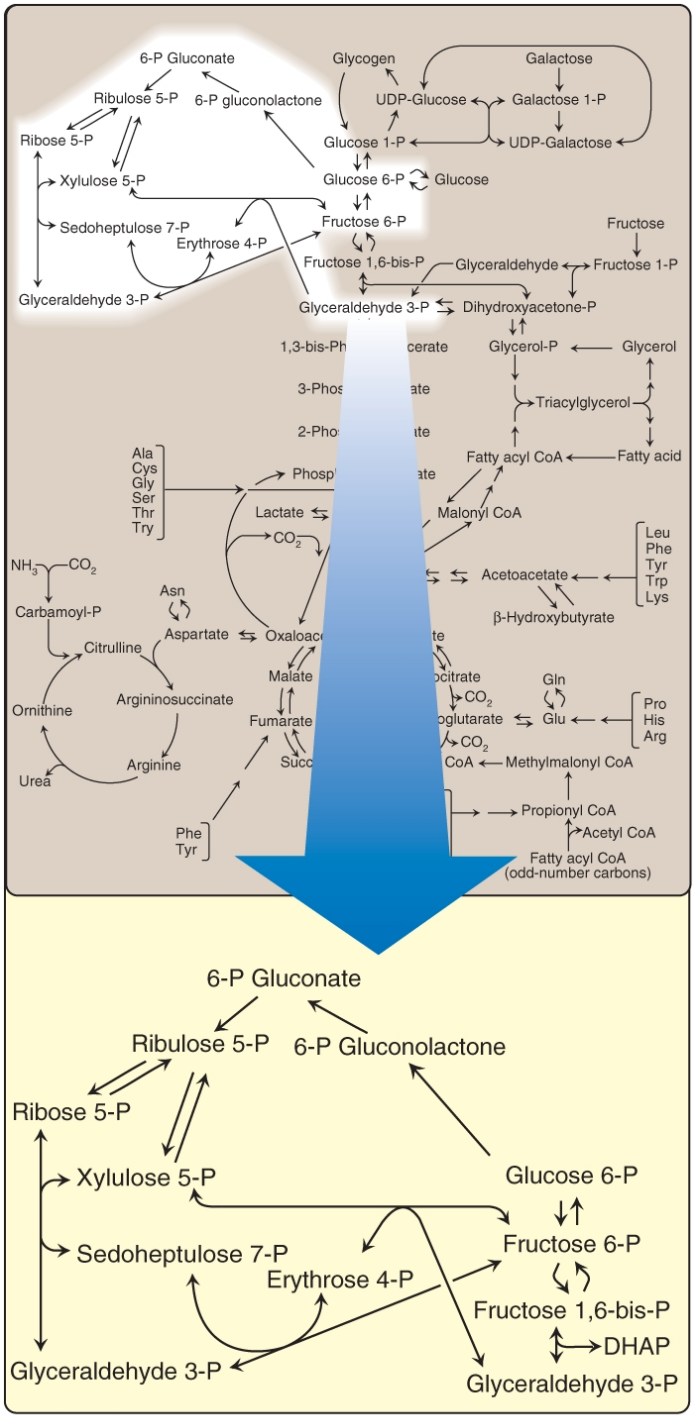
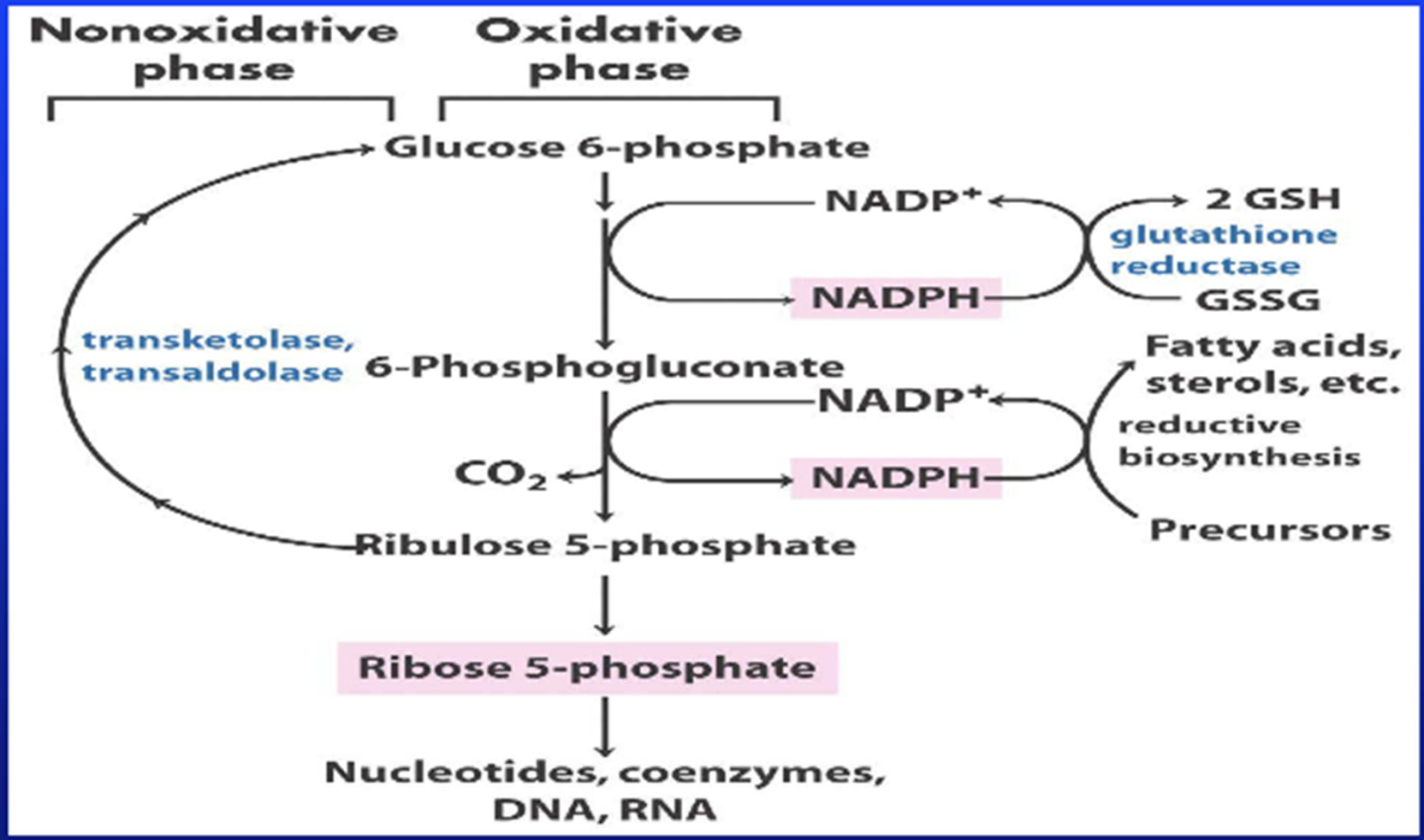
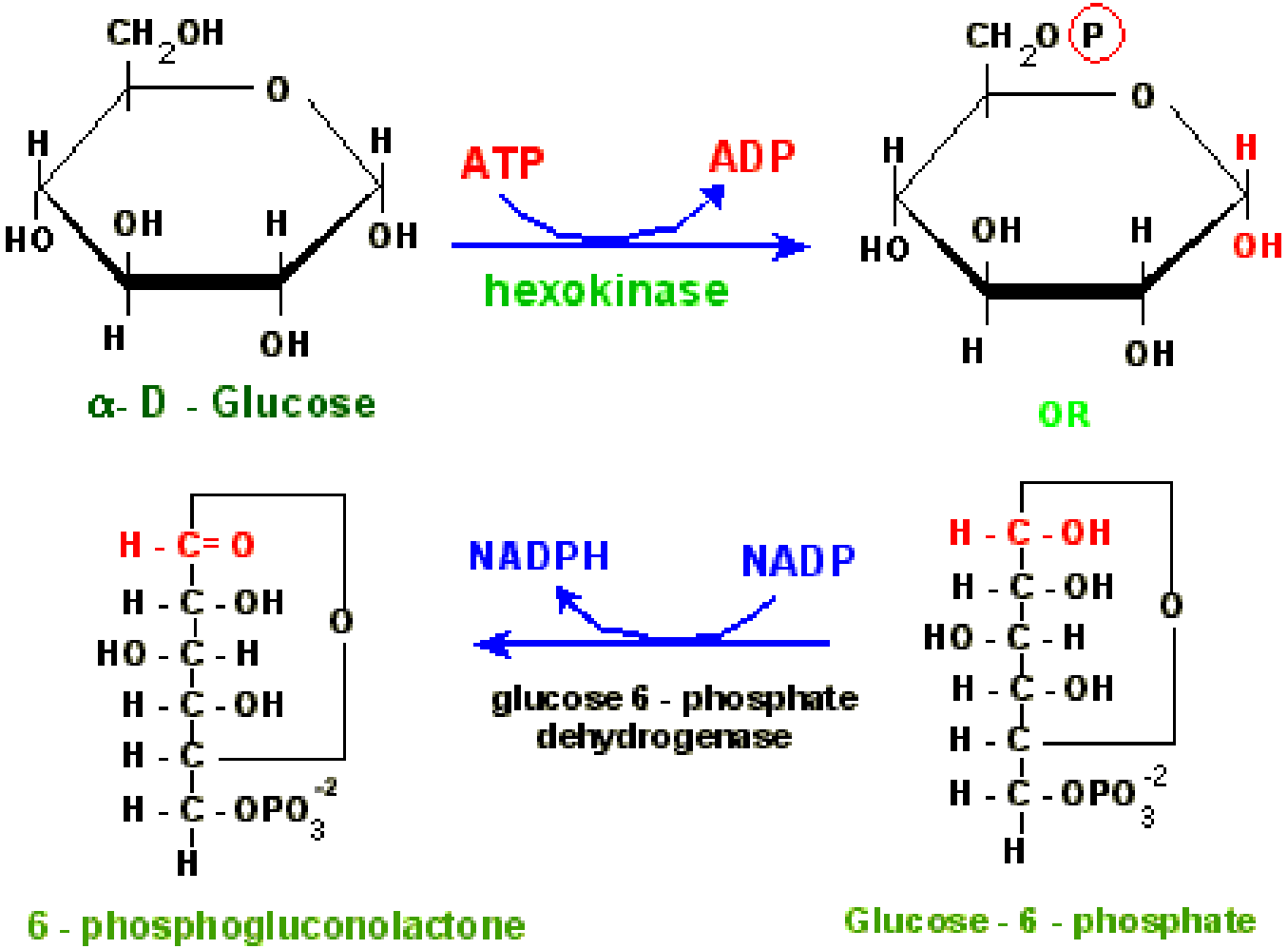


HMP also known as the Pentose phosphate pathway. Consists of two irreversible oxidative rxs followed by a series of reversible sugar phosphate interconversions. No ATP consumed or produced. Carbon 1 is released as CO_2 and two NADPH produced. Several directions. Occurs in the cytosol. NADPH necessary for synthesis of fatty acid and steroids. In liver, mammary glands and adrenal cortex. Produces ribose phosphate required for biosynthesis of nucleotides. An alternative pathway for the oxidation of glucose, the pentose phosphate pathway is not an important source of ATP in cells but provides a source for NADPH (required for many biosynthetic reductions) and ribose (for nucleic acid synthesis). The pathway begins from glucose-6-P with its oxidation to 6-phosphogluconate and the production of NADPH.

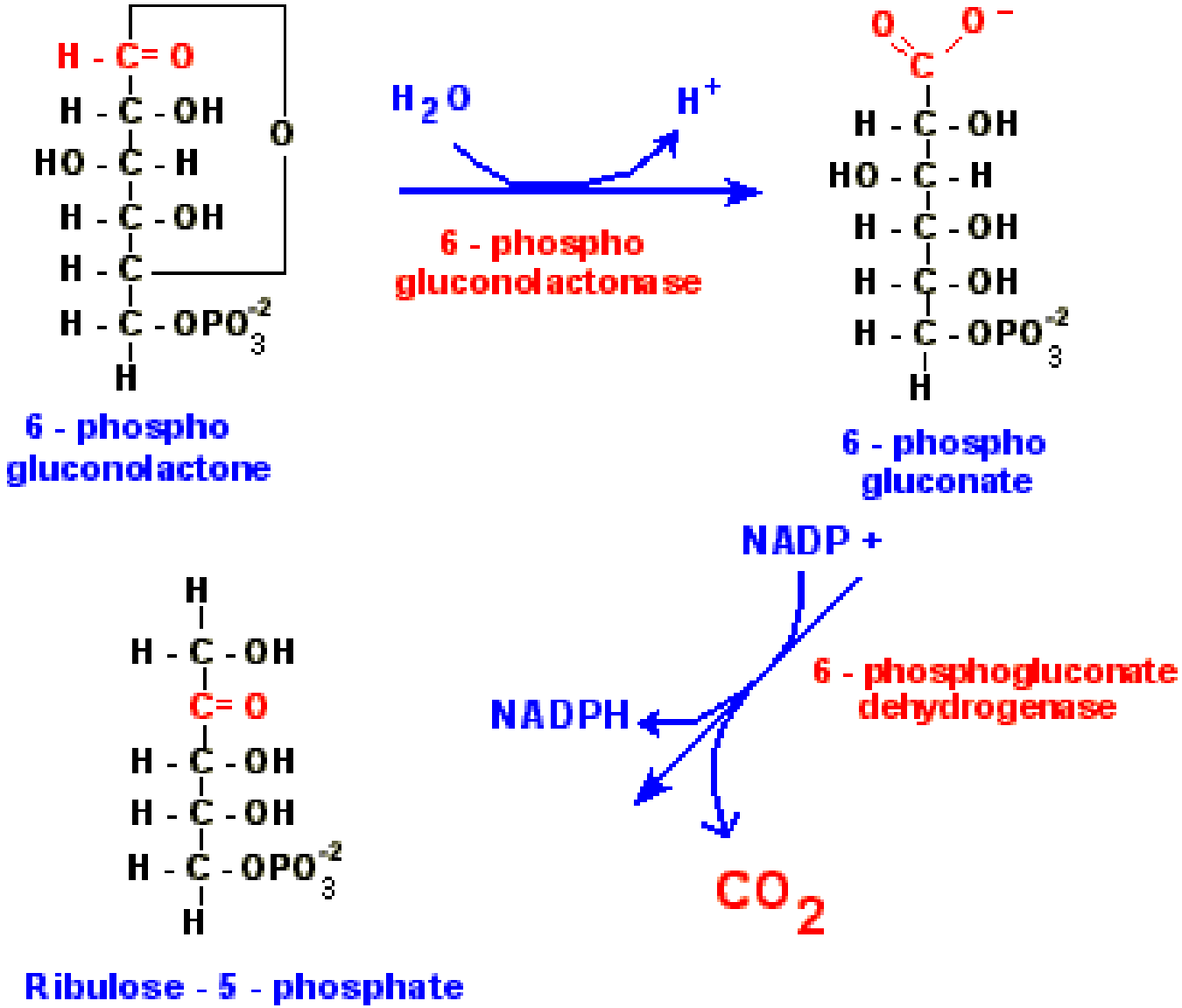
General Scheme of the Pentose Phosphate Pathway



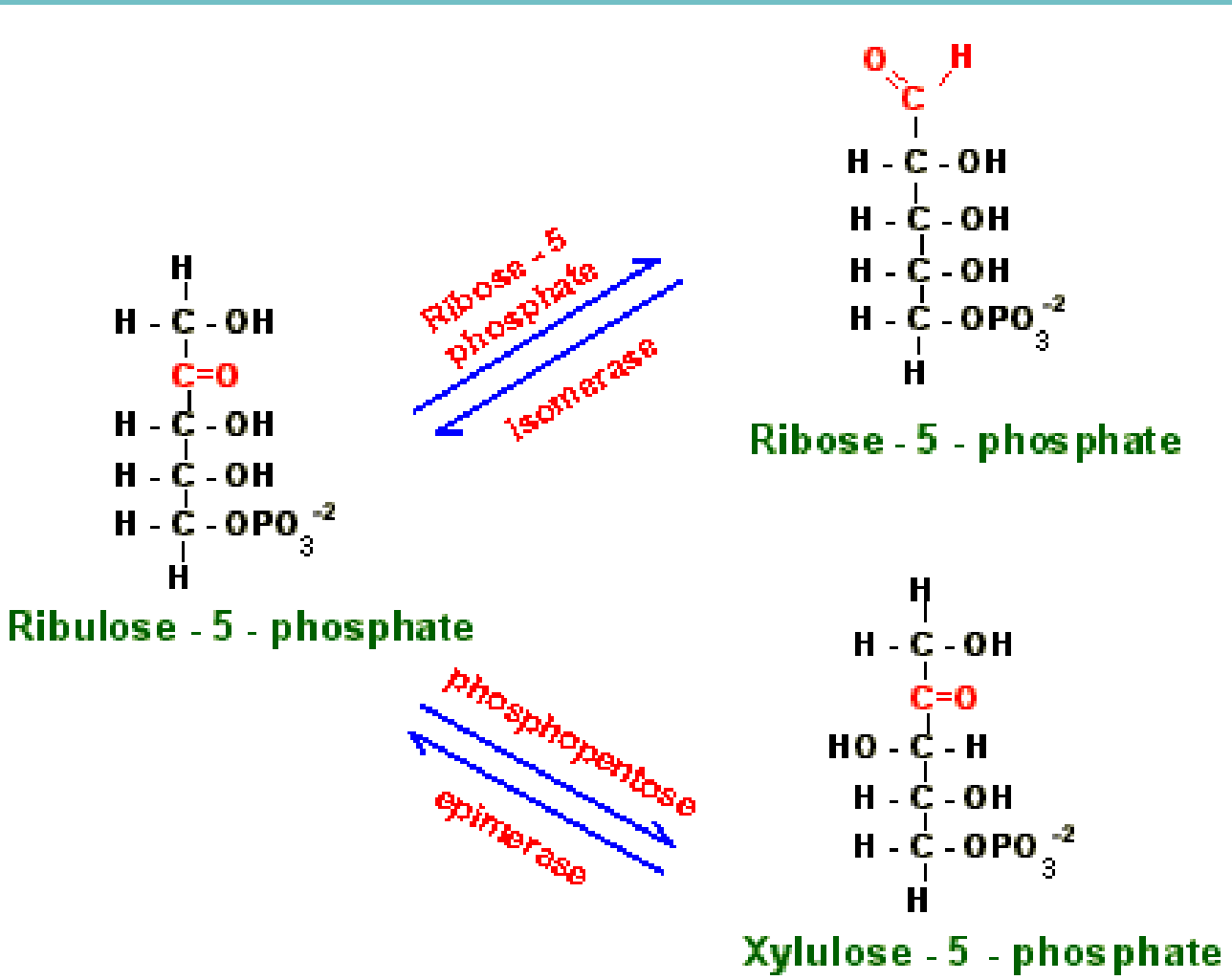
First oxidative reaction from G6P by G6PD (irreversible rx) specific for $NADP^+$ as coenzyme. NADPH is a competitive inhibitor of the enzyme. Therefore, low NADPH/NADP ratios induces enzyme act.

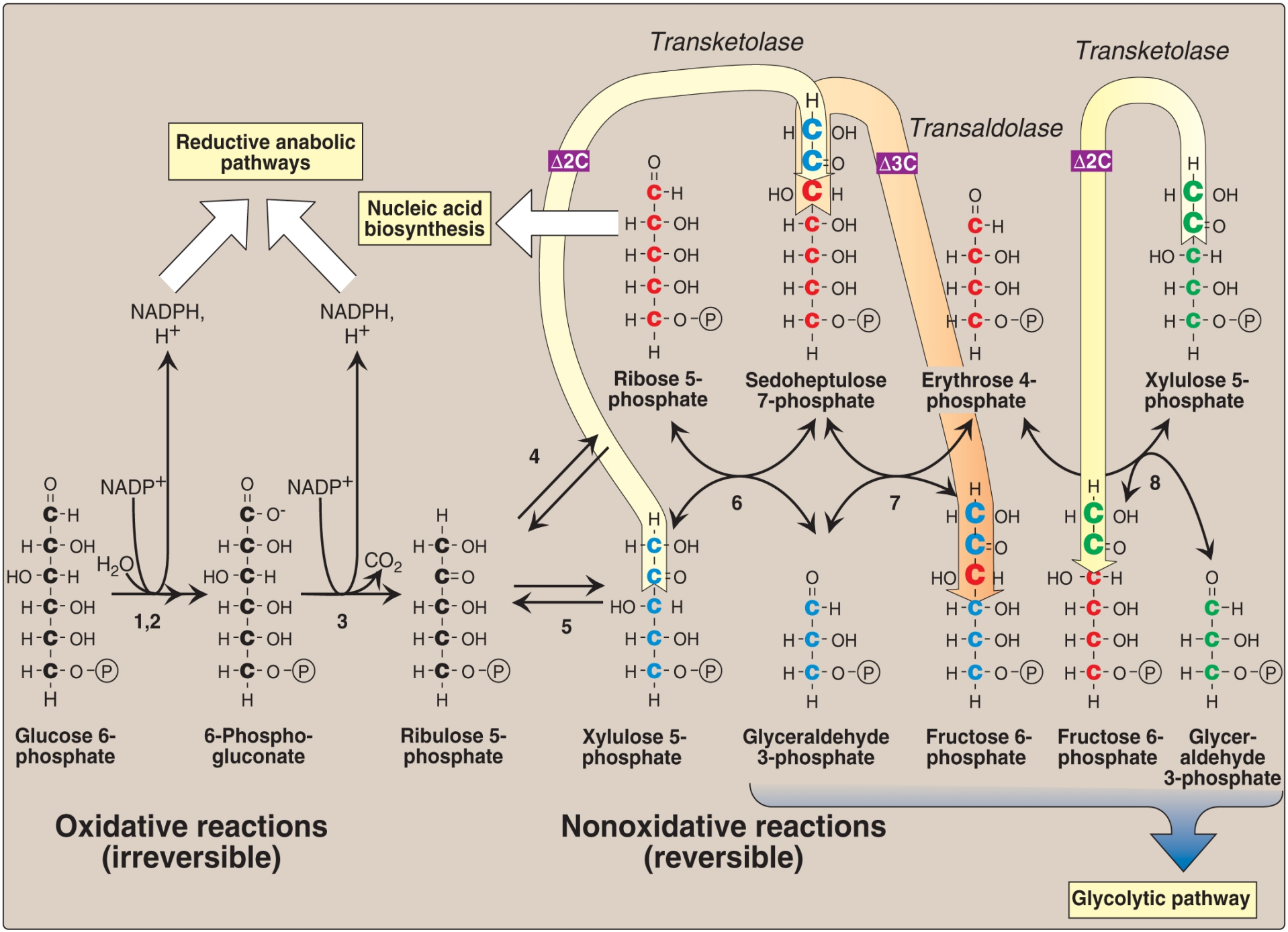


Second and third rx from the oxidative section reactions of the HMP pathway which produces the pentose sugar-phosphate and second NADPH

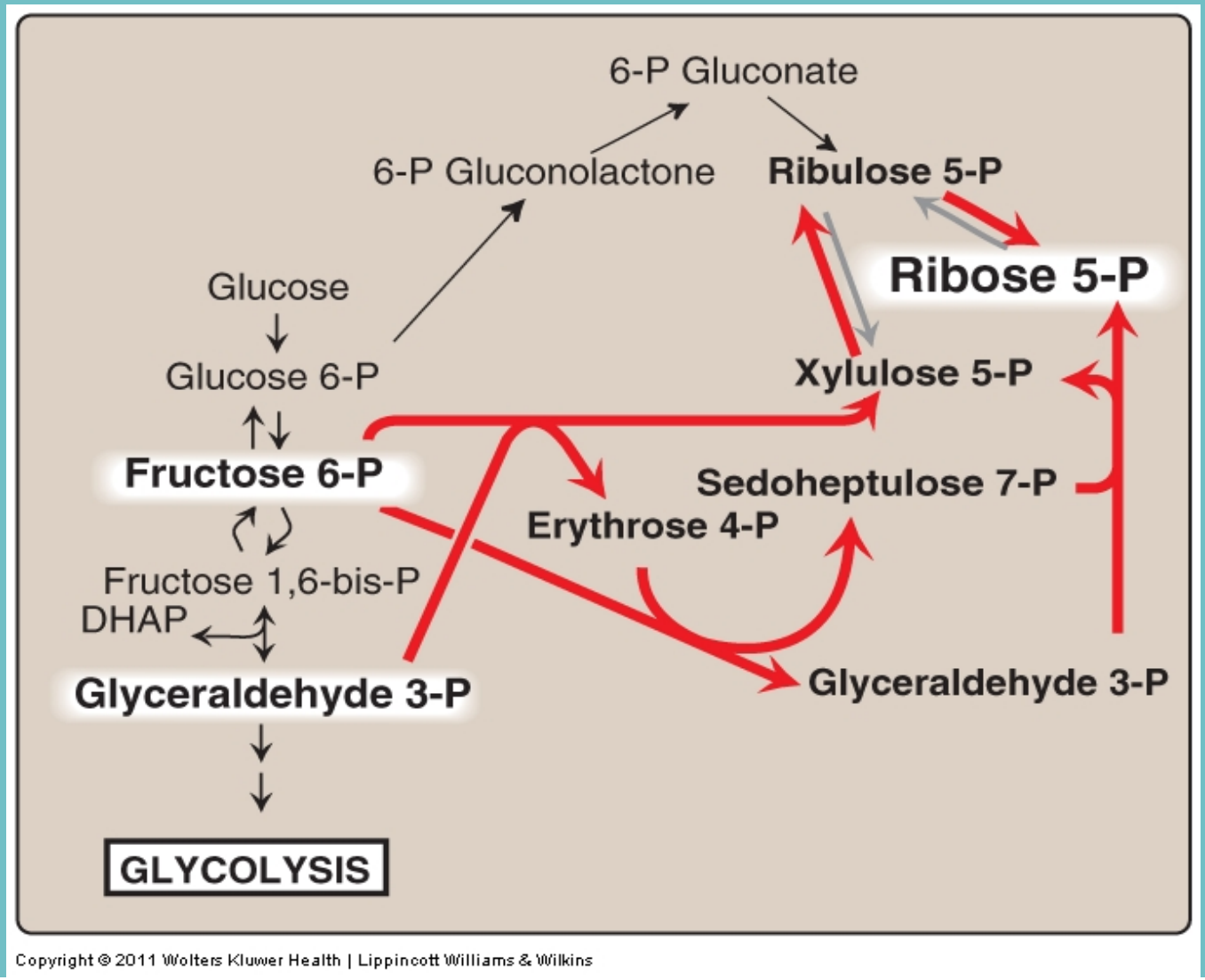


Non oxidative reactions. The pathway continues with the conversion of ribulose-5-P to ribose-5-P and xylulose-5 P. These are reversible rxs catalyzed by an isomerase and an epimerase. A series of condensation and rearrangement reactions ensues with the ultimate regeneration of fructose- 6-P and finally glucose.

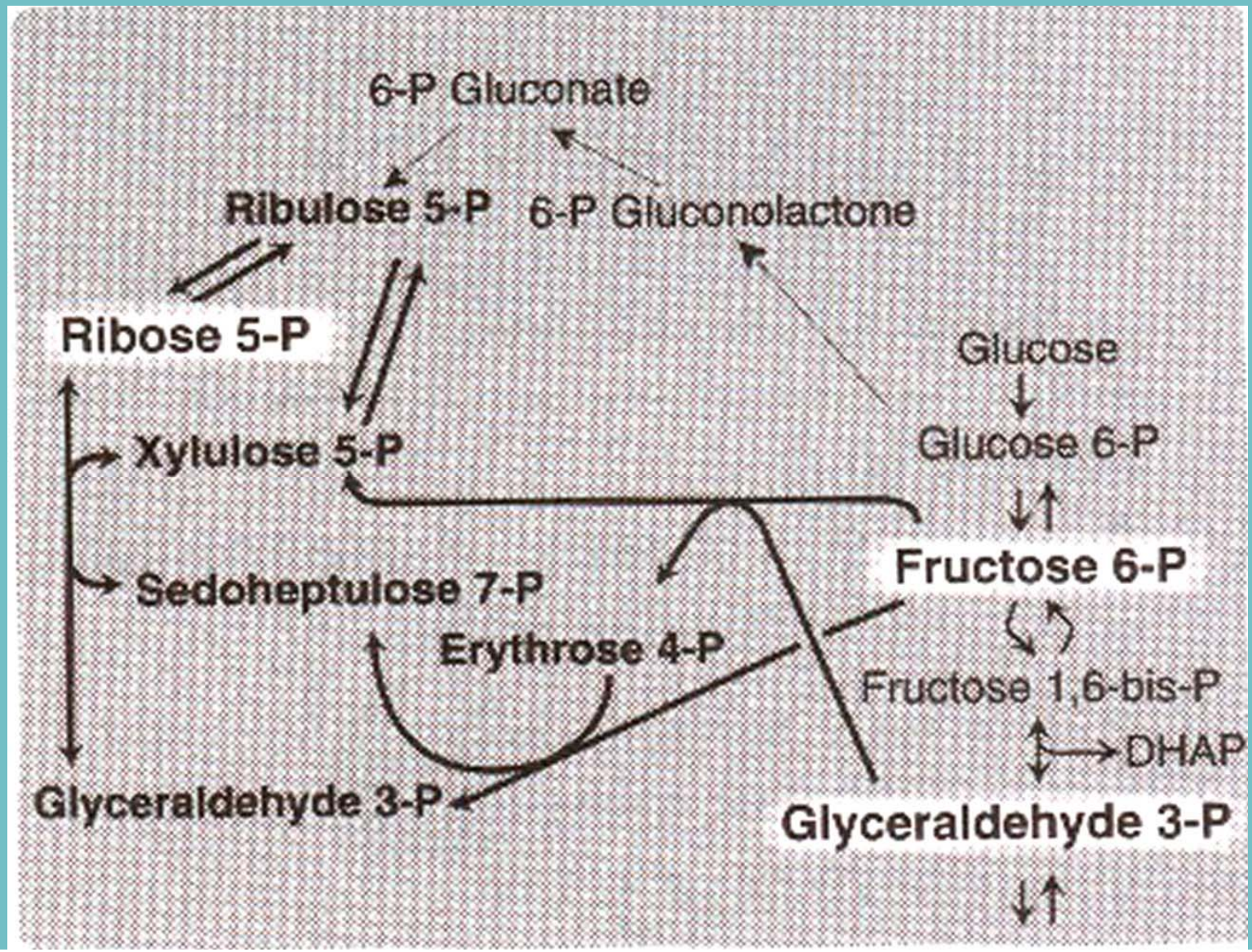




A summary of the pentose phosphate pathway carbon flow. These reactions permit Ribulose 5-P to be converted to ribose 5-P or to intermediates of 3-4-5 and 7 carbon sugars.



Ribose 5-P can be formed from non-oxidative rxs when nucleic acid synthesis is greater than NADPH needs (Fructose 6-P & G3-P).



The Pentose Phosphate Pathway Provides:

NADPH

Required for many biosynthetic reactions (reductions)

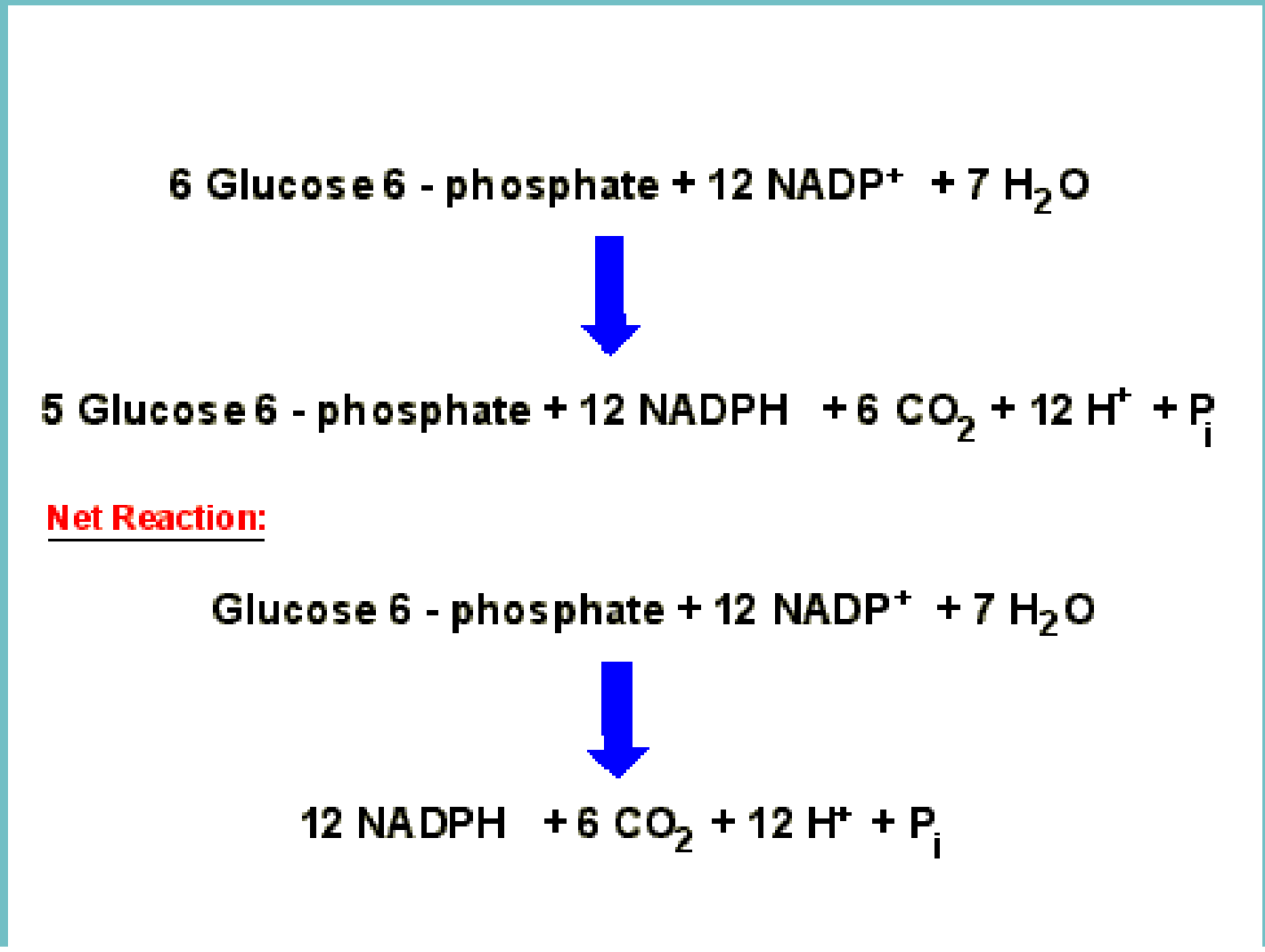
Necessary for maintenance of reduced glutathione in red blood cells.

Various tissues utilize this pathway to different degrees depending on their requirements for NADPH and Ribose 5-phosphate

Ribose 5-phosphate

Necessary for nucleotide and cofactor biosynthesis

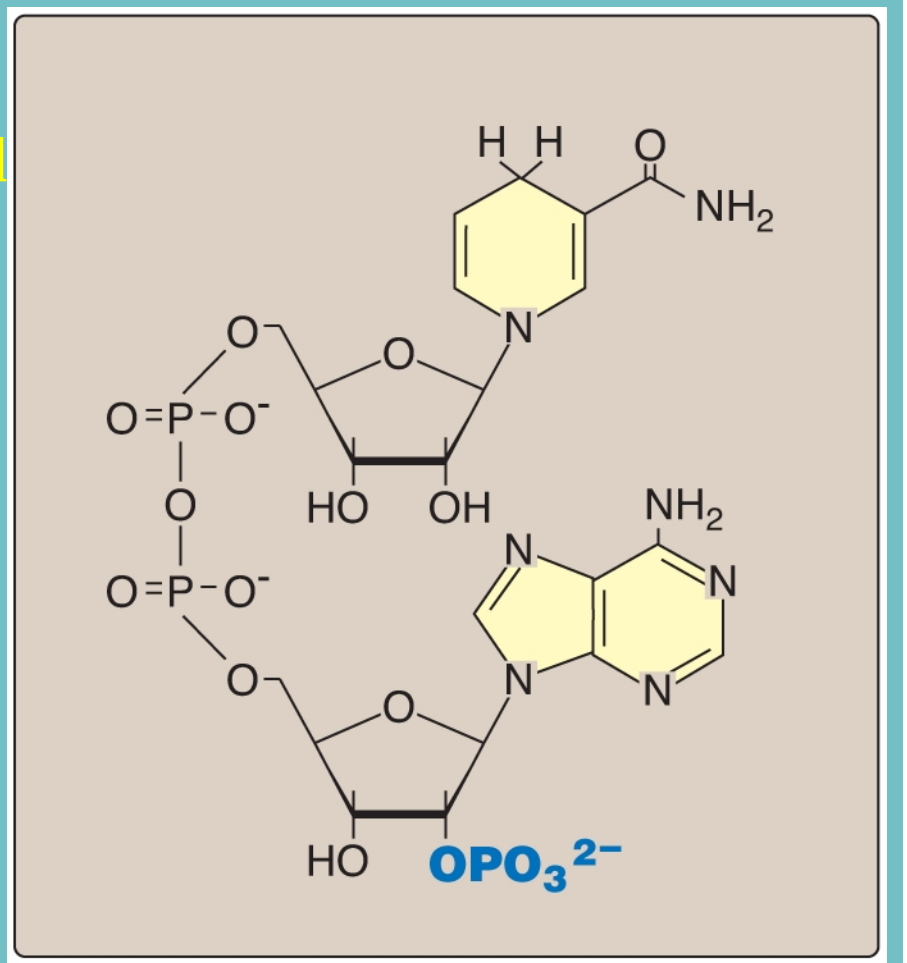
The pathway book keeping can be best visualized by considering the metabolism of six glucose molecules at a time. Looked at this way, the complete oxidation of a molecule of glucose to CO2 would produce 12 NADPH.



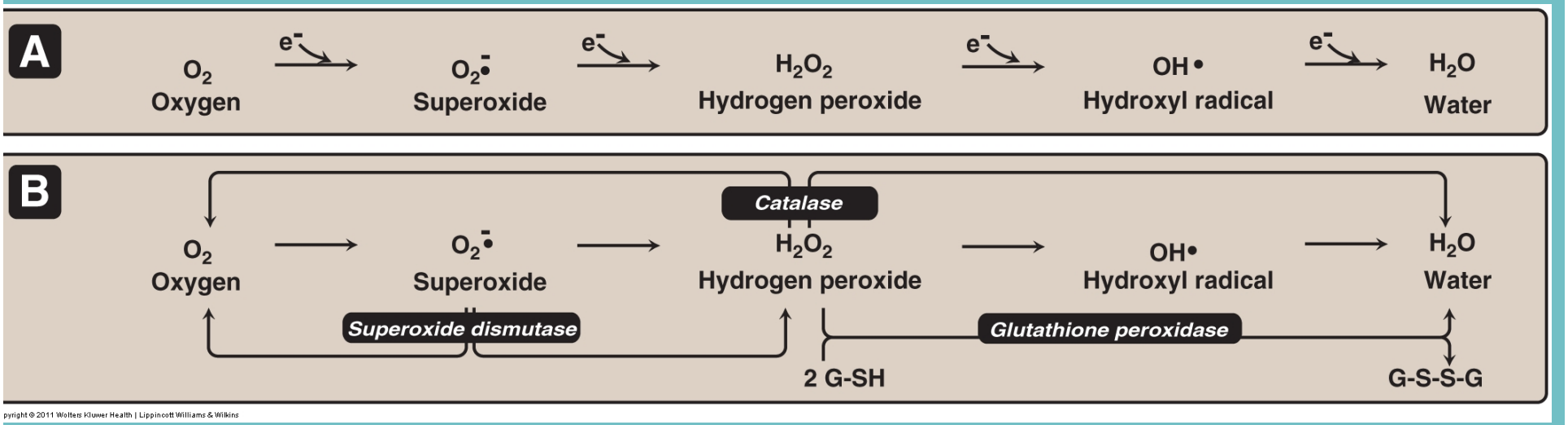
Uses of NADPH. Same as NAD but with a phosphoryl group on one of the ribose units. NADPH is a high energy molecule similar to NADH. Electrons are used in reductive biosynthesis rather than for transfer to O^2 (fatty acids and steroids) . $NADP^+$/NADPH in the cytosol of hepatocytes is approximately 0.1 which favors the use of NADPH in reductive biosynthesis while NAD^+/NADH is 1,000 which favors its oxidative role. Some uses

of NADPH as high electron-potential

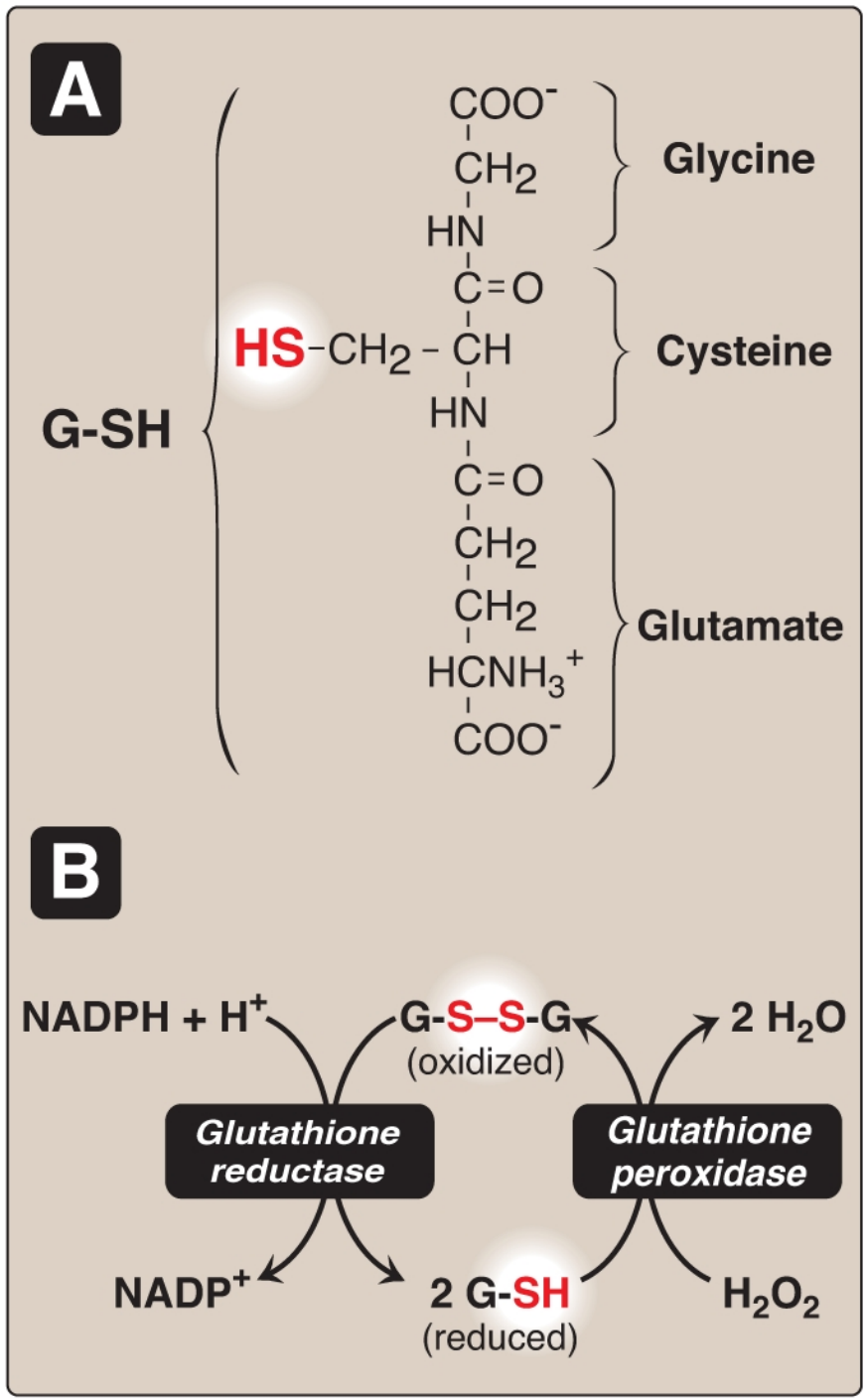
Donor follows in the next slide.



Formation of reactive intermediates from molecular oxygen. Some of these (A) superoxides, H_2O_2, hydroxyl radicals (involved in cell injury).

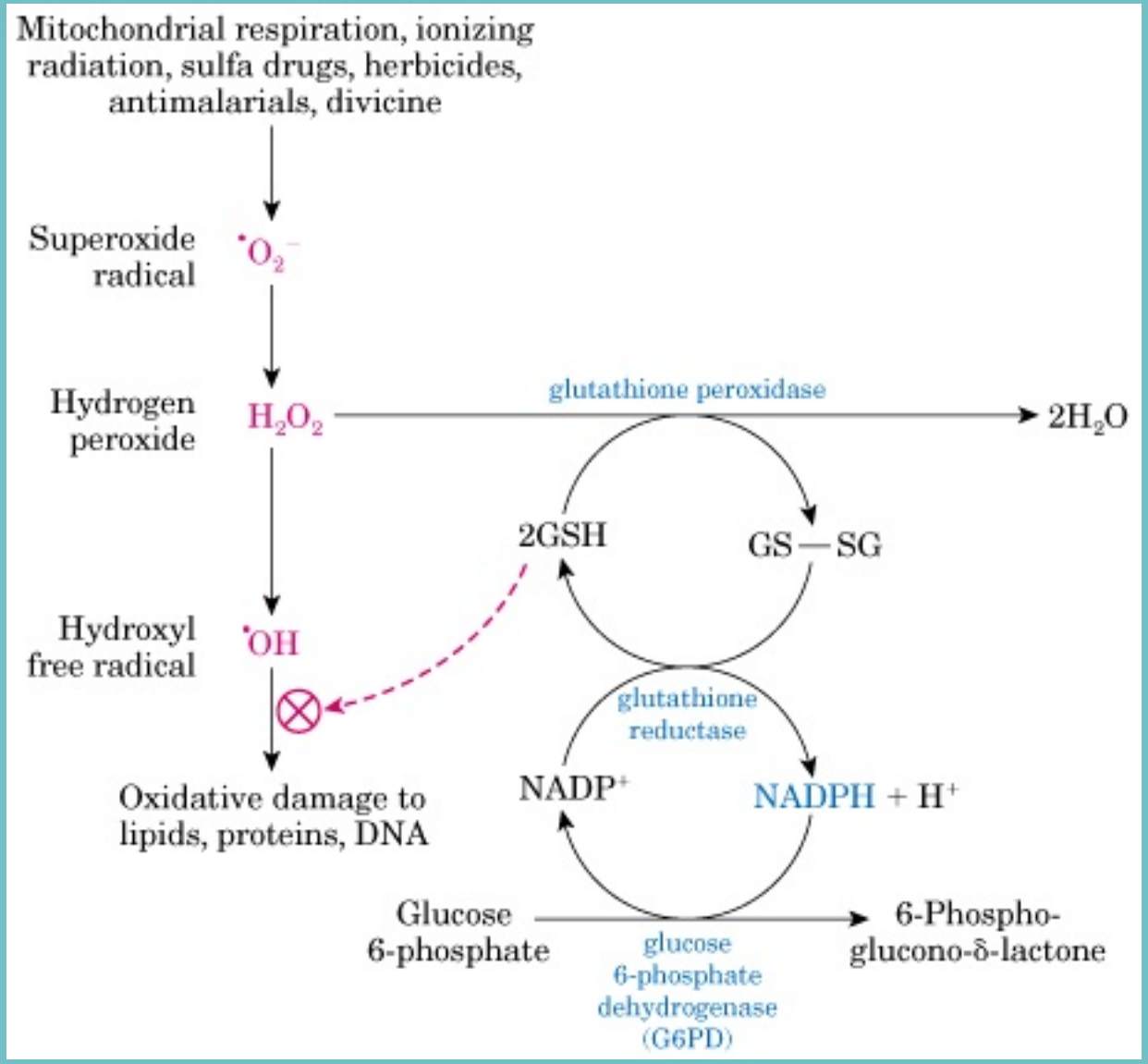


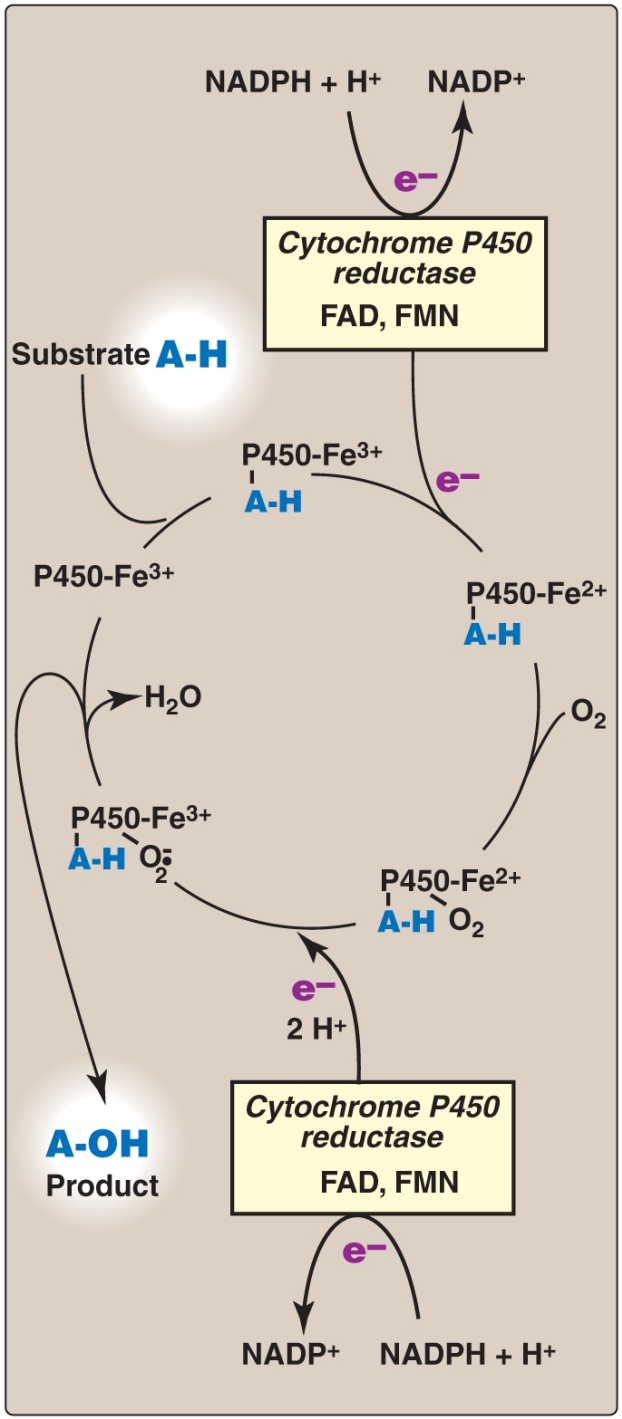
H_2O_2 is a reactive oxygen intermediate which is formed from aerobic metabolism and through reactions with xenobiotics. These can cause serious chemical damage to DNA, proteins and unsaturated lipids. Various enzymes catalyze antioxidant reactions (B). Catalases reduce H_2O_2. Reduced glutathione (a tripeptide-thiol G-SH) detoxifies H_2O_2 by glutathione peroxidase. Superoxide dismutase (SOD) is another enzyme involved in the reduction of oxygen radicals (superoxide).



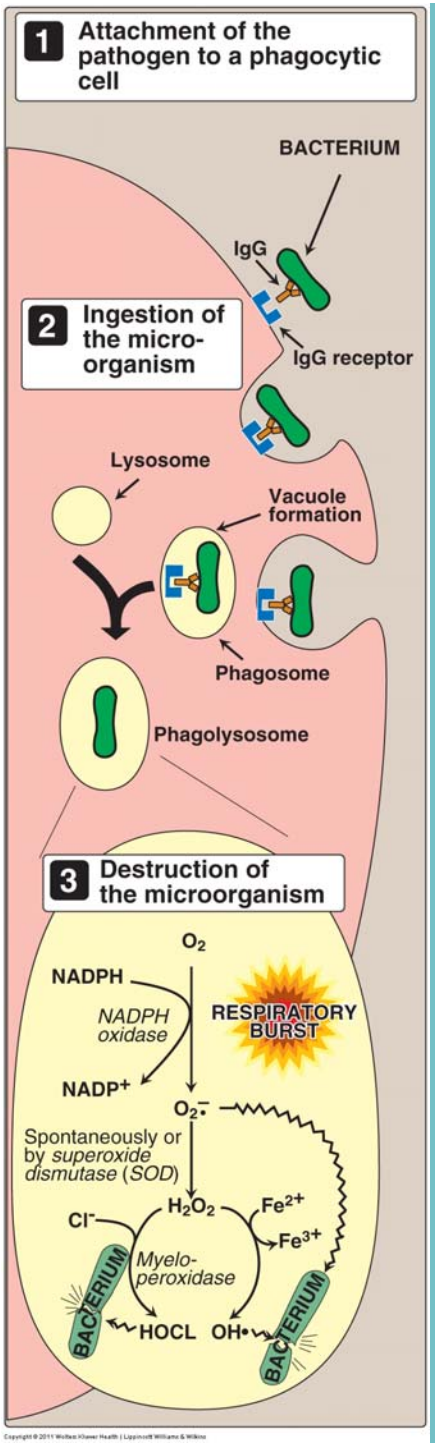
G-SH (γglutamylcysteinylglycine) tripeptide (A) that reduces H_2O_2. NADPH provides the electrons to reduce G-S-S-G through the enzyme Glutathione reductase (B). Thus indirectly it provides the e^- to reduce H_2O_2.

Antioxidant chemicals also able to reduce and detoxify intermediates are vitamin E, β carotene and ascorbate.

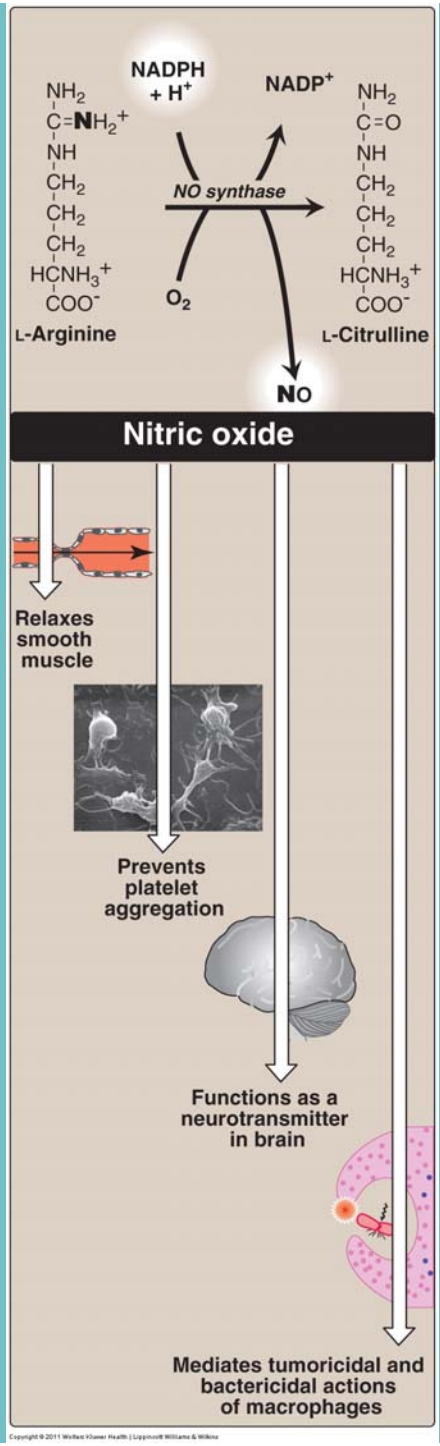

Mitochondrial respiration, ionizing radiation, sulfa drugs, herbicides, antimalarials, divicine
Superoxide radical
$^{\bullet}O_2^-$
Hydrogen peroxide
H_2O_2
glutathione peroxidase
$2H_2O$
2GSH
GS—SG
Hydroxyl free radical
$^{\bullet}OH$
glutathione reductase
NADP+
NADPH + H+
Oxidative damage to lipids, proteins, DNA
Glucose 6-phosphate
6-Phospho-glucono-δ-lactone
glucose 6-phosphate dehydrogenase (G6PD)



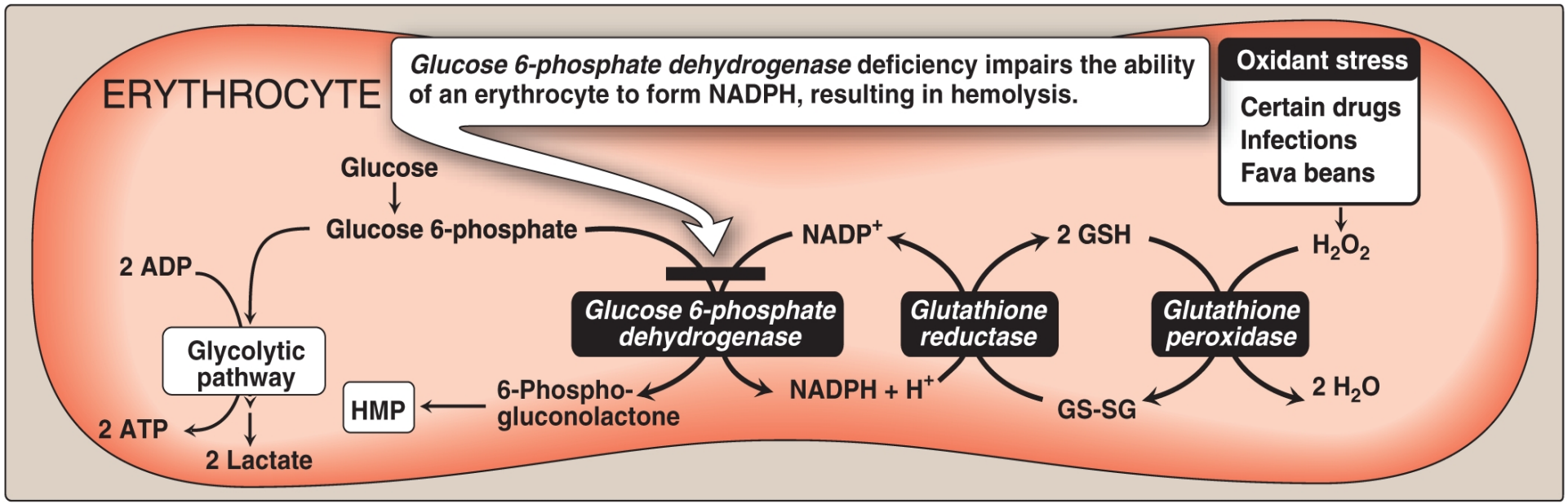
NADPH is critical for the liver in the detoxification of xenobiotic compounds by a family of enzymes known as the cytochrome P-450s CYP (monooxygenase system). What is so special about these enzymes? Why is liver so important in drug and pollutant metabolism? This is the major pathway for the hydroxylation of aromatic and aliphatic compounds such as steroids alcohols and many drugs. These enzymes also change the polarity of many compounds making them more water soluble and aiding excretion from body. The most abundant CYP3A4 in liver metabolizes more than 60% of drugs. Also important is the CYP2D6.



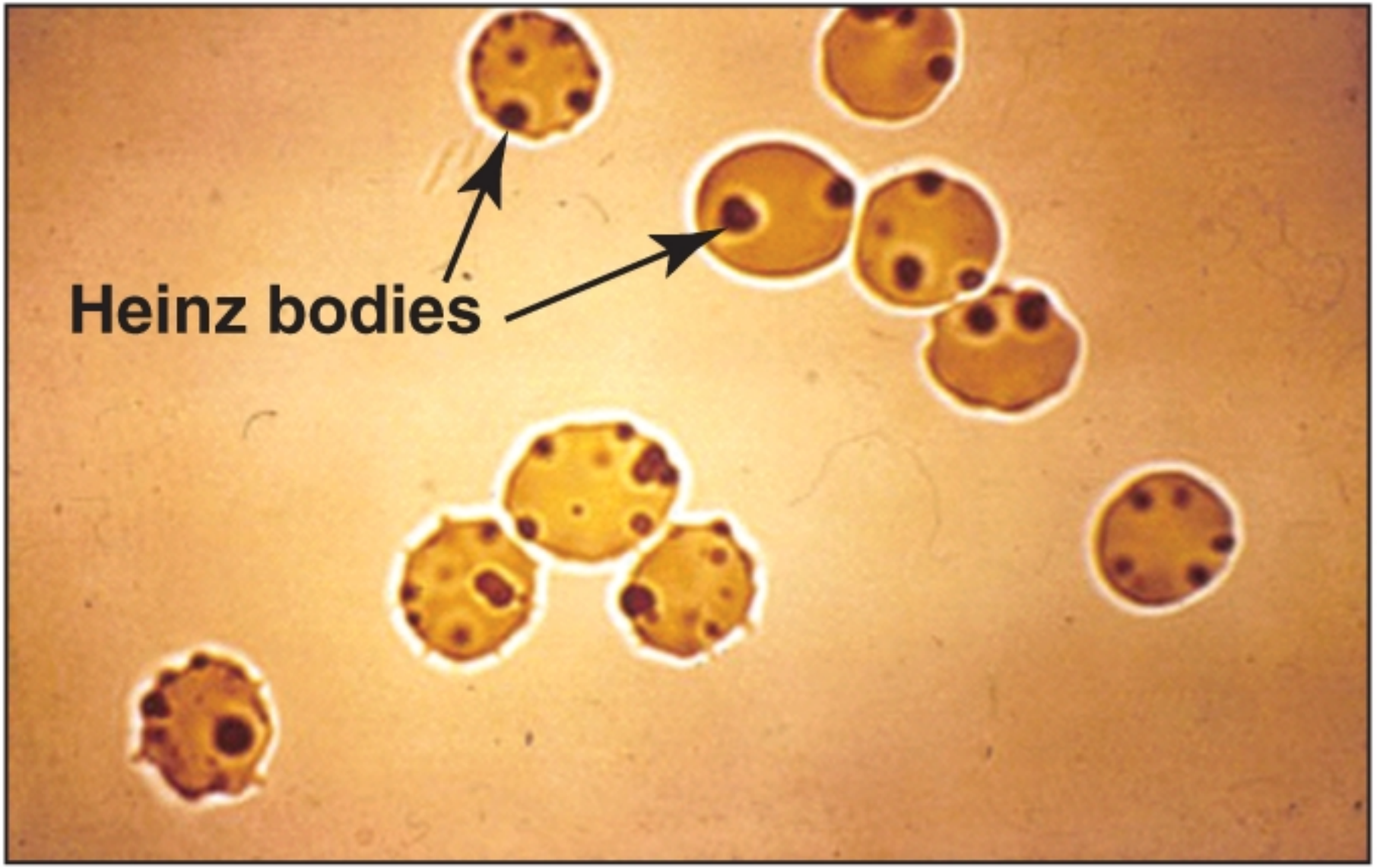
The use of NADPH in dealing with infections. Neutrophiles and macrophages engulf microorganisms and foreign particles by means of phagocytosis. These immune system cells are armed with oxygen dependent (OD) and oxygen independent (OI) mechanisms to kill bacteria. The OD mechanism include the myeloperoxidase (MOP) system and the generation of oxygen free radicals (phagolysosome). NADPH oxidase converts surrounding oxygen to superoxide. The rapid consumption of oxygen to produce superoxide is known as respiratory burst. The superoxide is converted to H_2O_2. H_2O_2 + Cl is converted to hypochlorous acid that kills bacteria. The OI system uses pH changes in phagolysosomes and lysosomal enzymes to destroy bacteria.



NO is a mediator in a broad array of biological system. NO is the endothelium-derived relaxing factor which causes vasodilation by relaxing vascular smooth muscle. It also acts as a neurotransmitter, prevents platelet aggregation, and plays an essential role in macrophage function. Not laughing gas (N_2O). It has short life in tissue (3-10 sec) reacts with O_2 and O_2^- and converted to nitrates and nitrites including pyroxynitrite ($O=NOO^-$) RNS. 3NO synthase. (3 types, 2 constitutive Ca^{+2} dependent ER and an inducible Ca^{+2} independent macrophage, hepatocytes, monocyte and neutrophils. Inducers, TNFα, ENX, inflammatory cytokines (IL6,IL8). Functions: produced by endothelial cells, relaxes muscle, activates cytosolic guanylate cyclase to form cGMP (similar to adenyl cyclase cAMP only that it is not membrane bound). cGMP activates protein Kinase G which phosphorylates Ca^{+2} channels causing decrease entry of Ca^{+2} into smooth muscle and decreasing myosin light chain kinase reducing contraction of muscle, and lowers blood pressure. Sildenafil citrate inhibits phosphodiesterase (PDE5) that degrades cGMP in corpus Cavernosum.



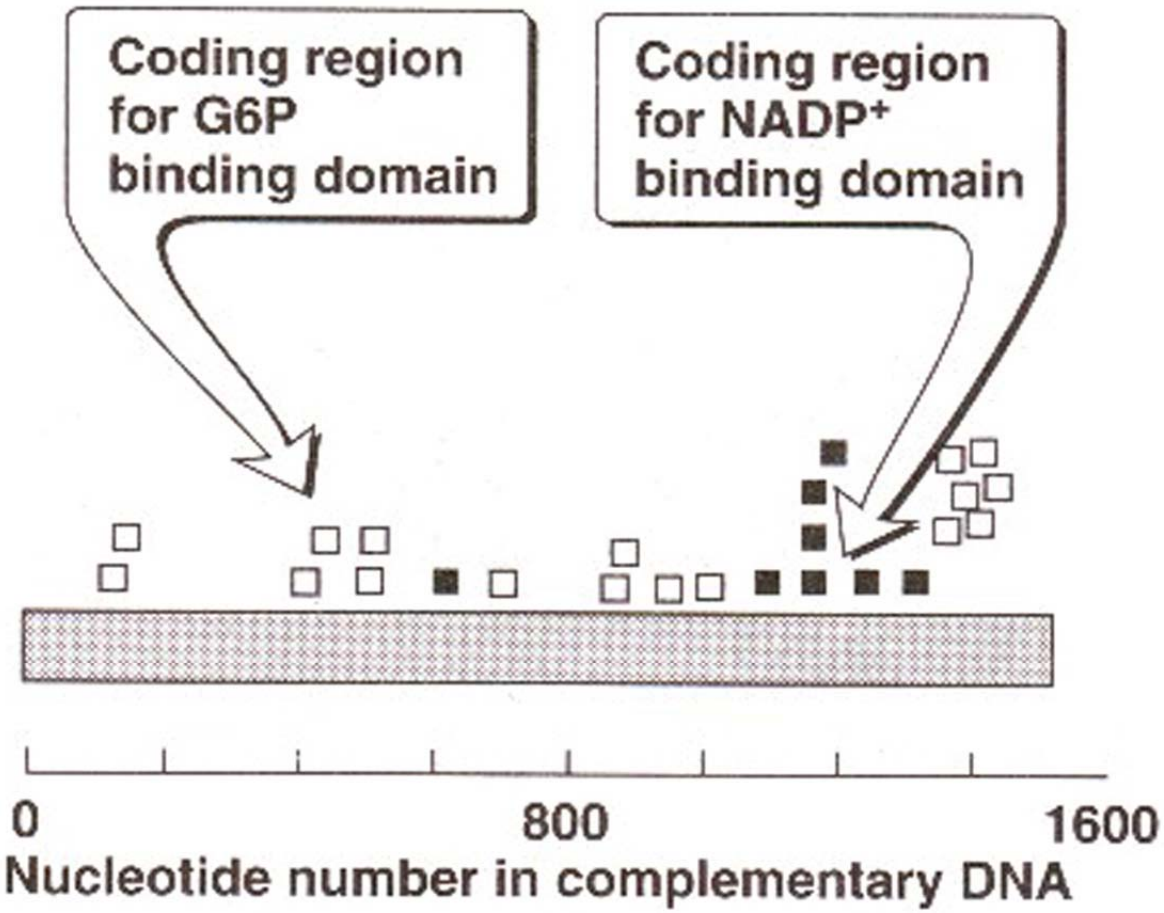
Glucose 6-P dehydrogenase deficiency (G6PD), a disease characterized by hemolytic anemia caused by the inability to detoxify oxidizing agents. It is the most common disease producing enzyme in humans. Affects more than 200 million people worldwide. Caused by over 400 mutations in the gene. RBC do not have alternative sources of producing NADPH cannot renew supply of enzymes, and cannot keep G-SH reduced. People with a mutation in this gene can develop clinical synthoms if treated with an oxidant drug, ingest fava beans or contract severe infections.



G6PD deficiency

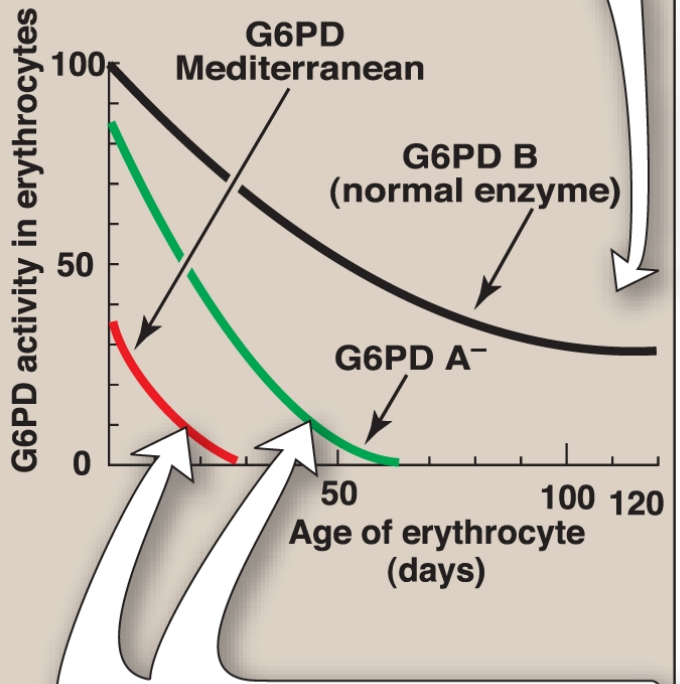
Class	Clinical symptoms	Residual enzyme activity
I	Very severe (Chronic hemolytic anemia)	<10%
II	Severe (Episodic hemolytic anemia)	<10%
III	Moderate	10–60%
IV	None	>60%

Oxidant drug commonly used can be remembered AAA= Antibiotic (sulfamethoxazole), Antimalarials (primaquine, debrisoquine), Antipyretics (acetanilid) Favism (mediterranean variant) Infection result in free radical formation that can diffuse to RBC causing oxidative damage. G6PD Mediterranean is prototype of (class I) more severe. G6PD A- is prototype of moderete class III



Mutations causing Nonspherocytic hemolytic anemia are clustered near the carboxyl end of the enzyme. Milder forms of the disease tend to be located at the amino end of the enzyme.

Although the activity of the normal enzyme declines as red cells age, even the oldest cells have a sufficient level of activity to provide protection against oxidative damage and hemolysis.



By contrast, very few *G6PD Mediterranean* red cells have sufficient enzyme activity to prevent oxidative damage, whereas a substantial fraction of young *G6PD A⁻* red cells are able to provide protection.