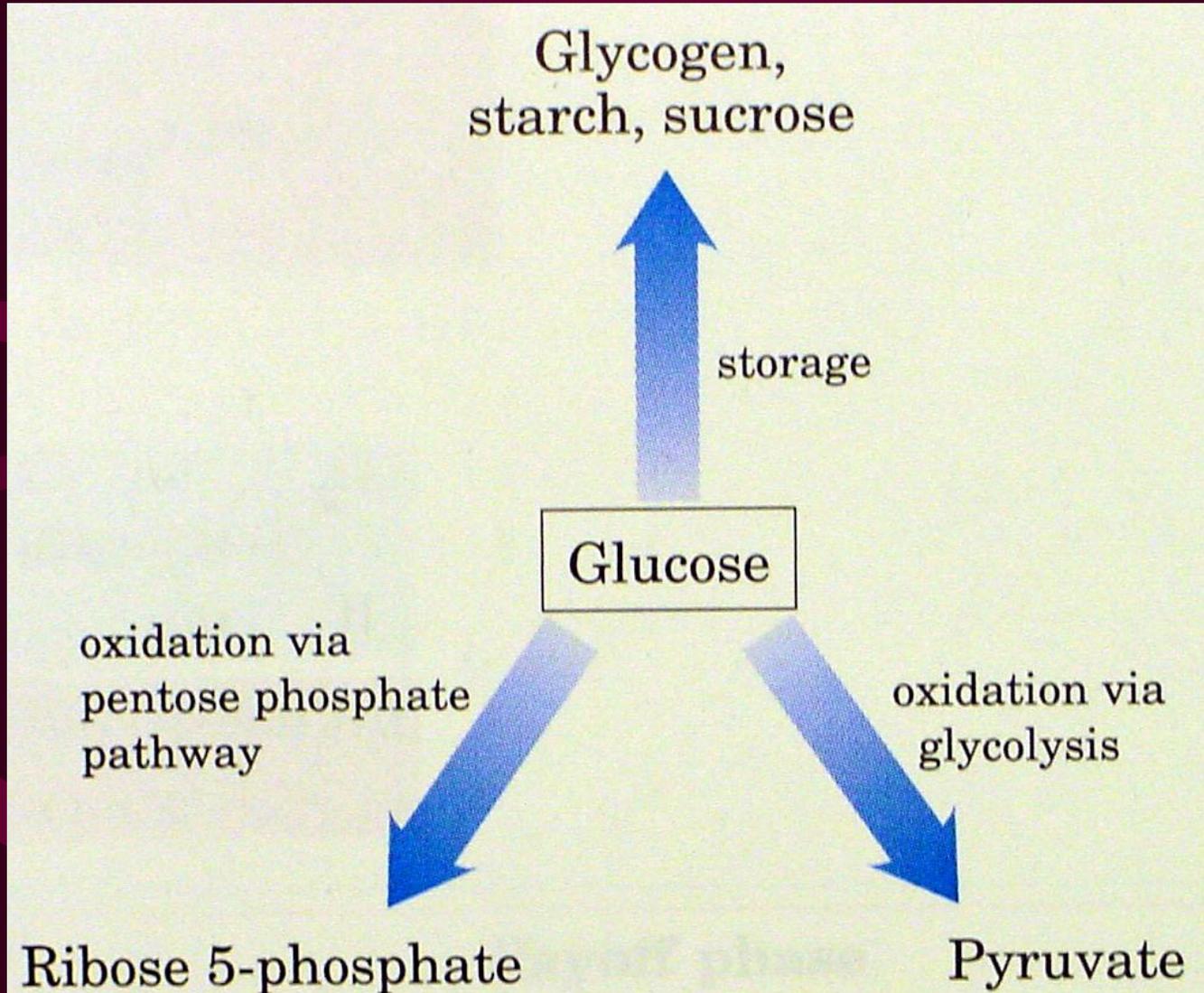


Pentose phosphate pathway (hexose monophosphate shunt)

OBJECTIVES

- To understand the function of the pentose phosphate pathway in production of NADPH and ribose precursors for nucleic acid synthesis.
- To examine the importance of NADPH in protection of cells against highly reactive oxygen species.
- To relate defects in the pentose phosphate pathway to disease conditions.

- The pentose phosphate pathway is an alternate route for the oxidation of glucose.



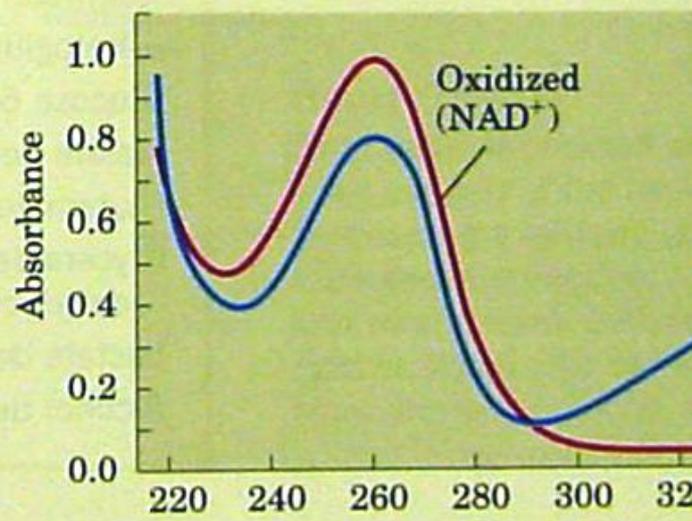
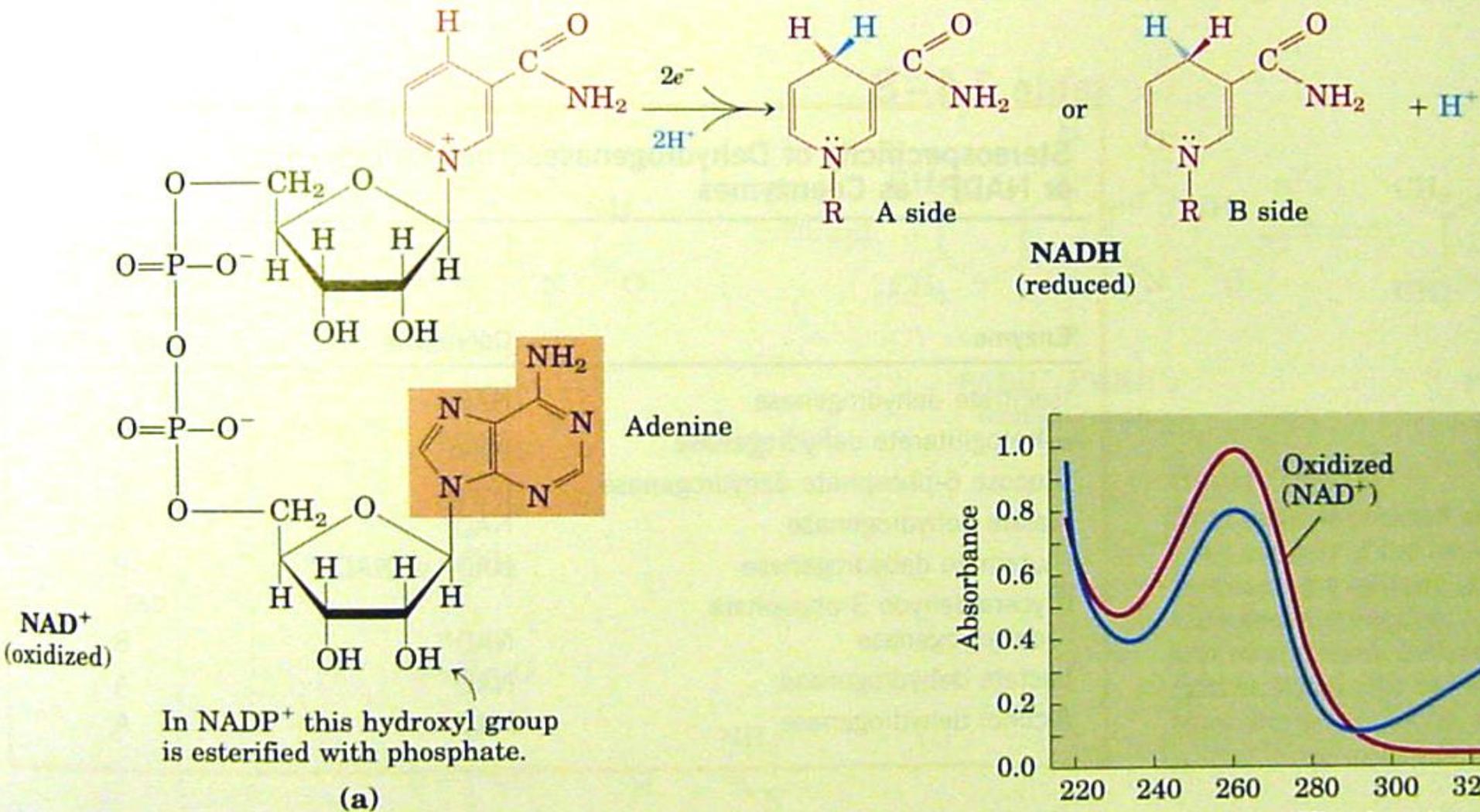
The pentose phosphate pathway has two main functions

- Generation of NADPH
 - mainly used for reductive syntheses of fatty acids, steroids, amino acids via glutamate dehydrogenase; and production of reduced glutathione in erythrocytes and other cells.
 - active in liver, adipose tissue, adrenal cortex, thyroid, erythrocytes, testes, and lactating mammary gland
 - not active in non-lactating mammary gland and has low activity in skeletal muscle.
- Production of ribose residues for nucleotide and nucleic acid synthesis.

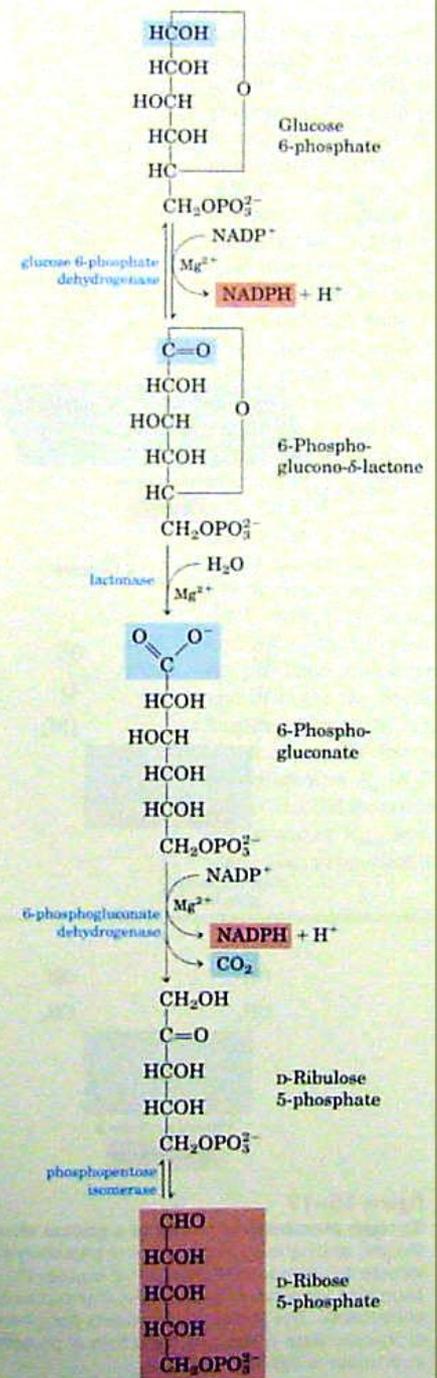
Reactions of the pentose phosphate pathway occur in the cytosol in two phases

- Oxidative non-reversible phase
- Non-oxidative reversible phase
- NADP^+ , not NAD^+ , is used as hydrogen acceptor
- 1st phase
 - Glucose 6-phosphate undergoes dehydrogenation and decarboxylation to give a pentose, ribulose 5-phosphate, which is converted to its isomer, D-ribose 5-phosphate.
 - Overall equation of 1st phase:

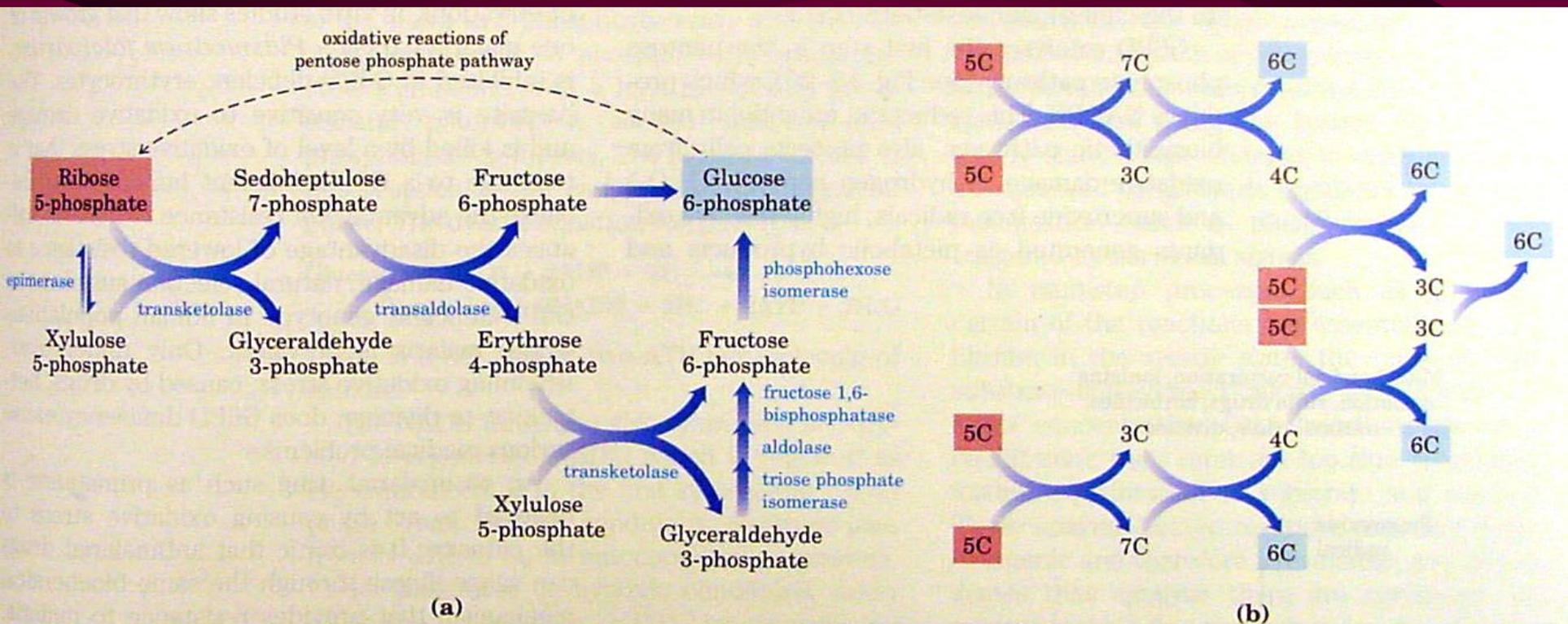




- Oxidative reactions of the pentose phosphate pathway. The end products are D-ribose 5-phosphate and NADPH

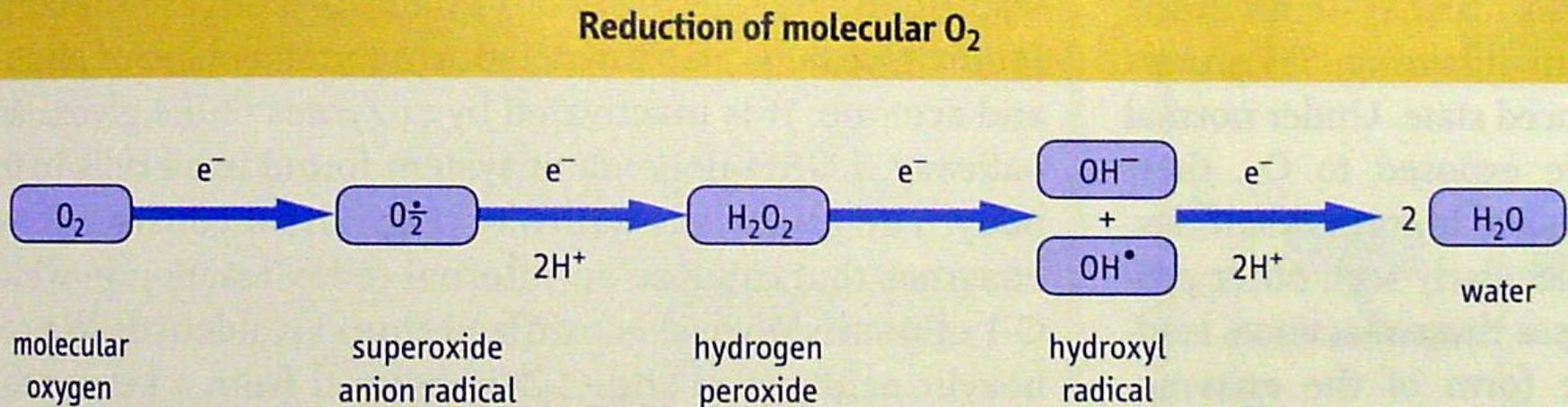


- In tissues requiring primarily NADPH rather than ribose 5-phosphate, these pentose phosphates can be recycled into glucose 6-phosphate. Overall, 6 five-carbon sugars are converted to 5 six-carbon sugars



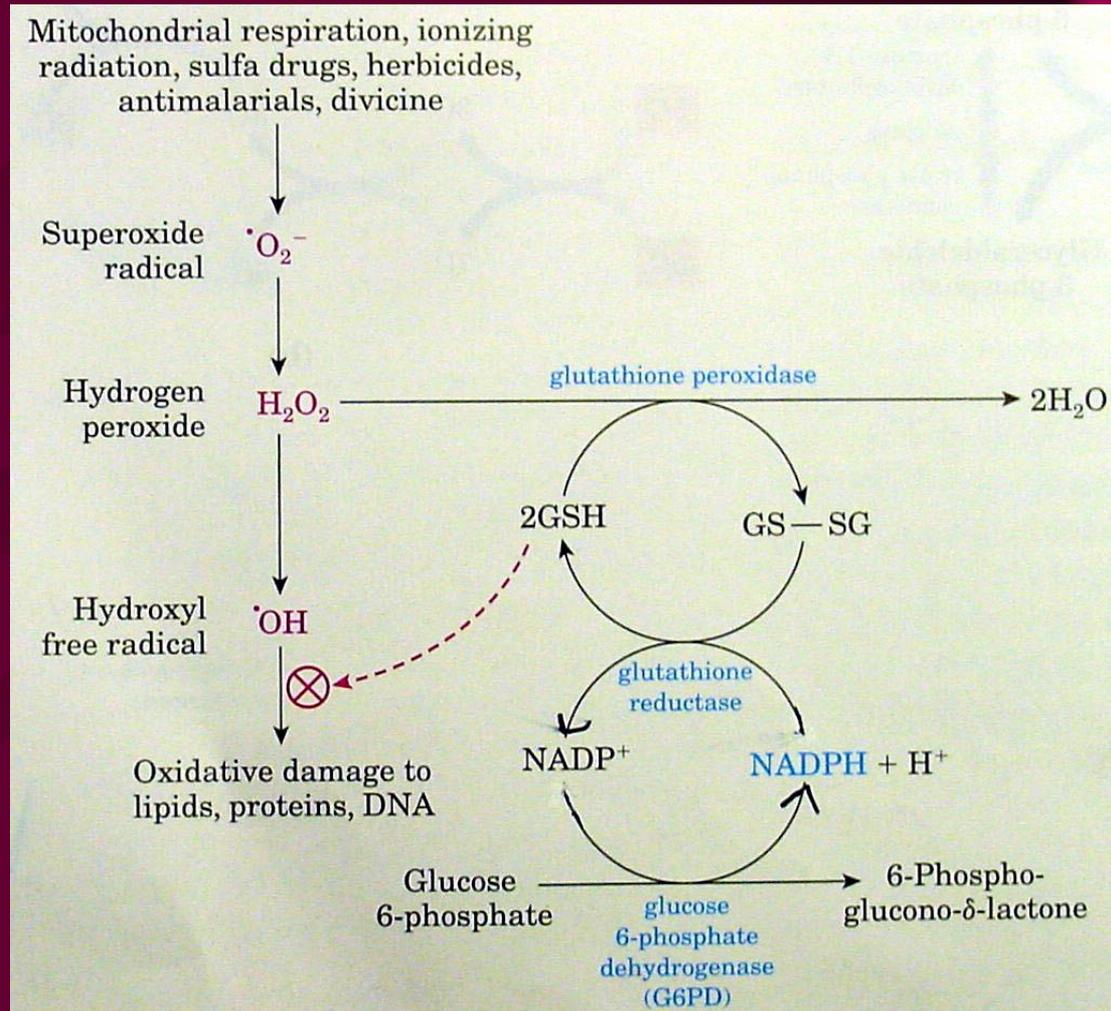
Pentose phosphate pathway protects cells against reactive oxygen species (ROS)

- Molecular oxygen and partially reduced, reactive forms of oxygen. Reduction of molecular O_2 in a series of one-electron steps yields superoxide, hydrogen peroxide, hydroxyl radical, and water. The intermediate, activated forms of oxygen are known as reactive oxygen species (ROS)



Role of NADPH and glutathione in protecting cells against ROS

- Role of NADPH and glutathione in protecting cells against highly reactive oxygen derivatives. Reduced glutathione (GSH) protects the cell by destroying hydrogen peroxide and hydroxyl free radicals. Regeneration of GSH from its oxidized form (GS-SG) requires the NADPH produced in the glucose 6-phosphate dehydrogenase reaction.



Glucose-6-phosphate dehydrogenase deficiency causes hemolytic anemia

- Mutations present in some populations causes a deficiency in glucose 6-phosphate dehydrogenase, with consequent impairment of NADPH production.
- Detoxification of H_2O_2 is inhibited, and cellular damage results - lipid peroxidation leads to erythrocyte membrane breakdown and hemolytic anemia.
- Most G6PD-deficient individuals are asymptomatic - only in combination with certain environmental factors (sulfa antibiotics, herbicides, antimalarials, *divicine) do clinical manifestations occur.

*toxic ingredient of fava beans

Table 9-1. Drugs and Chemicals That Have Been Shown to Cause Clinically Significant Hemolytic Anemia in G6PD Deficiency

Acetanilid	Pentaquine
Methylene blue	Sulfanilamide
Nalidixic acid (NegGram)	Sulfacetamide
Naphthalene	Sulfapyridine
Niridazole (Ambilhar)	Sulfamethoxazole (Gantanol)
Nitrofurantoin (Furadantin)	Thiazolesulfone
Phenylhydrazine	Toluidine blue
Primaquine	Trinitrotoluene (TNT)
Pamaquine	

Regulation of pentose phosphate pathway

- The entry of glucose 6-phosphate into the pentose phosphate pathway is controlled by the cellular concentration of NADPH
- NADPH is a strong inhibitor of glucose 6-phosphate dehydrogenase
- As NADPH is used in various pathways, inhibition is relieved, and the enzyme is accelerated to produce more NADPH
- The synthesis of glucose 6-phosphate dehydrogenase is induced by the increased insulin/glucagon ratio after a high carbohydrate meal.