

# Oxidative Stress

Cardiovascular System Block

# Objectives

By the end of this lecture, the First Year students will be able to:

- ❖ Define oxidative stress
- ❖ Understand the harmful effects of oxidative stress to the cell and its diseases
- ❖ List the types, sources and effects of Reactive Oxygen Species (ROS)
- ❖ List various antioxidants in the body
- ❖ Understand the role of glutathione system in detoxifying oxidants in the body
- ❖ Discuss how G6PD deficiency leads to oxidative stress
- ❖ Understand the role of Reactive Nitrogen Species (RNS) in contributing to oxidative stress
- ❖ Correlate the role of oxidative stress to pathogenesis of atherosclerosis

# Overview

- ❖ Oxidative stress
- ❖ Reactive Oxygen Species (ROS): types, sources, effects
- ❖ Antioxidants
- ❖ Glutathione system
- ❖ G6PD deficiency
- ❖ Nitric oxide (NO): Reactive Nitrogen Species (RNS)
- ❖ Oxidative stress and atherosclerosis

# Oxidative stress

- ❖ A condition in which cells are exposed to excessive levels of:
  - ❖ Reactive Oxygen Species (ROS) or
  - ❖ Reactive Nitrogen Species (RNS)
- ❖ Cells are unable to neutralize their deleterious effects with antioxidants
- ❖ Oxidative stress is implicated in atherosclerosis, CAD, ageing

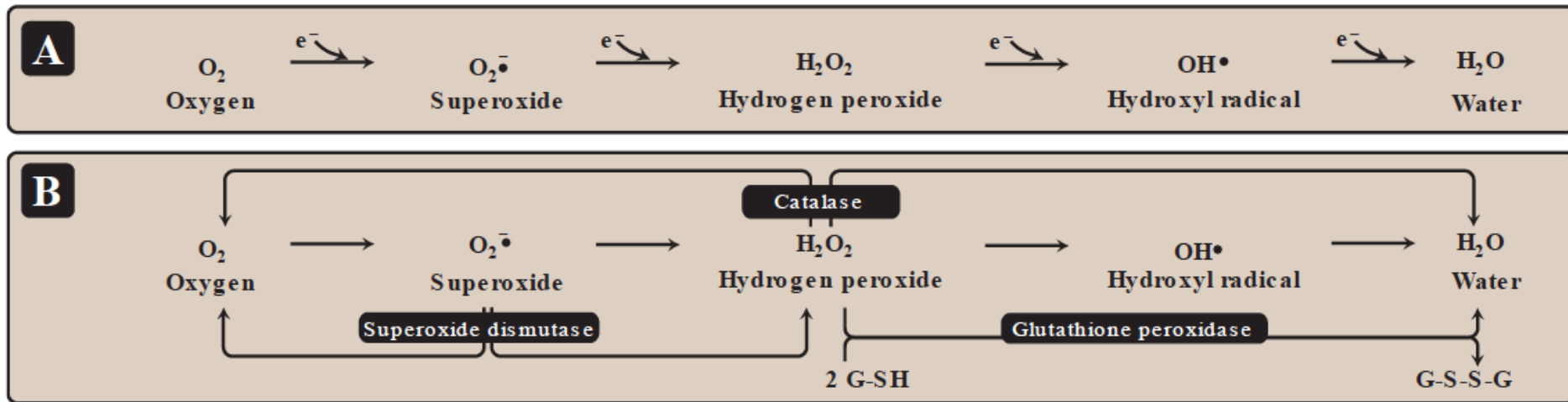
# Oxidative stress

- ❖ Cellular imbalance of oxidants and antioxidants damages:
  - ❖ DNA, proteins, lipids
- ❖ Diseases due to oxidative stress:
  - ❖ Inflammatory diseases (rheumatoid arthritis), atherosclerosis, CAD, obesity, cancer, G6PD deficiency hemolytic anemia

# Reactive Oxygen Species (ROS)

- ❖ Incomplete reduction of oxygen to water produces ROS
- ❖ ROS are continuously formed:
  - ❖ As byproducts of aerobic metabolism
  - ❖ Thru reactions with drugs and toxins
  - ❖ When cellular antioxidant level is low
  - ❖ Creating oxidative stress in cell
- ❖ ROS can damage DNA, proteins, unsaturated lipids → cell death
- ❖ Cells have protective antioxidant mechanisms that neutralize ROS

# Reactive Oxygen Species (ROS)



**Figure 13.5**

A. Formation of reactive intermediates from molecular oxygen.  $e^-$  = electrons. B. Actions of antioxidant enzymes. G-SH = reduced glutathione; G-S-S-G = oxidized glutathione. (See Figure 13.6B for the regeneration of G-SH.)

# Types and sources of ROS

- ❖ Free radicals:
  - ❖ Superoxide ( $O_2^{\bullet-}$ )
  - ❖ Hydroxyl radical ( $OH^{\bullet}$ )
- ❖ Non-free radical:
  - ❖ Hydrogen peroxide ( $H_2O_2$ )
- ❖ Sources:
  - ❖ Aerobic metabolism
  - ❖ Partial reduction of molecular oxygen in ETC
  - ❖ Ingestion of drugs, toxins, chemicals

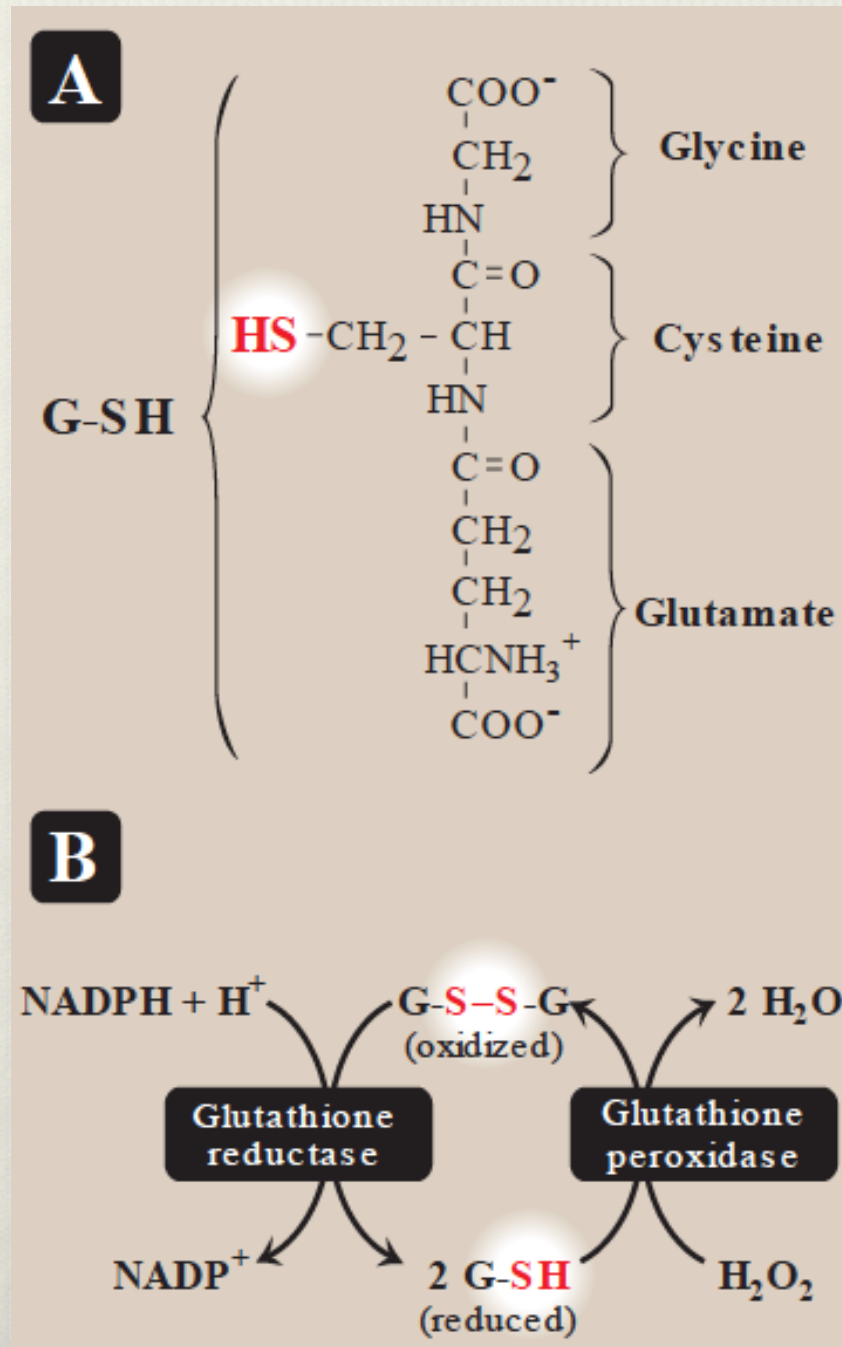


# Antioxidants

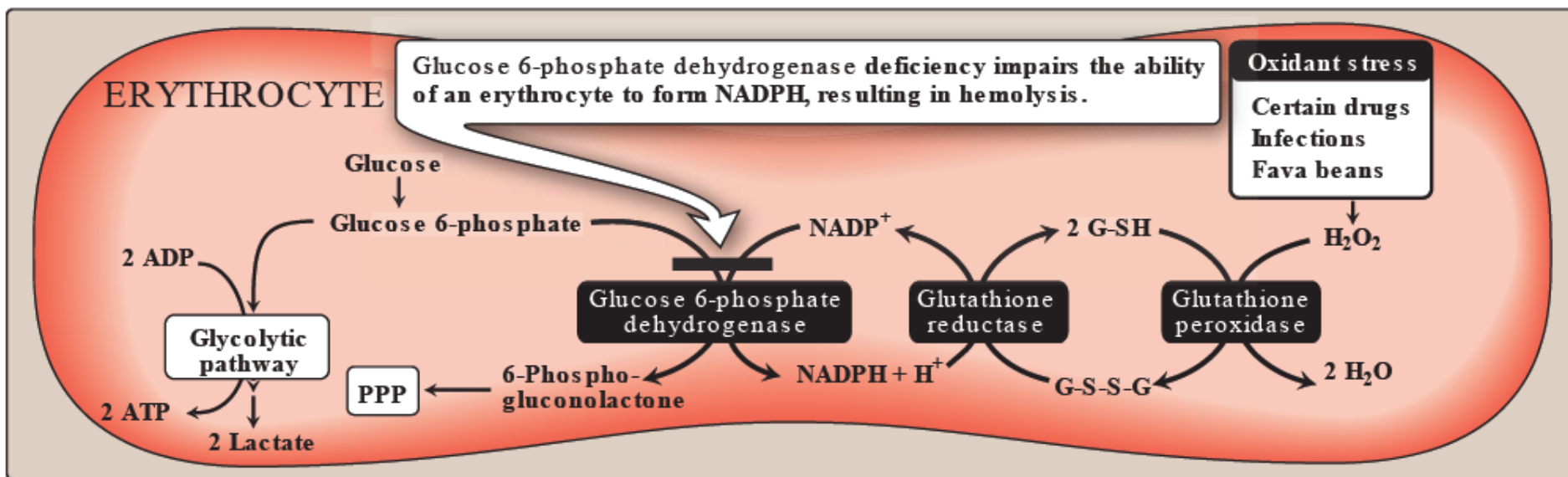
- ❖ Enzymes:
  - ❖ Superoxide dismutase
  - ❖ Catalase
  - ❖ Glutathione system
- ❖ Vitamins:
  - ❖ Vitamins A, C, E
  - ❖  $\beta$ -Carotene

# Glutathione system

- ❖ Present in most cells
- ❖ Chemically detoxifies  $\text{H}_2\text{O}_2$
- ❖ Catalyzed by glutathione reductase
- ❖ Produces NADPH that reduces  $\text{H}_2\text{O}_2$



# G6PD deficiency



**Figure 13.10**

Pathways of glucose 6-phosphate metabolism in the erythrocyte. NADP(H) = nicotinamide adenine dinucleotide phosphate; G-SH = reduced glutathione; G-S-S-G = oxidized glutathione; PPP = pentose phosphate pathway.

- ❖ Leads to NADPH deficiency
- ❖ Cells are unable to reduce free radicals
- ❖ Oxidation of cellular proteins is increased causing impaired cell functions

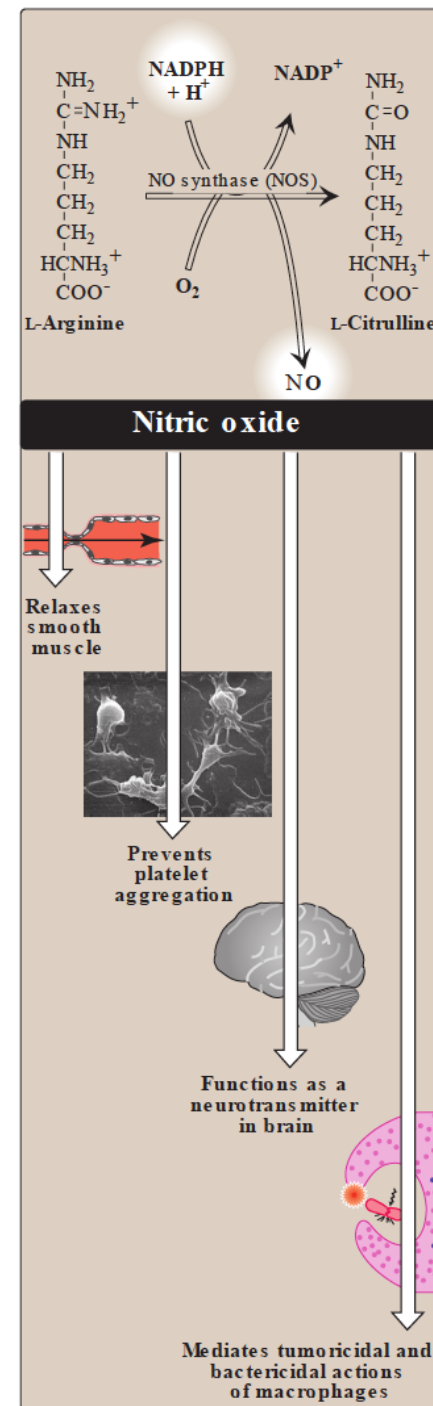
# Effects of ROS

- ❖ Lipid peroxidation (polyunsaturated fatty acids)
- ❖ DNA damage
- ❖ Protein denaturation
- ❖ Cytoskeletal damage
- ❖ Chemotaxis
- ❖ Cell signaling effects
  - ❖ Release of  $\text{Ca}^{2+}$  from intracellular stores
- ❖ Altered vascular tone
- ❖ Increased endothelial cell permeability

# Nitric oxide (NO)

- ❖ Endothelial-derived relaxing factor
- ❖ Causes vasodilation by relaxing vascular smooth muscle
- ❖ NO is a gas with short half-life (3-10 sec)
- ❖  $\text{NO} + \text{Oxygen/Superoxide} \rightarrow \text{Nitrates, Nitrites, Peroxynitrite (O=NOO}^-)$
- ❖ Peroxynitrite is a Reactive Nitrogen Species (RNS)

Synthesis and some of the actions of nitric oxide (NO). NADPH = reduced nicotinamide adenine dinucleotide phosphate. [Note: Flavin mononucleotide, flavin adenine dinucleotide, heme, and tetrahydrobiopterin are additional coenzymes required by NOS.]



# Nitric oxide (NO)

- ❖ NO is produced by nitric oxide synthase:
  - ❖ eNOS in the endothelium (vaso-relaxation)
  - ❖ nNOS in the neural tissue (neurotransmission)
  - ❖ iNOS in macrophages, neutrophils (infection)
  - ❖ bNOS (bacterial)
- ❖ iNOS activity (normally low) increased by infection and pro-inflammatory cytokines
- ❖ Activated macrophages produce  $O_2^{\bullet-}$  radical + NO → OH• radical → highly bactericidal
- ❖ Increased iNOS activity → free radicals → oxidative stress

# Oxidative stress and atherosclerosis

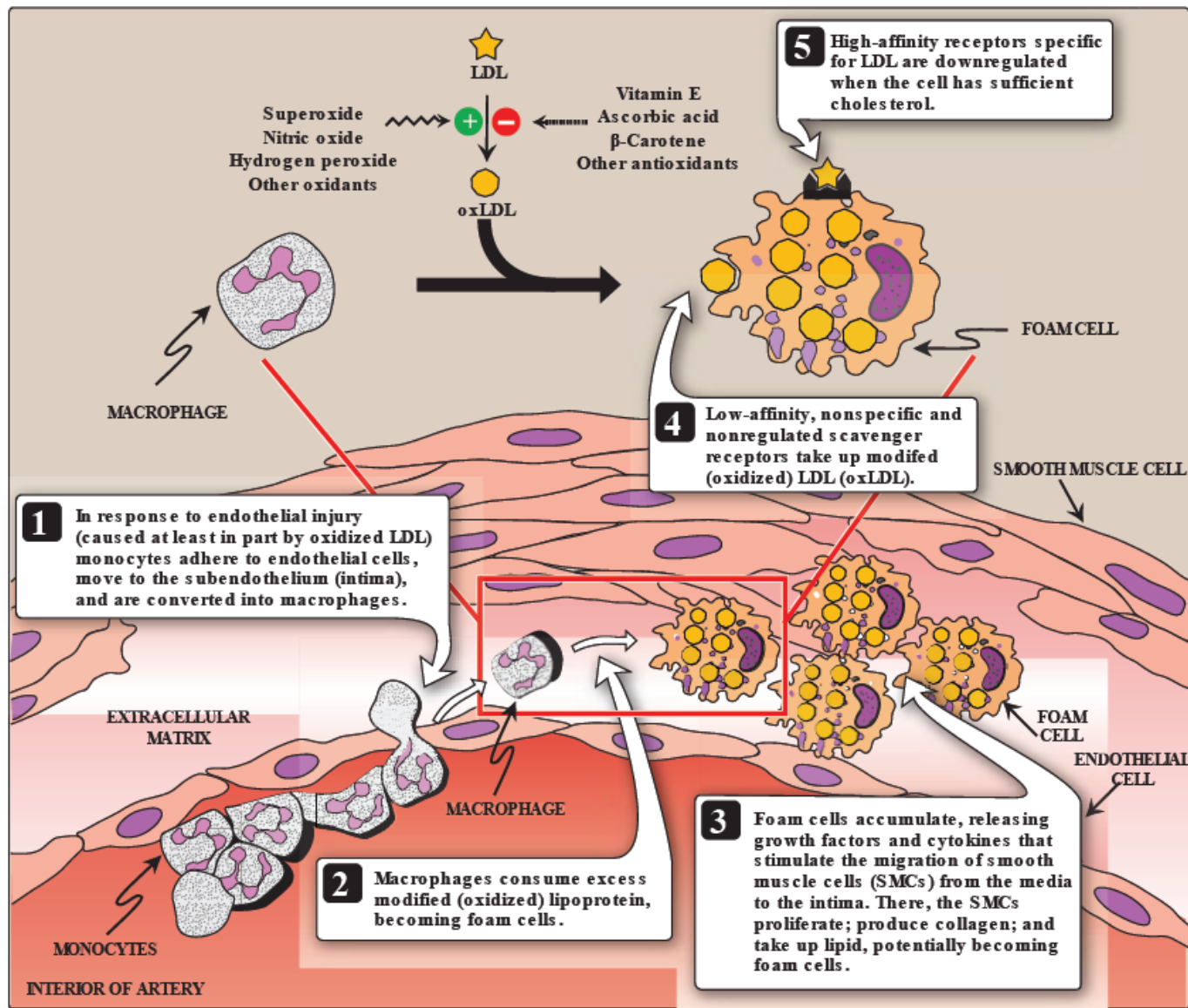


Figure 18.22

Role of oxidized lipoproteins in plaque formation in an arterial wall. LDL = low-density lipoprotein.



# Take home message

- ❖ Oxidative stress is due to excessive production of ROS and NOS in the cells.
- ❖ Cells neutralize these oxidants by a number of antioxidant processes.
- ❖ Imbalance between oxidants and antioxidants in the cells can result in the development of many diseases including atherosclerosis.

# References

- ❖ Lippincott's Biochemistry, 6<sup>th</sup> Edition, Chapter 13, pp. 148-152. Lippincott Williams & Wilkins, New York, USA.