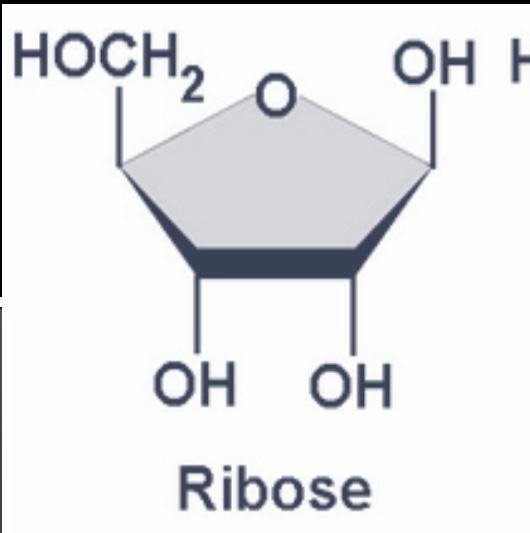


Pentose Phosphate Pathway



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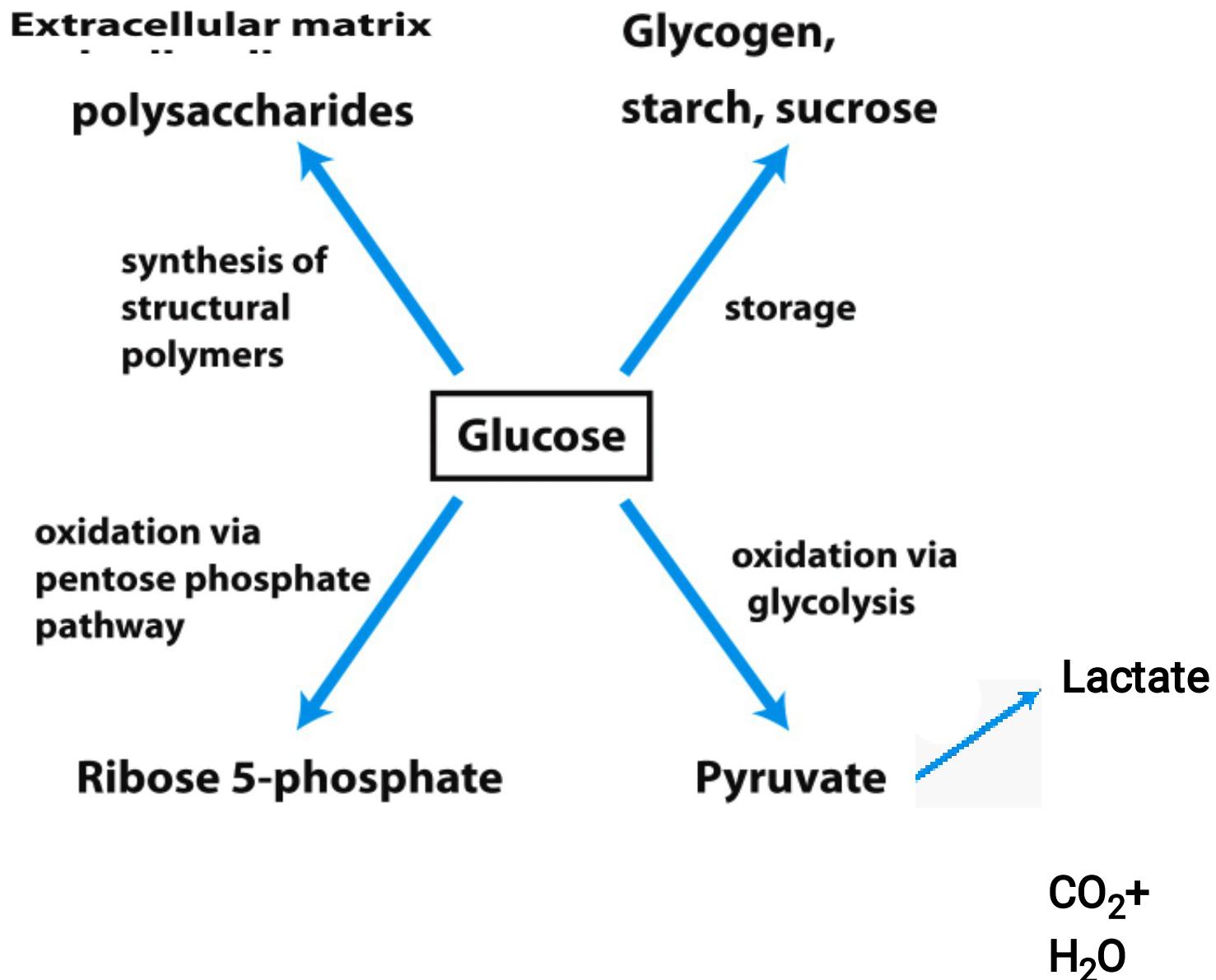
This is a 4-year old boy which presented to Al-Mafraq Hospital for Pediatrics and Gynecology at Al-Mafraq, Jordan on the 1st of March , 2010 complaining of Yellowish Discoloration in his sclera

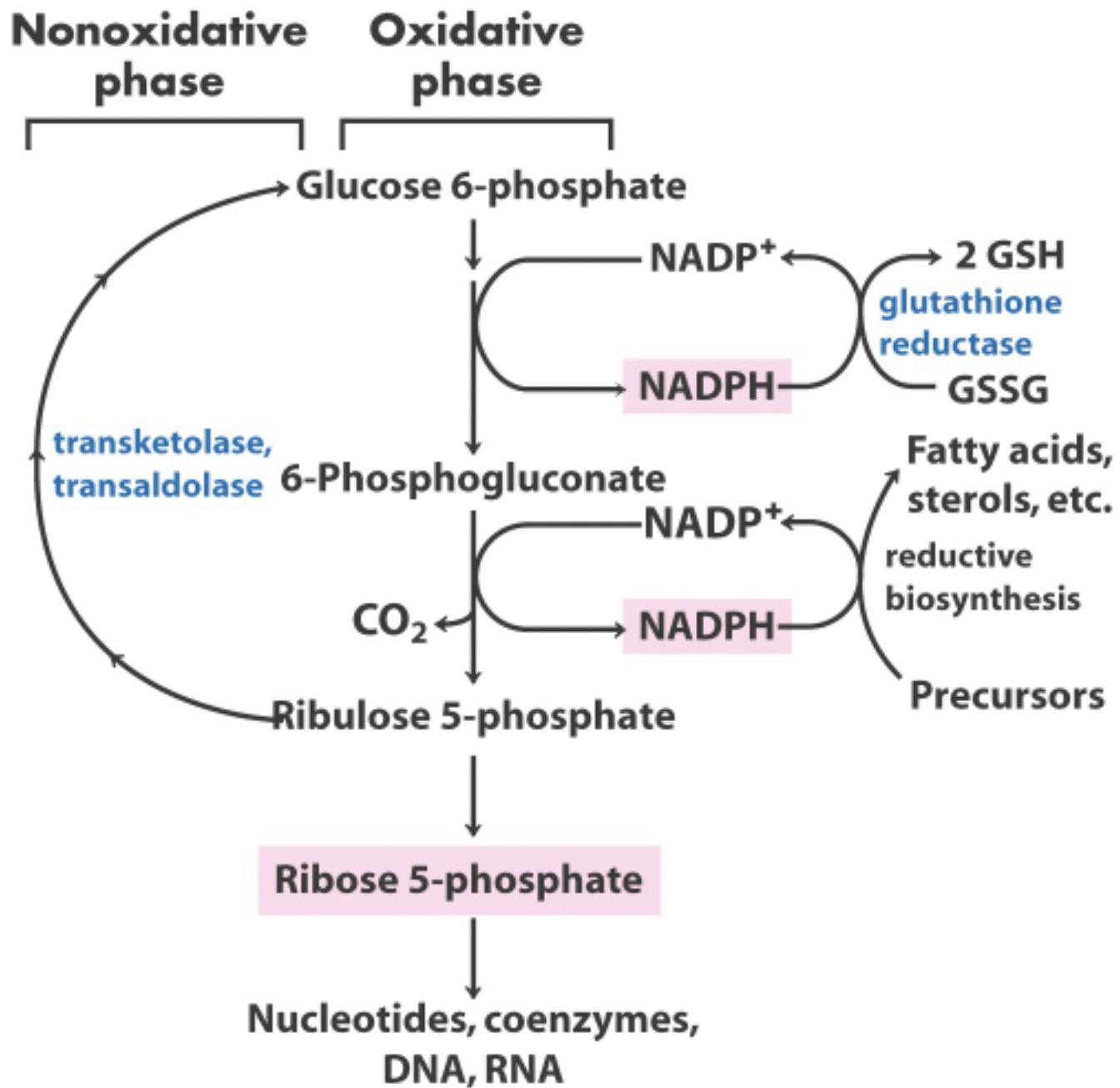
ILOs

At the end of this lecture student should be able to,

- outline Pentose phosphate pathway (PPP).
- explain the role of PPP in CH metabolism.
- list the tissue in which the PPP is active.
- discuss the significance of NADPH production.
- discuss clinical significance of PPP deficiencies.

Glucose metabolism





PPP overview

PPP overview

- Hexose mono-phosphate shunt
- Occurs in cytosol
- 2 Phases
 - Oxidative
 - Non-oxidative
- entry of G6P into the PPP is controlled by the cellular NADPH/NADP+
- It is important in tissues such as adipose, liver, mammary gland, and adrenal cortex (NADPH depended synthesis of steroids)
- Only source of NADPH in RBCs

Role of PPP

- Meet the NADPH demand of the cell
 - provide reducing power for biosynthetic reactions [FA, Nucleotide, Neurotransmitter, Cholesterol]
 - Reduction of oxidized glutathione
 - utilized by the cytochrome P₄₅₀ monooxygenase system
 - Generation of superoxide in phagocytes by NADPH oxidase
- Supply pentose sugars [ATP, CoA, NADP⁺, FAD, RNA, and DNA]

Oxidative (irreversible) Phase

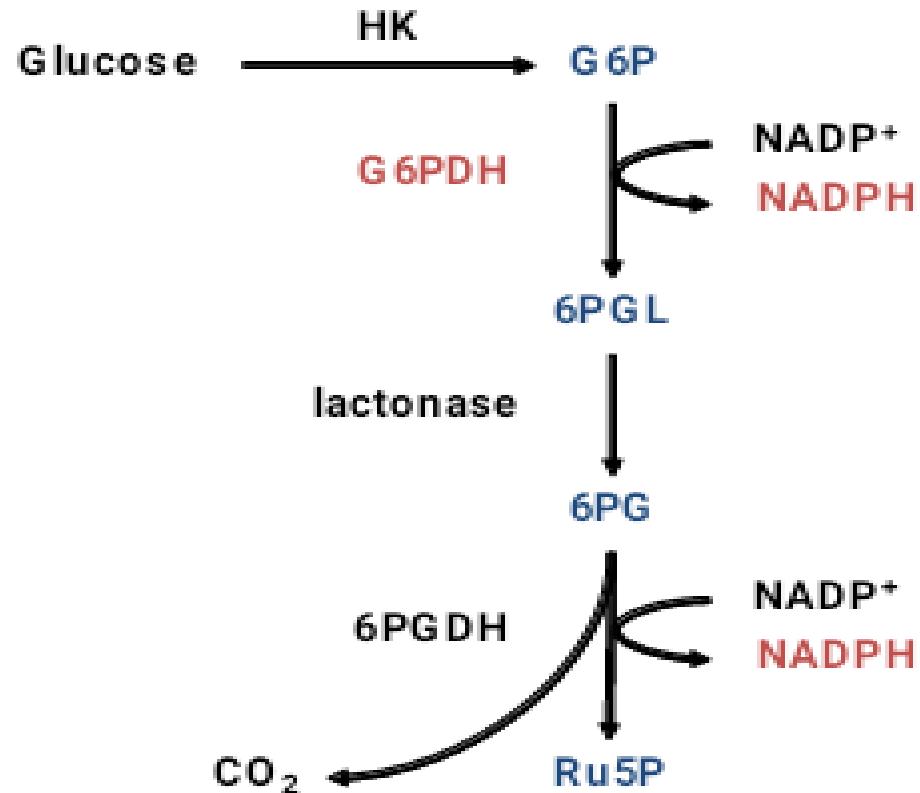
- **G6PDH: glucose-6-phosphate dehydrogenase**

Key regulatory enzyme

+ High NADP⁺/NADPH

+ high G6P

Transcription of gene under hormonal regulation.



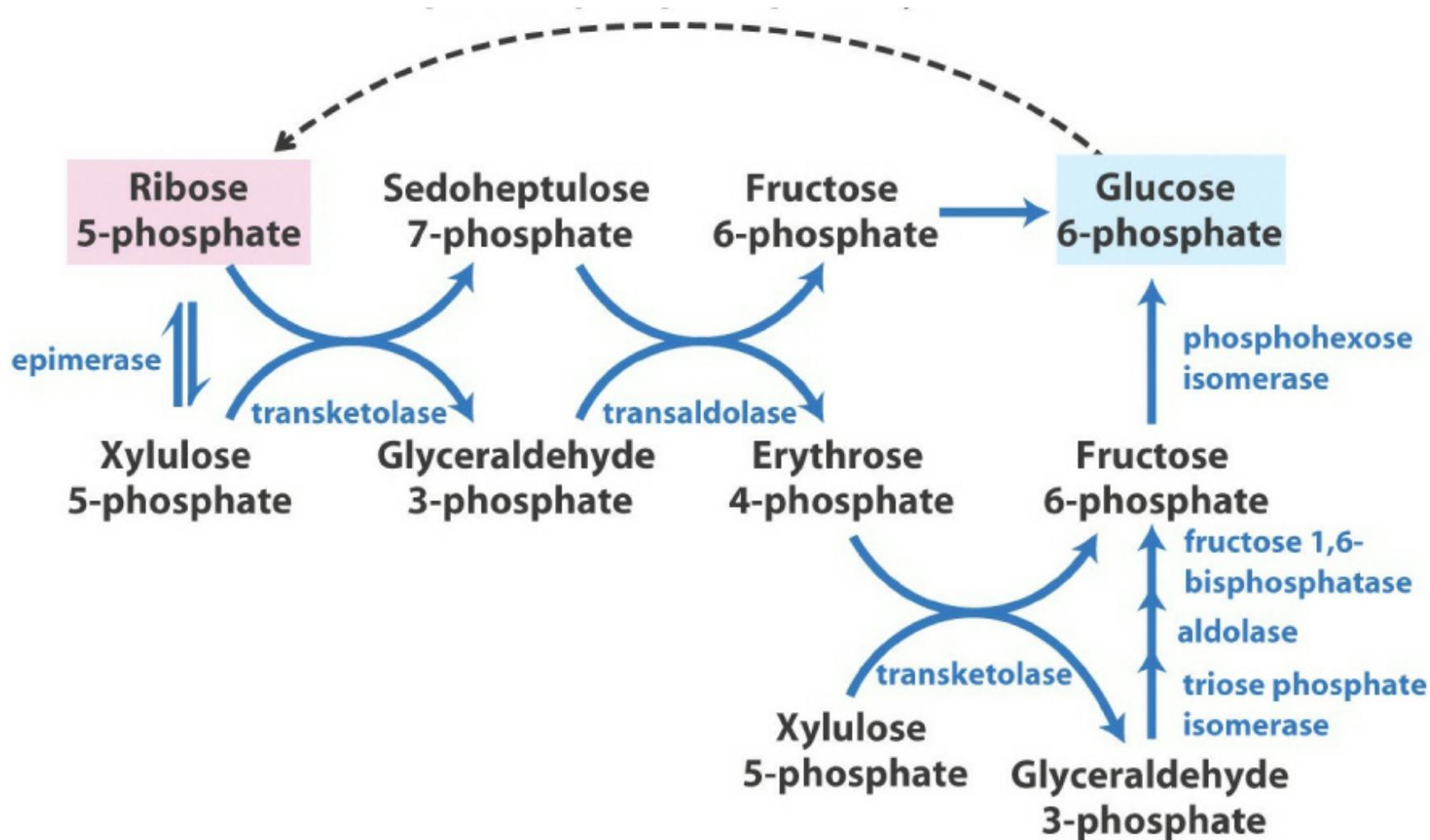
- **6PGDH: 6-phosphogluconate dehydrogenase**
- **6PGL: 6-phosphoglucono-δ-lactone**
- **6PG: 6-phosphogluconate**
- **Ru5P: ribulose-5-**

The Nonoxidative (reversible) phase

Five steps, only 4 types of reaction

- **Phosphopentose isomerase** : converts ketose to aldose
- **Phosphopentose Epimerase** : epimerizes at C-3
- **Transketolase** (TPP-dependent): transfer of two-carbon units
- **Transaldolase**: transfers a three-carbon unit

Non-oxidative phase



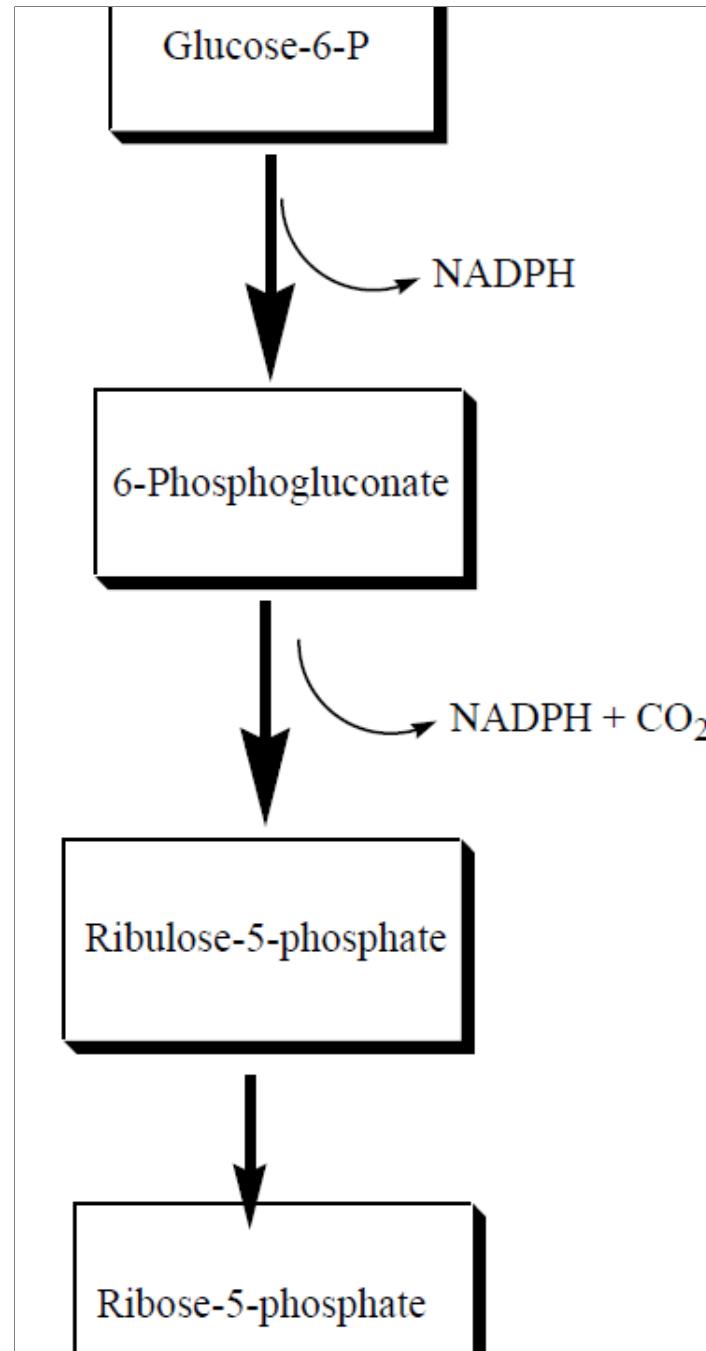
Why do we call it a shunt?

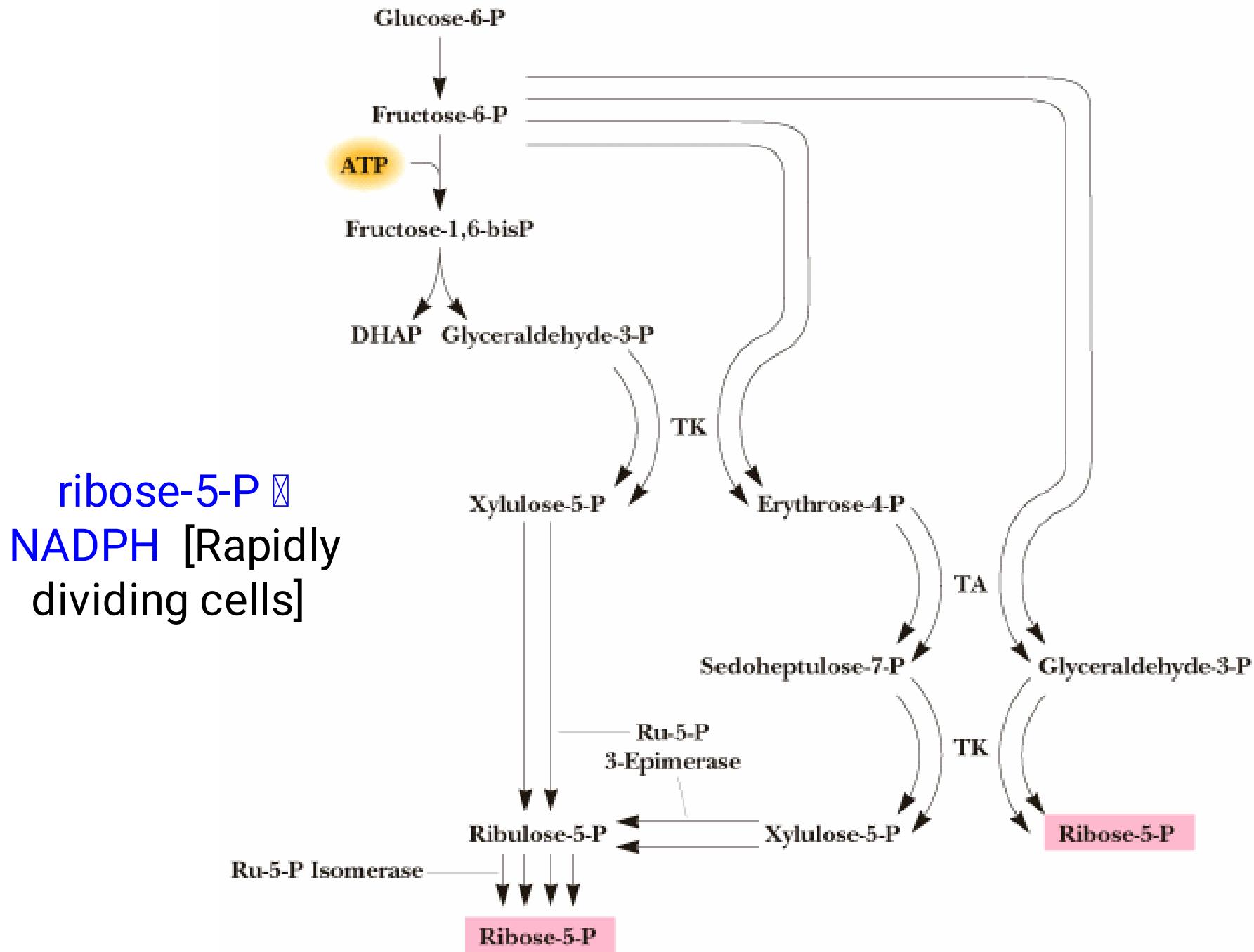
- Begins with the glycolytic intermediate G6P
- Reconnects with glycolysis
 - glyceraldehyde 3-P
 - fructose 6-P

PPP regulation

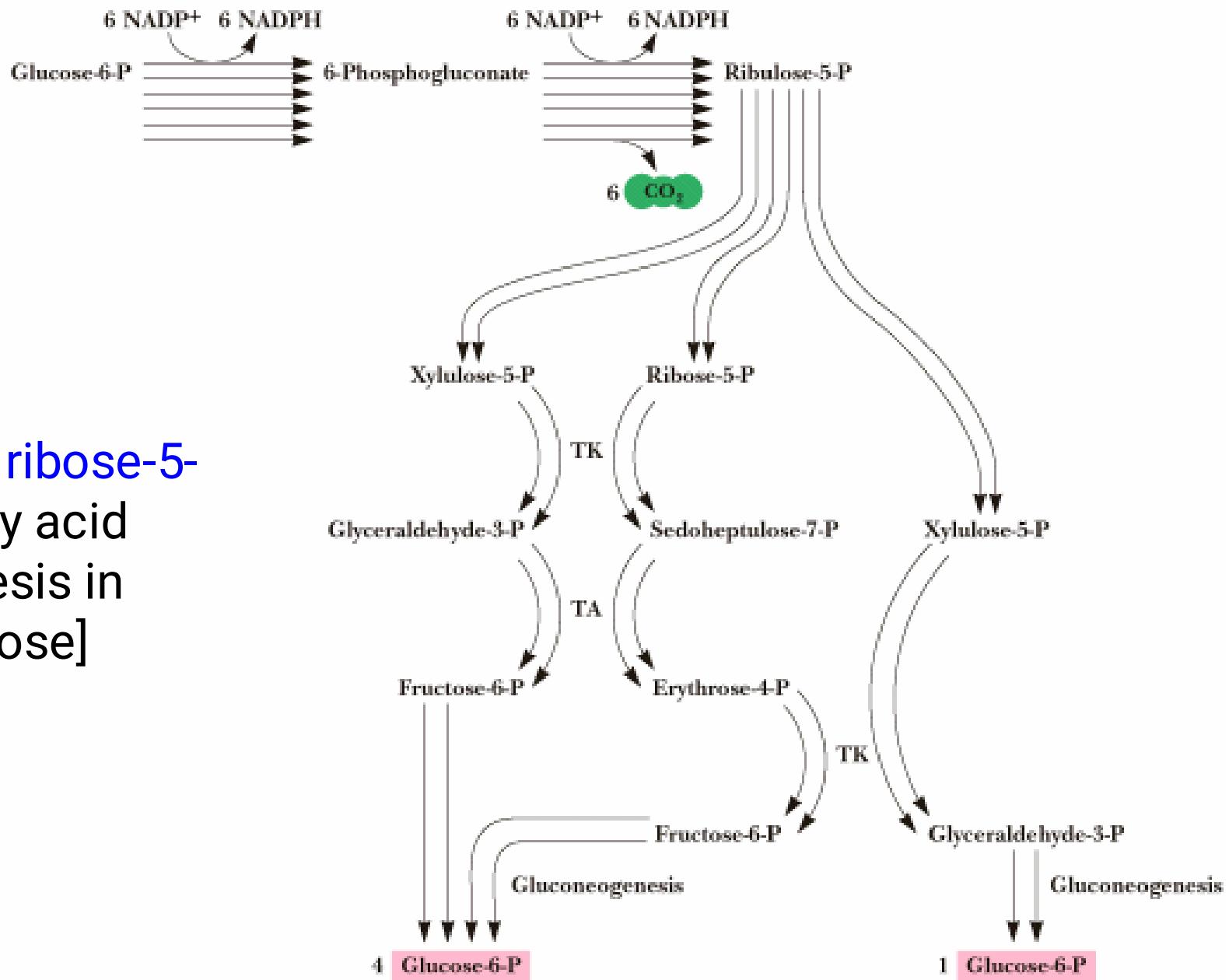
- The flow of Glc-6-P depends on the need for **NADPH, ribose 5-P, and ATP**
- Operates in different modes
 - i. both ribose-5-P and NADPH
 - ii. ribose-5-P \otimes NADPH [Rapidly dividing cells]
 - iii. NADPH \otimes ribose-5-P [Fatty acid synthesis in adipose]
 - iv. NADPH + ATP, not ribose-5-P

both ribose-5-P and NADPH

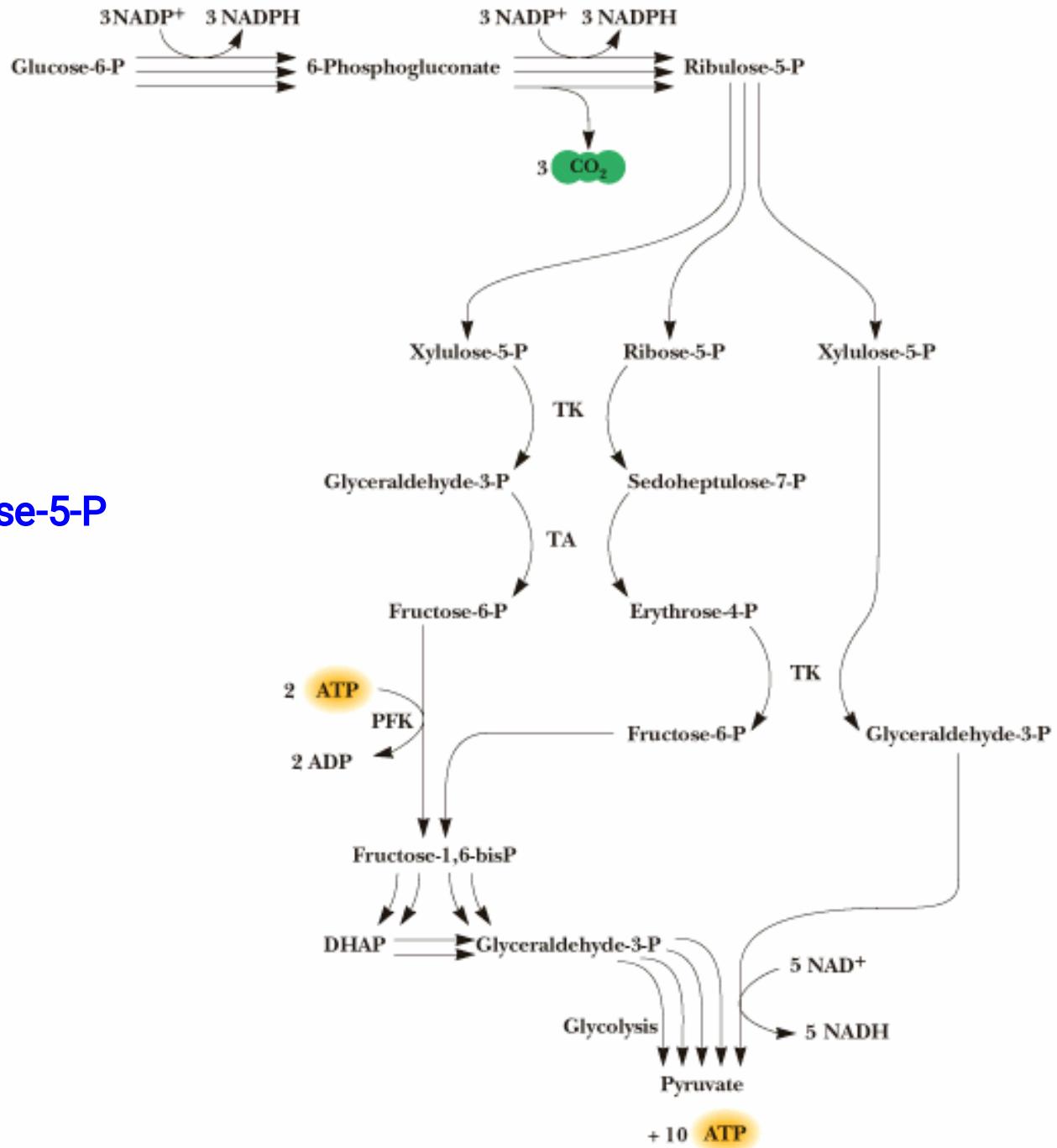




NADPH ⊗ ribose-5-P [Fatty acid synthesis in adipose]



NADPH + ATP, not ribose-5-P



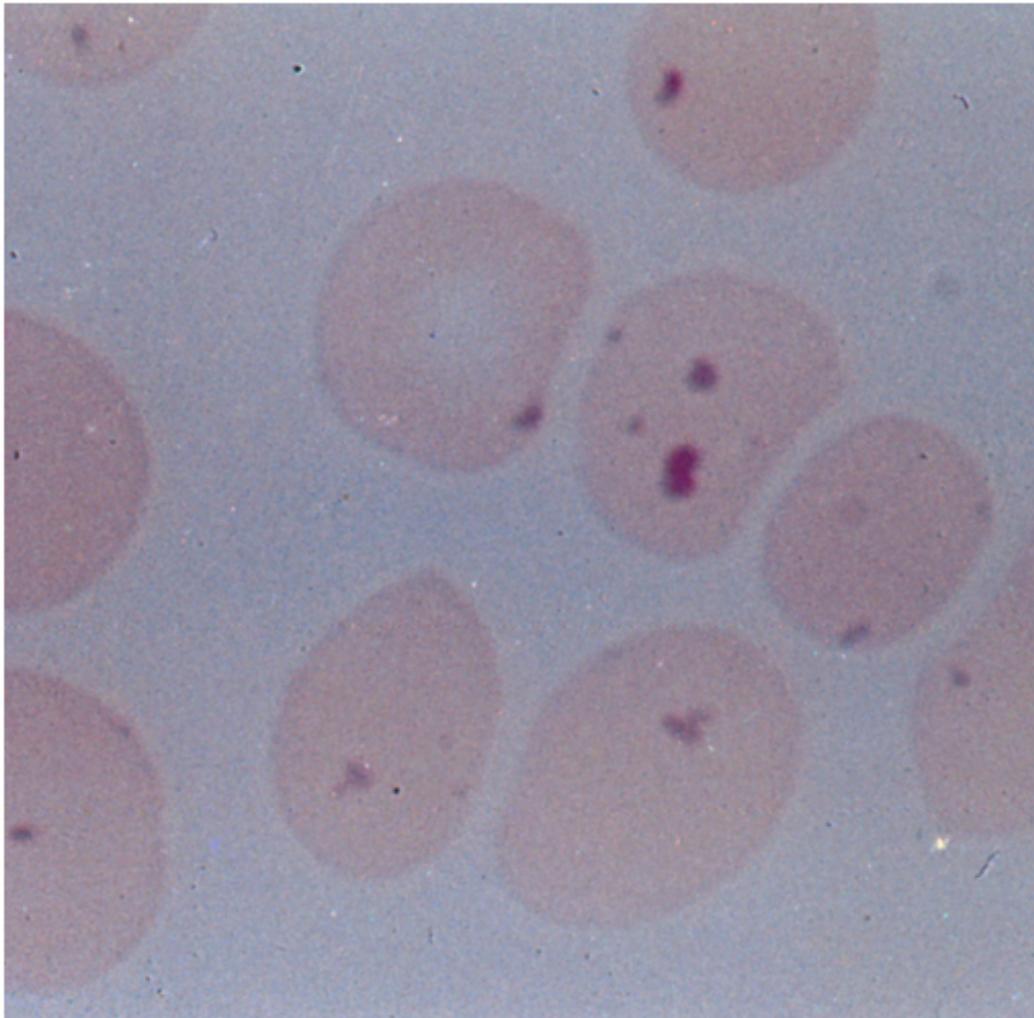
Glucose-6-phosphate dehydrogenase deficiency

- G6PD deficiency is an inheritable X-linked recessive disorder
- Over 300 genetic variants of the G6PD protein are known
- Most G6PD-deficient individuals are asymptomatic
- **Can cause haemolytic anaemia and jaundice due to excessive haemolysis**
- 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
- G6PD deficient individuals are resistant to malaria [Plasmodium falciparum]

Precipitating factors in G6PD deficiency

- Oxidant drugs
 - antimalarial agents [primaquine]
 - sulfonamides (antibiotic)
 - aspirin
- Favism
- exposure to certain chemicals – mothballs
- Infections

Glucose-6-phosphate dehydrogenase deficiency





This is a 4-year old boy presented to the Pediatrics and Gynecology unit at Al-Mafraq, Jordan with complaining of Yellowish Discoloration in his sclera which later proved to be a manifestation of hemolytic anemia due to G6PD deficiency following Fava beans consumption.

This early destruction of red blood cells is known as **hemolysis**, and it can eventually lead to **hemolytic anemia**.

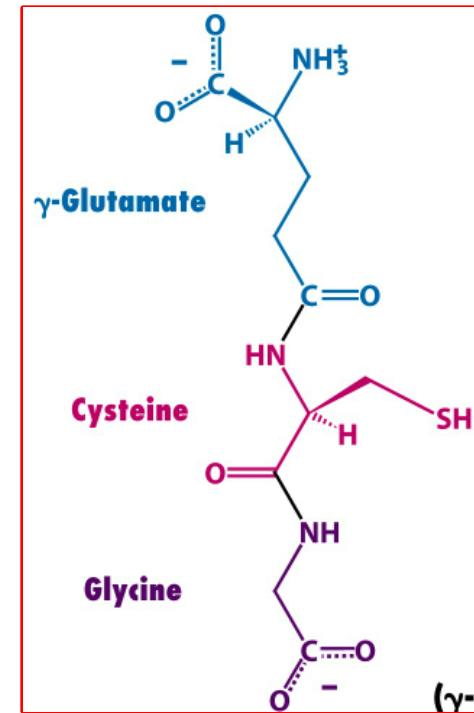
Jaundice: yellowing of the skin and eyes.

Cause: too much bilirubin in your system.

Bilirubin is a yellow pigment that is formed by the breakdown of red blood cells in the liver.

Glutathione and RBCs

- Tripeptide: glutamate, cysteine, glycine
- non-enzymatic thiol antioxidant
- Undergoes oxidation, protecting proteins , cellular organelles
- **GSH is essential for normal RBC structure and keeping hemoglobin in Fe^{++} state [Prevent Methemoglobin formation]**
- Glutathione reductase regenerates GSH
- Continuous NADPH supply is needed
- PPP is the sole NADPH supplier in RBCs



Glutathione and RBCs

