# Pentose Phosphate Pathway (PPP) or Hexose Monophosphate Shunt


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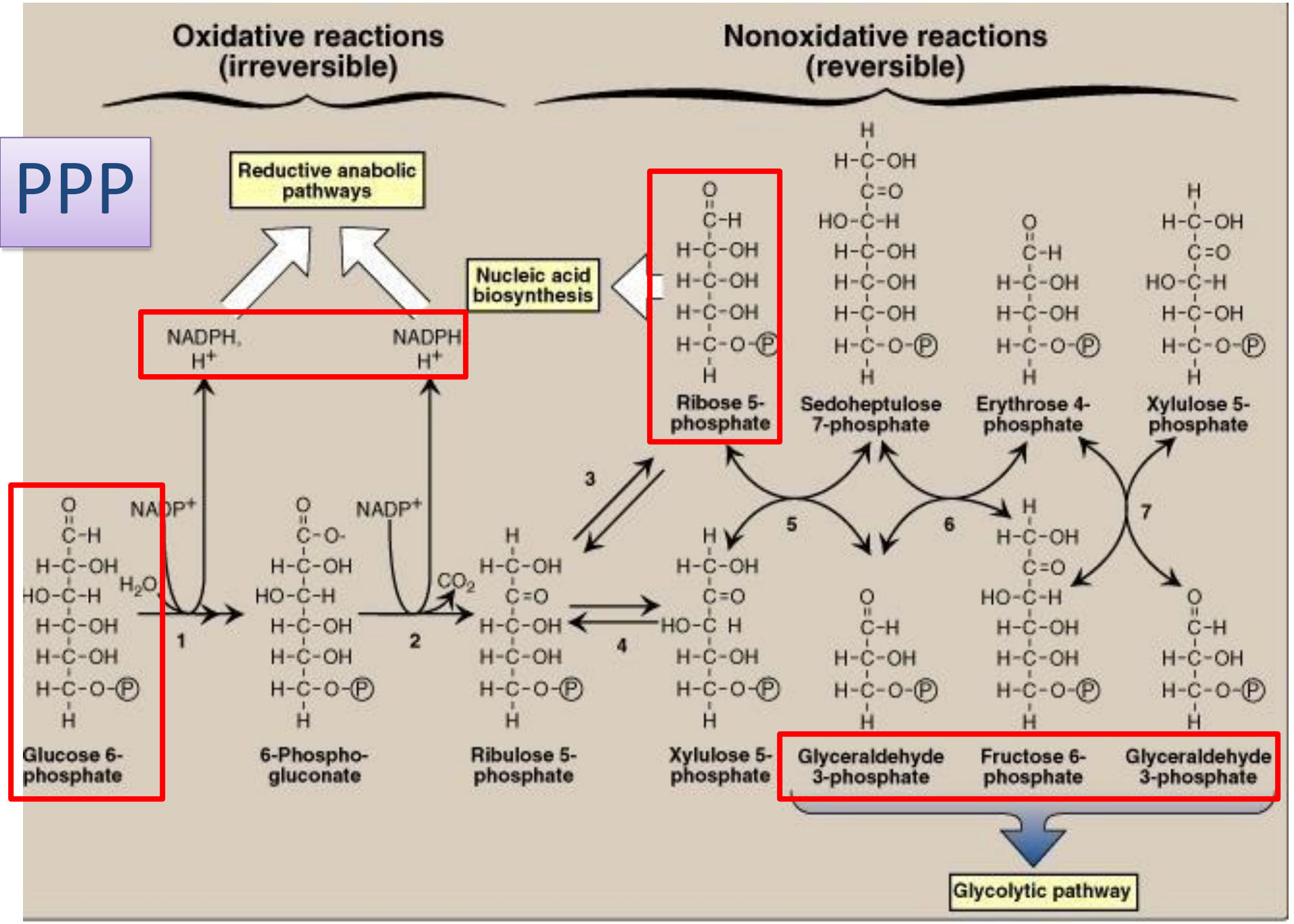
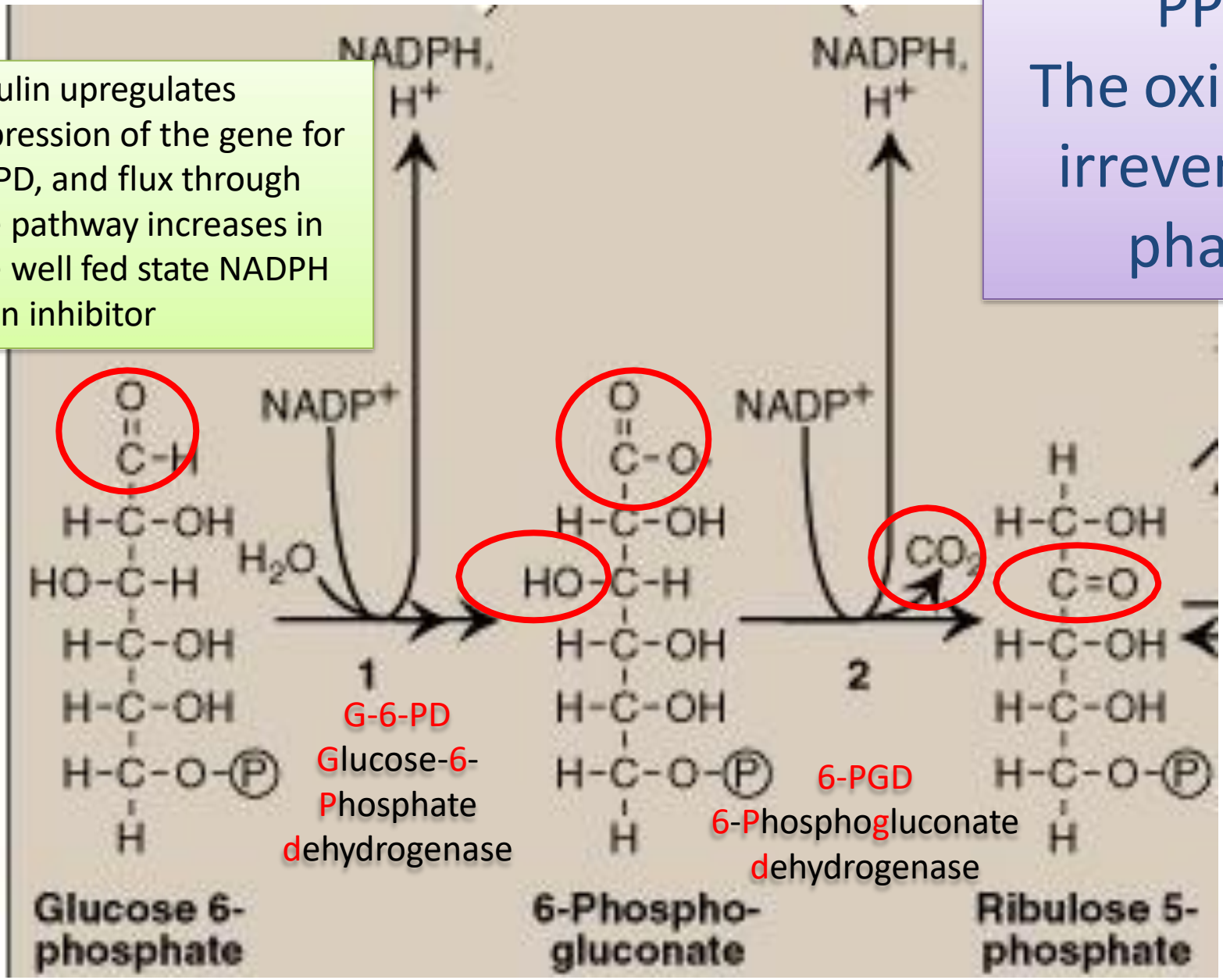

PPP
Oxidative reactions (irreversible)
Nonoxidative reactions (reversible)
Reductive anabolic pathways
Nucleic acid biosynthesis
NADPH, H+
NADPH H+
NADP+
NADP+
H2O
CO2
1
2
3
4
5
6
7
Glucose 6-phosphate
6-Phospho-gluconate
Ribulose 5-phosphate
Xylulose 5-phosphate
Ribose 5-phosphate
Sedoheptulose 7-phosphate
Erythrose 4-phosphate
Xylulose 5-phosphate
Glyceraldehyde 3-phosphate
Fructose 6-phosphate
Glyceraldehyde 3-phosphate
Glycolytic pathway

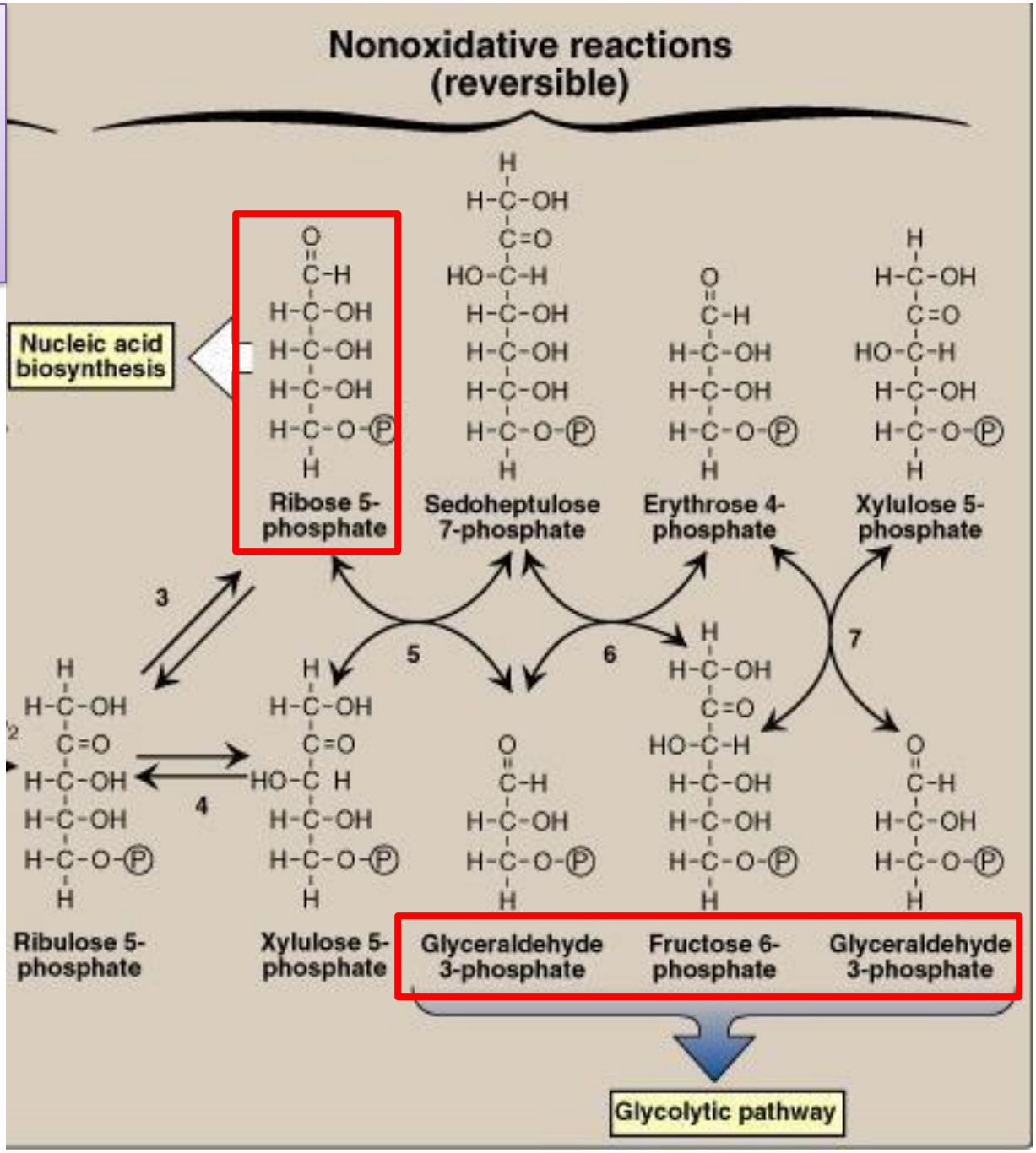
# PPP
# The oxidative irreversible phase

Insulin upregulates expression of the gene for G6PD, and flux through the pathway increases in the well fed state NADPH is an inhibitor




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

# PPP
# The non-oxidative reversible phase



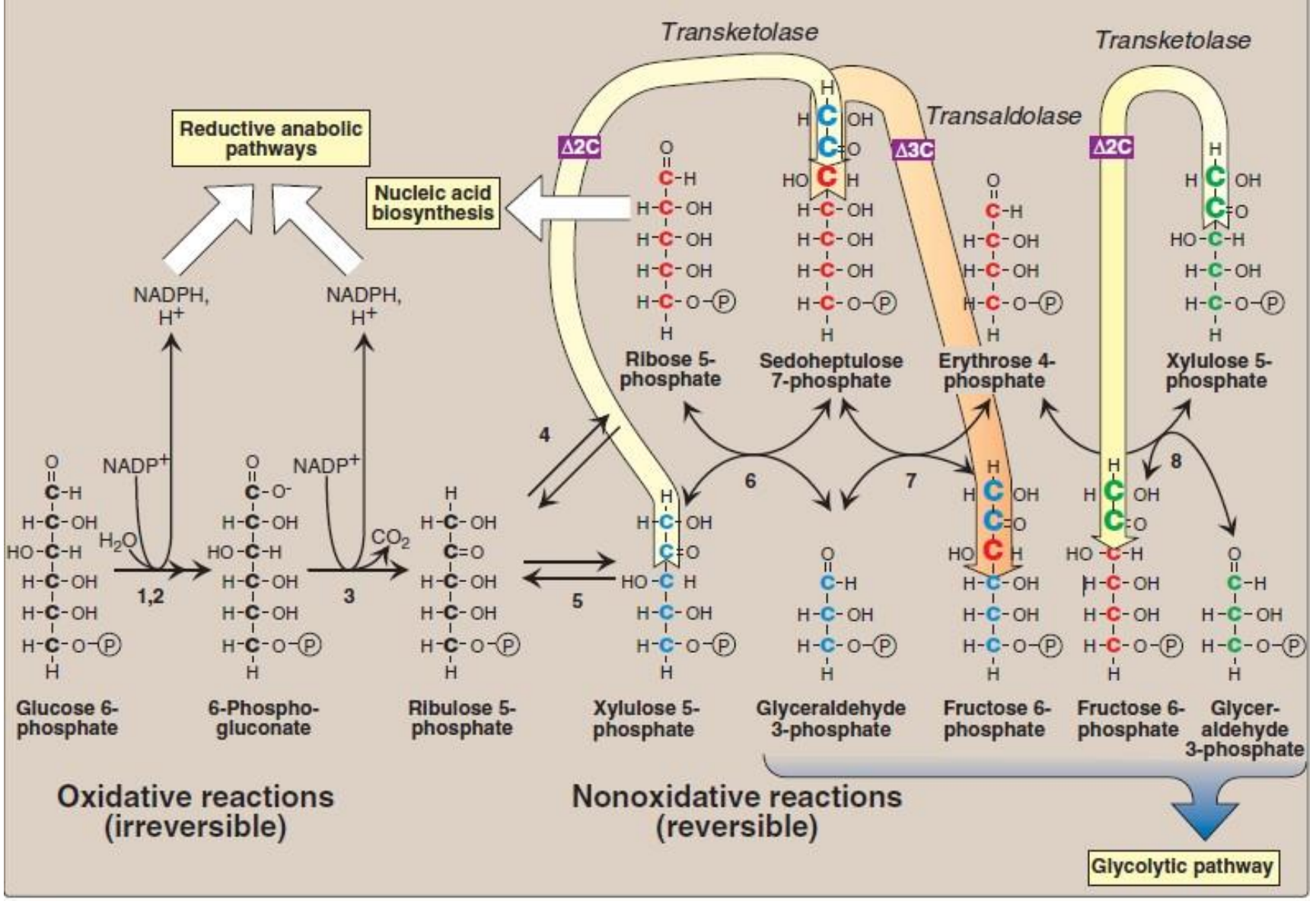



**Figure 13.2**

Reactions of the hexose monophosphate pathway. Enzymes numbered above are: 1,2) *glucose 6-phosphate dehydrogenase* and *6-phosphogluconolactone hydrolase*, 3) *6-phosphogluconate dehydrogenase*, 4) *ribose 5-phosphate isomerase*, 5) *phosphopentose epimerase*, 6) and 8) *transketolase* (coenzyme: thiamine pyrophosphate), and 7) *transaldolase*. Δ2C = two carbons are transferred in *transketolase* reactions; Δ3C = three carbons are transferred in the *transaldolase* reaction.

# Summary of the non-oxidative reactions

- Reversible reactions
- Transfer of 2 or 3 carbon fragment
- Transketolase (2C), Transaldolase (3C)
- Ketose + aldose ⇌ ketose + aldose
- From ketose to aldose

- Rearrangment of sugars
- 3 pentose phosph.. ⇌ { 2 hexose phosph + 1 triose phosph. }

# Net Products of the 2 Phases

3 Glc. 6-P + 6 $NADP^+$ → 2 Glc. 6-P + GA3P + 3 $CO_2$ + 6 NADPH

6 Glc. 6-P + 12 $NADP^+$ → 4 Glc. 6-P + 2 GA3P + 6 $CO_2$ + 12 NADPH

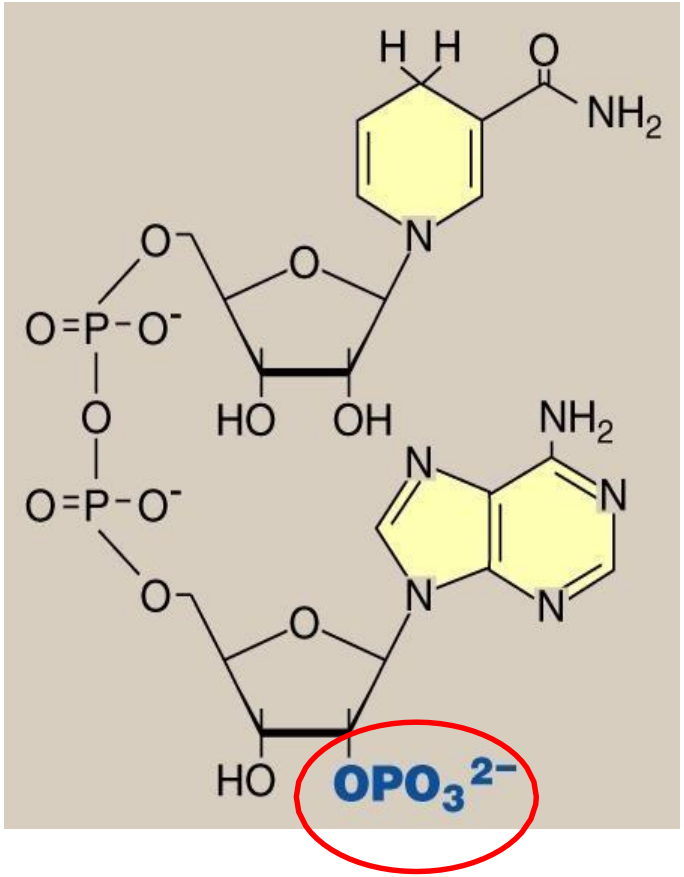
↓

Glc. 6-P

6 Glc. 6-P + 12 $NADP^+$ → 5 Glc. 6-P + 6 $CO_2$ + 12 NADPH

# Functions of the PPP

1. 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 reduced form in the RBCs

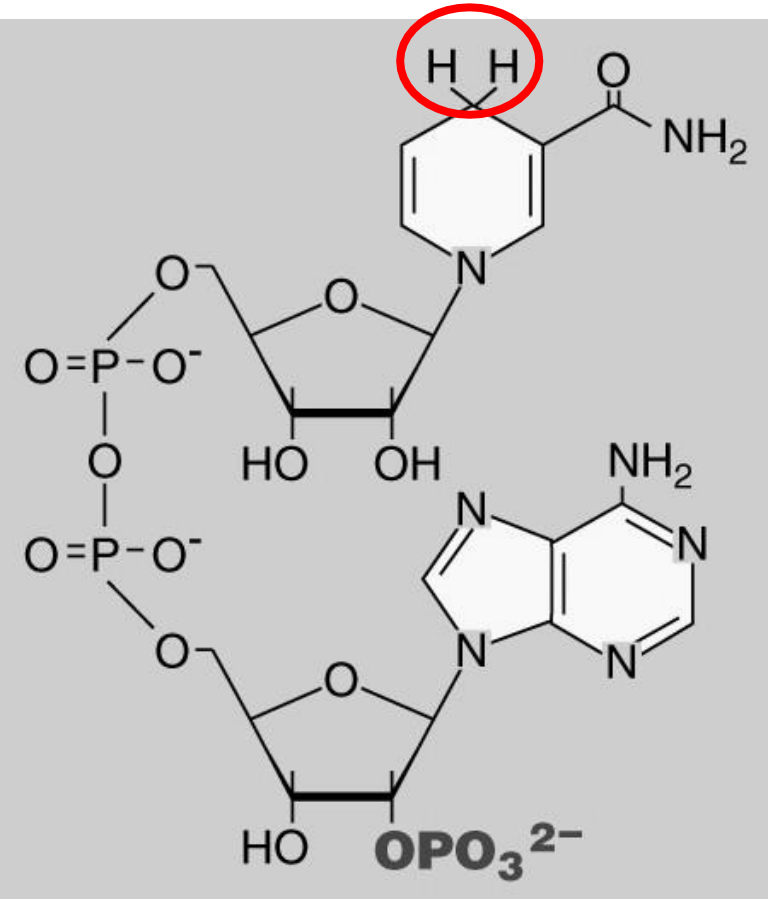



**OH in NADH**

2. Metabolism of five-carbon sugars (Pentoses)
   - Ribose 5-phosphate (nucleotide biosynthesis)
   - Metabolism of pentoses

# NADPH vs 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
  - $NADP^+/NADPH \approx 1/10$
  - $NAD^+/NADH \approx 1000/1$



# What are the uses of NADPH?

1. Reductive Biosynthesis

- Some biosynthetic reactions require high energy electron donor to produce reduced product
- Examples: Fatty acids, Steroids …

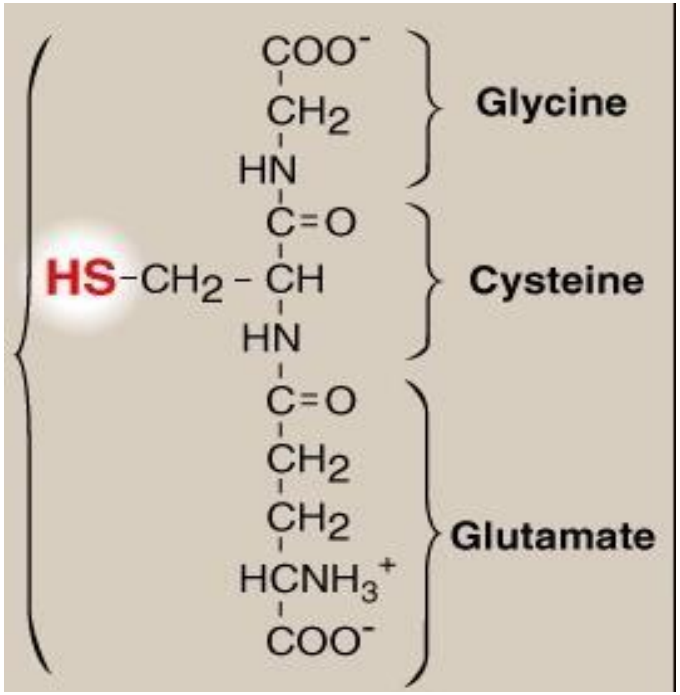
2. Reduction of Hydrogen Peroxide

- $H_2O_2$ 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

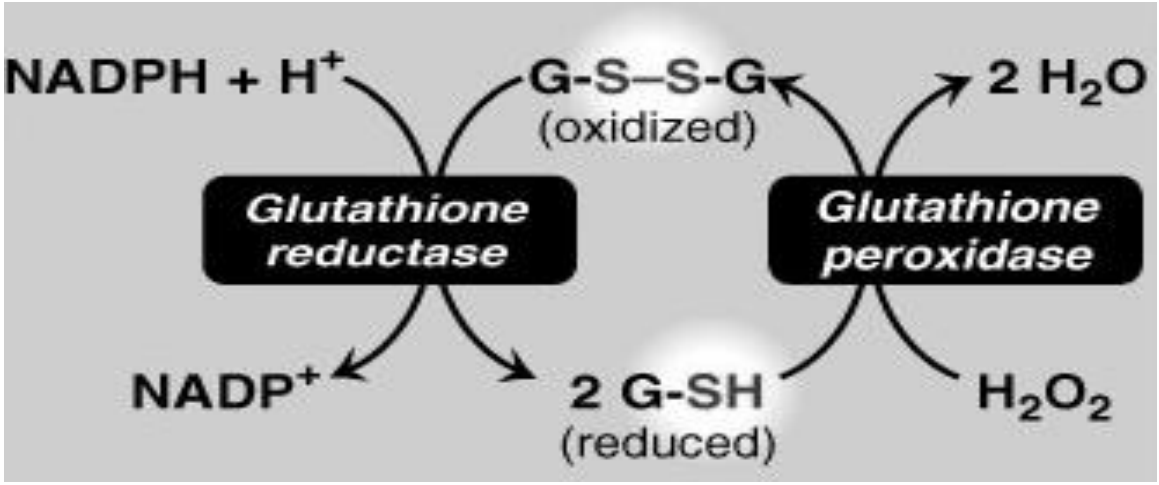
# Enzymes that catalyze antioxidant reactions

1. Glutathione peroxidase

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




Glutathione peroxidase is Selenium requiring Enzyme RBCs are totally dependent on PPP for NADPH production



# Enzymes that catalyze antioxidant reactions

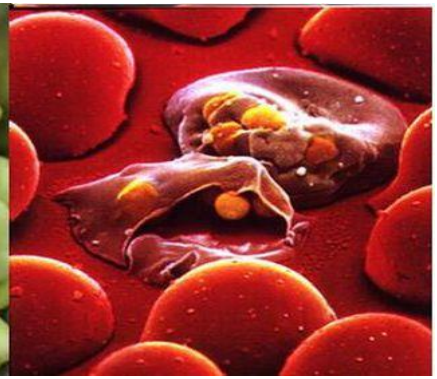
2. Super oxide dismutase (**SOD**)


3. Catalase


Anti oxidant chemicals

- Vitamin E, Vitamin C, Carotenoids

# Clinical Hint: G6PD Deficiency



- A 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

Precipitating Factors

- Oxidant drugs

– Antibiotics e.g. Sulfomethxazole

– Antimalaria e.g. Primaquine

– Antipyretics e.g. Acetanalid

- Favism due to vicine and covicine in fava beans in some G6PD deficient patients
- Infection
- Neonatal Jaundice

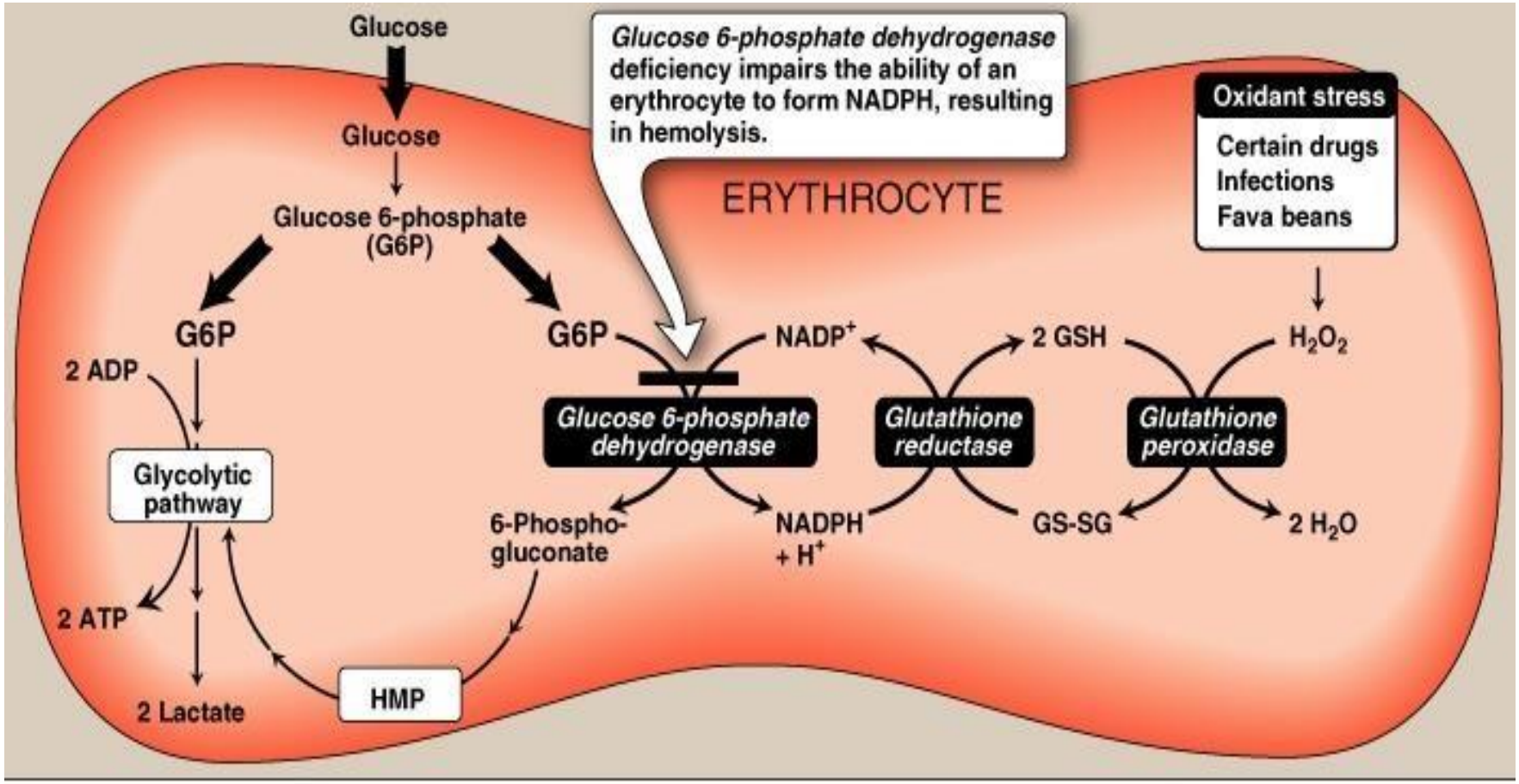
# Role of G6PD in red blood cells

$H_2O_2 + GSH \longrightarrow G\text{-}S\text{-}S\text{-}G + 2H_2O$

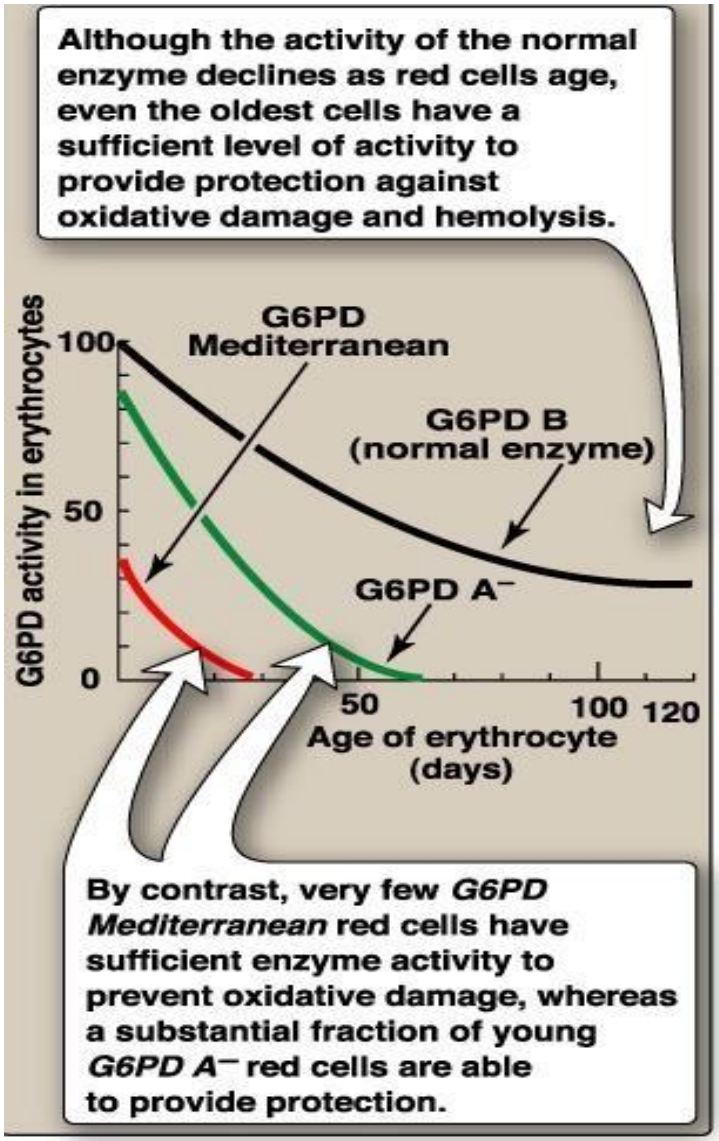
$G\text{-}S\text{-}S\text{-}G + NADPH \longrightarrow 2GSH + NADP+$

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

Oxidation ➔ denaturation of proteins and rigidity of the cells



# 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% |

- Wild type B
- Mediterranean Variant $B^-$ (Class II ) : 563C→T
- African Variant $A^-$ (Class III ); two point mutation
- Majority missense mutation, point mutation
- Large deletions or frame shift; Not Observed

# 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, thromboxanes, leukotrienes
- Coenzyme Q in Respiratory chain
- Respiratory Burst ( during phagocytosis) $O_2^-$, $OH^\bullet$, NO, HOCl, $H_2O_2$
- Ionizing Radiation $OH^\bullet$

# Cytochrome P450 Mono oxygenase

- Mixed function oxygenase
- Super family of structurally related enzymes

$$R\text{-}H + \mathbf{O_2} + NADPH + H^+ \longrightarrow R\text{-}\mathbf{O}H + H_2\mathbf{O} + NADP^+$$

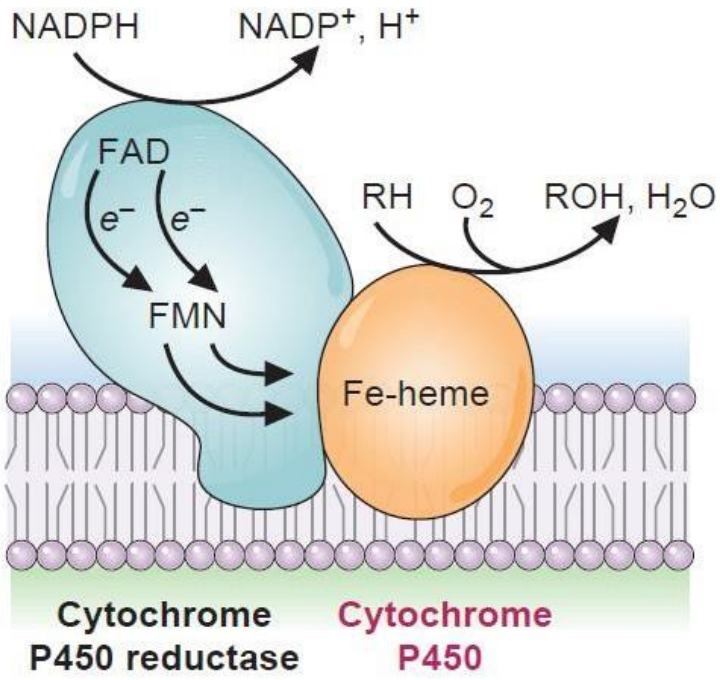
✓ Mitochondrialsystem

Synthesis by hydroxylation of steroids, bile acids, active form of Vit. D

✓ Microsomal system

Detoxification of foreign compounds Activation or inactivation of Drugs

Solublization to facilitate excretion in urine or feces

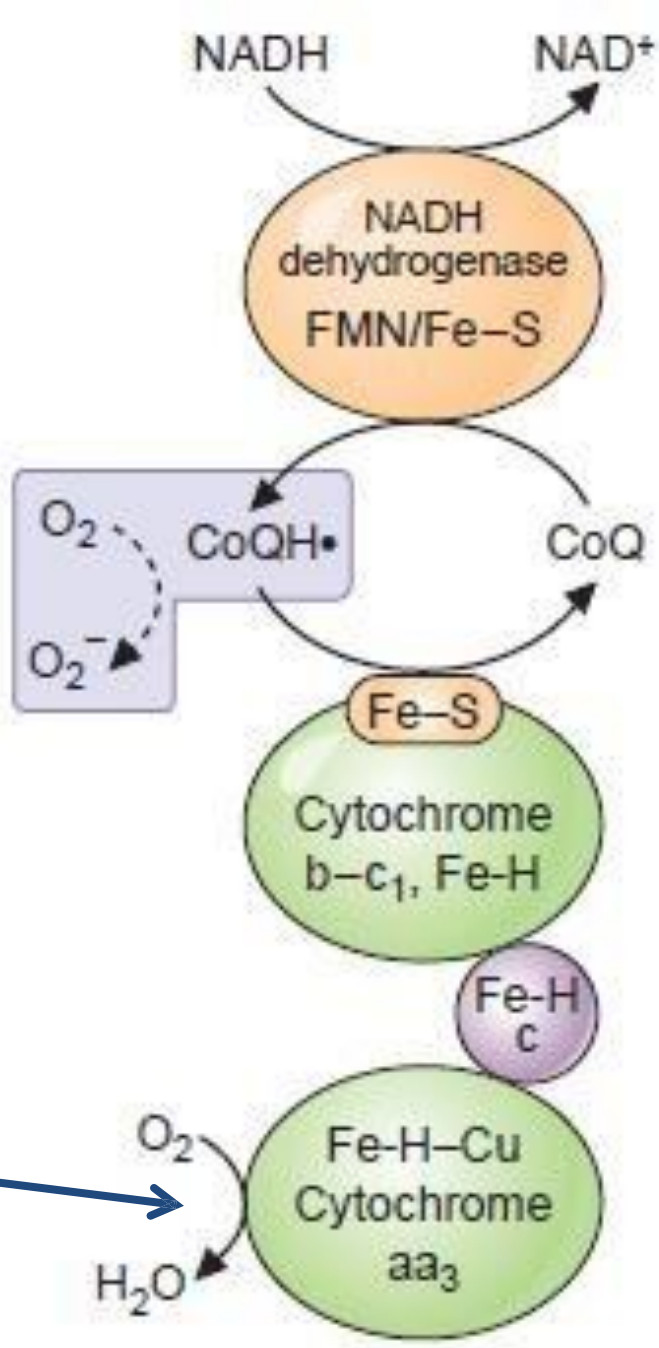


# Generation of $O_2^-$ by the respiratory chain

Accidental non-specific interaction

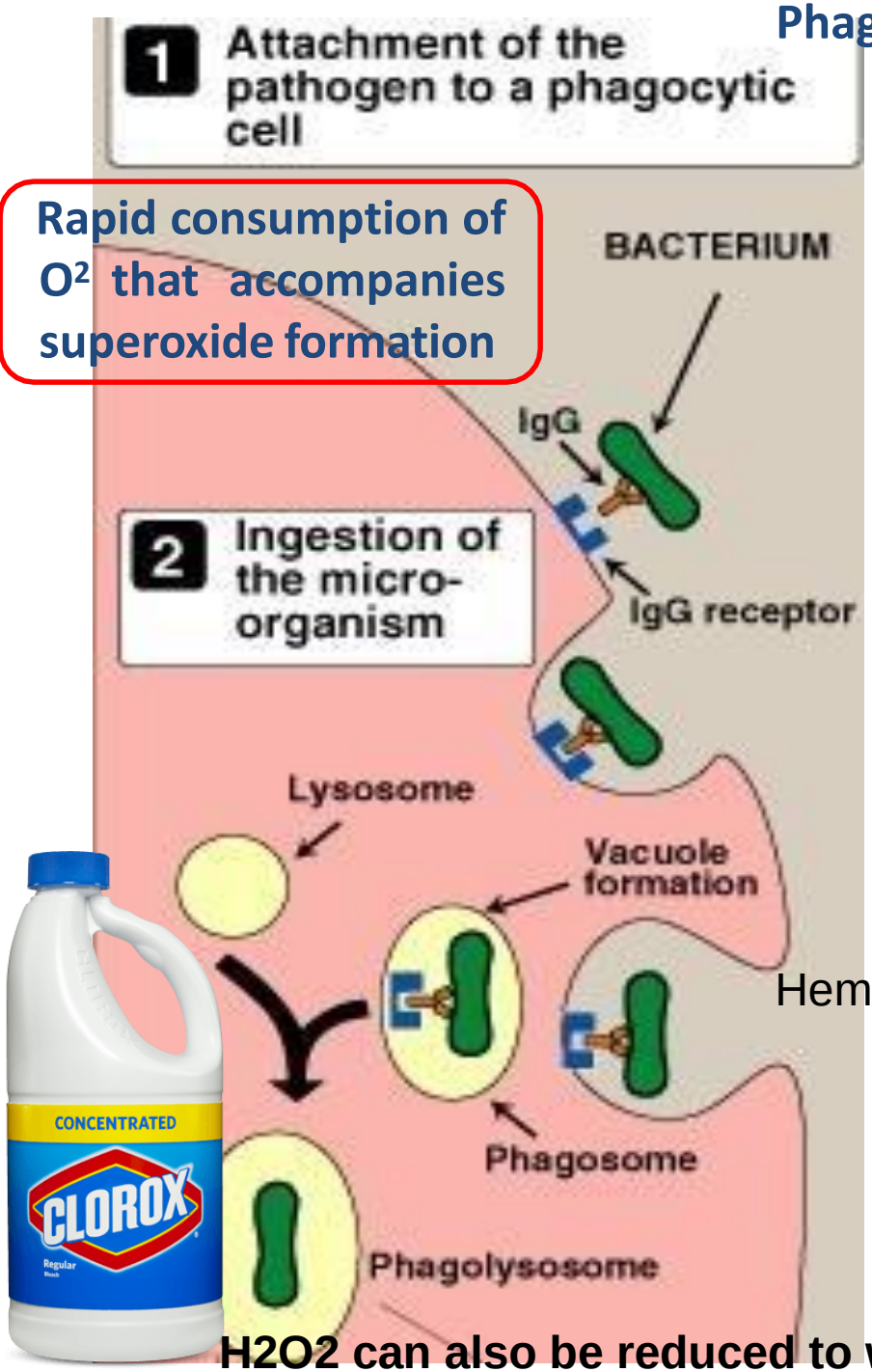
Major source of free radicals

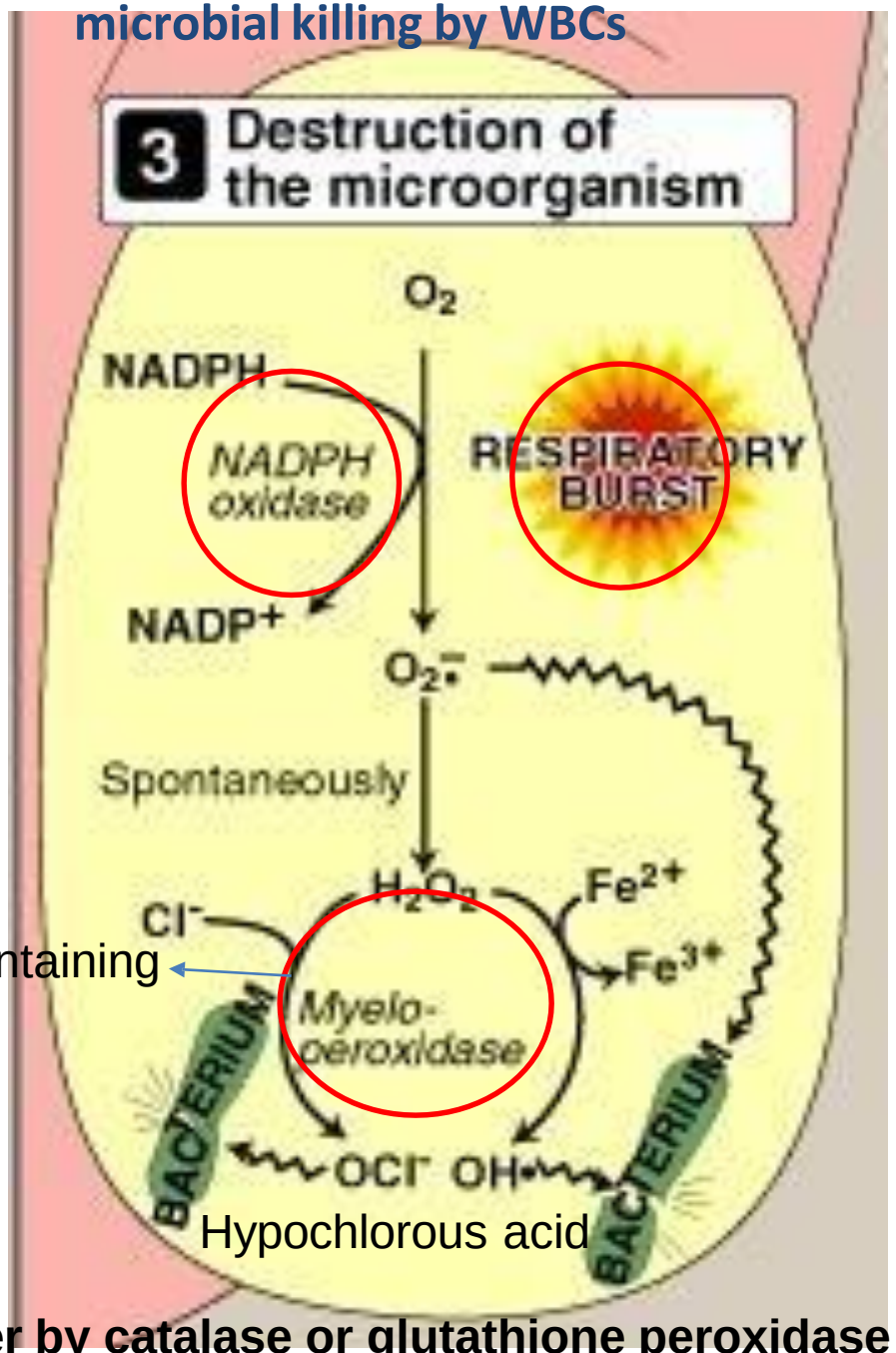
Binuclear center prevents release of free $O_2$ radicals



# Phagocytosis; the oxygen dependent pathway of microbial killing by WBCs

**Rapid consumption of $O^2$ that accompanies superoxide formation**

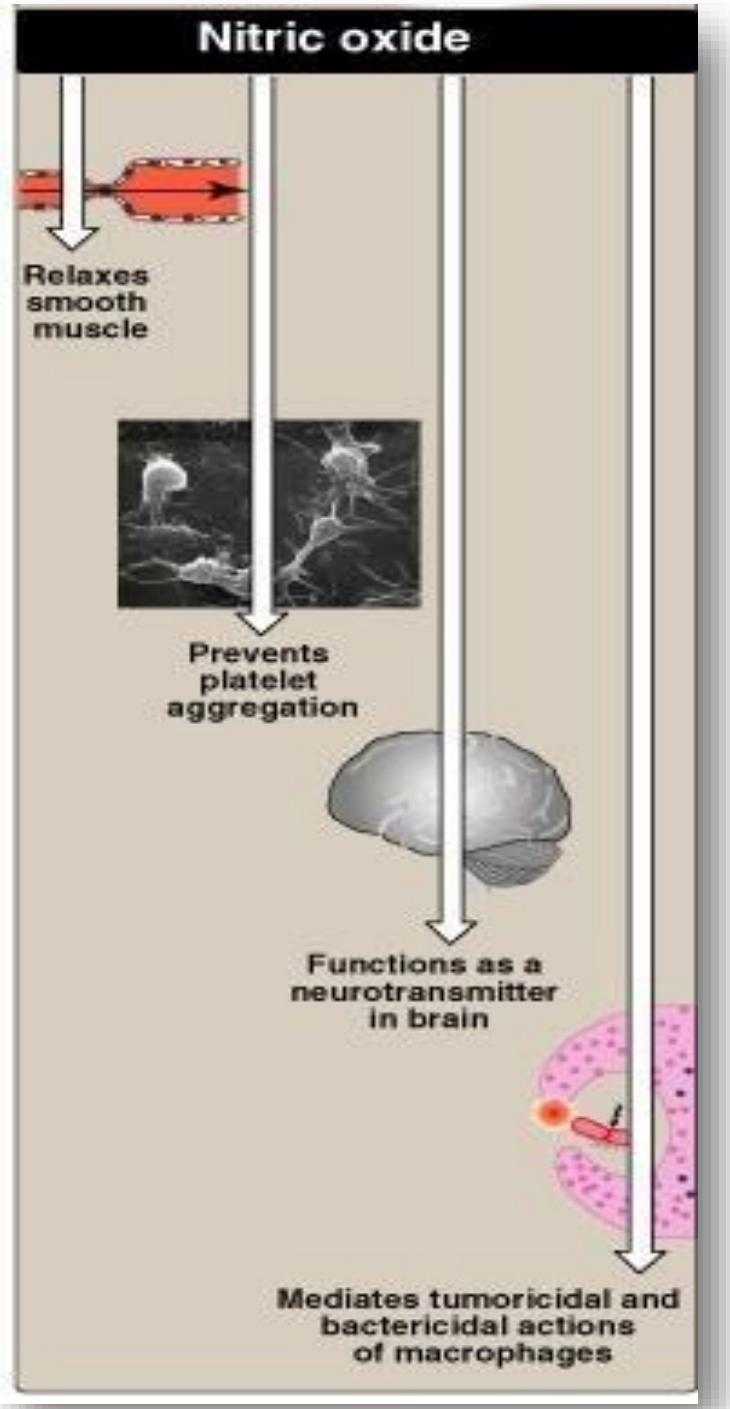


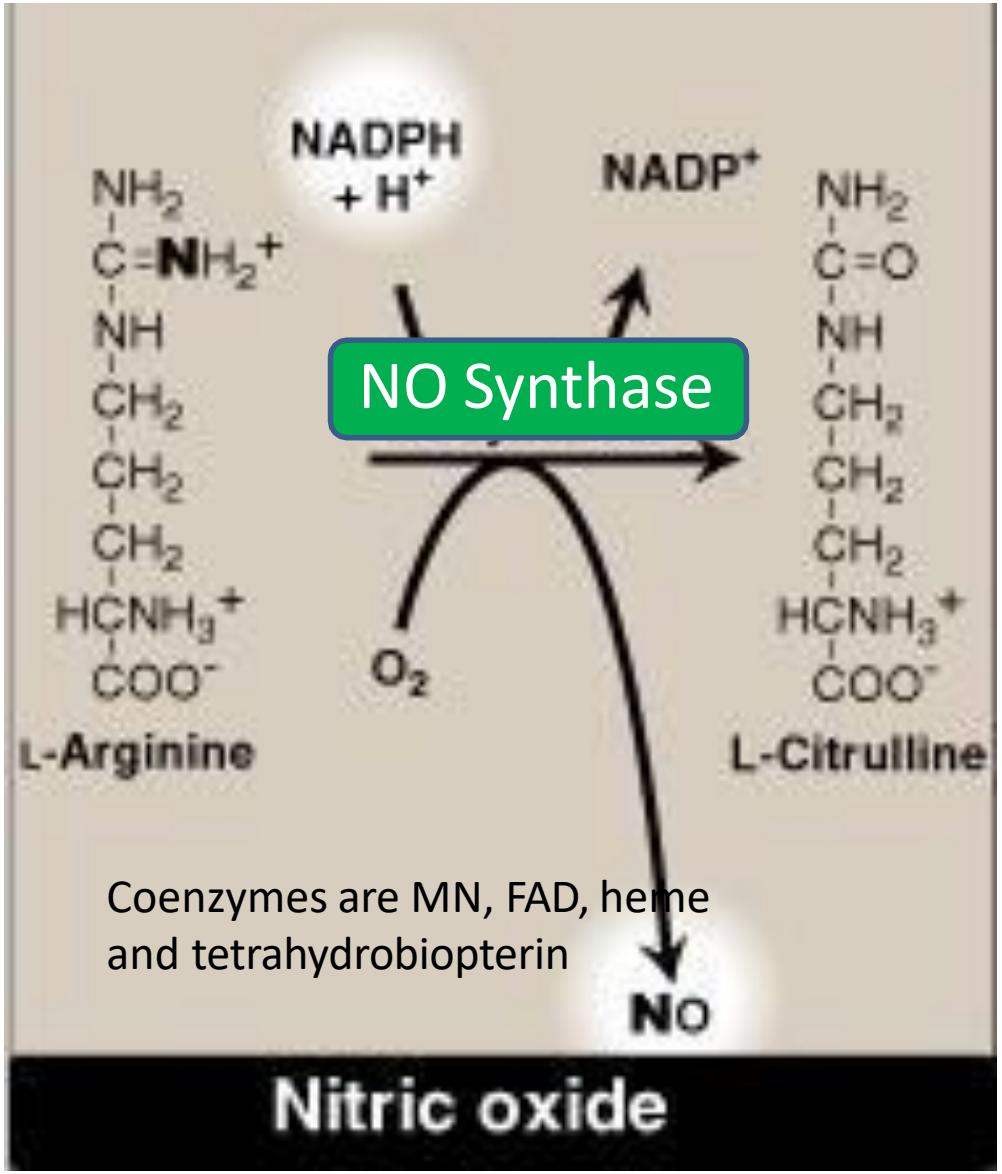

**H2O2 can also be reduced to water by catalase or glutathione peroxidase**

# NO and Reactive Nitrogen Oxygen Species (RNOS)

- 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

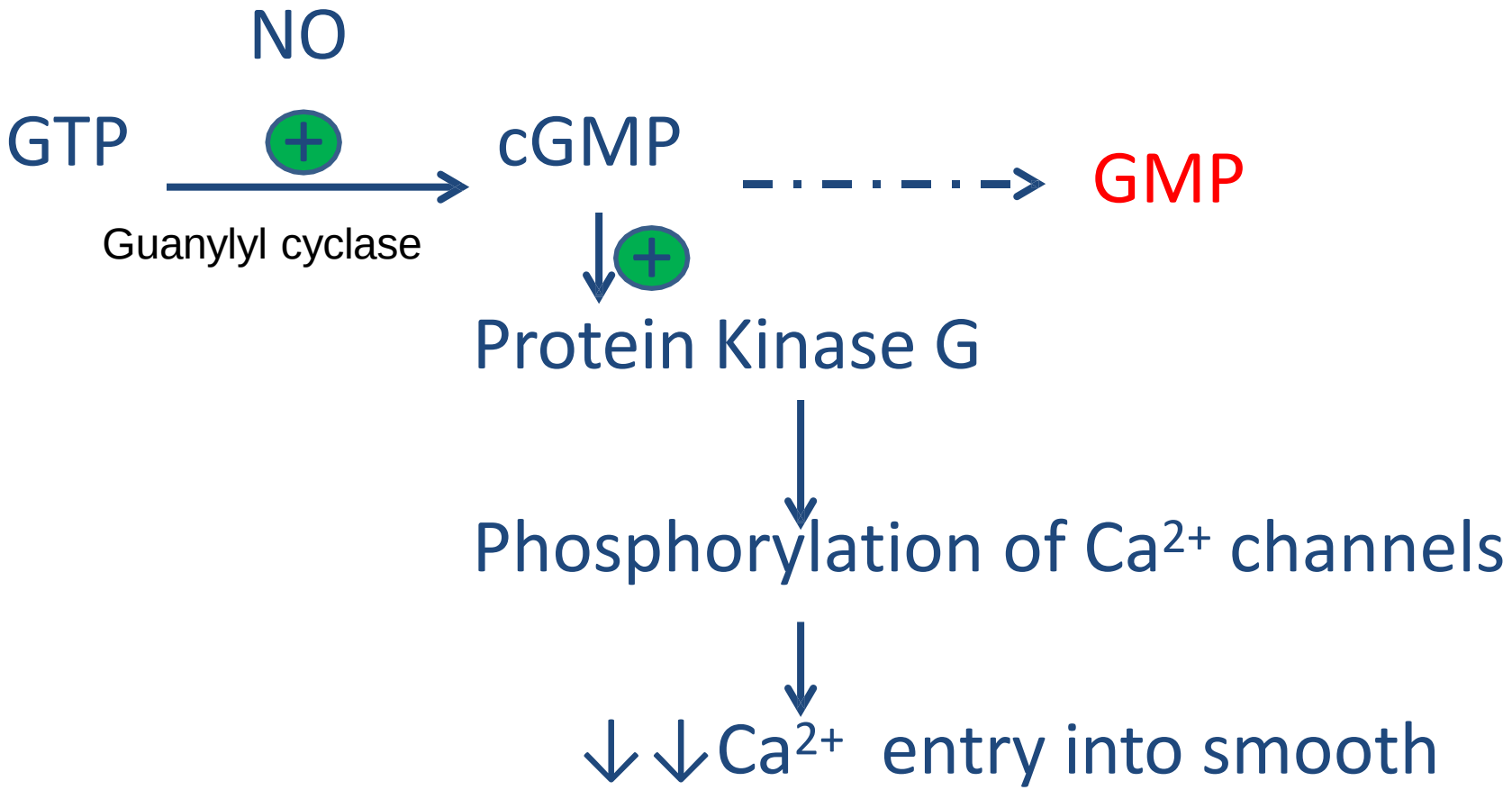



NO Synthase
Three isoforms
nNOS neural
eNOS endothelial
Both are constitutive

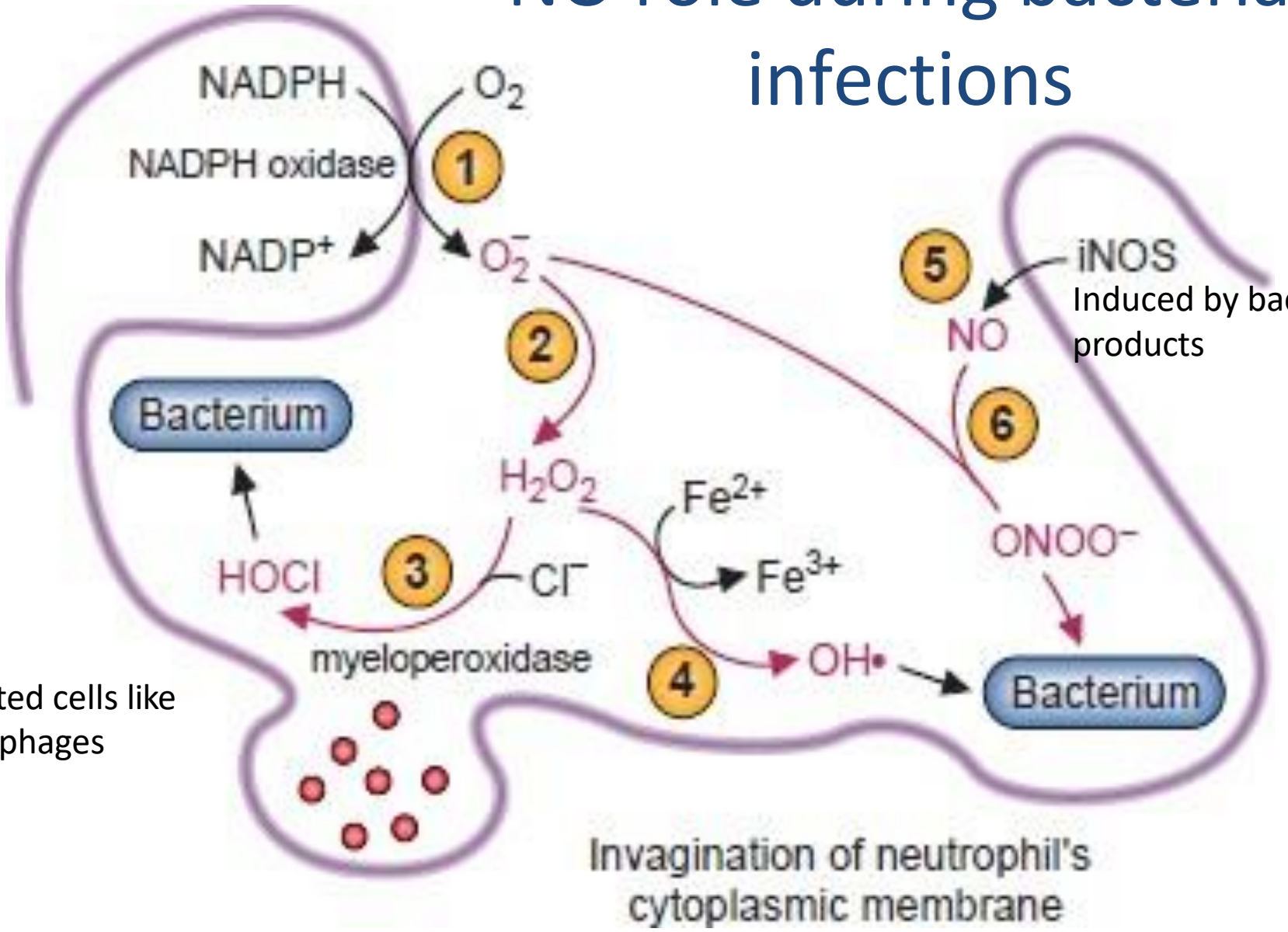
iNOS inducible Ca+2 independent
Induction of transcription in many cells of immune system➔↑↑ NO ➔ RNOS to kill invading bacteria

# Action of NO on vascular endothelium

Synthesis by endothelia cells → smooth muscle



# NO role during bacterial infections




Activated cells like macrophages

Hypochlorous acid