Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency Anemia

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Objectives:

By the end of this lecture, the student should be able to:

- Explain the biochemical basis of G6PD deficiency anemia
- Recognize the precipitating factors for G6PD deficiency anemia
- Classify various classes of G6PD deficiency anemia (variant enzymes)
- Describe the diagnostic methods for G6PD deficiency anemia

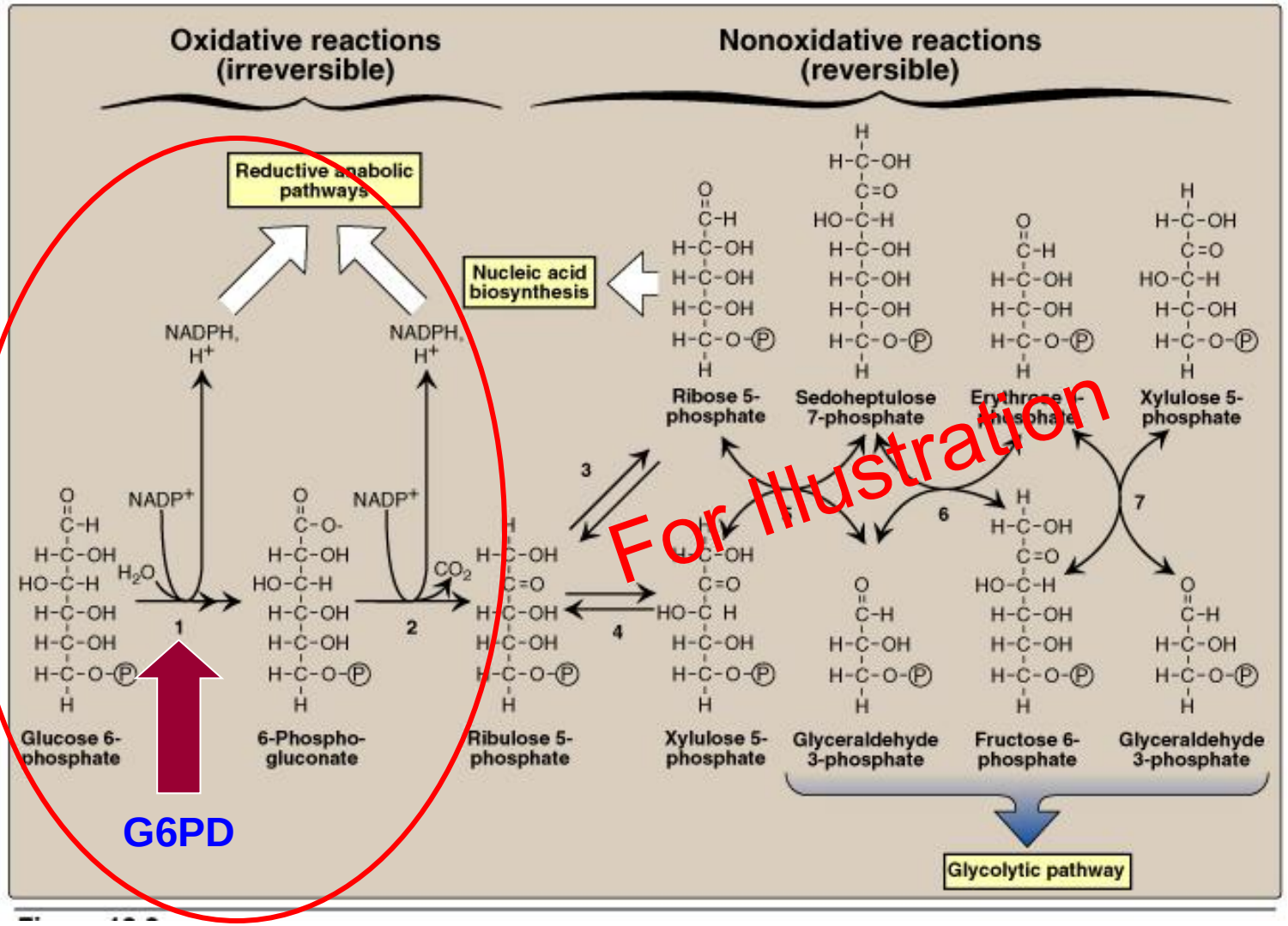
Background

Hexose monophosphate pathway (HMP) or

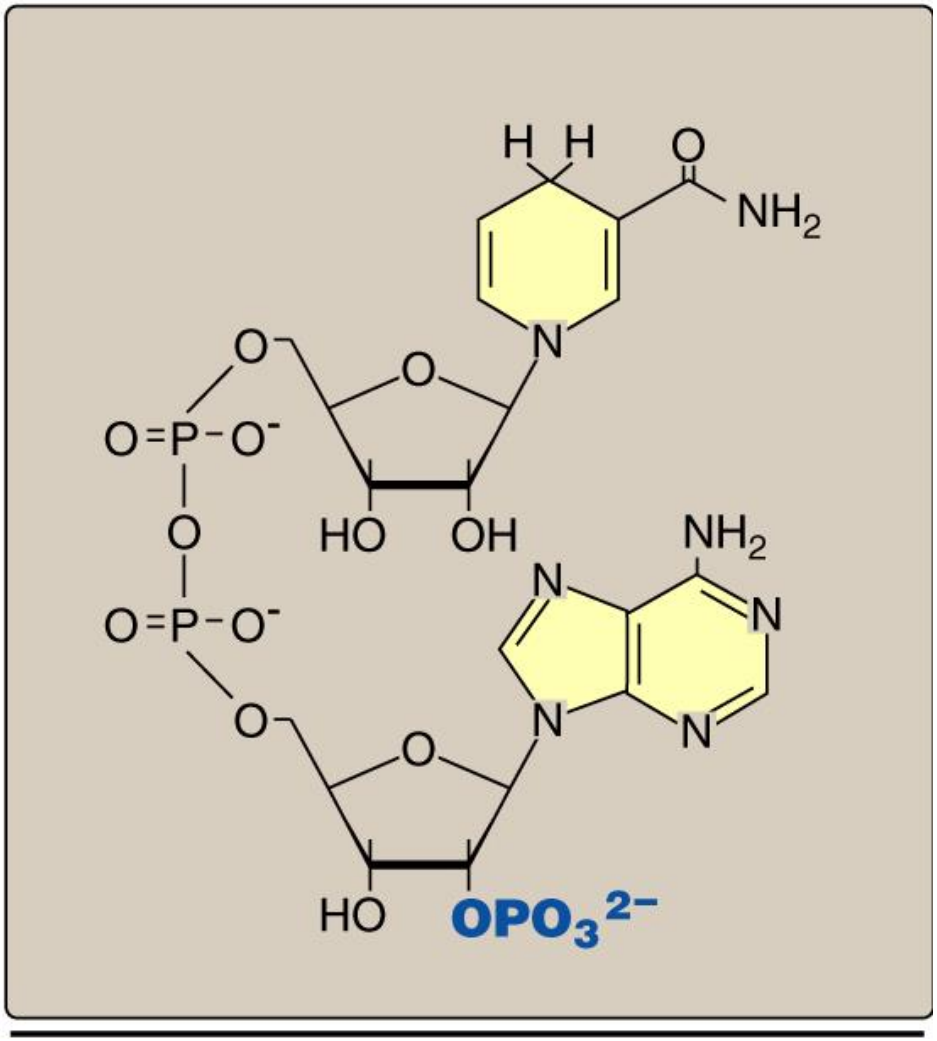
Pentose Phosphate Pathway (PPP):

- An alternative oxidative pathway for glucose
- No ATP production
- Major pathway for NADPH production
- Produces ribose-5-phosphate for nucleotide synthesis

Pentose Phosphate Pathway (PPP)



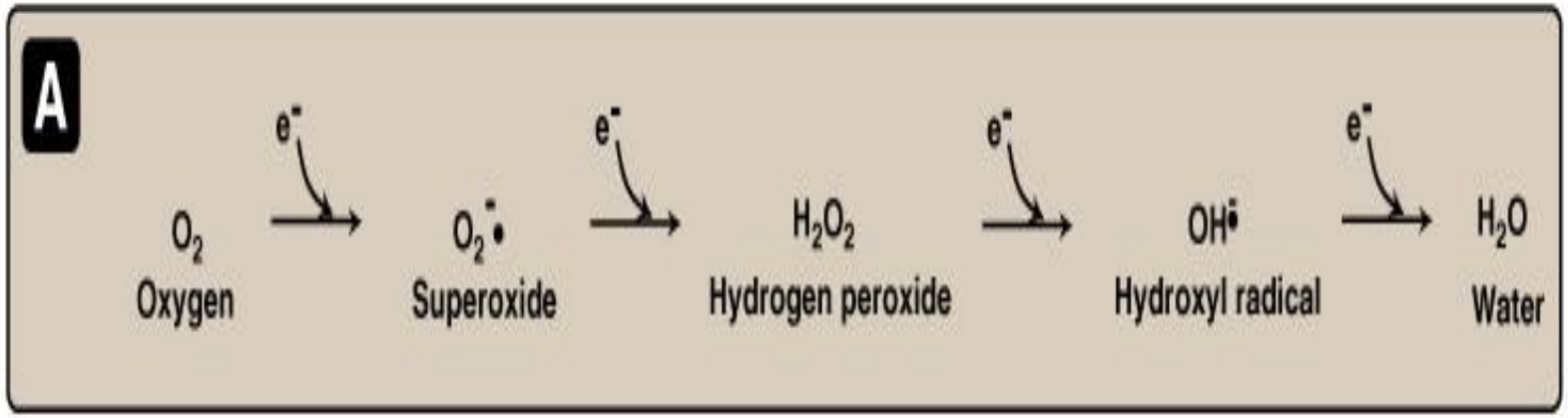
NADPH



Uses of NADPH

- Reductive biosynthesis e.g., fatty acid biosynthesis
- **Antioxidant (part of glutathione system)**
- Oxygen-dependent phagocytosis by WBCs
- Synthesis of nitric oxide (NO)

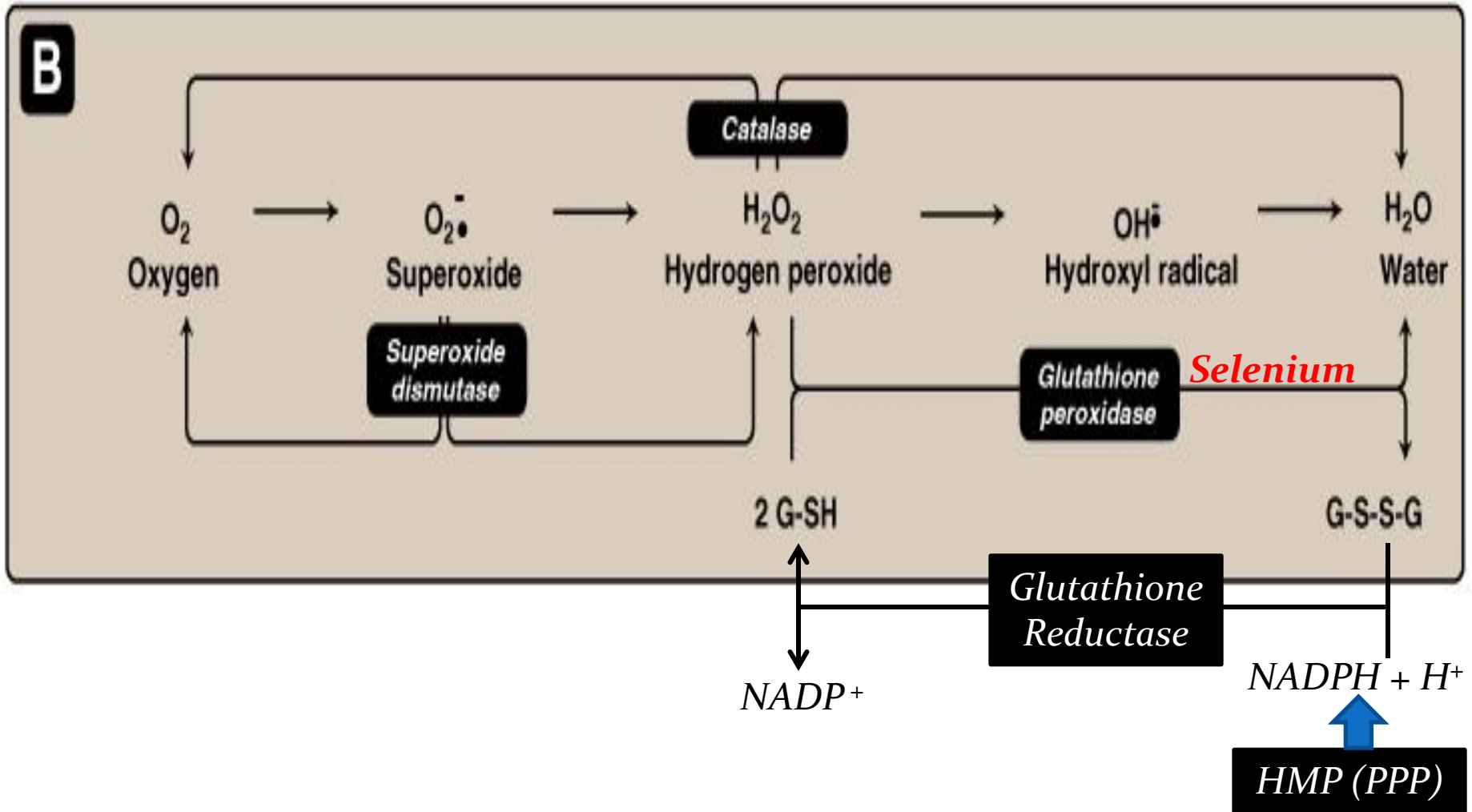
Reactive Oxygen Species (ROS)



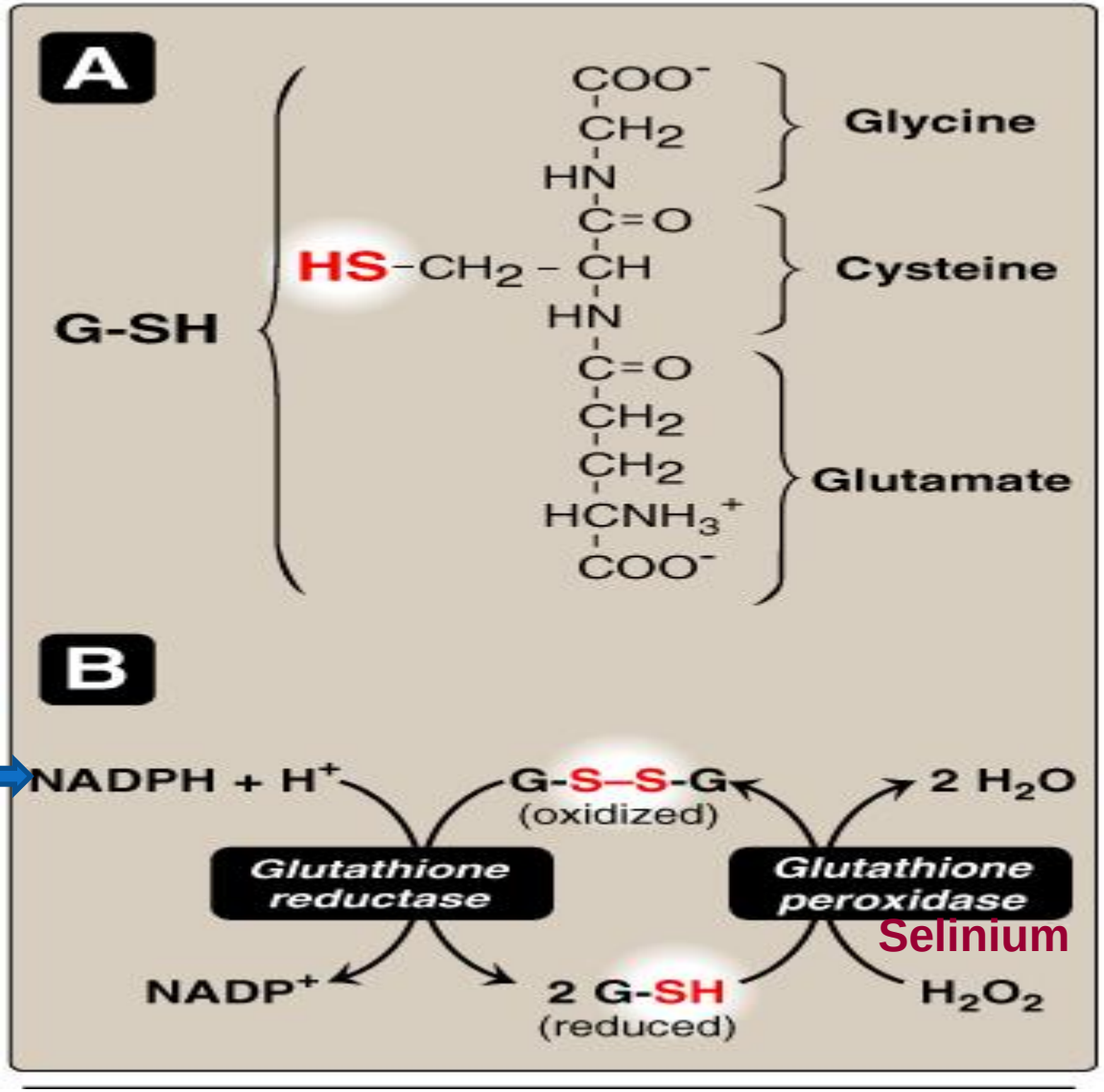
Oxygen-derived Free radicals :e.g., Superoxide and hydroxyl radicals

Non-free radical: Hydrogen peroxide

Antioxidant Mechanisms



Glutathione System



HMP (PPP)

Oxidative Stress

Imbalance between oxidant production and antioxidant mechanisms

Oxidative damage to:

DNA

Proteins

Lipids (unsaturated fatty acids)

Oxidative stress and diseases:

Inflammatory conditions e.g., Rheumatoid arthritis

Atherosclerosis and coronary heart diseases

Obesity

Cancers

G6PD deficiency hemolytic anemia

G6PD Deficiency Hemolytic Anemia

Inherited X-linked recessive disease

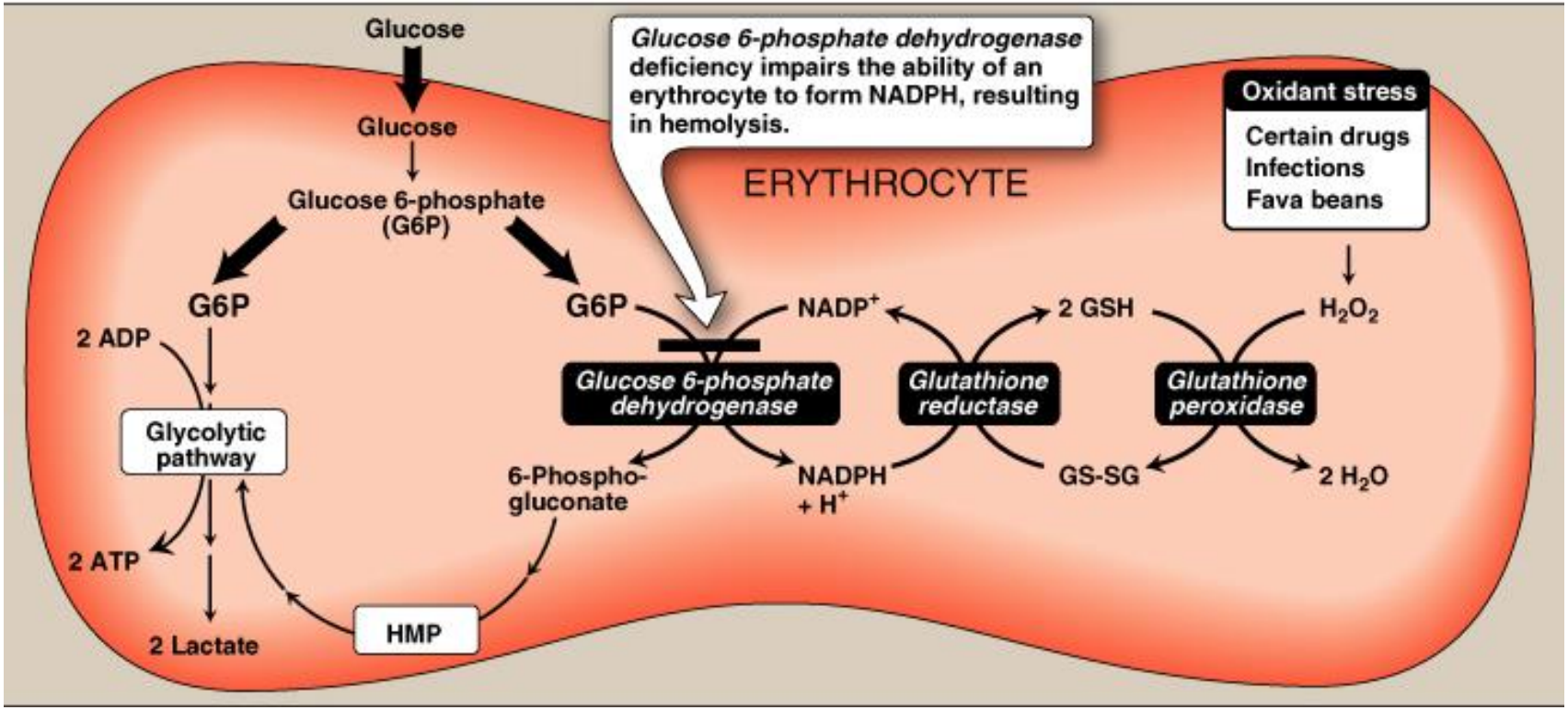
Most common enzyme-related hemolytic anemia

Highest prevalence: Middle East, Tropical Africa
Asia and Mediterranean

~400 different mutations affect G6PD gene, but only some can cause clinical hemolytic anemia

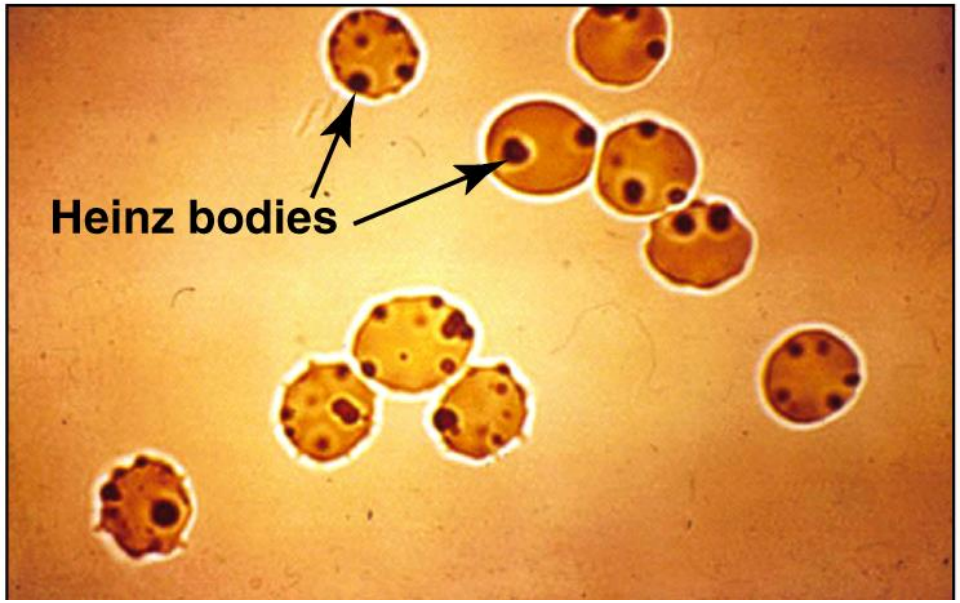
G6PD deficient patients have increased resistance to infestation by falciparum malaria

Biochemical Basis of G6PD Deficiency Hemolytic Anemia



Biochemical Basis of G6PD Deficiency Hemolytic Anemia, continued…

Oxidation of sulfhydryl (SH) groups of proteins inside RBCs causes protein denaturation and formation of insoluble masses (Heinz bodies) that attach to RBCs membranes



Biochemical Basis of G6PD Deficiency Hemolytic Anemia, continued…

Although G6PD deficiency affects all cells, it is most severe in RBCs …… Why?

Other cells have other sources for NADPH production:
e.g., Malic enzyme that converts malate into pyruvate

Precipitating Factors for G6PD Deficiency Hemolytic Anemia

G6PD deficient patients will develop hemolytic attack upon:

1. **Intake of oxidant drugs (AAA):**
   - **Antibiotics e.g., sulfa preparation**
   - **Antimalarial: e.g., Primaquine**
   - **Antipyretics**
2. **Exposure to infection**
3. **Ingestion of fava beans (favism, Mediterranean variant)**

Chronic nonspherocytic anemia: Hemolytic attack in absence of precipitating factors. Severe form due to class I mutation

Different Classes of G6PD Deficiency Hemolytic Anemia

- There are 4 different classes:
  - I (Very severe)
  - II (Severe, e.g. Mediterranean)
  - III: (Moderate: G6PD A-)
  - IV: (Normal)
- This classification is based on the residual enzyme activity (Least in class I, and Highest in class IV)

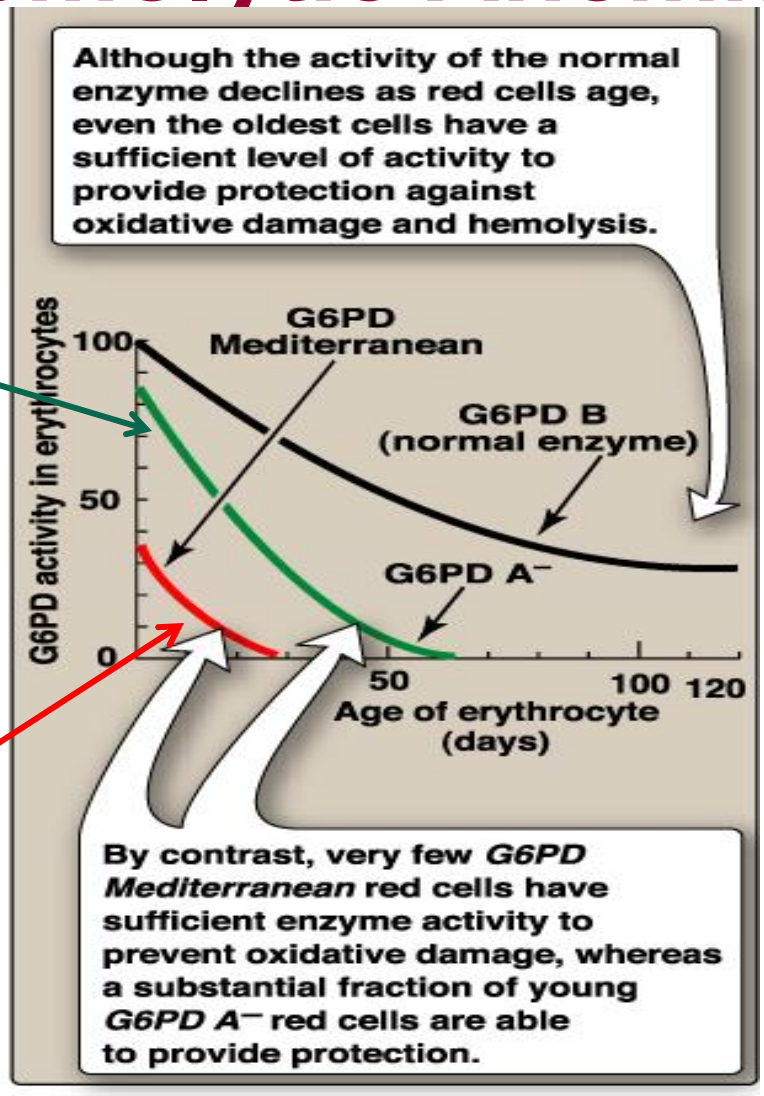
Variant Enzymes of G6PD Deficiency Hemolytic Anemia

G6PD A- (class III):

Moderate, young RBCs contain enzymatic activity. Unstable enzyme, but kinetically normal

G6PD Mediterranean (II)

Enzyme with decreased stability and activity (severe). Affect all RBCs (both young and old)



Diagnosis of G6PD Deficiency Hemolytic Anemia

Diagnosis of hemolytic anemia

Complete Blood Count (CBC) & reticulocytic count

Screening:

Qualitative assessment of G6PD enzymatic activity (UV-based test)

Confirmatory test:

Quantitative measurement of G6PD enzymatic activity

Molecular test:

Detection of G6PD gene mutation

Take Home Message

- G6PD deficiency impairs the ability of cells to form NADPH.
- RBCs are particularly affected because they do not have other sources of NADPH.
- NADPH is essential for the anti-oxidant activity of Glutathione peroxidase/reductase system

Take Home Message

- G6PD deficiency is an X-linked disease characterized by hemolytic anemia.
- The precipitating factors of hemolysis includes administration of oxidant drugs, ingestion of fava beans or severe infections.
- G6PD deficiency is classified according to the residual activity of the G6PD
- Class I variant (the most severe) class is associated with chronic nonspherocytic hemolytic anemia.

Reference

- Lippincott's Illustrated Reviews in Biochemistry, 6th edition, Chapter 13, pages 152-154