UNIVERSITY OF BASRAH
AL-ZAHRAA MEDICAL COLLEGE

MINISTRY OF HIGHER EDUCATION AND SCIENTIFIC RESEARCH

The module: Metabolism

Session 3, Lecture 1

Duration : 1 hr

Carbohydrate Metabolism 2.

Module staff

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Marks Essentials of Medical Biochemistry.

Ganong's Review of Medical Physiology .

For more discussion, questions or cases need help please post to the session group

Learning outcomes (LO)

1. Why the pentose phosphate pathway is an **important metabolic pathway** in some tissues.

2. The clinical condition of **Glucose 6-phosphate dehydrogenase deficiency** and the biochemical basis of the signs and symptoms.

3. The biochemical basis of the clinical conditions of **lactose intolerance** and **Galactosaemia**.

4. The key role of **pyruvate dehydrogenase** in glucose metabolism.

What is Pentose Phosphate Pathway ?

Pentose Phosphate Pathway (PPP) : LO 1

Also known as:

- **Pentose shunt .**
- **Hexose monophosphate shunt .**
- **Phosphogluconate pathway .**

- Is a process that breaks down **Glucose-6- phosphate (G6p)** into:
-

  1. **NADPH.**
  2. **Pentoses (5- carbon sugars).**

  for use in downstream biological processes.

- It occurs in the **cytosol.**

- It is an alternate route for the oxidation of glucose **without** direct consumption or generation of **ATP.**

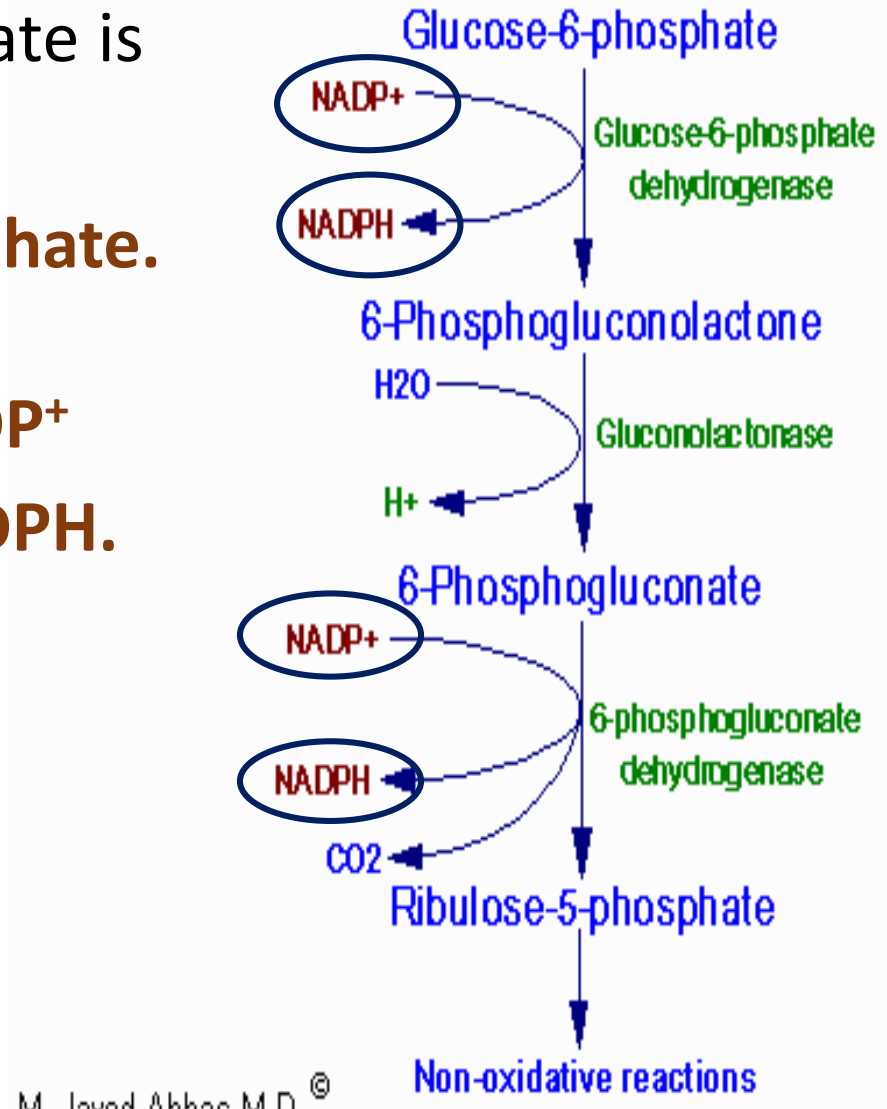
- Serves as an entry into Glycolysis for both **5-carbon** & **6-carbon sugars.**

- **2** Phases of pentose phosphate pathway:
    1) **The oxidative phase**.
    2) **The non-oxidative phase.**

a) Glucose-6-phosphate is converted to **Ribulose-5- phosphate.**

b) **2** molecules of **$NADP^+$** are reduced to **NADPH.**

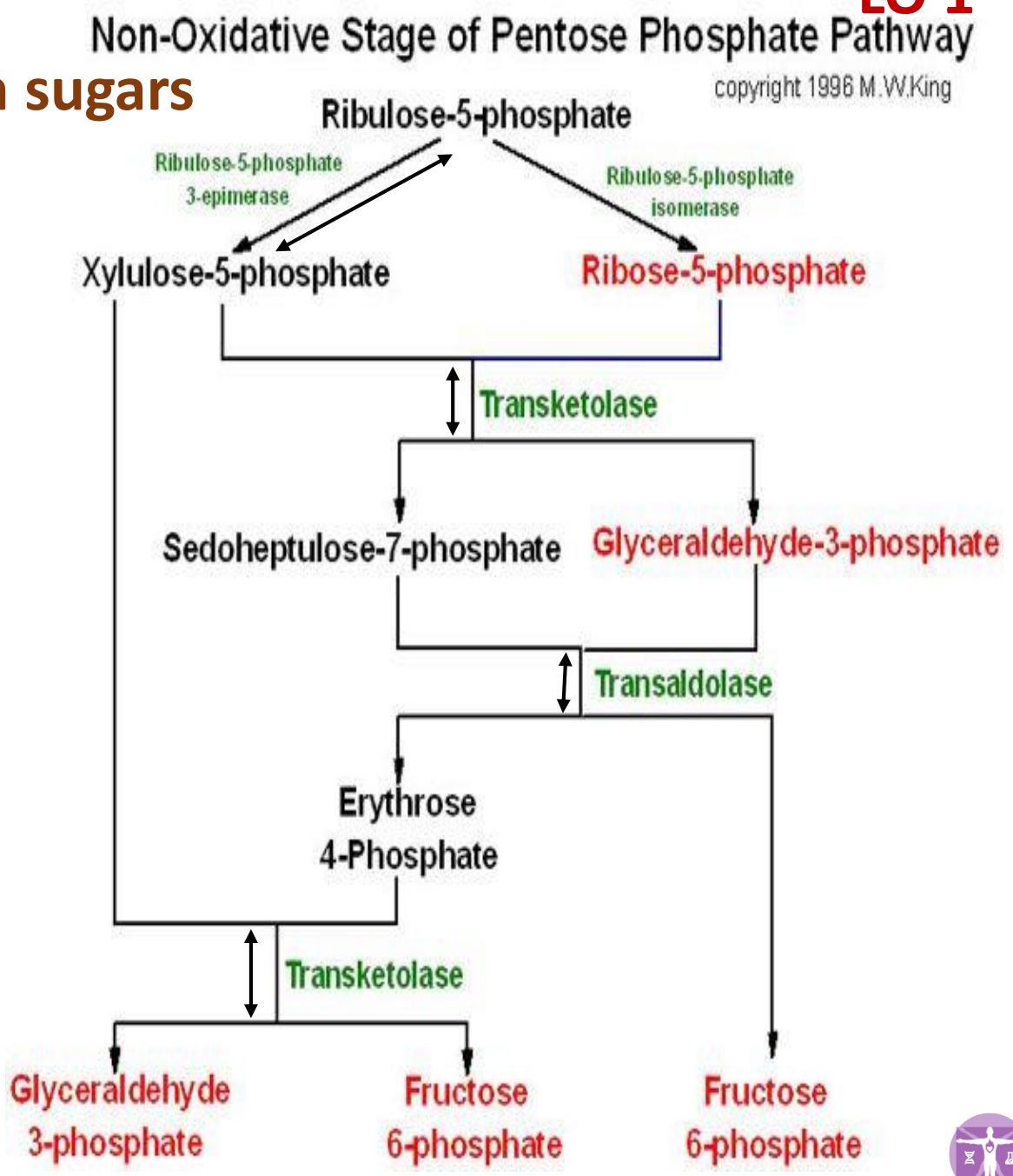
c) **-1 H_2O and + 1 CO_2**



LO 1

a) Generates **5-carbon sugars** which can be used in the synthesis of **nucleotides**.

b) These reactions are **reversible.**

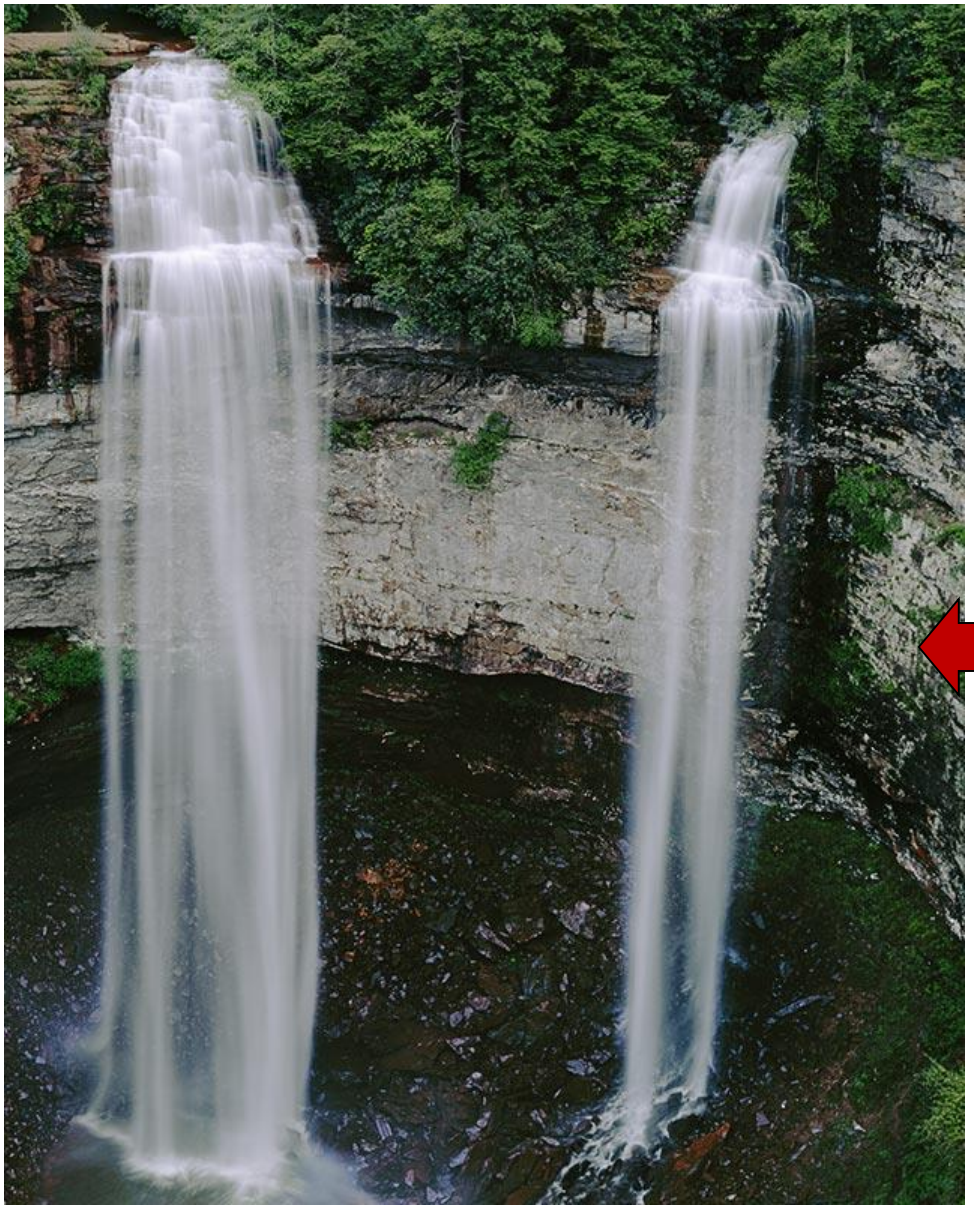


Moderate glucose flux

LO 1

Glycolysis only

Glycolysis



Pentose Phosphate Pathway

Importance of pentose phosphate pathway : LO 1

A. Generation of NADPH (reducing agents) oxidative steps

- **Mainly used for:**
  1. **Reductive synthesis** of fatty acids, cholesterol and steroid hormones, Neurotransmitters.
  2. Production of **reduced glutathione** in erythrocytes and other cells.

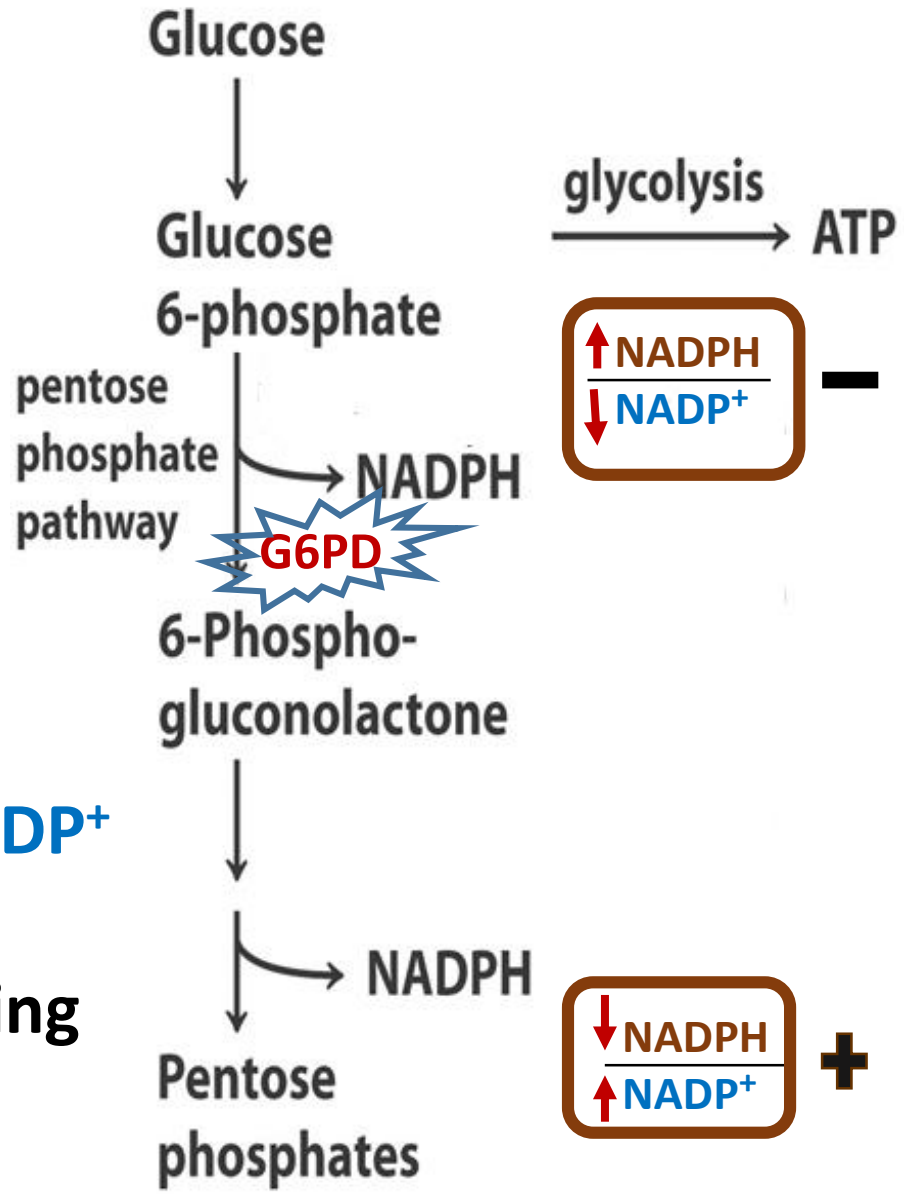
B. Production of ribose residues (Non oxidative steps):

- **Used for:**
  1. Nucleic acid synthesis (**DNA, RNA**).
  2. **ATP, NAD+, FAD** and **Coenzyme A** biosynthesis.

Regulation of the pentose phosphate pathway LO 1

- The pathway is regulated by controlling the activity of **Glucose 6-phosphate Dehydrogenase (G6PD)**, the first enzyme in the pathway.

- The activity of the enzyme is controlled by the **NADPH/NADP+** ratio in the cell, **NADPH inhibiting** and **NADP+ activating** the enzyme .



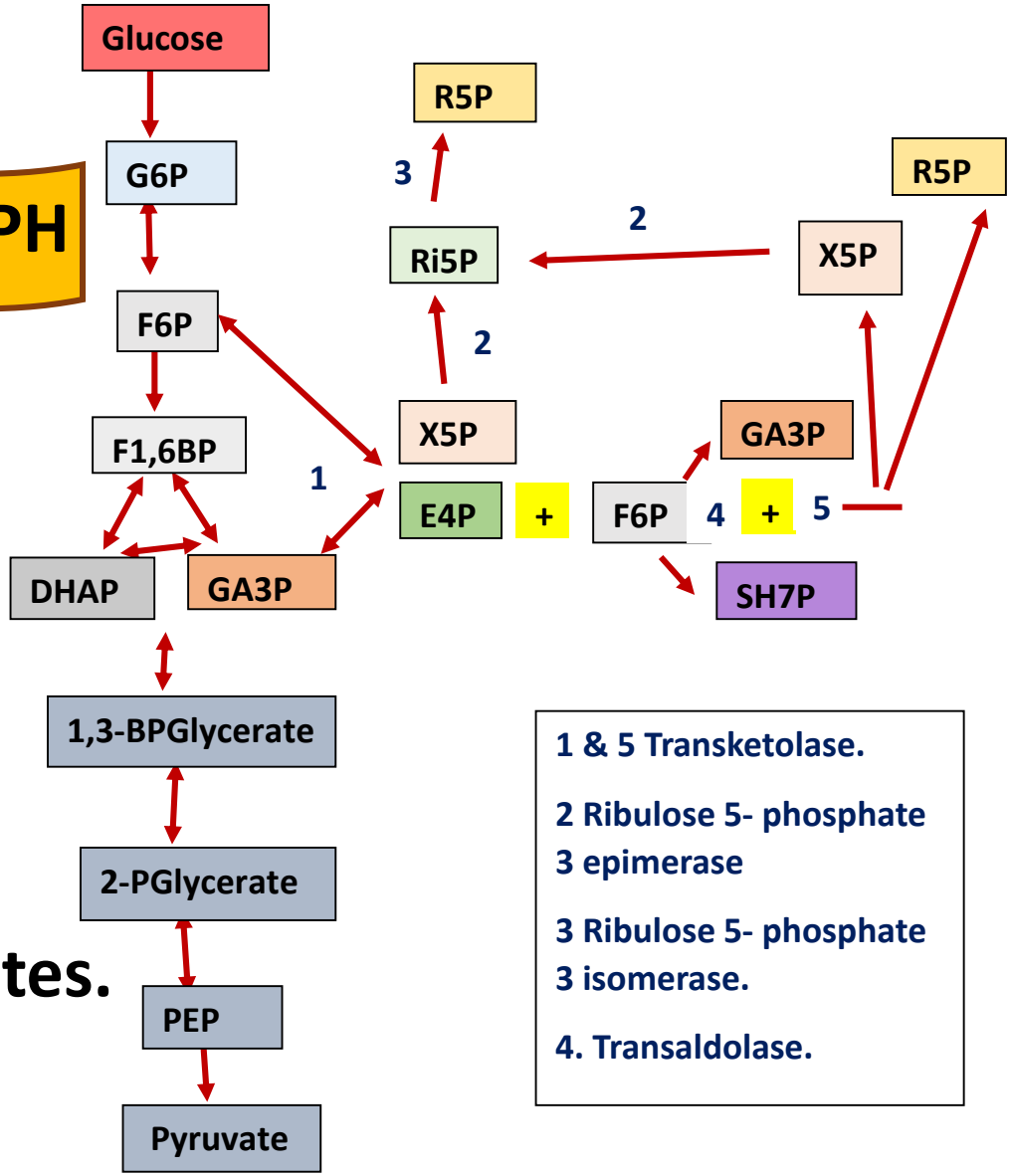
There are 4 scenario in regulation of PPP

LO 1

Scenario 1:

Ribose 5-phosphate > NADPH

1. In rapidly dividing cells.
2. Its non oxidative phase.
3. **3 Ribose 5 phosphate (R5P)** will be generated From **glycolytic intermediates.**



1 & 5 Transketolase.

2 Ribulose 5- phosphate 3 epimerase

3 Ribulose 5- phosphate 3 isomerase.

4. Transaldolase.

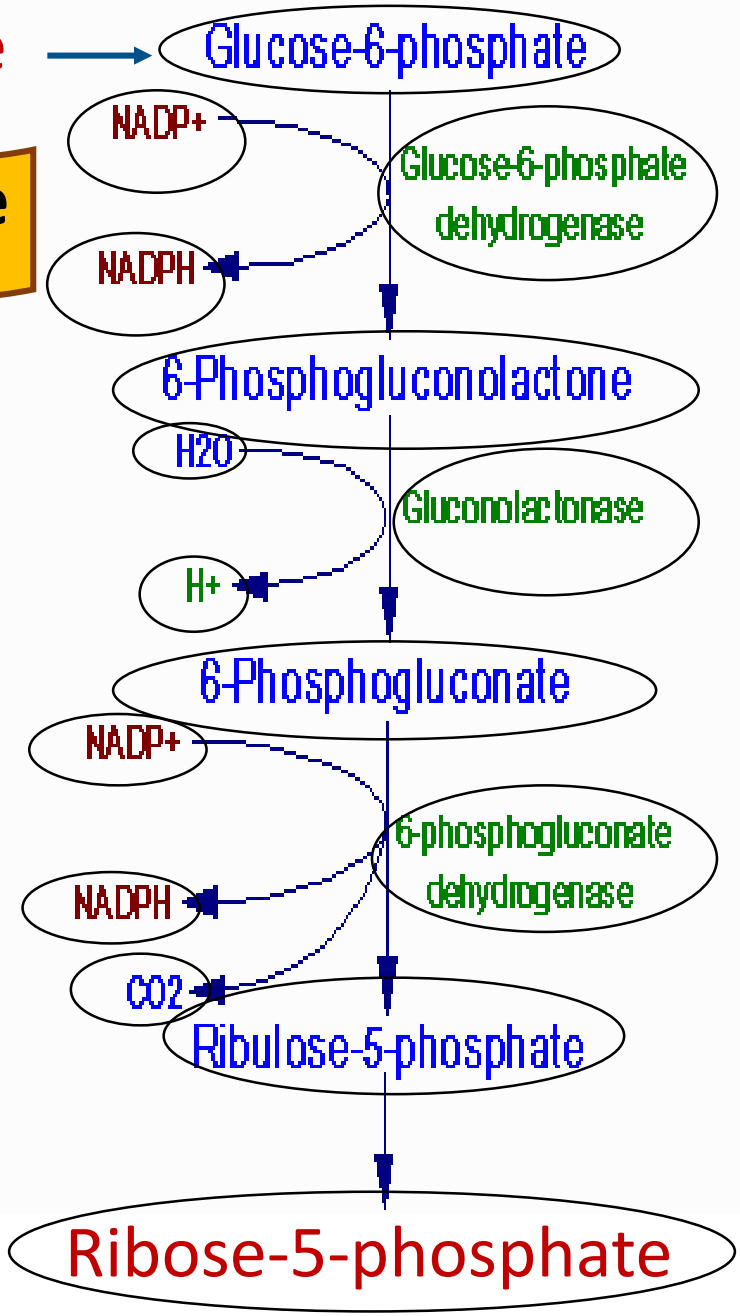
Scenario 2:

LO 1

NADPH = Ribose 5 phosphate

1. This occur during cell replication.

2. Oxidative phase.

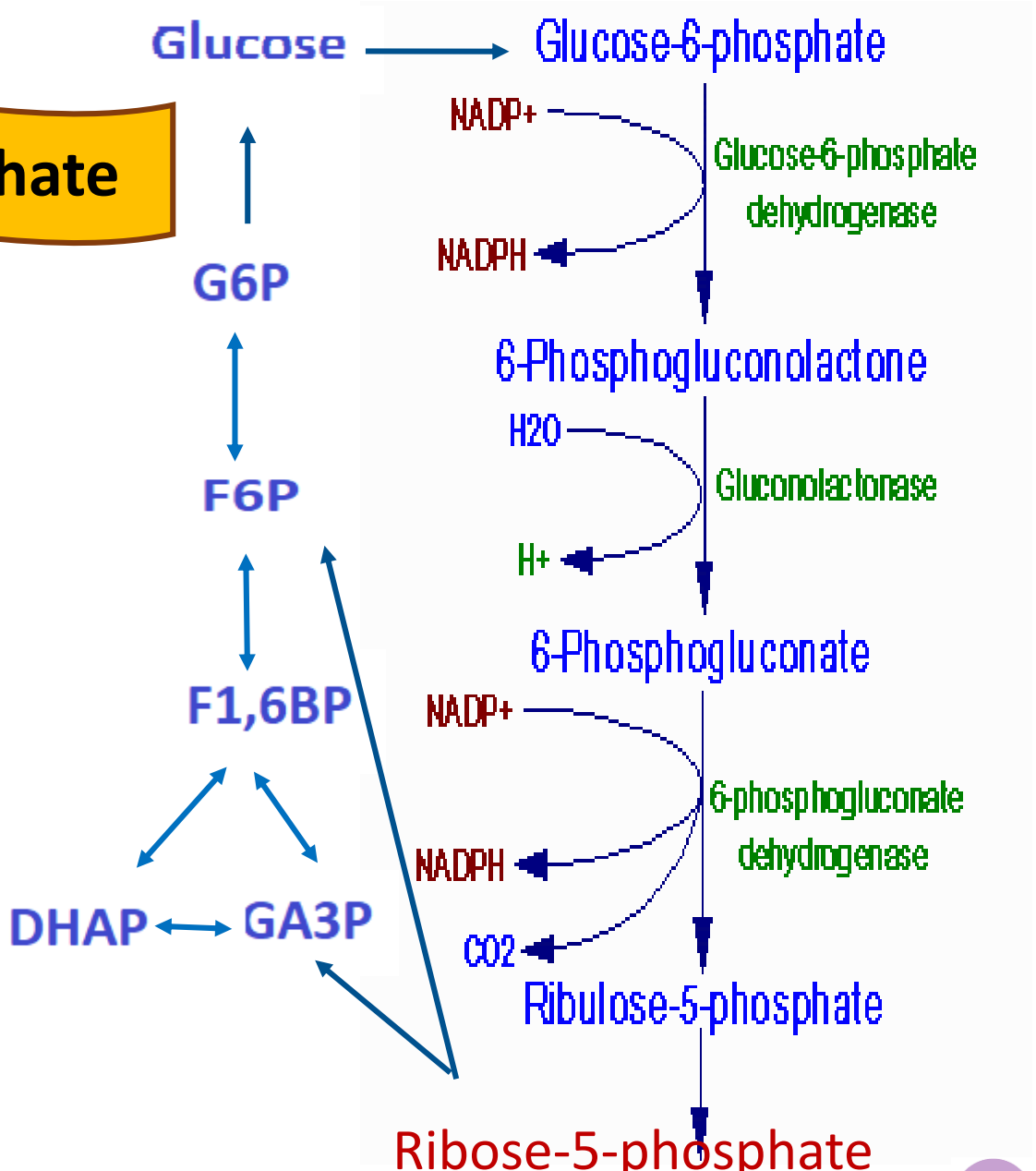


Scenario 3:

LO 1

NADPH > ribose 5-phosphate

Oxidative phase and Gluconeogenesis

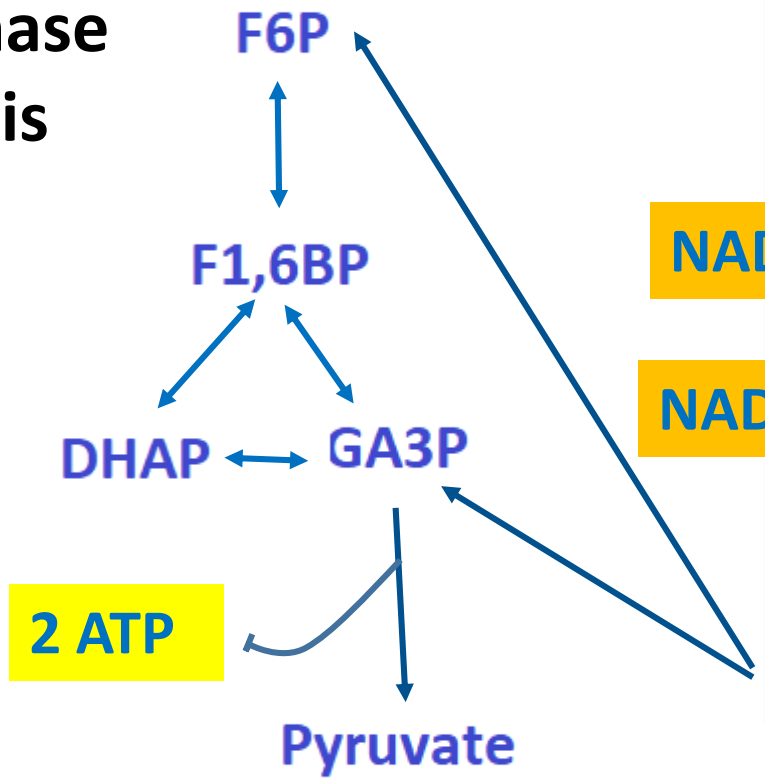


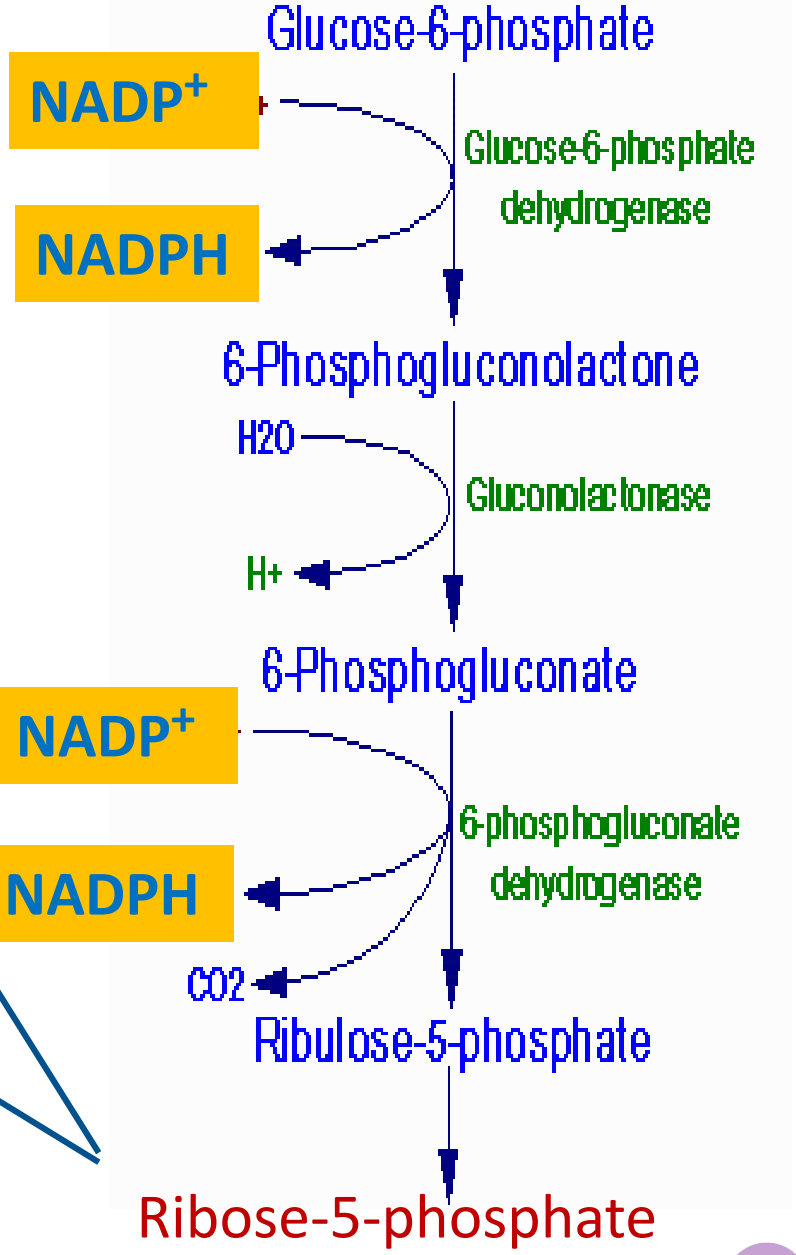
Scenario 4:

LO 1

The cell needs both NADPH and ATP

Oxidative phase and Glycolysis





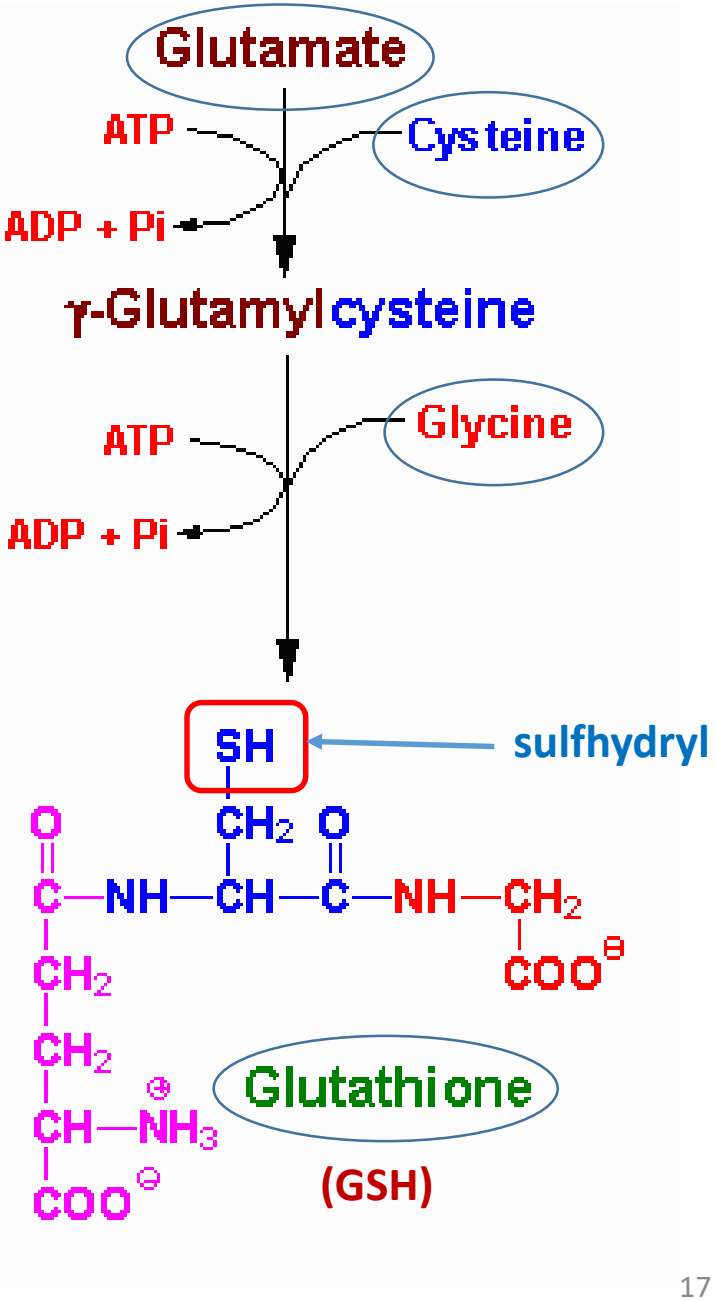
Glutathione and NADPH

LO 1

- ✓ What is glutathione?
- ✓ Why is it important?
- ✓ How is it related to NADPH?

Glutathione

- ✓ Glutathione is a tripeptide composed of **glutamate**, **cysteine**, **glycine**.
- ✓ Reduced glutathione (GSH) maintains the normal reduced state of the cell.



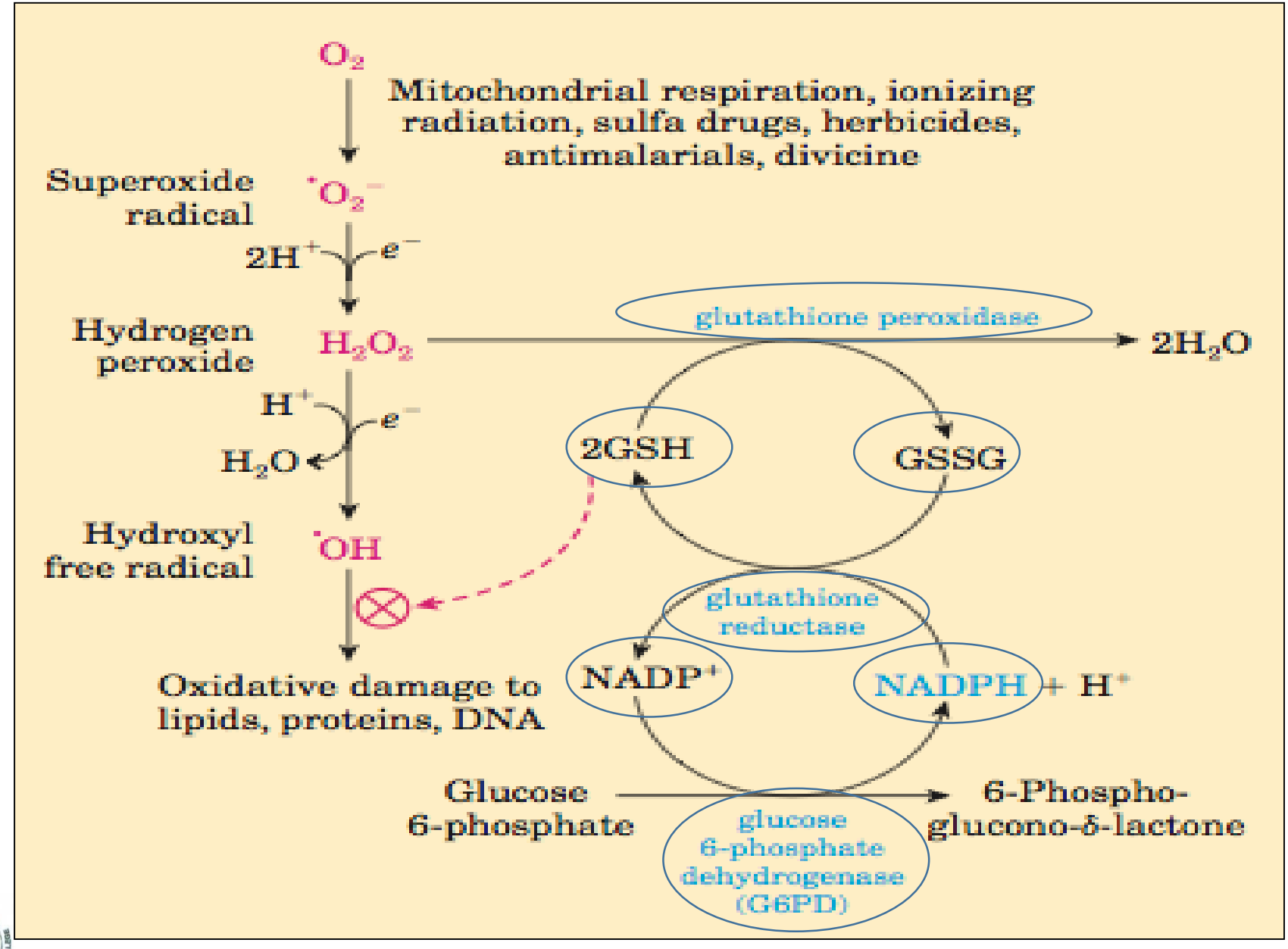
Role of NADPH and Glutathione in RBCs :

LO 1

- In RBCs, reactive oxygen species **(superoxide and hydrogen peroxide)** are formed normally during the process of oxygen transport as in the following:

$$Hb\text{-}Fe^{+2}\text{-}O_2 \rightarrow Hb\text{-}Fe^{+3} + O_2\cdot^{-}$$ **(superoxide anion)**

- This reaction is spontaneous, **1%** of inspired O_2/h reacts in this Reaction.


O_2
Mitochondrial respiration, ionizing radiation, sulfa drugs, herbicides, antimalarials, divicine
Superoxide radical
$^{\cdot}O_2^-$
$2H^+$
e^-
Hydrogen peroxide
H_2O_2
glutathione peroxidase
$2H_2O$
H^+
e^-
H_2O
2GSH
GSSG
Hydroxyl free radical
$^{\cdot}OH$
glutathione reductase
NADP+
NADPH + H+
Oxidative damage to lipids, proteins, DNA
Glucose 6-phosphate
glucose 6-phosphate dehydrogenase (G6PD)
6-Phospho-glucono-δ-lactone

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

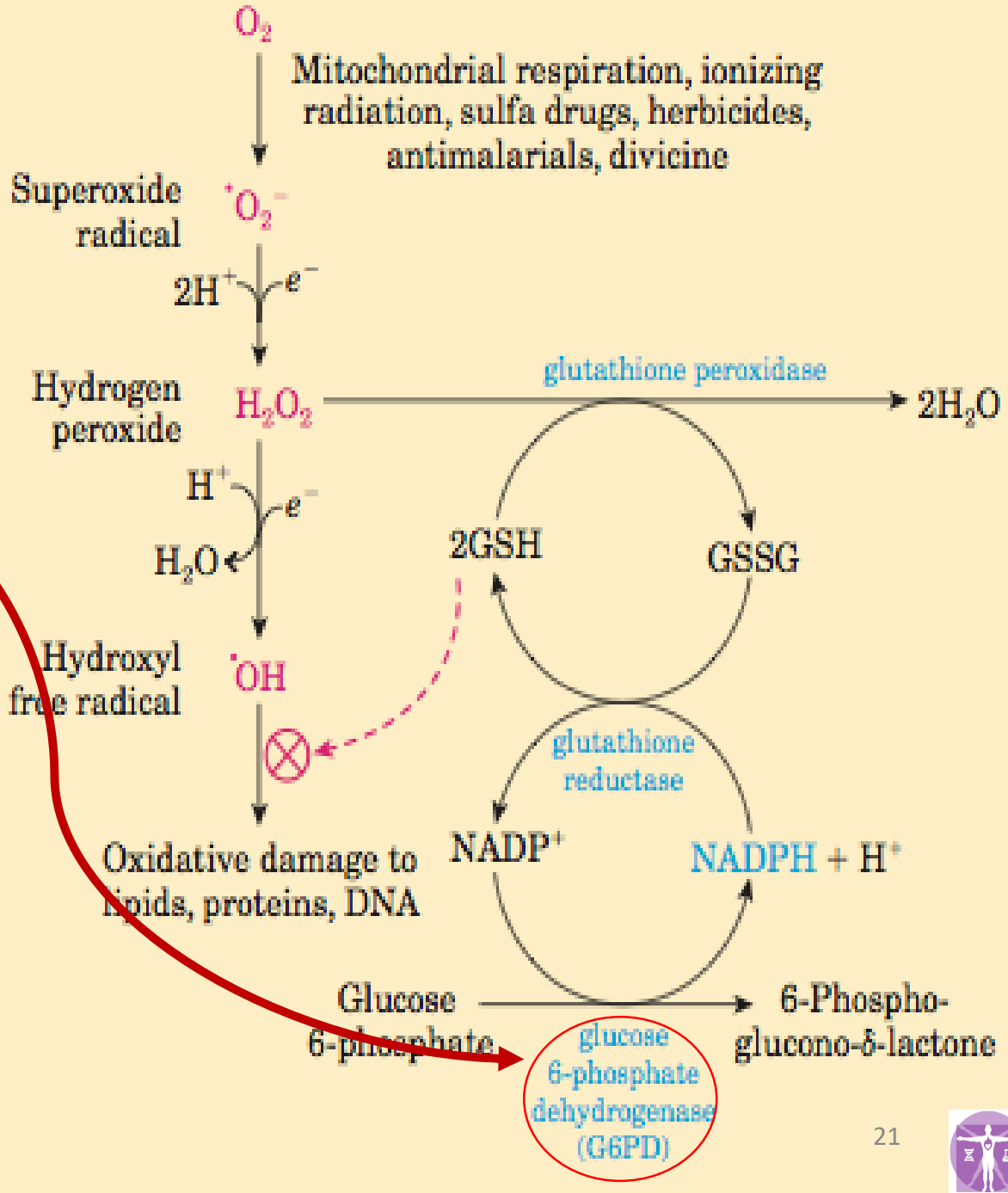
✓Glutathione Peroxidase catalyzes degradation of organic hydroperoxides by reduction, as two glutathione molecules are oxidized to a disulfide GSSG

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

LO 2

What happen if this enzyme defected?

G6PD Deficiency

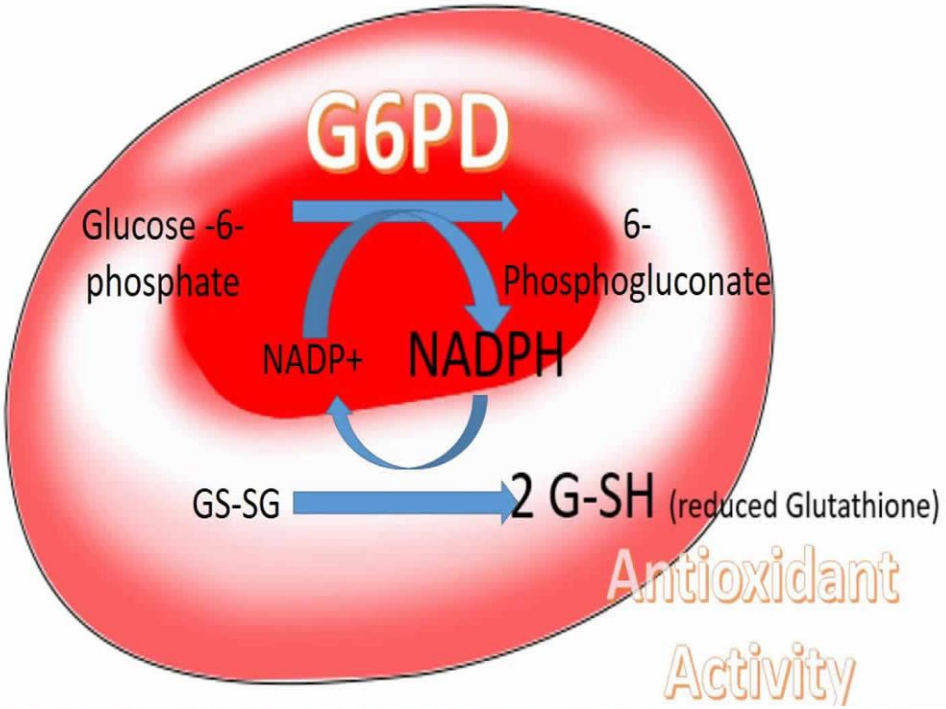


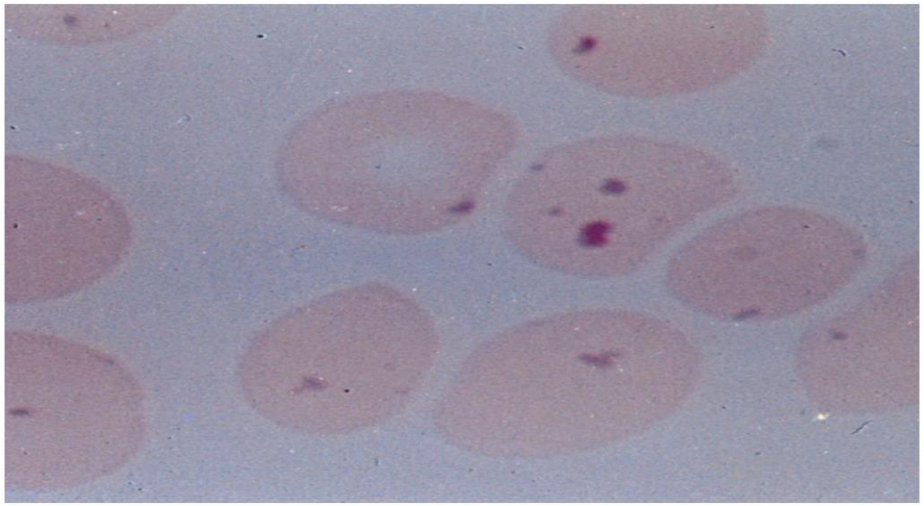
LO 2

Glucose 6-phosphate dehydrogenase deficiency (G6PD deficiency)

- The gene encodes G6PD is found on chromosome **X.**
- In some individuals this gene is mutated.
- If **G6PD** is not functioning well, **NADPH production will be impaired.**
- **Low NADPH** leads to **oxidative damage of cells.**

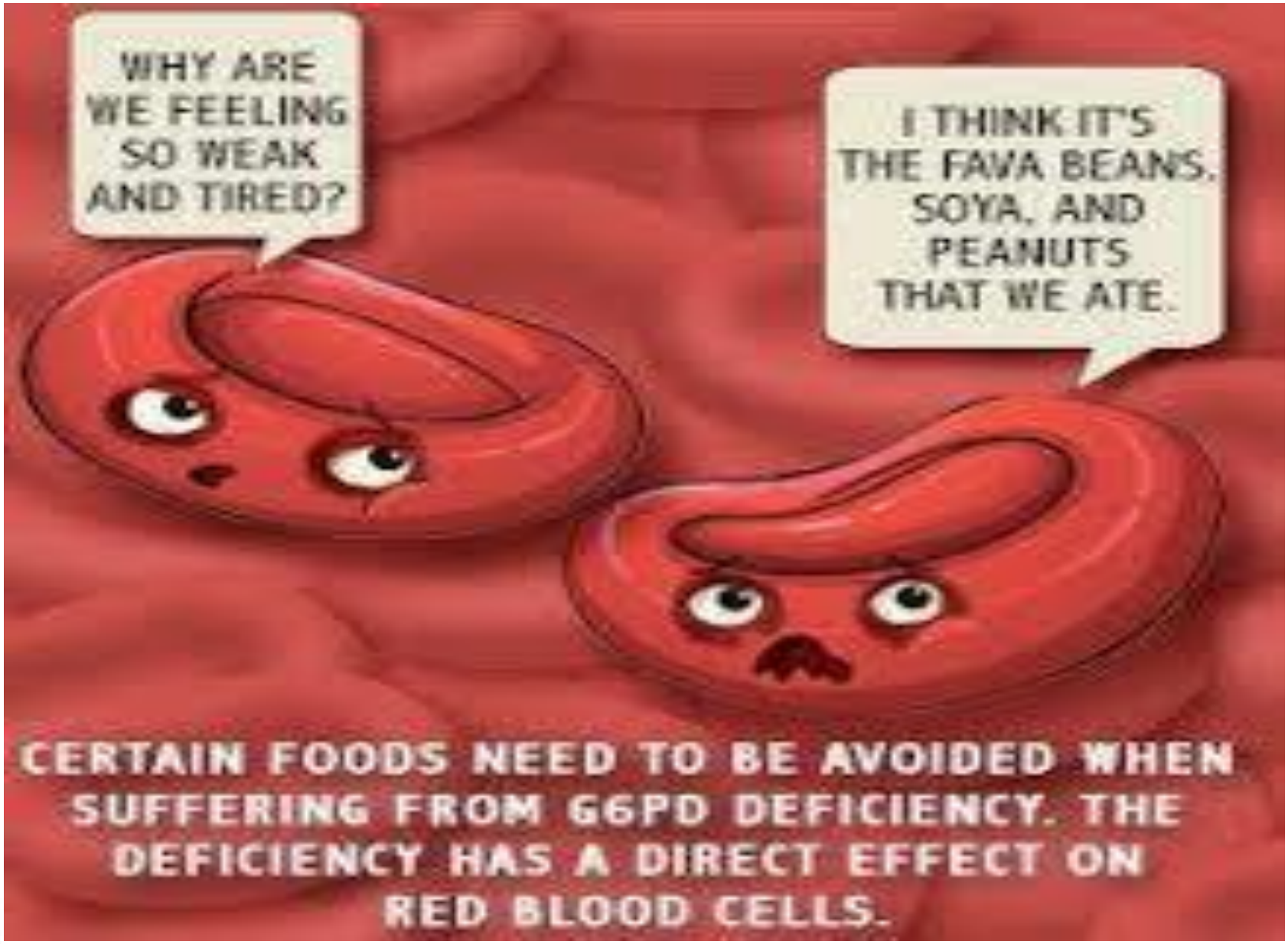
- Hydrogen peroxide accumulates in RBCs
- Consequent oxidation of Hb and other proteins.
- Hb becomes cross-linked by disulphide bonds to form insoluble aggregates called **Heinz bodies.**





- Oxidation of Hb leads to premature destruction of RBCs and causes **Acute haemolytic episodes** .
- Some chemicals increase the oxidative stress (e.g. sulphonamides, aspirin, NSAIDs and antimalarials like primaquine).
- It occurs when affected individuals have eaten fava beans which contain glycosides (vicine & isouramil).
- For this reason it is called **favism.**

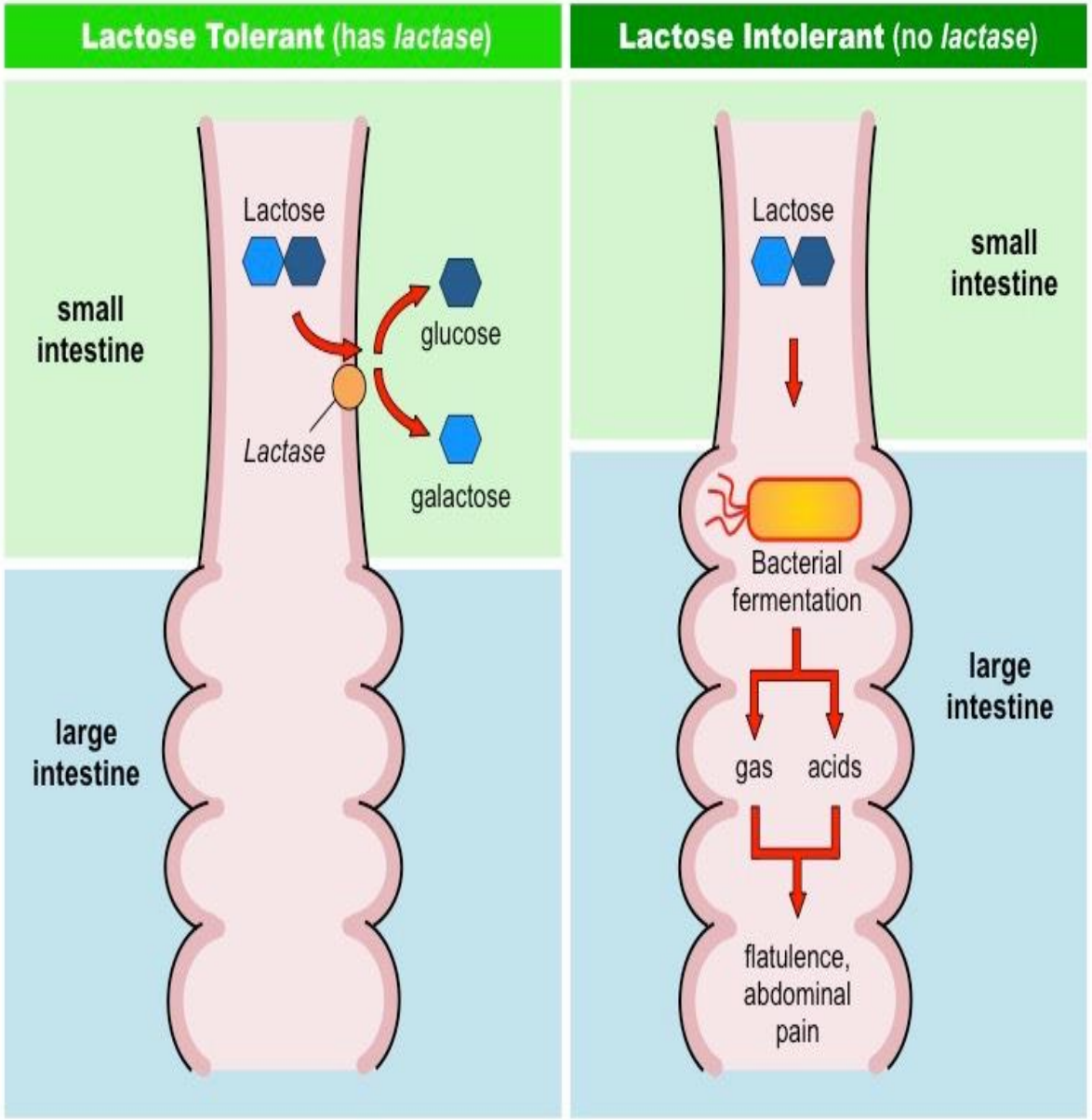
LO 2


WHY ARE WE FEELING SO WEAK AND TIRED?
I THINK IT'S THE FAVA BEANS, SOYA, AND PEANUTS THAT WE ATE.
CERTAIN FOODS NEED TO BE AVOIDED WHEN SUFFERING FROM G6PD DEFICIENCY. THE DEFICIENCY HAS A DIRECT EFFECT ON RED BLOOD CELLS.

Lactose intolerance :

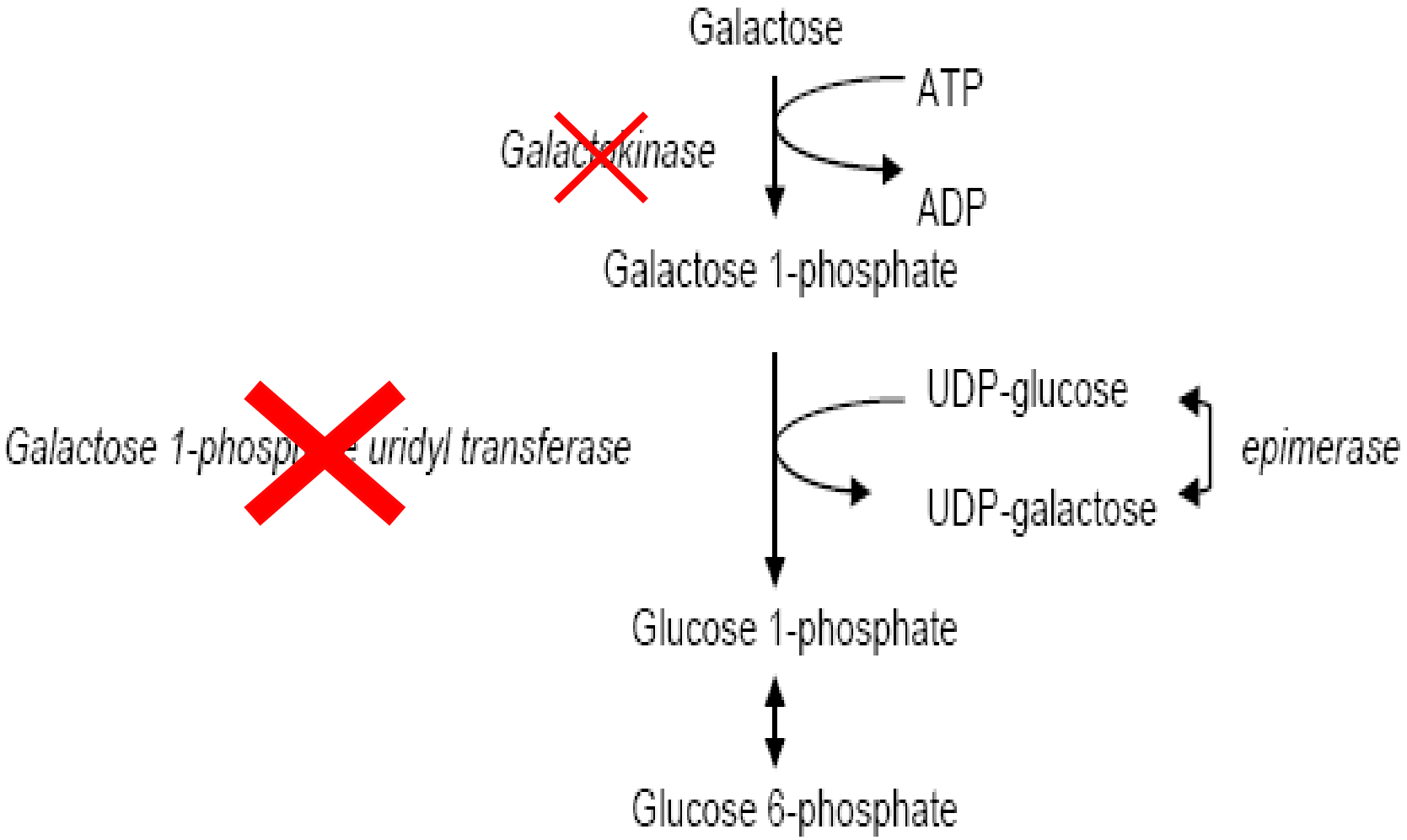
LO 3

Low activity of *lactase* (acquired or inherited) is associated with a reduced ability to digest the lactose present in milk products and may produce the clinical condition of lactose intolerance .



Metabolism of Galactose :

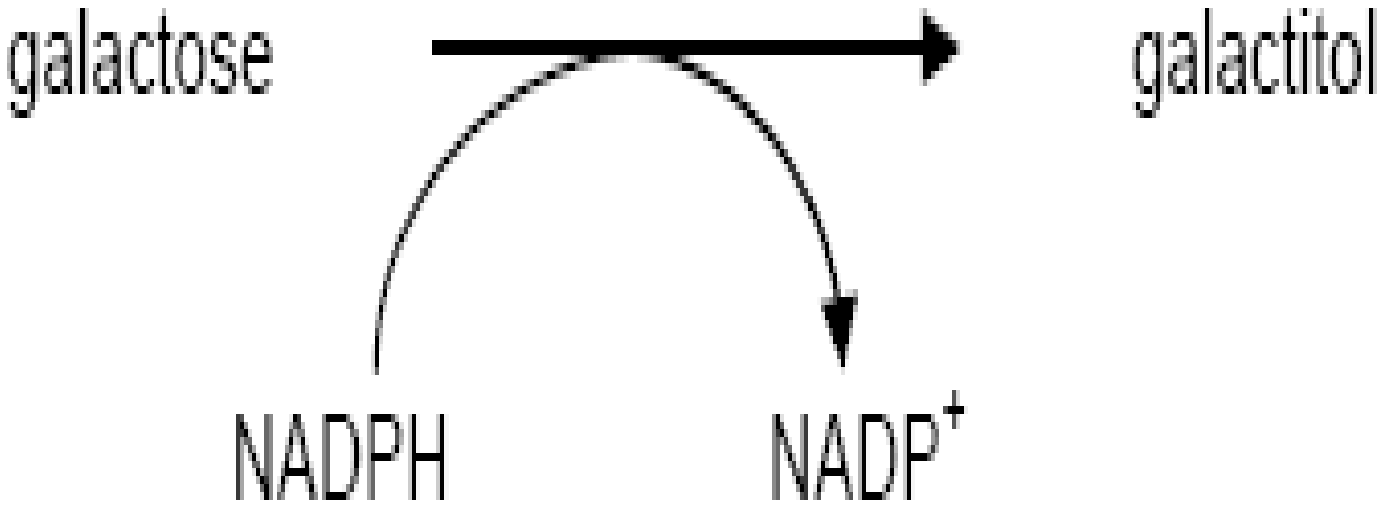
LO 3



Galactosaemia:

- Genetic defect leads to a lack of the **kinase or transferase** enzyme.
- The absence of the **kinase** is relatively rare and is characterized by accumulation of **galactose** in tissues.
- The absence of the **transferase** is more common and more serious as both **galactose and galactose-1-P** accumulate in tissues.

- Accumulated galactose in tissues is reduced to **galactitol** (aldehyde group reduced to alcohol group) by the activity of the enzyme **aldose reductase:**



This reaction depletes tissues NADPH

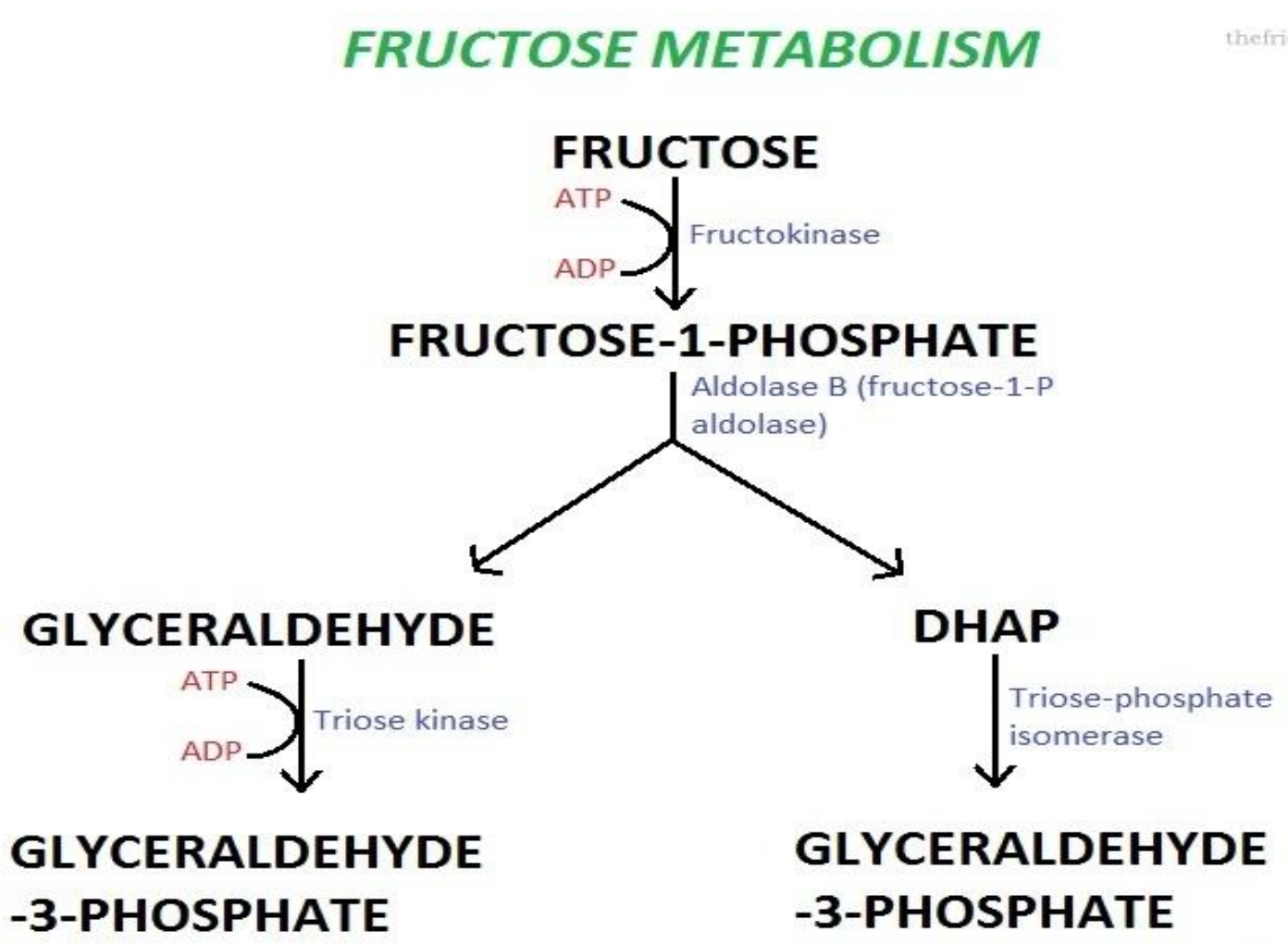
Consequences of Galactosemia:

LO 3

- ✓ Accumulation of galactose in the eye damages the lens structure, resulting in **cataract** .
- ✓ Accumulation of galactose and galactitol in the eye may raise the **intra-ocular pressure (glaucoma)** which if untreated may cause blindness .
- ✓ Accumulation of galactose-1-phosphate in tissues causes damage to the **liver, kidney** and **brain.**

Metabolism of Fructose:

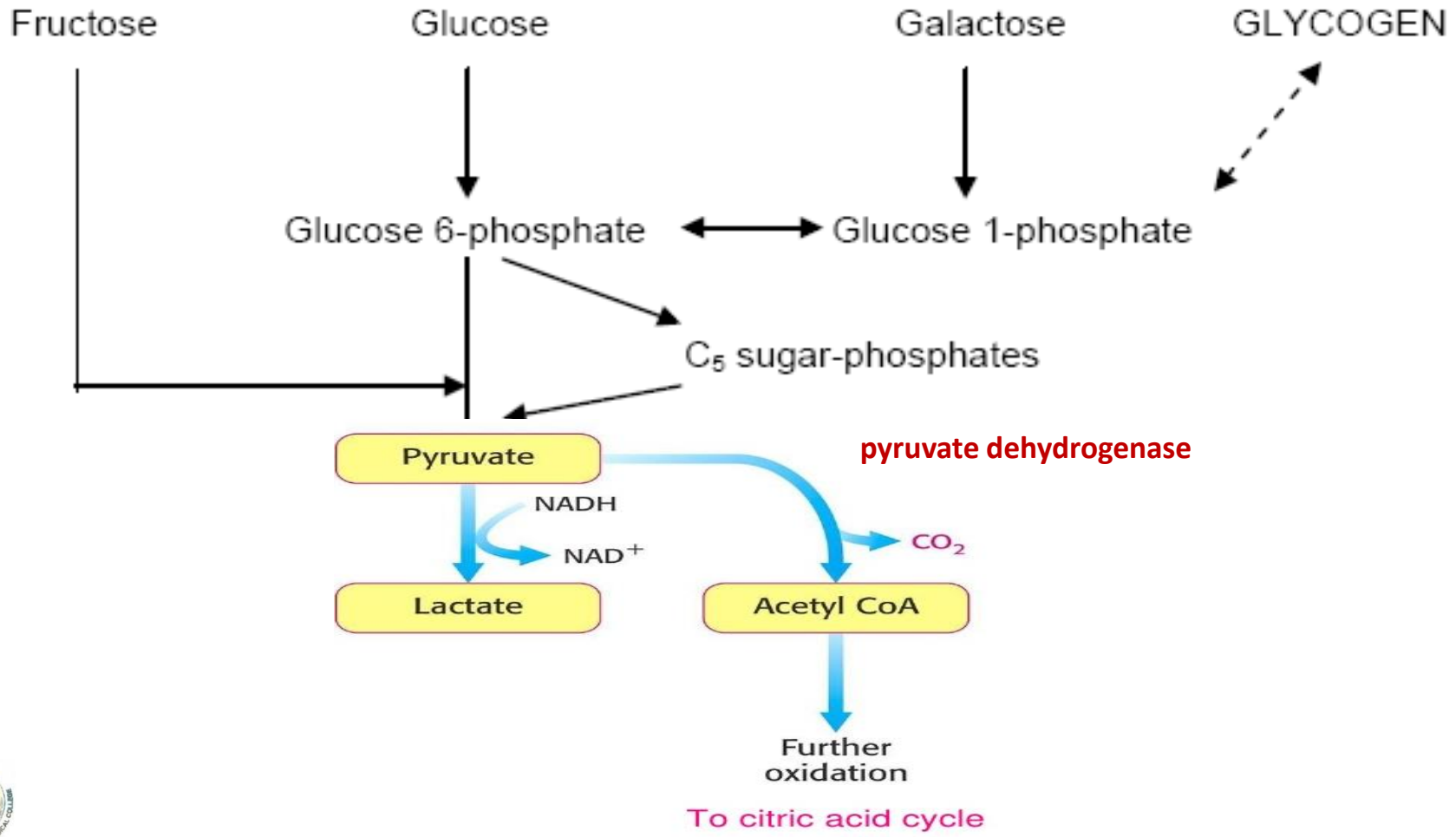
LO 4



Metabolism of Pyruvate:

LO 4

- Pyruvate does not enter stage 3 of catabolism directly but is first converted to acetyl~CoA by the enzyme pyruvate dehydrogenase (PDH).



Regulation of PDH reaction

LO 4

- Allosterically: the reaction is sensitive to the energy status of the cell so it is regulated by:

1. Negative effectors:
Acetyl CoA, ATP & NADH

2. Positive effectors :
ADP and pyruvate

- Hormonally: **Insulin activates** the enzyme by promoting its dephosphorylation.

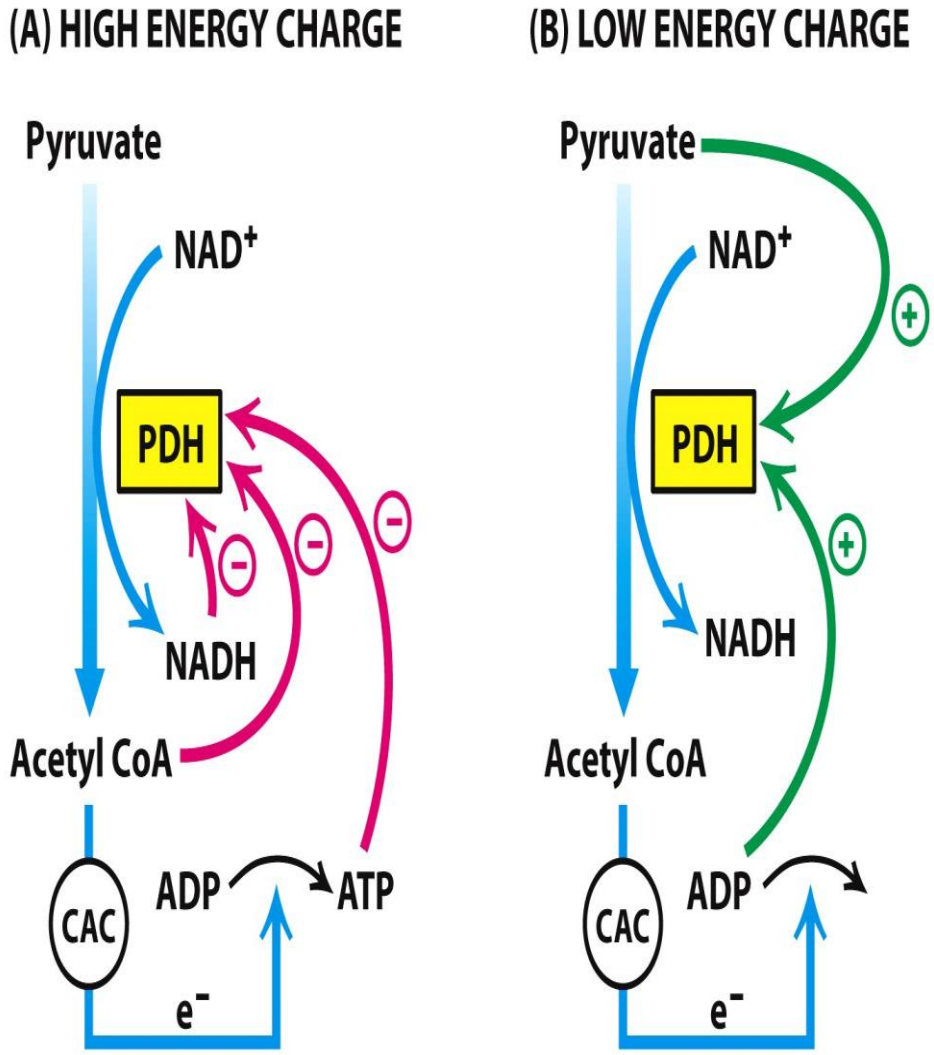


Figure 17.18
Biochemistry, Seventh Edition


THANKS!