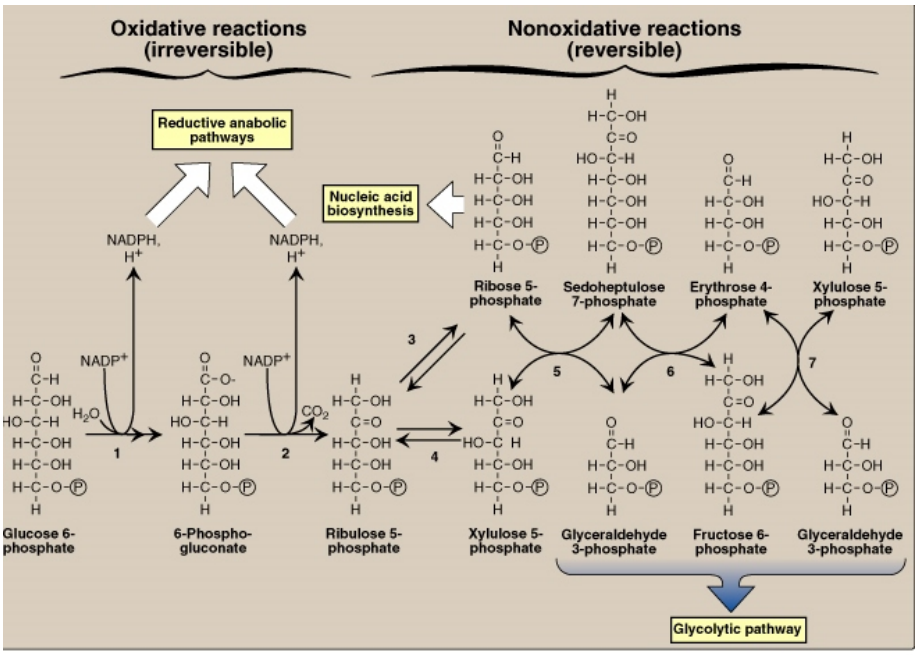
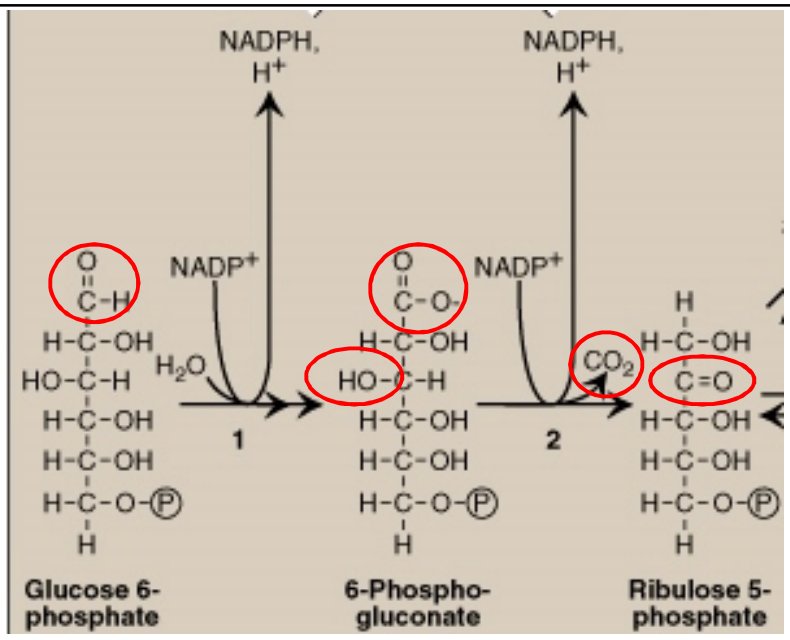
Pentose Phosphate Pathway (PPP)
or
Hexose Monophosphate Shunt

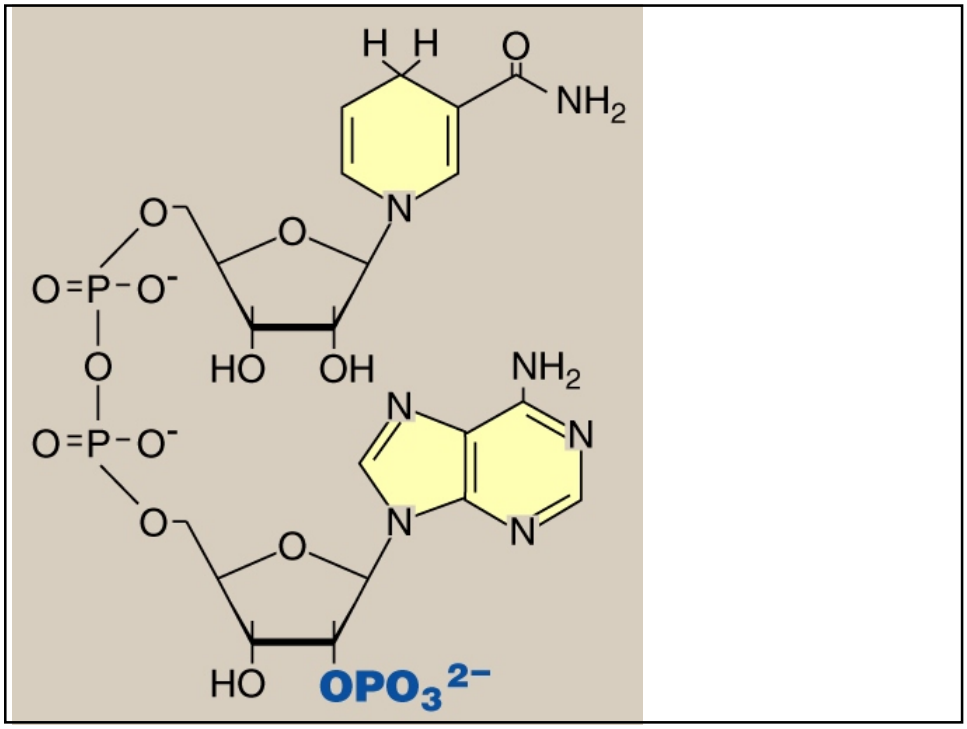
Functions of the PPP

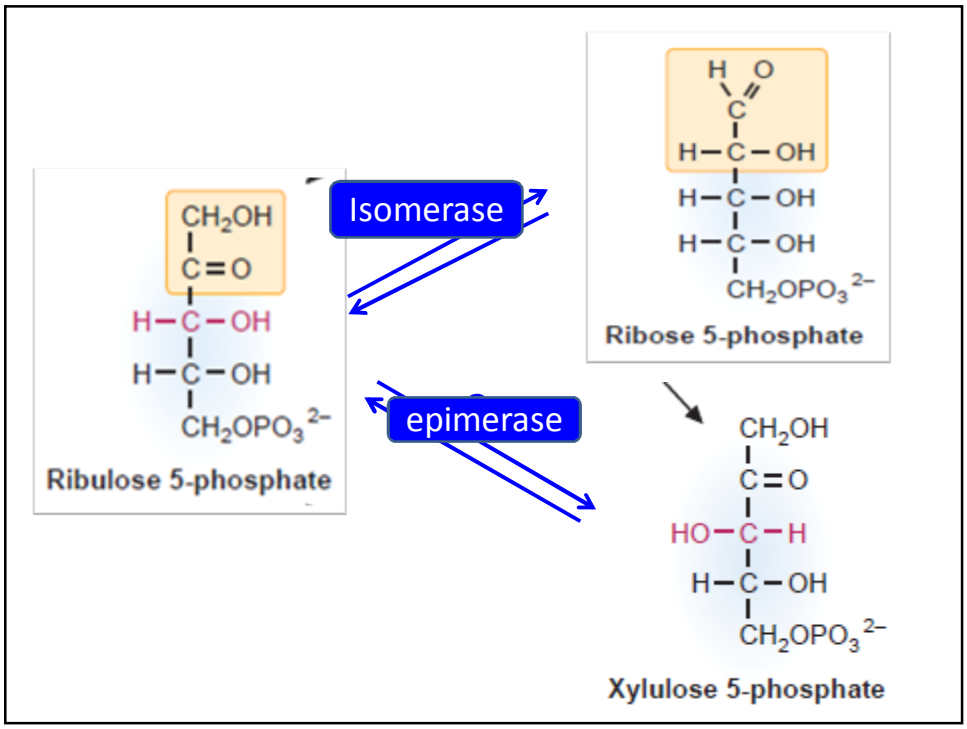
- Production of NADPH
  - NADPH dependent biosynthesis of fatty acids
    - Liver, lactating mammary glands, adipose tissue
  - NADPH dependent biosynthesis of steroid hormones
    - Testes, ovaries, placenta, and adrenal cortex
  - Maintenance of Glutathione (GSH) in the reuced form in the RBCs
- Metabolism of five-carbon sugars (Pentoses)
  - Ribose 5-phosphate (nucleotide biosynthesis)
  - Metabolism of pentoses





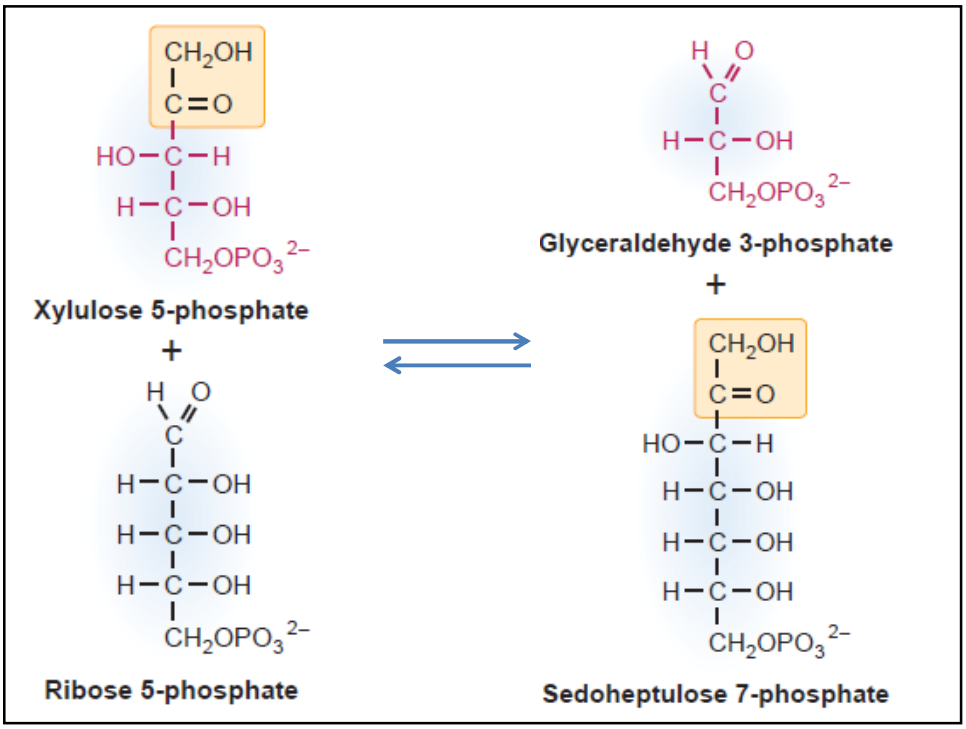
Glc. 6 Phosph. +2 $NADP^+$ ⟶ Ribulose 5-Phosph. + CO_2 + 2 NADPH

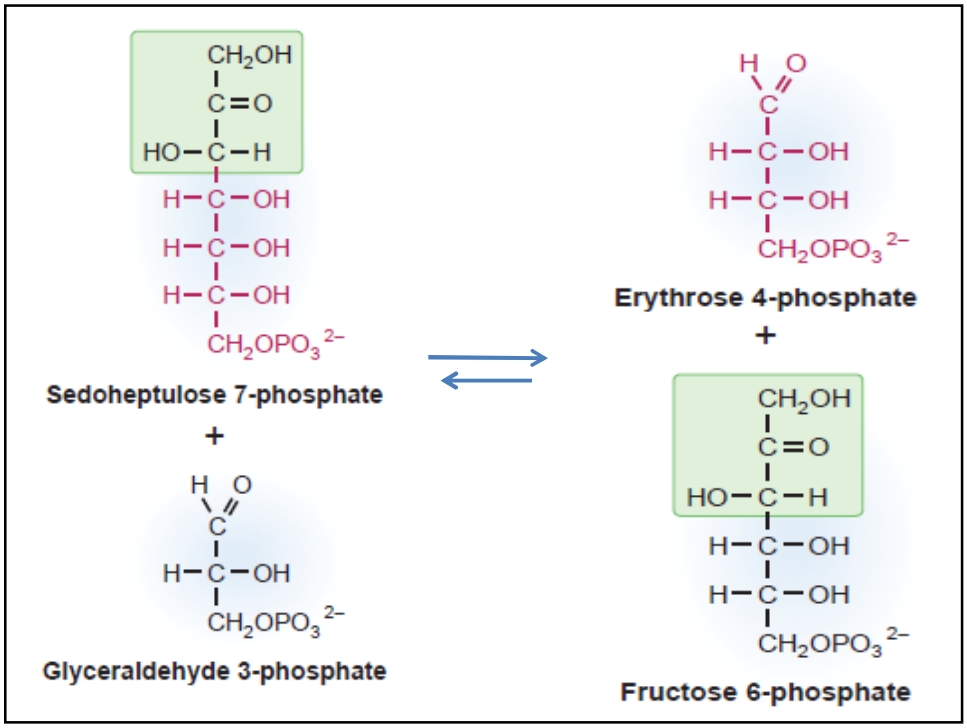

H H
O
NH2
N
O
O=P-O-
O
HO
OH
NH2
N
N
N
N
O=P-O-
O
O
N
HO
OPO3 2–

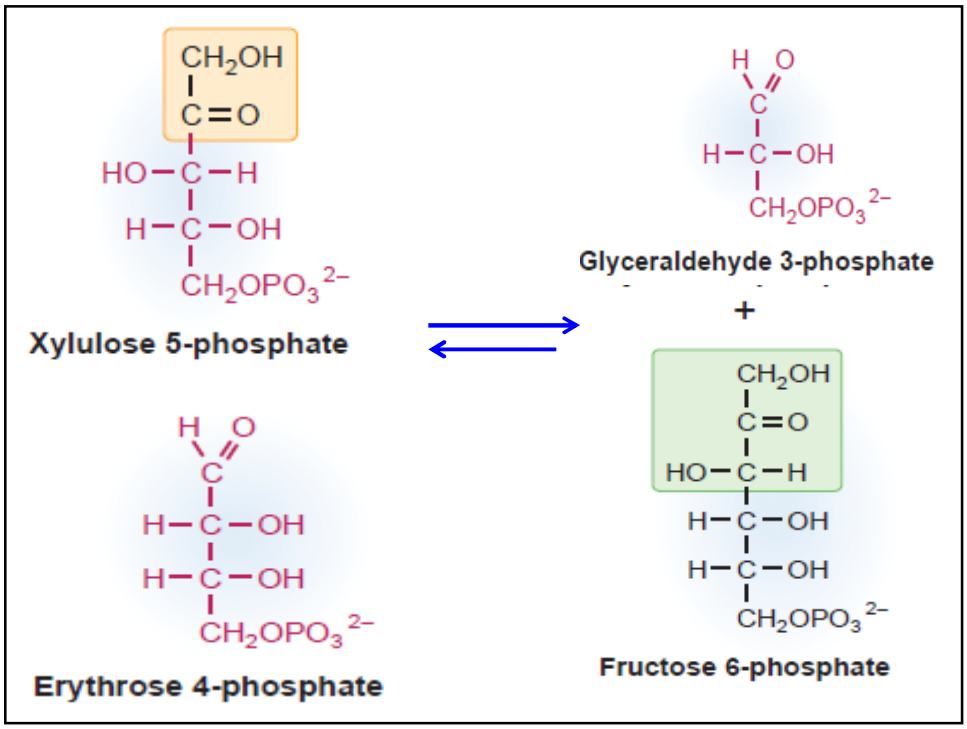

Isomerase
epimerase
Ribulose 5-phosphate
Ribose 5-phosphate
Xylulose 5-phosphate

Summary of the non-oxidative reactions

- Rearrangment of sugars
- 3 pentose phosph.. ⇌ { 2 hexose phosph + 1 triose phosph. }
- Reversible reactions
- Transfer of 2 or 3 carbon fragment
- Transketolase (3C), Transaldolase (2C)
- Ketose + aldose ⇌ ketose + aldose
- From ketose to aldose




Sedoheptulose 7-phosphate
+
Glyceraldehyde 3-phosphate
Erythrose 4-phosphate
+
Fructose 6-phosphate

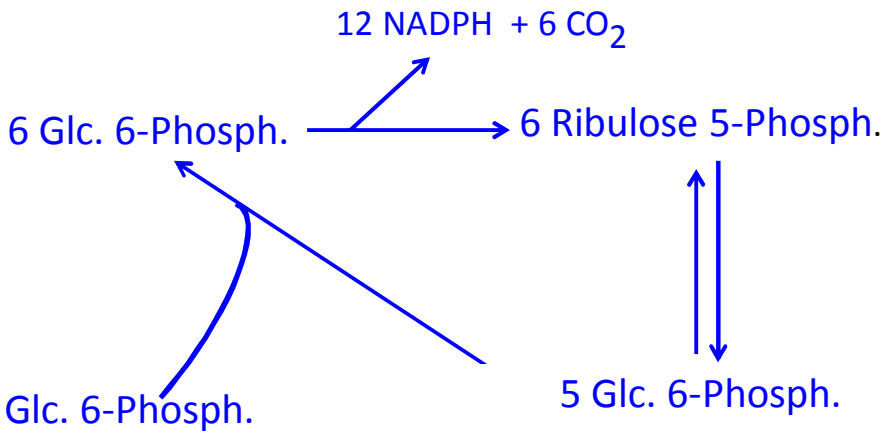

Xylulose 5-phosphate
Erythrose 4-phosphate
Glyceraldehyde 3-phosphate
+
Fructose 6-phosphate

The net non-oxidative reaction

- 3 Ribulose 5-phosph. ⇌ { 2 Fructose 6-phosph. + Glyceraldehyde 3-phosph. }
- Multiply by 2
- 6 Ribulose 5-phosph. ⇌ { 4 Fructose 6-phosph. + 2 Glyceraldehyde 3-phosph. }

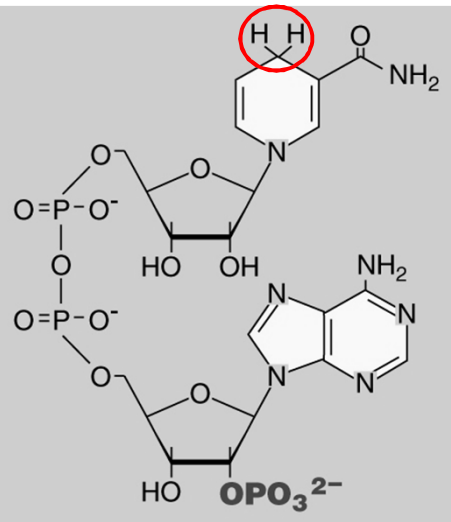
↓

5 Glc. 6-Phosph.

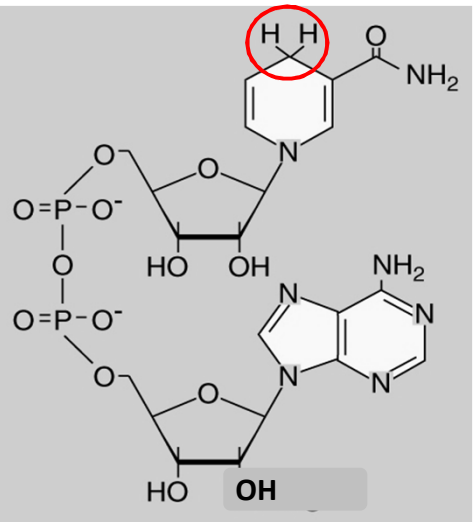


Uses of NADPH

NADPH



NADH



Why NADPH and NADH

- Enzymes can specifically use one NOT the other
- NADPH and NADH have different roles
- NADPH exists mainly in the reduced form (NADPH)
- NADH exists mainly in the oxidized form (NAD^+)
- In the cytosol of hepatocyte
  - $NADP^+/NADPH \approx 1/10$
  - $NAD^+/NADH \approx 1000/1$

Uses of NADPH
Reductive Biosynthesis

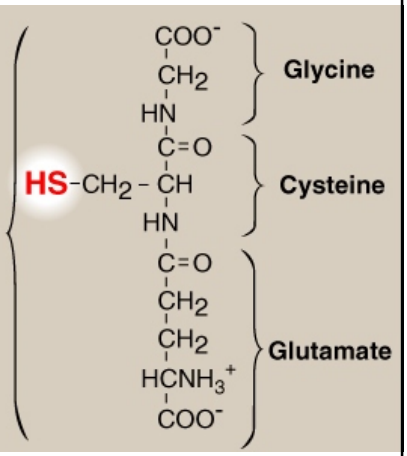
- Some biosynthetic require high energy electron donor to produce reduced product
- Examples: Fatty acids, Steroids …
- 8 CH_3COO ➔ $C_{15}H_{33}COO$

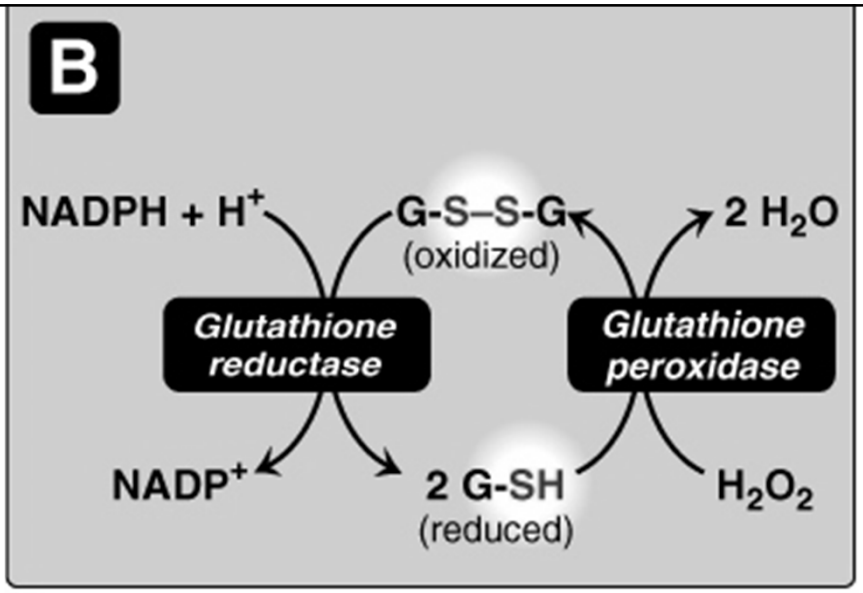
Uses of NADPH
Reduction of Hydrogen Peroxide

- H_2O_2 one of a family of compounds known as Reactive Oxygen Species (**ROS**)
- Other: Super oxide, hydroxyl radical,
- Formed continuously
  - As by products of aerobic metabolism
  - Interaction with drugs and environmental toxins
- Can cause chemical damage to proteins, lipids and DNA ➔ cancer, inflammatory disease, cell death

Enzymes that catalyze antioxidant reactions

- Glutathione peroxidase
- Glutathione is a reducing agent
- Tripeptide
- GSH is the reduced form
- Oxidation ➔two molecules joined by disulfide (GSSG)
- 2 GSH ⟶ GSSG





Glutathione peroxidase is Selenium requiring Enzyme
RBCs are totally dependent on Pentose Phosphate Pathway for NADPH production

Enzymes that catalyze antioxidant reactions

- Super oxide dismutase (**SOD**)

$$2O_2\bullet^- + 2H^+ \longrightarrow O_2 \quad H_2O_2$$

- Catalase

$$2H_2O_2 \longrightarrow O_2 + 2H_2O$$

Anti oxidant chemicals

- Vitamin E, Vitamin C, Carotenoids

Sources of ROS in the cell

- Oxidases

$$e^- + O_2$$

Most oxidases produce H_2O_2 (peroxidase)

Oxidases are confined to sites equipped with protective enzymes

- Oxygenases
  - Mono oxygenases (hydroxylases)
  - Dioxygenases in the synthesis of prostaglandins, Thromboxans, leucotrienes
- Coenzyme Q in Respiratory chain

Sources of ROS in the cell

- Respiratory Burst (during phagocytosis)

  O_2 H_2O_2 $OH^{\bullet}$ NO HOCl

- Ionizing Radiation

  $OH^{\bullet}$

Cytochrome P450 Mono oxygenase

- Mixed function oxygenase
- Super family of structurally related enzymes

$$R\text{-}H + O_2 + NADPH + H^+ \longrightarrow R\text{-}OH + H_2O + NADP^+$$

Mitochondrial system

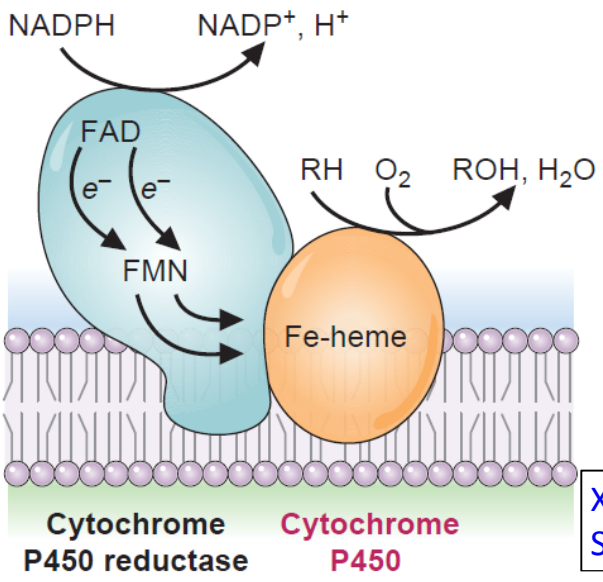
Hydroxylation of steroids, bile acids, active form of Vit. D

Microsomal system

Detoxification of foreign compounds

activation or inactivation of Drugs

solublization



Accidental release of free radical intermediates may occur

XH2: electron donor
S: substrate

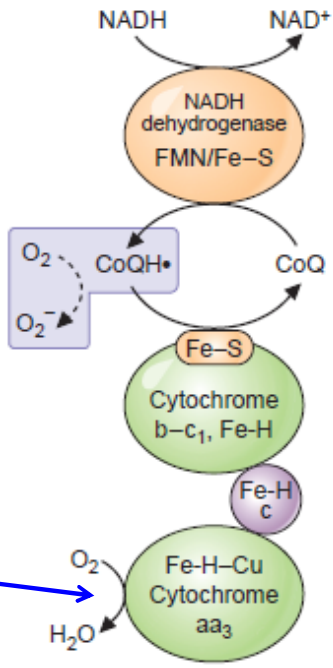
$O_2 + S + XH_2 \longrightarrow H_2O + SOH + X$

Generation of O_2^- by respiratory chain

Accidental non-specific interaction

Major source of free radicals

Binuclear center prevents release of free O2 radicals



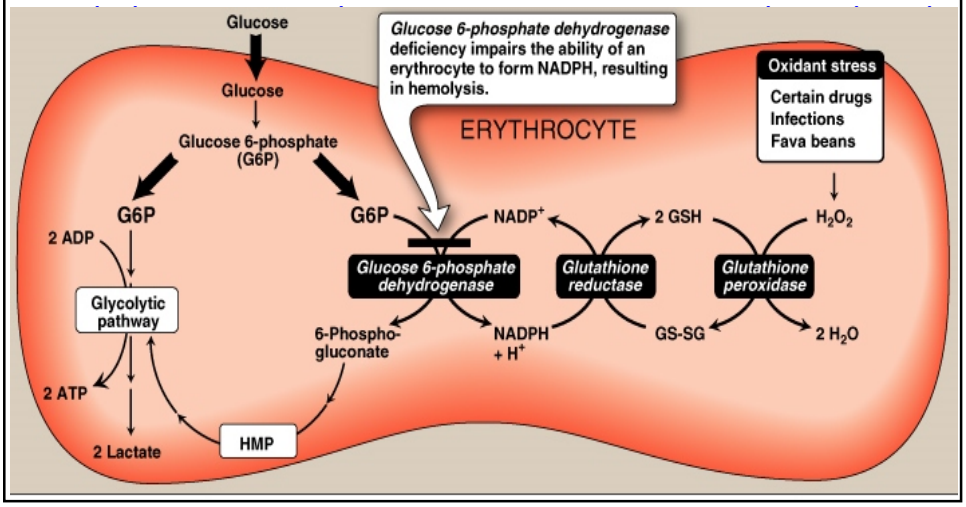
G6PD Deficiency

- Common disease
- characterized by hemolytic anemia
- 200 – 400 millions individuals worldwide
- Highest prevalence in Middle East, S.E. Asia, Mediterranean
- X-linked inheritance
- > 400 different mutations
- Deficiency provides resistance to falciparum malaria

Role of G6PD in red blood cells

Peroxides + GSH ⟶ G-S-S-G + $2H_2O$

G-S-S-G + NADPH ⟶ 2GSH + NADP+



Precipitating Factors inG6PD Deficiency

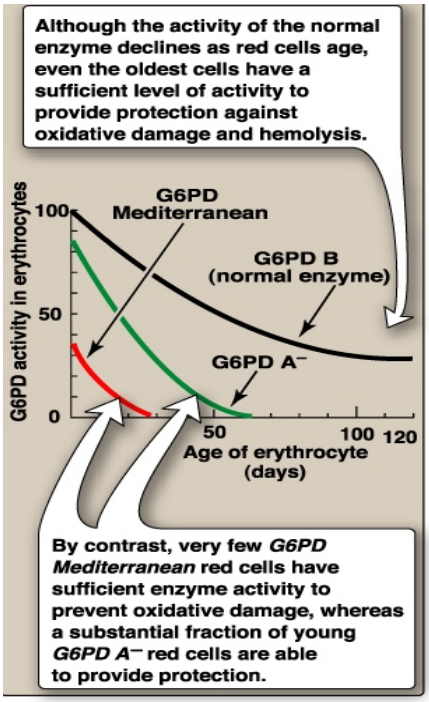
- Oxidant drugs
  - Antibiotics e.g. Sulfomethxazole
  - Antimalaria Primaquine
  - Antipyretics Acetanalid
- Favisim
- Infection
- Neonatal Jaundice

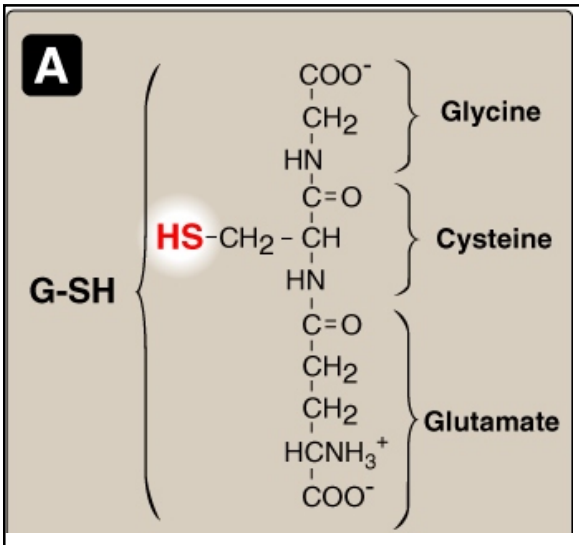
G6PD Deficiency Variants

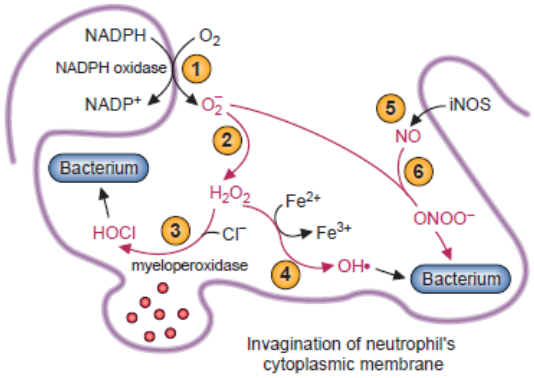
- Wild type B
- Med. Variant B^- (Class II) : 563C → T
- African Variant A^- (Class III); two point mutation
- African Variant A; Normal activity 80%
- Very severe deficiency (Class I)
- Majority missense mutation point mutation
- Large deletions or frame shift; Not Observed

Classification of G6PD Deficiency Variants

Class	Clinical symptoms	Residual enzyme activity
I	Very severe	<2%
II	Severe	<10%
III	Moderate	10–50%
IV	None	60–150%




A
G-SH
HS-CH2-CH
COO-
CH2
HN
C=O
CH2
CH2
HCNH3+
COO-
Glycine
Cysteine
Glutamate



NO and RNOS Synthesis

- Free radical diffuses readily
- Essential for life and toxic
- Neurotransmitter , vasodilator
- Platelet aggregation
- At high concentration combines with O2 or O2 to form RNOS ➔ neurodegenerative diseases

NO synthase isoforms

- I nNOS (neural)