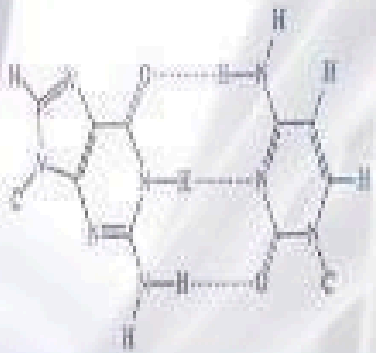
Medical Committee
The University of Jordan

SLIDE SHEET

SLIDE : 9-(PPP)-HMS

DR.NAME: Dr. Nayef

Biochemistry



Majida Al-Foqaraa'

- 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

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

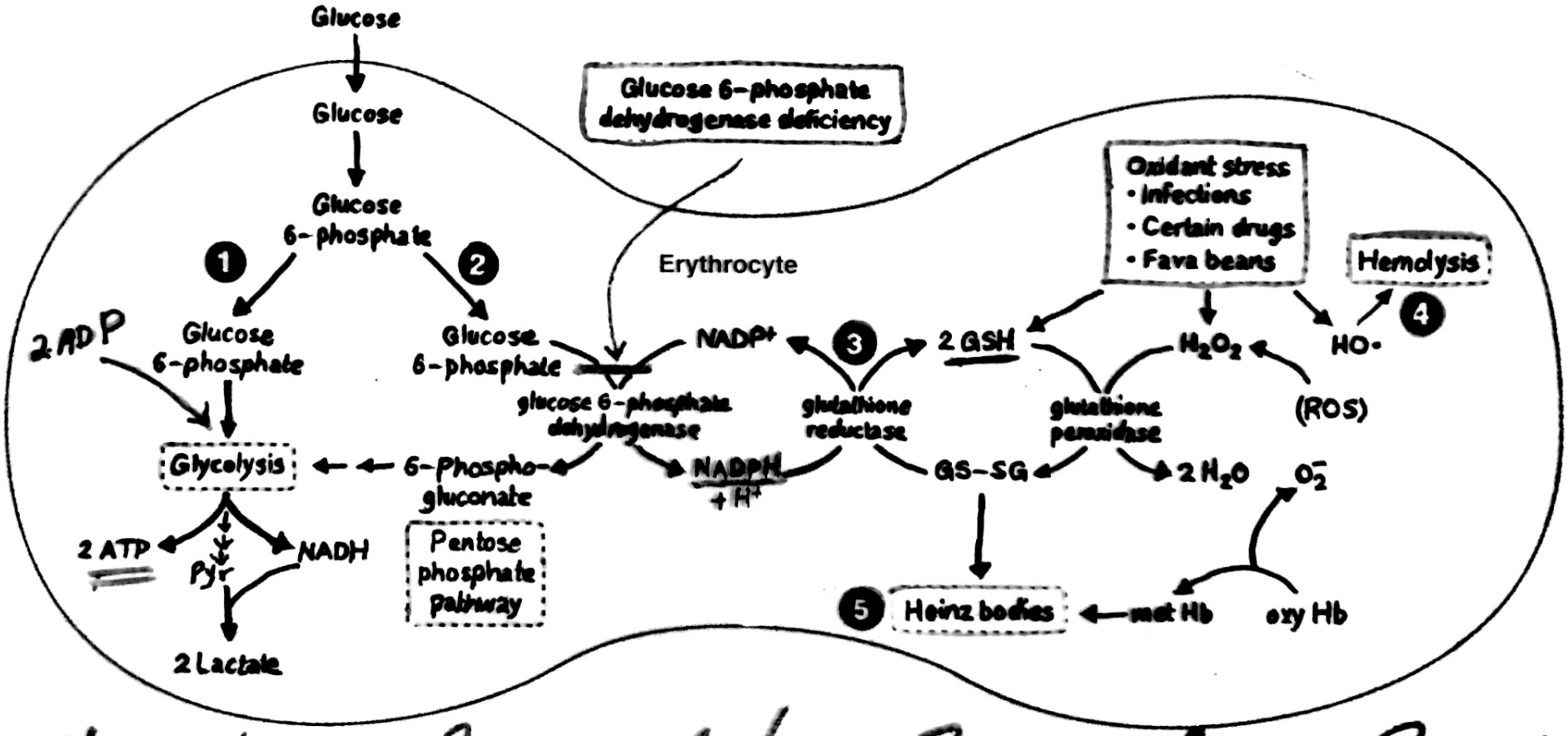
- Variants
  - Wild type - B
  - Med. variant - B^- (class II) Ser → Phe < 10% residual activity
    - 563C → T
  - African variant - A^- (class III) 10 - 20%
    - two points mutation
    - 376 A → G + 202 G → A Val → Met
  - African variant A^- - normal activity 80%
    - 376 A → G Asn → Asp < 2%
  - 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 $\xrightarrow[\text{reductase}]{\text{GSH}}$ 2GSH + $NADP^+$
  - G6P + NADP $\xrightarrow{\text{G6PD}}$ NADPH + 6PG

Table 28.1. Pathways That Require NADPH

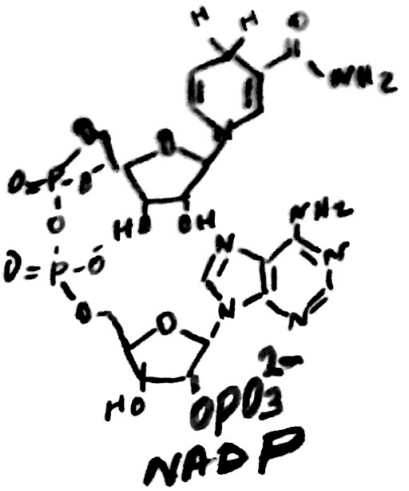
Functions of NADPH :-

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

$NADP/NADPH = 0.1$ (In cytosol of hepatocytes)

$NAD/NADH = 1000$

A- Reductive Biosynthesis
Biosynthesis of fatty acids
" " Steroids

B- Reduction of Hydrogen Peroxide, Oxidised Glutathione

aerobic metabolism
Drugs
Enviromental toxins
} → reactive oxygen intermediates (species) ROS
e.g. H_2O_2 ; O_2^- ; OH^-
→ Oxidants

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

1. Enzymes catalyze anti oxidant reactions

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

$2H_2O_2 \xrightarrow{Catalase} O_2 + 2H_2O$

$H_2O_2 + 2GSH \xrightarrow[Peroxidase]{GSH} 2H_2O + \underline{G\text{-}S\text{-}S\text{-}G}$ (oxd. GSH)

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

2. Antioxidant chemicals
Vit. E
Vit C
Carotenoids

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

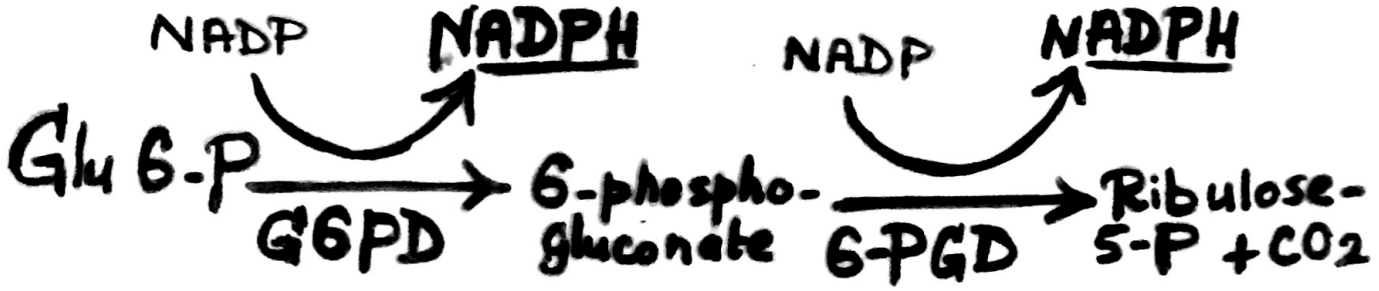
3- NADPH is required by the RBC → GSH maintenance

B- Five-carbons sugars metabolism:-

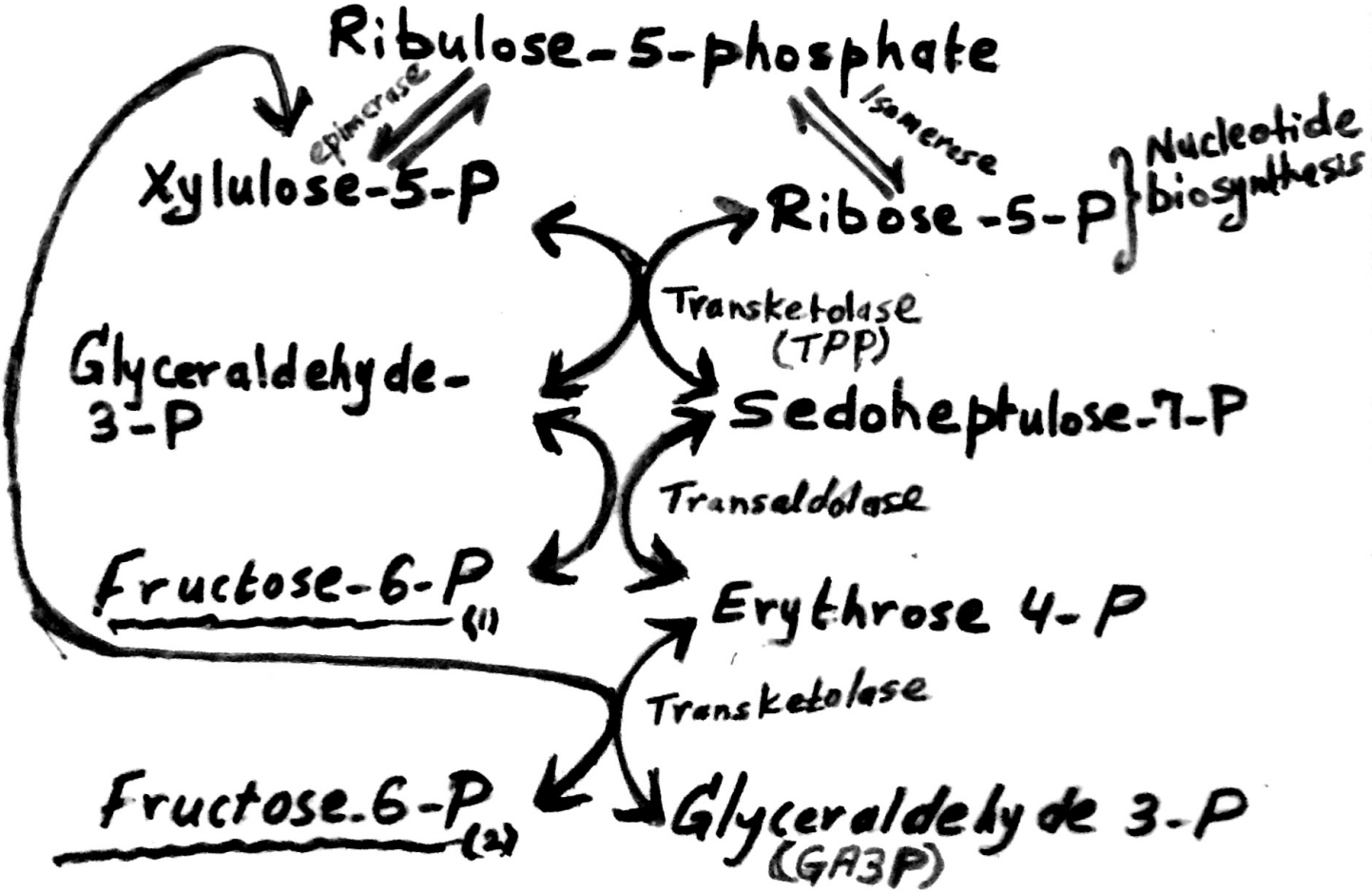
- Ribose-5-phosphate for nucleotides biosynthesis
- Metabolic use of 5-carbon sugars from diet or degradation.

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

The Oxidative phase - irreversible



The non oxidative phase



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

$\xrightarrow{2\,FBP}$

IRREVERSIBLE OXIDATIVE REACTIONS

$\longrightarrow$ 2 NADPH

- NADPH-dependent biosynthesis of fatty acids in Liver; lactating mammary glands; adipose tissue
- NADPH-dependent biosynthesis of steroid hormones in the testes; ovaries; placenta and adrenal cortex.
- to keep <u>reduced</u> glutathione especially in the red blood cells (RBCs)

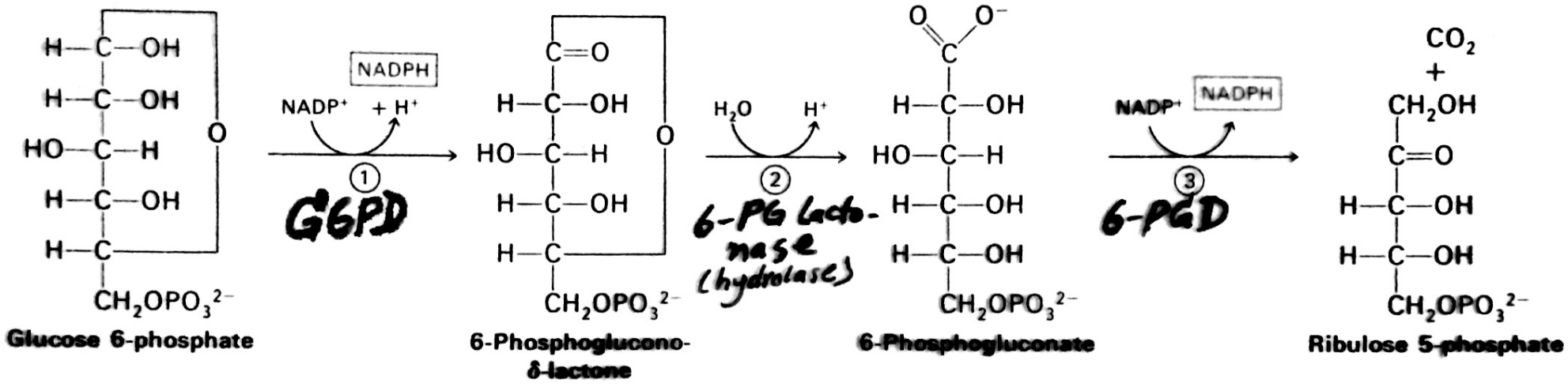
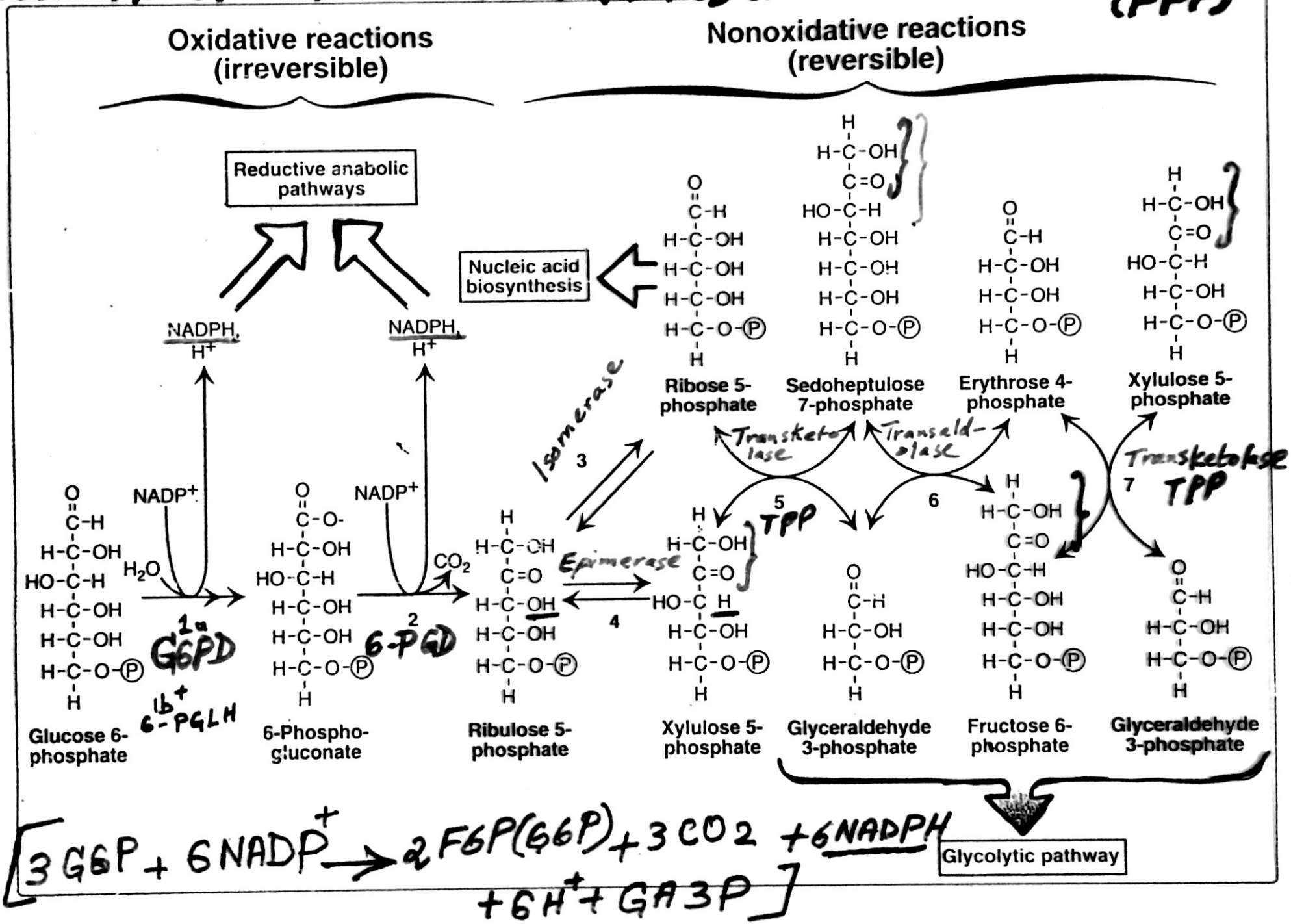


Figure 18-1

Stryer: *Biochemistry*, Third Edition

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



net $[3\,G6P + 6\,NADP^+ \rightarrow 2\,F6P(G6P) + 3\,CO_2 + 6\,NADPH + 6\,H^+ + GA3P]$

6PGLH = 6-phosphogluconolactone hydrolase