Faculty of Pharmacy
Biochemistry-2

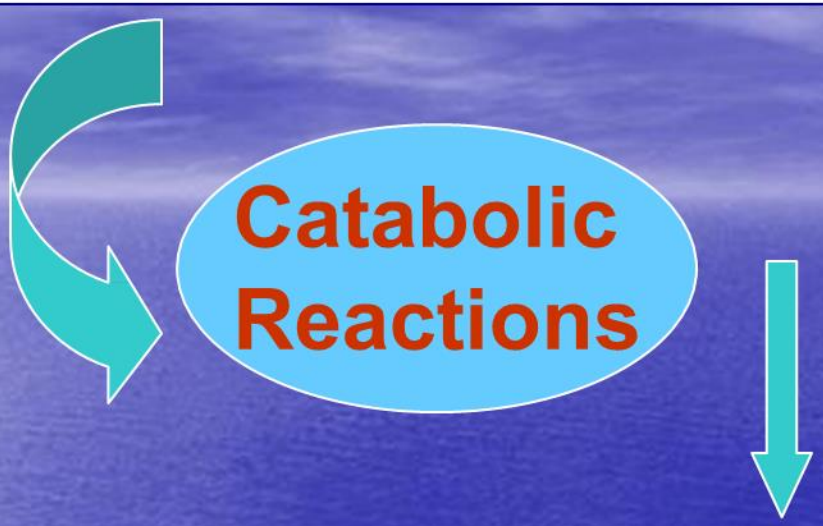
Edited By:

Dr. Abdalkareem Maghmomeh

Lecturer of Biochemestry

Lecture 3

Utilization of Glucose



1) Glycolysis
2) Kreb's Cycle
3) Pentose Shunt
4) Formation of Uronic acids

Hexose Monophosphate Pathway (HMP)

- HMP is a minor oxidation pathway for glucose.

- It is an alternative pathway which involves **phospho–pentoses** as intermediates for purposes other than energy production.

HMP Shunt

- **HMP occurs in the Cytoplasm of:**

1. **Liver**
2. **Lactating mammary gland**
3. **Adipose tissue**
4. **Red blood cells**
5. **Adrenal cortex**

The pentose phosphate pathway has two main functions

1- **Generation of NADPH**

mainly used for syntheses of fatty acids, steroids, amino acids and production of reduced glutathione.

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

Reactions of the pentose phosphate pathway occur in the cytosol in two phases

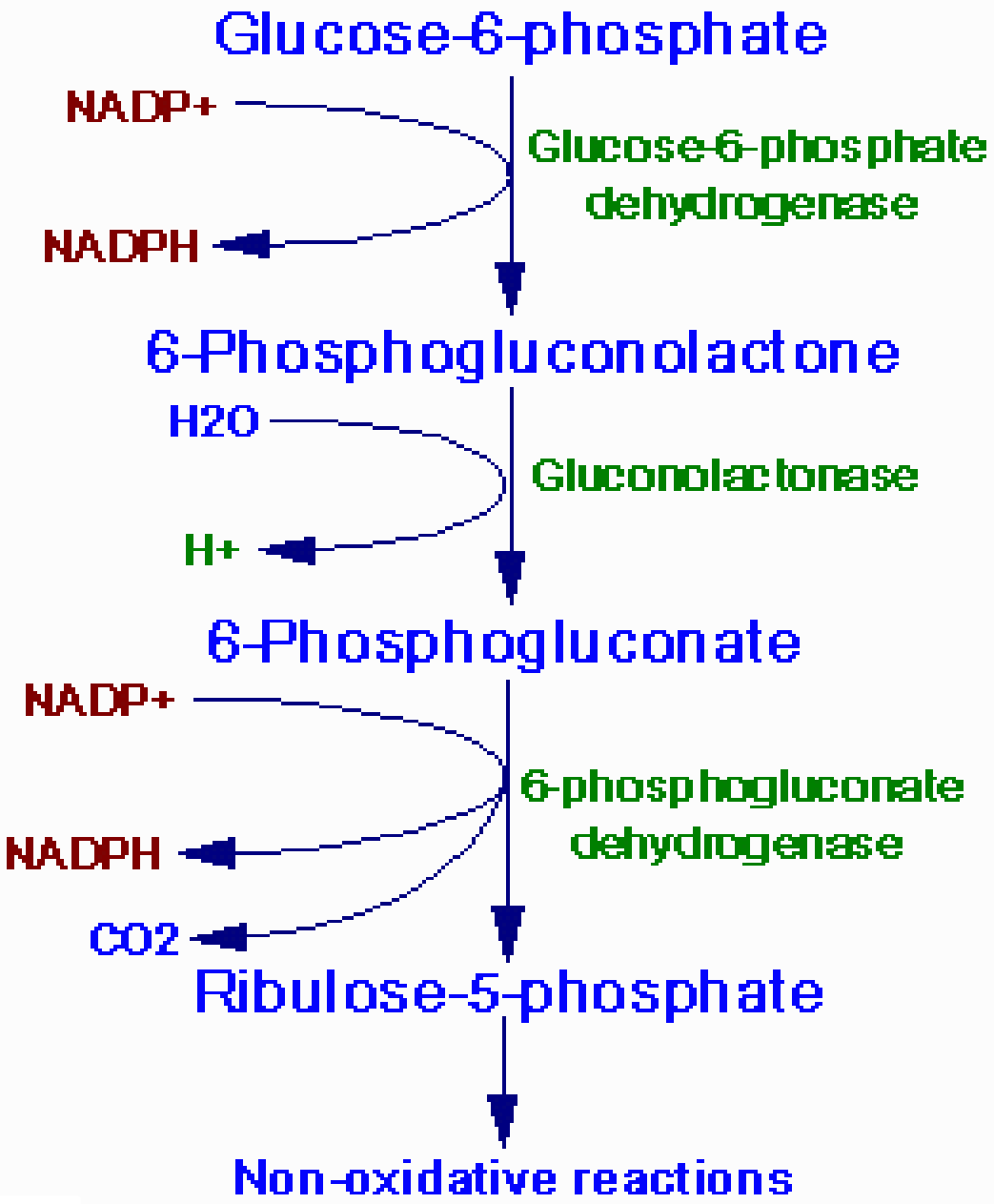
- **Oxidative non-reversible phase**
- **Non-oxidative reversible phase**
- $NADP^+$, not NAD $^+$, is used as hydrogen acceptor
- **1st phase**

  - Glucose 6-phosphate undergoes dehydrogenation and decarboxylation to give a pentose, ribulose 5-phosphate, which is converted to its isomer, D-ribose 5-phosphate.

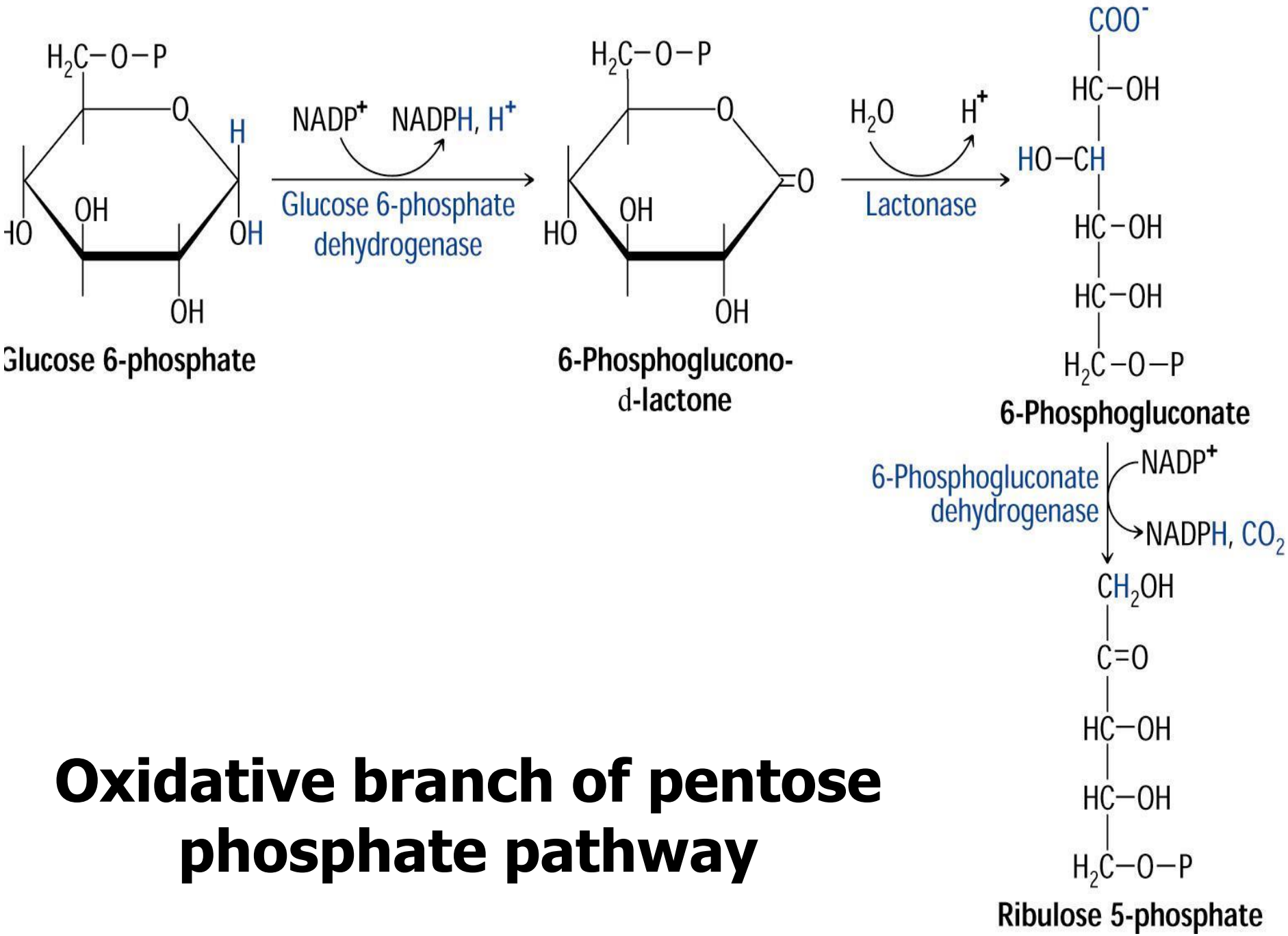
  - Overall equation of 1st phase:

$$\text{Glucose 6-phosphate} + 2\ NADP^+ + H_2O \rightarrow$$
$$\text{ribose 5-phosphate} + CO_2 + 2\ NADPH + 2\ H^+$$

Oxidative Stage of Pentose Phosphate Pathway

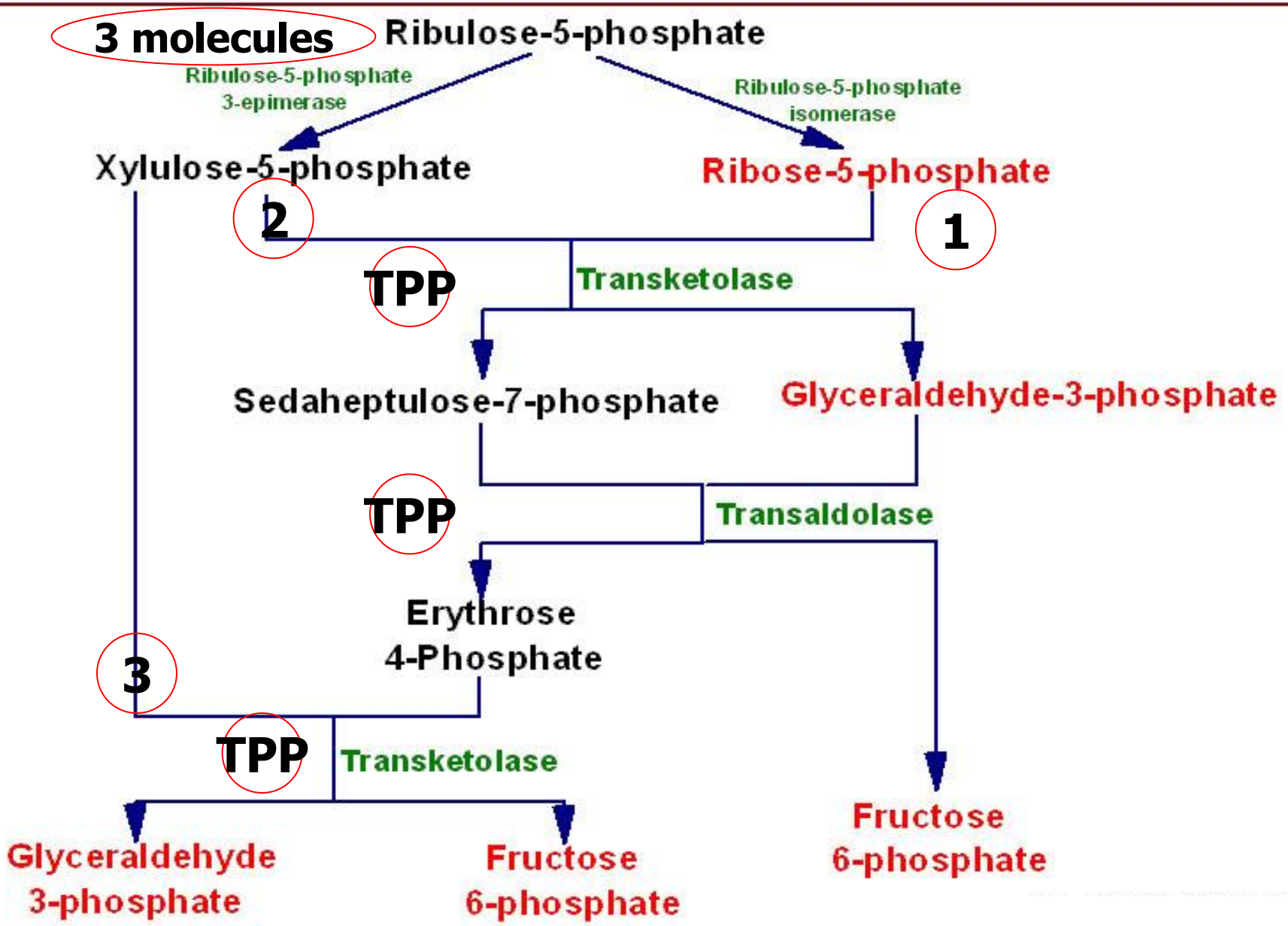


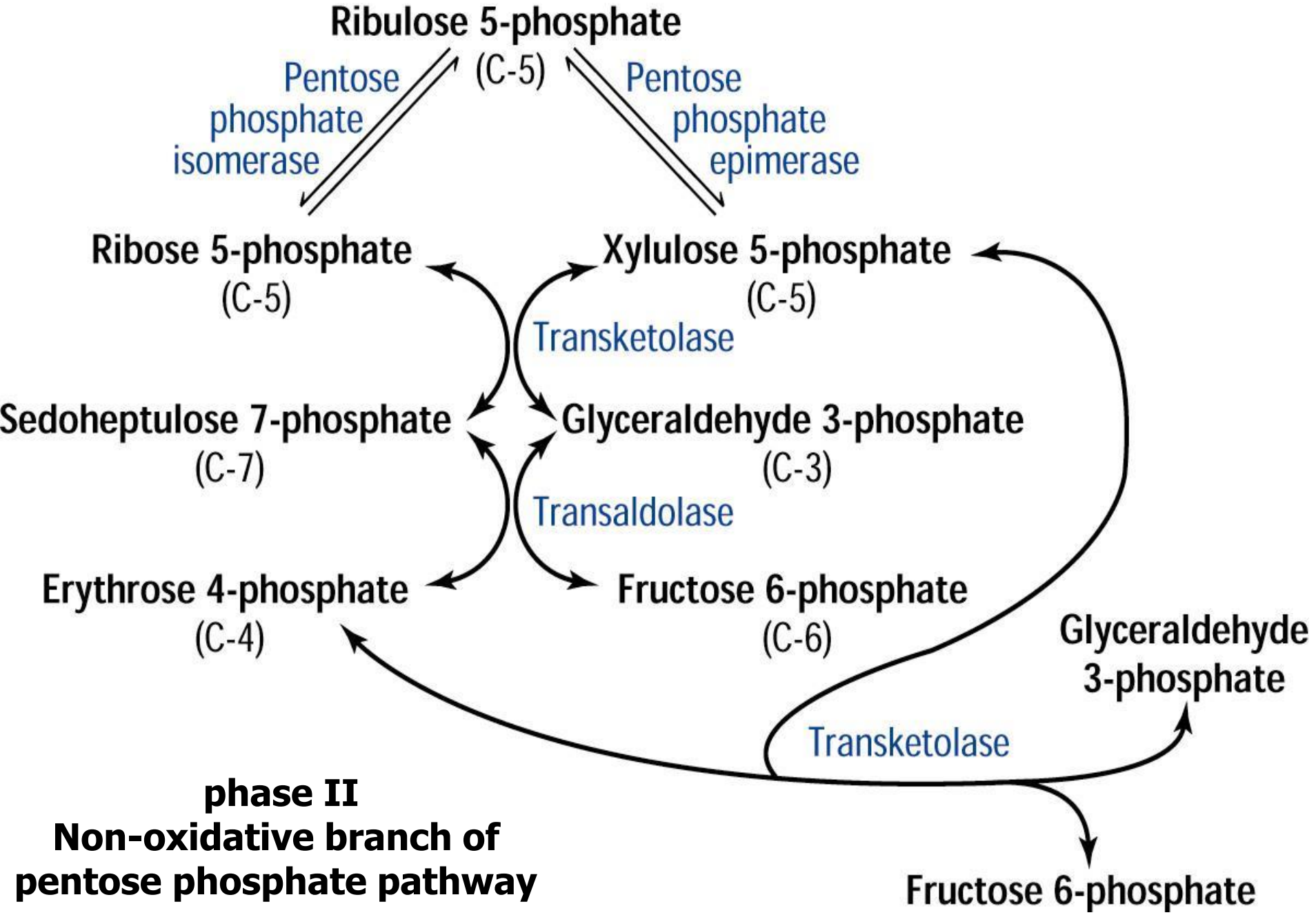
Rate limiting enzyme



Oxidative branch of pentose phosphate pathway

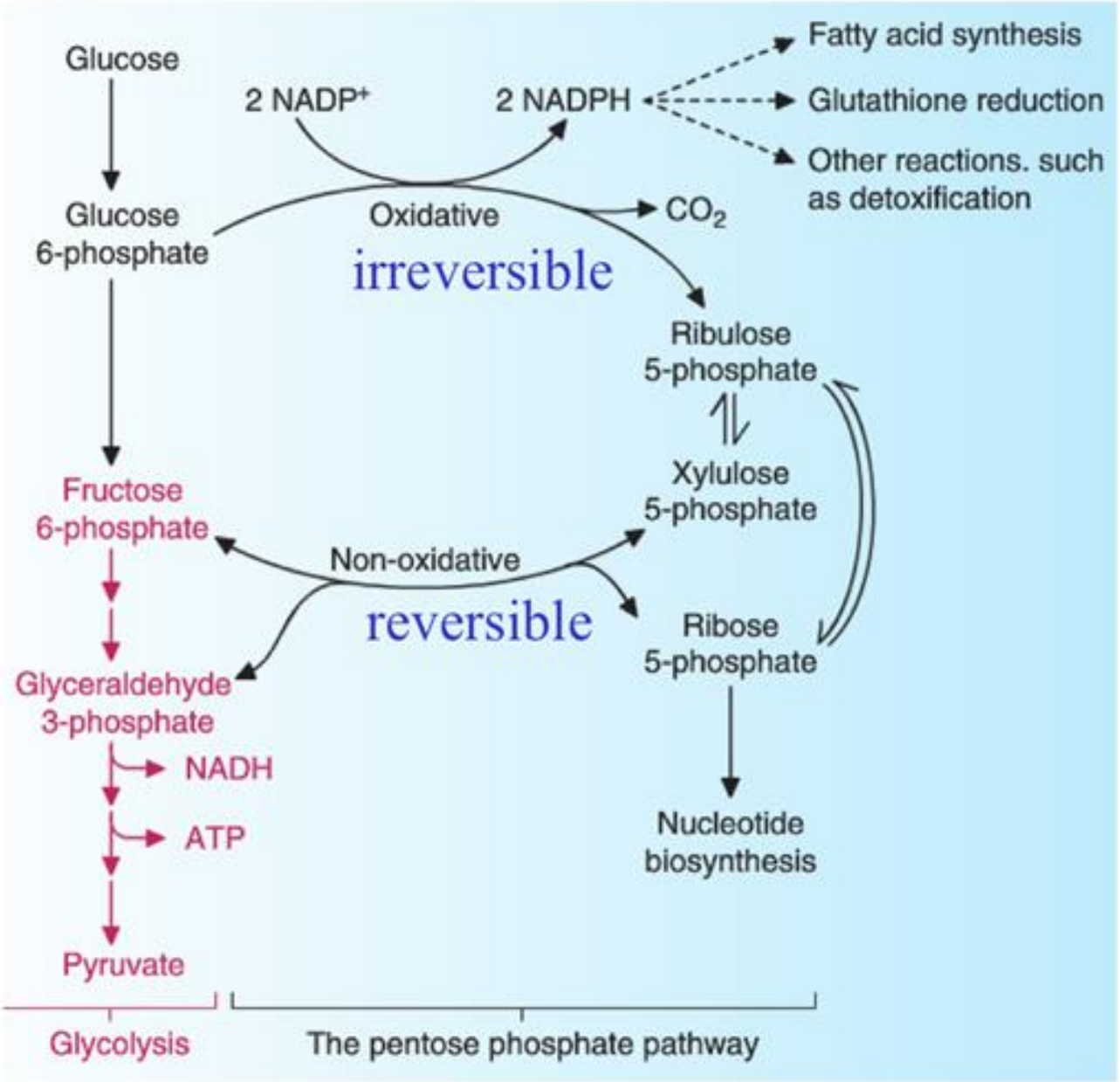
Non-Oxidative Stage of Pentose Phosphate Pathway





phase II
Non-oxidative branch of pentose phosphate pathway

Pentose phosphate pathway and its link to glycolysis



- NADPH
- Ribose 5-P
- Glucose 6-P dehydrogenase deficiency

Metabolic Significance of HMP Shunt

1) **It is the only source of <u>phosphorylated pentoses</u> which used for the synthesis of:**

A. Nucleotides: ATP & GTP.

B. Coenzymes: FAD, NAD^+.

C. Certain vitamins: B_2 & B_{12}.

D. Nucleic acids: DNA & RNA.

Metabolic Significance of HMP Shunt

2) It is the major source of NADPH$^+$ which is essential for:

A. Fatty acid synthesis for lipogenesis which occurs in liver, adipose tissue & lactating mammary gland.

B. Steroid synthesis (Adrenal cortical hormones, Sex hormones) which is active in adrenal cortex, testes, ovaries & placenta.

C. Act as coenzyme of glutathione reductase which keeps GSH in reduced state.

Metabolic Significance of HMP Shunt

3) There is a relation between G-6-P DH in the RBCs and fragility of the cell wall of RBCs, since reduced G-SH is essential for:

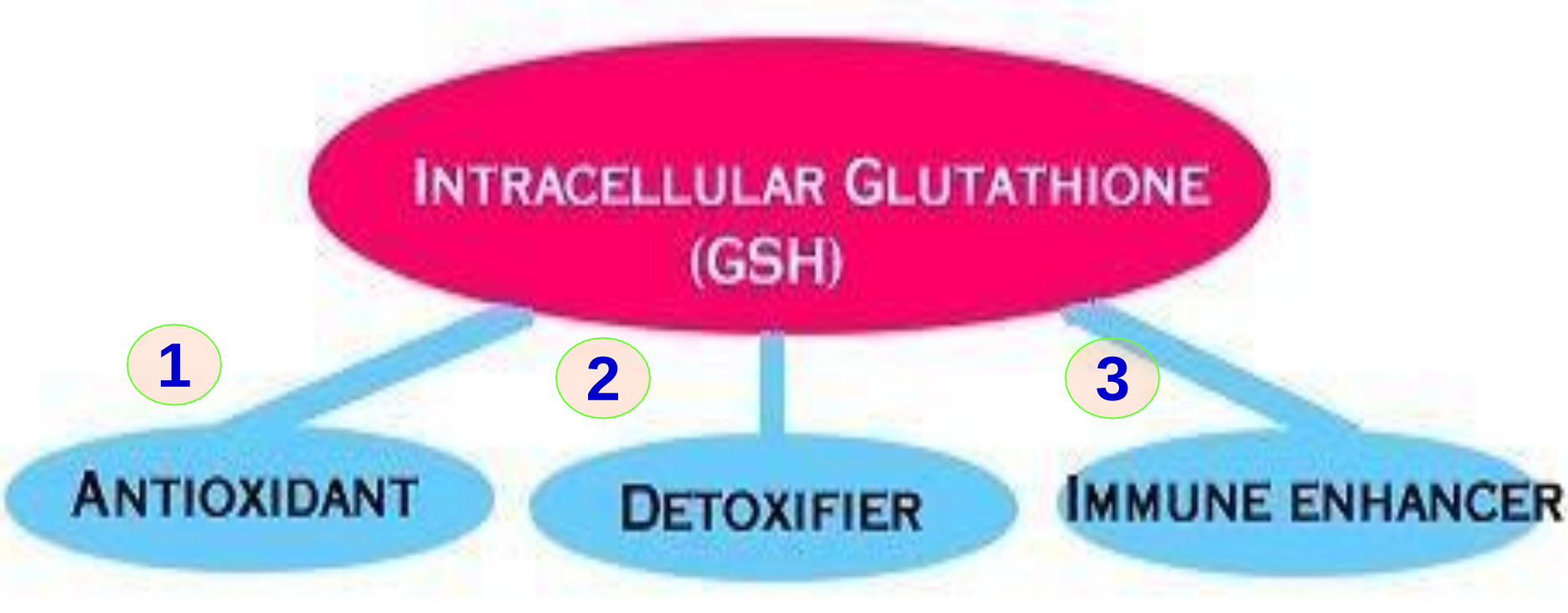
A. Keeping iron of Hb in Ferrous state (Fe^{2+}).

B. Keeping globin of Hb in native structure.

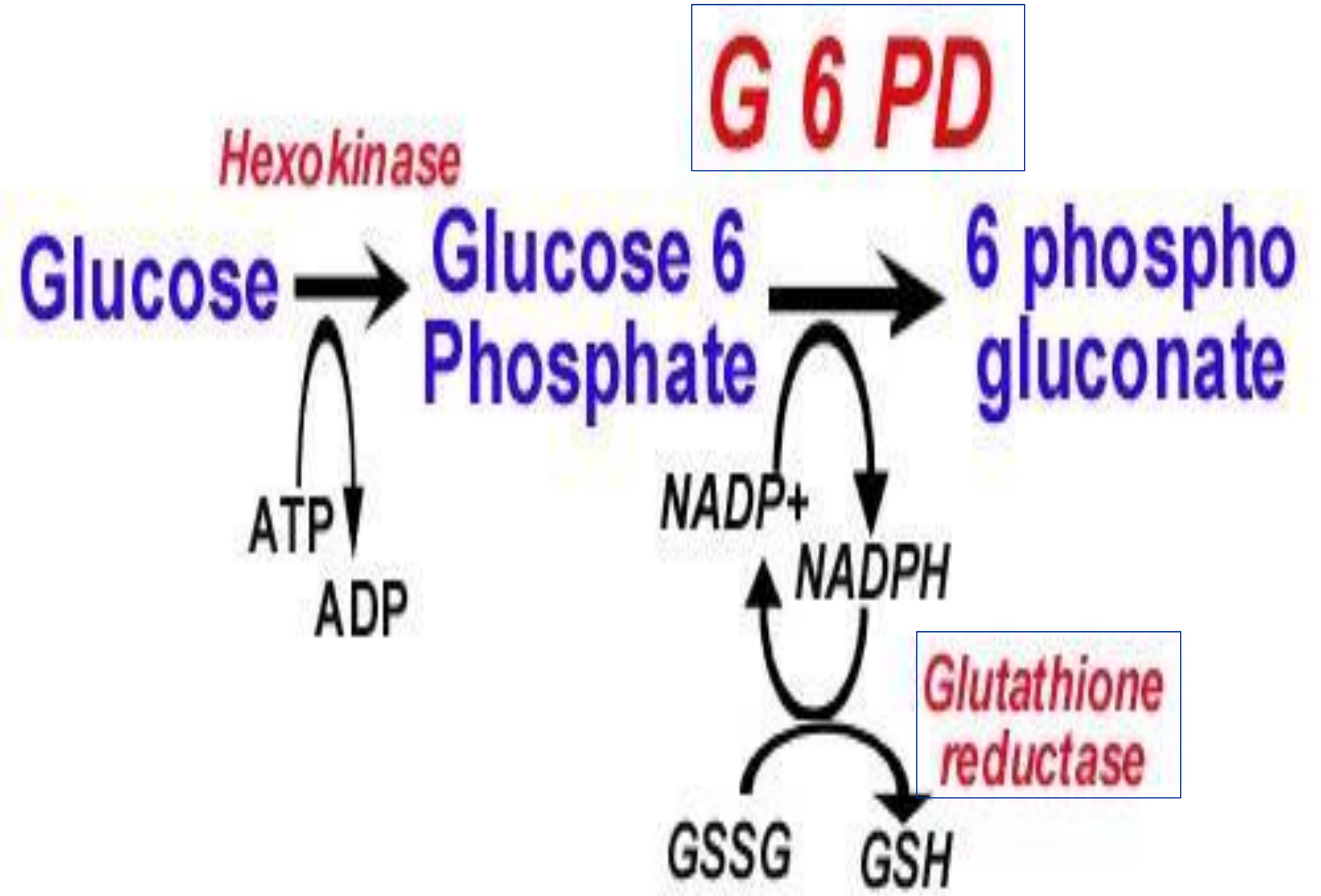
C. Preventing accumulation of free radicals & H_2O_2 in RBCs.

D. Keeping RBCs wall intact preventing hemolysis.

Glutathione Protects us from Oxidation



4 **Protects RBC's against hemolysis**


G 6 PD
Hexokinase
Glucose
Glucose 6 Phosphate
6 phospho gluconate
ATP
ADP
NADP+
NADPH
Glutathione reductase
GSSG
GSH
Oxidized Glutathione
Reduced Glutathione

G6PD (glucose 6-phosphate dehydrogenase) deficiency

- Blocks hexose monophosphate shunt
- Reduced supply of NADPH
- Reduced GSH/Increased oxidative stress (H_2O_2)
- Causes hemolysis

Glucose-6-phosphate dehydrogenase deficiency causes hemolytic anemia

- Mutations present in some populations causes a deficiency in **glucose 6-phosphate dehydrogenase**, with consequent impairment of NADPH production.
- Detoxification of H_2O_2 is inhibited, and cellular damage results - lipid peroxidation leads to erythrocyte membrane breakdown and hemolytic anemia.
- Most G6PD-deficient individuals are asymptomatic - only in combination with certain environmental factors (sulfa antibiotics, herbicides, antimalarials, *divicine) do clinical manifestations occur.

*toxic ingredient of fava beans

favism

Resulting from deficiency of glucose 6-phophate dehydrogenase enzyme

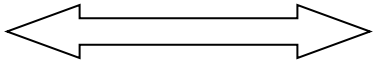
It is type of hemolytic anaemia (destruction of RBCs) after ingestion of fava beans and some other compounds

Main presentation of this patient: jaundice, and decreased hemoglobin concentration.

Child with Favism

With signs of anemia (decreased red blood cell count, jaundice, etc.)

Other $NADPH^+$ Source

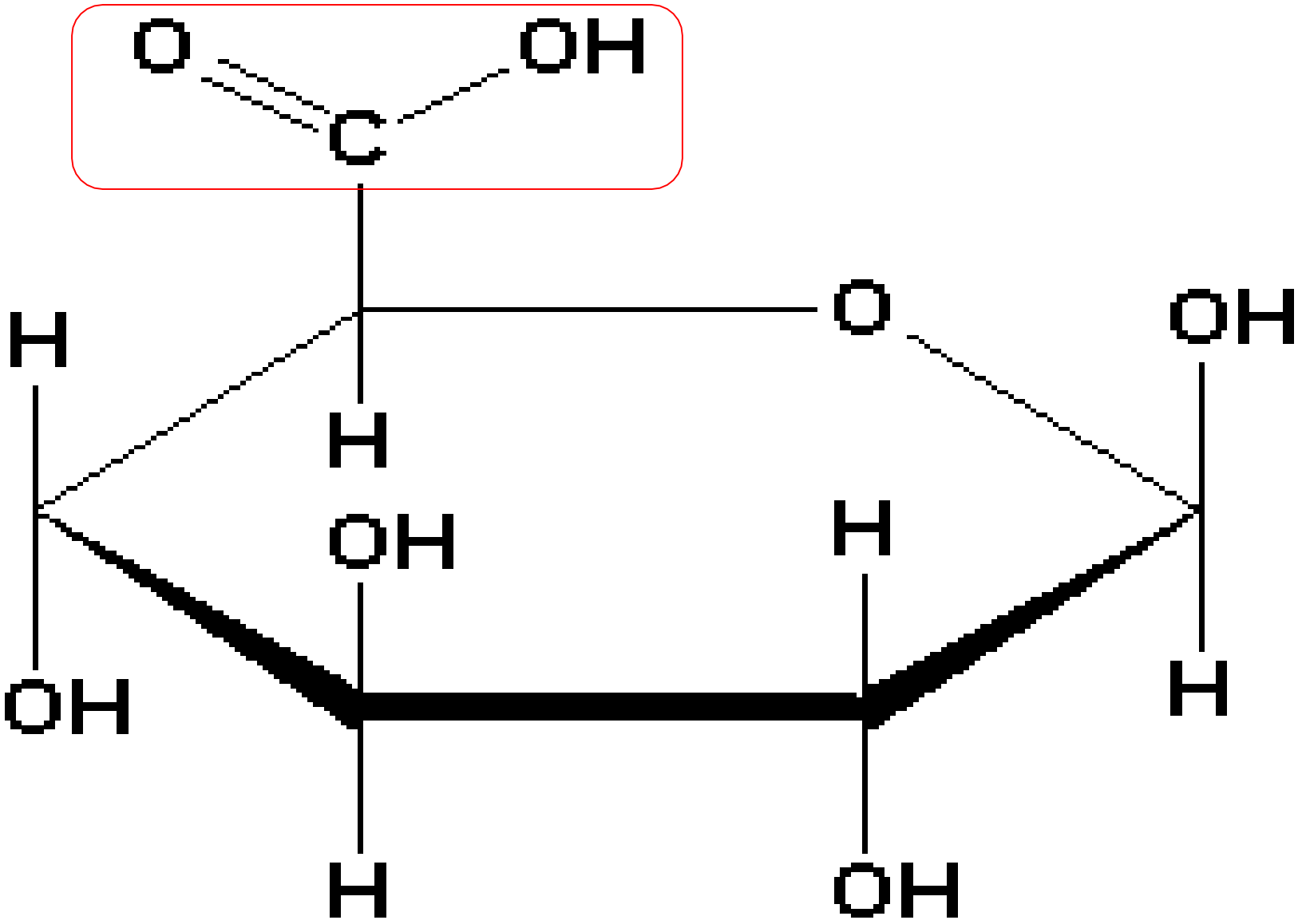
- Malic enzymes (In the cytoplasm) catalyze the oxidative decarboxylation of malate to pyruvate and CO_2, with the concomitant reduction of the cofactor $NADP^+$ to NADPH.
- Reaction catalyzed:
- Malate + $NADP^+$  Pyruvate + CO_2 + NADPH

Regulation of HMP shunt:

Glucose-6- phosphate dehydrogenase is the key enzyme of HMP-shunt.

- **Stimulated by: insulin and NADP+**
- **Inhibited by NADPH, H+ and acetyl CoA.**

Glucuronic Acid Synthesis (Oxidation of Glucose into Glucuronic acid)

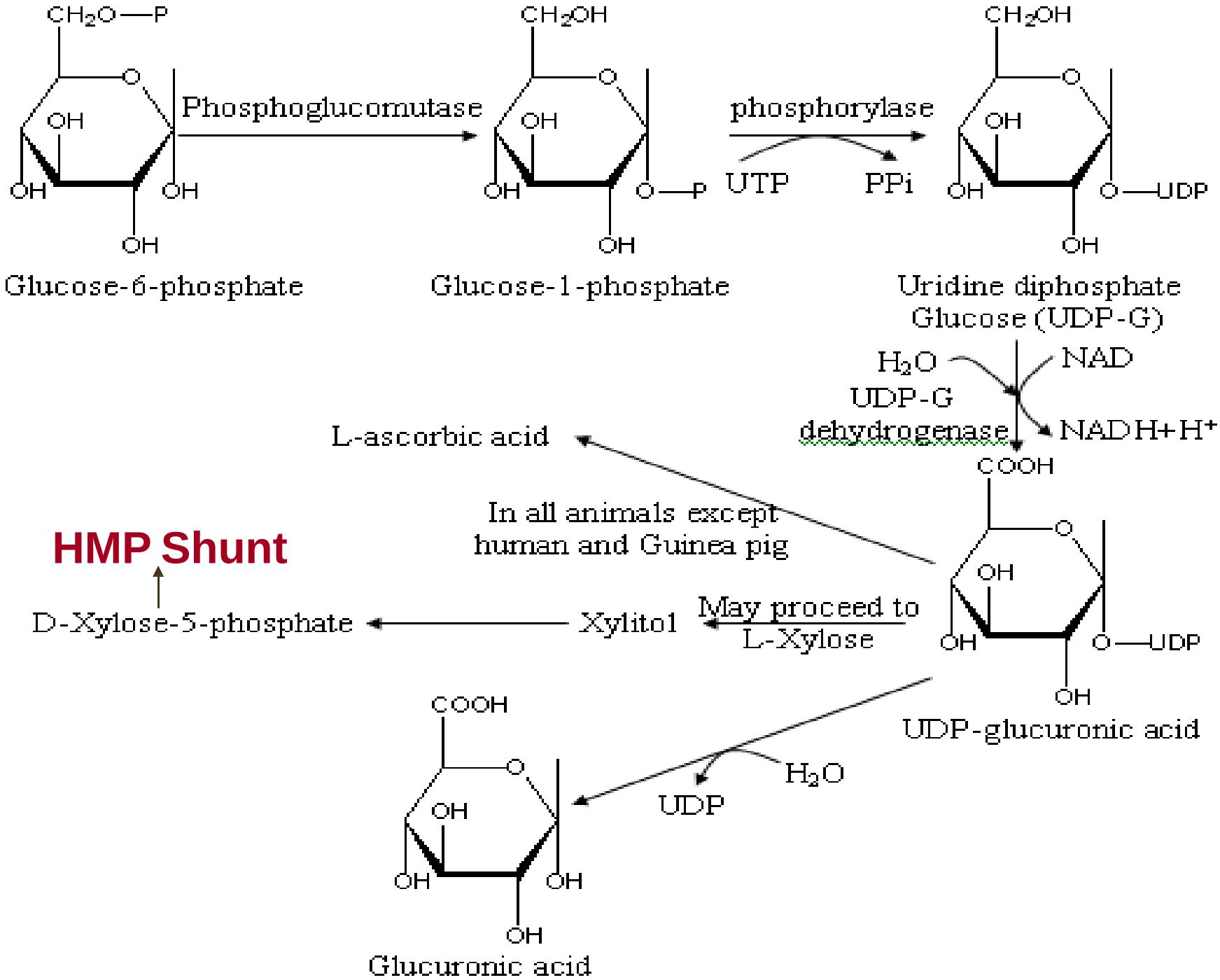


Glucuronic Acid

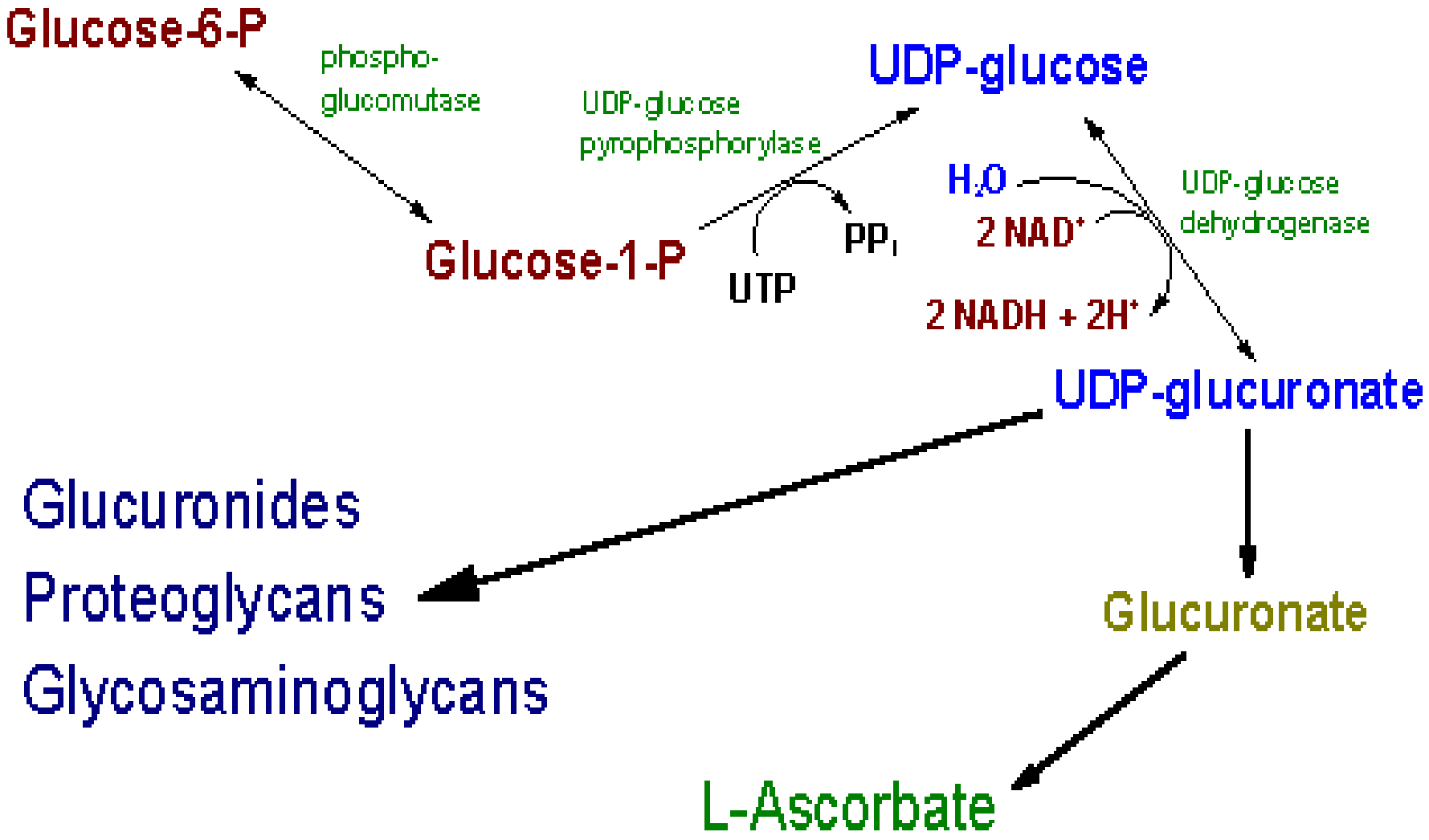
Uronic acid pathway

It is a minor pathway, to convert the glucose into glucuronic acid

Location: intracellular : cytosol
Organ location : mainly in the liver


CH2O—P
OH
OH
OH
OH
Phosphoglucomutase
CH2OH
OH
OH
O—P
OH
phosphorylase
UTP
PPi
CH2OH
OH
OH
O—UDP
OH
Glucose-6-phosphate
Glucose-1-phosphate
Uridine diphosphate
Glucose (UDP-G)
H2O
NAD
UDP-G
dehydrogenase
NADH+H+
L-ascorbic acid
In all animals except
human and Guinea pig
COOH
O
OH
OH
O—UDP
OH
HMP Shunt
D-Xylose-5-phosphate
Xylitol
May proceed to
L-Xylose
UDP-glucuronic acid
COOH
O
OH
OH
OH
OH
UDP
H2O
Glucuronic acid

Glucuronic Acid Usage



Metabolic Significance of Glucuronic Acid

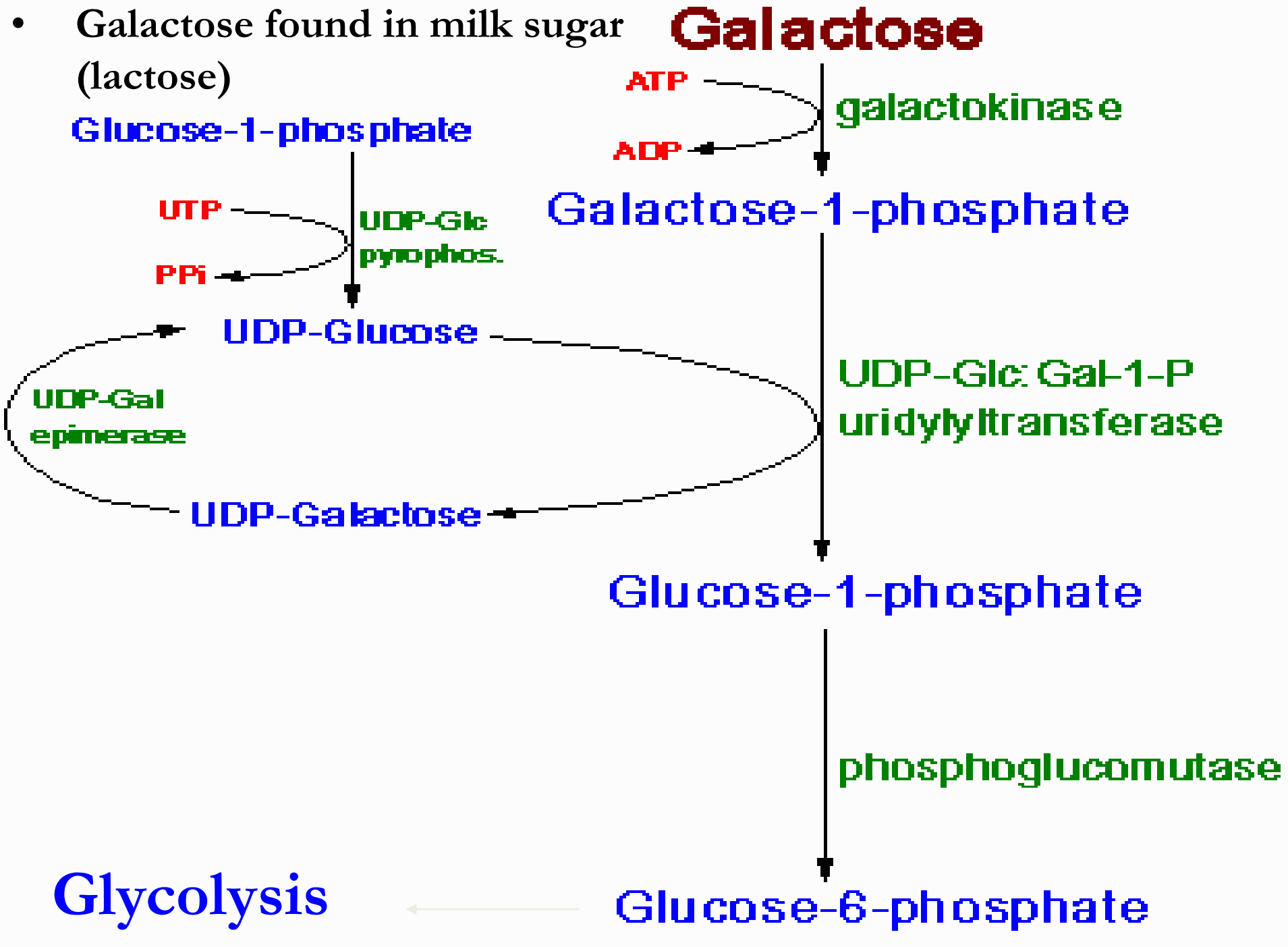
- **Glucuronic acid is used in:**

1. **Synthesis Mucopoly saccharides, Glycosaminoglycans, GAGs).**
2. **Excretion of Bilirubin and Steroid compounds**
3. **Detoxification of certain drugs and their metabolites by increasing their solubility**

Galactose Metabolism

- Galactose is found in **milk** containing diet and it is rather slowly converted to glucose in **the liver**.
- Galactose is synthesized from glucose in large quantities in actively **secreting mammary gland**, and the blood and urine of pregenant and lactating women may contain both galactose and lactose.

- Galactose found in milk sugar (lactose)



Galactosemia

Galactosemia: Congenital disease caused by deficiency of **galactose-1-P-uridyl transferase**. It's characterized by galactosemia and galactosuria and cataract. Cataract which occurs in case of galactosemia is due to:

1-Accumulation of galactose in the eye which is reduced in the eye lens to its alcohol , this alcohol overhydrates the eye lens, causing cataract.

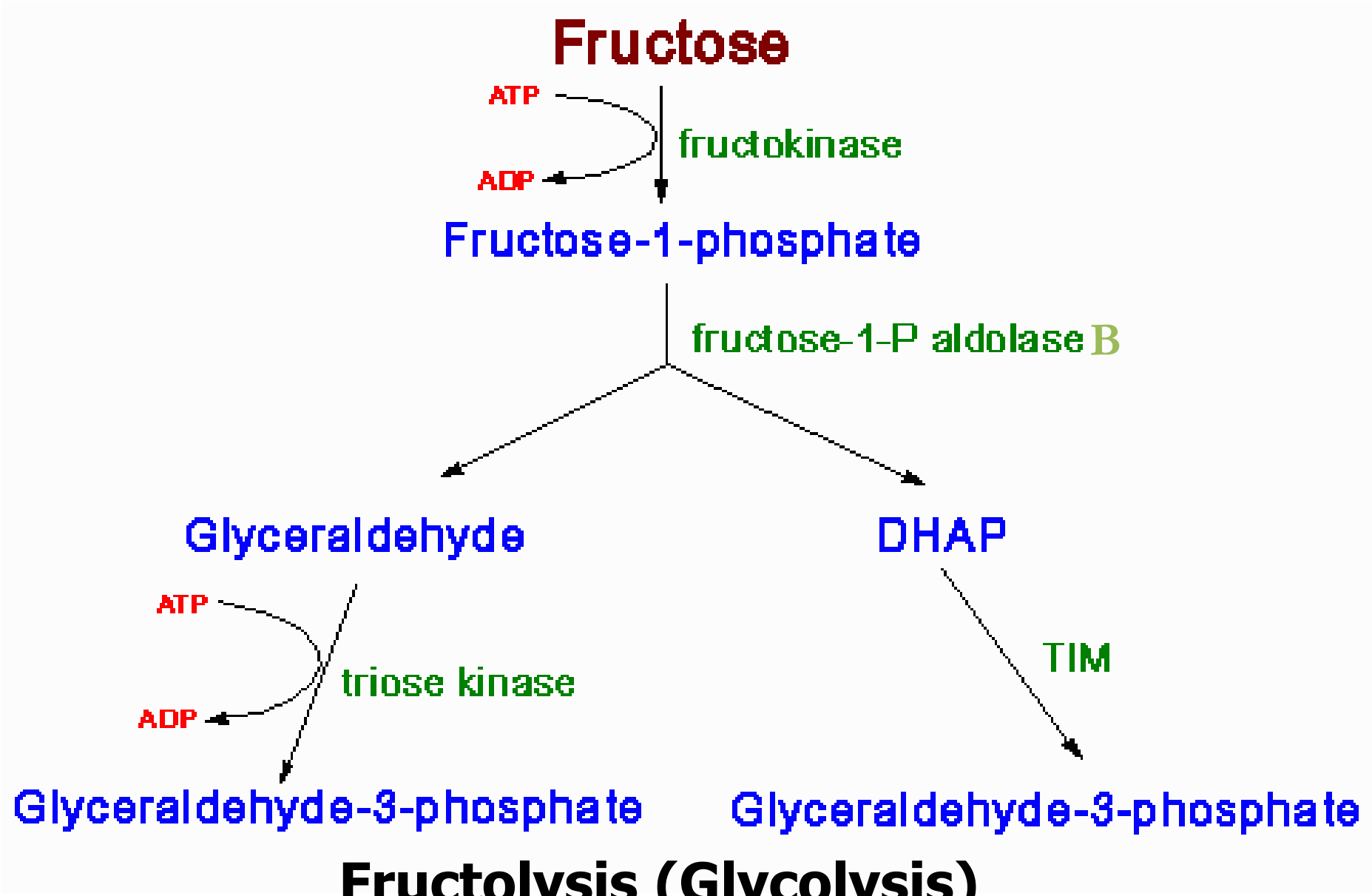
2-Increased galactose levels inhibit glucose-6-P dehydrogenase, the key enzyme of HMP shunt which is one source of energy to the eye lens.

Fructose Metabolism

- People eating diets containing large amounts of sucrose, can utilize fructose as a major source of energy.
- The pathway for utilization of fructose differs in muscle and liver.
- Muscle which contains only *hexokinase* can phosphorylate fructose into F-6-P which is a direct glycolytic intermediate.

- **In the liver, glucokinase does not activate fructose**
- **Fructokinase produces F1P**
- **This is cleaved by type B aldolase to glyceraldehyde + DHAP**

Entry of fructose carbon atoms into the glycolytic pathway in hepatocytes



Fructolysis (Glycolysis)

Deficiency for aldolase B (Hereditary Fructose Intolerance) leads to:

1. Accumulation of Fructose & F-1-P.
2. F-1-P inhibits glycogen phosphorylase enzyme leading to hypoglycemia especially after ingestion of fructose.

Synthesis of Fructose in Seminal Vesicles

- Estimation of seminal fructose is used as a Male Fertility Test.
- Aldose reductase (NADPH-linked) can reduces glucose into Sorbitol.
- Sorbitol dehydrogenase converts Sorbitol into fructose.

Metabolism of Sorbitol

- Aldose reductase is found in significant amounts in:
  - Liver.
  - Seminal vesicle.
  - Epithelium of the eye lens.
  - Schwann cells of peripheral nerves.
  - kidney.

- **While Sorbitol dehydrogenase is present <u>only</u> in liver & Seminal vesicle.**

In Diabetes Mellitus:

- Glucose enters tissues freely (requires no insulin).
- In hyperglycemia large amounts of glucose enter these tissues & converted into sorbitol which is dead metabolite in the retina, kidney & peripheral nerves, due to absence of Sorbitol DH.
- Sorbitol will accumulates in these cells, causing many physiologic & pathologic manifestation including:
- Cataract.
- Retinopathy of eye lens.
- Peripheral neuropathy of peripheral nerves.
- Nephropathy of kidney.
- Vascular problems (Atherosclerosis).

References:

- **Lippincott's Illustrated Reviews: Biochemistry Fifth Edition**

  Richard A. Harvey and Denise R. Ferrier.