Feeder pathways for glycolysis

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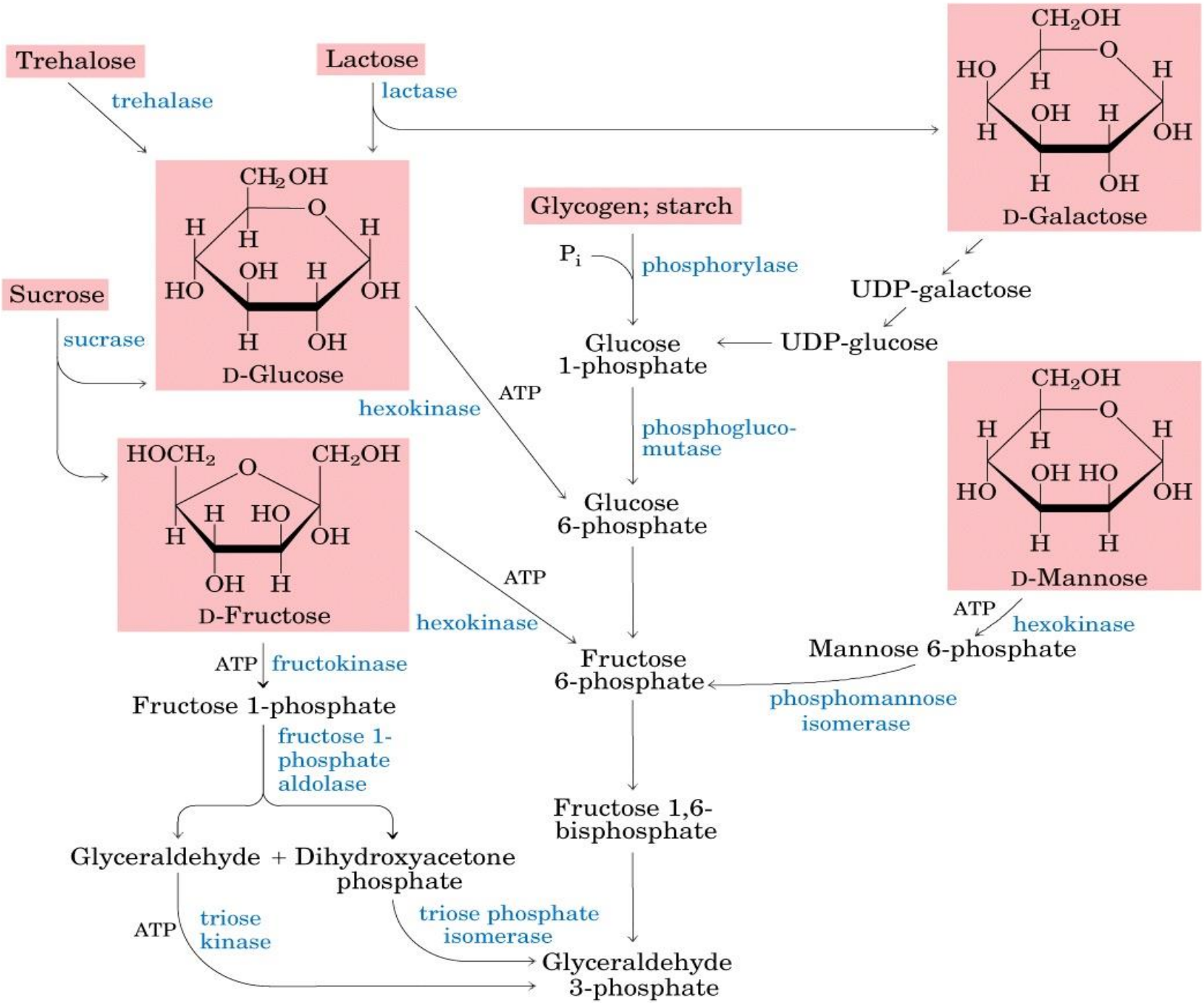
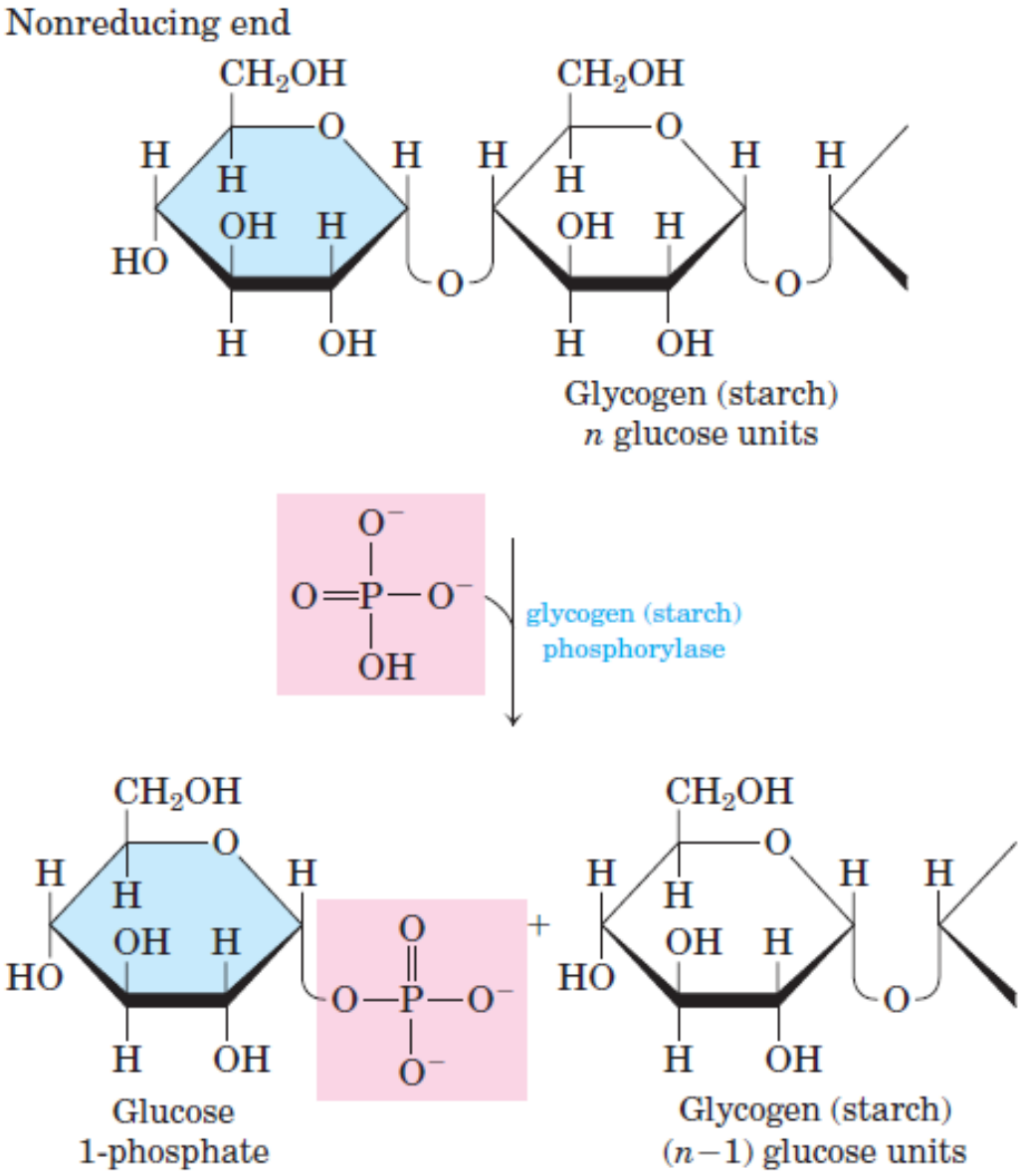
Entry of Carbohydrates into glycolysis





Phosphorolysis **NOT** hydrolysis

$$\text{Dextrin} + n\text{H}_2\text{O} \xrightarrow[\text{dextrinase}]{} n \text{ D-glucose}$$

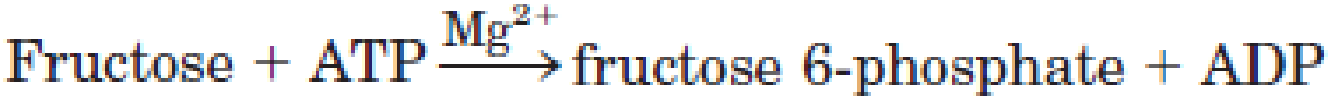
$$\text{Maltose} + \text{H}_2\text{O} \xrightarrow[\text{maltase}]{} 2 \text{ D-glucose}$$

$$\text{Lactose} + \text{H}_2\text{O} \xrightarrow[\text{lactase}]{} \text{D-galactose} + \text{D-glucose}$$

$$\text{Sucrose} + \text{H}_2\text{O} \xrightarrow[\text{sucrase}]{} \text{D-fructose} + \text{D-glucose}$$

$$\text{Trehalose} + \text{H}_2\text{O} \xrightarrow[\text{trehalase}]{} 2 \text{ D-glucose}$$

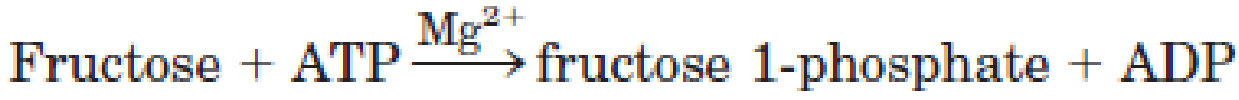
HK



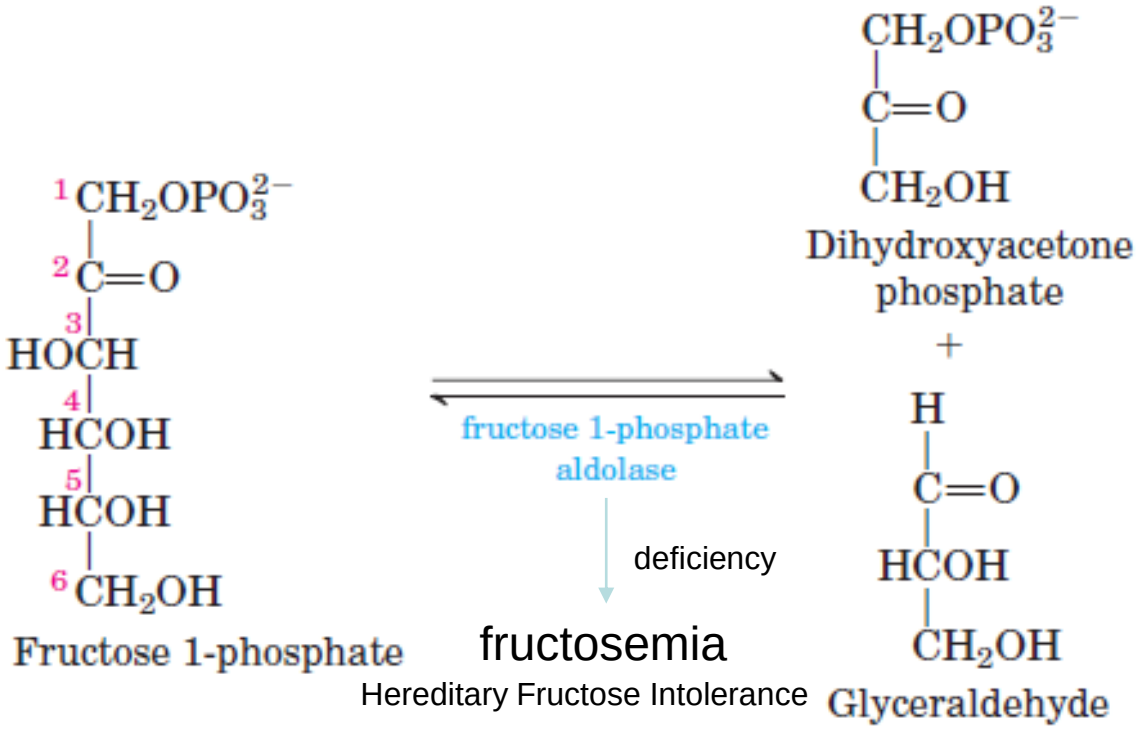
(Muscle)

deficiency

fructosuria ← FK

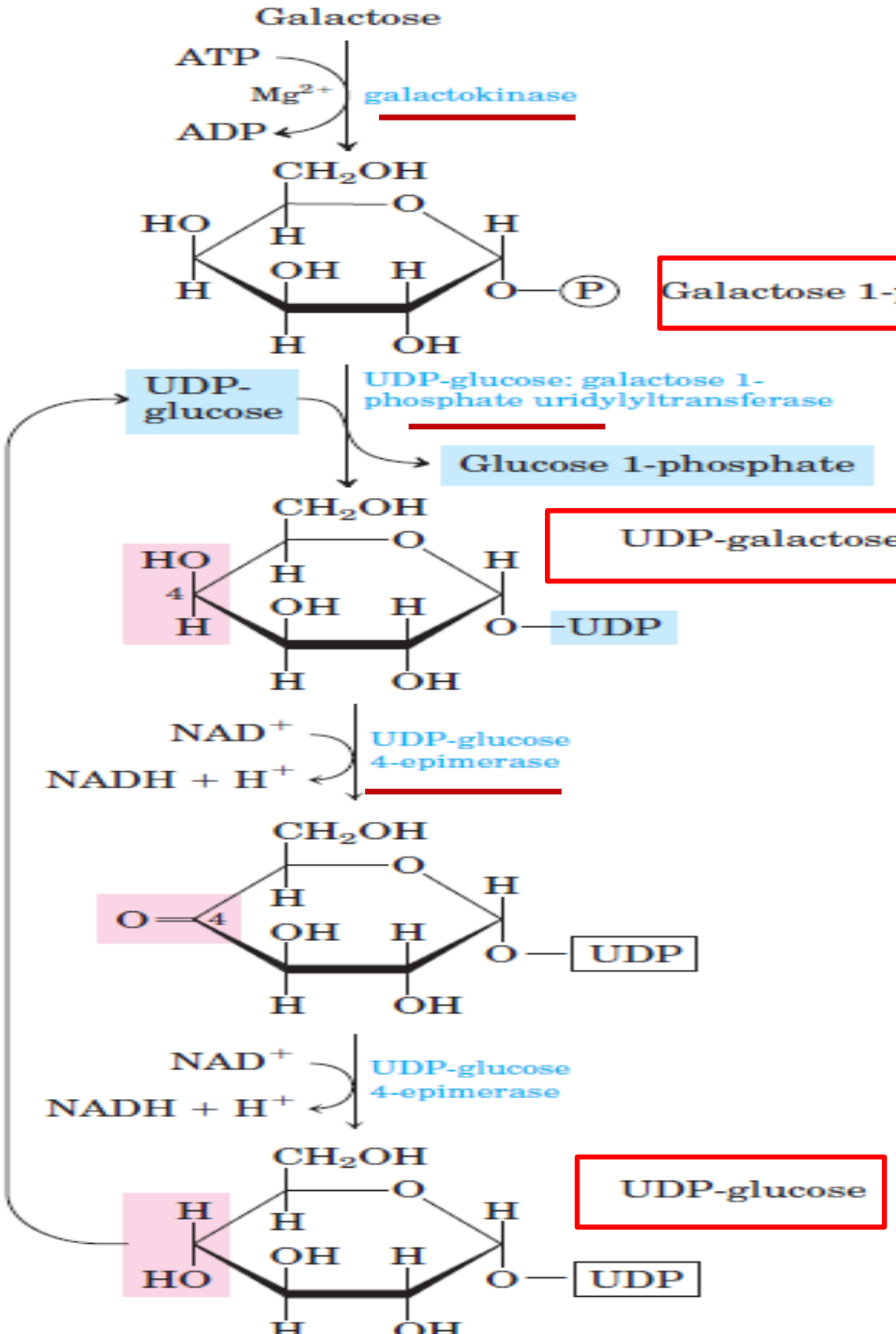


(liver)



both products of fructose 1-phosphate hydrolysis enter the glycolytic pathway as glyceraldehyde 3-phosphate.

Conversion of galactose to glucose 1-phosphate



Defects in any of the three enzymes in this pathway cause **galactosemia in humans.** In galacto kinase deficiency galactosemia, high galactose concentrations are found in blood and urine. Infants develop cataracts, Transferase-deficiency galactosemia is more serious it is characterized by poor growth in children, speech abnormality, mental deficiency, and liver damage that may be fatal.

Lactose intolerance

Lactose cannot be completely digested and absorbed in the small intestine and passes into the large intestine, where bacteria convert it to toxic products that cause abdominal cramps and diarrhea. The problem is further complicated because undigested lactose and its metabolites increase the osmolarity of the intestinal contents, favoring the retention of water in the intestine.

Conversion of galactose to glucose 1-phosphate.

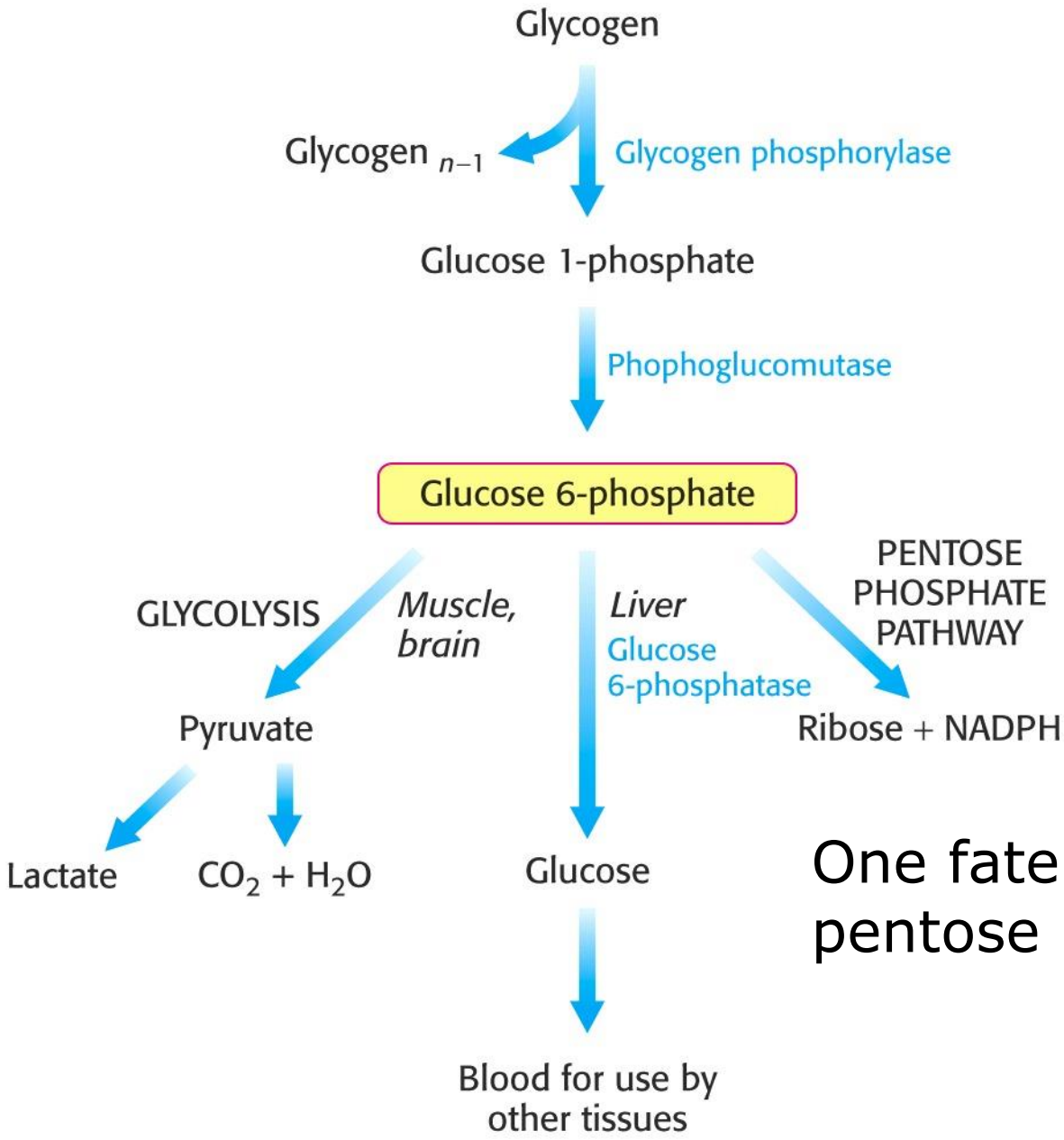
The conversion proceeds through a sugar-nucleotide derivative, UDP galactose, which is formed when galactose 1-phosphate displaces glucose1-phosphate from UDP-glucose. UDP-galactose is then converted by UDP-glucose 4-epimerase to UDP-glucose, in a reaction that involves oxidation of C-4 (pink) by NAD, then reduction of C-4 by NADH; the result is inversion of the configuration at C-4.

The UDP glucose is recycled through another round of the same reaction. The net effect of this cycle is the conversion of galactose 1-phosphate to glucose 1-phosphate; there is NO net production or consumption of UDP-galactose or UDP-glucose.

PENTOSE PHOSPHATE PATHWAY

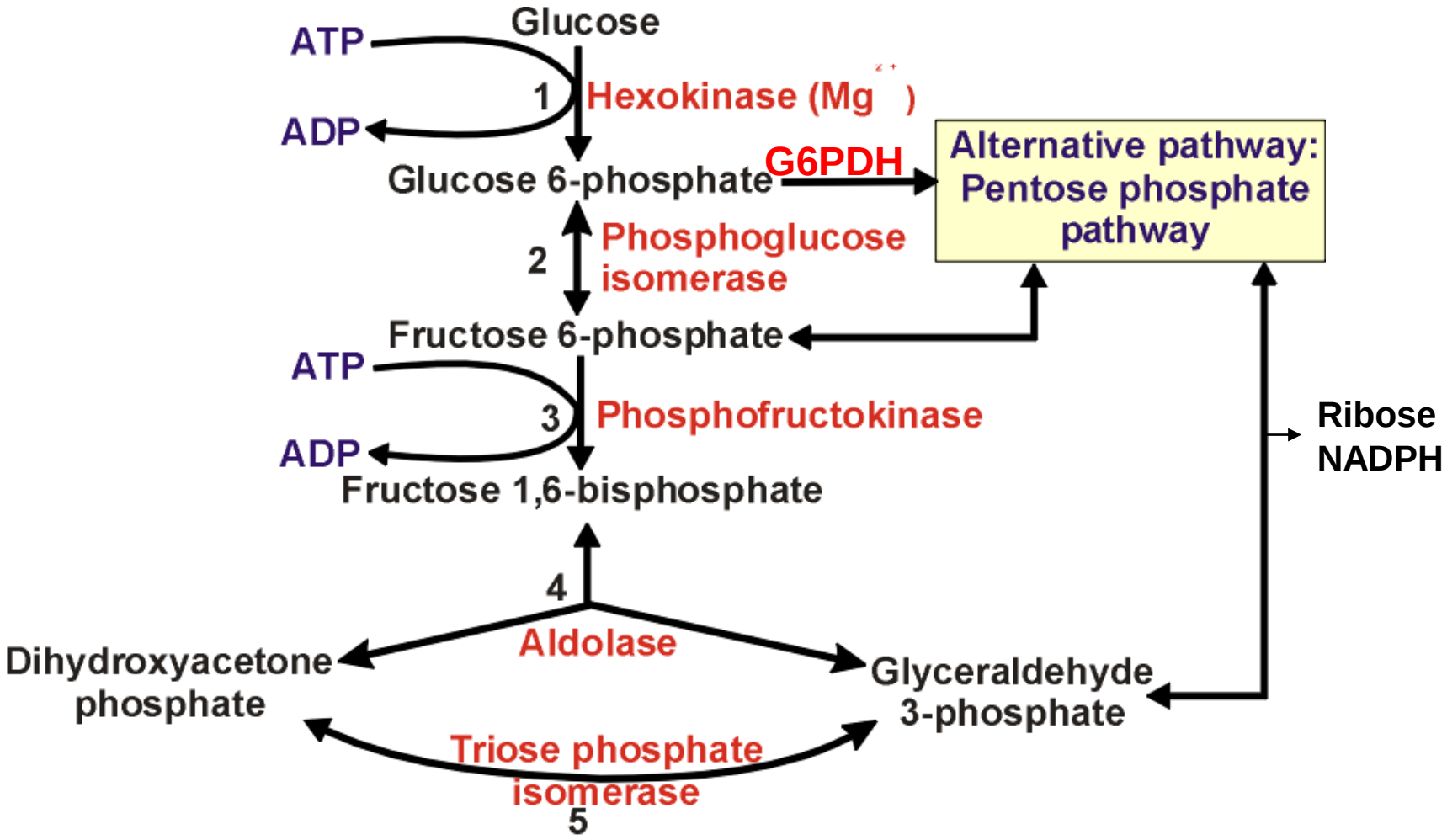
Phosphogluconate pathway

Hexose monophosphate pathway



One fate of G6P is the pentose pathway.

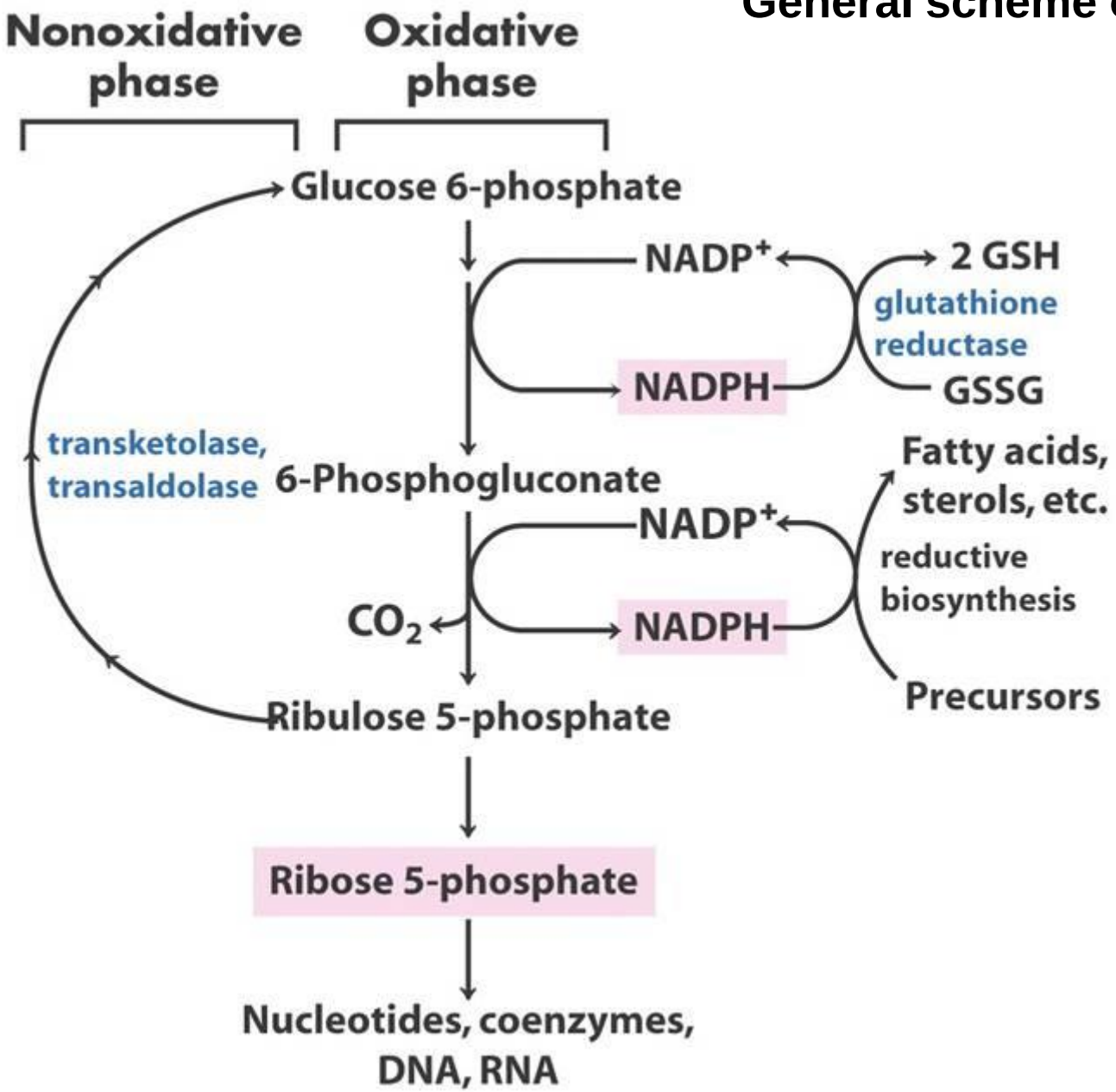
It’s a shunt


Glucose
ATP
ADP
1
Hexokinase (Mg++)
Glucose 6-phosphate
G6PDH
Alternative pathway:
Pentose phosphate
pathway
2
Phosphoglucose
isomerase
Fructose 6-phosphate
ATP
ADP
3
Phosphofructokinase
Fructose 1,6-bisphosphate
Ribose
NADPH
4
Aldolase
Dihydroxyacetone
phosphate
Glyceraldehyde
3-phosphate
Triose phosphate
isomerase
5

General scheme of the pentose phosphate pathway

- NADPH formed in the oxidative phase is used to reduce glutathione and to support reductive biosynthesis.
- The other product of the oxidative phase is ribose 5-phosphate, which serves as precursor for nucleotides, coenzymes, and nucleic acids.
- In cells that are not using ribose 5-phosphate for biosynthesis, the nonoxidative phase recycles **six** molecules of the pentose into **five** molecules of the hexose glucose 6-phosphate, allowing continued production of NADPH and converting glucose 6-phosphate to CO_2.

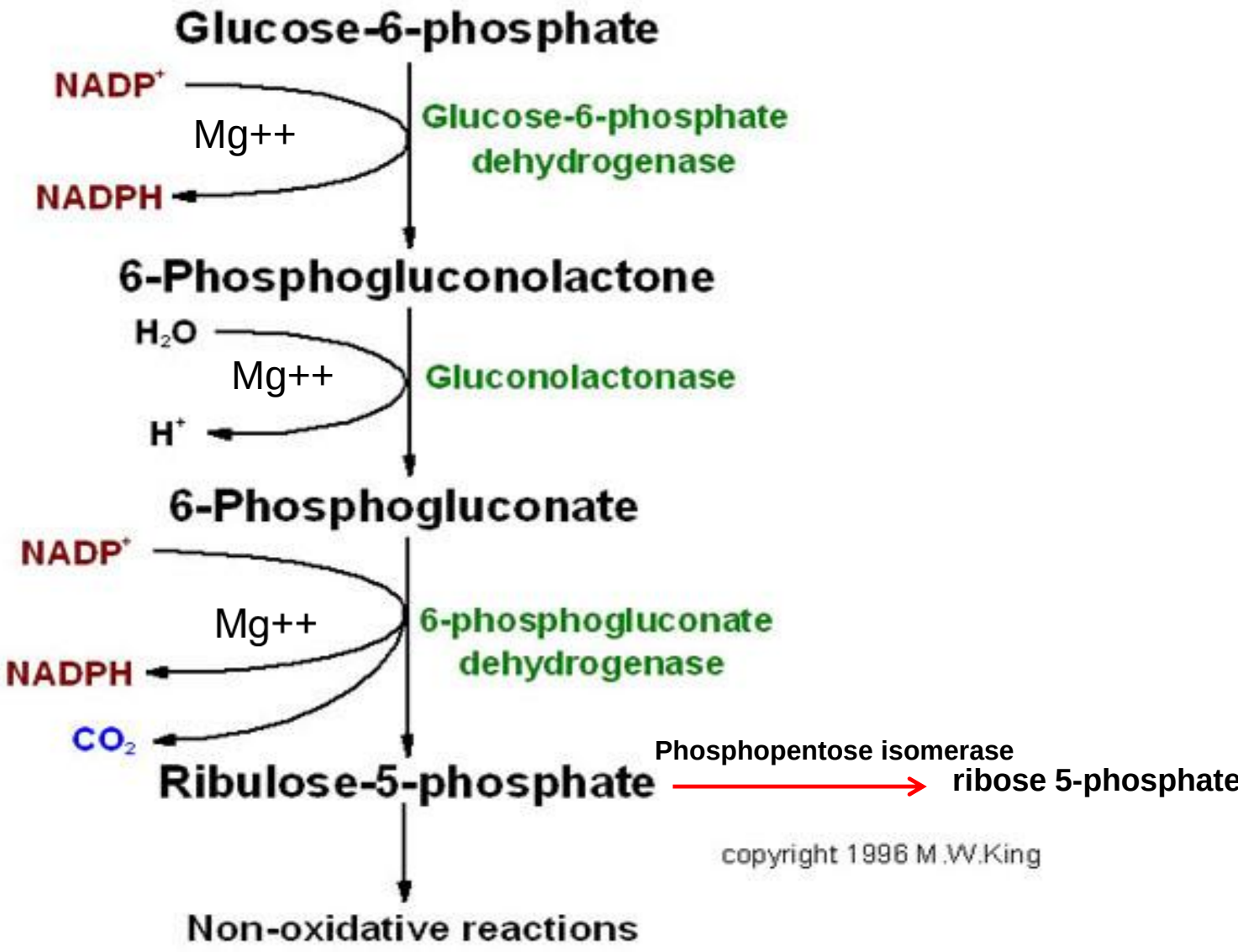
General scheme of PPP



Pentose Phosphate Pathway is the major source of NADPH used for:

- Biosynthesis of:
  - fatty acids (within liver, adipose tissue, lactating mammary gland).
  - cholesterol (in liver, adrenal gland cortex, skin, gonads).
  - catecholamines (nervous system, adrenal medulla).
- preserving the transparency of the eye lens, keeping crystalline (eye lens protein) in the active reduced state).
- to preserve erythrocyte membrane integrity.

Oxidative Stage of Pentose Phosphate Pathway



The Oxidative Phase Produces Pentose Phosphates and NADPH

In some tissues, the pentose phosphate pathway ends at this point, and its overall equation is:

Glucose 6-phosphate + 2NADP + H2O ⟶

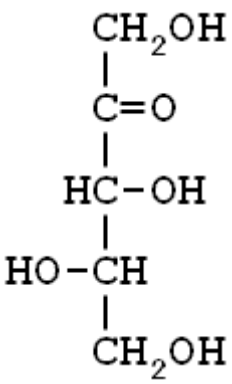
Ribose 5-phosphate + CO2 + 2NADPH + 2H

The net result is the production of:

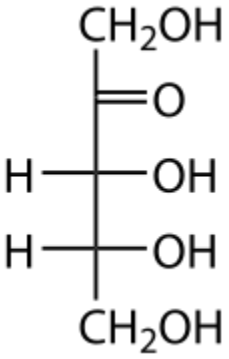
- ***NADPH,*** *a reductant for biosynthetic reactions,*
- ***Ribose 5-phosphate****, a precursor for nucleotide synthesis.*

The Nonoxidative Phase Recycles Pentose Phosphates to Glucose 6-Phosphate

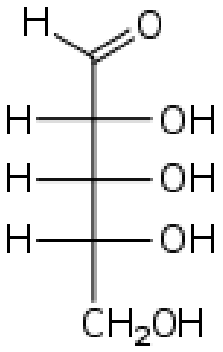
Ribulose 5-phosphate is first epimerized to xylulose 5-phosphate.



Xylulose



Ribulose

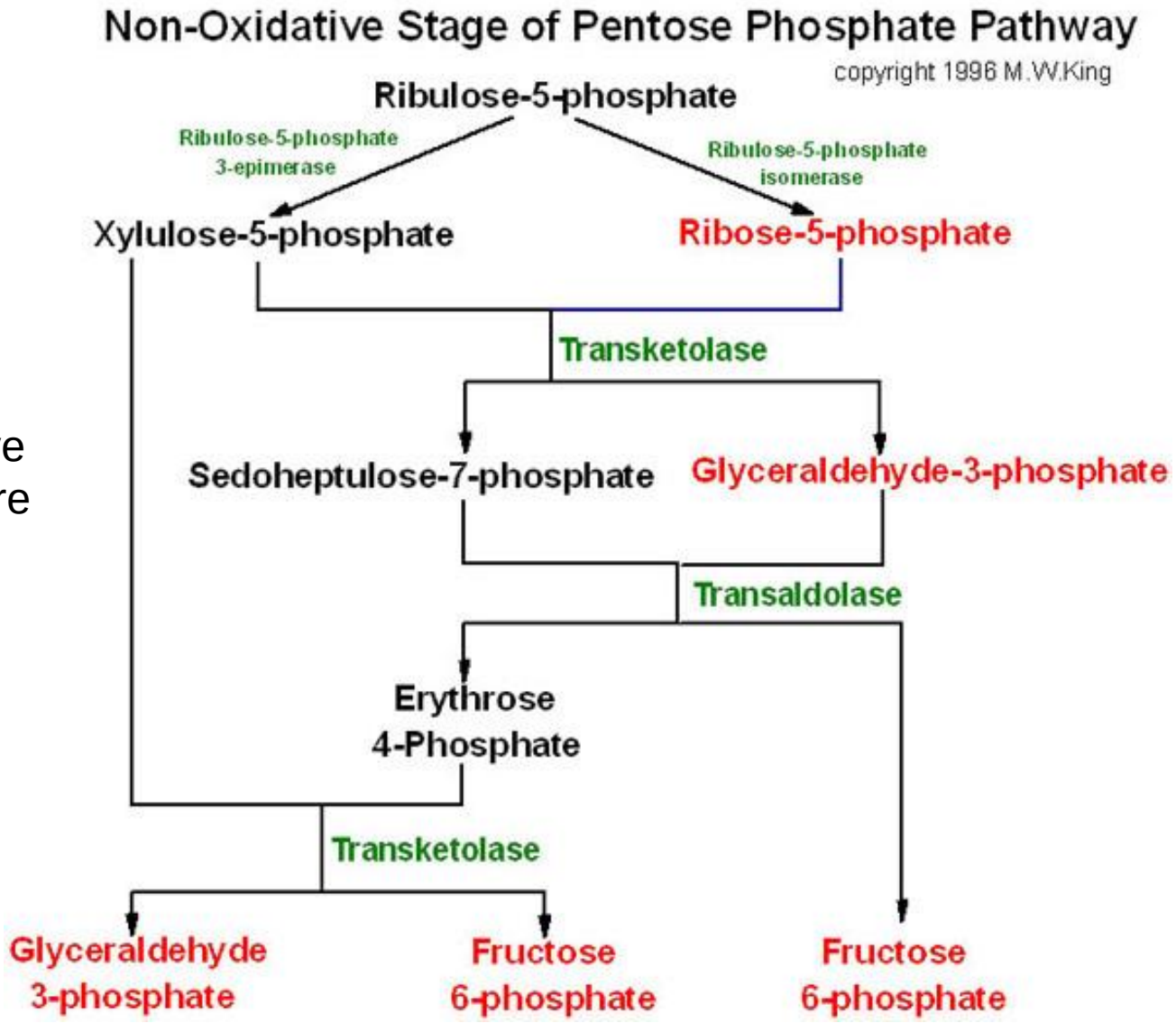


Ribose

Then, in a series of rearrangements of the carbon skeletons , six pentoses(five-carbon sugar) are converted to five hexoses (six-carbon sugar), completing the cycle and allowing continued oxidation of glucose 6-phosphate with production of NADPH.

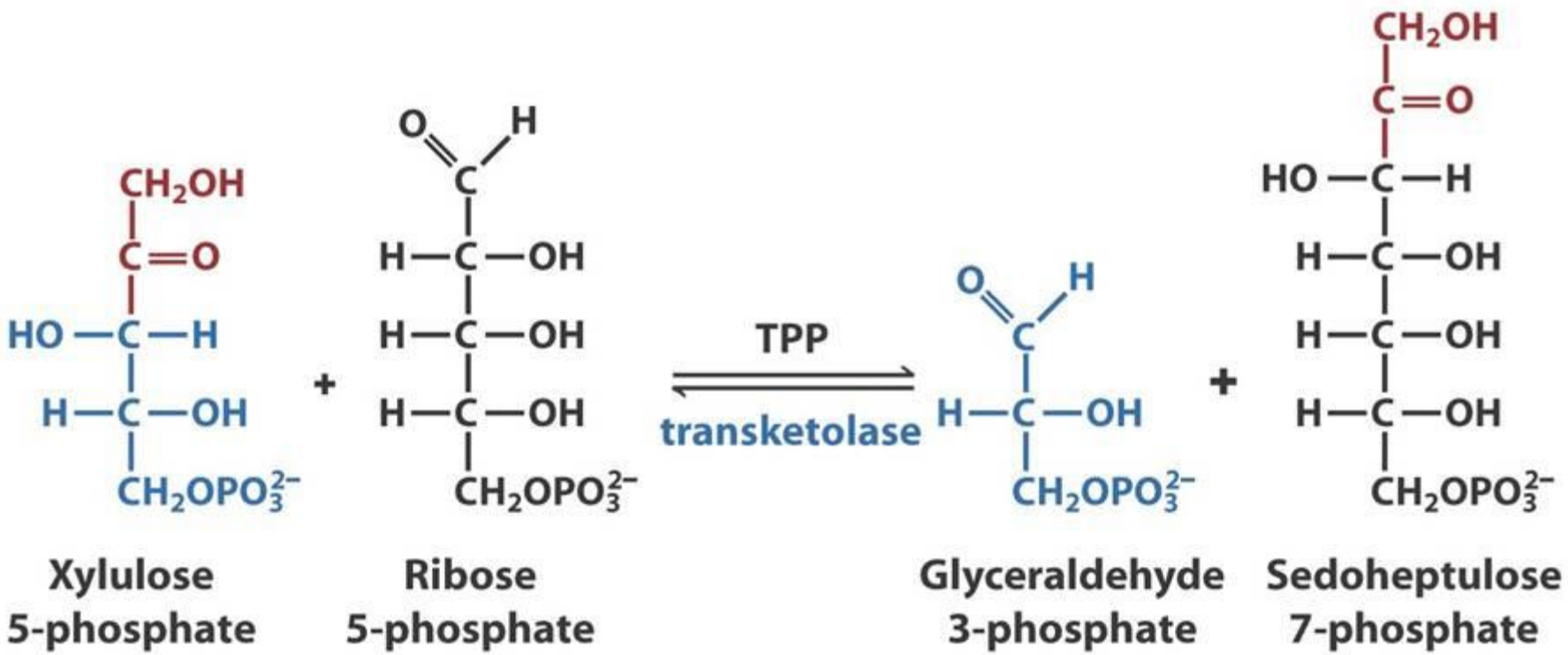
Continued recycling leads ultimately to the conversion of glucose 6-phosphate to six CO2.

In tissues that require primarily **NADPH,** the pentose phosphates produced in the oxidative phase of the pathway are recycled into glucose 6-phosphate.



See detailed reactions below

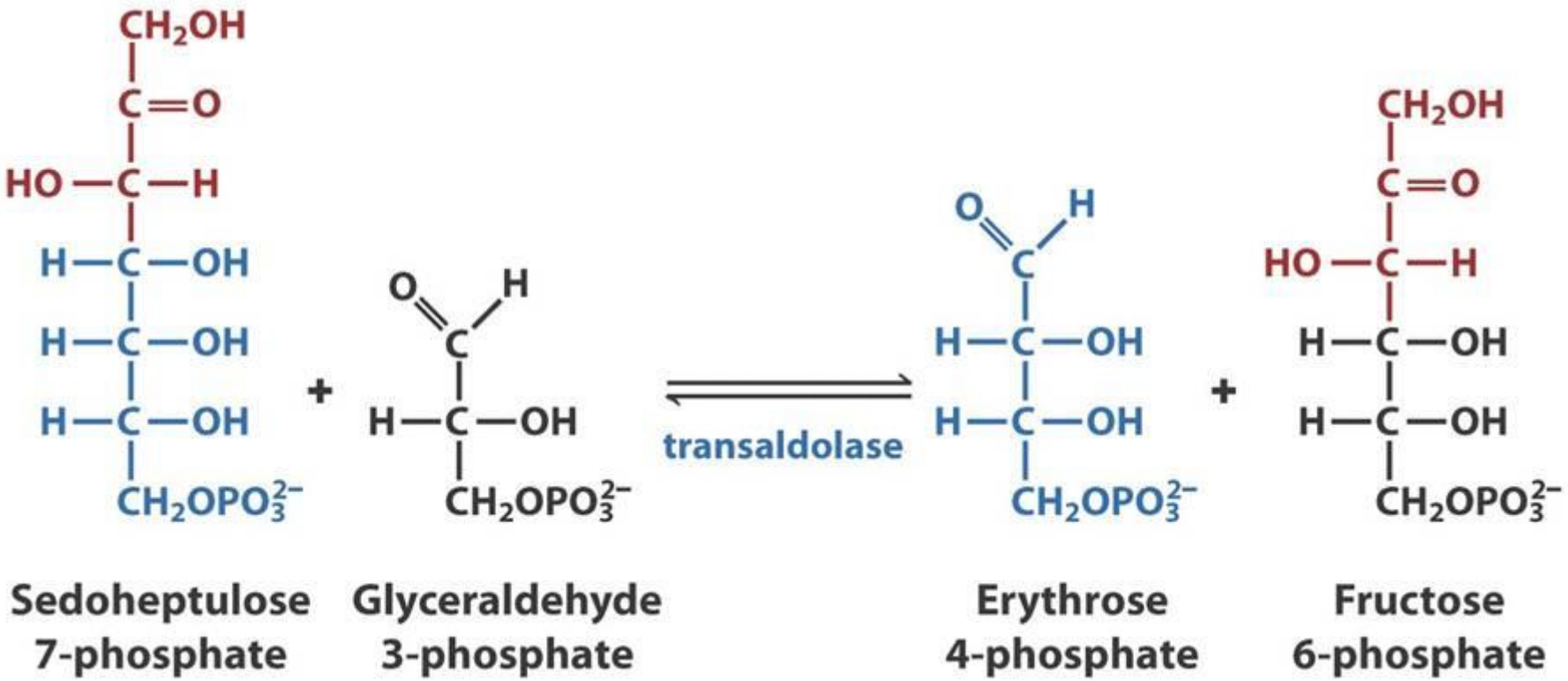
First



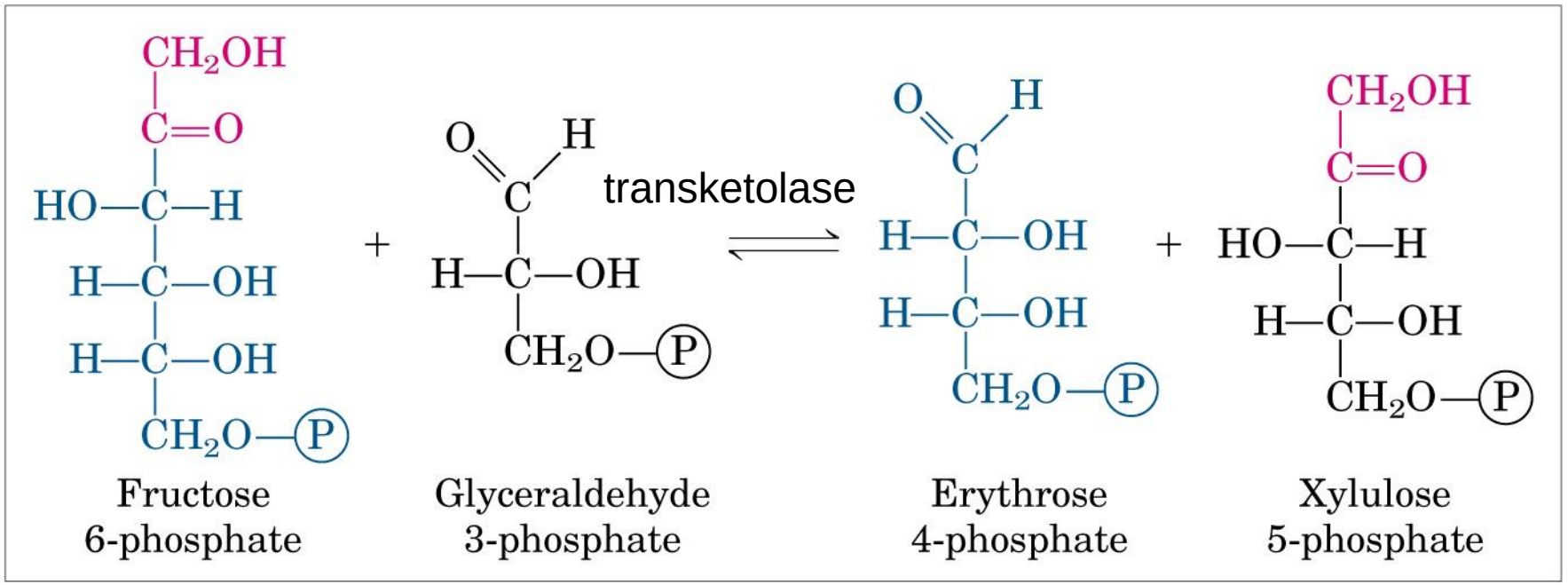
Ketose donor

Aldose acceptor

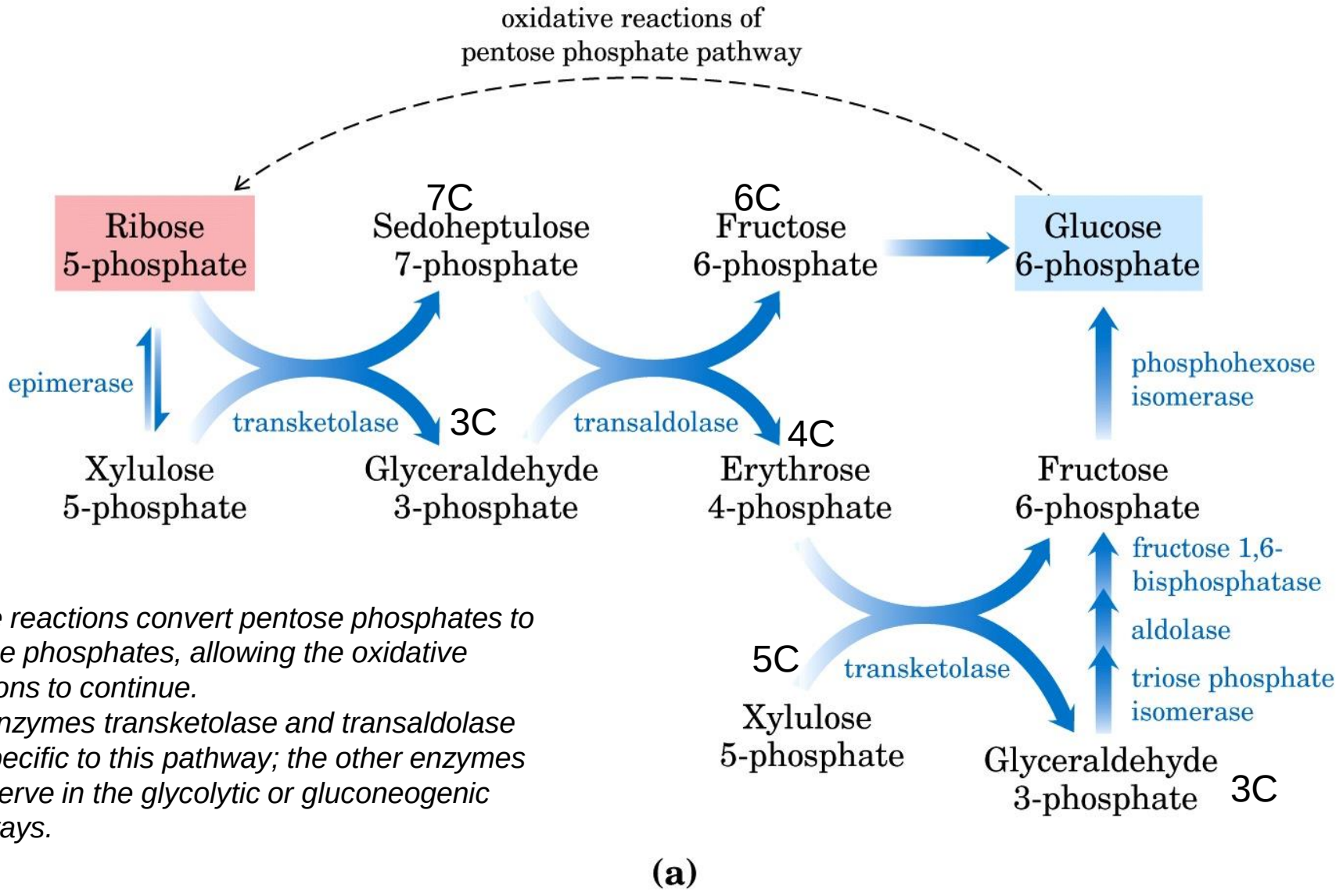
second


CH2OH
C=O
HO—C—H
H—C—OH
H—C—OH
H—C—OH
CH2OPO3 2–
+
O
H
C
H—C—OH
CH2OPO3 2–
transaldolase
O
H
C
H—C—OH
H—C—OH
CH2OPO3 2–
+
CH2OH
C=O
HO—C—H
H—C—OH
H—C—OH
CH2OPO3 2–
Sedoheptulose 7-phosphate
Glyceraldehyde 3-phosphate
Erythrose 4-phosphate
Fructose 6-phosphate

Third


transketolase
Fructose 6-phosphate
Glyceraldehyde 3-phosphate
Erythrose 4-phosphate
Xylulose 5-phosphate

(b)



These reactions convert pentose phosphates to hexose phosphates, allowing the oxidative reactions to continue.
The enzymes transketolase and transaldolase are specific to this pathway; the other enzymes also serve in the glycolytic or gluconeogenic pathways.
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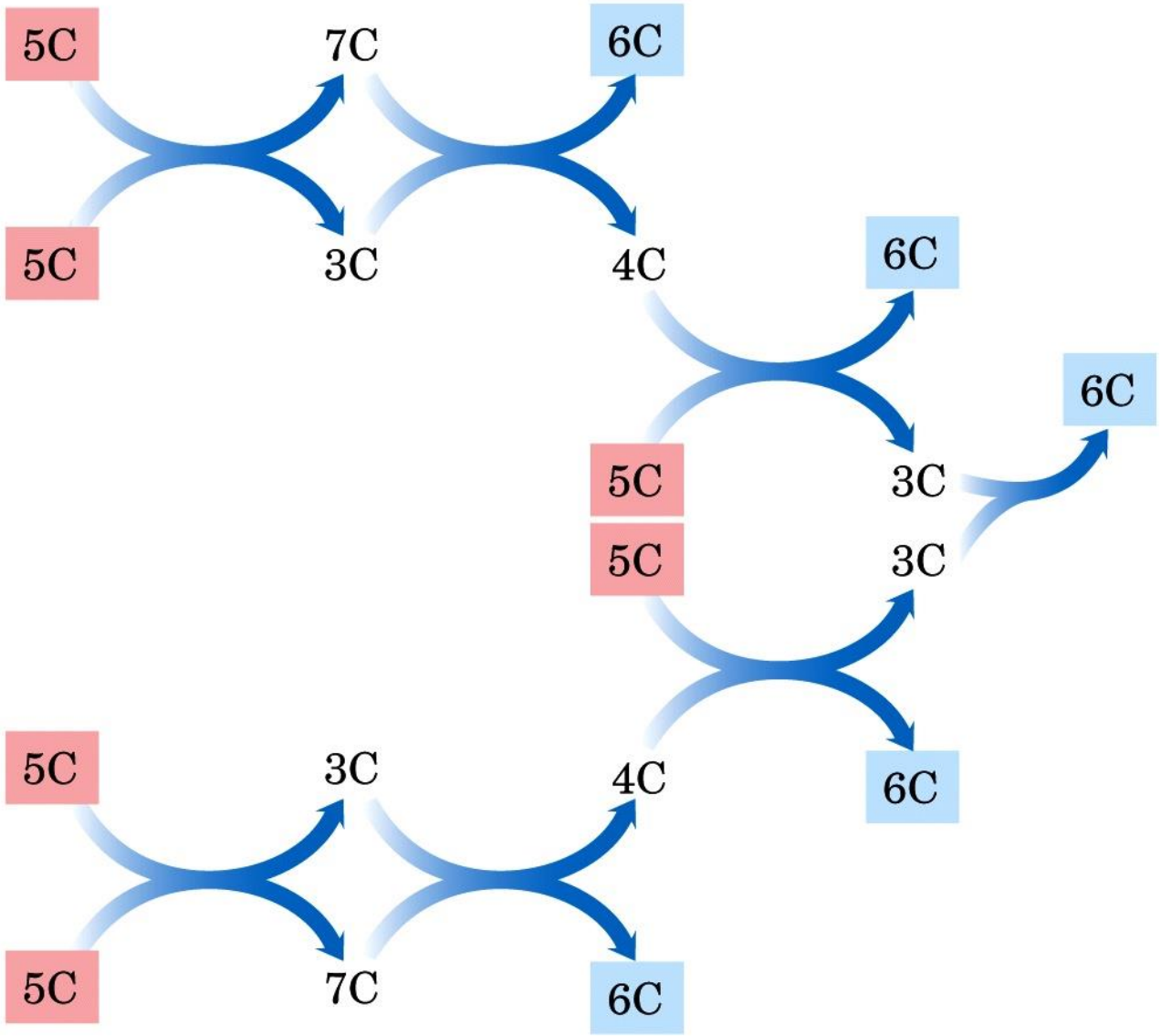
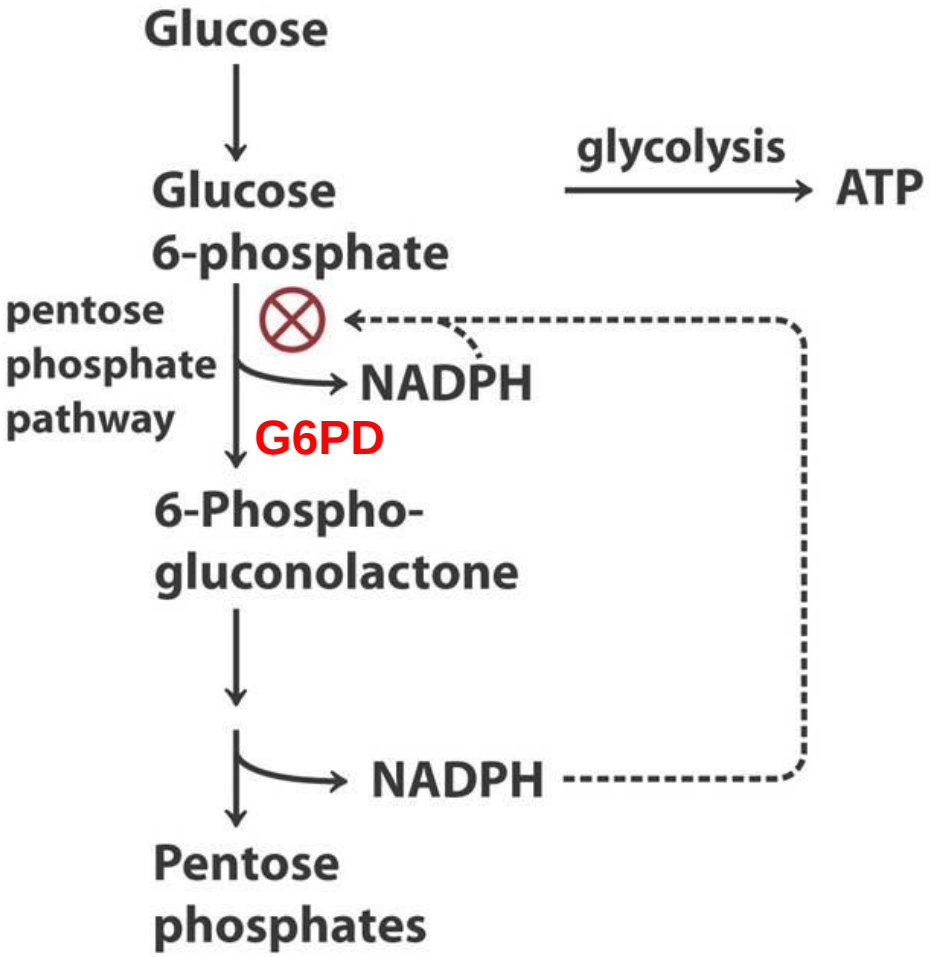
The fate of the trioses is determined by the cell's relative needs for pentose phosphates, NADPH, and ATP.



(b)

PPP_Regulation



When NADPH is forming faster than it is being used for biosynthesis and glutathione reduction

First step
Rate limiting
Feedback inhibited by NADPH

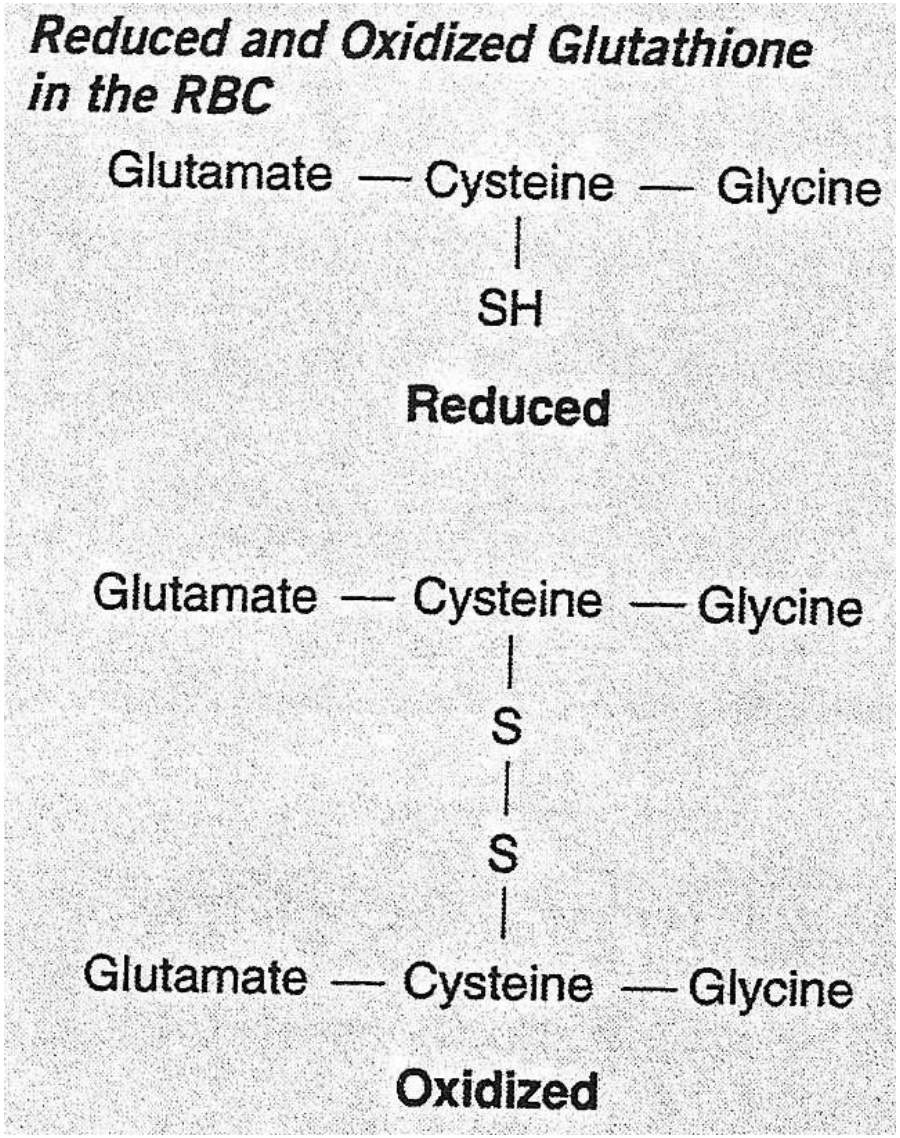
Regulation

Glucose-6-phosphate dehydrogenase is the rate-controlling enzyme of this pathway.

It is allosterically stimulated by NADP+. The ratio of NADPH:NADP+ is normally about 100:1 in liver cytosol. This makes the cytosol a highly-reducing environment.

An NADPH-utilizing pathway forms NADP+, which stimulates Glucose-6-phosphate dehydrogenase.

Glutathione and NDPH

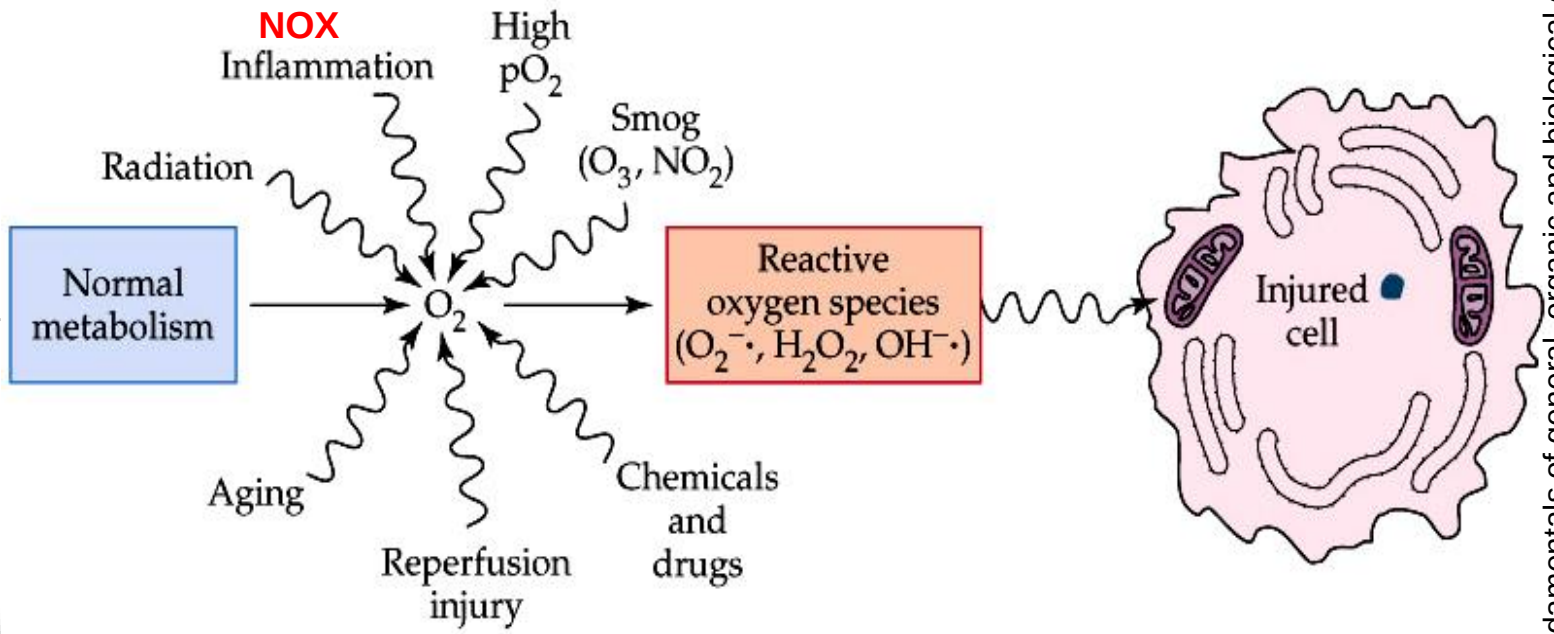


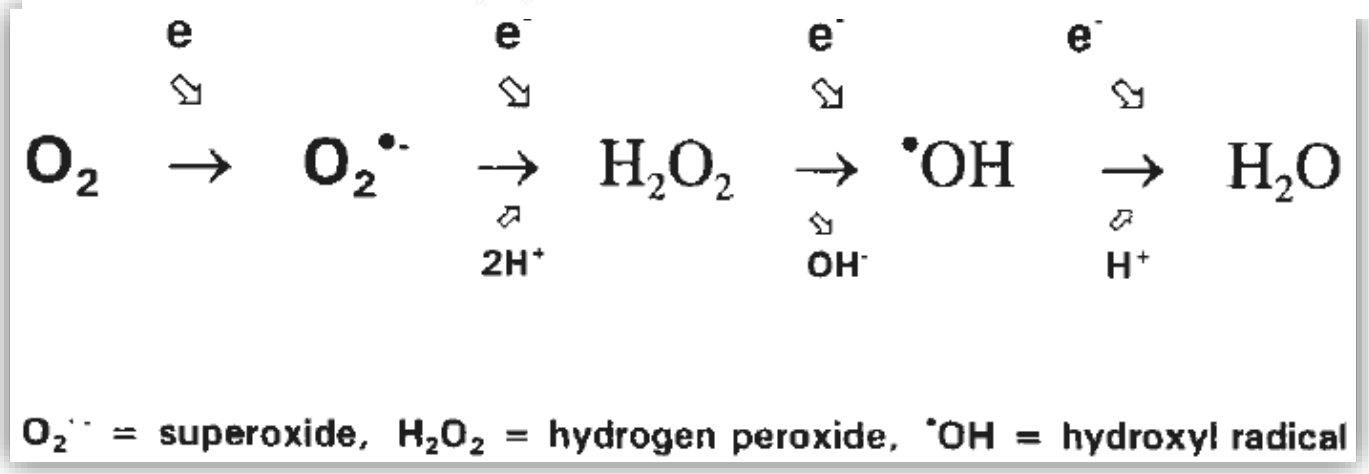
Glutathione Function

- 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.
  - rearrangement of protein disulfide bonds.

Reactive Oxygen Species(ROS)

Peroxisome
Mitochondria
Cyto. P450

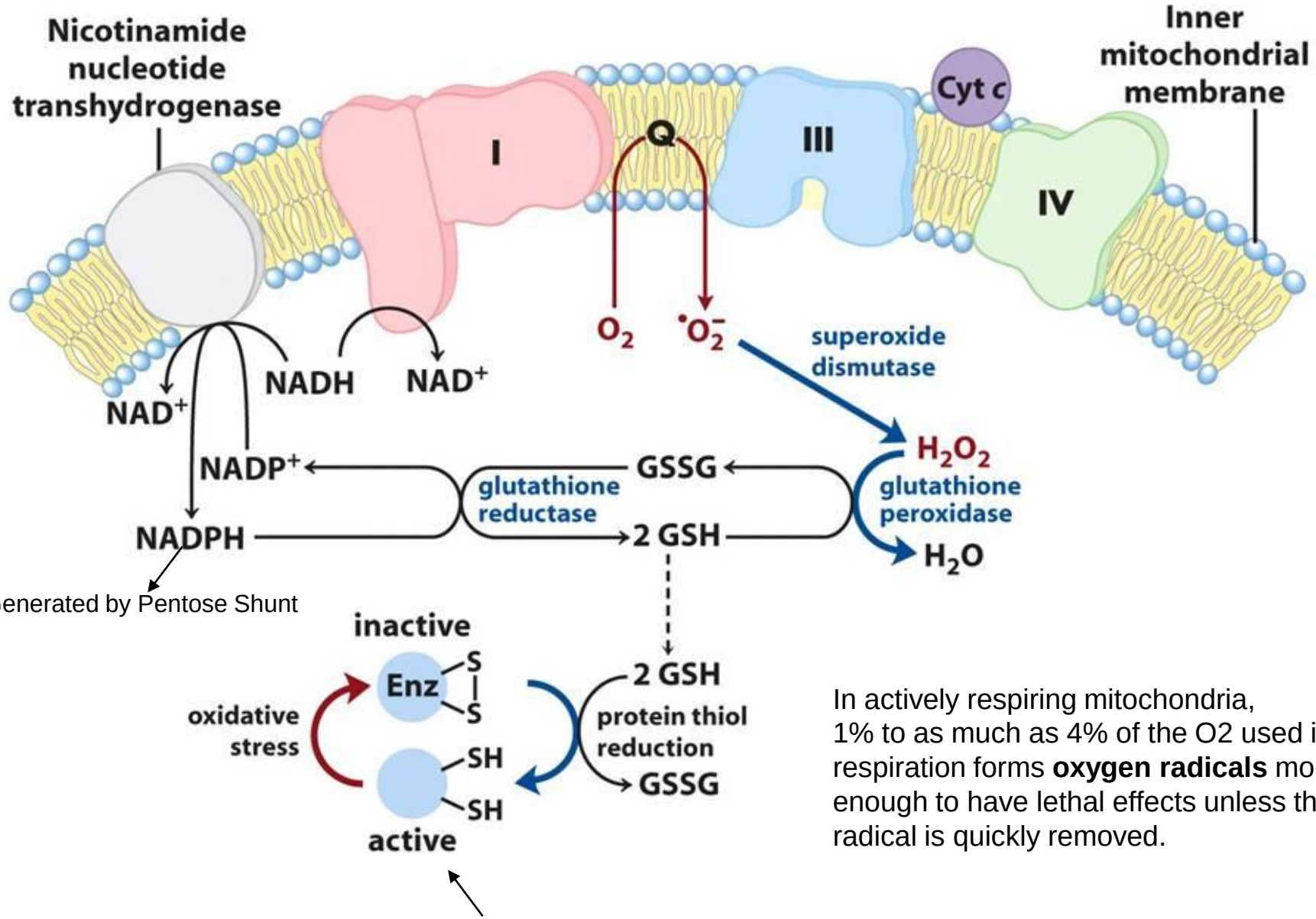




From: McMurry and Castellion "Fundamentals of general, organic and biological chemistry"

Detoxification of Superoxide Anion and Hydrogen Peroxide

- Antioxidant enzymes
  - Superoxide dismutase
  - Glutathione peroxidase
  - Glutathione reductase
  - Catalase
- ascorbic acid (vitamin C)
- The tocopherol (vitamin E)
- Carotenoids



In actively respiring mitochondria, 1% to as much as 4% of the O2 used in respiration forms **oxygen radicals** more than enough to have lethal effects unless the free radical is quickly removed.

Reduced glutathione also serves to keep protein sulfhydryl groups in their reduced state, preventing some of the deleterious effects of oxidative stress

Role of NADPH in the RBC

The oxidation of glucose-6-phosphate to ribulose-5-phosphate and CO_2 is very active in mammalian red blood cells, where the NADPH produced by the reaction is used to keep the glutathione inside the cell in a reduced state. Reduced glutathione helps prevent the oxidation of the iron in hemoglobin from Fe(II) to Fe(III). Hemoglobin containing Fe(III) is not effective in binding O_2.

Glucose 6 –phosphate dehydrogenase (G6PD) deficiency

- In favism, erythrocytes begin to lyse 24 to 48 hours after ingestion of the beans, releasing free hemoglobin into the blood. Jaundice and sometimes kidney failure can result.

- Similar symptoms can occur with ingestion of the antimalarial drug primaquine or of sulfa antibiotics, or following exposure to certain herbicides. These symptoms have a genetic basis: G6PD deficiency, which affects about 400 million people worldwide.

- Most G6PD-deficient individuals are asymptomatic; only the combination of G6PD deficiency and certain environmental factors produces the clinical manifestations

Wernicke-Korsakoff Syndrome

- Wernicke-Korsakoff syndrome is a disorder caused by a severe deficiency of thiamine, a component of TPP.
- The syndrome is more common Among people with alcoholism than in the general population, because chronic, heavy alcohol consumption interferes with the intestinal absorption of thiamine.
- The syndrome can be exacerbated by a mutation in the gene for transketolase that results in an enzyme with a lowered affinity for thiamine.
- This defect makes individuals much more sensitive to a thiamine deficiency. The result is a slowing down of the whole pentose phosphate pathway.In people with Wernicke-Korsakoff syndrome this results in a worsening of symptoms, which can include severe memory loss, mental confusion, and partial paralysis.