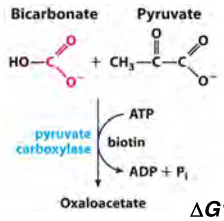
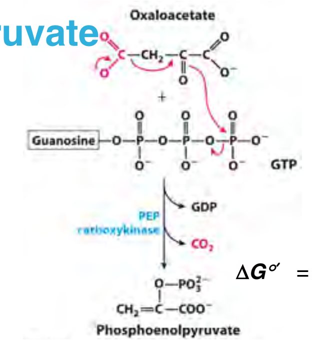
# Gluconeogenesis

## Pyruvate to Phosphoenolpyruvate




$\Delta G^{\circ\prime}$ = –0.5 kcal/mol



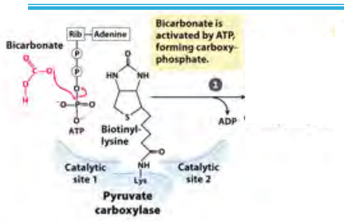

$\Delta G^{\circ\prime}$ = +0.7 kcal/mol

- Requires two energy-consuming steps
- The first step, pyruvate carboxylase (PC) converts pyruvate to oxaloacetate.
  - carboxylation using a biotin cofactor
  - This enzyme is only in the mitochondria; requires transport of pyruvate
- The second step, phosphoenolpyruvate carboxykinase converts oxaloacetate to PEP.
  - phosphorylation from GTP and decarboxylation
  - occurs in mitochondria or cytosol depending on the organism

During this conversion, the same carbon from $CO_2$ is added and immediately removed from the structure.

Lets look at the PC mechanism more closely…..

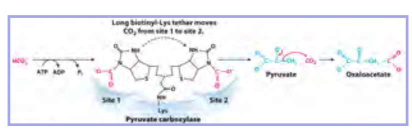
# Gluconeogenesis




## Biotin is a $CO_2$ Carrier

**Pyruvate Carboxylase**

*Mechanism*

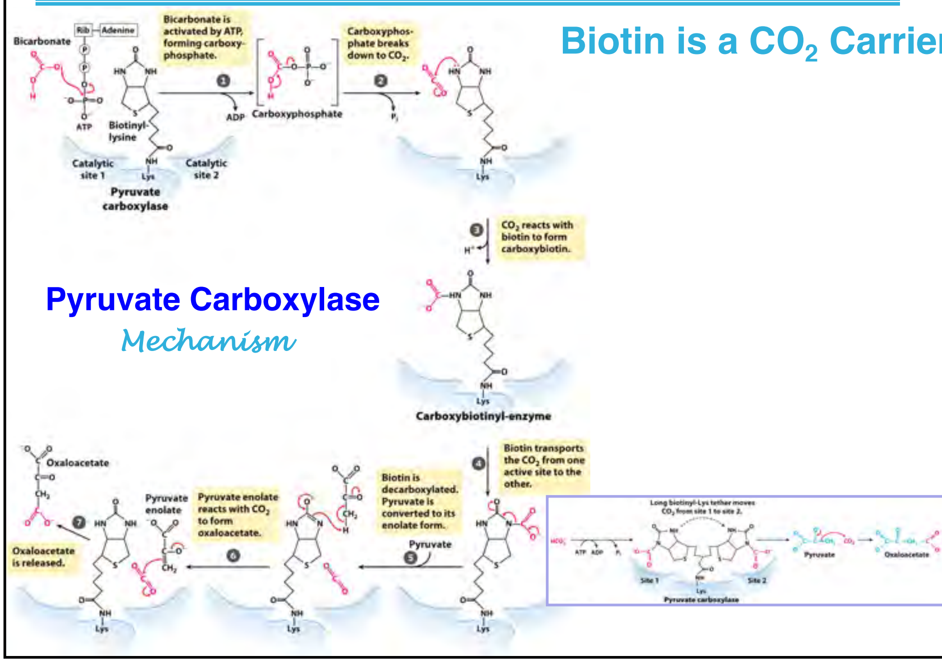


# Gluconeogenesis

## Biotin is a $CO_2$ Carrier

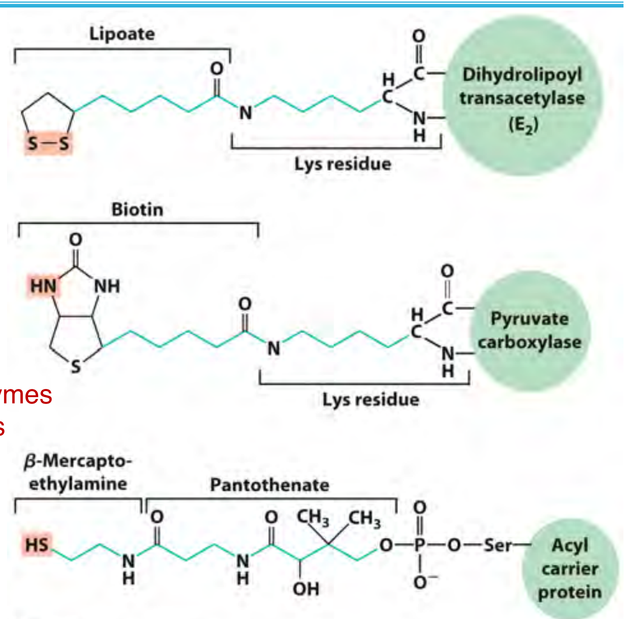
**Pyruvate Carboxylase**

*Mechanism*




# Gluconeogenesis

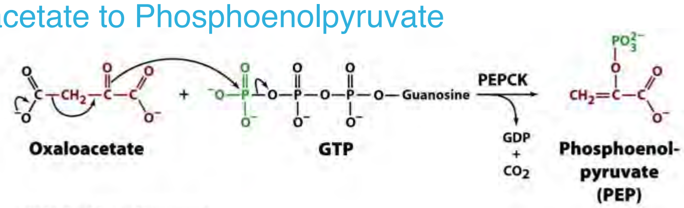
## Biological Tethers Allow Flexibility




Can you name the enzymes we've seen that use this concept?

# Gluconeogenesis

Oxaloacetate to Phosphoenolpyruvate

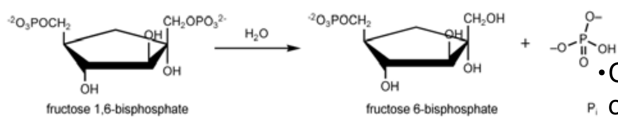



**Phosphoenolpyruvate Carboxykinase (PEPCK)**

Phosphoenolpyruvate to Fru 6-P

[PEP→2PGA→3PGA→1,3BPGA→GA3P→DHAP→Fru 1,6$P_2$]

–3 –0.5 –1 0 –2 +5 –1.3




**Fructose 1,6-bisphosphatase**

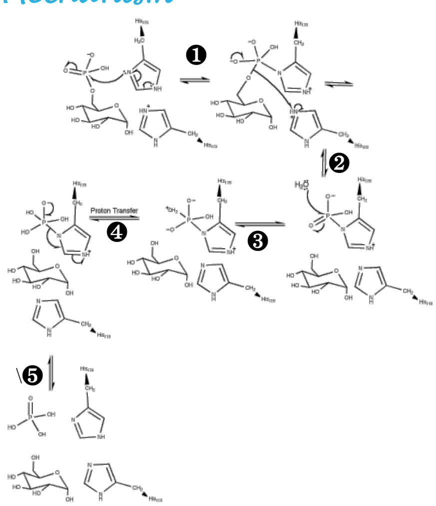
$\Delta G^{\circ\prime}$ = –4 kcal/mol

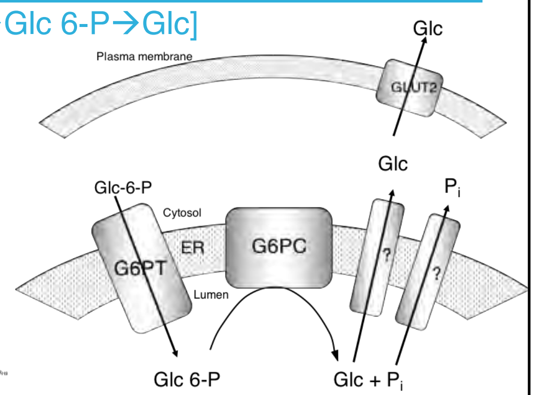
- Catalyze reverse reaction of opposing step in glycolysis
- Fructose 1,6-bisphosphate → fructose 6-phosphate
  - by fructose 1,6-bisphosphatase-1
  - coordinately/oppositely regulated with PFK
  - cleaves phosphate with water
  - DOES NOT generate ATP

# Gluconeogenesis

Fru 6-P to Glucose [Fru 6-P→Glc 6-P→Glc]

*Mechanism*




**Glucose 6-phosphatase**

$\Delta G^{\circ\prime}$ = –3.3 kcal/mol

- Glucose 6-phosphate → glucose
  - by glucose 6-phosphatase
  - segregated in the endoplasmic reticulum
  - cleaves phosphate with His at active site
  - Water hydrolyzes the His-$P_i$
  - DOES NOT generate ATP

# Gluconeogenesis

Why do we need glucose?

RECALL:

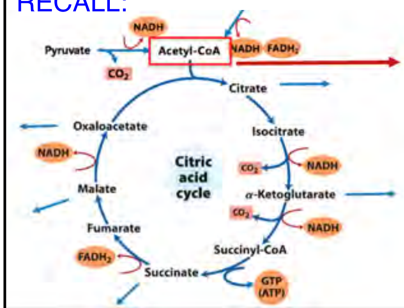



**TABLE 14-4** Glucogenic Amino Acids, Grouped by Site of Entry

| **Pyruvate** | **Succinyl-CoA** |
|---|---|
| Alanine | Isoleucine[a] |
| Cysteine | Methionine |
| Glycine | Threonine |
| Serine | Valine |
| Threonine | **Fumarate** |
| Tryptophan[a] | Phenylalanine[a] |
| **α-Ketoglutarate** | Tyrosine[a] |
| Arginine | **Oxaloacetate** |
| Glutamate | Asparagine |
| Glutamine | Aspartate |
| Histidine | |
| Proline | |

Note: All these amino acids are precursors of blood glucose or liver glycogen, because they can be converted to pyruvate or citric acid cycle intermediates. Of the 20 common amino acids, only leucine and lysine are unable to furnish carbon for net glucose synthesis.
[a]These amino acids are also ketogenic (see Fig. 18-15).

- Physiologically necessary: Brain, nervous system, and red blood cells generate ATP ONLY from glucose.
- When can't get it from pyruvate, amino acids are utilized, which allows generation of glucose when glycogen stores are depleted:
  - during starvation
  - during vigorous exercise
  - can generate glucose from amino acids, but not fatty acids
- Costs 4 ATP, 2 GTP, and 2 NADH. Net reaction:

2 Pyruvate + 4 ATP + 2 GTP + 2 NADH + 2 $H^+$ + 4 $H_2O$ → $\Delta G^{\circ\prime}$ = –9 kcal/mol

Glucose + 4 ADP + 2 GDP + 6 $P_i$ + 2 $NAD^+$

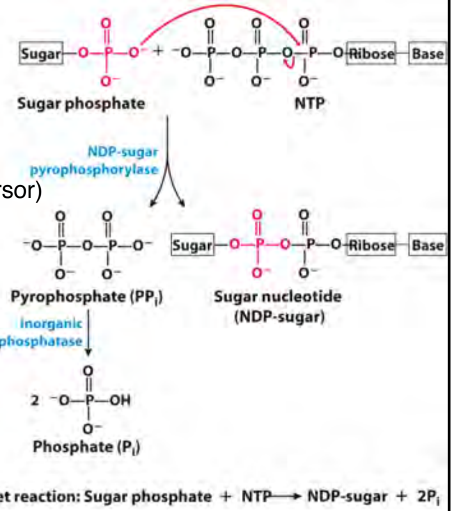
# Glycogen Synthesis

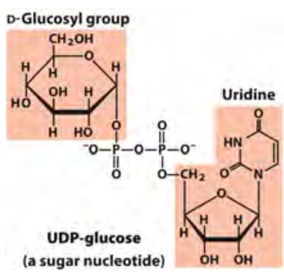
## Storing a ready-reserve of carbohydrate

# Glycogen Synthesis

- Synthesis of glycogen requires two enzymes, whereas glycogen degradation, only used phosphorylase. Both pathways use $\alpha$-phosphoglucomutase; the start and end junction is Glc 1-P.

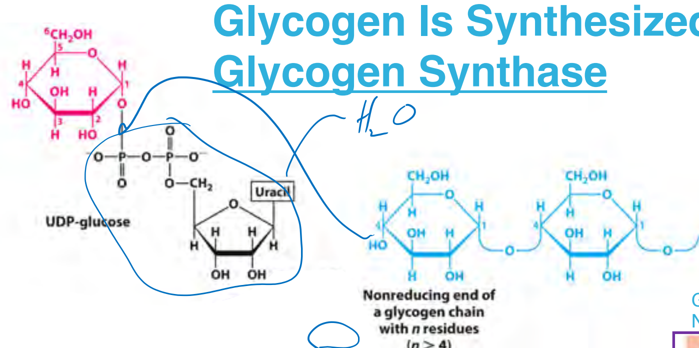
- Blood glucose must be:
  - Phosphorylated: Glc → Glc-6-P
  - Then converted: Glc 6-P → Glc 1-P
  - Activated with UDP (UDP-Glc is the precursor)
  - Added to glycogen

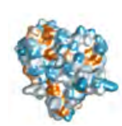


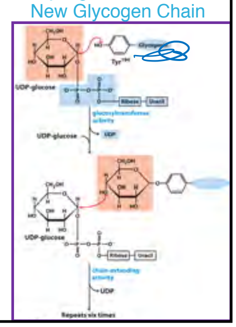

# Glycogen Synthesis

## Glycogen Is Synthesized by Glycogen Synthase



Glycogenin Starts a New Glycogen Chain



# Glycogen Synthesis

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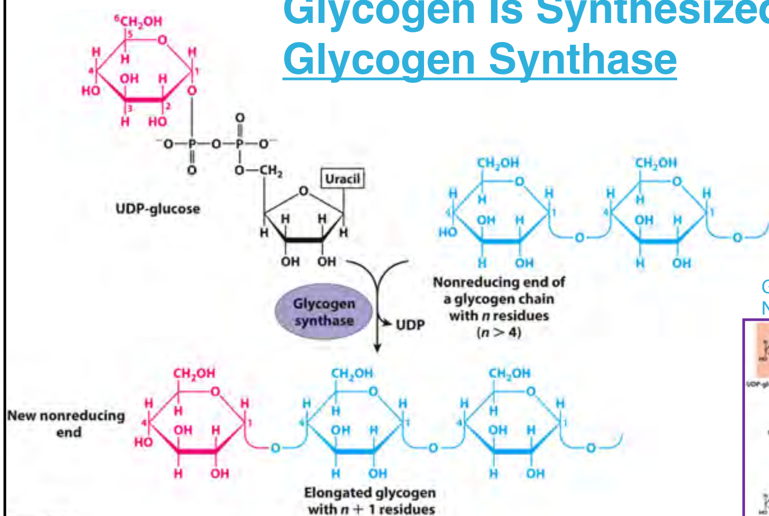


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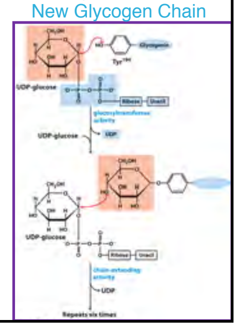
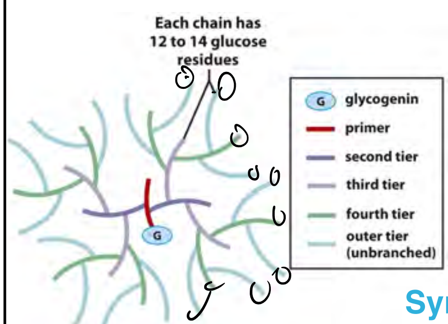
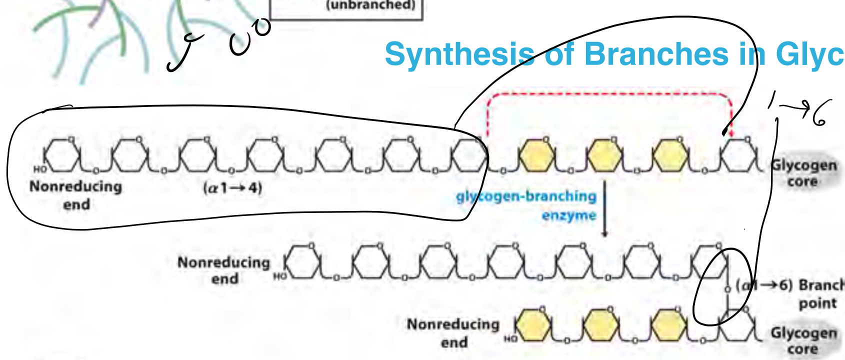


# Glycogen Synthesis

## General Structure of a Glycogen Particle




## Synthesis of Branches in Glycogen

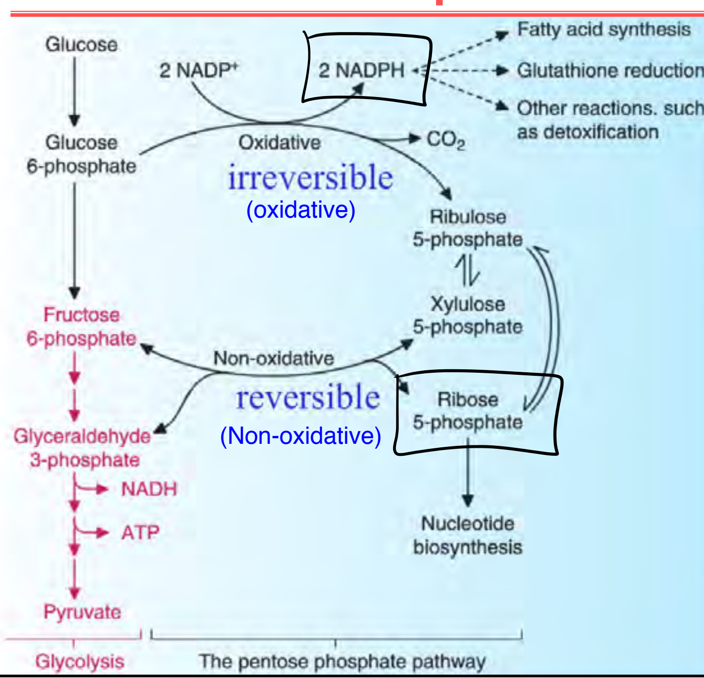


# Pentose Phosphate Pathway

NADPH

**Providing reduced electrons and ribose**

## Pentose Phosphate Pathway

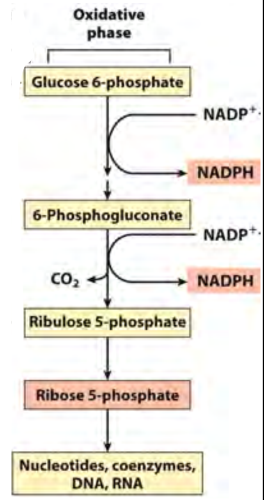



Pentose Phosphate Pathway, sometimes called the pentose-phosphate shunt, is linked to Glycolysis

Dr. Kornberg:
**Lecture 02.13.17**
**(7:30-8:50) 1.5 min**

# Pentose Phosphate Pathway

- Included in Anabolism because it provides the NADPH needed for so many biosynthetic reduction reactions, as well as the synthesis of pentoses.
- But, can also be used for a shunt in the catabolism of Glc 6-P.
- The main products are NADPH and ribose 5-phosphate (Rib 5-P).
- Oxidative Phase oxidizes Glc 6-P to make NADPH
- Non-oxidative Phase re-cycles pentoses to hexoses if not needed for biosynthesis.



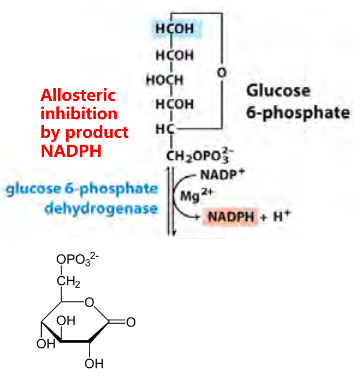

## Uses of PPP:

➢NADPH is an electron donor.
- reductive biosynthesis of fatty acids and steroids
- repair of oxidative damage

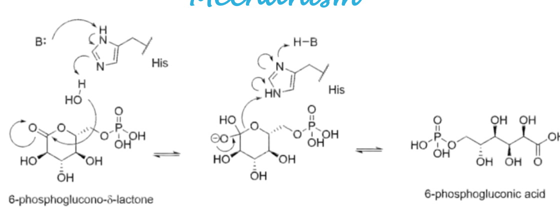
➢Ribose 5-phosphate is a biosynthetic precursor of nucleotides.
- used in DNA and RNA synthesis
- or synthesis of some coenzymes

# Pentose Phosphate Pathway

## Oxidative Phase Generates NADPH and a Pentose




*Mechanism*



# Pentose Phosphate Pathway

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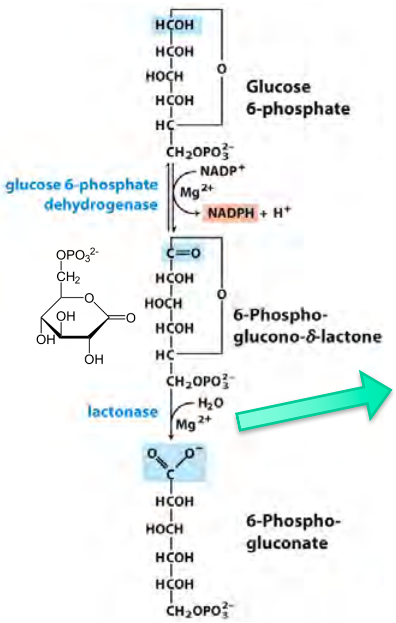
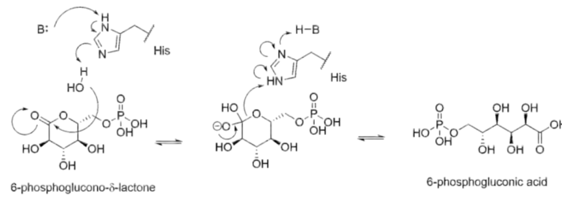
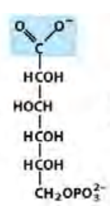



Mechanism

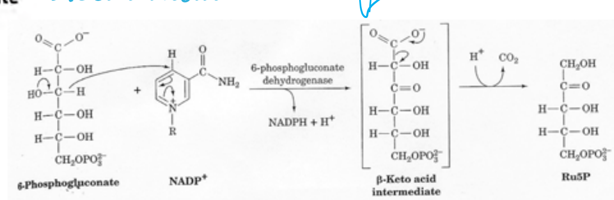



# Pentose Phosphate Pathway

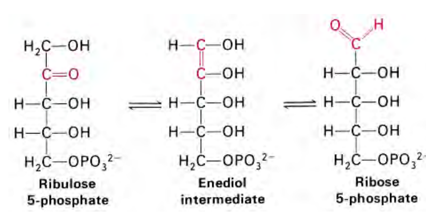



recall Rubisco

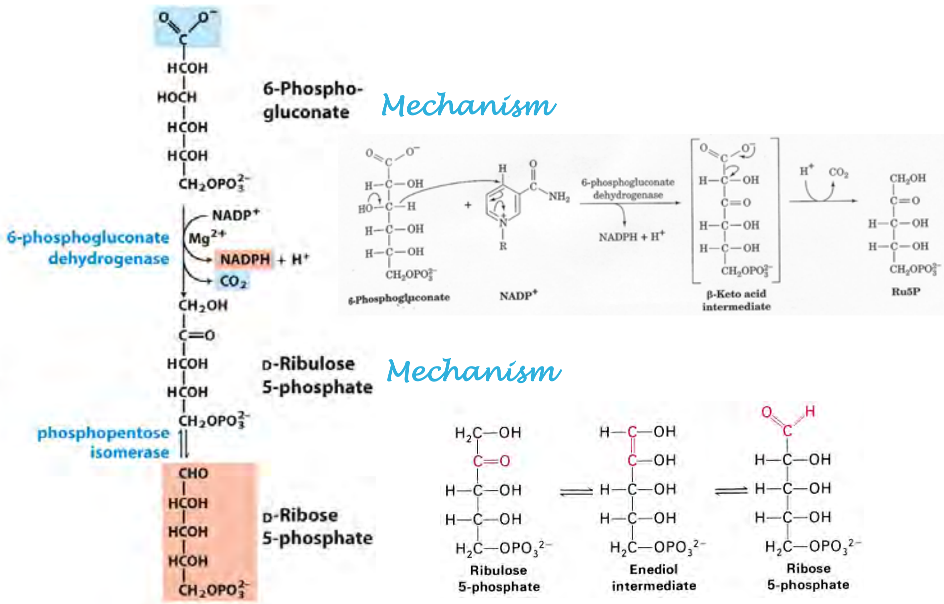
Mechanism




Mechanism



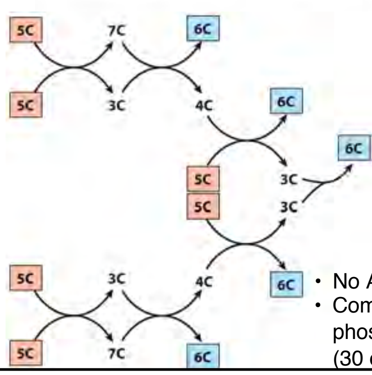
# Pentose Phosphate Pathway




# Pentose Phosphate Pathway

(aldose)

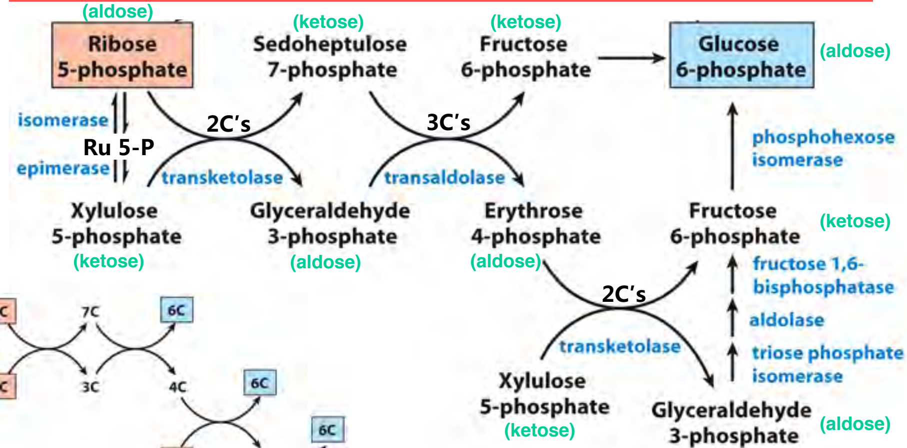
**Ribose 5-phosphate**

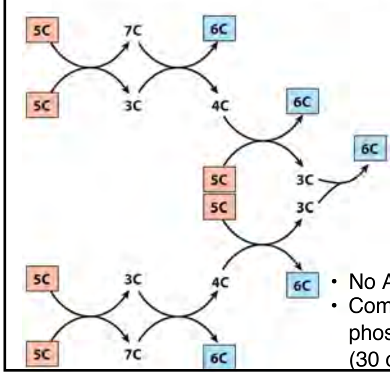



**Non-oxidative Phase**
**Interconverts Rib 5-P to form Glc 6-P**

- No ATP is used in the non-oxidative phase.
- Complete conversion of ribose-5-phosphate to glucose-6-phosphate requires 6 Rib 5-P (30 carbons) to make 5 Glc 6-P (30 carbons).

# Pentose Phosphate Pathway

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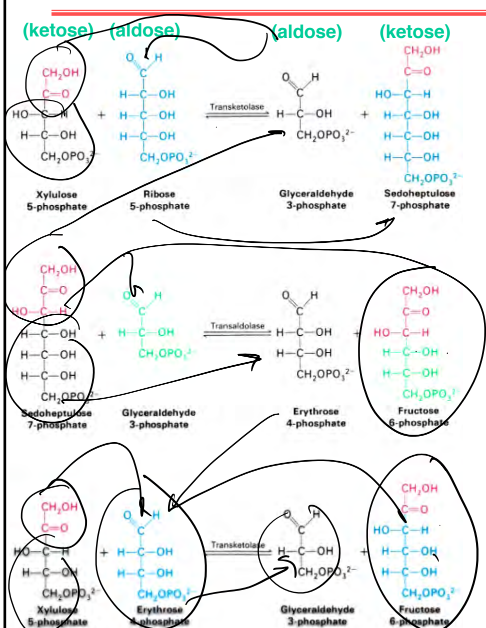
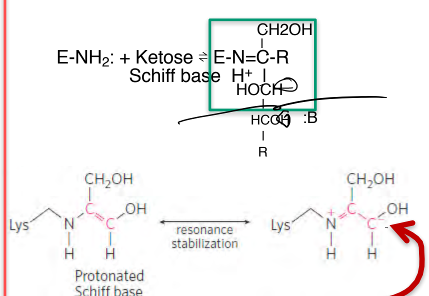
# Pentose Phosphate Pathway




**Transaldolase** *Mechanism*

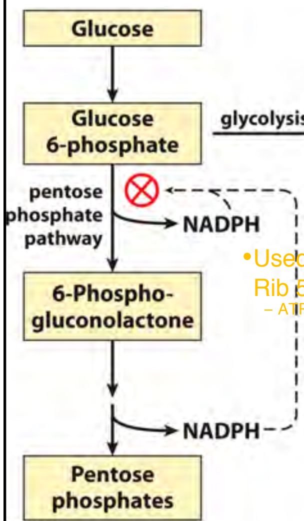


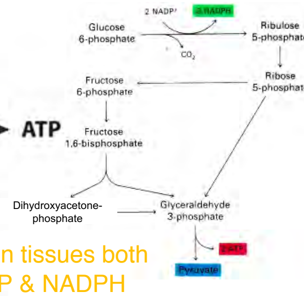

This carbanion is protonated in aldolase and transaldolase it's a nucleophile to attack the aldehyde of the substrate aldose. Substrate-phosphates differ

- Ribulose-5-phosphate can be used to generate ribose-5-phosphate for DNA/RNA.
- Ribulose-5-phosphate can also be used to generate xylulose-5-phosphate for Non-oxidative PPP.

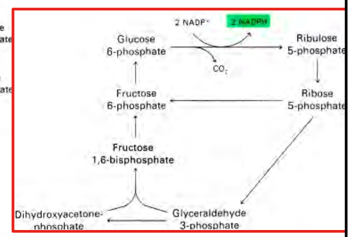
# Pentose Phosphate Pathway

## NADPH Regulates Partitioning into Glycolysis versus Pentose Phosphate Pathway

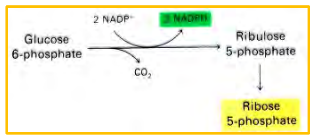


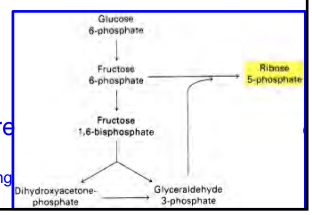

- Used in tissues both Rib 5-P & NADPH
  - ATP is plentiful




- Used in tissues requiring more NADPH than Rib 5-P
  - such as the liver and adipose tissue

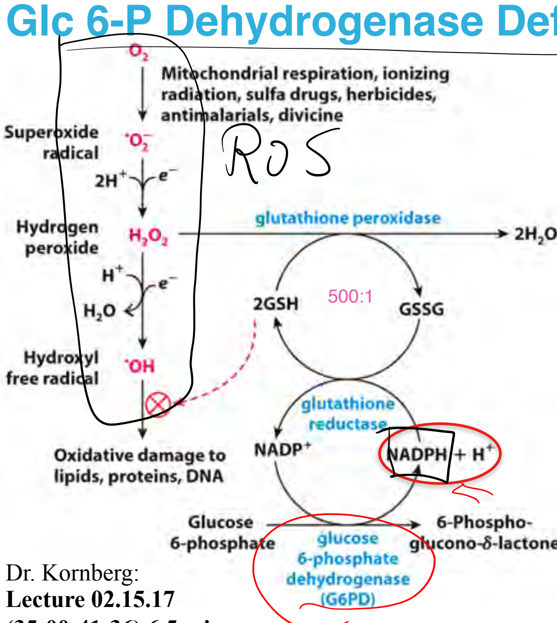



- Used in tissues requiring more Rib 5-P than NADPH
  - such as the lymphocytes and fast growing tissues/cancer cells




# Pentose Phosphate Pathway

## Glc 6-P Dehydrogenase Deficiency*



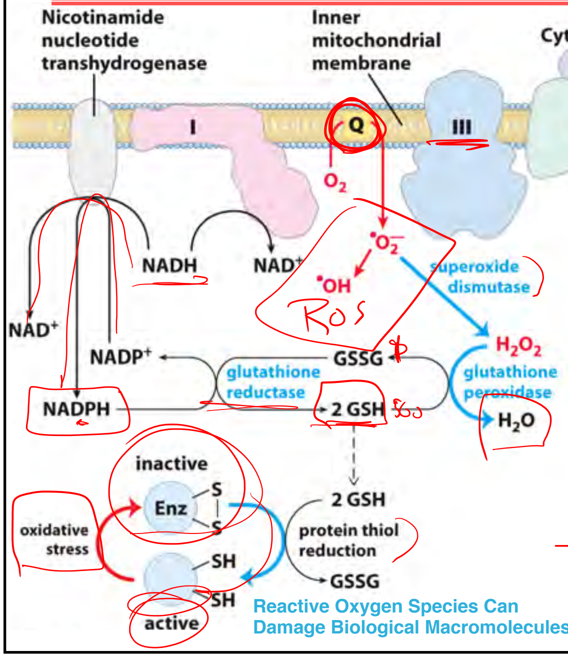

- Can be fatal in cases of high oxidative stress. Hemolytic anemia
  - certain drugs, herbicides, and some foods (fava beans)
- Resistance to malaria due to high oxidative stress in red blood cells
- X-linked heterozygous advantage

Essential for red-blood cells

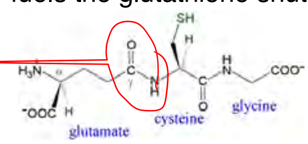
Dr. Kornberg:
**Lecture 02.15.17**
**(35:00-41:36) 6.5 min**

*Total lack of G6PDH is lethal

## Pentose Phosphate Pathway




- Ubiquinone is naturally "leaky" and facilitates partial reduction of non-Complex III targets.
  - Single electron transfers result in free radicals.
- One method by which the cell can correct free-radical production of reduced glutathione (GSH), which fuels the glutathione shuttle

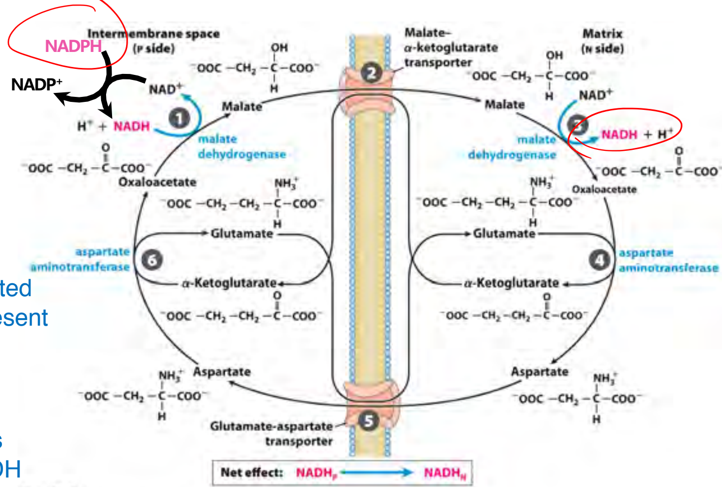



Glutathione

## Pentose Phosphate Pathway

### Malate-Aspartate Shuttle

### Converting Cytosolic Electron Carriers (NADH & NADPH) to the Mitochondria




- This more complicated shuttle is mostly present in liver, heart, and kidney.
- It moves NADH & NADPH equivalents from cytosol to NADH equivalents to the mitochondria.