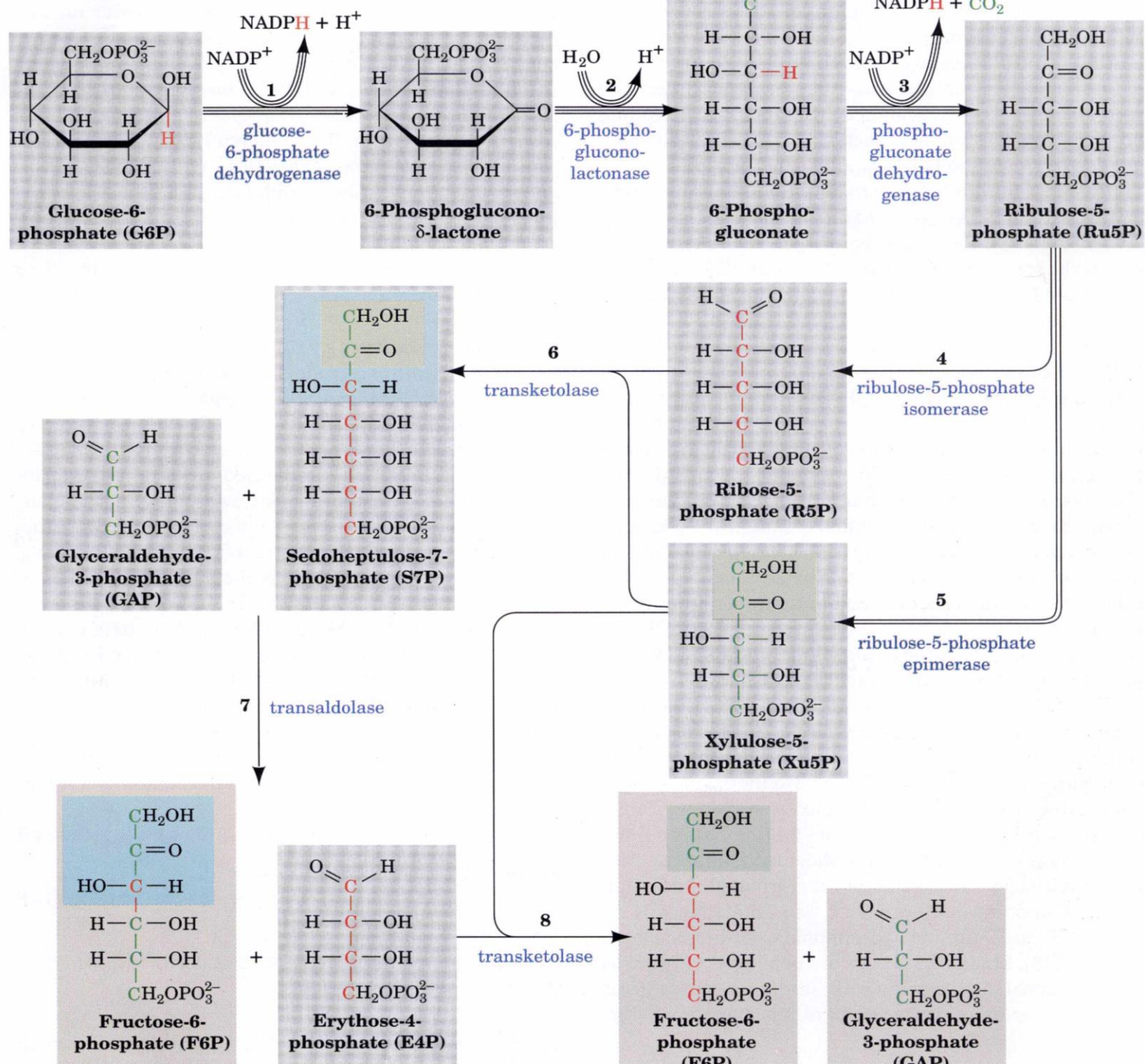


(Pentose phosphate pathway)
Hexose monophosphate shunt

- The aim of this pathway is to produce NADPH and (ribose-5-phosphate for nucleotide synthesis) .
- The NADPH needed for fatty acid synthesis , cholesterol synthesis , glutathione reduction , neurotransmitter synthesis and detoxification reaction.
- NADPH is used in hydroxylation reaction during metabolism of phenyl alanine and tryptophan and also NADPH is used for synthesis of NO nitric oxide from arginine (NO act as a neurotransmitter in brain) (NO potent inhibitors of platelet aggregation also NO in macrophages is effective against viral , fungal protozoal infections) (NO is a laughing gas used as anesthetic , causes smooth relaxation of vascular smooth muscles) .
- HMP occurs in the liver , mammary gland , RBCs , adipose tissues , testis and adrenal cortex .
- This pathway found in active tissues with rapid turnover (so need more nucleic acid synthesis) and in tissues which synthesize lipid and steroid .
- For most organism , the PPP take place in the cytosol while in plants most step take place in plastids .



(Why hemolysis occurs)

1 . RBCs lack mitochondria and thus lack the enzyme of citric acid cycle . Therefore , glucose is metabolized exclusively by glycolytic pathway (90 %) and pentose phosphate pathway (10 %) .

2. RBCs need NADPH production to keep glutathione in the reduced state .

3. NADPH act a cofactor with the glutathione reductase to converted oxidized GSSG to reduced GSH .

GSH is a important reducing substance in the cell , it is a peptide contain 3 amino acids (glutamic acid , cysteine and glycine) , cysteine contain a SH group , this SH group maintain integrety of SH group enzyme , Hb , proteins of the cell membrane .

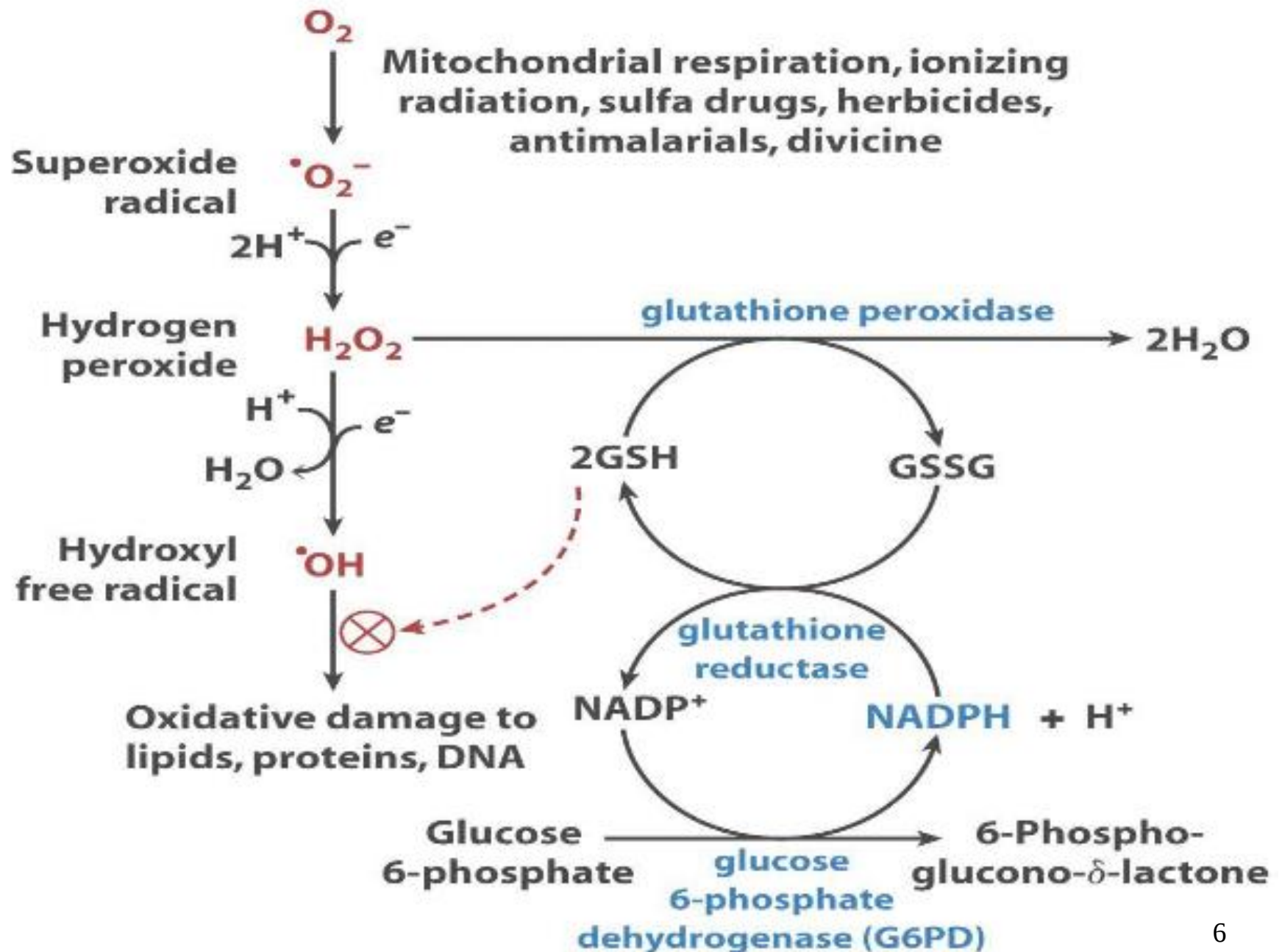
4. GSH remove H_2O_2 come from metabolic process in the presence of glutathione peroxidase.

So if there deficiency of G6PD, so deficiency of NADPH, this cause failure in the conversion of GSSG to a GSH, so it cannot remove H_2O_2 .

This lead to accumulation of H_2O_2 in the cell, as H_2O_2 is oxidizing agent so oxidized Hb, cell membrane SH, enzyme and protein.

This result ↓ in metabolic function so ↓ life and make cell easily to hemolyzed and die.

Other reducing substance in the cell except NADPH as vitamin C and vitamin E.



- Reduced glutathione (GSH) protects the cell by destroying hydrogen peroxide and hydroxyl free radicals .
- Reduction of molecular oxygen yields superoxide anion radical .
- In erythrocytes , electrons from glutathione are used to keep cysteine residue in hemoglobin in the reduced state , and for reducing harmful reactive oxygen specie and hydroxyl free radicals that damage protein and lipids through oxidation induced cleavage reactions .

(G6PD deficiency)

In peoples with low G6PD , certain drugs will cause haemolytic anemia . Example of these drugs :

1. Antimalarial drugs (Primaquine , Paraquine) .
2. Sulfonamides (Sulphacetamide , Sulphonamide , Sulphopyridine)
3. Analgesic (Acetailid)
4. Antibacterial (Nitrofurantone)

Notes :

- Fava beans can cause favism (favism caused by G6PD defect) .
- One of the active compound in the fava beans is called vicine (a toxic glycoside that induces oxidative stress in erythrocytes) .
- People having deficiency of G6PD cannot tolerate primaquine because their erythrocytes do not hold enough GSH to detoxify the reactive oxygen species produced by the compound .

Laboratory Diagnosis :

The laboratory workup for glucose-6-phosphate deficiency includes the following :

- 1 . Measurement of G6PD activity .
- 2 . A complete blood cell (CBC) count with the reticulocyte count to determine the level of anemia .
- 3 . Indirect bilirubinemia occurs with excessive hemoglobin degradation and can produce clinical jaundice.
- 4 . Serum haptoglobin levels serve as an index of hemolysis and will be decreased .
- 5 . LDH is high and so is the unconjugated bilirubin , indicating that there is also extravascular hemolysis .⁹

Notes :

- Reduced glutathione is needed for glutathione peroxidase , which destroy hydrogen peroxide and organic peroxides. This enzyme requires selenium as a cofactor.**
- G6PD is absent or only present in very small amount in muscle so this pathway not exist in muscle .**
- NADPH is not utilized as source of energy because it can not oxidized directly in Respi – chain (The aim of this pathway is not to produce ATP) .**
- Transketolase requires thiamine pyrophosphate (TPP) : chronic thiamine deficiency → defective transketolase and lead to Wernicke - karsakoff syndrome (symtomes are weakness , paralysis and impaired mental functions) .**