- Precipitating factors in G6PD deficiency
  - Few individuals show chronic hemolysis
  - Most individuals show clinical manifestations (develop hemolytic anemia) if :-
    - treated with oxidant drugs
    - ingested fava beans (favism)
      fava beans contain purine glycosides as vicin and isouramil
    - contract a severe infection
  - Neonatal jaundice

- Molecular Biology of G6PD
  more than 300 different mutations - most of them are missense, point mutations
  No frame shift or large deletion - since complete deficiency is lethal

G6PD Deficiency

- Prevalence and Geographic Distribution
  - 200 to 400 million individuals worldwide
  - Highest prevelance in Middle East, tropical Africa, S.E. Asia & Mediterranean
  - X-linked deficiency
  - Deficiency provides resistance to falciparum malaia

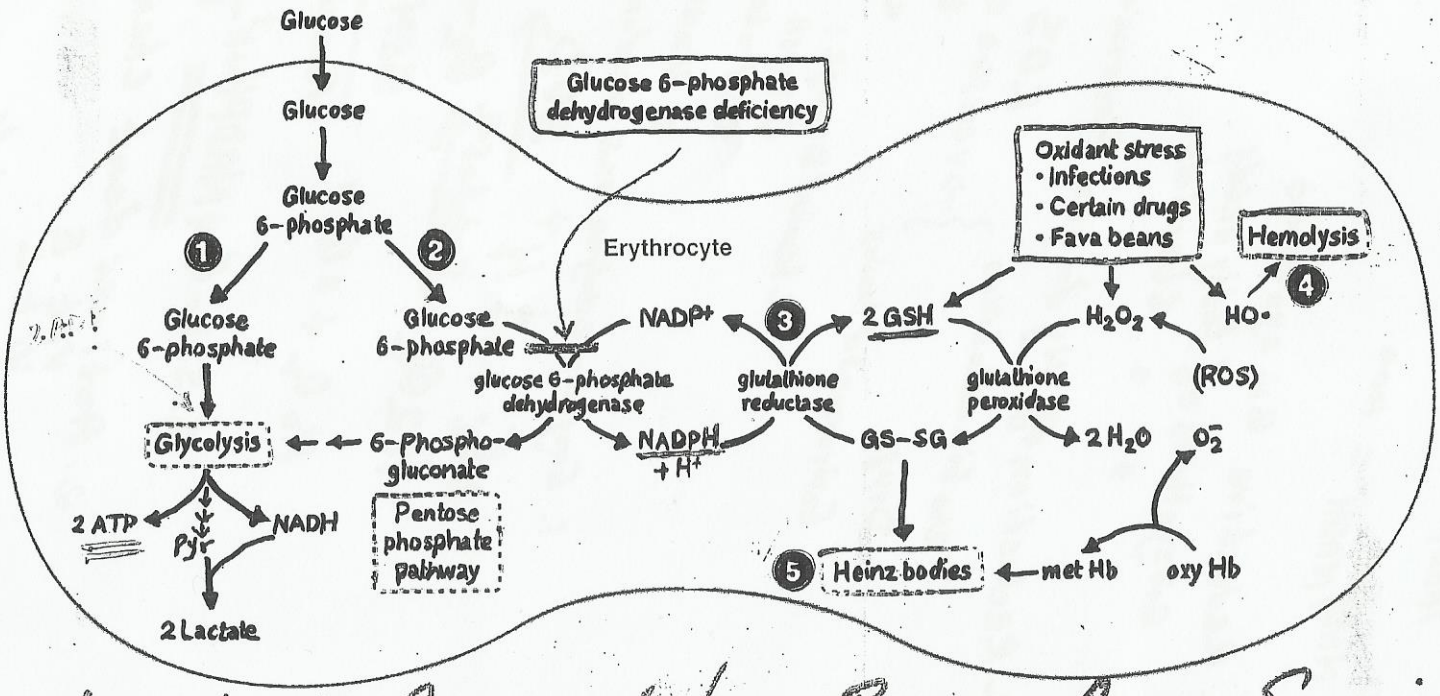
- Variants
  - Wild type – B^- (class !!) Ser → Phe < 10% residual activity
  - Med. variant – B^- (class !!!) 563C → T 10 – 20%
  - African variant – A^- (class !!!) two points mutation 376 A → G + 202 G → A Val → Met 80%
  - Africans variant A^- normal activity 376 A → G Asn → Asp < 2%
  - r. severe deficiency

- Role of G6PD in red blood cells
  - Peroxides + GSH $\xrightarrow{\text{Peroxidase}}$ G-S-S-G + 2 H_2O
  - G-S-S-G + NADPH $\xrightarrow{\text{GSH reductase}}$ 2 GSH + $NADP^+$
  - G6P + $NADP^+$ $\xrightarrow{\text{G6PD}}$ NADPH + 6PG

Table 28.1. Pathways That Require NADPH

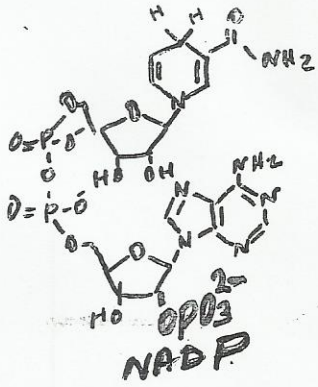
Functions of NADPH :-

1) Detoxification
   - Reduction of oxidized glutathione
   - Cytochrome P450 monooxygenases
2) Reductive synthesis
   - Fatty acid synthesis
   - Fatty acid chain elongation
   - Cholesterol synthesis
   - Neurotransmitter synthesis
   - Nucleotide synthesis



Hemolysis Caused by Reactive Oxygen Species

USES of NADPH



NADP/NADPH = 0.1 (In cytosol of hepatocytes)

NAD/NADH = 1000

A- Reductive Biosynthesis
Biosynthesis of fatty acids
" " Steroids

B- Reduction of Hydrogen Peroxide, Oxidized Glutathione

ROS (species)

aerobic metabolism
Drugs
Environmental toxins } → reactive oxygen intermediates e.g. H_2O_2 ; $O_2^{\cdot-}$; $OH^{\cdot}$ → Oxidants

Chemical Damage:
1) DNA
2) Proteins
3) Unsat. lipids } → Pathologic Process

1. Enzymes catalyze anti oxidant reactions

$$2O_2^{\cdot-} + 2H^+ \xrightarrow{SOD} O_2 + H_2O_2$$

$$H_2O_2 \xrightarrow{Catalase} O_2 + H_2O$$

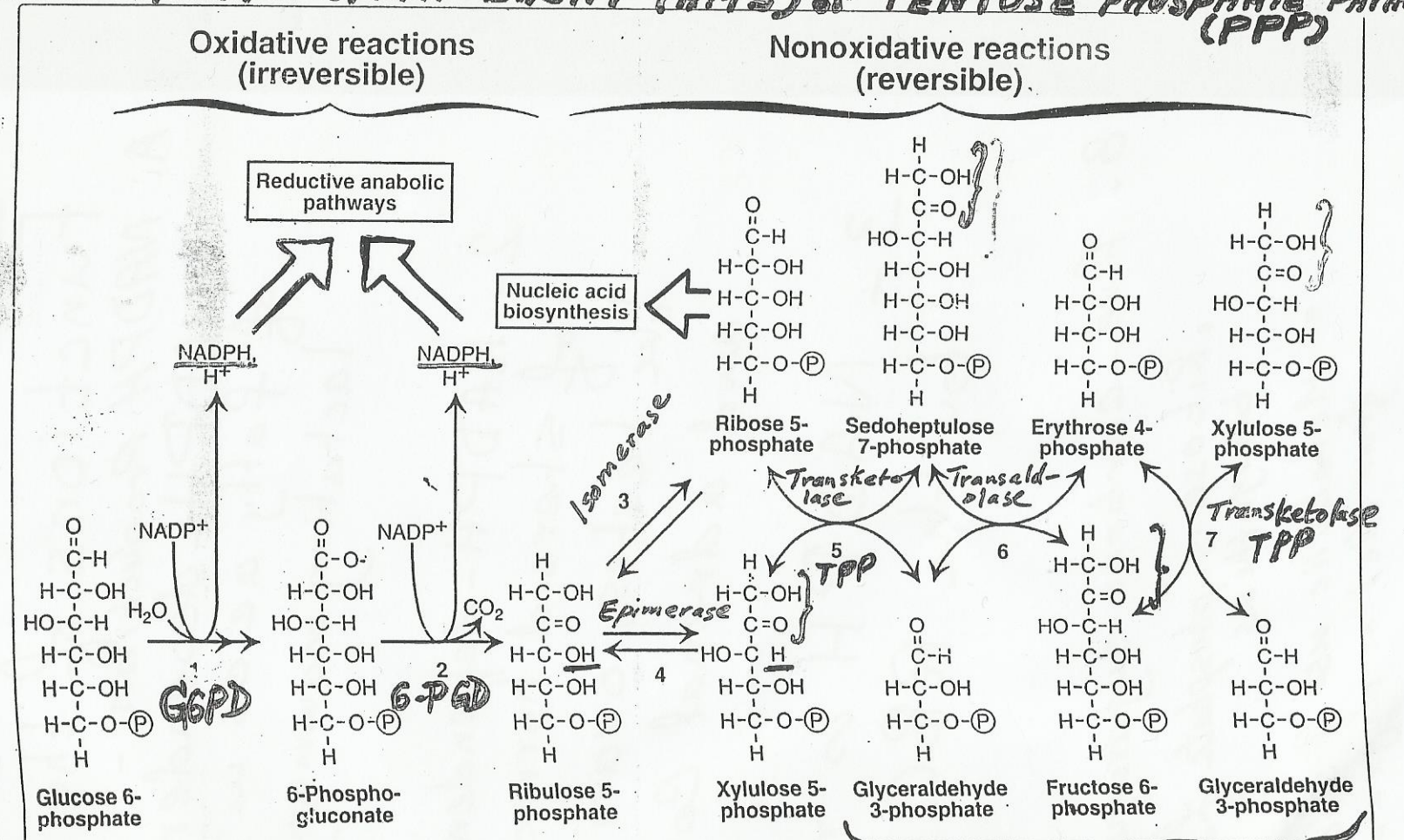
$$H_2O_2 + 2GSH \xrightarrow[Peroxidase]{GSH} 2H_2O + G\text{-}S\text{-}S\text{-}G$$

oxd. GSH

$$G\text{-}S\text{-}S\text{-}G + NADPH + H^+ \xrightarrow[reductase]{GSH} 2GSH + NADP^+$$

2. Antioxidant chemicals
Vit. E
Vit C
Carotenoids

HEXOSE MONOPHOSPHAT SHUNT (HMS) or PENTOSE PHOSPHATE PATHWAY (PPP)



net [3 G6P + 6 NADP+ → 2 F6P(G6P) + 3 CO2 + 6 NADPH + 6 H+ + GA3P]

PENTOSE PHOSPHATE PATHWAY

Functions of the PPP

A: NADPH Production:-

1. NADPH-dependent biosynthesis of fatty acids in liver, lactating mammary gland & adipose

2- NADPH-dependent biosynthesis of steroid hormones in the testes, ovaries, placenta and adrenal Cortex

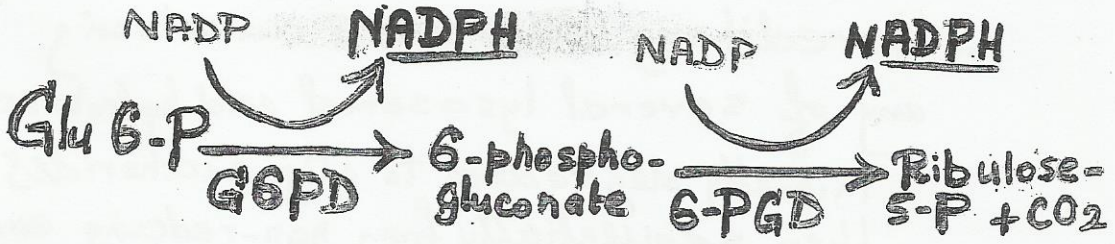
3- NADPH is required by the RBC → GSH maintenance

B- Five-carbons sugars metabolism:-

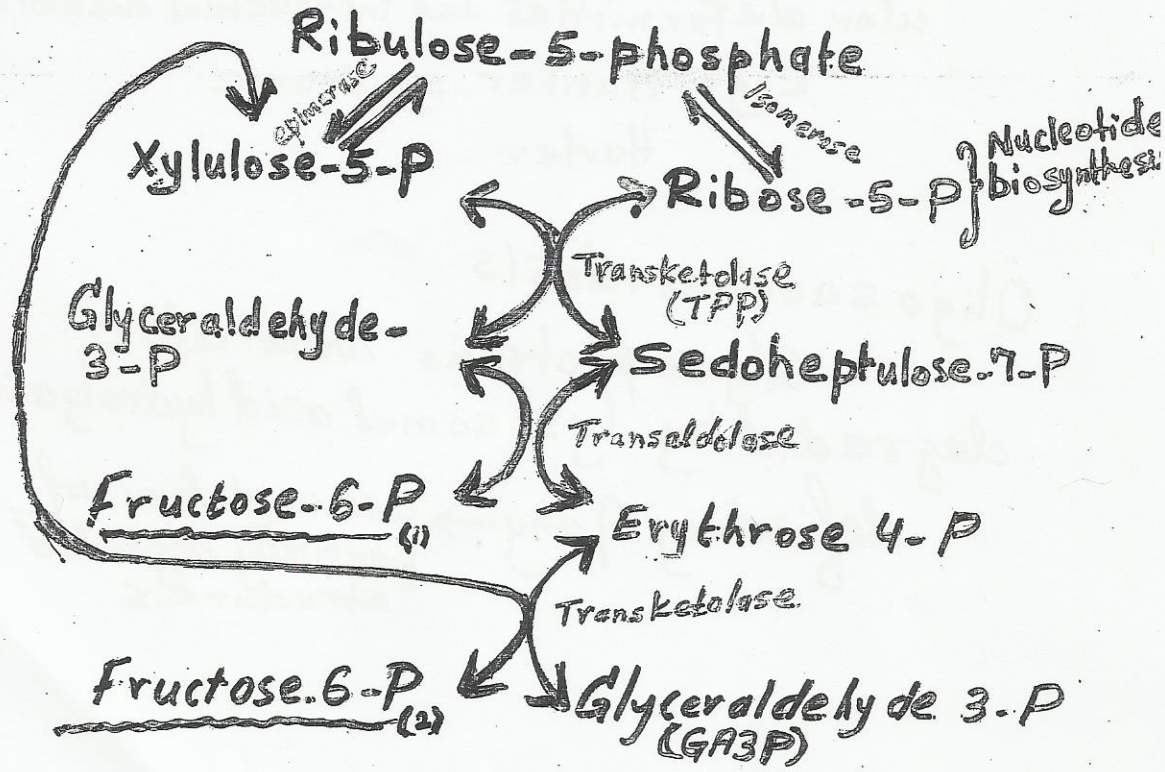
- Ribose-5-phosphate for nucleotides biosynthesis
- Metabolic use of 5-carbon sugars from diet or degradation.

The Pentose-phosphate Pathway
The Hexose Monophosphate Shunt "HMS"

The Oxidative phase - irreversible



The non oxidative phase



$$3\,G6P + 6\,NADP \rightarrow 2\,G6P + GA3P + 3\,CO_2 + 6H^+ + 6\,NADPH$$

2F6P