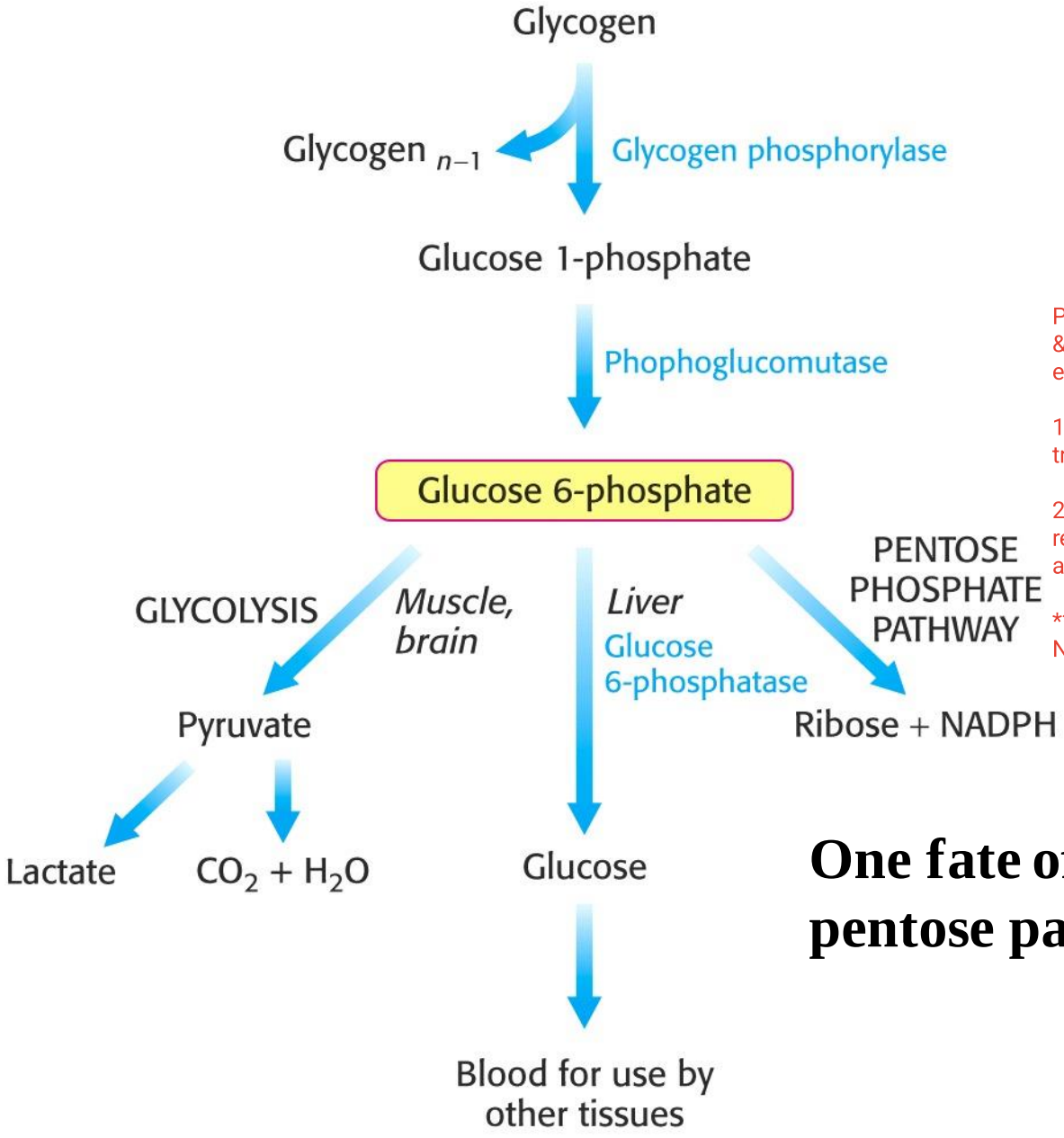
Pentose Phosphate Pathway



PPP can produce energy but indirectly by NADH & FADH2 only , NADPH are not participate in energy production , why ??

1) because the phosphate group is limiting the transfer of Hydrogen atom to ETC

2) the hydrogen of NADPH are needed in reduction of many reactions and there are alternative of it .

**** NADP+ —> it is a phosphorelated form of NAD+

One fate of G6P is the pentose pathway.

The pentose pathway is a shunt.

- The pathway begins with the glycolytic intermediate glucose 6-P.
- It reconnects with glycolysis because two of the end products of the pentose pathway are glyceraldehyde 3-P and fructose 6-P; two intermediates further down in the glycolytic pathway.
- It is for this reason that the pentose pathway is often referred to as a shunt.
- The pathway yields reducing potential in the form of NADPH to be used in anabolic reactions requiring electrons.
- The pathway yields ribose 5-phosphate.

Nucleotide biosynthesis leading to: DNA, RNA

Various cofactors (CoA, FAD, SAM, NAD+/NADP+).

It's a shunt

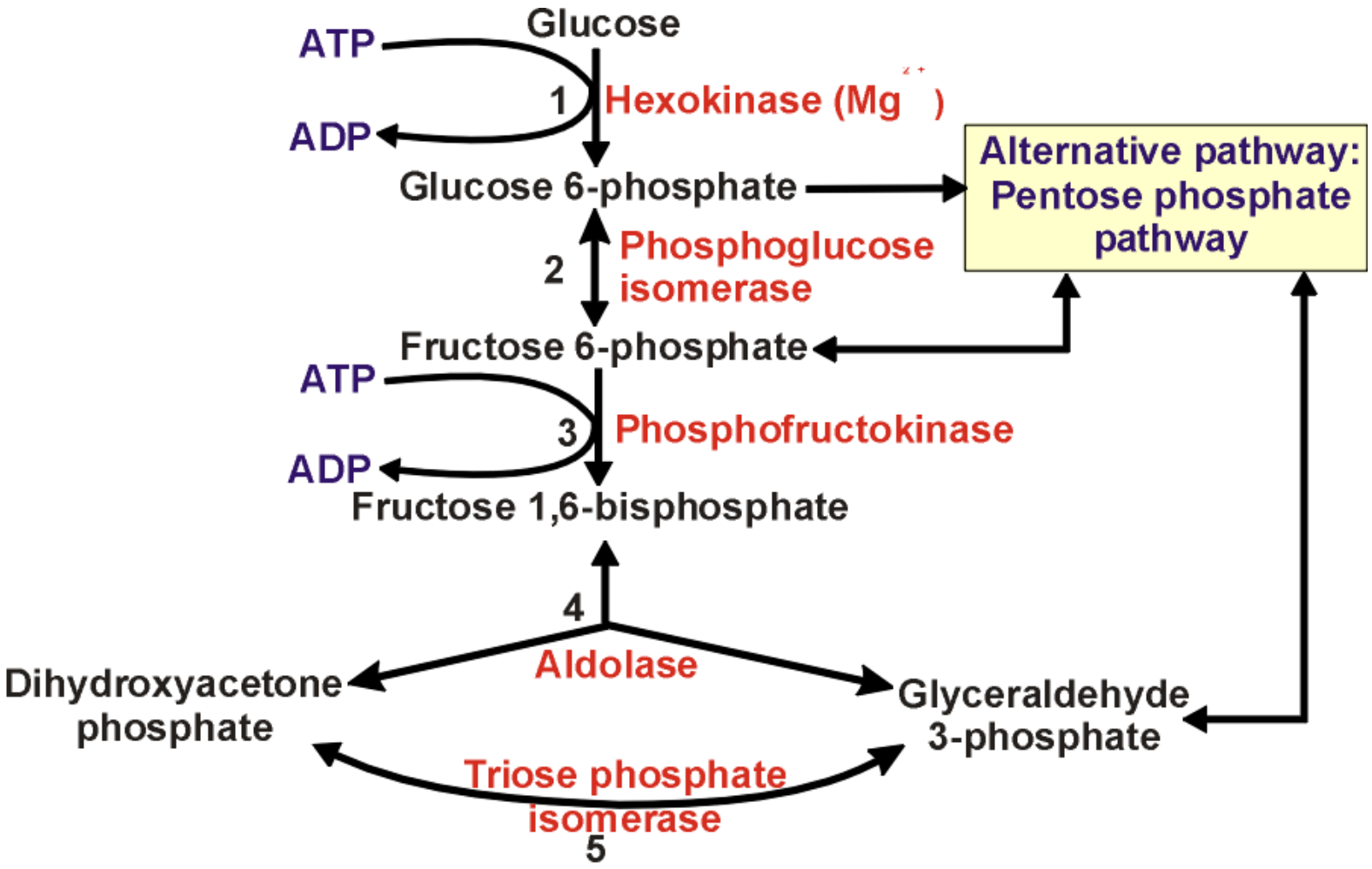

Glucose
ATP
ADP
1
Hexokinase (Mg++)
Glucose 6-phosphate
Alternative pathway:
Pentose phosphate
pathway
2
Phosphoglucose
isomerase
Fructose 6-phosphate
ATP
ADP
3
Phosphofructokinase
Fructose 1,6-bisphosphate
4
Aldolase
Dihydroxyacetone
phosphate
Glyceraldehyde
3-phosphate
Triose phosphate
isomerase
5

TABLE 20.2 Pathways requiring NADPH

Synthesis

Fatty acid biosynthesis

Cholesterol biosynthesis

Neurotransmitter biosynthesis

Nucleotide biosynthesis

Detoxification

Reduction of oxidized glutathione

Cytochrome P450 monooxygenases

why do not muscles proceed PPP??

because they are lacking of oxidative irreversible phase .

**** PPP diveded into to phases :
1) oxidative irreversible phase
2) non-oxidative reversible phase .

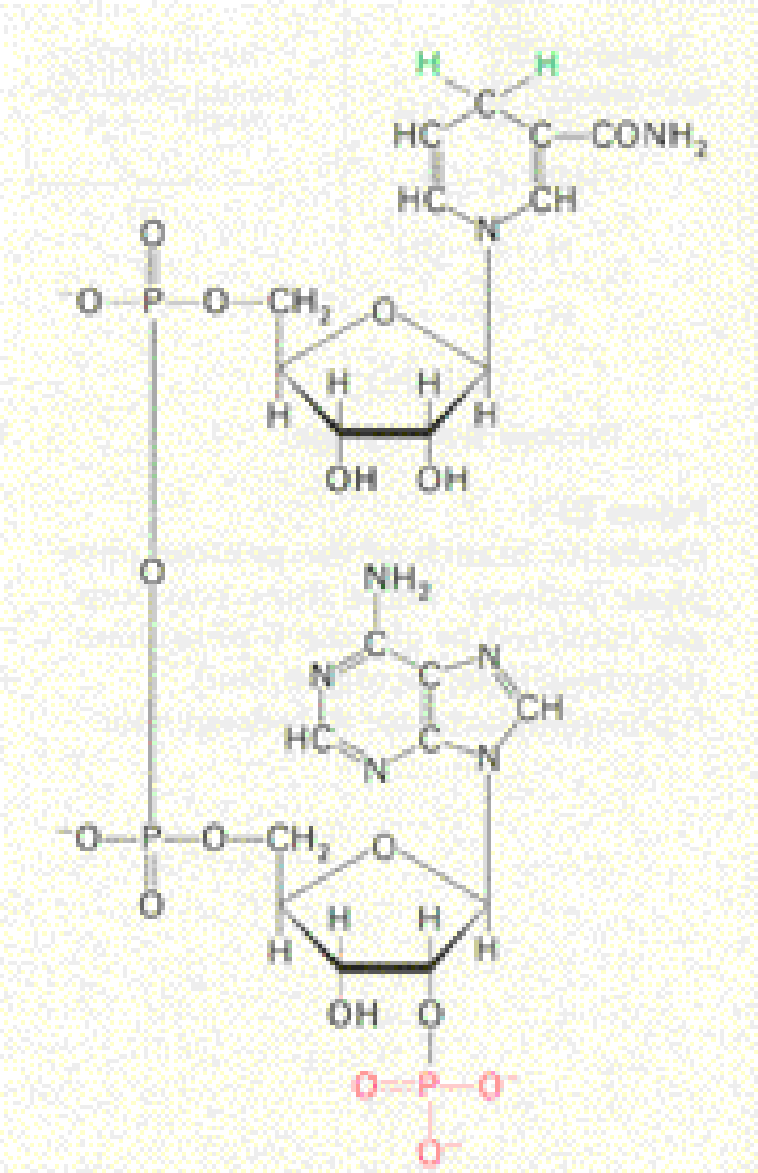
**** tissues that are active in PPP has alot of dehydrogenases that are responsible for oxidative irreversible phase.

TABLE 20.4 Tissues with active pentose phosphate pathways

Tissue	Function
Adrenal gland	Steroid synthesis
Liver	Fatty acid and cholesterol synthesis
Testes	Steroid synthesis
Adipose tissue	Fatty acid synthesis
Ovary	Steroid synthesis
Mammary gland	Fatty acid synthesis
Red blood cells	Maintenance of reduced glutathione

- NADPH is a phosphorylated form of NADH.

- In general, with some exceptions, NADH is used to drive the phosphorylation of ADP to ATP. NADPH is used where reducing potential is required for synthetic reactions.



Reduced nicotinamide adenine dinucleotide phosphate (NADPH)

The pentose pathway can be divided into two phases.

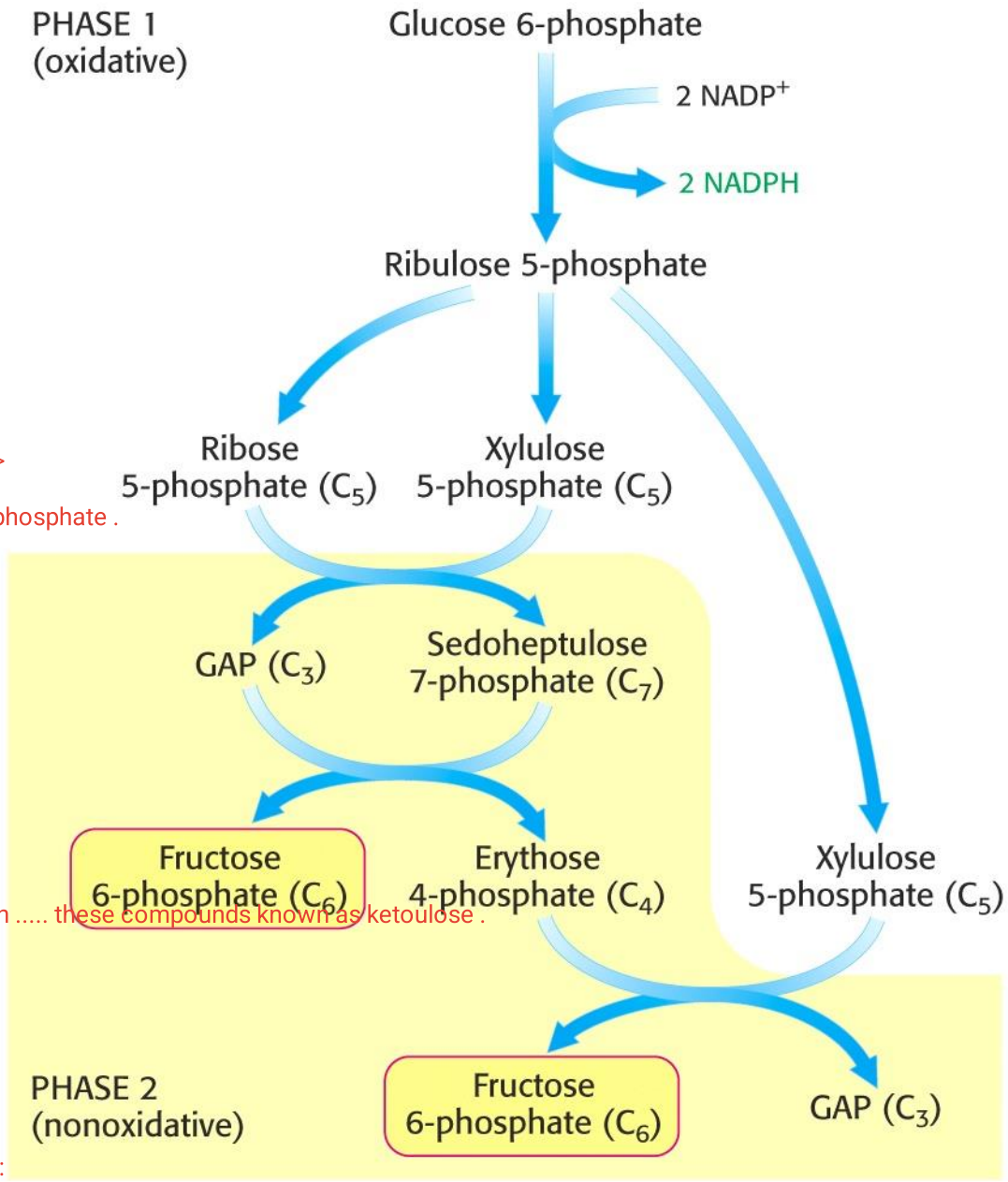
1- Oxidative

oxidative irreversible phase ----->

- phase from G6P to ribulose 5 phosphate .

- produce 2 NADPH+H & 1 CO2

2- Non-oxidative interconversion of sugars



ribulose 5 phosphate ---->
has keto functional group , it contains active & functional group keton ..... these compounds known as ketoulose .

ribose 5 phosphate ------>
contain functional group aldehyde , so it is aldoulose .

xyloulose ---->
epimer of ribulose 5 phosphate

***** ribulose will convert to one of two forms by on of two enzymes :
1) ribulose to ribose ----> by isomerase enzyme known as aldo-keto isomerase ..... it reaction is reversable

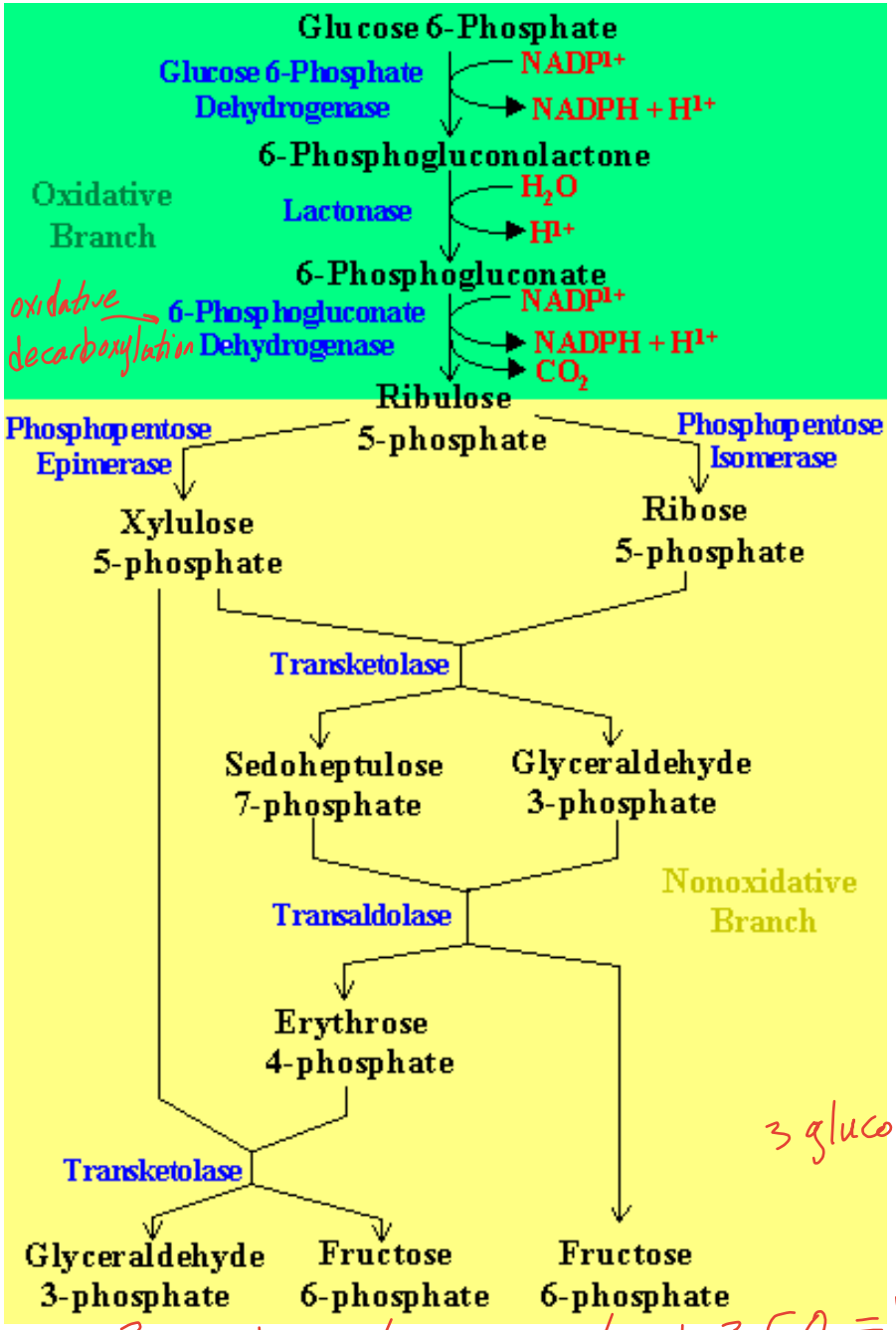
2) xyloulose ----> by epimerase enzyme

NADPH + H^+ is formed from two separate reactions.

The glucose 6-phosphate dehydrogenase reaction is the rate limiting step and is essentially irreversible.

key regulatory enzyme

Cells have a greater need for NADPH than ribose 5-phosphate.



3 glucose

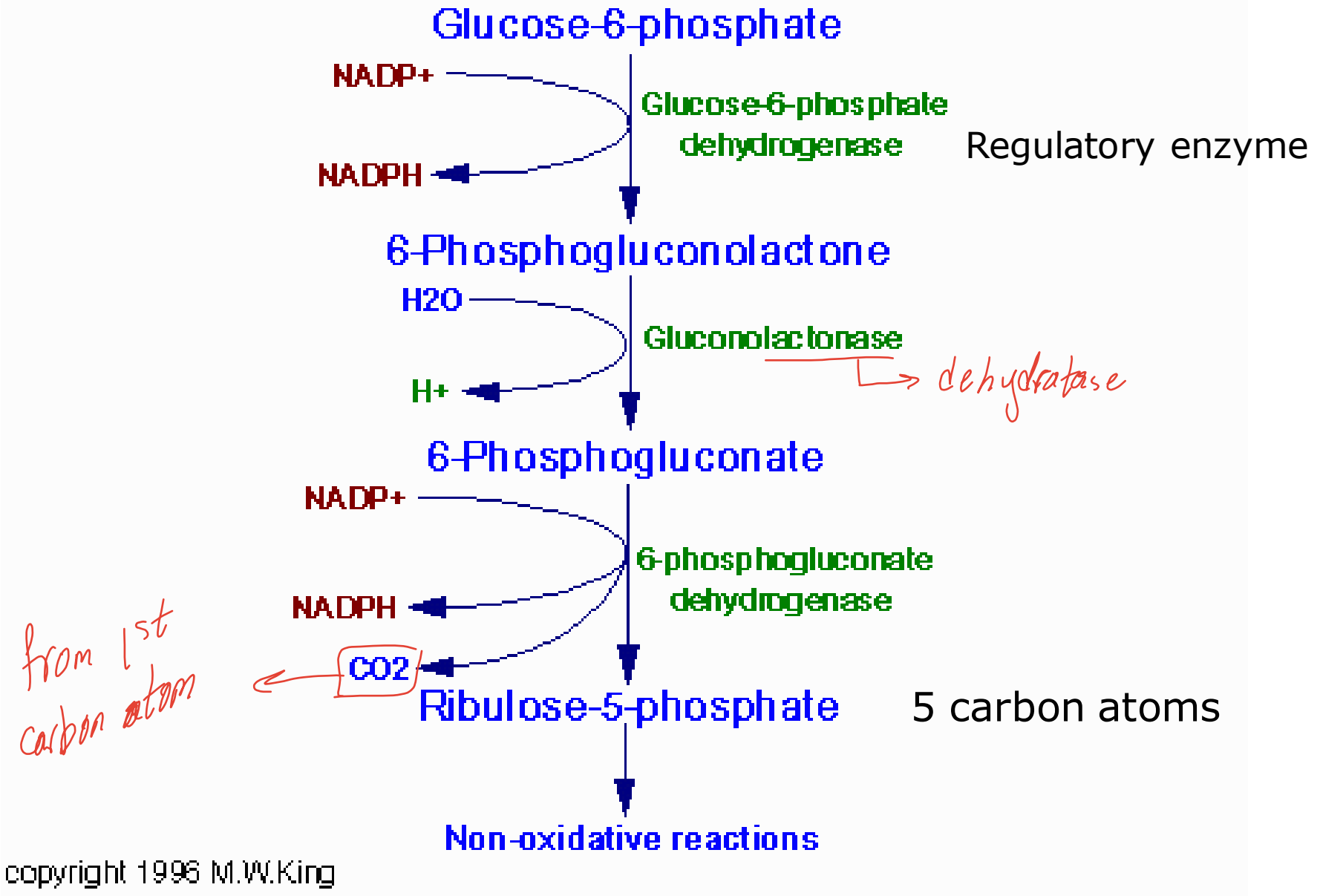
3 + 6 + 6 + $3CO_2$ = 18C

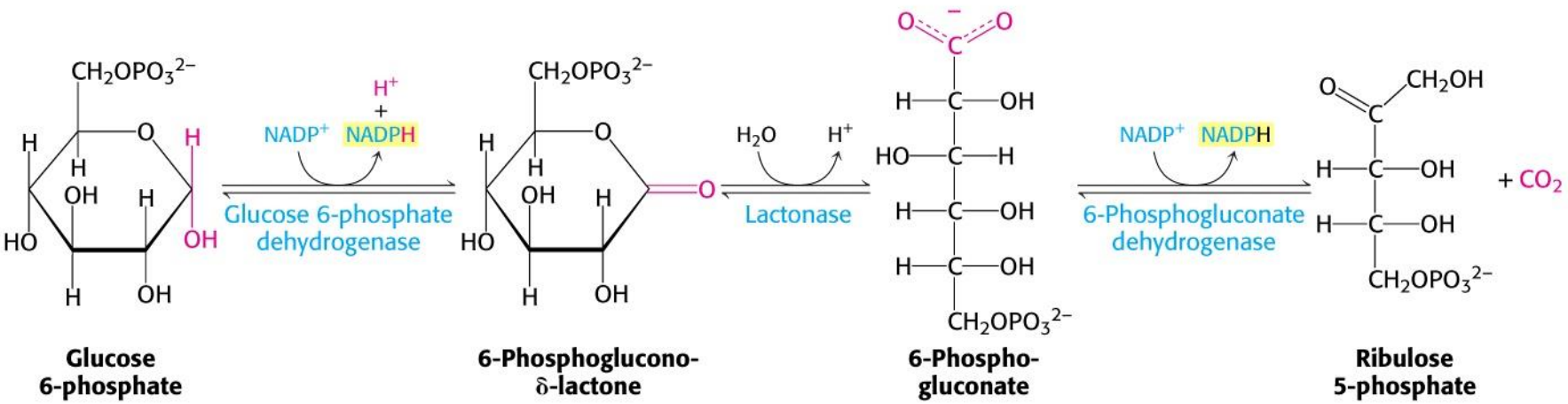
Homework :-

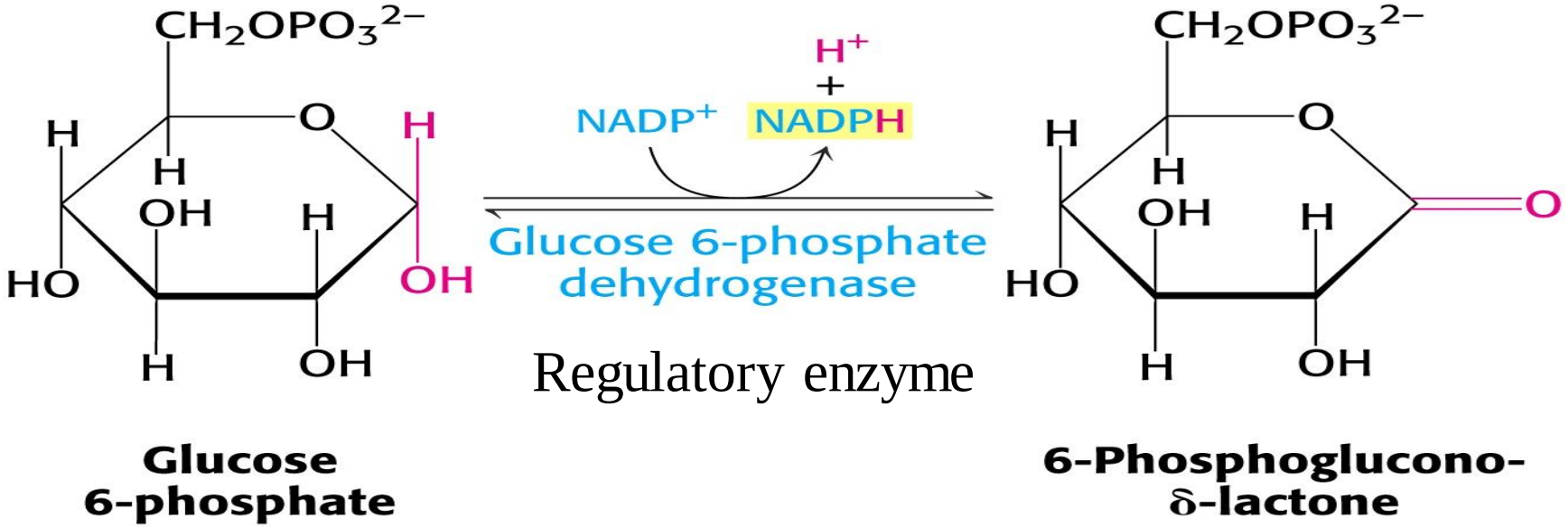
Energy produced under aerobic conditions with aspartate malate shuttle

85 ATP

Oxidative Stage of Pentose Phosphate Pathway

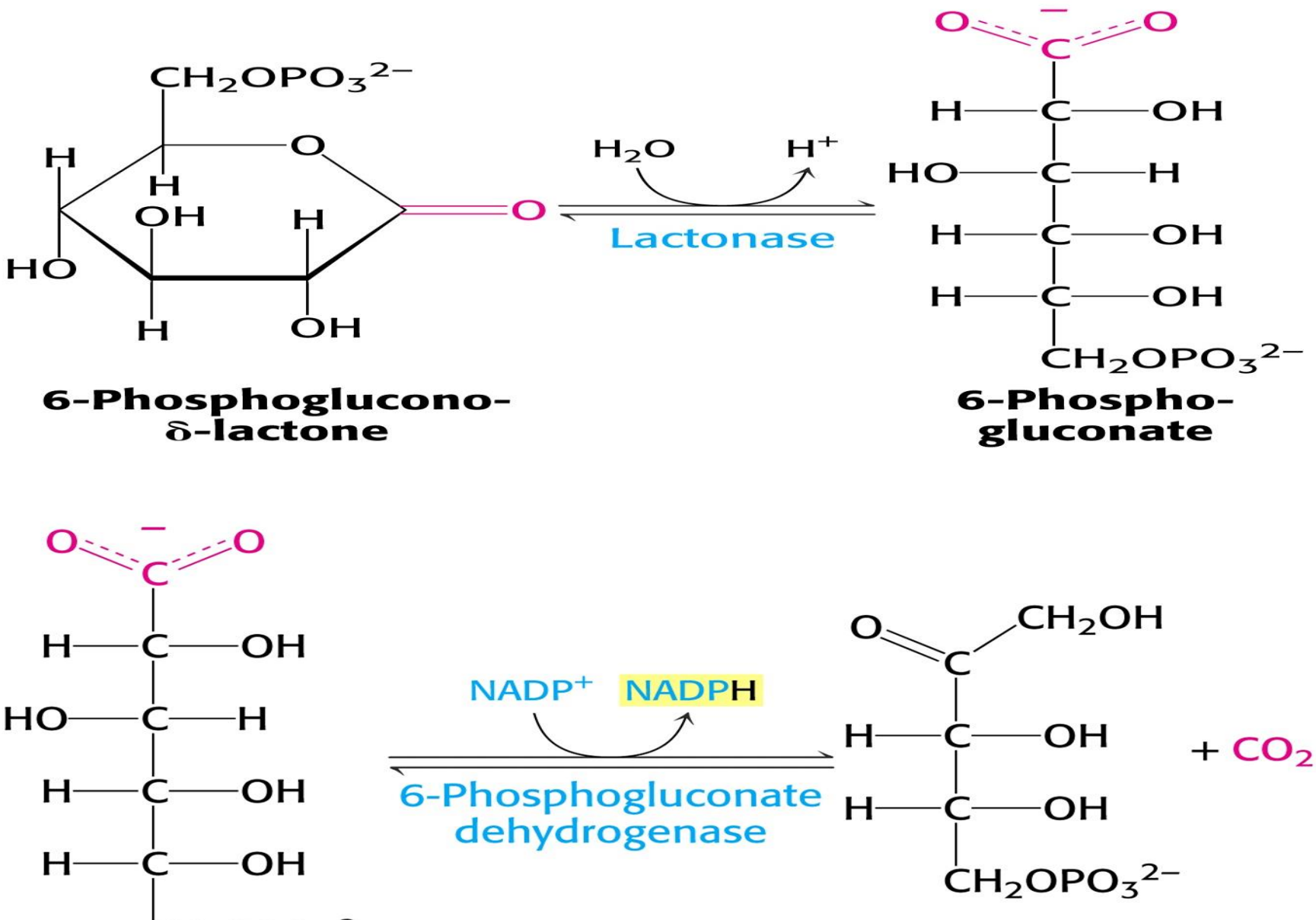






Regulatory enzyme

- The enzyme is highly specific for NADP+; the Km for NAD+ is 1000 greater than for NADP+.

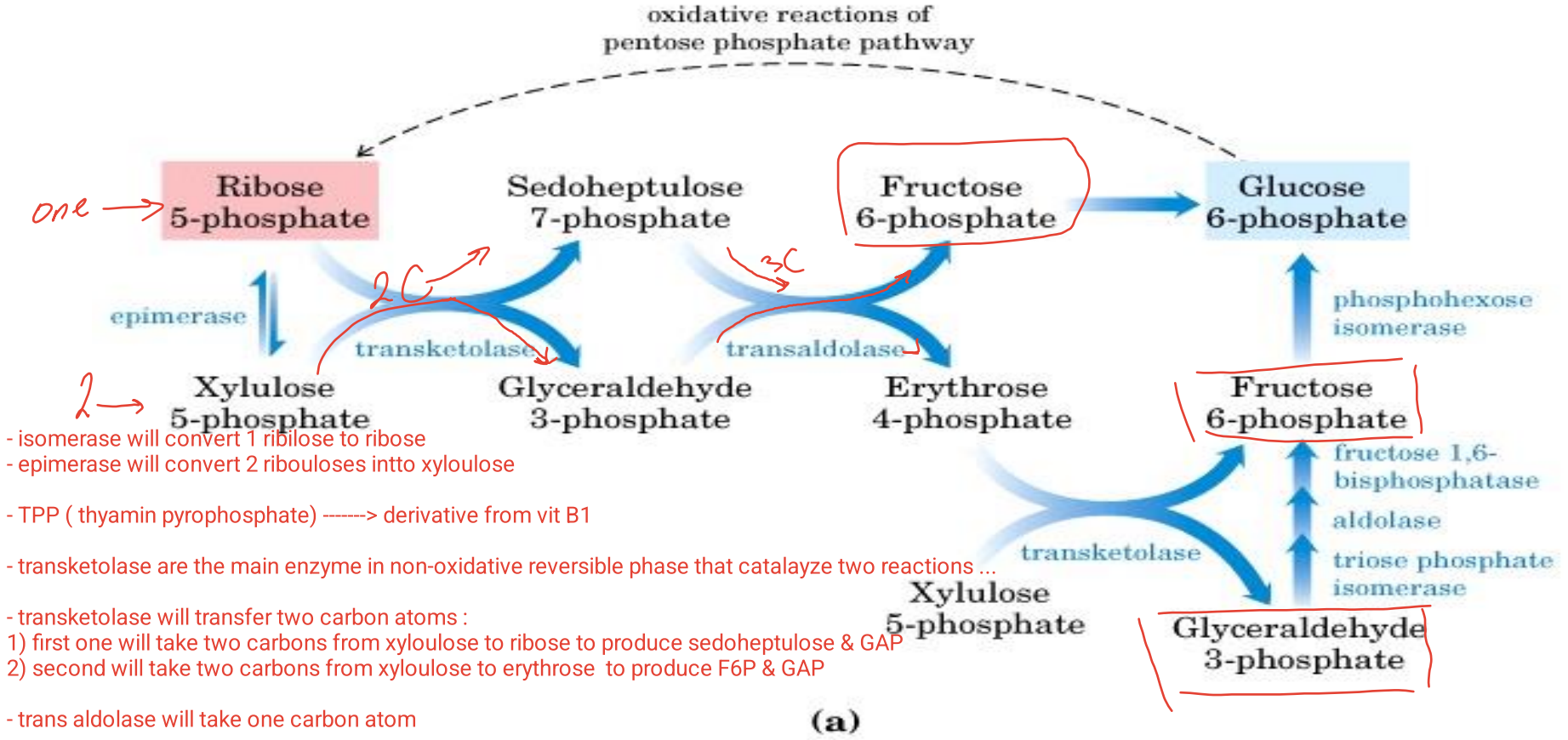

$CH_2OPO_3^{2-}$
H
O
H
OH
H
HO
H
OH
O
H_2O
H^+
Lactonase
6-Phosphogluconono-
δ-lactone
O
O
O
H
C
OH
HO
H
H
OH
H
OH
$CH_2OPO_3^{2-}$
6-Phospho-
gluconate
$NADP^+$
NADPH
6-Phosphogluconate
dehydrogenase
CH_2OH
+ CO_2
Ribulose
5-phosphate

Don’t panic, you need not know all the reactions in detail; stay tuned.

TABLE 20.3 Pentose phosphate pathway

Reaction	Enzyme
Oxidative phase	
Glucose 6-phosphate + $NADP^+$ $\longrightarrow$ 6-phosphoglucono-δ-lactone + NADPH + H^+	Glucose 6-phosphate dehydrogenase
6-Phosphoglucono-δ-lactone + H_2O $\longrightarrow$ 6-phosphogluconate + H^+	Lactonase
6-Phosphogluconate + $NADP^+$ $\longrightarrow$ ribulose 5-phosphate + CO_2 + NADPH	6-Phosphogluconate dehydrogenase
Nonoxidative Phase	
Ribulose 5-phosphate $\rightleftharpoons$ ribose 5-phosphate	Phosphopentose isomerase
Ribulose 5-phosphate $\rightleftharpoons$ xylulose 5-phosphate	Phosphopentose epimerase
Xylulose 5-phosphate + ribose 5-phosphate $\rightleftharpoons$ sedoheptulose 7-phosphate + glyceraldehyde 3-phosphate	Transketolase
Sedoheptulose 7-phosphate + glyceraldehyde 3-phosphate $\rightleftharpoons$ fructose 6-phosphate + erythrose 4-phosphate	Transaldolase
Xylulose 5-phosphate + erythrose 4-phosphate $\rightleftharpoons$ fructose 6-phosphate + glyceraldehyde 3-phosphate	Transketolase

The non-oxidative phase of the pentose pathway



- isomerase will convert 1 ribilose to ribose
- epimerase will convert 2 ribouloses intto xyloulose

- TPP (thyamin pyrophosphate) -------> derivative from vit B1

- transketolase are the main enzyme in non-oxidative reversible phase that catalayze two reactions ...

- transketolase will transfer two carbon atoms :
1) first one will take two carbons from xyloulose to ribose to produce sedoheptulose & GAP
2) second will take two carbons from xyloulose to erythrose to produce F6P & GAP

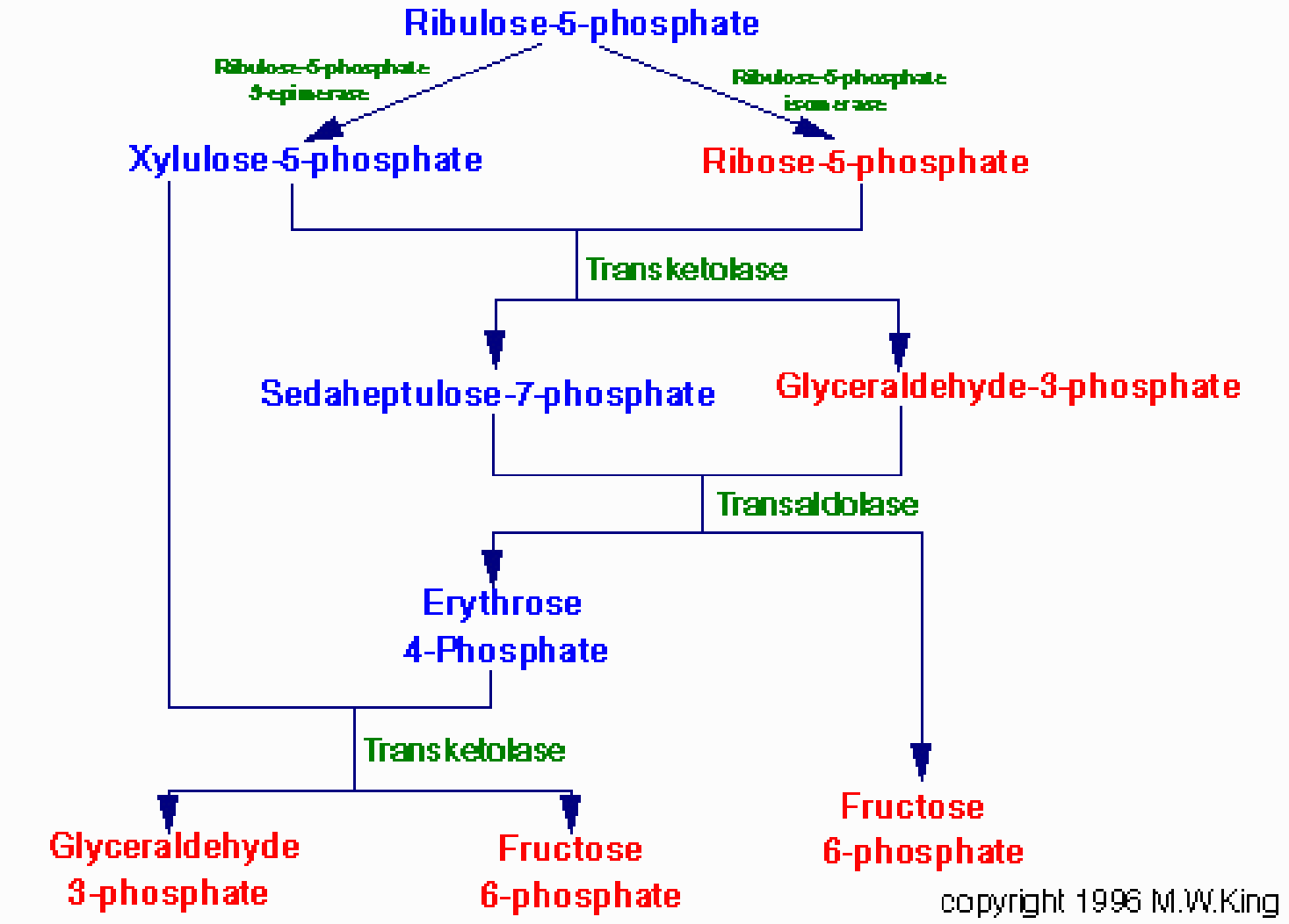
- trans aldolase will take one carbon atom

- Transketolase requires the coenzyme TPP, the transaldolase does not.
- Transketolase (TPP) and transaldolase are the link back to glycolysis.

Glyceraldehyde 3-phosphate

Fructose 6-phosphate Net result: $3C5 \rightarrow 2C6 + C3$

Non-Oxidative Stage of Pentose Phosphate Pathway



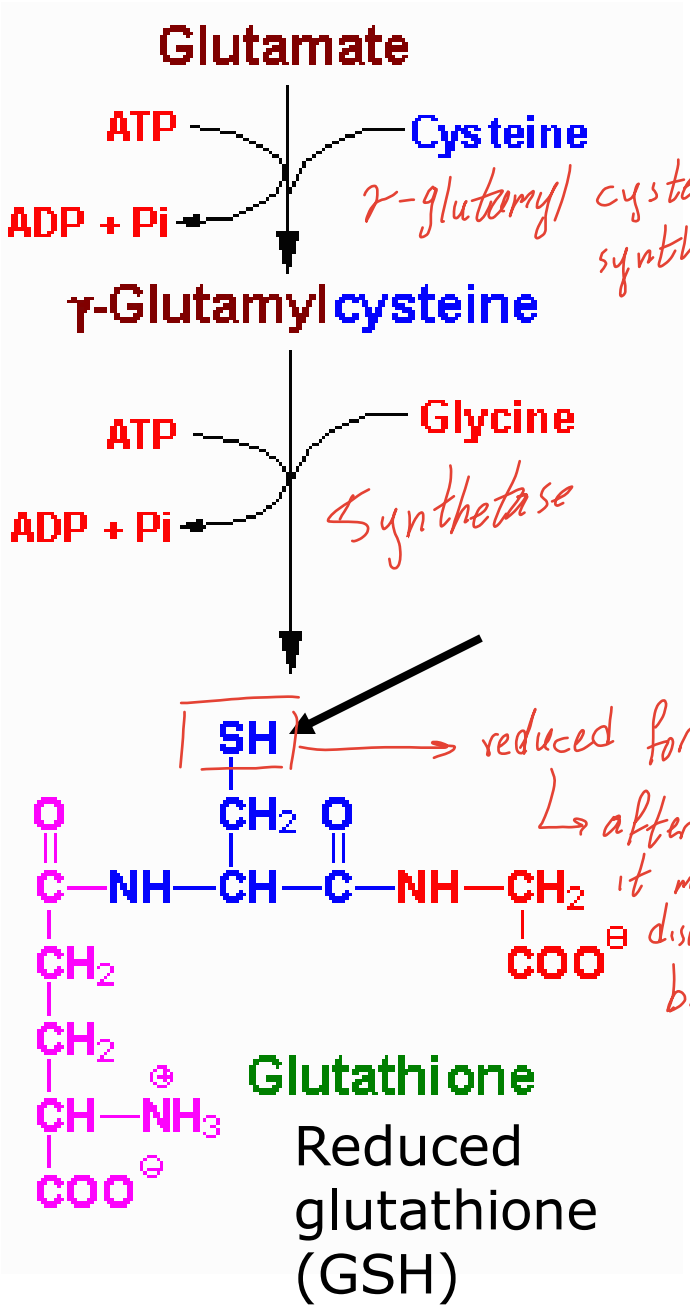
Regulation of the Pentose Pathway

- Glucose 6-phosphate dehydrogenase is the regulatory enzyme.
- NADPH is a potent competitive inhibitor of the enzyme.
- Usually the ratio NADPH/$NADP^+$ is high so the enzyme is inhibited.
- But, with increased demand for NADPH, the ratio decreases and enzyme activity is stimulated.
- The reactions of the non-oxidative portion of the pentose pathway are readily reversible.
- The concentrations of the products and reactants can shift depending on the metabolic needs of a particular cell or tissue.

Glutathione and NADPH

Glutathione is a tripeptide composed of glutamate, cysteine, glycine.

Reduced glutathione (GSH) maintains the normal reduced state of the cell.



2 enzymes & 2 ATP molecules are required

* Glutathione acts as hydrogen carrier (anti-oxidant)

Glutathione Functions

- glutathion work as hydrogen carriers, it take hydrogen by gluta reductase and lose it by peroxidase, peroxidase has cofactor known as selenium

- vit C & E and selenium are antioxidants
- selenium are race element , and we need it little .
- selenium are main component of antioxidant drugs .

- It serves as a reductant.
- Conjugates to drugs making them water soluble.
- Involved in amino acid transport across cell membranes.
- Cofactor in some enzymatic reactions.

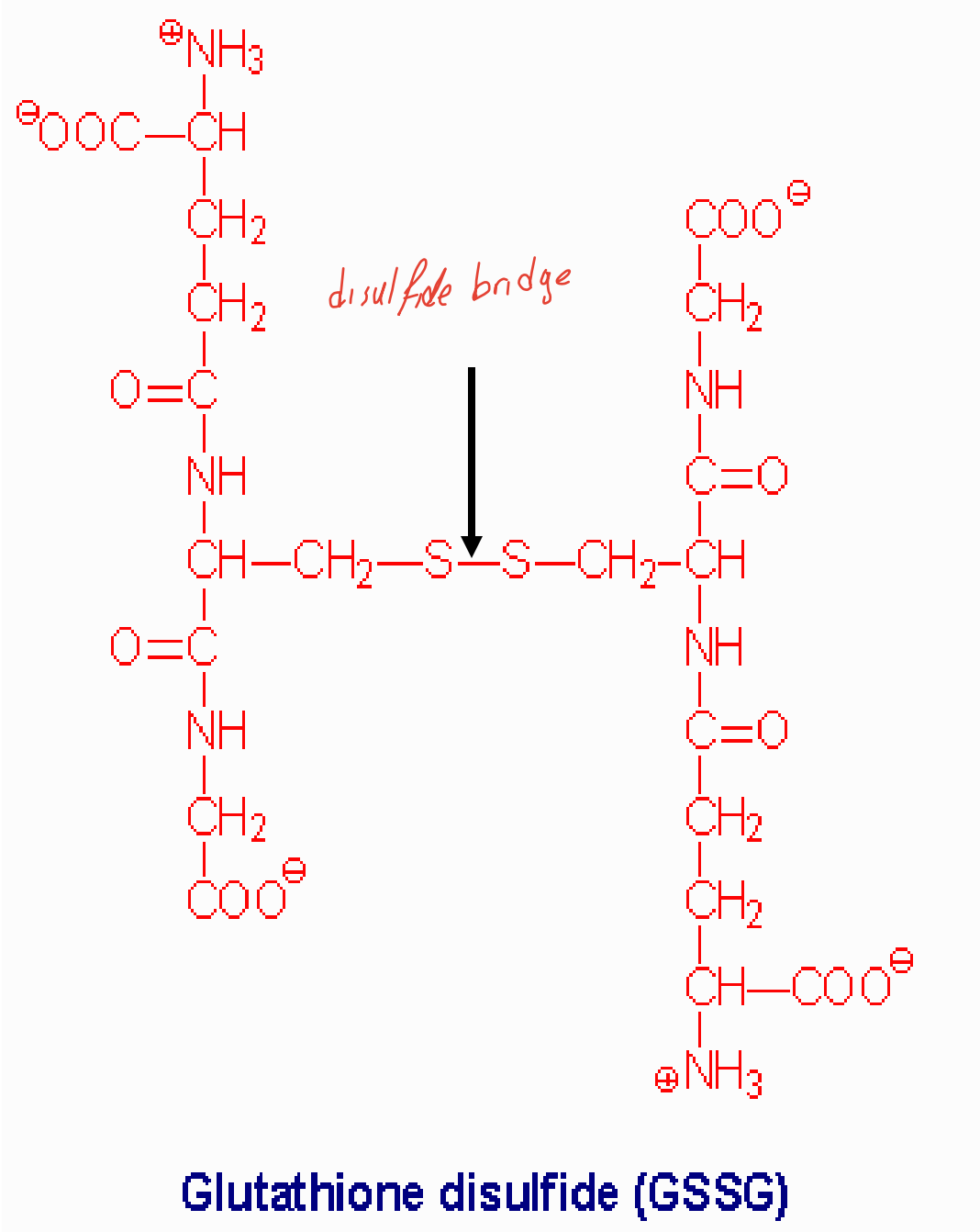
- The sulfhydryl of GSH is used to reduce peroxides (ROS) formed during oxygen transport. ROS can affect DNA, RNA, and proteins leading to cell death.

- The resulting oxidized form of GSH is two molecules linked by a disulfide bridge (GSSG).

* CYP450 is a mono-oxygenase (hydroxylase enzyme)

-The enzyme glutathione reductase uses NADPH as a cofactor to reduce GSSG back to two moles of GSH.

-Thus, the pentose pathway is linked to the supply of adequate amounts of GSH.



Glutathione disulfide (GSSG)

Glutathione and Erythrocytes

- GSH is extremely important particularly in the highly oxidizing environment of the red blood cell.
- Mature RBCs have no mitochondria and are totally dependent on NADPH from the pentose phosphate pathway to regenerate GSH from GSSG via glutathione reductase.
- In fact, as much as 10% of glucose consumption, by erythrocytes, is mediated by the pentose pathway.
- The reduced form of glutathione serves as a sulfhydryl buffer, it maintains cysteine residues in hemoglobin and other proteins in a reduced state.
- GSH is essential for normal RBC structure and keeping hemoglobin in Fe++ state.

* Phospholipids of cell membrane.-
  - Glycerol
  - saturated f.a
  - unsaturated f.a
  - PO_4 – nitrogenous compound

- Reduced glutathione also detoxifies peroxides.

$$2GSH + ROOH \rightarrow GSSG + H_2O + ROH$$

- Cells with low levels of GSH are susceptible hemolysis.
- Individuals with reduced GSH are subject to hemolysis.
- This is often clinically seen as black urine under certain conditions.

hydrogen peroxide (H2O2) is not a free radicl , but it is a source of free radicals, it is unstable so it can easly convert to water & single free oxygen.. this single free oxygen are considerd as the most dangerous ROS because it's carry an Extra electron .

So , accumulation of hydrogen peroxide (H2O2) can lead to peroxide formation caused by saturation of double bond of poly unsaturated fatty acid in the membrane

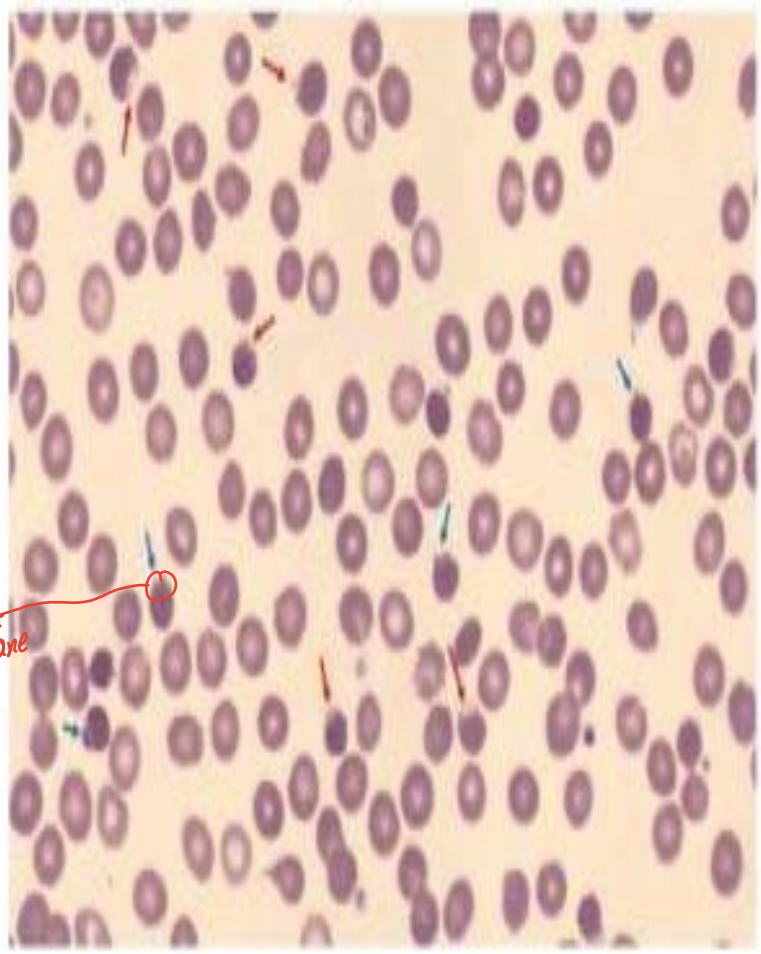
Conditions for hemolytic anemia related G6PD deficiency

- The ingestion of oxidative agents that generate peroxides or reactive oxygen species (ROS), such as antimalarial drugs, purine glycoside from fava beans, aspirin and sulfa drugs
- Individuals with G6PD deficiency can not produce sufficient GSH to cope with the ROS.
- Proteins become cross linked leading to Heinz body formation and cell lysis.

G6PD produce NADPH,.... NADPH are cofactor for glutathion reductase , so deficiency of G6PD will lead to decreasing in glutathion function and amounts .

this disease was known as phaphism ...
it is asymptomatic until patient ingest oxidative agents that generate peroxides or reactive oxygen species (ROS) .

- Glucose 6-phosphate dehydrogenase deficiency and non-spherocytic hemolytic anemia.
- Over 300 genetic variants of the G6PD protein are known.
- Thus, there is a remarkable variation in the clinical spectrum.
- G6PD deficiency is an inheritable X-linked recessive disorder.
- Approximately 10-14% of the male African American population is affected.
- It is also seen in Caucasians from the Mediterranean Basin.



- People with the disorder are not normally anemic and display no evidence of the disease until the red cells are exposed to an oxidant or stress.

treated by avoiding causes .... if it not avoided you take antioxidant, if hemolysis occur the treatment will be blood transfusion & iron calutorto prevent hemosederosis