

G6PD

Editing File

Color Index

- Main Text
- Important
- Extra
- Dr.'s Notes
- Girls slides
- Boys slides

Objectives



Explain the biochemical basis of G6PD deficiency anemia



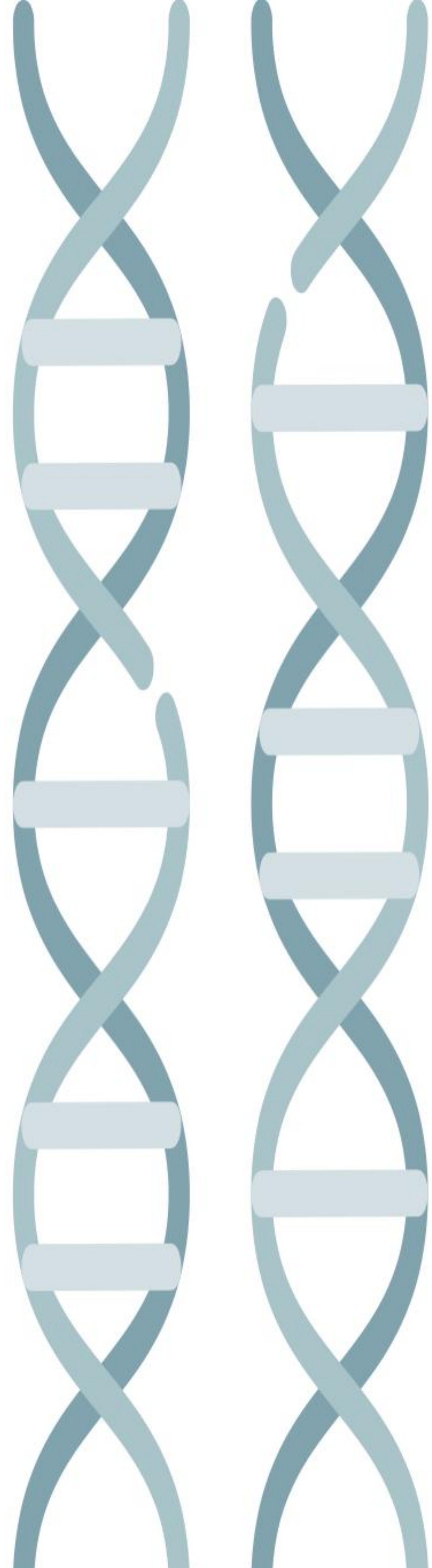
Recognize the precipitating factors for G6PD deficiency anemia



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):

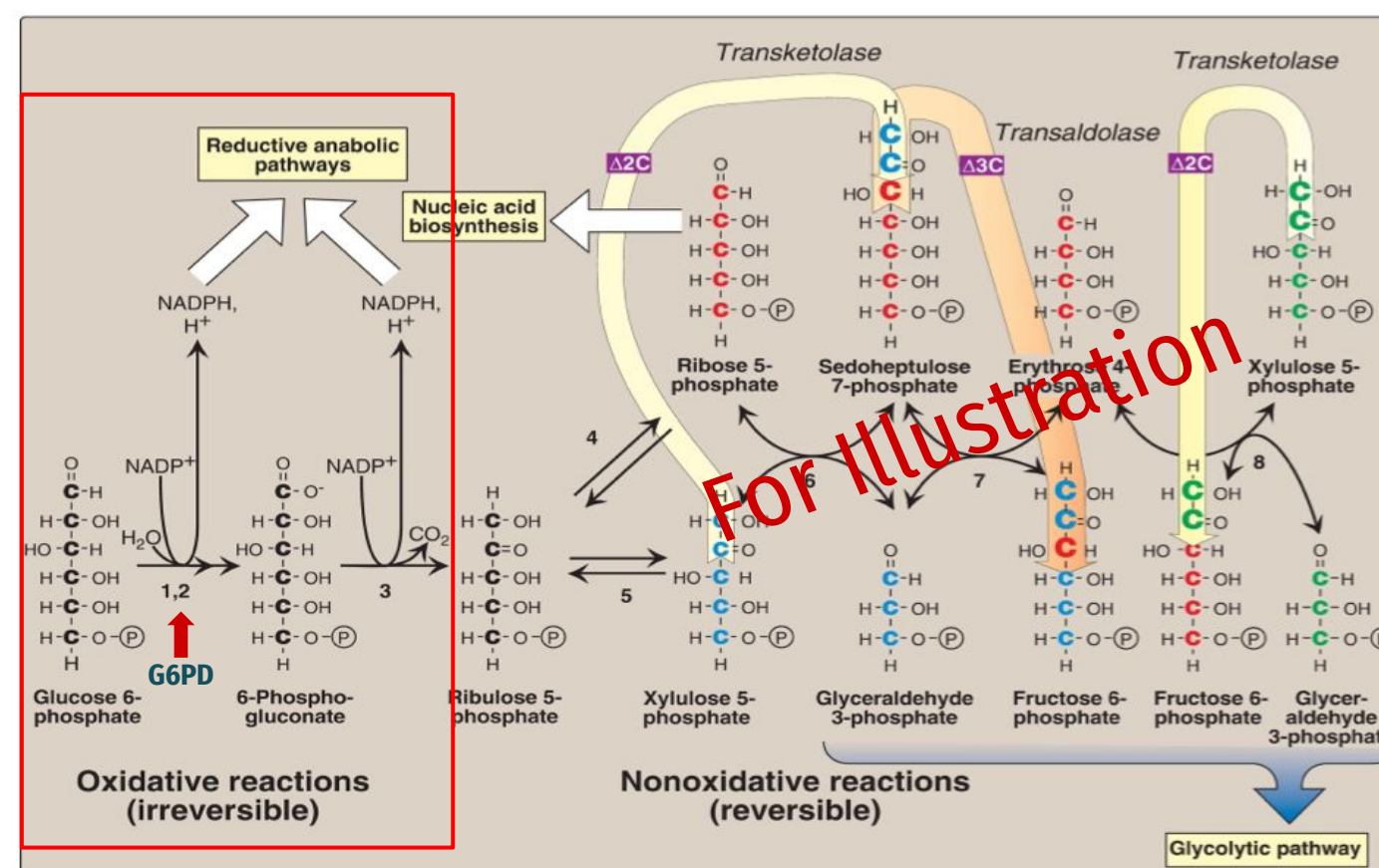
Major pathway for **NADPH** production.

An **alternative** oxidative pathway for **glucose**.

No ATP production.

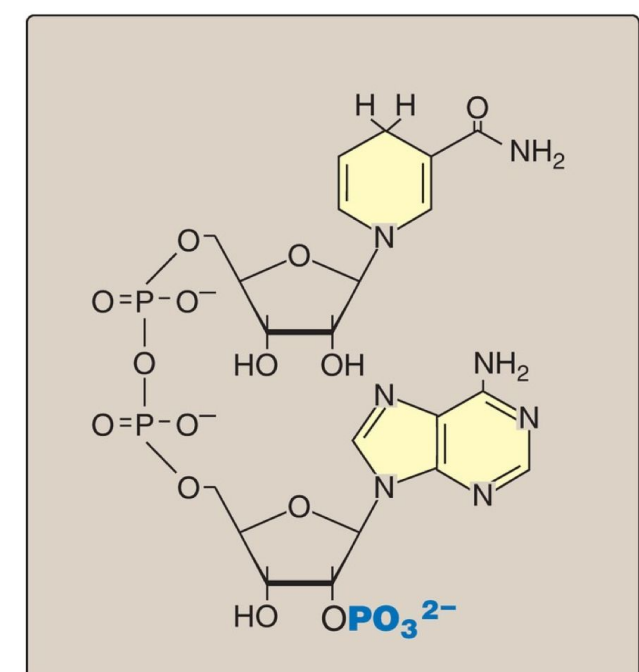
Produces **ribose-5-phosphate** for nucleotide synthesis

Pentose Phosphate Pathway (PPP)



Uses of NADPH

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



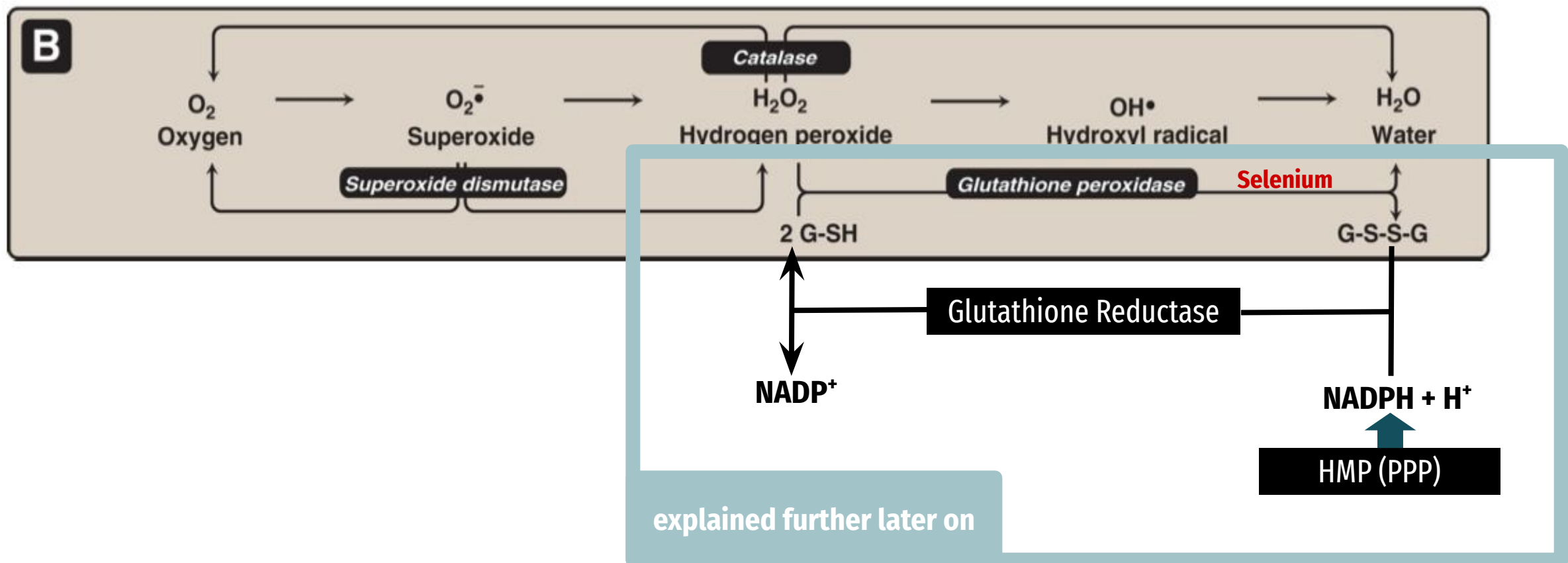
Structure of NADPH

Antioxidant Mechanisms

Let's start with Anti-oxidant mechanisms to understand the relationship between **G6PD** and **Anemia**!

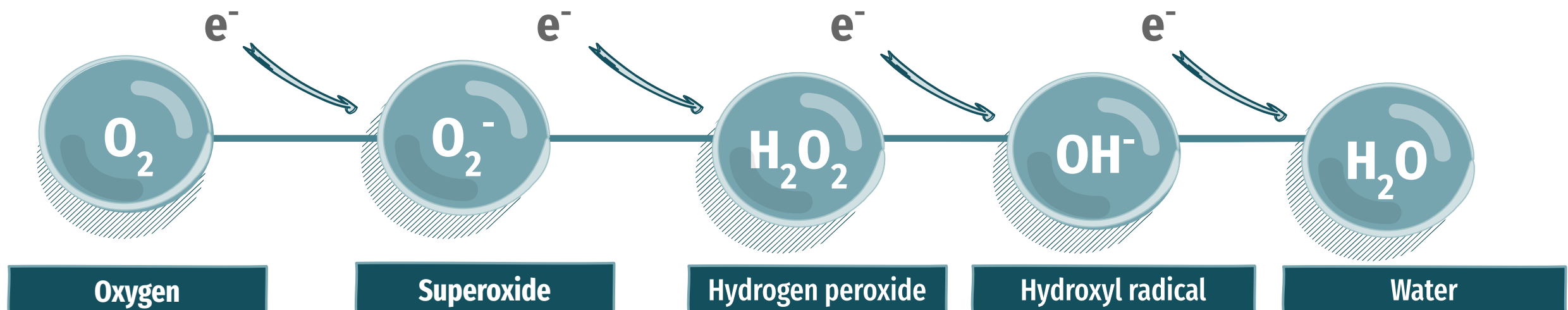
: Harmless **أولاً، الغاية ننتهي بنتيجة**

H₂O₂ transform to H₂O by Glutathione system



Reactive Oxygen Species (ROS)

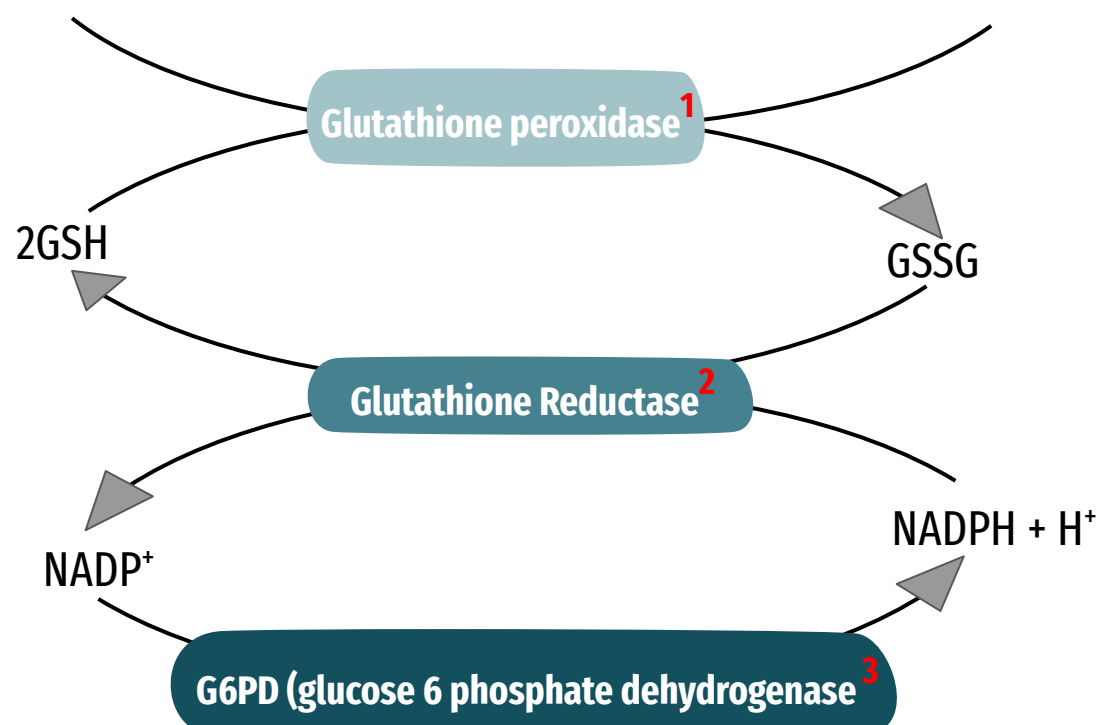
[Click here for the original picture](#)



⊙ **Oxygen-derived Free radicals:** **Superoxide** and **Hydroxyl radicals**

⊙ **Non-free radical:** **Hydrogen peroxide**

Glutathione System



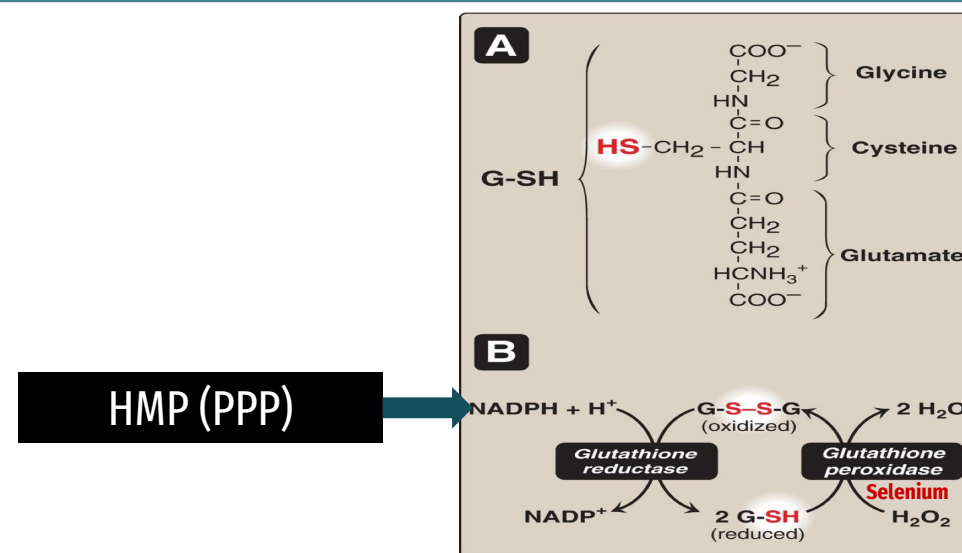
G6PD is a **key and rate limiting enzyme** in the **pentose phosphate pathway (PPP)**
Aka: **Hexose monophosphate pathway (HMP)**

This information was written/drawn in the pictures of the dr's slides.
The original picture in the next slide.

	Substrate	End product	Action
glutathione peroxidase ¹	2GSH (Reduced form)	GSSG (Oxidized form)	Oxidase > loss of e ⁻ from reduced form 2GSH > become oxidized > GSSG
Glutathione Reductase² (يحتاج مساعد مايشغل ل حاله)	GSSG (Oxidized form)	2GSH (Reduced form) Reduced glutathione is essential for maintaining the normal structure of red blood cells and for keeping hemoglobin in the ferrous state.	Reductase > gain of e ⁻ from NADPH give e ⁻ to the oxidized form (GSSG) > become reduced (2GSH)
G6PD (المساعد: Glucose 6 phosphate dehydrogenase)	NADP (Oxidized form)	NADPH + H (Reduced form)	-

- معنى ذلك ان **NADPH** هو أصل كل العملية
- How NADPH + H can be formed ? By G6PD
- In which pathway ? **pentose phosphate pathway (PPP)**
- so **deficiency** in this enzyme will decrease the anti-oxidant sequence > oxidation stress in many cells but **much severe in RBCs** > lead to **hemolysis** > **hemolytic anemia**
- why the oxidation stress is server in RBCs? Because the Other cells have other sources for NADPH production.

Glutathione System cont..



This picture was explained in details in previous slide

Oxidative Stress

Imbalance between **oxidant production** and **antioxidant mechanisms**
Whenever oxidation is increased, RBC will need G6PD > if G6PD is insufficient > the oxidative stress will occur

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:

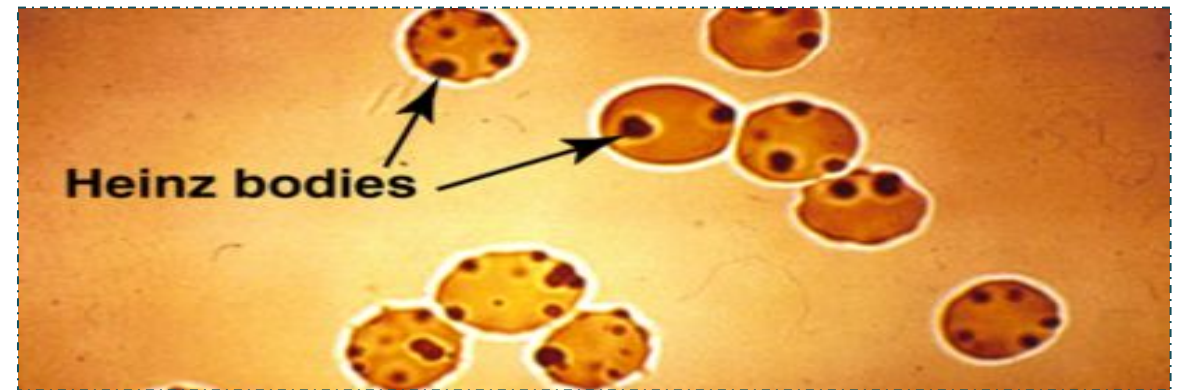
- Inherited X-linked recessive disease
- Most common enzyme-related hemolytic anemia
- Highest prevalence: Middle East, Tropical Africa Asia and Mediterranean
- ~400 different mutations affect G6PD gene, but only some can cause clinical hemolytic anemia.
- G6PD deficient patients have increased resistance to infestation by falciparum malaria ¹

1) This happens because

- Malaria cannot live well in the RBCs if they are hemolyzed
- G6PD deficiency will cause an increase in free radicals which will also damage the parasite

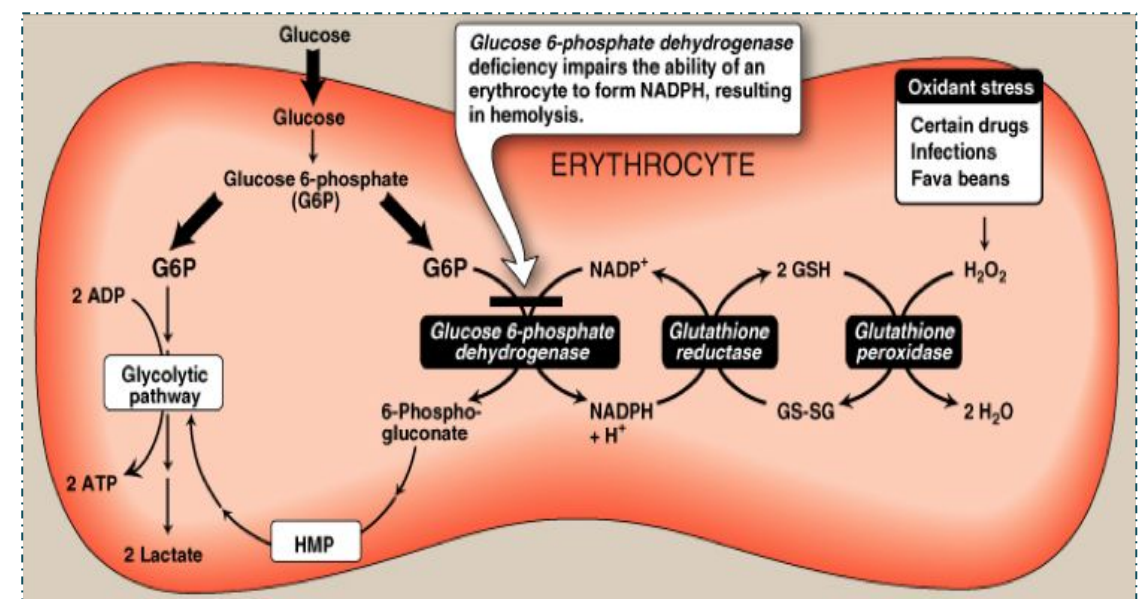
Biochemical Basis of G6PD Deficiency Hemolytic Anemia

Oxidation of sulfhydryl [because there is little or no reductive agents (NADPH)] (SH) groups of proteins inside RBCs causes protein denaturation and formation of insoluble masses (**Heinz bodies**) that attach to RBCs membranes



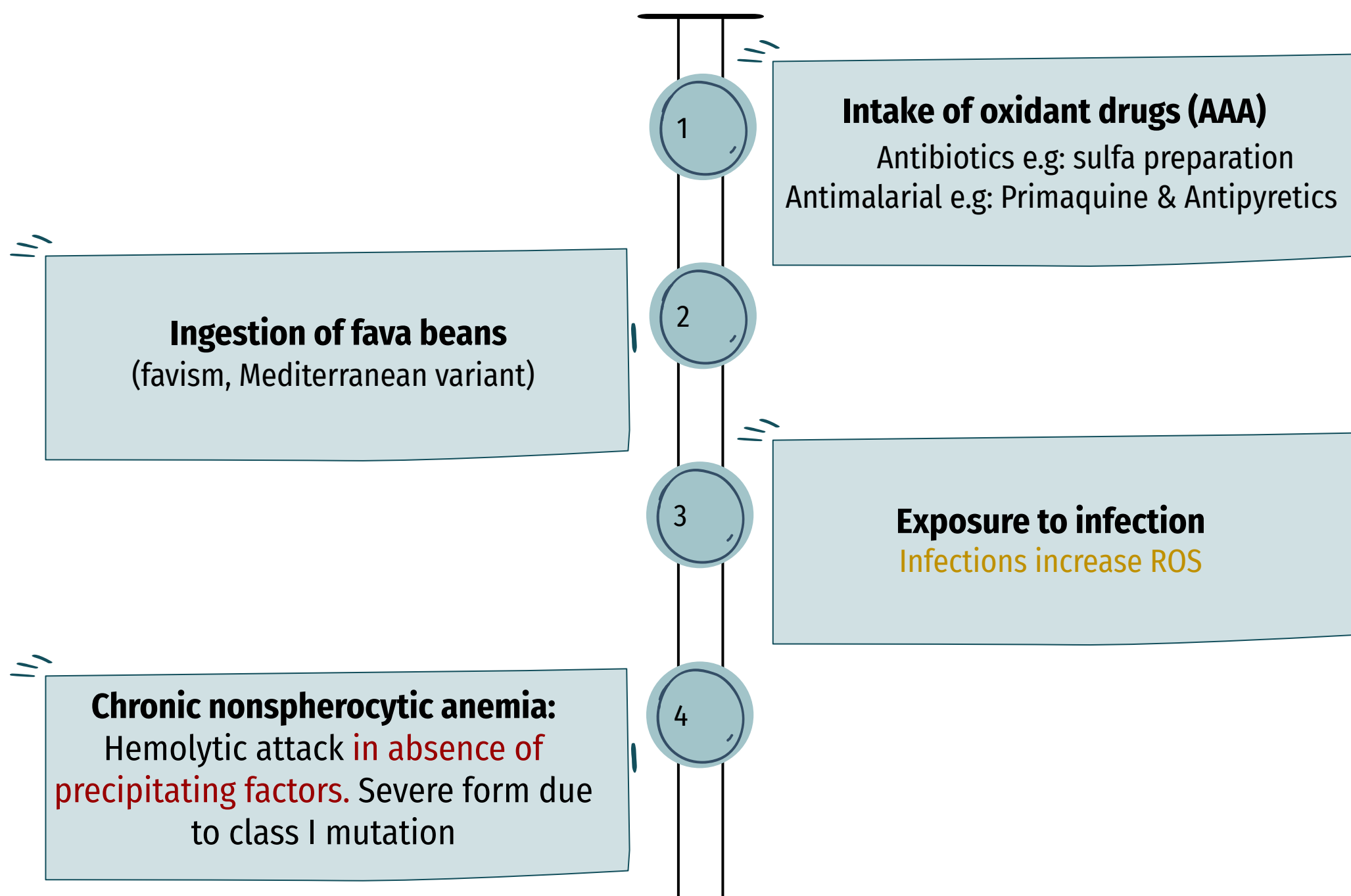
طيب للحين مافهمنا، وإذا لصقت كتل على جدار الخلية شبيصير؟
RBCs will pass through spleen
طبعا يستقعد عليها
Spleen by its macrophages in sinusoids
بيروح يأكل المكان اللي فيه الترسبات هذي، فالشكل الناتج للخلية بيصير مشوهة كأنه أكل معروف أو معضوض
Known as bite cell

Al though 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



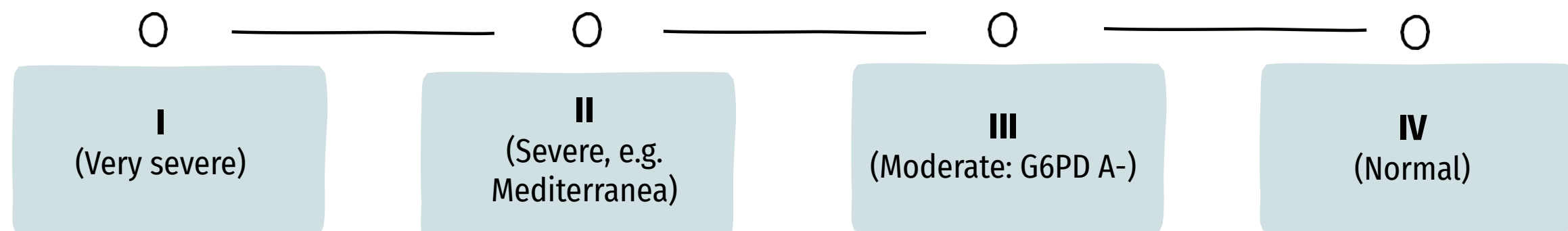
Precipitating Factors for G6PD Deficiency Hemolytic Anemia

G6PD deficient patients will develop hemolytic attack upon:



Different Classes of G6PD Deficiency Hemolytic Anemia

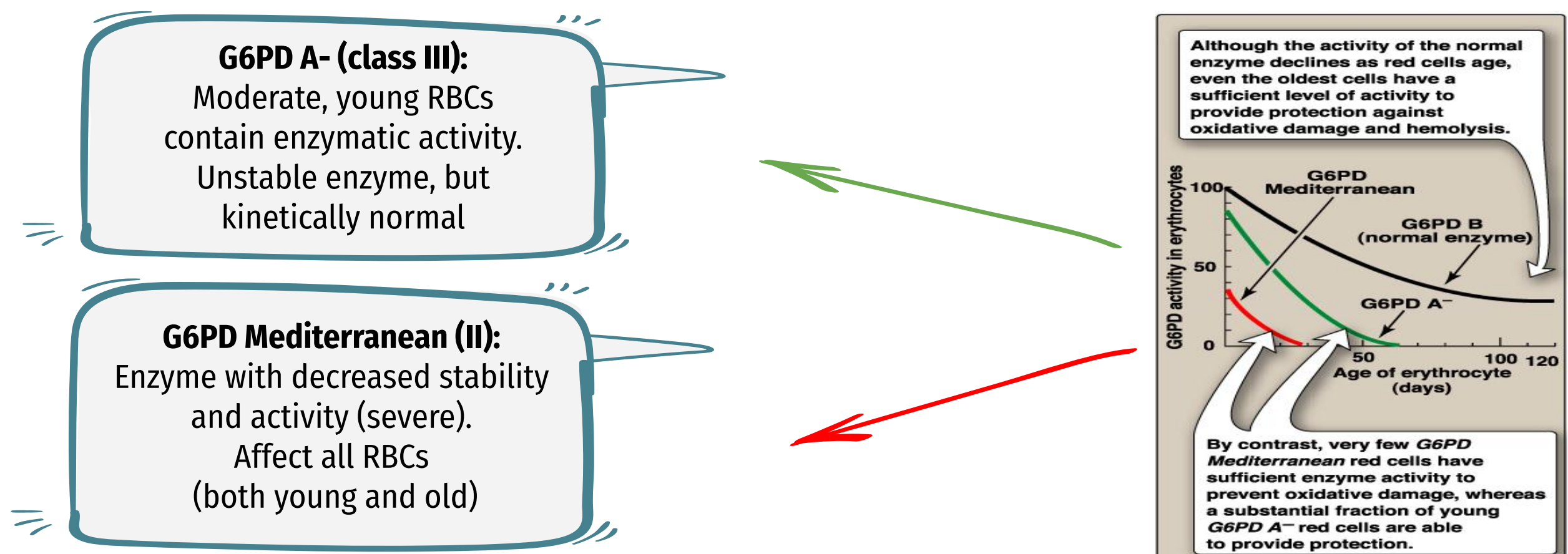
There are 4 different classes:



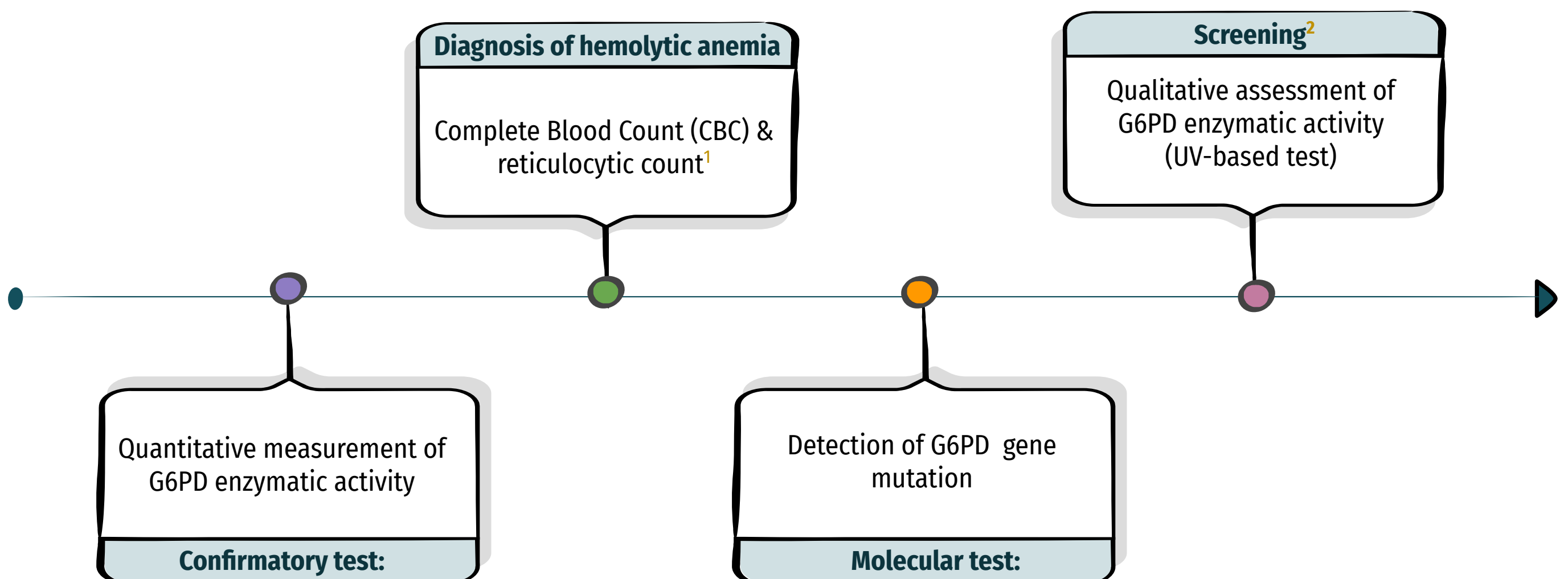
Enzymes are measured through 2 criteria:
1- Stability
2- Activity (used in this classification)

- 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



Diagnosis of G6PD Deficiency Hemolytic Anemia










1) Results:

-RBCs → decreased

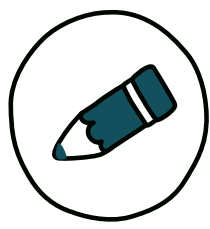
-Reticulocyte count → Increased (due to compensation)

2) Screening is used in some african countries. Since malaria is prevalent in that area, these tests are done before giving anti malaria drugs to prevent extra oxidative stress.

Take Home Messages

-  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
-  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.





Summary

NADPH		
Production	Uses	Disease
<p>The Major pathway for NADPH production is HMP (hexose monophosphate pathway):</p> <ul style="list-style-type: none"> • An alternative oxidative pathway for glucose • No ATP production •Major pathway for NADPH production • Produces ribose-5-phosphate for nucleotide synthesis 	<ul style="list-style-type: none"> • Antioxidant (part of glutathione system) • Reductive biosynthesis e.g., fatty acid biosynthesis • Oxygen-dependent phagocytosis by WBCs • Synthesis of nitric oxide (NO) 	<p>Low NADPH cause oxidative strree What makes NADPH low? G6PD Deficiency hemolytic anemia</p>
G6PD Deficiency Hemolytic Anemia		
General:	When they develop hemolytic attack?	Claasses of G6PD Deficiency Hemolytic Anemia (based on the residual enzyme activity (Least in class I, and Highest in class IV)
<ul style="list-style-type: none"> • Inherited X-linked recessive disease • Most common enzyme-related hemolytic anemia • ~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 	<ul style="list-style-type: none"> • Intake of oxidant drugs (AAA): Antibiotics e.g., sulfa preparation Antimalarial: e.g., Primaquine Antipyretics • Exposure to infection • Ingestion of fava beans (favism, Mediterranean variant) 	<p>I (Very severe)</p> <ul style="list-style-type: none"> <input type="checkbox"/> II (Severe, e.g. Mediterranean) <input type="checkbox"/> III: (Moderate: G6PD A-) <input type="checkbox"/> IV: (Normal)



 **MCQs**

1- HMP Is major pathway for production of:

A-ATP

B-NADPH

C-NADH

D-FADH

2- G6PD deficient patients have increased resistance to:

A-Cholera

B-salmonella

C- Giardia Lamblia

D-malaria

3--HMP Produces for nucleotide synthesis

A-ribose-3-phosphate

B- glucose -5-phosphate

C-fructose-5-phosphate

D-ribose-5-phosphate

4-Oxidation of sulfhydryl (SH) groups of proteins inside RBCs will lead to :

A-Formation of insoluble masses (Heinz bodies)

B- Production ATP

C-Reductive biosynthesis

D-None of them

5- Which one of the following enzymes converts H₂O₂ to H₂O ?

A- Glutathione Synthetase

B-Glutathione Peroxidase

C-Glutathione Reductase

D-Superoxide dismutase

6-Which one of these can produce NADPH ?

A-Superoxide dismutase

B- Malic enzyme

C-Glutathione Reductase

D-all of them

Answers key

1- B

2- D

3- D

4- A

5- B

6- B

SAQs

1- Although G6PD deficiency affects all cells, why it is most severe in RBCs?

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

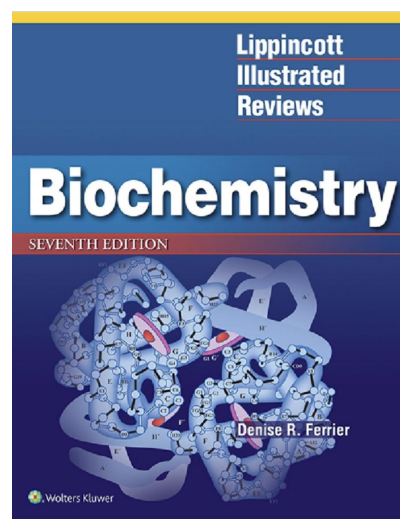
2- what is the Uses of NADPH

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

3- Mention 2 factors which will lead to Hemolytic attacks in G6PD Deficient patients ?

1. Exposure to infection
2. Intake of oxidant drugs

Resources Click on the book to download the resource





Leaders



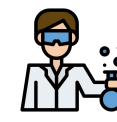
Albandari Alanazi



Sara Alharbi



Abdulaziz Alrabiah



Khalid Almutlaq

Reviser

Abdulaziz Alghuligah

NoteTakers

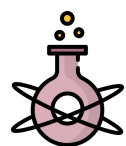
Teif Almutiri

Homoud Algadheb

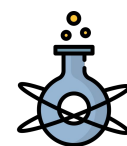
Organizer

Hessa Alalyan

Members



- **Noura Alkathiri**



- **Abdullah Alhumimidi**



Special thanks to Sara Alharbi



Special thanks to Fahad AlAjmi for designing our team's logo.