Glycogen Storage Diseases

(A group of genetic diseases)

Glycogen Storage Diseases (GSD)

- Inherited genetic defects related to glycogen metabolism.
- Glycogenosis.
- Characterized by deposition of glycogen in the specific tissues, mainly Liver, Muscle, Spleen, Renal tubules..
- Some of the more common 6 major forms of these diseases……

Type	Name	Enzyme affected	Primary organ involved	Clinical Manifestations
I	Von Gierke's disease or (type I glycogenosis)	G-6-P'ase	Liver, kidney and intestine	Hypoglycemia, hyperlipemia, Ketosis, hyperuricemia(Gout), Lactic phosphatase acidemia, hepatomegaly etc
II	Pompe's disease	Lysosomal α-1, 4 glucosidase or (acid maltase)	All organs with Lysosomes	Infantile form, early death, Cardiac failure, Accumulation of glycogen in lysosomes
III	Cori's disease or (Limit dextrinosis) or Forbe's disease)	Absence of Debranching enzyme or (Amylo α-1,6-glucosidase)	Liver, muscle, heart, leucocytes	Branched chain glycogen accumulates; liver enlarged; clinical manifestations are similar to von Gierke's disease.

Type	Name	Enzyme affected	Primary organ involved	Clinical Manifestations
IV	Andersen's disease Or Amylopectinosis	Absence of Branching enzyme	Liver	Accumulation of abnormal glycogen having few branches, Early death due to cardiac or liver failure
V	Mc-Ardle's syndrome	Absence of Muscle glycogen phosphorylase	Skeletal muscle	Muscle do not get energy, Excessive induced muscular pain, cramps, decrease serum lactate after exercise.

Type	Name	Enzyme affected	Primary organ involved	Clinical Manifestations
VI	Her's disease	Liver glycogen phosphorylase	Liver	High content of liver glycogen, mild hypoglycemia and ketosis
VII	Tarui's disease	Phosphofructo kinase (PFK) in muscle and erythrocytes	Muscle and RBC	As in type V, in addition hemolytic anemia

Hexose Monophosphate Pathway (HMP)

(PPP Shunt)

Definition:

It is an alternative minor pathway for glucose oxidation.

Does not produce ATP nor utilize it.

Producing $NADPH+H^+$ (Biosyn Lipids) and Ribose (Synthesis of NA).

Intracellular site and tissue distribution:

Cytosolic in tissues namely: liver, Adipose tissues, Lactating mammary gland, RBCs, Suprarenal cortex, Thyroid and testis.

Not active in non-lactating mammary gland, and in skeletal muscles.

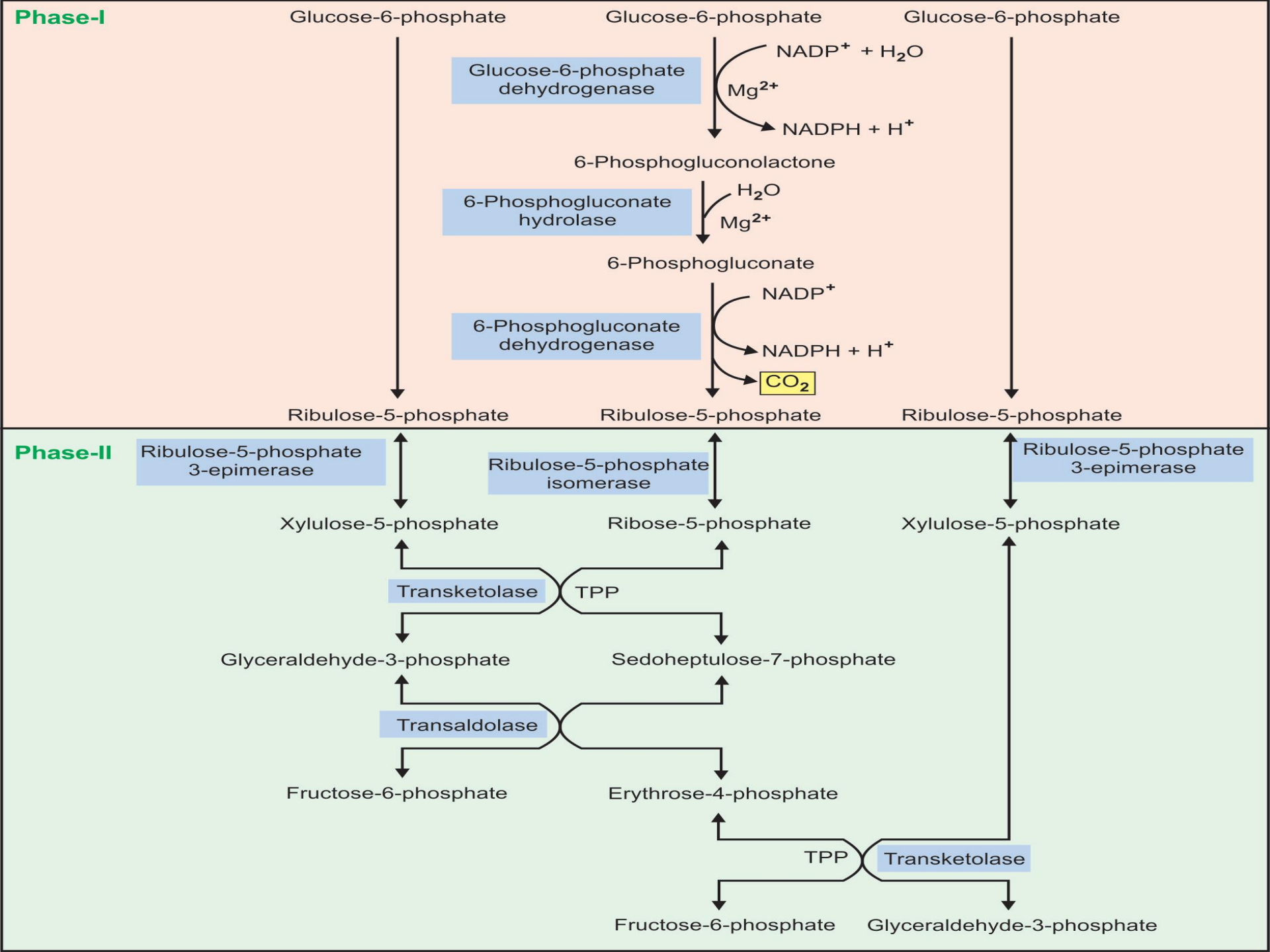
Reactions of the Pentose Phosphate Pathway

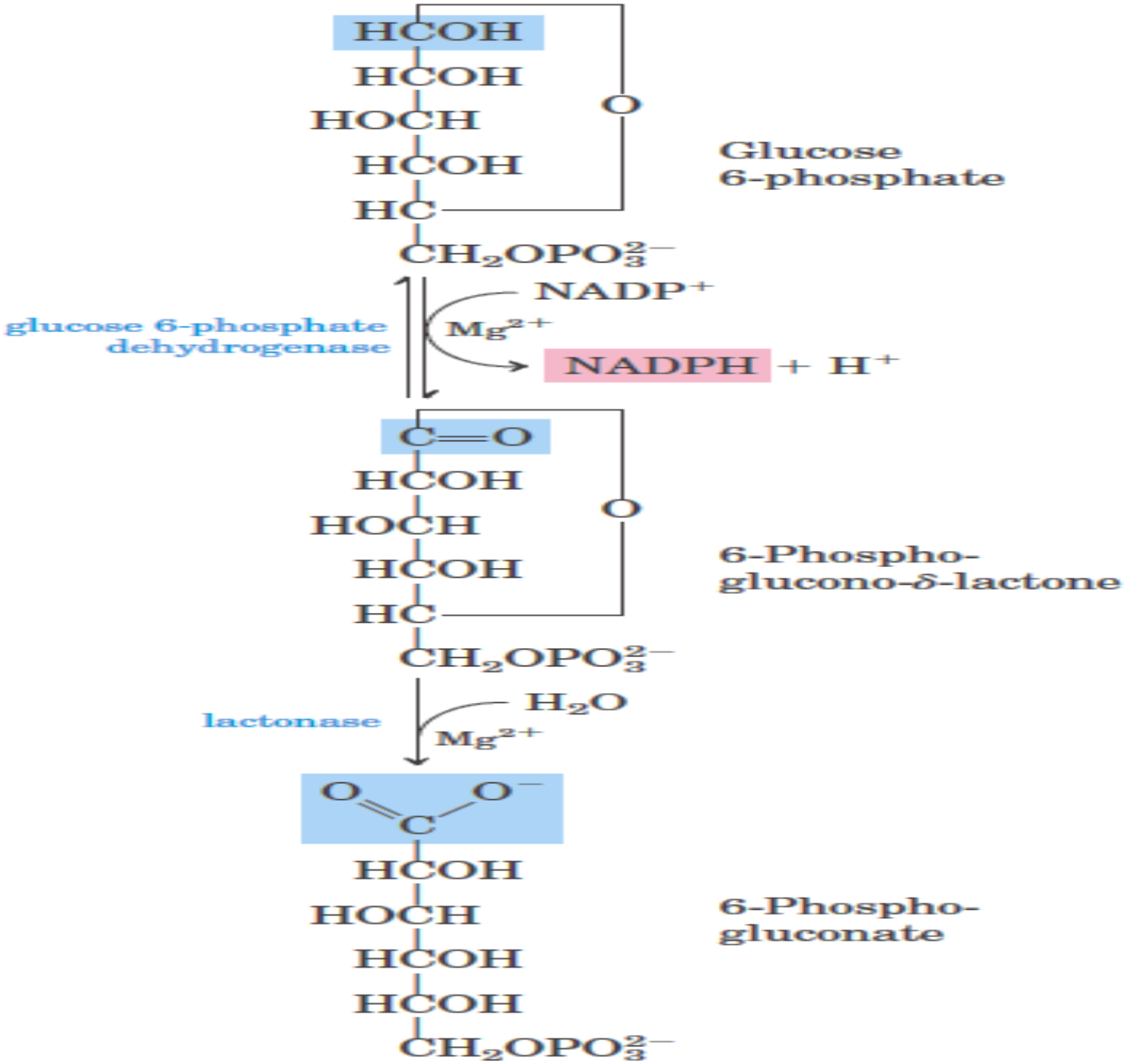
The pathway are divided into **two phases:**

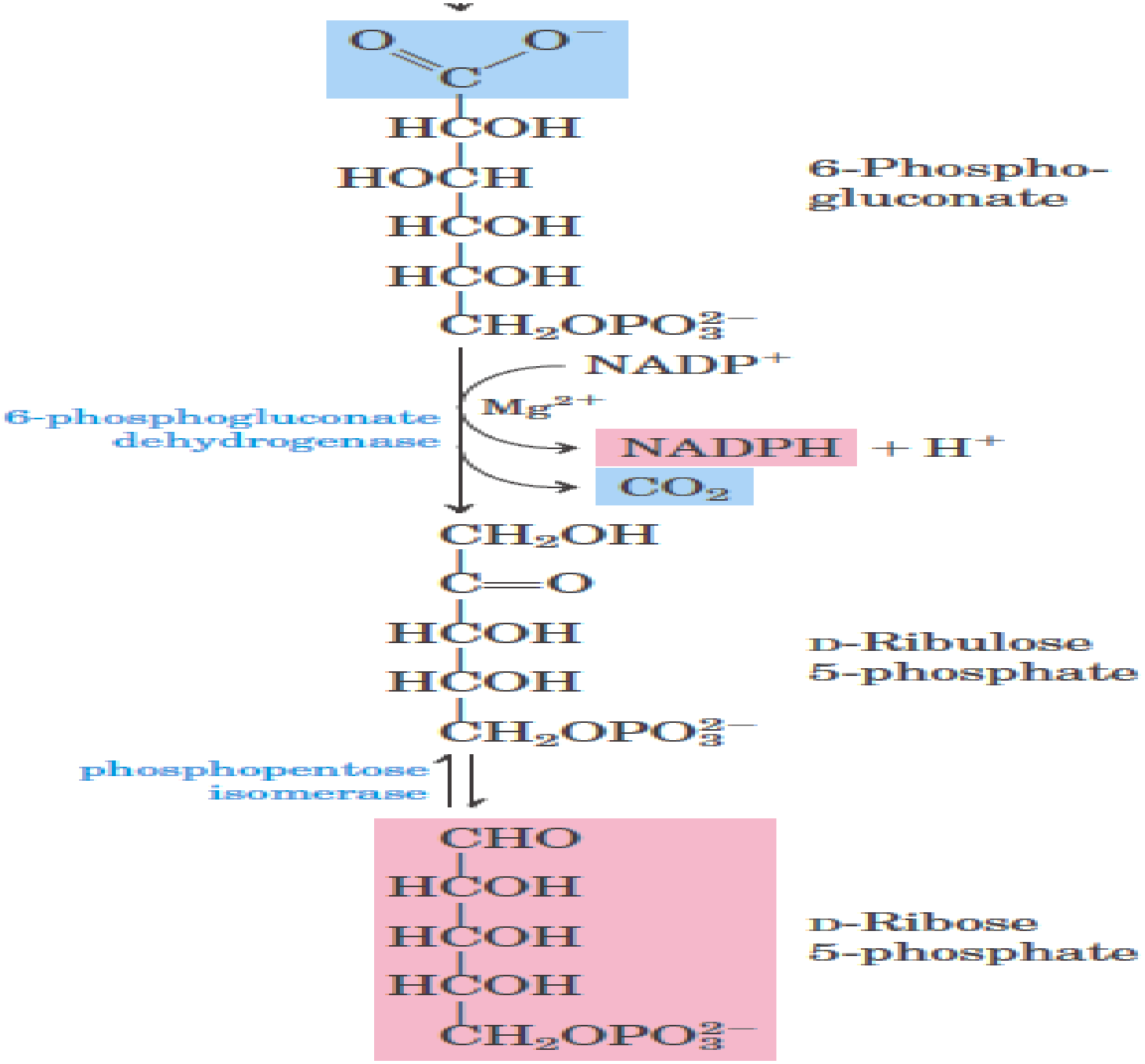
1. **Phase I : Oxidative irreversible phase**
2. **Phase II : Non-oxidative reversible phase.**

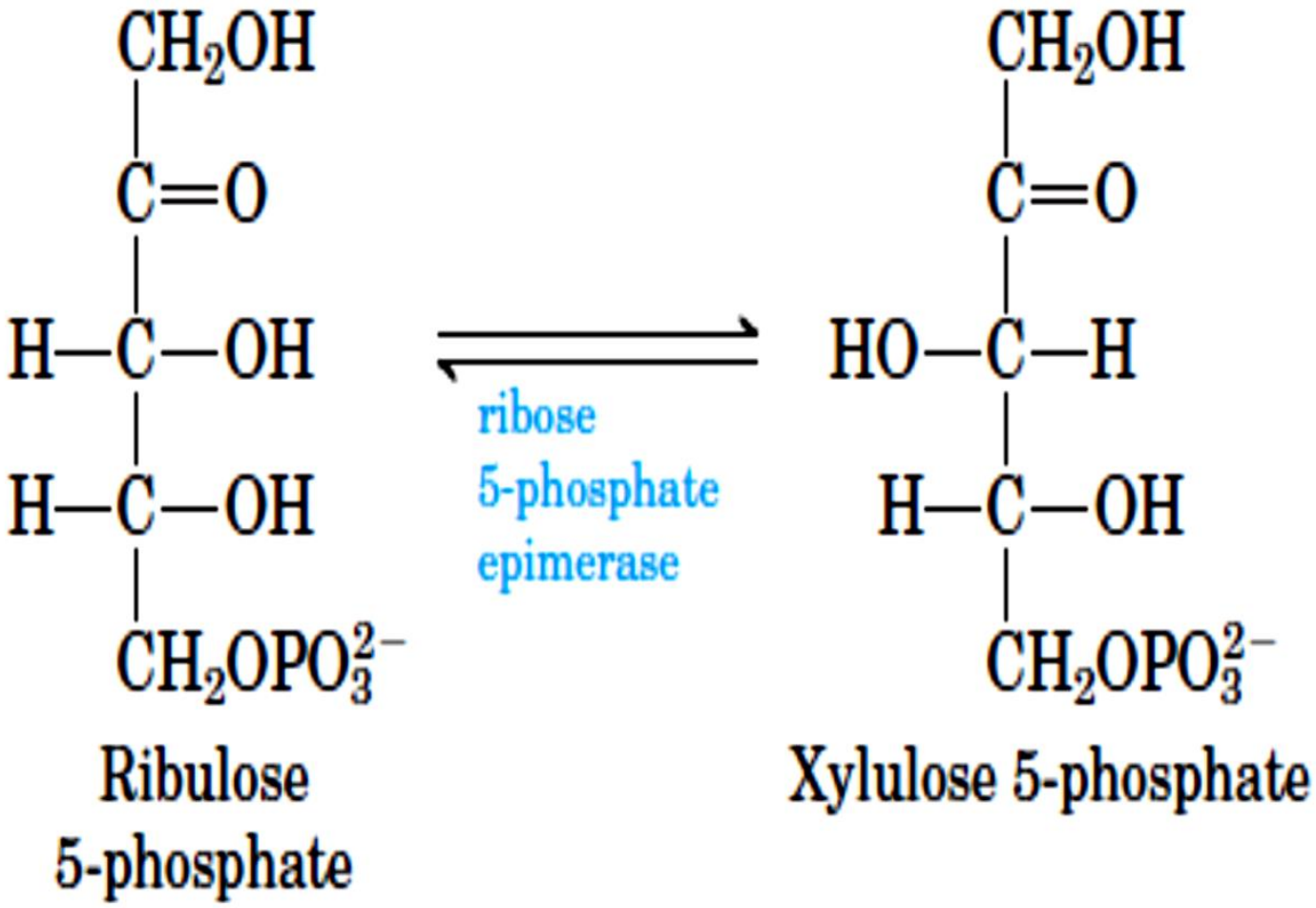
Reactions of phase I (oxidative irreversible phase):

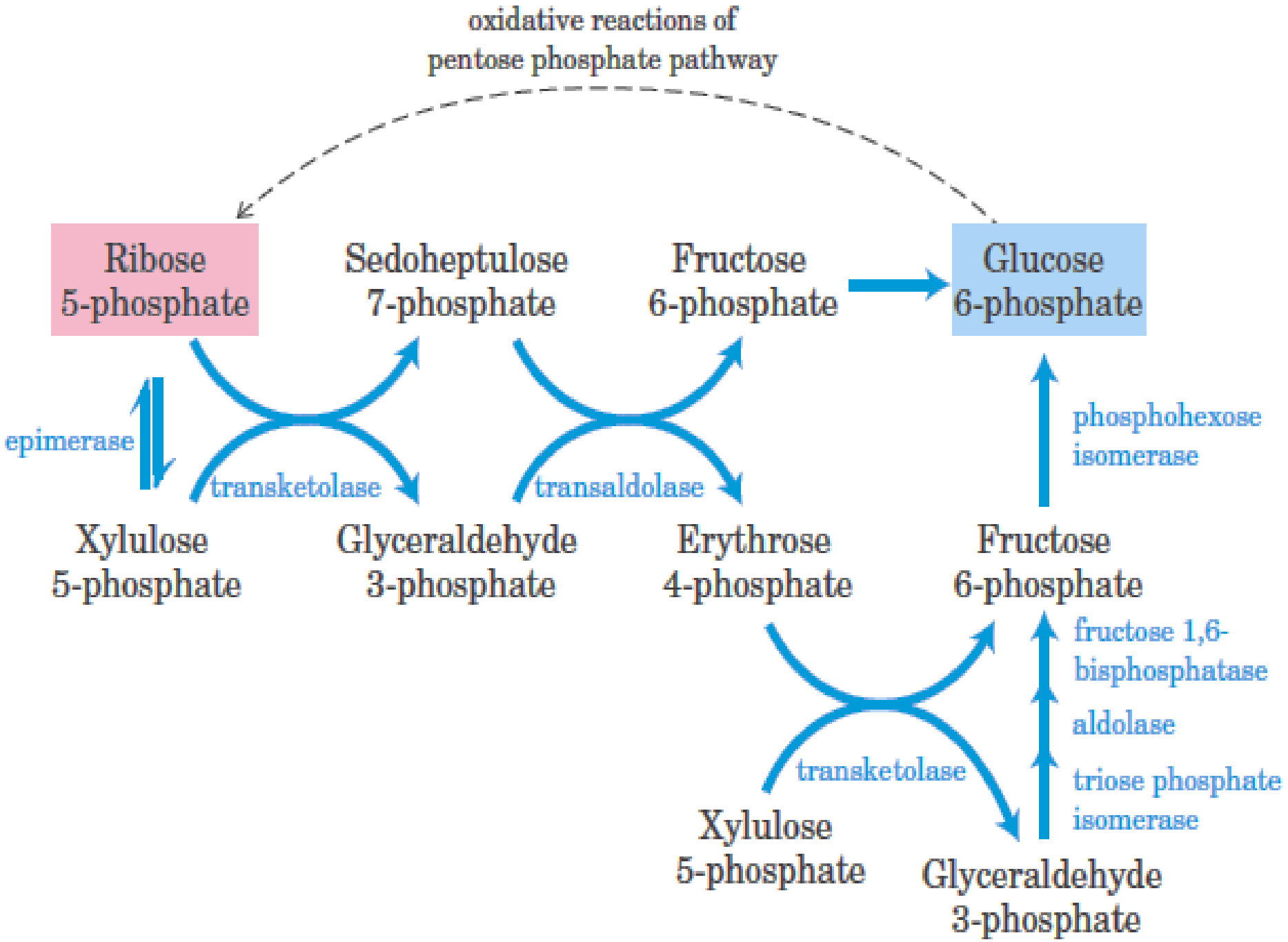
In the first phase, glucose-6-phosphate undergoes dehydrogenation and decarboxylation to give pentose, ribulose-5-phosphate with generation of NADPH.

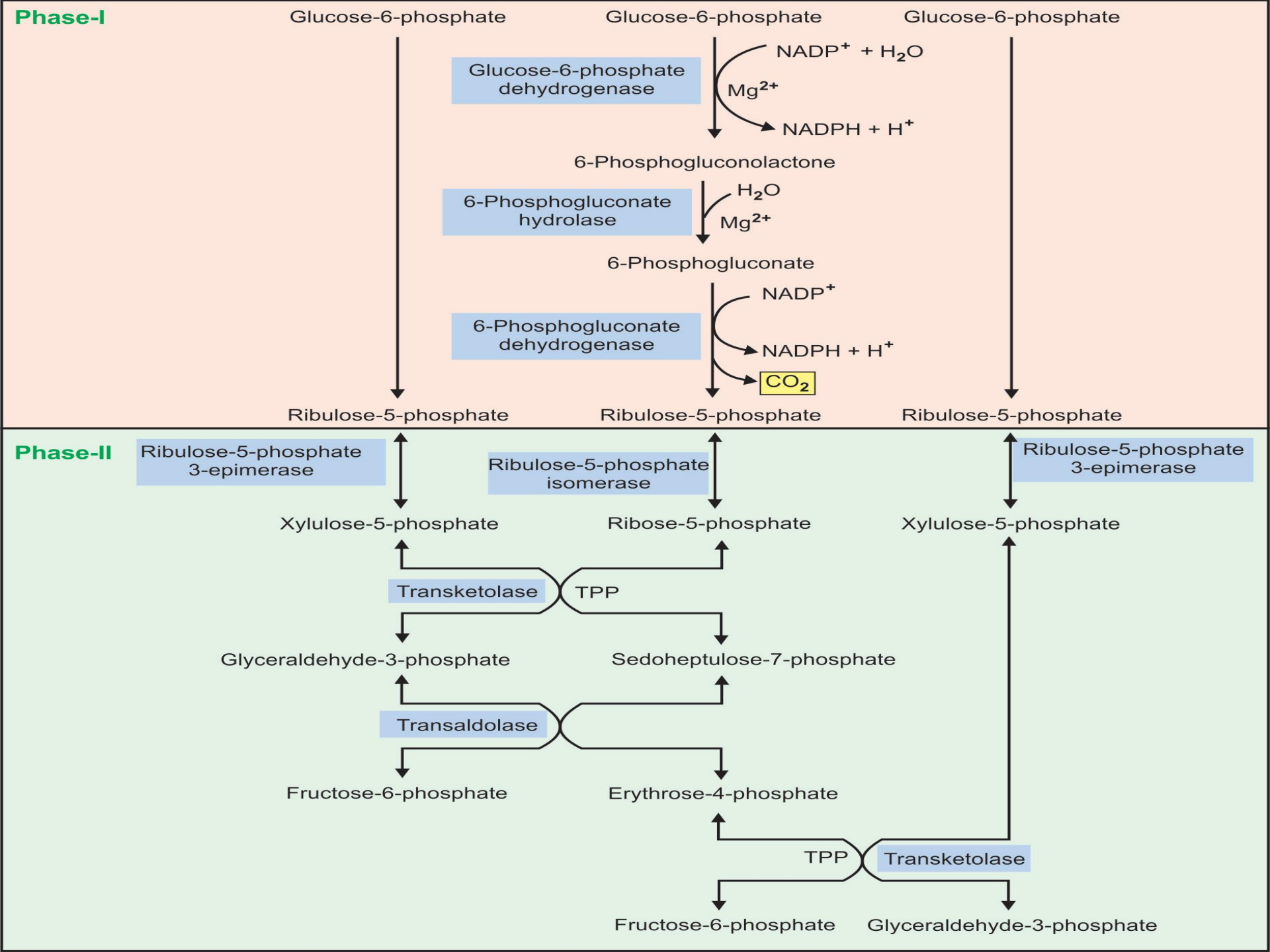

Phase-I
Glucose-6-phosphate
Glucose-6-phosphate
Glucose-6-phosphate
Glucose-6-phosphate dehydrogenase
NADP+ + H2O
Mg2+
NADPH + H+
6-Phosphogluconolactone
6-Phosphogluconate hydrolase
H2O
Mg2+
6-Phosphogluconate
6-Phosphogluconate dehydrogenase
NADP+
NADPH + H+
CO2
Ribulose-5-phosphate
Ribulose-5-phosphate
Ribulose-5-phosphate
Phase-II
Ribulose-5-phosphate 3-epimerase
Ribulose-5-phosphate isomerase
Ribulose-5-phosphate 3-epimerase
Xylulose-5-phosphate
Ribose-5-phosphate
Xylulose-5-phosphate
Transketolase
TPP
Glyceraldehyde-3-phosphate
Sedoheptulose-7-phosphate
Transaldolase
Fructose-6-phosphate
Erythrose-4-phosphate
TPP
Transketolase
Fructose-6-phosphate
Glyceraldehyde-3-phosphate


HCOH
HCOH
HOCH
HCOH
HC
O
CH2OPO3 2−
Glucose 6-phosphate
NADP+
glucose 6-phosphate dehydrogenase
Mg2+
NADPH + H+
C=O
HCOH
HOCH
HCOH
HC
O
CH2OPO3 2−
6-Phospho-glucono-δ-lactone
H2O
lactonase
Mg2+
O
O−
C
HCOH
HOCH
HCOH
HCOH
CH2OPO3 2−
6-Phospho-gluconate


6-Phospho-
gluconate
NADP+
Mg2+
6-phosphogluconate
dehydrogenase
NADPH + H+
CO2
D-Ribulose
5-phosphate
phosphopentose
isomerase
D-Ribose
5-phosphate


CH2OH
C=O
H—C—OH
H—C—OH
CH2OPO3 2−
ribose
5-phosphate
epimerase
CH2OH
C=O
HO—C—H
H—C—OH
CH2OPO3 2−
Ribulose
5-phosphate
Xylulose 5-phosphate


oxidative reactions of
pentose phosphate pathway
Ribose
5-phosphate
Sedoheptulose
7-phosphate
Fructose
6-phosphate
Glucose
6-phosphate
epimerase
transketolase
transaldolase
phosphohexose
isomerase
Xylulose
5-phosphate
Glyceraldehyde
3-phosphate
Erythrose
4-phosphate
Fructose
6-phosphate
fructose 1,6-
bisphosphatase
aldolase
triose phosphate
isomerase
transketolase
Xylulose
5-phosphate
Glyceraldehyde
3-phosphate


Phase-I
Glucose-6-phosphate
Glucose-6-phosphate
Glucose-6-phosphate
Glucose-6-phosphate dehydrogenase
NADP+ + H2O
Mg2+
NADPH + H+
6-Phosphogluconolactone
6-Phosphogluconate hydrolase
H2O
Mg2+
6-Phosphogluconate
6-Phosphogluconate dehydrogenase
NADP+
NADPH + H+
CO2
Ribulose-5-phosphate
Ribulose-5-phosphate
Ribulose-5-phosphate
Phase-II
Ribulose-5-phosphate 3-epimerase
Ribulose-5-phosphate isomerase
Ribulose-5-phosphate 3-epimerase
Xylulose-5-phosphate
Ribose-5-phosphate
Xylulose-5-phosphate
Transketolase
TPP
Glyceraldehyde-3-phosphate
Sedoheptulose-7-phosphate
Transaldolase
Fructose-6-phosphate
Erythrose-4-phosphate
TPP
Transketolase
Fructose-6-phosphate
Glyceraldehyde-3-phosphate

Regulation of HMP shunt: -

The key regulatory enzymes are G-6-PD and 6-phospho-gluconate dehydrogenases.

They are activated by **fed state**, glucose, insulin, thyroxine and NADP.

But….

They are inhibited during starvation, diabetes mellitus and with high $NADPH.H^{+}/NADP$ ratio.

Functions and metabolic importance of HMP shunt:

I- Production of pentoses:

Tissues must satisfy their own requirement of pentoses since dietary pentoses are not utilizable and ribose is not a significant constituent of systemic blood.

Pentoses are used for:

1. Nucleic acids, Ribose for RNA and Deoxyribose for DNA.
2. Coenzymes synthesis, e.g., NAD+, FAD, CoASH.
3. Free nucleotide Coenzymes, e.g., ATP, GTP,
4. Synthesis of certain vitamins, e.g., B_2 and B_{12}.

HMP pathway is the major human source for production of NADPH.H$^+$ required for:

1. Fatty acid synthesis (lipogenesis) and fatty acid desaturation.
2. Cholesterol and other steroid synthesis.
3. Synthesis of sphingosine and cerebrosides.
4. Synthesis of non-essential amino acids, e.g., glutamate and tyrosine from phenylalanine.
5. Regeneration of reduced glutathione (G-S-H).
6. Metabolic hydroxylation with cytp_{450}.

F a v i s m
(G-6-PD Deficiency)

Glucose-6-phosphate dehydrogenase deficiency :

-- Sometimes also called **G6PD deficiency**, or **favism** is a hereditary disease.

-- As it is linked to the X chromosome, most people who suffer from it are male.

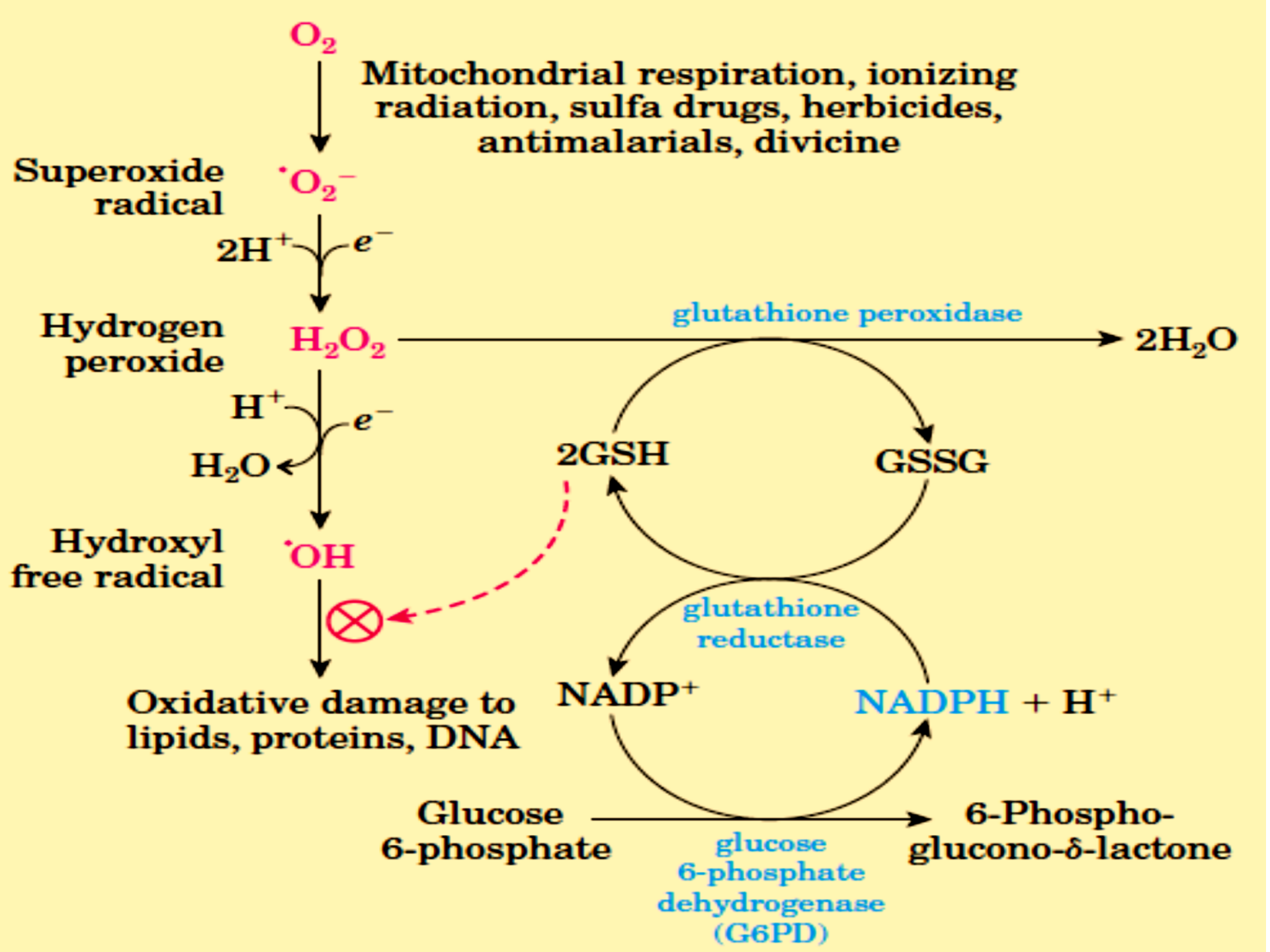
-- Sufferers can not make the enzyme G-6-PD.

-- This will mean the circulation of sugar in their body is different.

-- G6PD (first step in the PPP), which **produces** NADPH (reductant) which essential in many biosynthetic pathways.

-- **Also protects** cells from oxidative damage (ROS) like hydrogen peroxide (H_2O_2) and superoxide free radicals (metabolic byproducts).

-- Through the actions of drugs such as primaquine and natural products such as divicine—the toxic ingredient of fava beans.


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
6-Phospho-glucono-δ-lactone
glucose 6-phosphate dehydrogenase (G6PD)

G-6-PD deficiency and resistance to malaria:

The malarial parasite, Plasmodium falciparum infects the red blood cell, where it depends on the reduced glutathione and the products of the pentose phosphate pathway for its optimum growth.

Therefore, persons with G-6-PD deficiency cannot support growth of this parasite and thus are less prone to malaria than the normal person.

Wernicke-Korsakoff syndrome

- This is a genetic disorder.
- Due to reduced activity of TPP-dependent transketolase enzyme.

- Chronic thiamine deficiency a much reduced activity of transketolase leading to the Wernicke-Korsakoff syndrome.

- Symptoms :

Weakness, Mental disorder, Memory loss, Paralysis, etc.

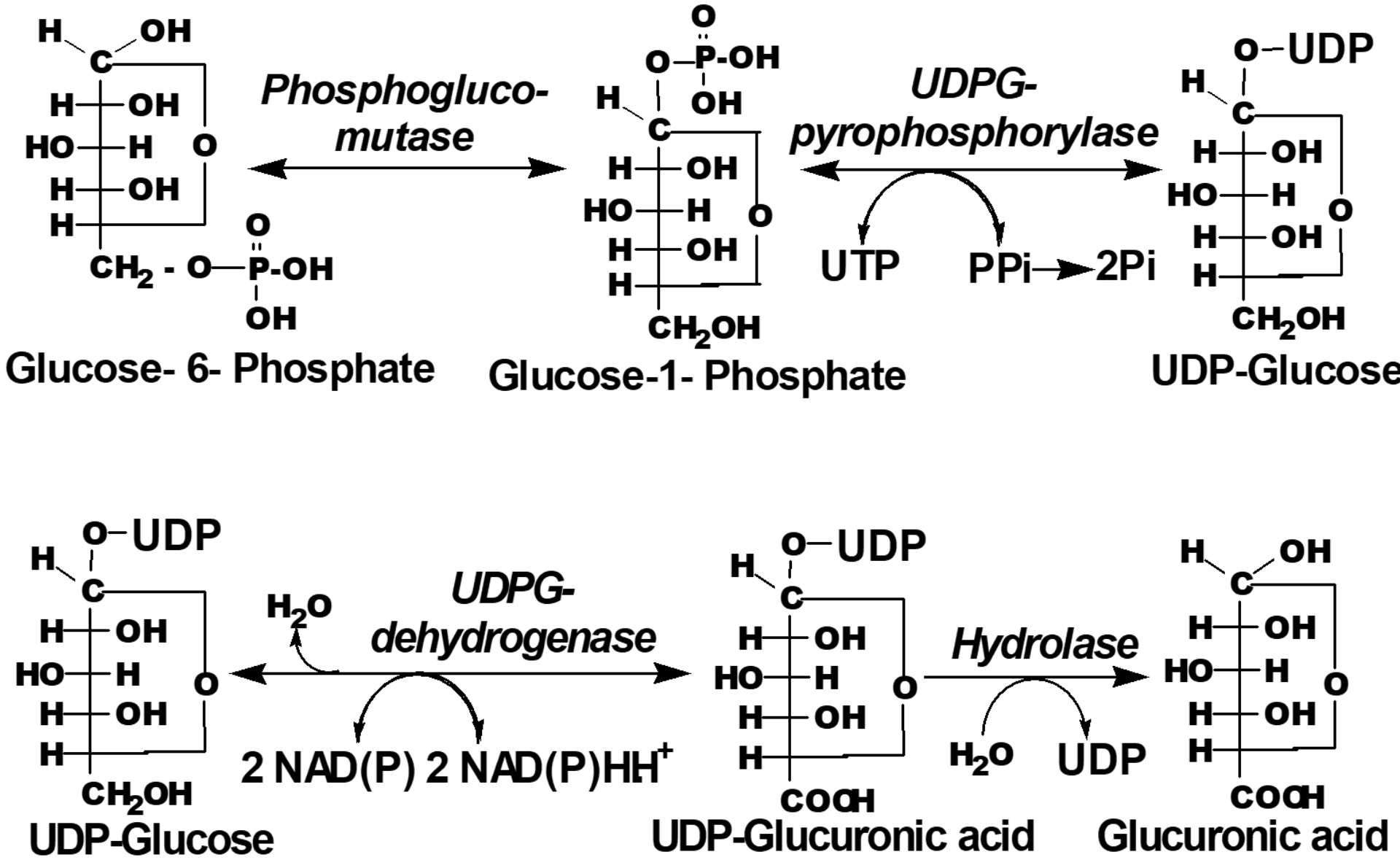
Uronic acid Pathway

It is another minor alternative pathway for glucose oxidation by which glucuronic acid, ascorbic acid and pentoses are obtained from glucose.

Like HMP shunt, it does not need nor generate ATP.

Site:

In cytosol of many tissues, especially liver, kidney and intestine.


Phosphogluco-
mutase
UDPG-
pyrophosphorylase
UTP
PPi
2Pi
Glucose- 6- Phosphate
Glucose-1- Phosphate
UDP-Glucose
UDPG-
dehydrogenase
2 NAD(P) 2 NAD(P)H
Hydrolase
UDP
UDP-Glucose
UDP-Glucuronic acid
Glucuronic acid

Biological importance of Uronic Acid Pathway:

1-Production of UDP-glucuronic acid,
metabolically active form of glucuronic acid.

Enters in:

- Synthesis of mucopolysaccharides.
- Detoxification by conjugation: UDP-glucuronic acid is used to detoxify steroid hormones, drugs and toxins.
- Formation of conjugated bilirubin.

2-Formation of pentoses.

Disorder of Glucuronic Acid Pathway

Essential pentosuria:

It is a benign (harmless) inborn error of metabolism.

Sugar L-xylulose is excreted in the urine in excess.

Due to defect in NADP+ linked ***L-xylulose dehydrogenase***, *(*glucuronic acid pathway).

It is necessary to accomplish reduction of L-xylulose to xylitol.

GALACTOSE METABOLISM AND GALACTOSEMIA

- Galactose is derived from disaccharide, lactose (**Milk sugar**) of the diet.
- Galactose is **readily converted** in the liver to glucose
- It is important for the formation of:
  - Glycolipids
  - Glycoproteins
  - Proteoglycans
  - Lactose during lactation.

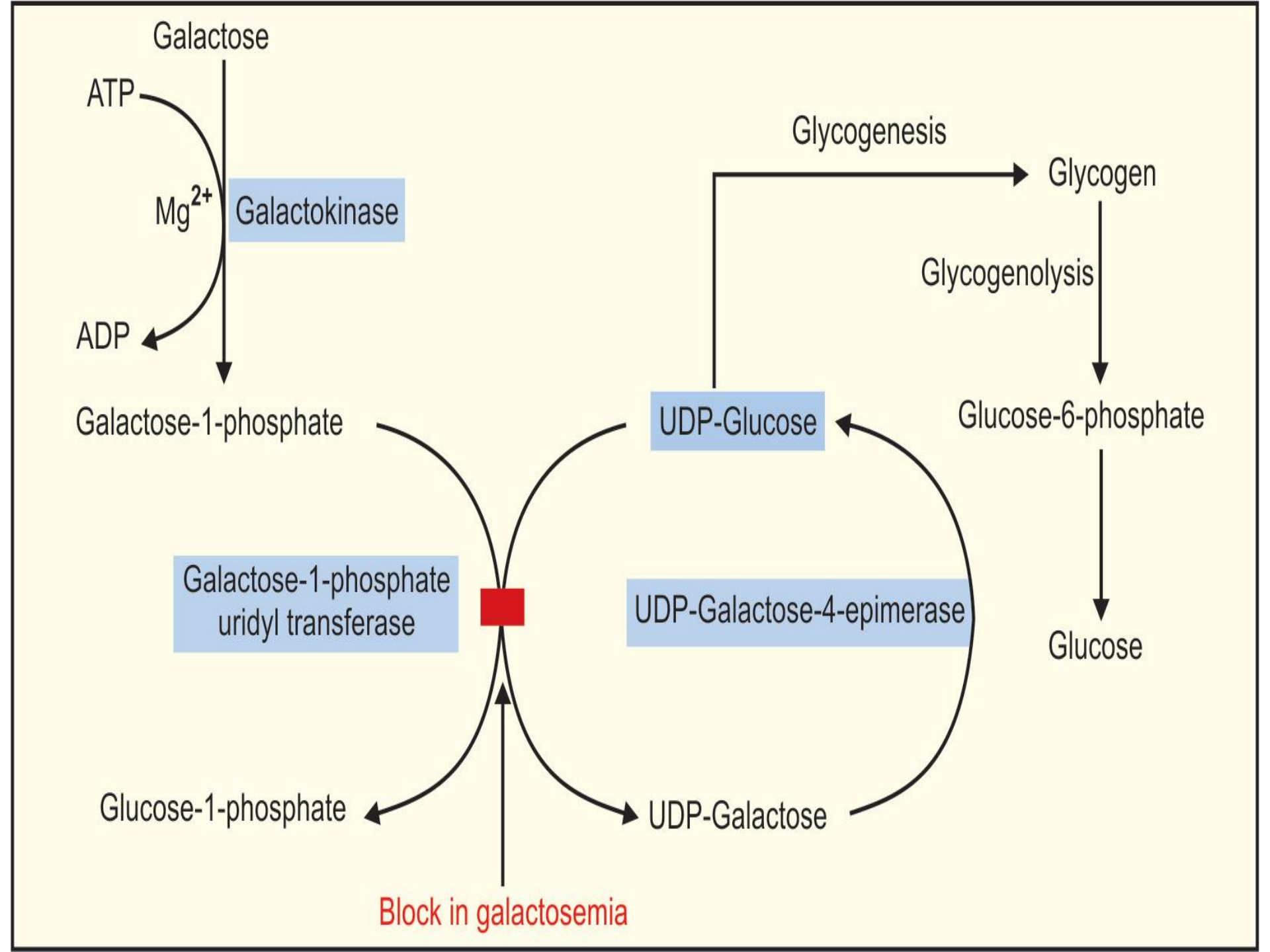
Reactions of the Pathway

I. Phosphorylation of galactose to galactose-1-phosphate by ***Galactokinase,*** using ATP.

II. Galactose displaces a glucose of UDP-glucose by ***Galactose-1-phosphate uridyl-transferase***.

III. UDP-galactose to UDP-glucose by ***Epimerase.***

IV. Finally, glucose is liberated from UDP-glucose for glycogenesis and glycogenolysis.


Galactose
ATP
Mg^{2+}
Galactokinase
ADP
Galactose-1-phosphate
Glycogenesis
Glycogen
Glycogenolysis
UDP-Glucose
Glucose-6-phosphate
Galactose-1-phosphate uridyl transferase
UDP-Galactose-4-epimerase
Glucose
Glucose-1-phosphate
UDP-Galactose
Block in galactosemia

Disorder of Galactose Metabolism

- *Galactosemia:* (An inborn error)

- Deficiency of **galactose-1- phosphate uridyl transferase.**

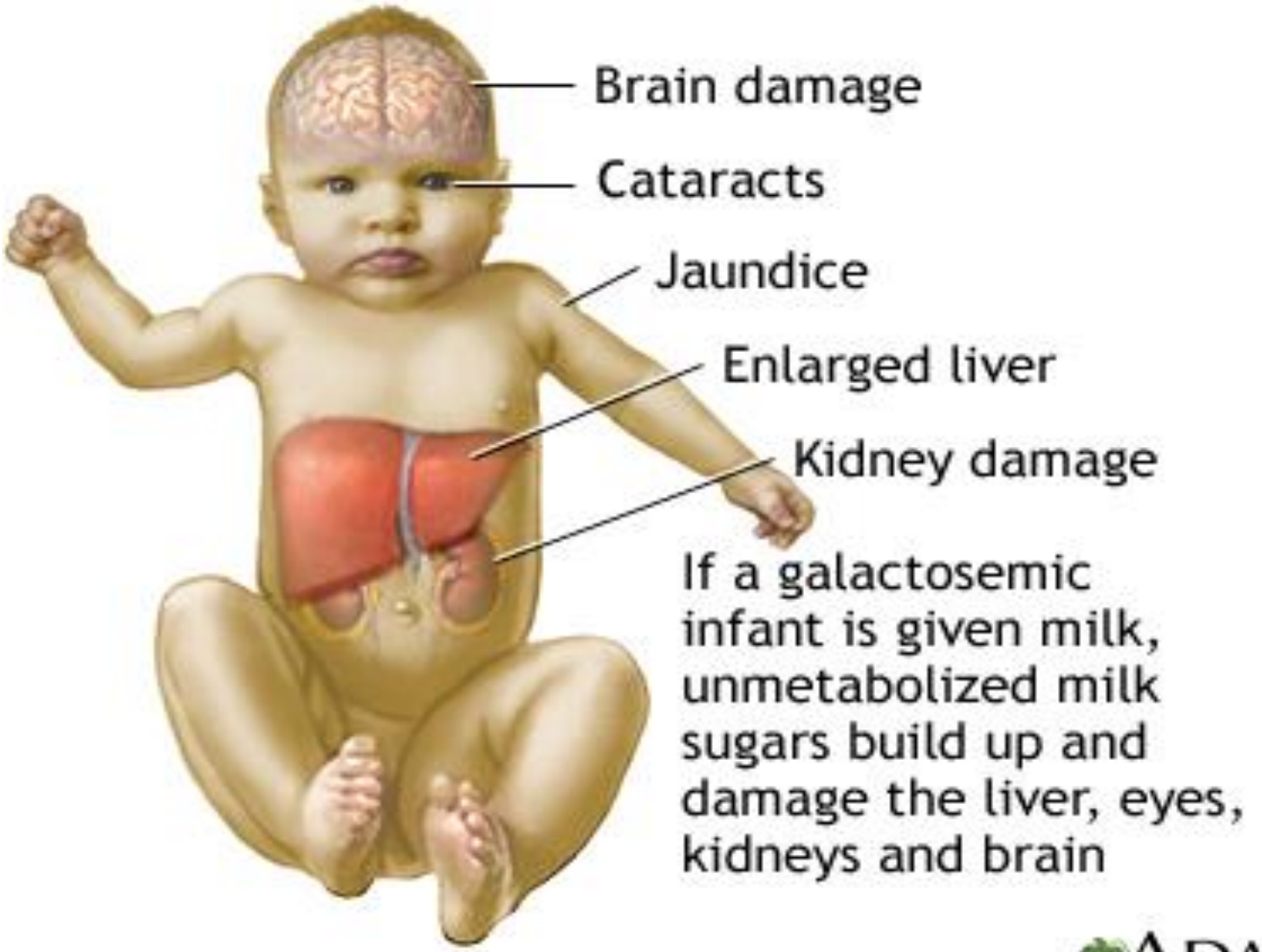
Prevents conversion of galactose to glucose and leads to **accumulation** of galactose and galactose-1-phosphate in blood, liver, brain, kidney and eye lenses.

-- In these organs, the galactose is reduced to galactitol (dulcitol) by **aldose reductase.**

- **Clinical findings:**

- The accumulation of galactitol and galactose-1-phosphate in liver, brain and eye lenses.

- Causes :
- liver failure (hepatomegaly/cirrhosis), mental retardation and cataract formation, etc.


Brain damage
Cataracts
Jaundice
Enlarged liver
Kidney damage
If a galactosemic infant is given milk, unmetabolized milk sugars build up and damage the liver, eyes, kidneys and brain
A.D.A.M.

Glycosuria/Glucosuria

- **Definition :**
- **Conditions:**

1.Glucosuria (excretion of glucose) mainly in diabetes and renal diabetes.

2.Lactosuria: during pregnancy and lactation

3.Galactosuria: found in galactosemia

Types

1.Hyperglycemic glycosuria: blood glucose level exceeds Renal Sugar Threshold (RST).

Ex: DM, Hyper secretion of Thyroid hormones, Cortisol etc.

2.Renal glycosuria: RST lower due to reabsorption capacity of renal tubules diminished (BSL normal).

3.Alimentary glycosuria: after carbohydrate rich meal due to excess absorption from intestine.

4.Glycosuria of pregnancy: decreased RST

5.Transient glycosuria: Emotional stress, excessive production of catecholamine's.

Once stress is removed glycosuria disappears

THANK YOU