

# **Major Metabolic Pathways of Glucose and Glucose Transport**

**Clinical Chemistry Unit Pathology  
Department  
College of Medicine, KSU**

# Objectives

- ***By the end of the lecture, students are expected to:***
  - Define a metabolic pathway.
  - Describe the general metabolic pathways for glucose (production and utilization)
  - Briefly describe the HMP
  - Recognize the mechanisms of glucose transport

# Metabolic Pathway

**Definition**

**Site:**

**Cellular (tissue) and Subcellular**

**Reactions**

**Rate-limiting enzyme(s)**

**Regulatory mechanism(s):**

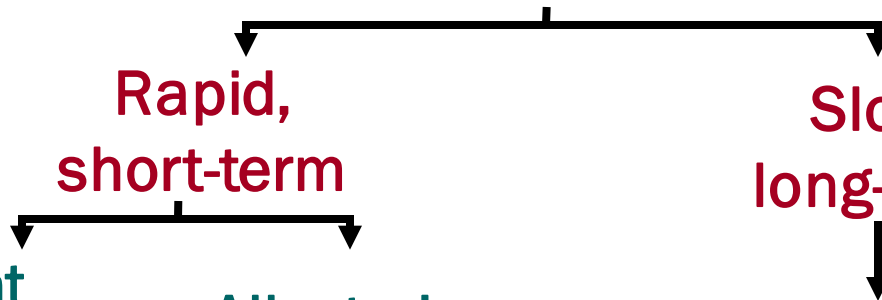
**Rapid,  
short-term**

**Slow,  
long-term**

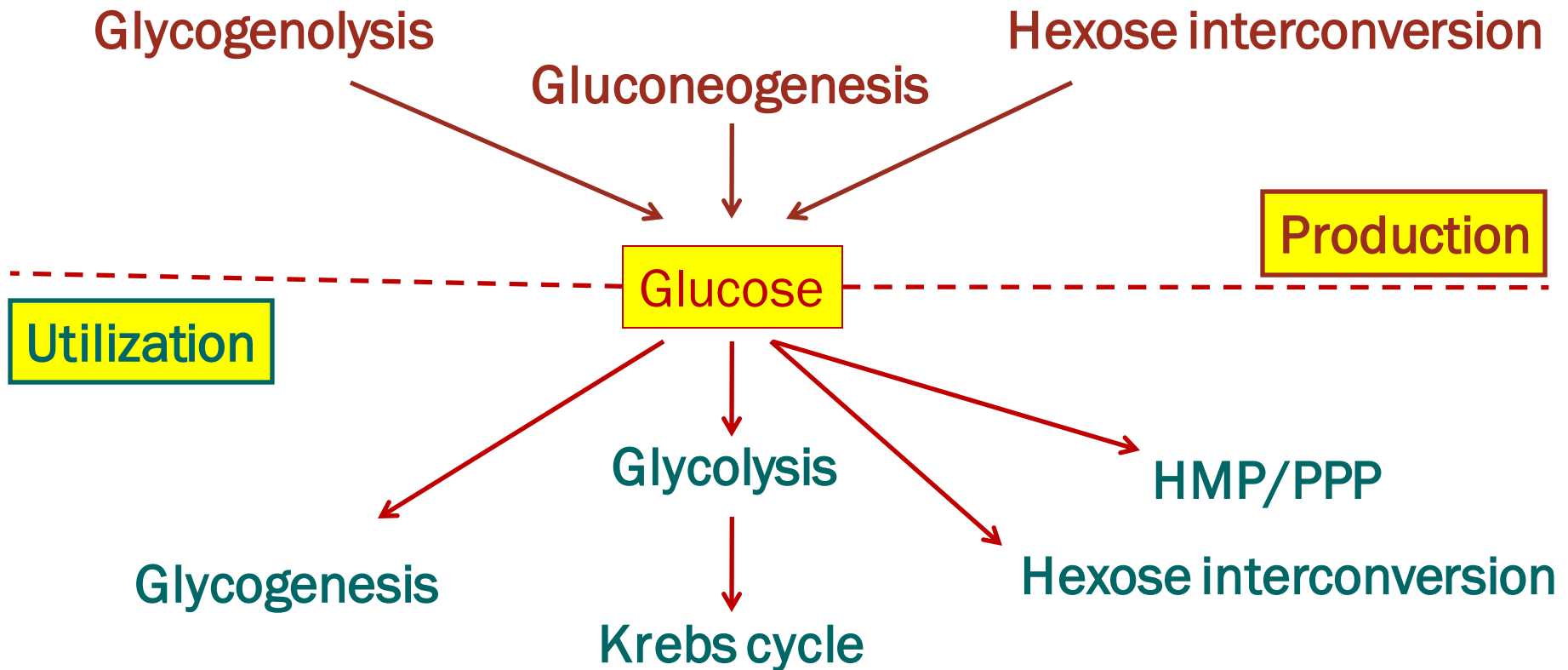
**Covalent  
modification**

**Allosteric**

**Induction/repression**



# Metabolic Pathways of Glucose-production and utilization



# Metabolic Pathways of Glucose- catabolic and anabolic

## Catabolic cycles

Glycolysis (Mainly)

Krebs (Mainly)

Glycogenolysis

HMP

## Anabolic cycles

Gluconeogenesis

Glycogenesis

# Glycolysis

- Oxidation of glucose to provide energy.
- Pyruvate is the end product of glycolysis in cells with mitochondria and an adequate supply of oxygen- aerobic glycolysis
- In absence of oxygen and in cells that lack mitochondria, the end product is lactate- anaerobic glycolysis

# Glycogenesis and Glycogenolysis

## **Glycogenesis:**

Synthesis of glycogen from glucose  
Mainly liver and muscle, Cytosol

## **Glycogenolysis**

Degradation of glycogen into glucose  
Mainly liver and muscle, Cytosol

# Gluconeogenesis

- Synthesis of glucose from non-carbohydrate precursors.
- The precursors could be lactate, pyruvate, glycerol and alpha-keto acids.
- It requires both mitochondria and cytosolic enzymes
- Liver and kidney



# Hexose Monophosphate shunt(HMP) or Pentose Phosphate Pathway (PPP)

- HMP shunt is an alternative pathway of glucose oxidation
- It is not involved in the generation of energy
- Around 10% of glucose is entered in this pathway
- In liver and kidney, this percentage is upto 30%

# Biomedical Importance

- It has two main functions-
  1. Provides NADPH which is required for –
    - synthesis of fatty acids, steroid and some amino acids
    - Detoxification of drugs by cytochrome p450
    - In scavenging the free radicals
  2. Provides Pentoses
    - This pentose and its derivatives are useful in the synthesis of
      - Nucleic acids (DNA and RNA)
      - Nucleotides (ATP, NAD, FAD and CoA)

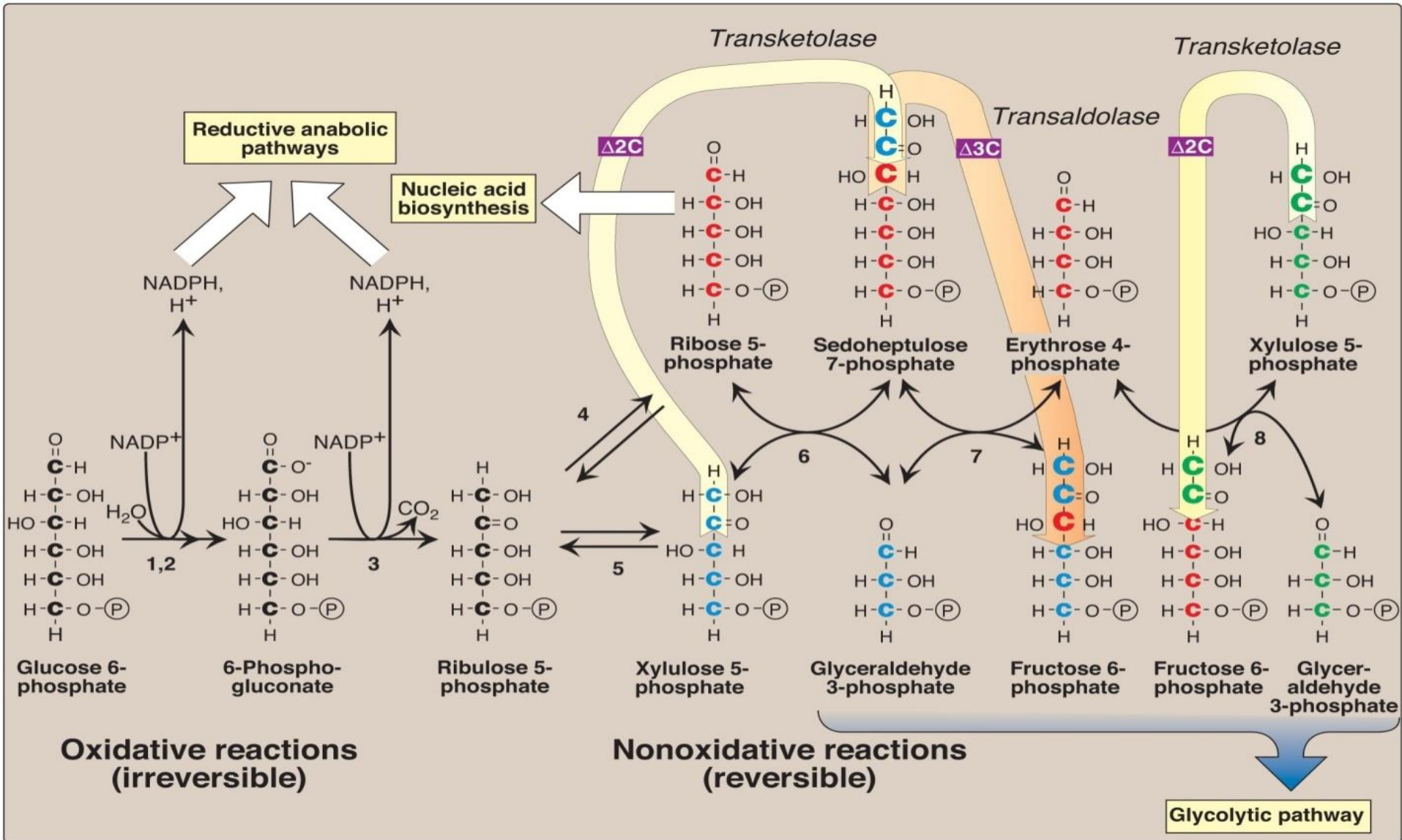
# Tissue Distribution

## Location- Cytosol

- Liver
- Lactating mammary gland
- Adrenal cortex
- Gonads
- Adipose tissue
- Erythrocytes to reduce glutathione
- Lens and cornea

# Phases of HMP Shunt

- It has two phases-
  - Oxidative phase
  - Non-oxidative phase

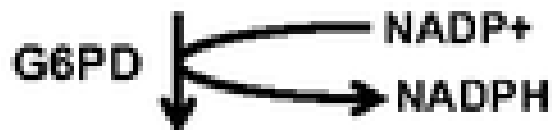


Enzymes numbered above are: 1, 2) *glucose 6-phosphate dehydrogenase* and *6-phosphogluconolactone hydrolase*, 3) *6-phosphogluconate dehydrogenase*, 4) *ribose 5-phosphate isomerase*, 5) *phosphopentose epimerase*, 6 and 8) *transketolase* (coenzyme: thiamine pyrophosphate), and 7) *transaldolase*.

# Phase 1- Oxidative pathway

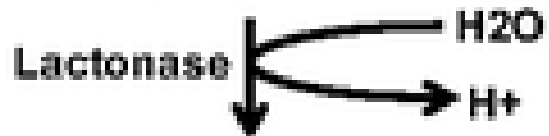
## Oxidative Phase

Glucose 6-phosphate



**G6PD**- Glucose 6-Phosphate Dehydrogenase

6-Phosphogluconolactone



**Lactonase**- 6 phosphogluconolactone hydrolase

6-Phosphogluconate



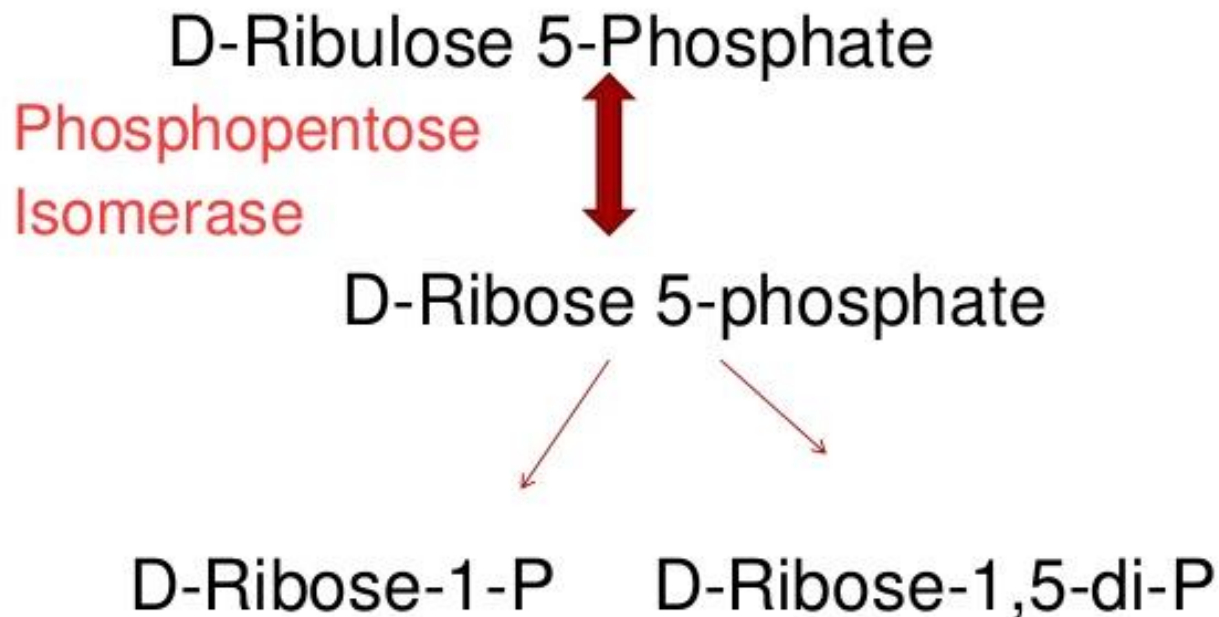
**6PGD**- 6 phosphogluconate dehydrogenase

Ribulose 5-phosphate

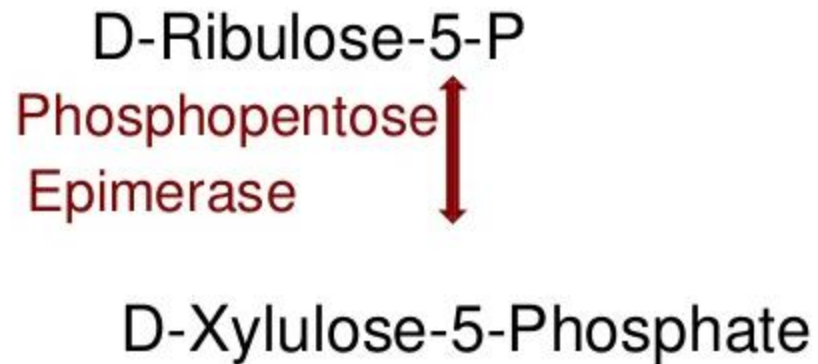
Non-oxidative phase

# Phase 2- Non-oxidative

## a) Interconversion of pentoses




# Phase 2- Non-oxidative





## Phase 2- Non-oxidative

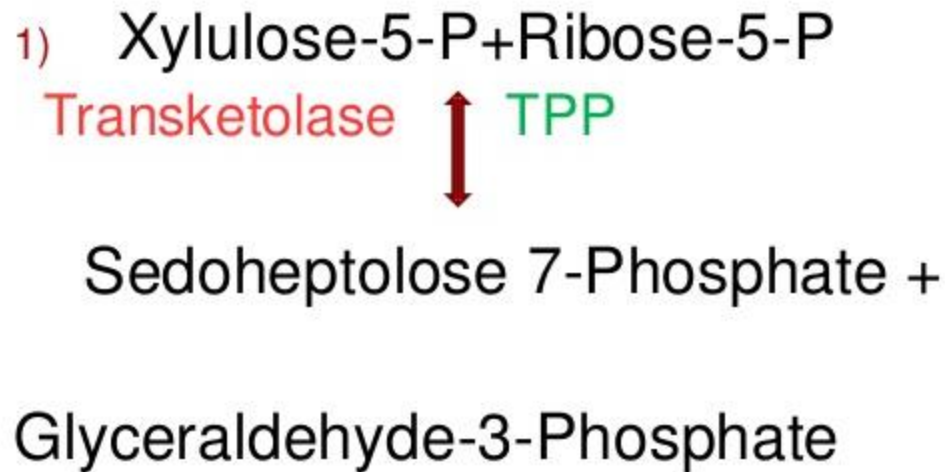
a) Conversion of pentose phosphate to hexose phosphates

 2 Particular Enzymes are required:

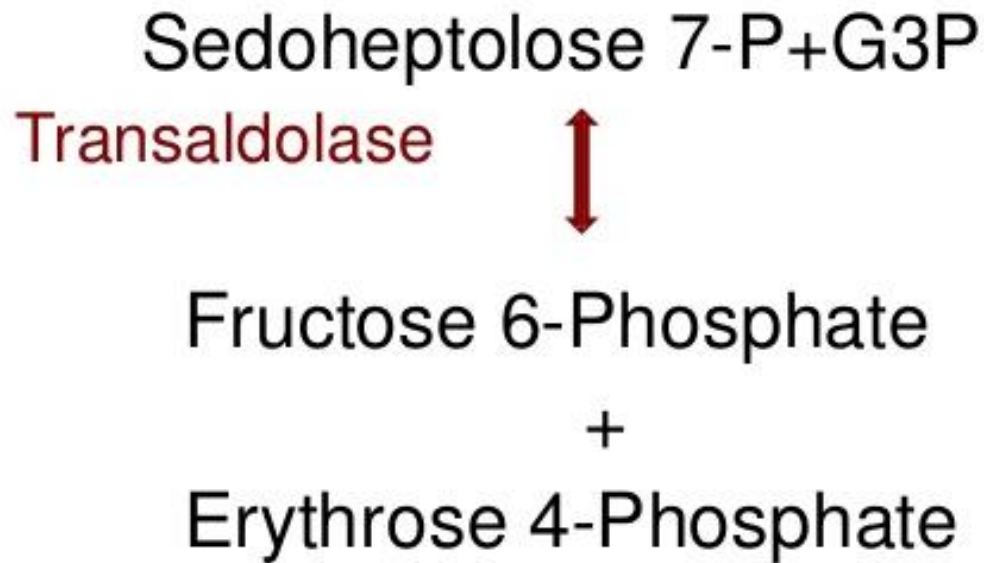
1) TRANSKETOLASE

2) TRANSALDOLASE

# Transketolation



# Transaldolation



# Transketolation

2) Xylulose 5-P + Erythrose 4-P

Transketolase  $\updownarrow$  TPP

Fructose 6-Phosphate + G3P

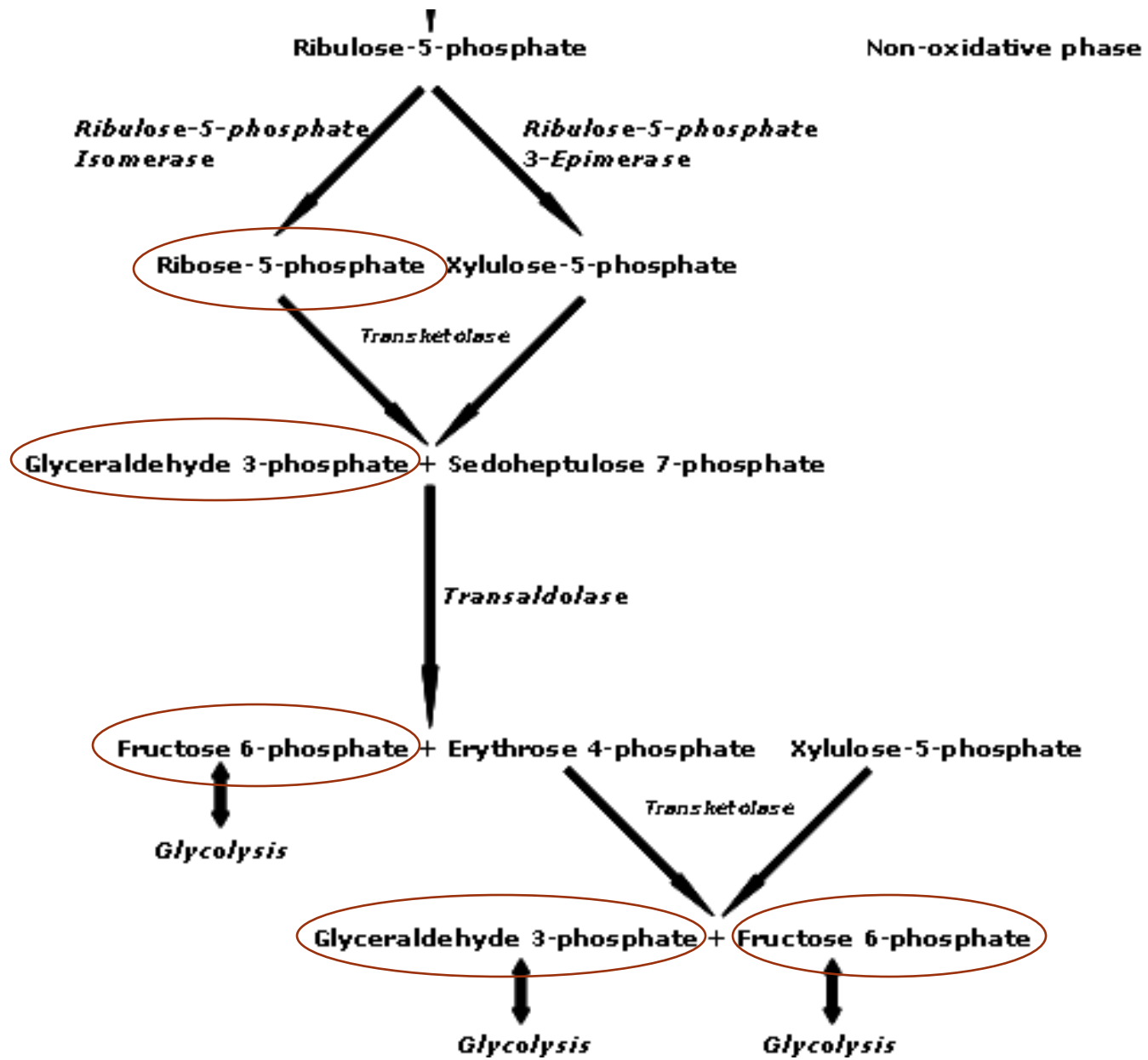
$\updownarrow$   
Dihydroxy-acetone-P + G3P

$\updownarrow$   
Fructose-1,6-bi-P

Recycles  
the Pathway

$\updownarrow$   
Glucose-6-P  $\rightleftharpoons$  Fructose-6-P





# Clinical Correlations

**G-6-PD** deficiency results in:

➤ Hemolytic Anemia

➤ Neonatal Jaundice

➤ Kidney failure

# Glucose Transport

## Na<sup>+</sup>-Monosaccharide Cotransporter:

Against concentration gradient

Energy dependent

Carrier-mediated

Coupled to Na<sup>+</sup> transport

Small intestine, renal tubules & choroid plexus

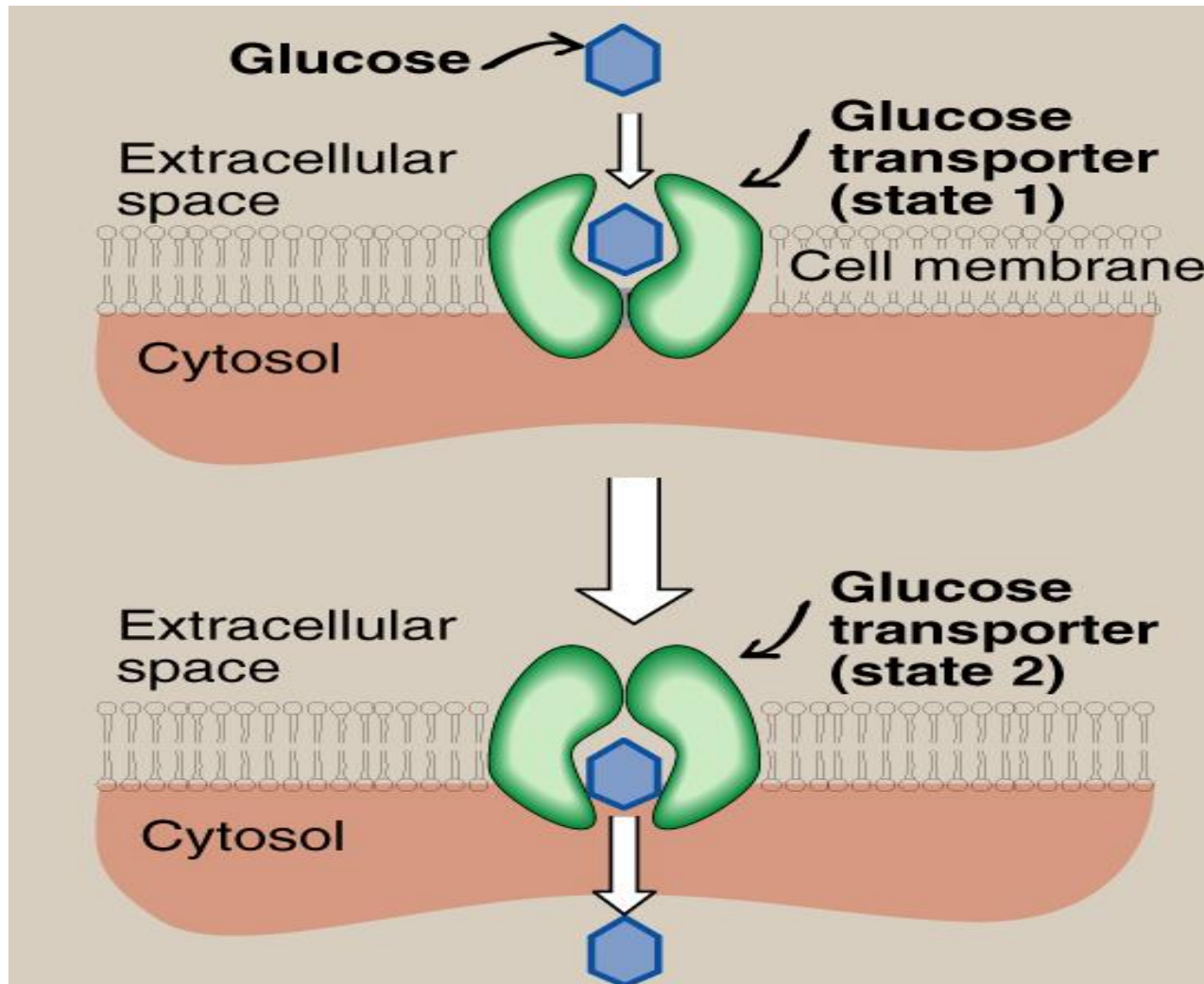
## Na<sup>+</sup>-Independent Facilitated Diffusion:

Down the concentration gradient

Energy Independent

Glucose Transporters (GLUT 1-14)

# Glucose Transport: Facilitated Diffusion





# Glucose Transporters

- **Tissue-specific expression pattern**

GLUT-1

RBCs and brain

GLUT-2

Liver, kidney & pancreas

GLUT-3

Neurons

**GLUT-4**

**Adipose tissue & skeletal muscle**

GLUT-5

Small intestine & testes

GLUT-7

Liver (ER-membrane)

- **Functions:**

GLUT-1, 3 & 4 Glucose uptake from blood

GLUT-2

Blood & cells (either direction)

GLUT-5

Fructose transport

# Take Home Message

- There are multiple pathways for glucose that can be grouped in to catabolic (utilizing glucose) or anabolic (producing glucose)
- Glycolysis is the major metabolic pathway of glucose breakdown to provide energy

# Take Home Message - HMP

- Alternative pathway for glucose oxidation but not meant for producing energy
- Has two phases- oxidative and non-oxidative
- During oxidative phase, glucose-6-P is oxidized with generation of 2 moles of NADPH, and one mole of pentose phosphate, with liberation of CO<sub>2</sub>
- During non-oxidative phase, pentose phosphate is converted to intermediates of glycolysis

# References

- Lippincott's Illustrated Reviews- Biochemistry 6<sup>th</sup> Edition-  
pages: 96-97,117,126,128,145-147
- <http://www.biochemden.com/the-hexose-monophosphate-shunt/>

# Non Oxidative phase

- 5 reactions
- Ribu 5P=R5P, Isomerase
- Ribu 5P= X5P, Epimerase
  
- $X5P + \mathbf{R5P} = \text{Sedo } 7P + \mathbf{G3P}$ , TK (10)
- $\text{Sedo } 7P + G3P = \text{Ery}4P + \mathbf{F6P}$ , TA (10)
- $X5P + \text{Ery}4P = \mathbf{F6P} + \mathbf{G3P}$ , TK (9)

R5P- Nucleotide biosynthesis

G3P and F6P- Glycolytic intermediates