BIOCHEMISTRY

Hexose Monophosphate Pathway

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Chapter Description

- Overview

  This pathway important to generate pentose sugar and reduced NADP.

- Expected Outcomes

  You should be able to understand the importance of this pathway in converting hexose to pentose sugar for various essential biochemical components. Also in supplying NADPH.

- Other related Information

  Some relevant questions been provided for improving your understanding of the topic. You are expected to search for external sources for information to adequately answer the questions. All pictures and figures within this chapter categorized as creative commons for the purpose of education only.

Alternative Glucose Metabolism

Glucose utilization by tissues:

- Glucose may undergo one of the following fate:

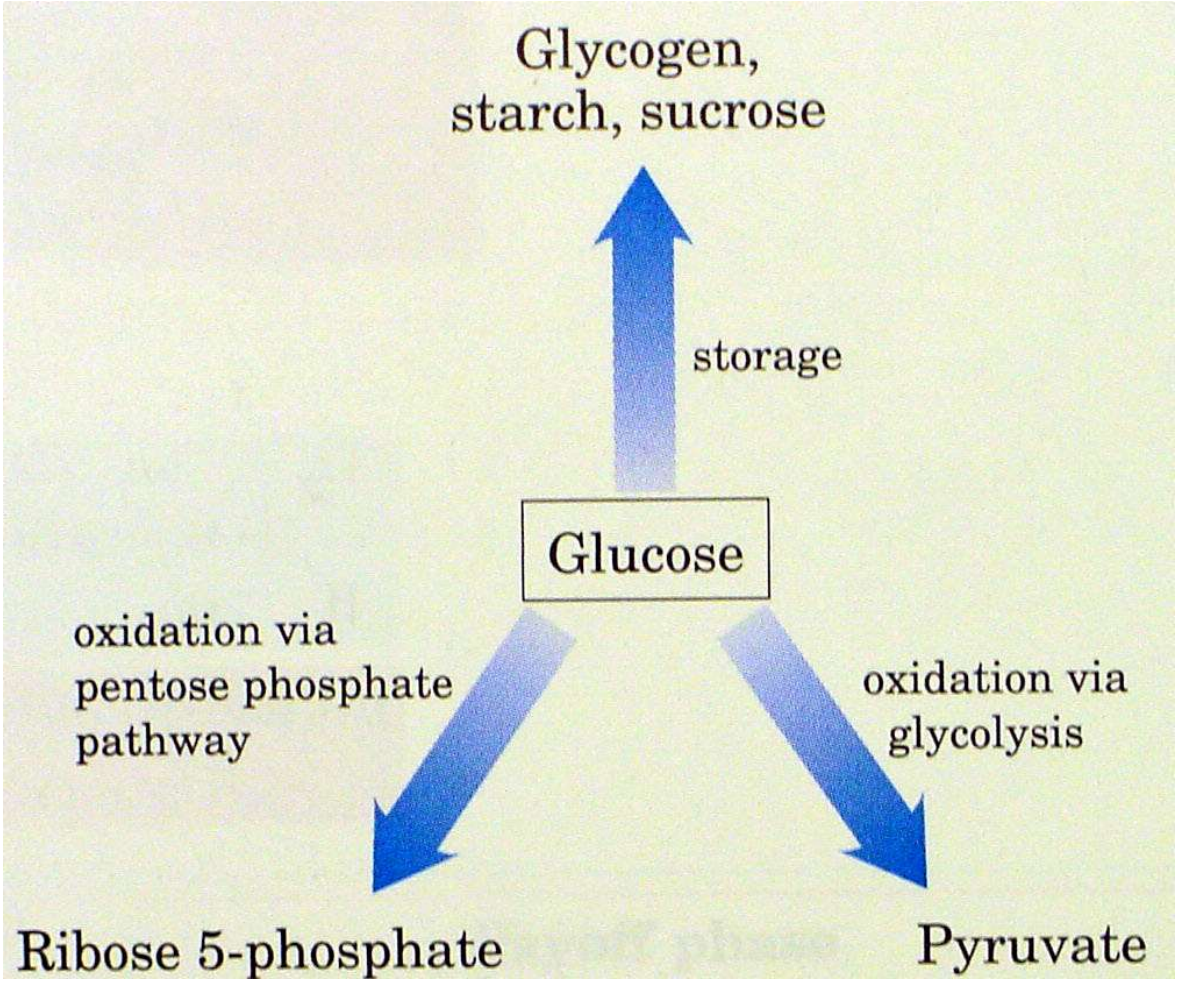
1. **Oxidation**
2. **Storage (as fat and glycogen)**
3. **Conversion (to substances of biological importance)**

Alternatives to Glycolysis

- Two pathways
  - Pentose phosphate pathway
  - Entner-Doudoroff pathway
    - Occurs only in prokaryotes
    - Yield different from glycolysis

    i.e 1ATP, 1NADH or 1NADPH
    - Uses different set of enzymes

The pentose phosphate pathway (HMP) is an alternate route for the oxidation of glucose.



Pentose phosphate pathway has two main functions

- **Generation of NADPH**

  - mainly used for reductive synthesis of fatty acids, steroids, amino acids via glutamate dehydrogenase; and production of reduced glutathione in erythrocytes and other cells.

  - active in liver, adipose tissue, adrenal cortex, thyroid, erythrocytes, testis, and lactating mammary gland

  - not active in non-lactating mammary gland and has low activity in skeletal muscle.

- **Production of ribose** residues for nucleotide and nucleic acid synthesis.

Pentose Phosphate Pathway(PPP) / Phosphogluconate Pathway(PGP) / Hexose Mono Phosphate(HMP) Shunt

- Is anabolic in nature and is a process that generates NADPH and pentoses.

  - *The **first phase** is the oxidative phase, in which NADPH is generated*
  - *The **second phase** is the non-oxidative phase which results in the synthesis of 5-carbon sugars (pentoses)*

- While it does involve oxidation of glucose, its primary role is anabolic rather than catabolic and this cycle takes place in **cytosol**.

Importance of the HMP/PPP

- **the function of the pentose phosphate pathway in production of NADPH and ribose precursors for nucleic acid synthesis.**
- **the importance of NADPH in protection of cells against highly reactive oxygen species.**
- **defects in the pentose phosphate pathway leads to disease conditions.**

Site :

➢In the cytoplasm of all cells **except muscle**, and nonlactating mammary gland (low activity)

- Generation of NADPH

  - mainly used for reductive syntheses of fatty acids, steroids/cholesterol, amino acids via glutamate dehydrogenase; and production of reduced glutathione in erythrocytes and other cells.

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NADPH for H_2O_2 elimination

- **In the Erythrocytes, Pulmonary Cells, and Liver Cells :**

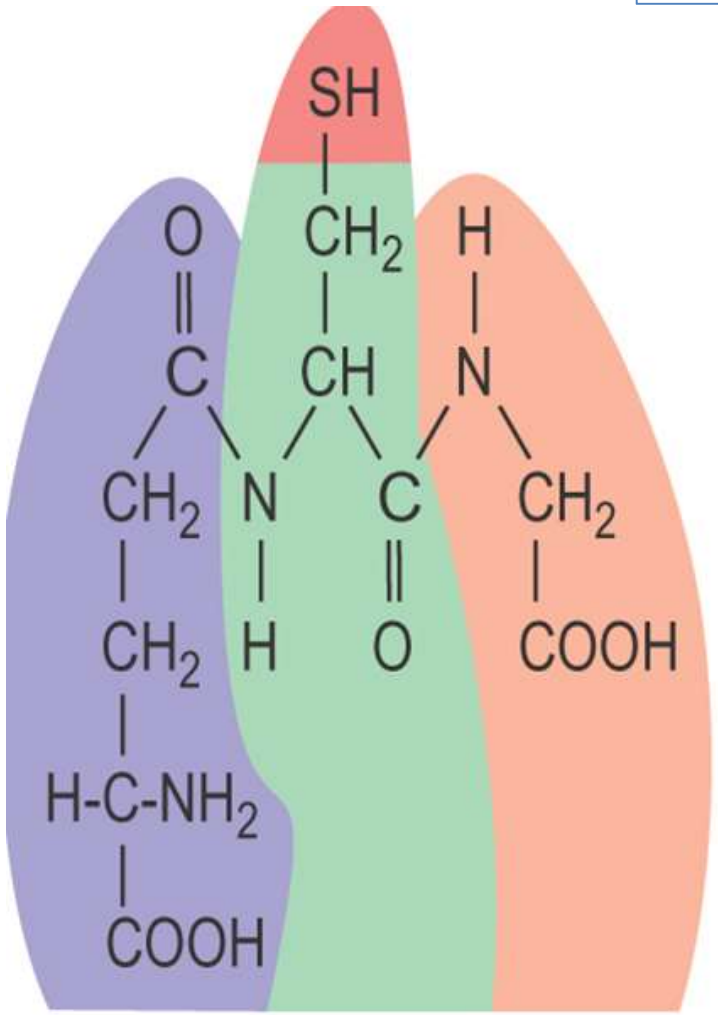
H_2O_2 + GSH (glutathione) → GS-SG + H_2O (1)

GS-SG + 2 NADPH → 2 GSH + 2 NADP (2)

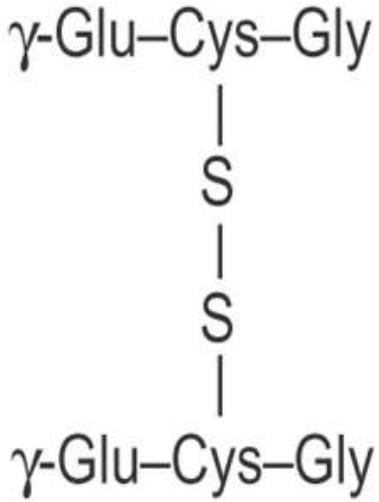
Enzyme 1.Glutathione peroxidase

Enzyme 2.Glutathione reductase

reduced glutathione (GSH) and oxidized glutathione (GSSG).

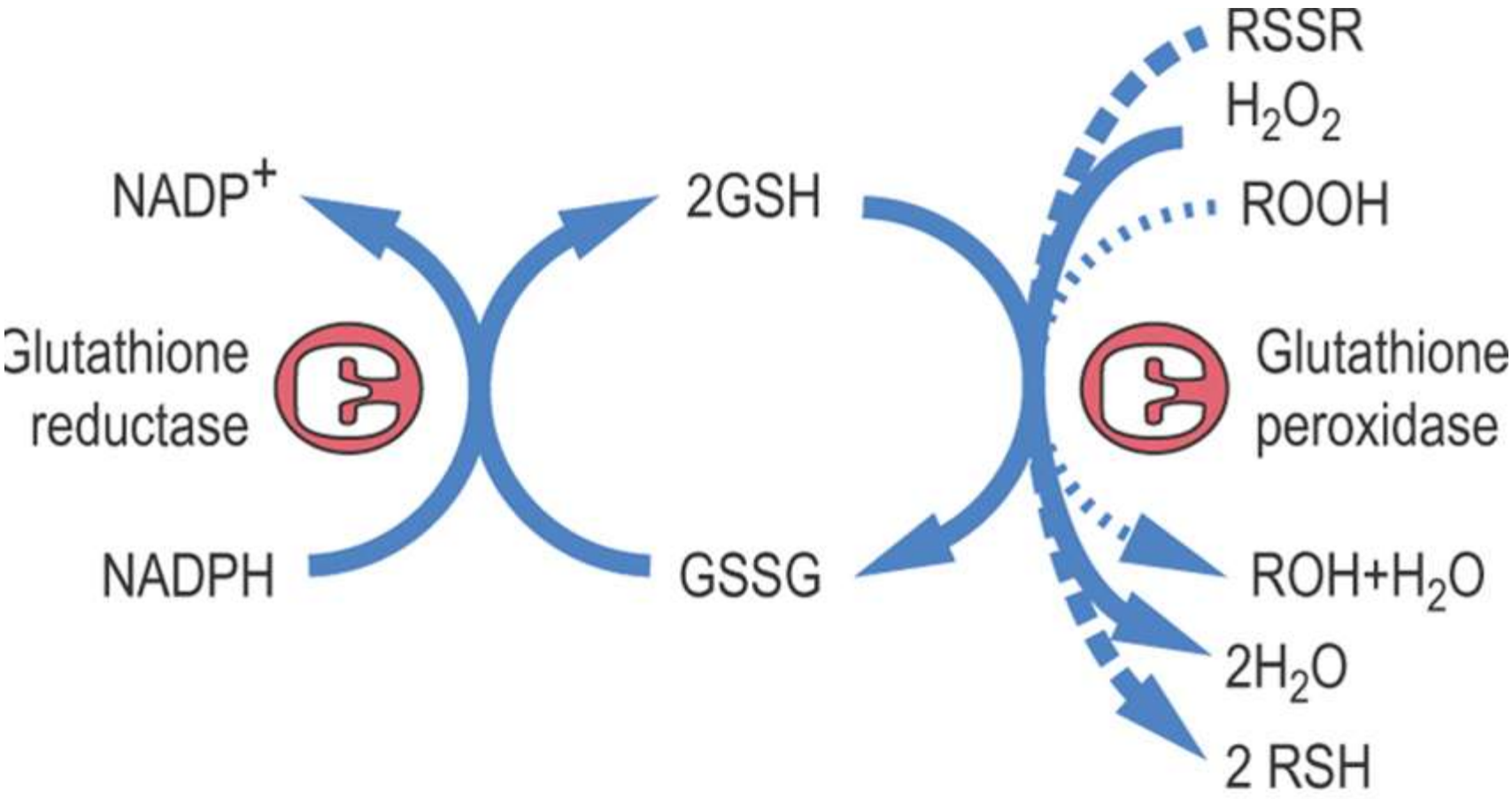


GSH



GSSG

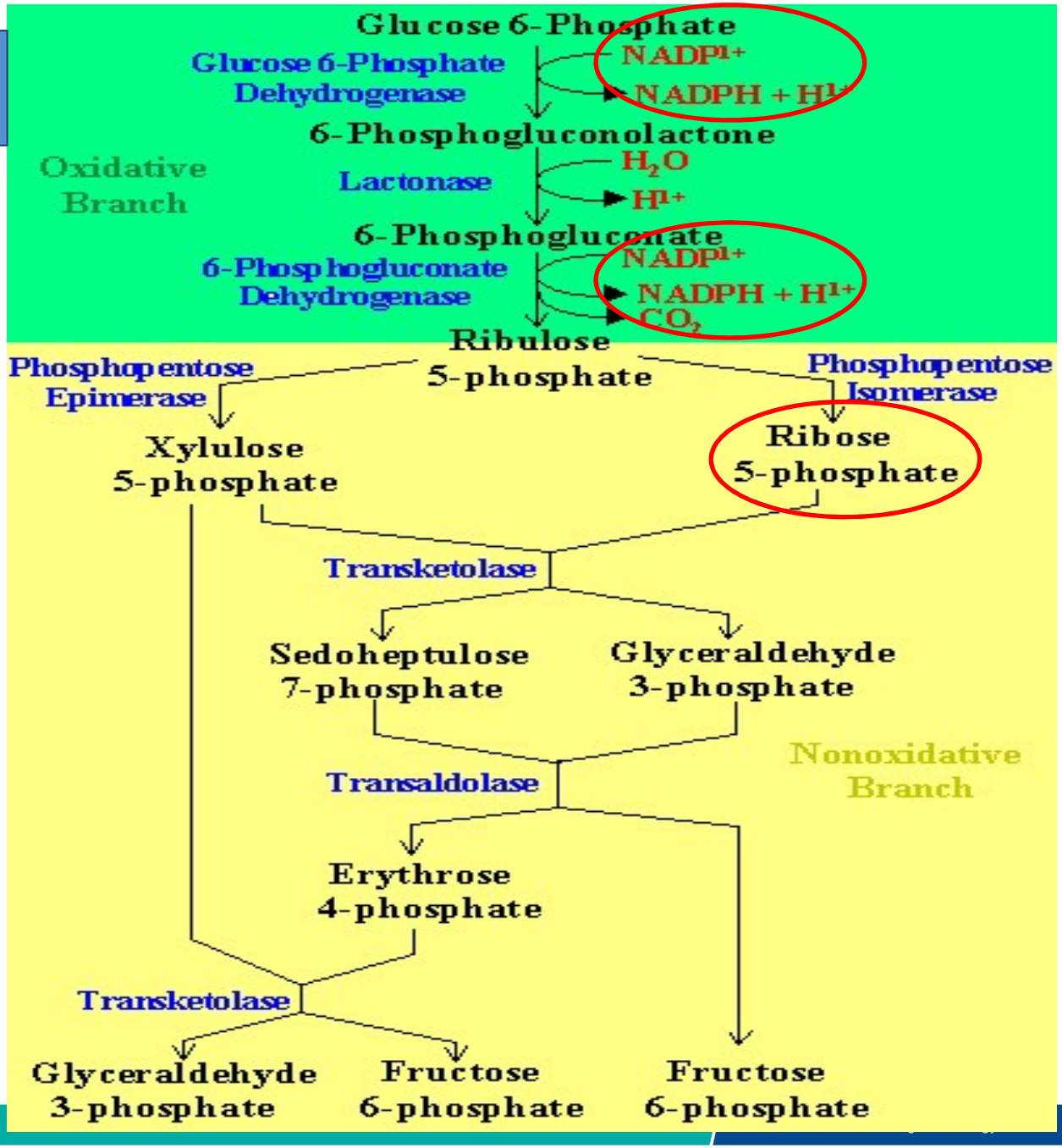
GSH has a range of protective functions (antioxidant) in the cell

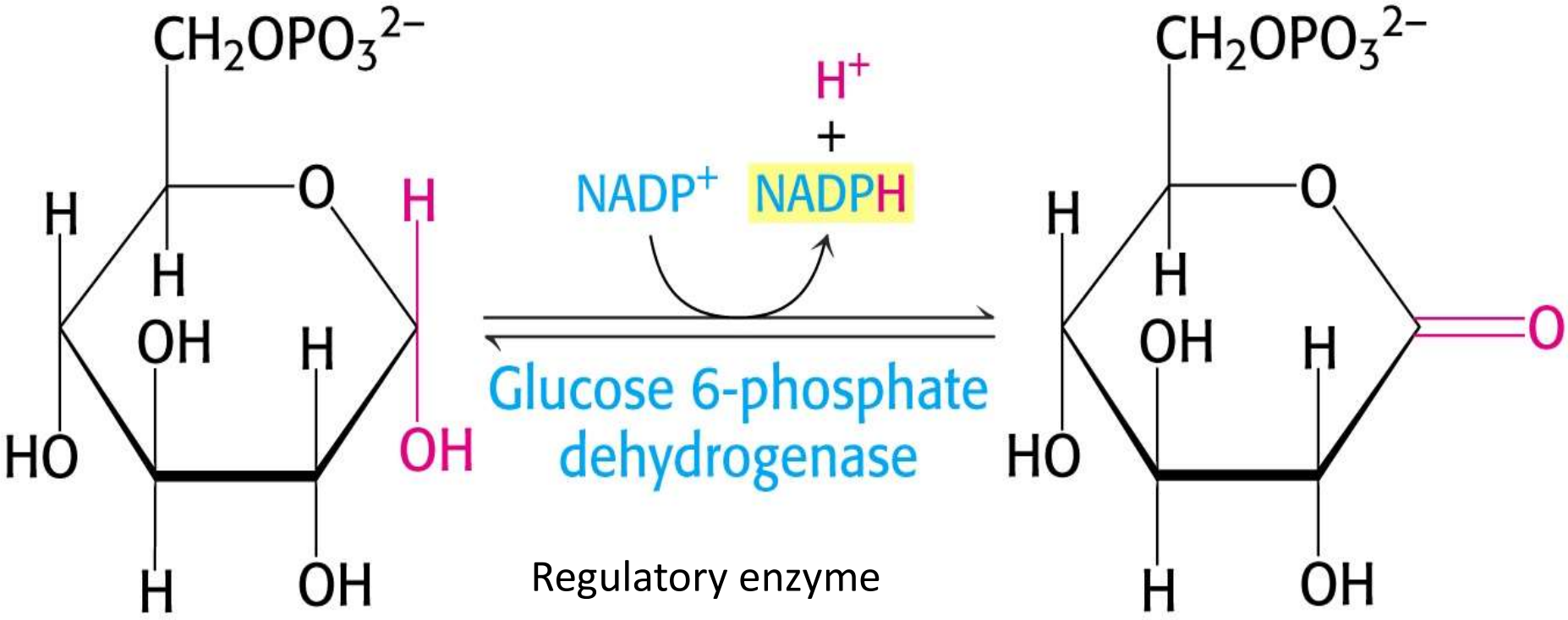


NADPH + H^+ is formed from two separate reactions.

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

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

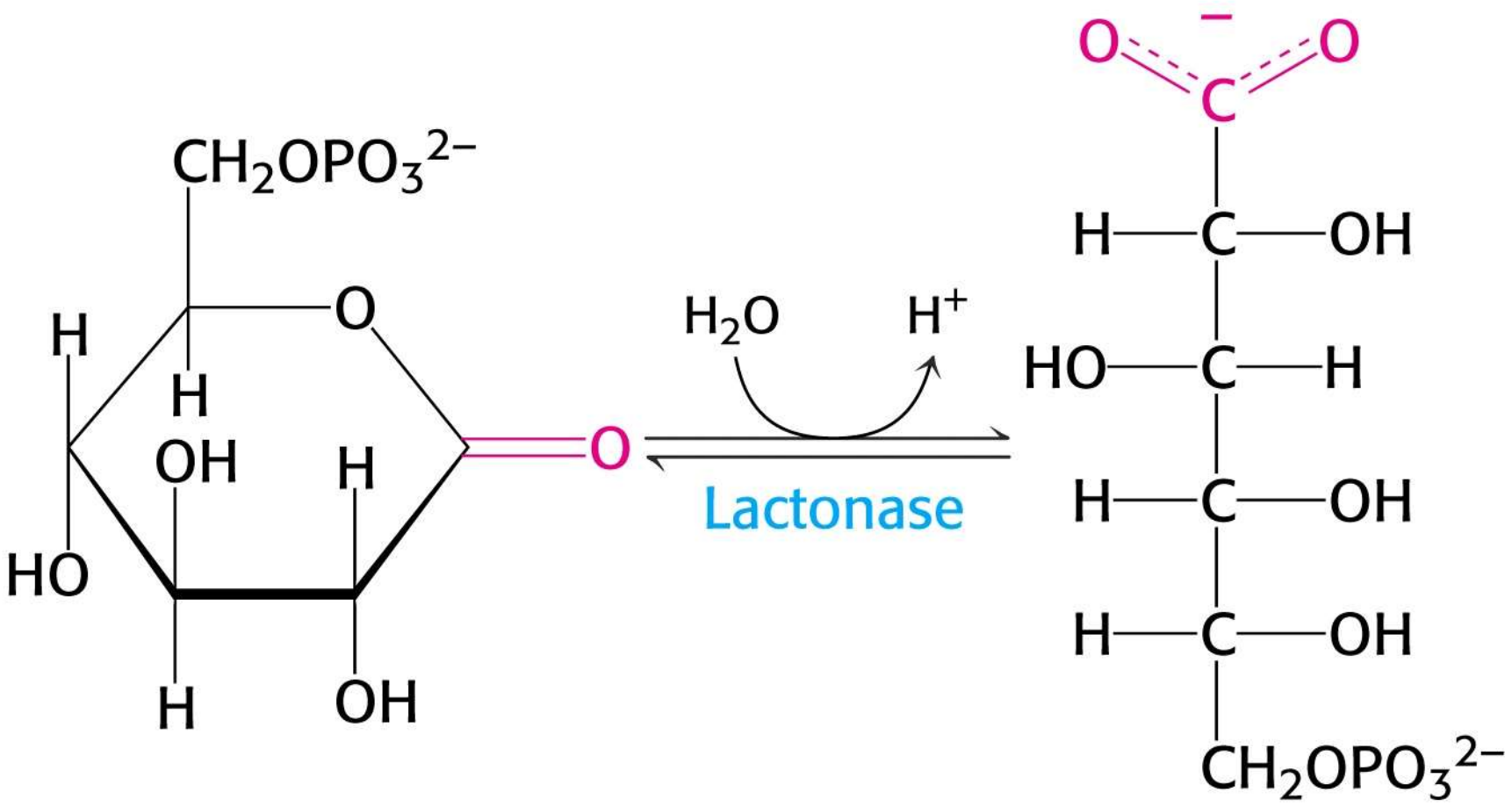




Glucose 6-phosphate

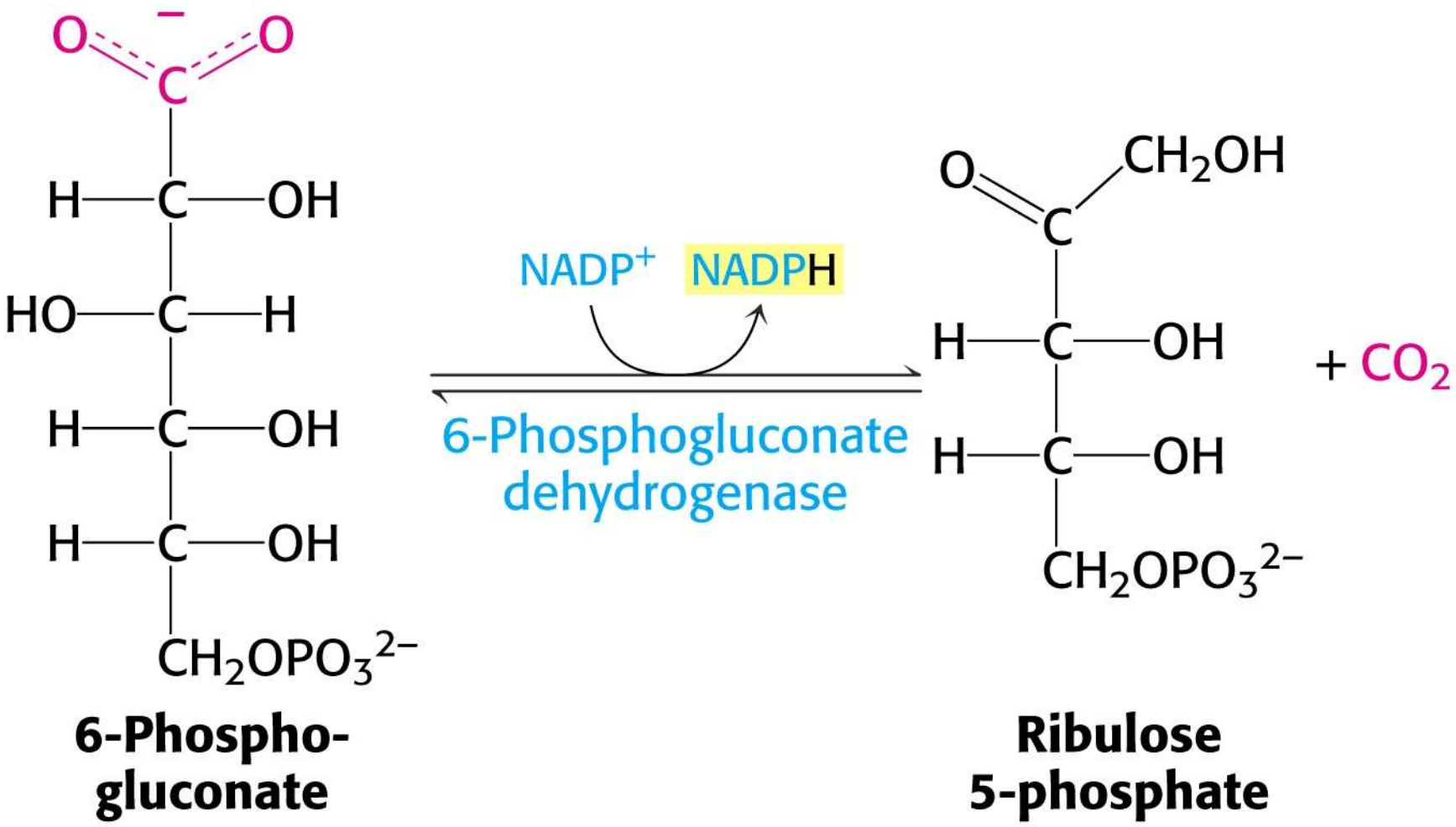
6-Phosphoglucono-δ-lactone

The enzyme is highly specific for $NADP^+$; the K_m for NAD^+ is 1000 greater than for $NADP^+$.



6-Phosphoglucono-δ-lactone

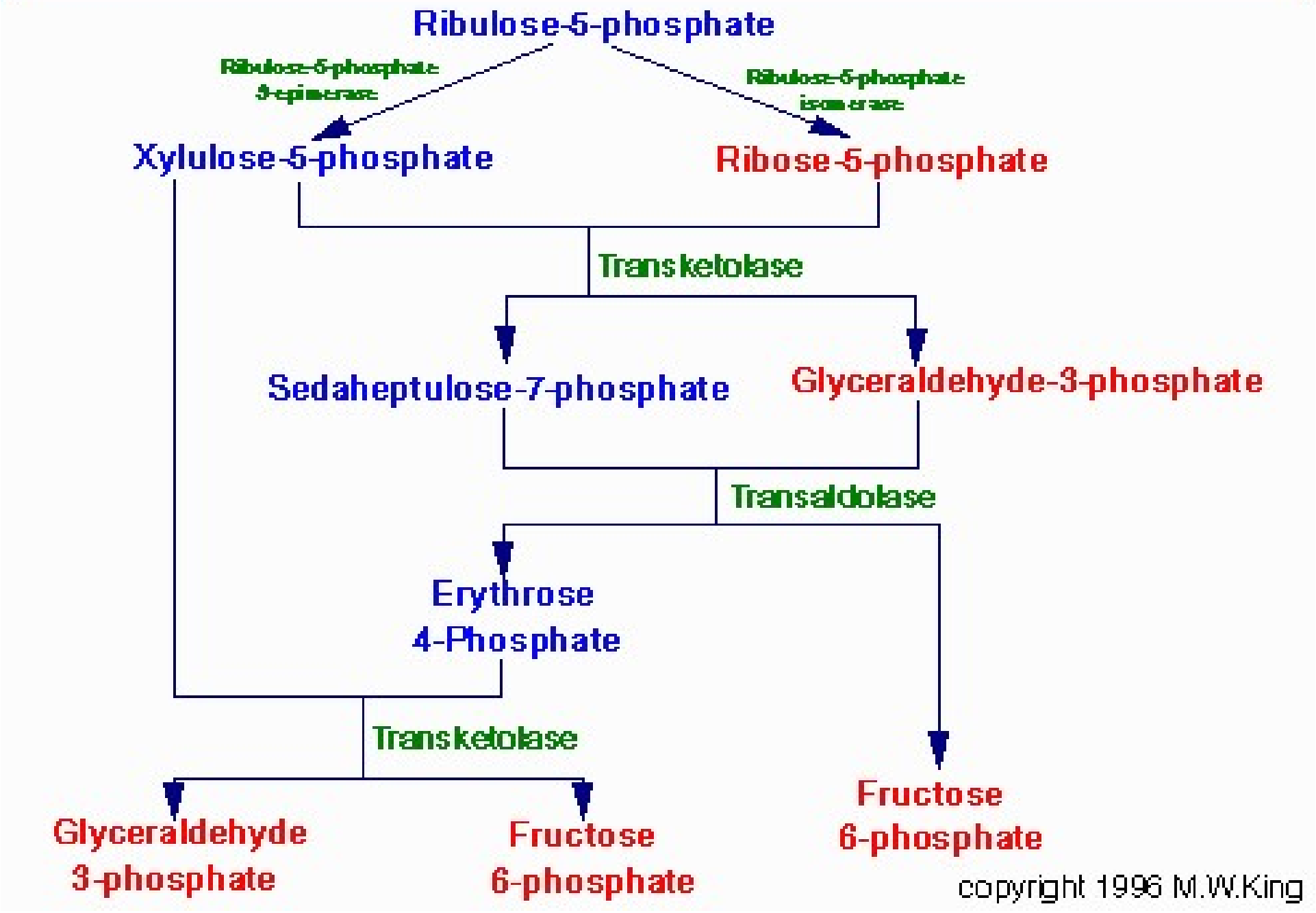
6-Phospho-gluconate



6-Phospho-gluconate

Ribulose 5-phosphate

Non-Oxidative Stage of Pentose Phosphate Pathway



- Transketolase (TPP) and transaldolase are the link back to glycolysis.
- Glyceraldehyde 3-phosphate
- Fructose 6-phosphate
- Net result:

$$3C_5 \leftrightarrows 2C_6 + C_3$$

In the muscle

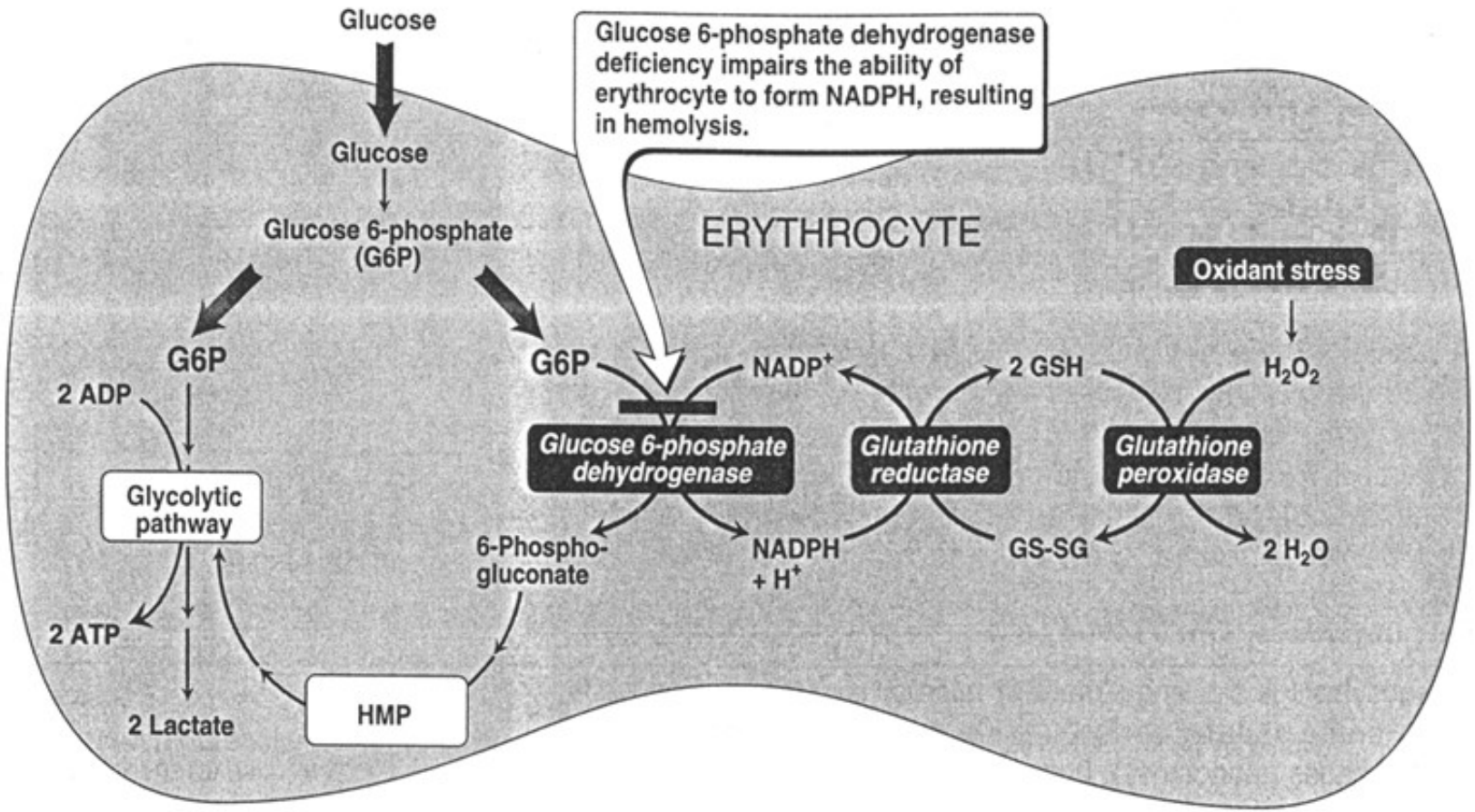
- HMP Shunt **inactive** because G 6P Dehydrogenase and 6 P Gluconate Dehydrogenase deficient

- Ribose 5 P synthesized in the way of reverse HMP Shunt or through Transketolase path.

Regulation of HMP

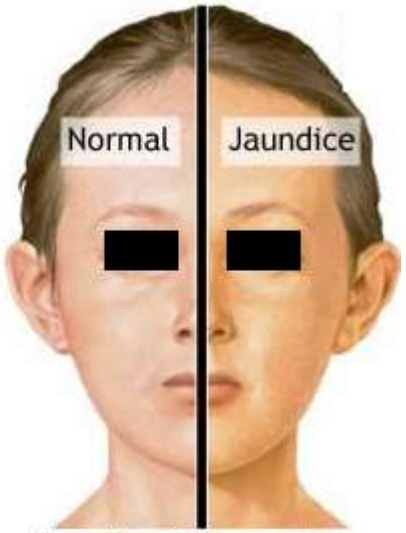
- Glucose-6-P dehydrogenase
  - First step
  - Rate limiting
- Allosteric Regulation
  - Feedback inhibited by NADPH
- Inducible enzyme
  - Induced by insulin

HMP in the RBC



GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY CAUSES HEMOLYTIC ANEMIA

- Some persons have **a genetic defect in G6PDH**, typically yielding an unstable enzyme that has a shorter half-life in the RBC or is unusually sensitive to inhibition by NADPH.
- because of the decreased activity of this enzyme and insufficient production of NADPH the cell's ability to recycle GSSG to GSH is impaired
- leads to excessive damage and **lysis of RBCs** (hemolysis) and hemolytic anemia.
- **Bilirubin**, a product of heme metabolism, overloads hepatic detoxification pathways, and also accumulates in plasma and tissues, causing **jaundice**.



Jaundice is a symptom where the skin and eyes become yellow

What is glucose-6-phosphate dehydrogenase deficiency?

- a genetic disorder that occurs most often in males.
- a defect in the enzyme causes red blood cells to break down prematurely . This destruction of red blood cells is called hemolysis hemolytic anemia
- Glucose-6-dehydrogenase deficiency is also a significant cause of mild to severe jaundice in newborns.
- Mutations in the G6PD gene located in the X-chromosomal cause glucose-6-phosphate dehydrogenase deficiency.
- Chemical reactions involving glucose-6-phosphate dehydrogenase produce compounds that prevent reactive oxygen species such as superoxide, hydrogen peroxide, and hydroxyl from building up to toxic levels within red blood cells.

Pentose Phosphate Pathway

Three main functions:

1) Supply the cell with NADPH in order to:

a) provide reducing power for biosynthetic reactions.
b) serve as a biochemical reductant (e .g., maintain glutathione levels).
c) be utilized by the cytochrome P450 monooxygenase system.
d) as the electron source for reduction of ribo-to deoxyribonucleotides for DNA synthesis.

2) Convert hexoses into pentoses

(which are essential components of ATP, CoA, NADP+, FAD, RNA, and DNA).

3) Enable the complete oxidative degradation of pentoses

by converting them into hexoses and trioses which can then enter the glycolytic pathway.

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