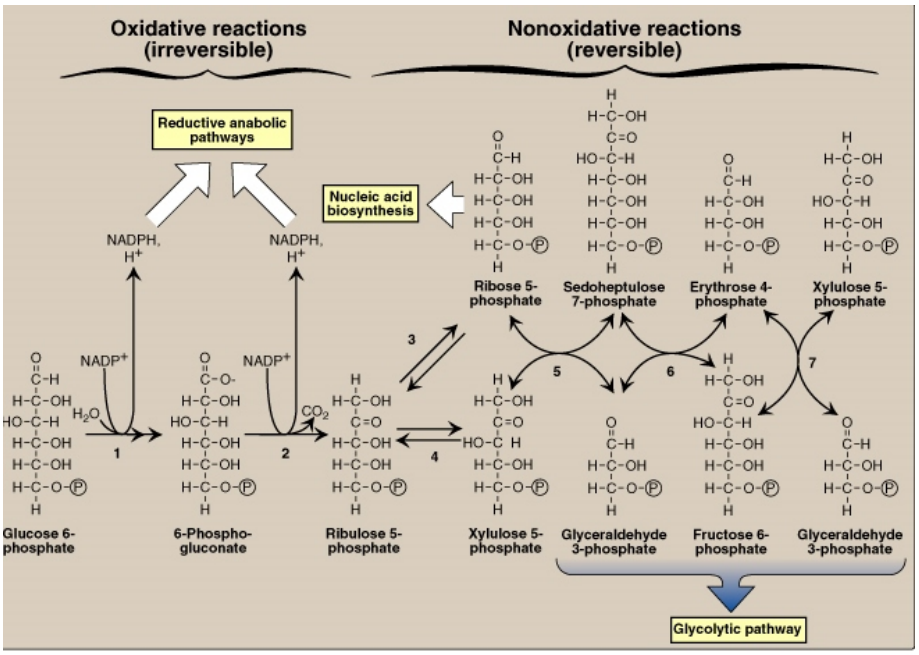
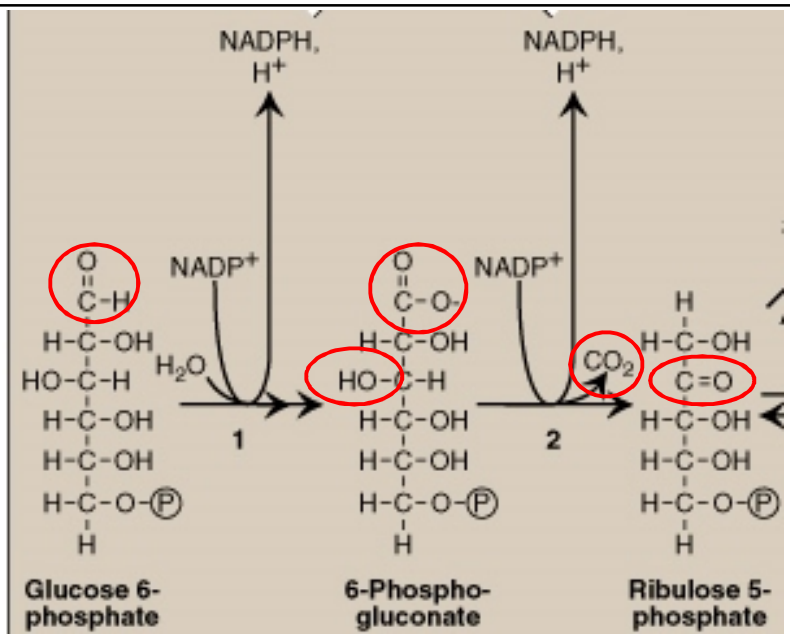
Pentose Phosphate Pathway (PPP)
or
Hexose Monophosphate Shunt

Lippincott's Chapter 13

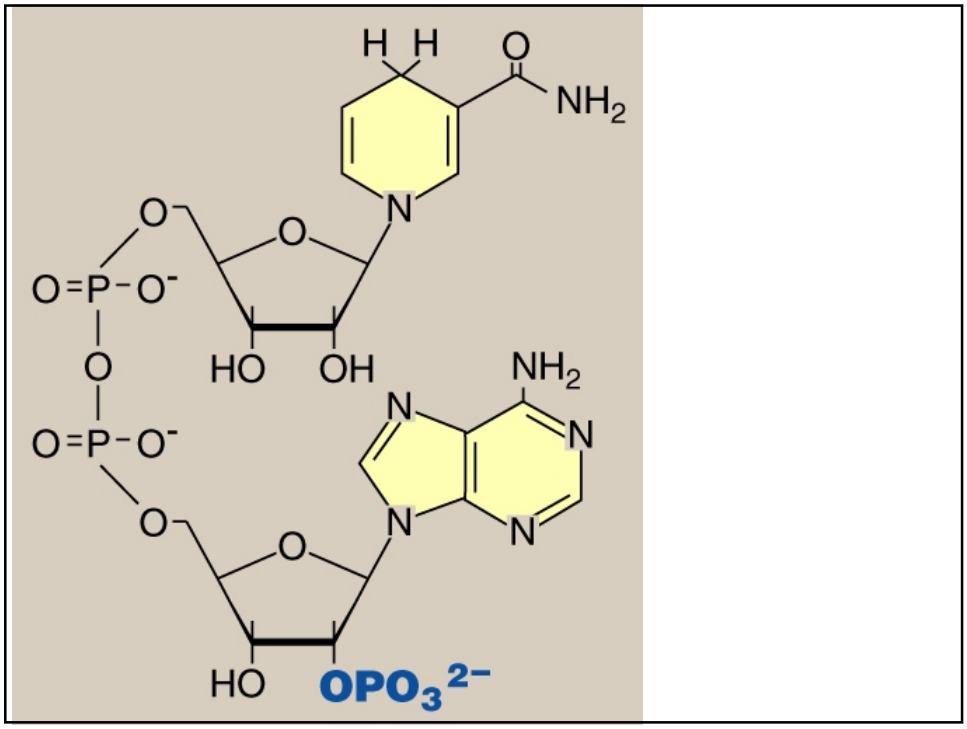
Functions of the PPP

- 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
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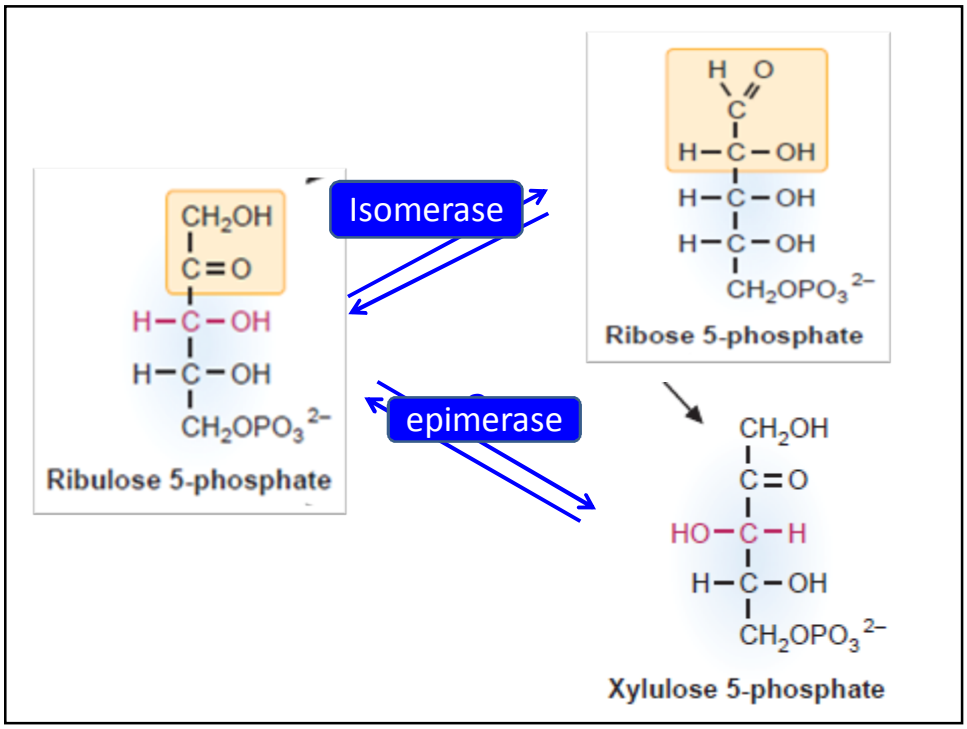
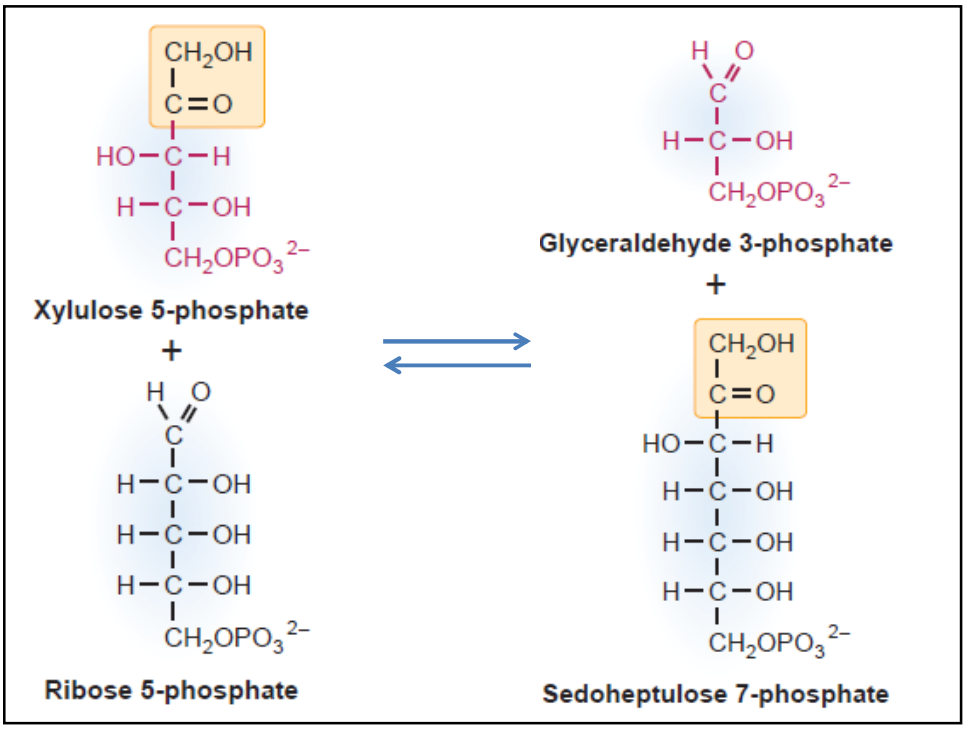
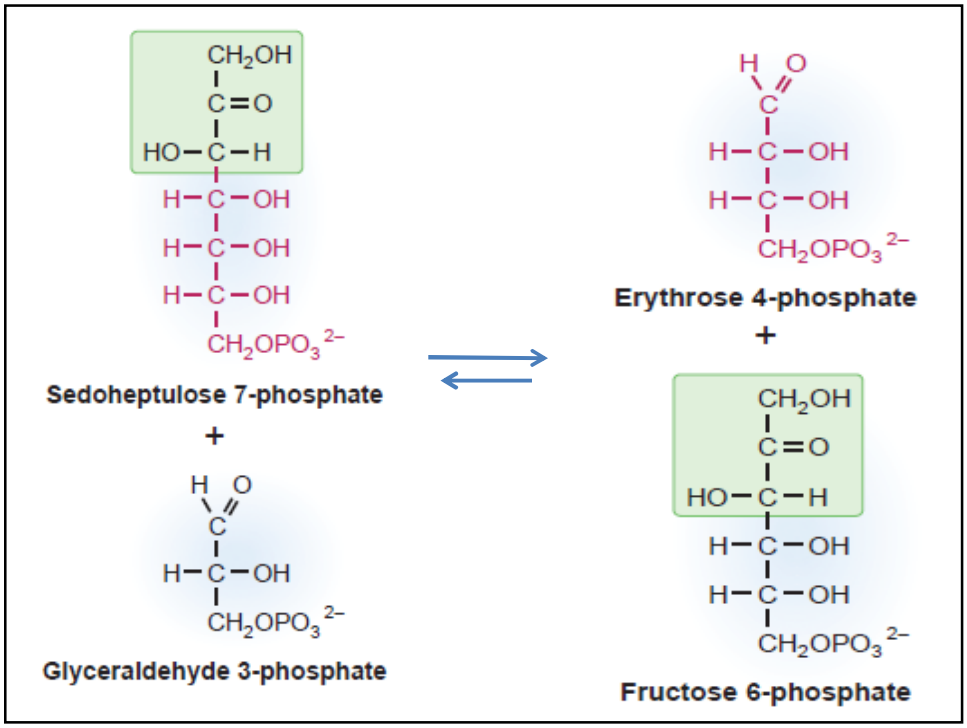
N
N
O=P-O-
O
O
N
HO
OPO3 2–

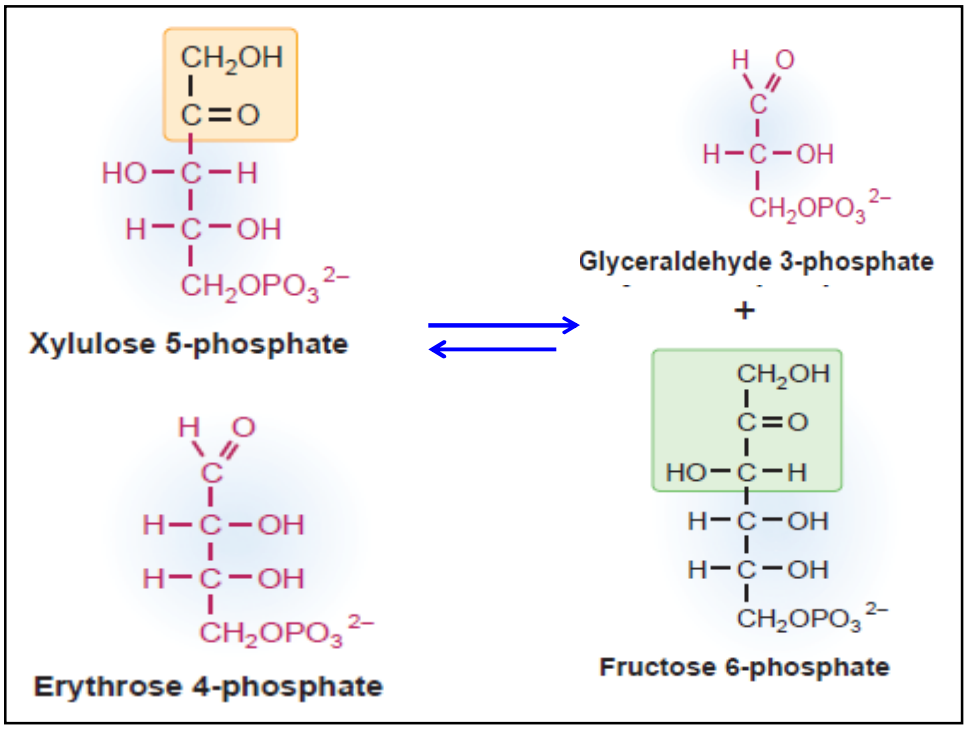

Isomerase
epimerase
Ribulose 5-phosphate
Ribose 5-phosphate
Xylulose 5-phosphate

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

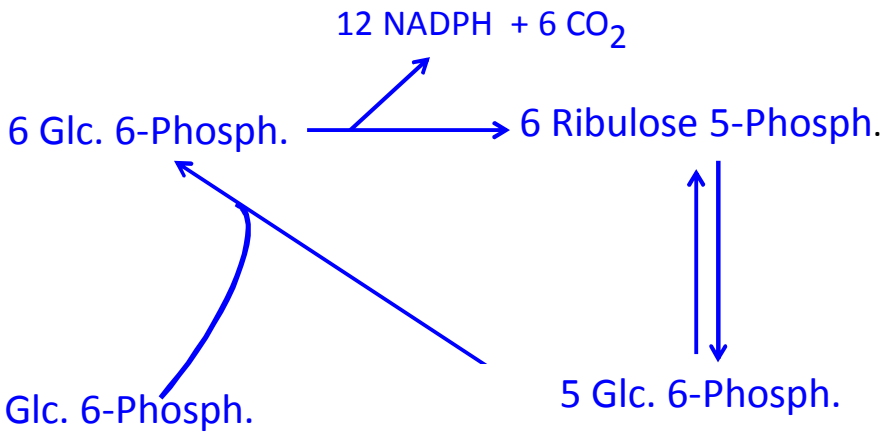

Xylulose 5-phosphate
Erythrose 4-phosphate
Glyceraldehyde 3-phosphate
+
Fructose 6-phosphate

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. }

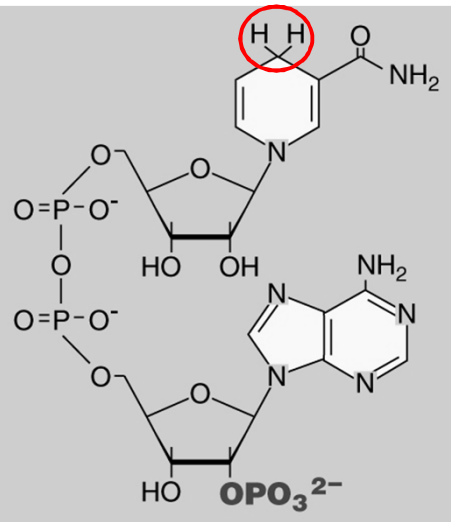
↓

5 Glc. 6-Phosph.

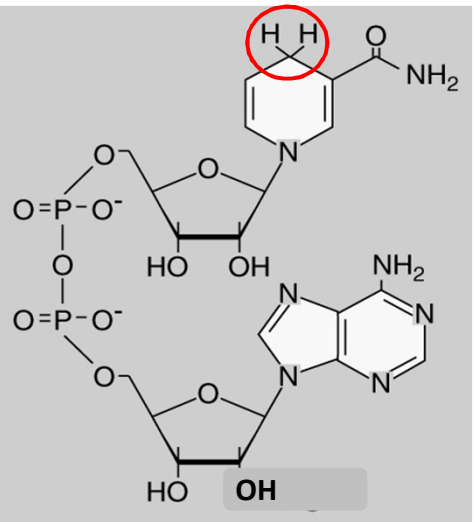


Uses of NADPH

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

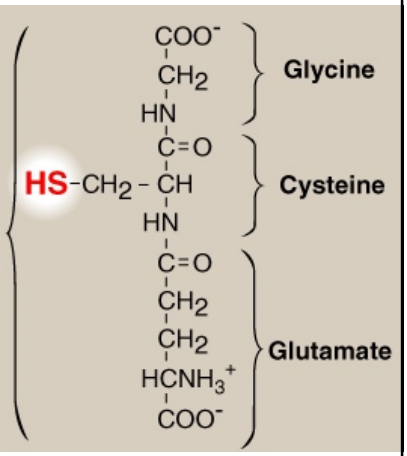
- Some biosynthetic require high energy electron donor to produce reduced product
- Examples: Fatty acids, Steroids …
- 8 CH_3COO ➔ $C_{15}H_{33}COO$

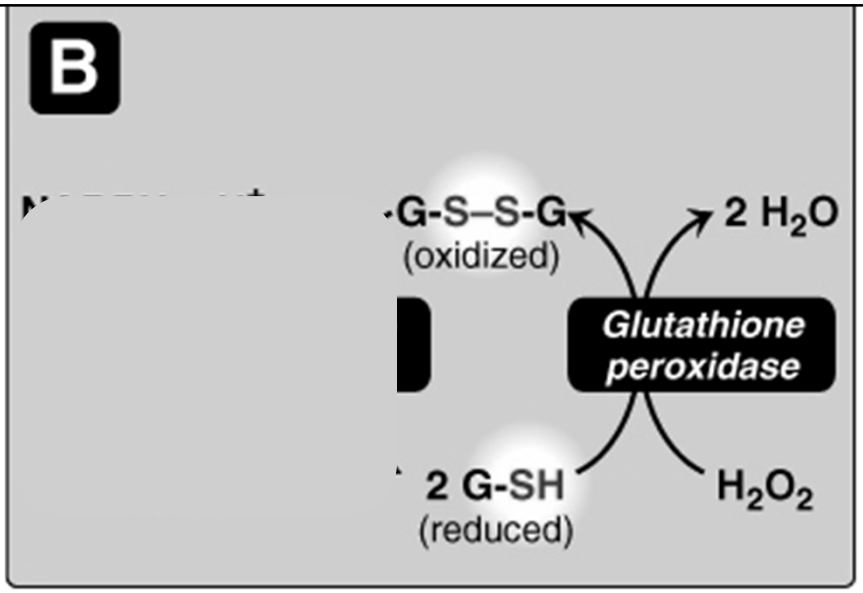
Uses of NADPH
Reduction of Hydrogen Peroxide

- 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

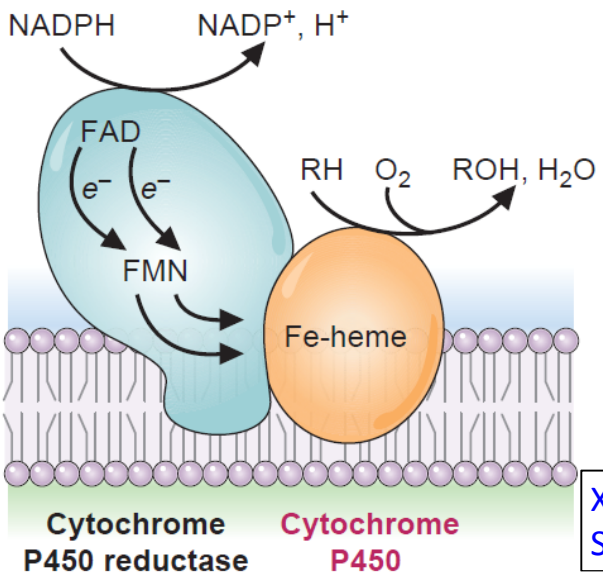
Hydroxylation of steroids, bile acids, active form of Vit. D

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

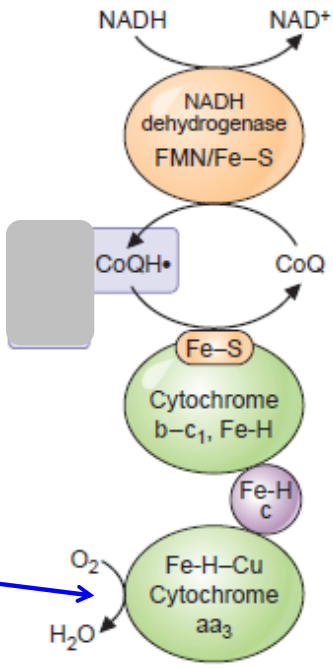
$O_2 + S + XH_2 \longrightarrow H_2O + SOH + X$

Generation of O_2^- by respiratory chain

Accidental non-specific interaction

Major source of free radicals

Binuclear center prevents release of free O_2 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

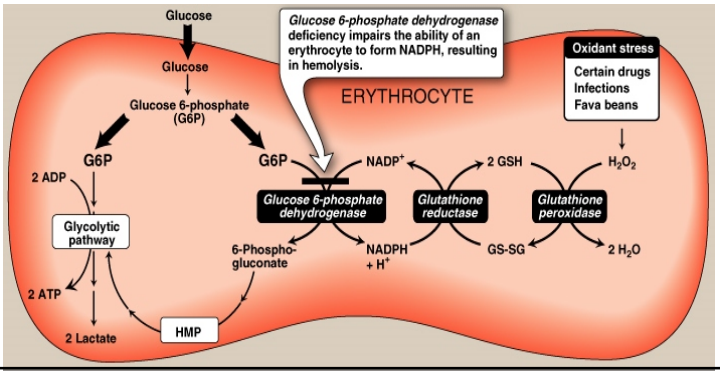
Role of G6PD in red blood cells

H_2O_2 + GSH ⟶ G-S-S-G + $2H_2O$

G-S-S-G + NADPH ⟶ 2GSH + NADP+

GSH helps maintain the SH groups in proteins in the reduced state

Oxidation ➔ denaturation of proteins and rigidity of the cells



Precipitating Factors inG6PD Deficiency

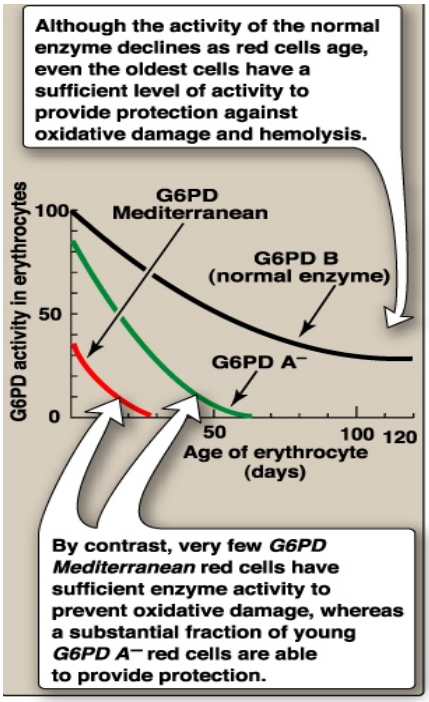
- Oxidant drugs
  - Antibiotics e.g. Sulfomethxazole
  - Antimalaria Primaquine
  - Antipyretics Acetanalid
- Favism
- Infection
- Neonatal Jaundice

G6PD Deficiency Variants

- Wild type B
- Mediterranean 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

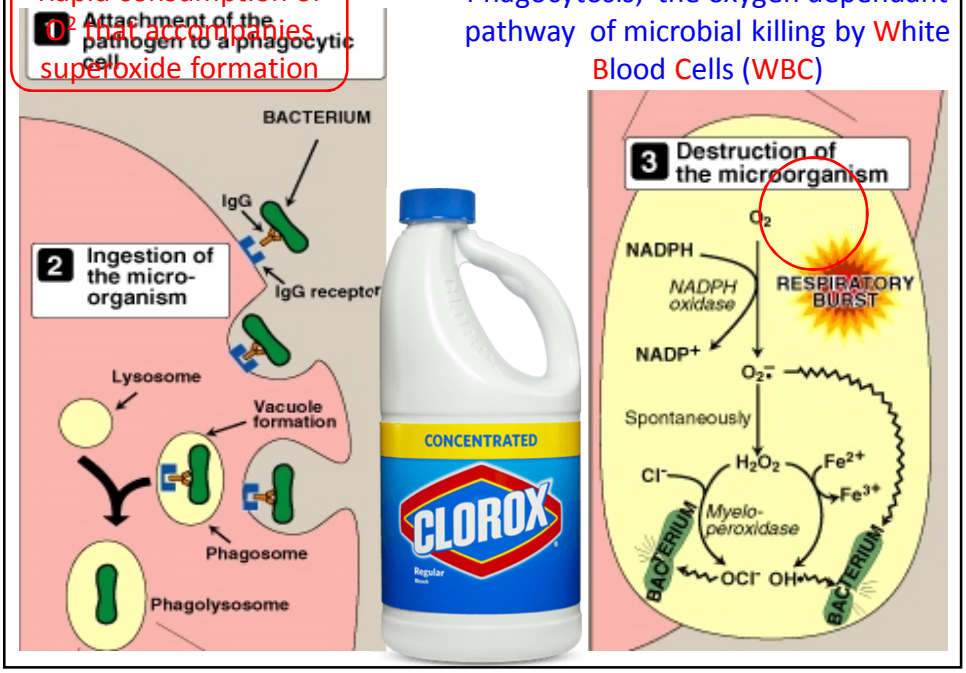
Classification of G6PD Deficiency Variants

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



Rapid consumption of O_2 that accompanies superoxide formation

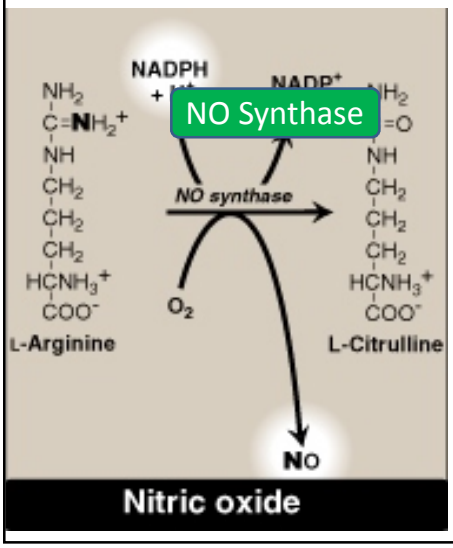
Phagocytosis; the oxygen dependant pathway of microbial killing by White Blood Cells (WBC)



NO and Reactive Nitrogen Oxygen Spciese (RNOS)

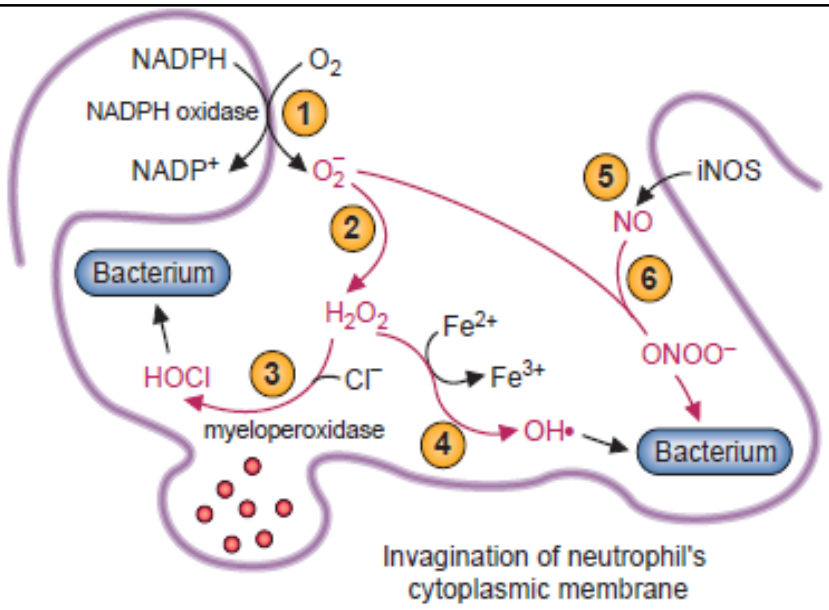
- Free radical diffuses readily
- Essential for life and toxic
- Neurotransmitter , vasodilator
- ↓Platelet aggregation
- At high concentration combines with $O_2^{\bullet-}$ or O_2 to form **RNOS**
- **RNOS** are involved in neurodegenerative diseases and inflammatory diseases

NO Synthesis



NO Synthase
Three isoforms
nNOS neural
eNOS endothelial
Both are constitutive

iNOS inducible
Induction of transcription in many cells of immune system➔↑↑ NO ➔ RNOS to kill invading bacteria



Hypoclorous acid

Action of NO on vascular endothelium

Synthesis by endothelia cells → smooth muscle

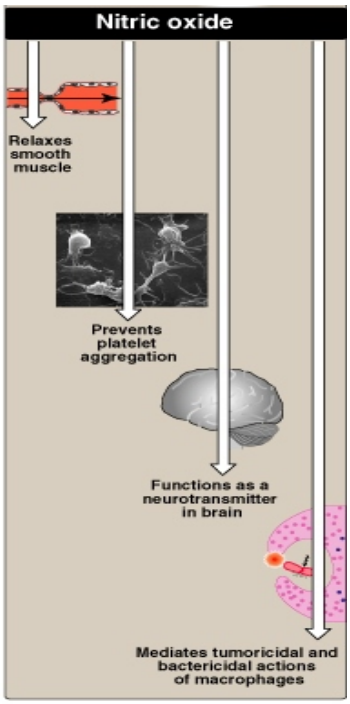
NO (+)

GTP → cGMP - - - - → GMP

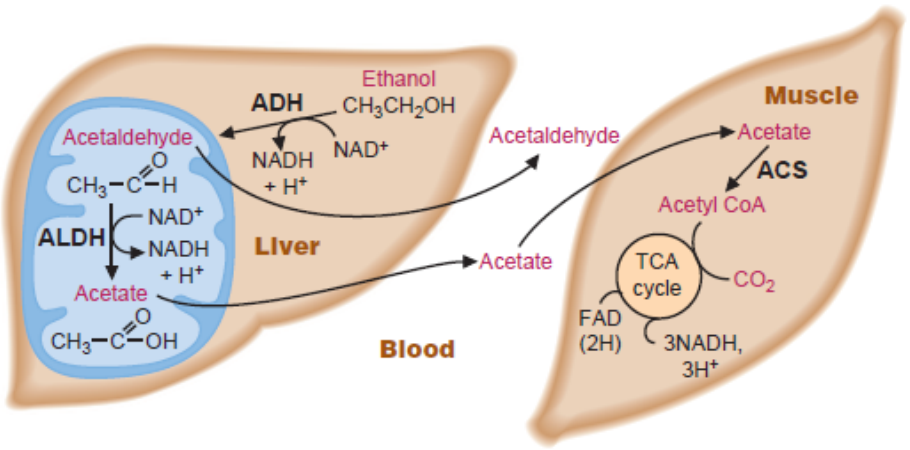
cGMP (+) → Protein Kinase G

Protein Kinase G → Phosphorylation of Ca^{2+} channels

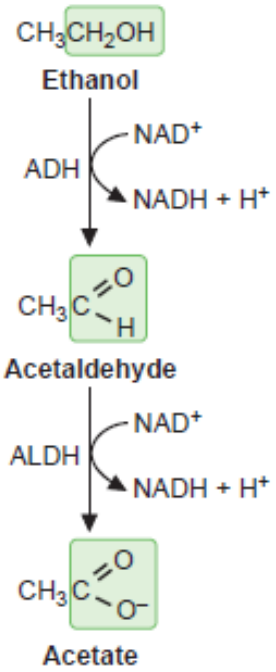
Phosphorylation of Ca^{2+} channels → ↓↓Ca^{2+} muscle relaxation

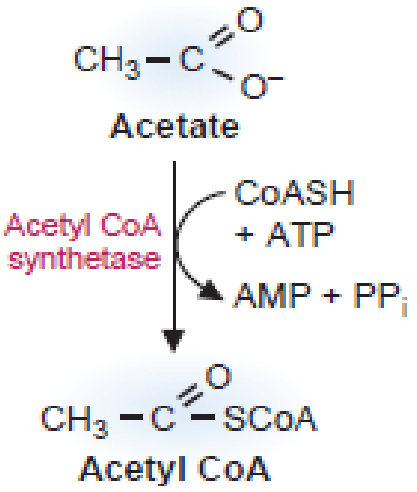


Metabolism of Alcohol



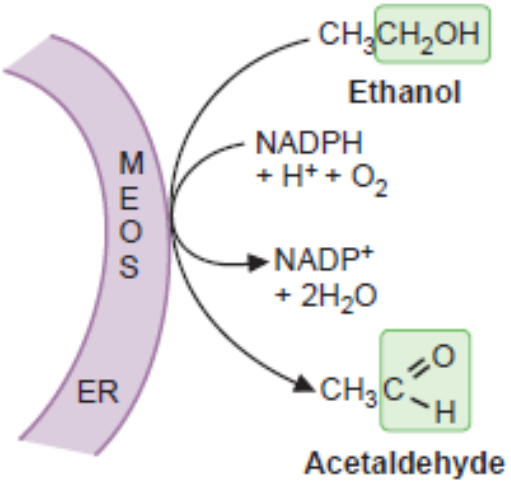
ADH: Alcohol Dehydrogenase
ALDH: Acetaldehyde Dehydrogenase
ACS: Acetyl CoA Synthetase



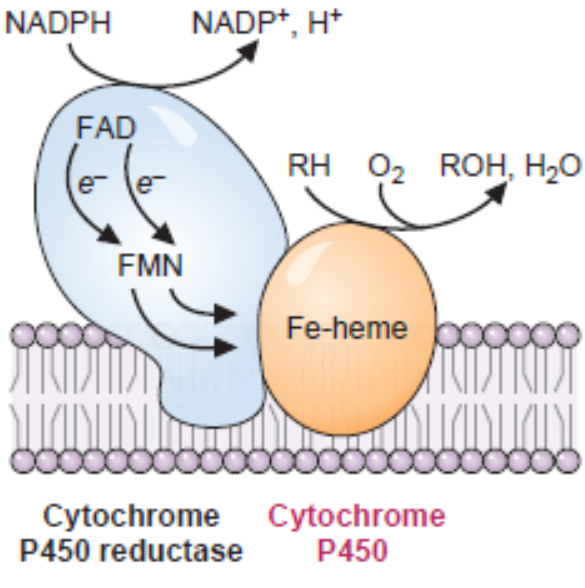


High NADH/NAD^+
Inhibition of FA oxidation
Inhibition of gluconeogenesis
Lactic acidosis

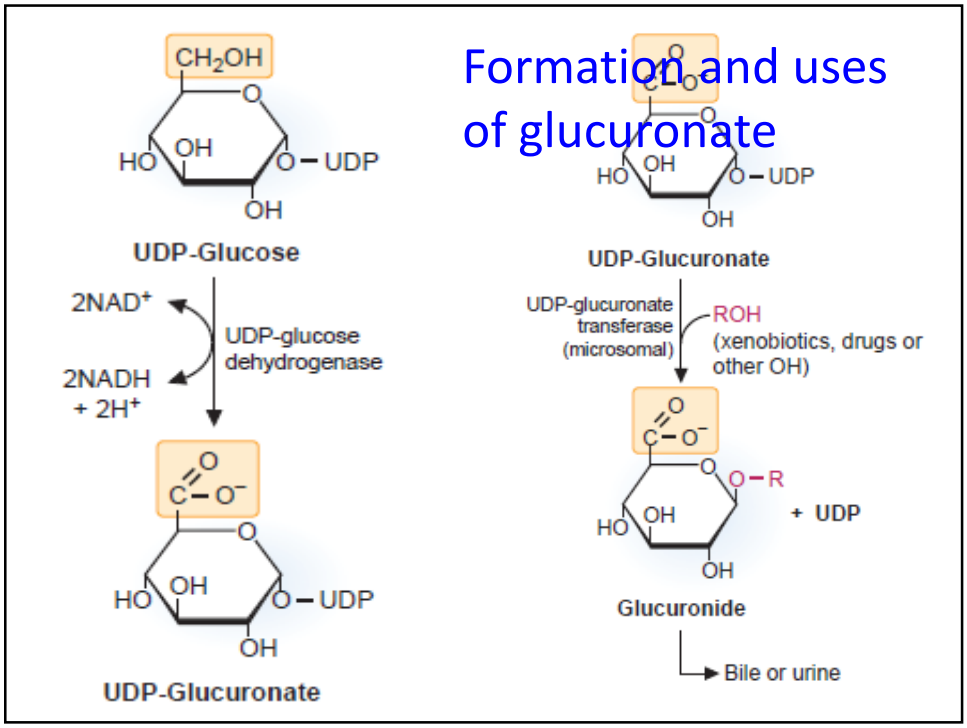
MEOS: Microsomal Oxidizing System

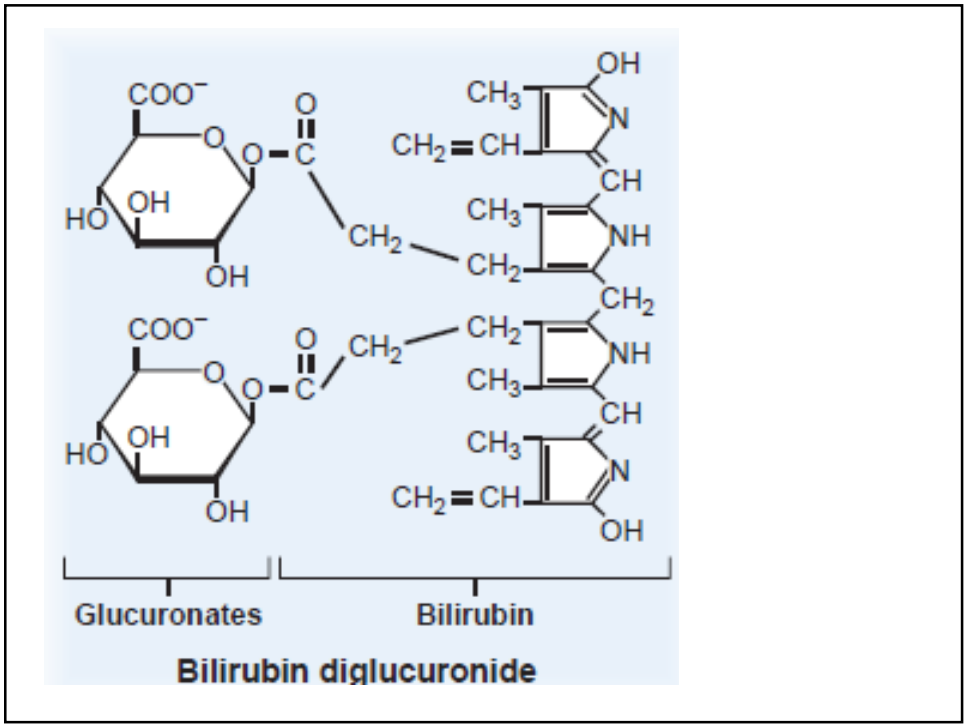


10-20% of the ingested ethanol
Cytochrome P450 (CYP2E1)
High K_m for ethanol
Inducible by ethanol



Formation and uses of glucuronate





The Role of UDP-Glucose in Metabolism