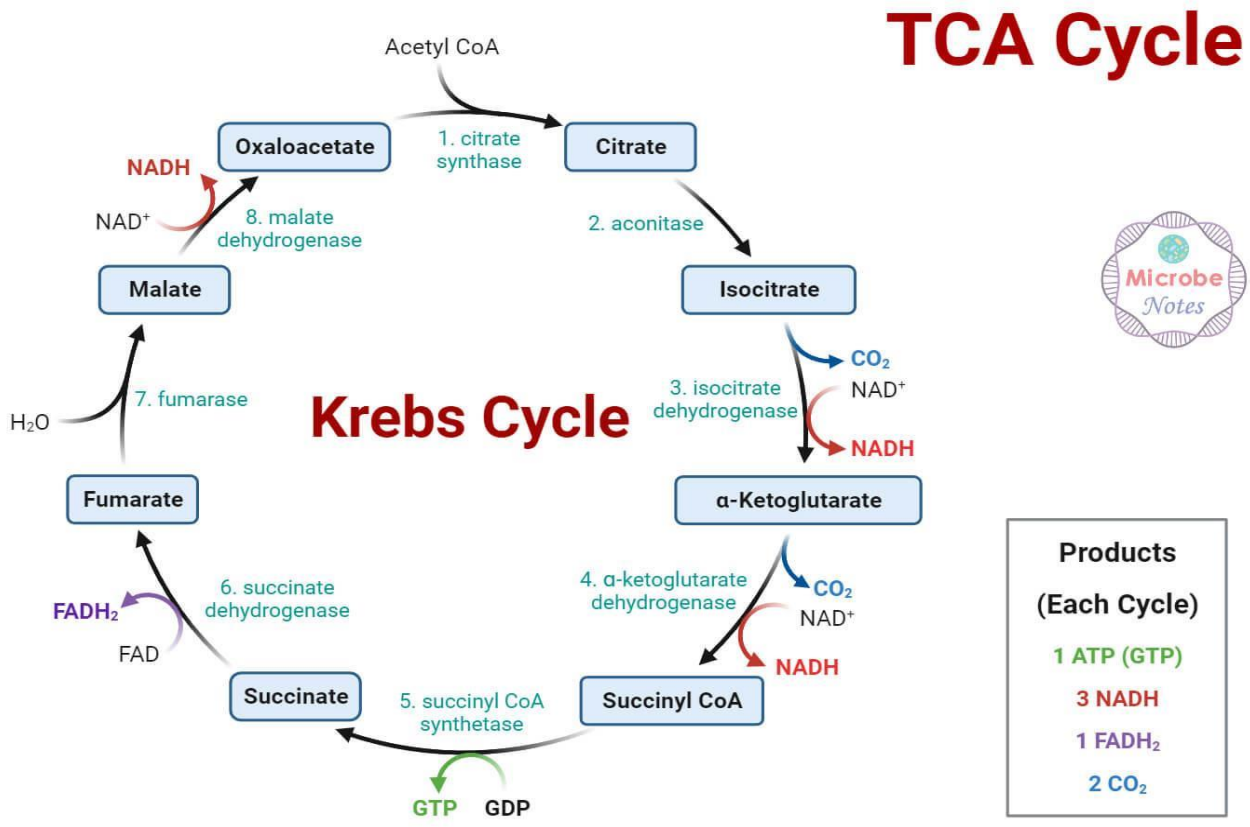
Glucose Oxidation II

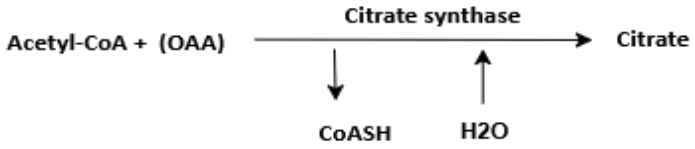
Krebs cycle

Definition:	• *It is a series of biochemical reactions that are responsible for **oxidation of Acetyl CoA** to 2 molecules of CO2 liberating reduced coenzymes (**NADH and FADH2**) which then oxidized through the electron transport chain for **ATP synthesis**.*
Other names:	• *Tricarboxylic acid cycle (TCA).* • *Citric acid cycle.*
Site:	• *Mitochondria of all cells **except** RBCs (as they do not contain mitochondria).* • *All enzymes are present in mitochondrial matrix **except** succinate dehydrogenase present in inner mitochondrial membrane.* **MCQ**



- ***Steps:***

1



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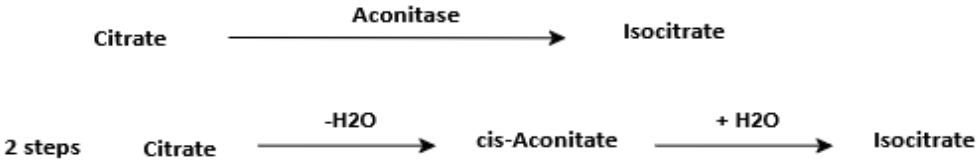

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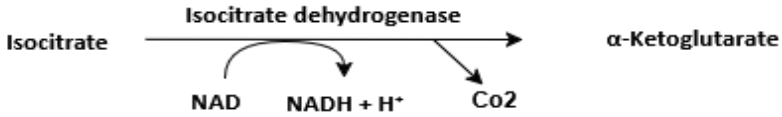

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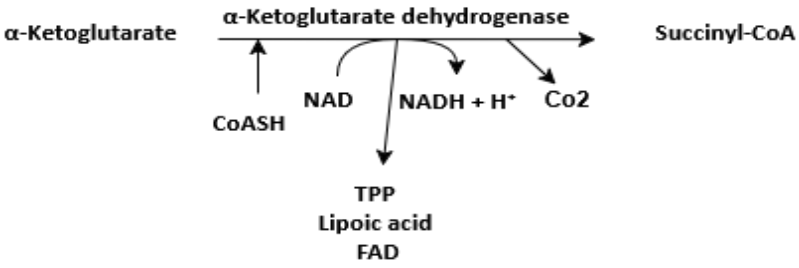

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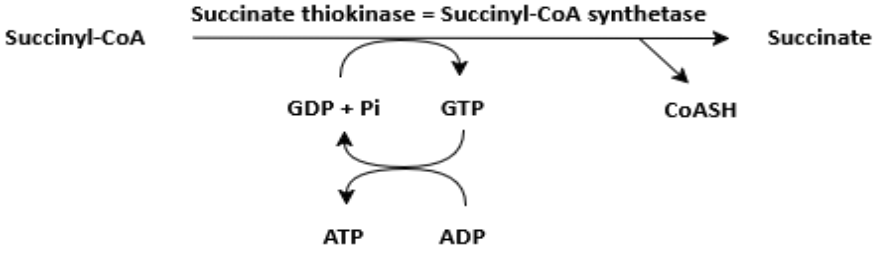

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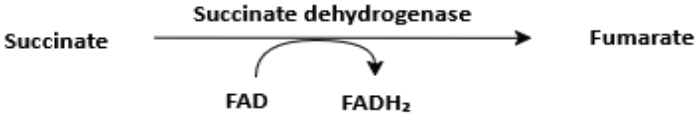

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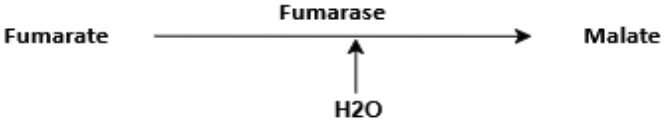

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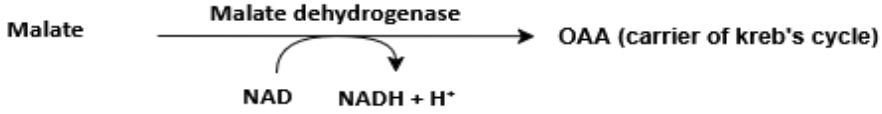


- ***Products:***
  - ***Two cycles*** *are required per one glucose molecule.*
  - ***So, the overall reaction is as follows:***

$$2\ Acetyl\ CoA + 6\ NAD^{+} + 2\ FAD + 2\ GDP\ (ADP) + 2\ Pi \rightarrow$$
$$4\ CO_2 + 6\ NADH{+}H^{+} + 2\ FADH_2 + 2\ GTP\ (ATP).$$

- ***ATP Generating Steps in Krebs cycle:*** **MCQ**

Step	Reaction	Method of ATP production	No. of ATP
3	Oxidative decarboxylation of isocitrate → α-ketoglutarate	Oxidation of NADH+H+ by ETC	3
4	Oxidative decarboxylation of α-ketoglutarate → succinyl CoA	Oxidation of NADH+H+ by ETC	3
5	Cleavage of succinyl CoA → succinate	Substrate level phosphorylation	1
6	Oxidation of succinate → fumarate	Oxidation of FADH2 by ETC	2
8	Oxidation of malate → oxaloacetate	Oxidation of NADH+H+ by ETC	3

Importance of Krebs cycle (Amphibolic in nature)

1- It is the final common metabolic pathway for oxidation of carbohydrates, fats, and proteins (amino acids). (Acetyl CoA).

2- <u>Complete Oxidation of Acetyl CoA (CO2 removal steps):</u>

- *Acetyl CoA contains 2 carbon atoms which are removed as CO2 in steps 3 and 4 in the citric acid cycle.*

  a) Step 3: *conversion of isocitrate to alpha ketoglutarate.*

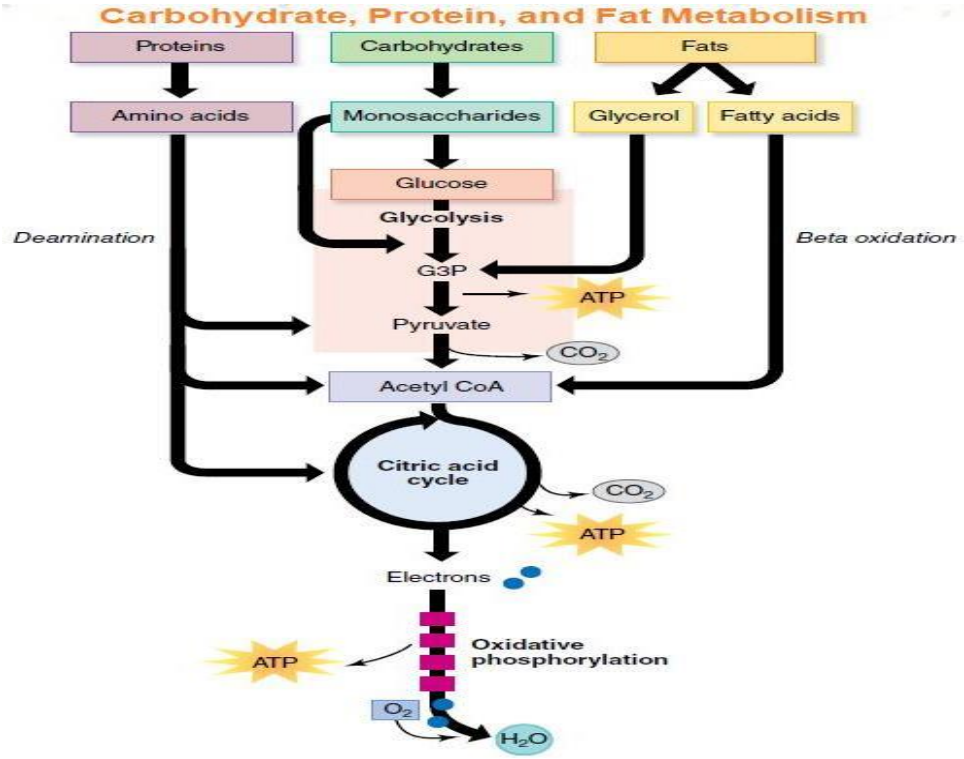
  b) Step 4: *conversion of alpha ketoglutarate to succinyl CoA.*

3- <u>Energy production</u>: ***MCQ***

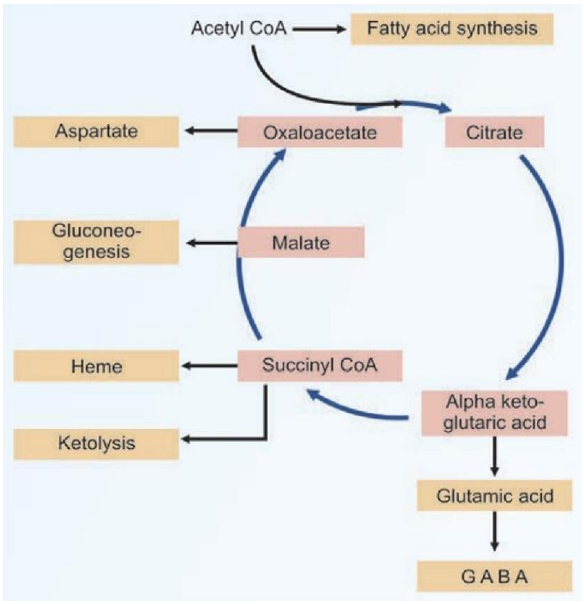
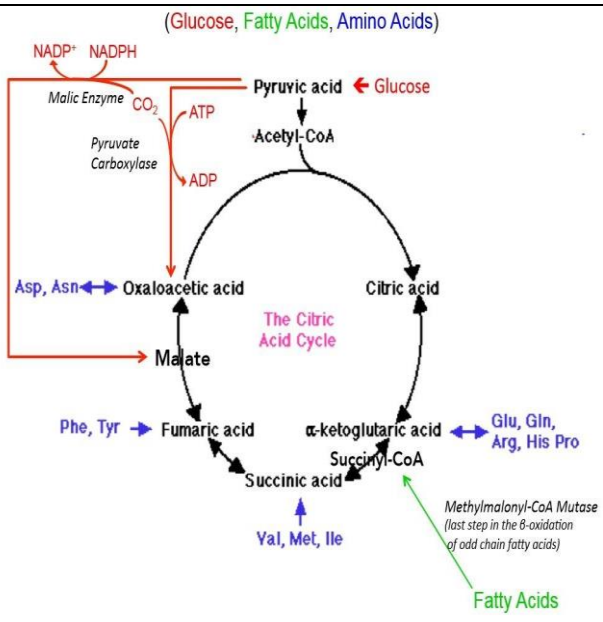
- *3 $NADH+H^+$ → **9 ATP** by ETC*
- *1 $FADH_2$ → **2 ATP** by ETC*
- *1 GTP (ATP) → at substrate level phosphorylation.*

NB:

- ***1 molecule of acetyl CoA*** → *12 ATP*
- ***1 glucose molecule → 2 Acetyl CoA → 2 X 12 ATP*** = *24 ATP*



4- Anabolic & Anaplerotic reactions of Krebs cycle:

	Anabolic or synthetic	Anaplerotic reactions
Def	• *Several intermediates of the cycle may* ***serve other functions***	• *They are metabolic reactions that* ***refill or replenish intermediates of Krebs cycle.***
Example	1. ***Citrate*** *may leave mitochondria (citrate shuttle) to deliver* ***acetyl CoA*** *into the cytoplasm for* ***fatty acid and cholesterol synthesis.*** 2. ***α-ketoglutarate*** *can be used for glutamate and GABA synthesis.* 3. ***Succinyl-CoA*** *can be used for heme synthesis.* 4. ***Malate*** *can leave mitochondria (malate shuttle) for gluconeogenesis.* 5. ***Oxaloacetate*** *is the precursor of aspartate.*	1. ***Pyruvate carboxylase:*** *Catalyzes the conversion of pyruvate into oxaloacetate.* 2. ***Transamination reactions:*** *Can generate α-ketoglutarate from glutamate and oxaloacetate from aspartate.* 3. ***NADP+ dependent malic enzyme:*** *This enzyme can carboxylate pyruvate to malate.*
		

- ***Regulation and key regulatory (irreversible rate limiting) enzymes of Krebs cycle:*** **MCQ**

1) Citrate synthase	• *Inhibited by its product* ***citrate, NADH and ATP.***
2) Isocitrate dehydrogenase	• *It is the* ***most potent*** *rate limiting enzyme of krebs cycle* • *Allosterically activated by* ***ADP*** *& inhibited by* ***ATP & NADH.***
3) α-ketoglutarate dehydrogenase complex	• *Inhibited by its products* ***succinyl CoA and NADH*** • *Activated by* ***Ca2+.***

- ***Role of vitamins in Krebs cycle:*** **written Q**
  - *Four vitamins of vitamin B complex play a role in Krebs cycle.*
  - ***They act as cofactors for enzymes:***

Vitamin	Co-enzyme derivation
B1 (Thiamine)	*TPP*
B2 (Riboflavin)	*FAD*
B3 (Niacin)	*NAD*
B5 (pantothenic acid)	*part of CoA*

  - *The α-ketoglutarate dehydrogenase complex requires* ***the same cofactors as the pyruvate dehydrogenase complex*** *(TPP, lipoic acid, CoASH, FAD and NAD+).*

- ***Inhibitors of Krebs cycle:*** **MCQ**

1. ***Fluoroacetate*** *inhibits aconitase.*
2. ***Arsenite*** *inhibits α-ketoglutarate dehydrogenase.*
3. ***Malonate*** *inhibits succinate dehydrogenase.*

NB: CO_2 fixation reactions:

- ***CO_2 produced in TCA cycle is used in the following reactions:***

  1) Pyruvate + CO_2 → Oxaloacetate → ***Gluconeogenesis.***

  2) Acetyl CoA + CO_2 → Malonyl CoA → ***Fatty acids.***

  3) Propionyl CoA + CO_2 → Methyl malonyl CoA → Succinyl CoA.

  4) Ammonia + CO_2 → Carbamoyl phosphate → ***Urea and Pyrimidine.***

  5) Formation of C6 in ***Purine ring.***

  6) Synthesis of ***H_2CO_3/HCO_3.***

Summary for complete oxidation of glucose

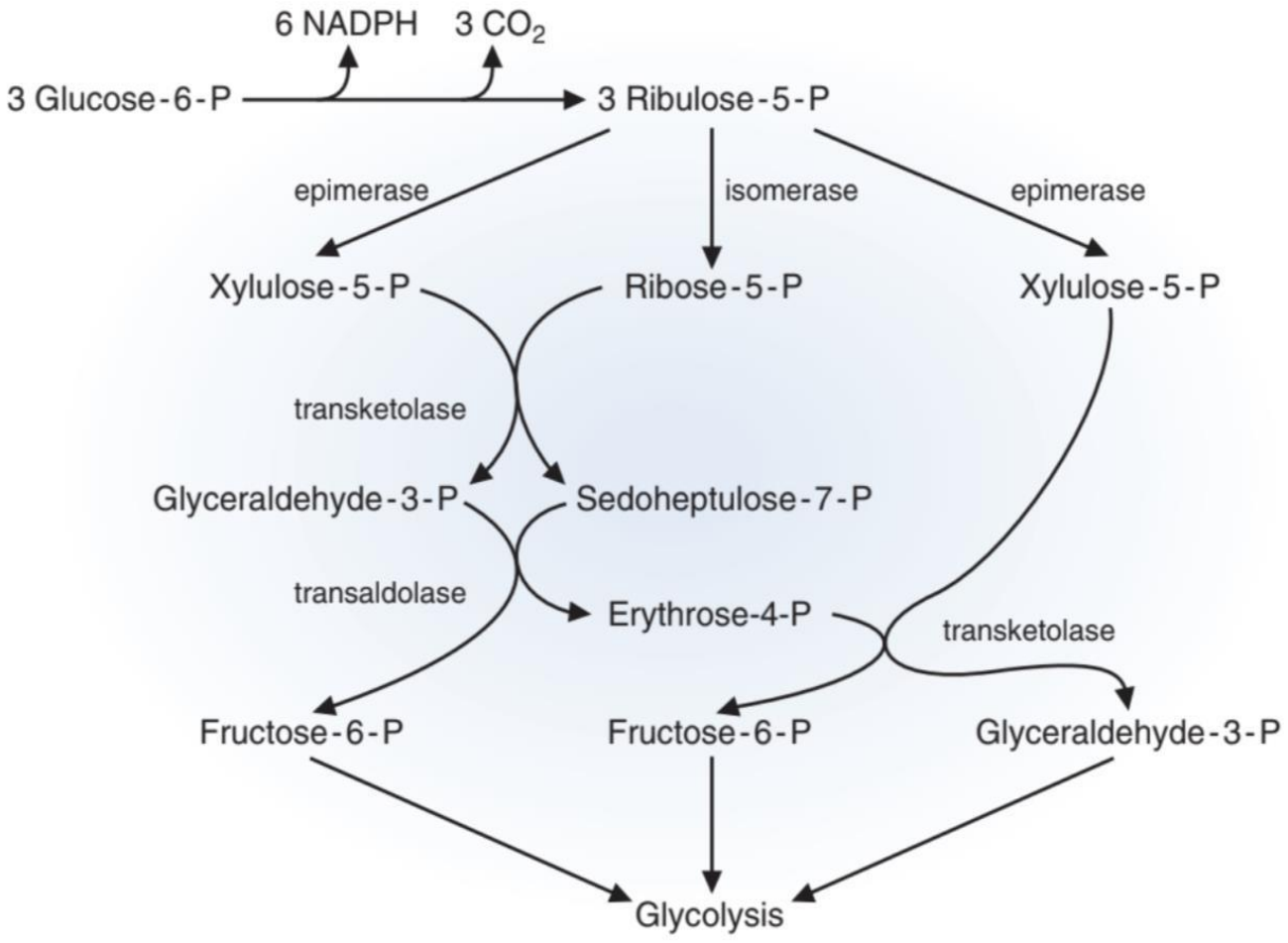
- *Complete* ***aerobic oxidation*** *of 1 molecule of glucose produces 6 CO_2, 6 H_2O and 38 molecules of ATP.*
- *Complete* ***Anaerobic oxidation*** *of 1 molecule of glucose (anaerobic glycolysis) produces 2 lactic acid and 2 molecules of ATP (citric acid cycle and electron transport chain* ***will not occur*** *due to absence of O_2).*

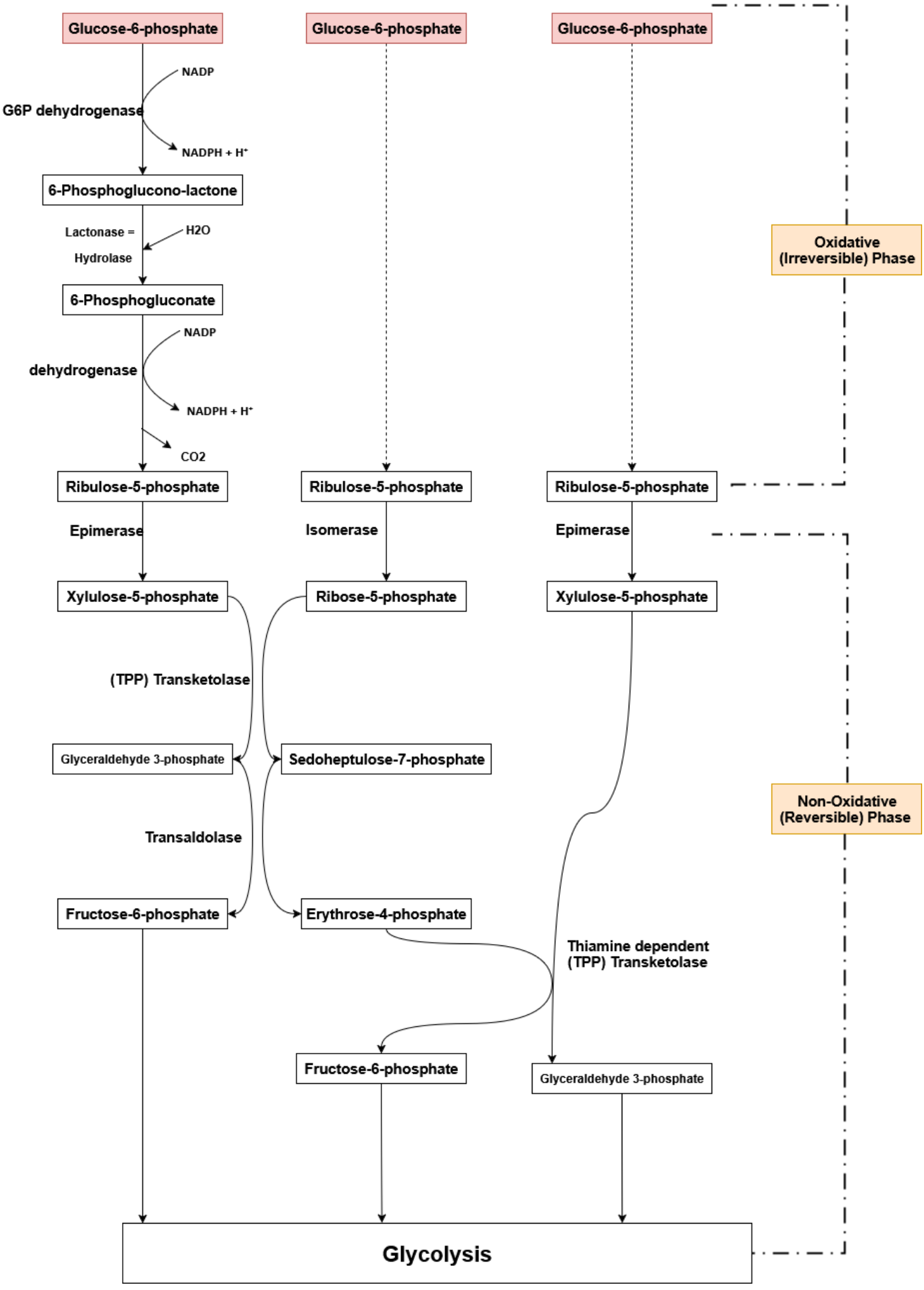
Pathway	ATP	$NADH+H^+$	$FADH_2$	Total ATP /Pathway
Glycolysis	2	2	0	8
Oxidative decarboxylation of 2 pyruvic	0	2	0	6
Kreb's Cycle (2 acetyl coA)	1 X 2	3 X 2	1 X 2	24
Total:	38 ATP			

Hexose monophosphate pathway (HMP) = Pentose shunt

Definition:	• *It is an **alternative pathway** for glucose oxidation without direct consumption or generation of ATP.* • *It is a pathway by which glucose is converted into **pentose phosphate** with production of **NADPH**.* **MCQ**
Site:	• ***Cytosol of many cells e.g.:** liver, mammary gland, adipose tissue, red blood cells, adrenal cortex, ovaries, testes, etc*
Steps:	***A- Oxidative (irreversible) phase.*** ***B- Non-oxidative (reversible) phase.***

- **Overall reactions of the pentose phosphate pathway:**




Glucose-6-phosphate
Glucose-6-phosphate
Glucose-6-phosphate
NADP
G6P dehydrogenase
NADPH + H+
6-Phosphoglucono-lactone
Lactonase =
Hydrolase
H2O
6-Phosphogluconate
NADP
dehydrogenase
NADPH + H+
CO2
Oxidative
(Irreversible) Phase
Ribulose-5-phosphate
Ribulose-5-phosphate
Ribulose-5-phosphate
Epimerase
Isomerase
Epimerase
Xylulose-5-phosphate
Ribose-5-phosphate
Xylulose-5-phosphate
(TPP) Transketolase
Glyceraldehyde 3-phosphate
Sedoheptulose-7-phosphate
Non-Oxidative
(Reversible) Phase
Transaldolase
Fructose-6-phosphate
Erythrose-4-phosphate
Thiamine dependent
(TPP) Transketolase
Fructose-6-phosphate
Glyceraldehyde 3-phosphate
Glycolysis

NB:

- ***Summary of oxidative irreversible phase :***

$$Glucose\ 6\text{-}P + H_2O + 2\ NADP^+ \rightarrow ribulose\ 5\text{-}P + CO_2 + 2\ NADPH$$

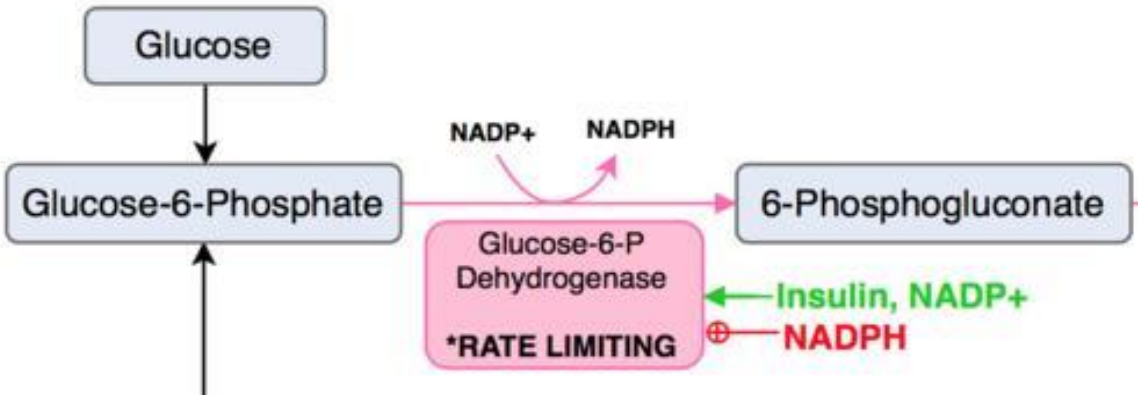
- *Ribulose-5-phosphate provides* ***ribose-5-phosphate*** *for nucleotide biosynthesis or generates* ***pentose phosphates****, which enter non-oxidative portion of pathway.*

▪ Regulation:

- *The key rate limiting enzyme is* ***glucose 6-P dehydrogenase (G6PD).*** MCQ
- ***This enzyme is controlled by:***

  a) Allosteric Regulation: *Feedback inhibition by* ***NADPH.***

  b) Hormonal control: Insulin *induces the synthesis of glucose 6-P dehydrogenase and thus increases the activity of HMP pathway.*



▪ Importance: written Q

1- Production of pentoses:

- *Formation of ribose and deoxy ribose which are essential for* ***nucleotide and nucleic acid biosynthesis.***

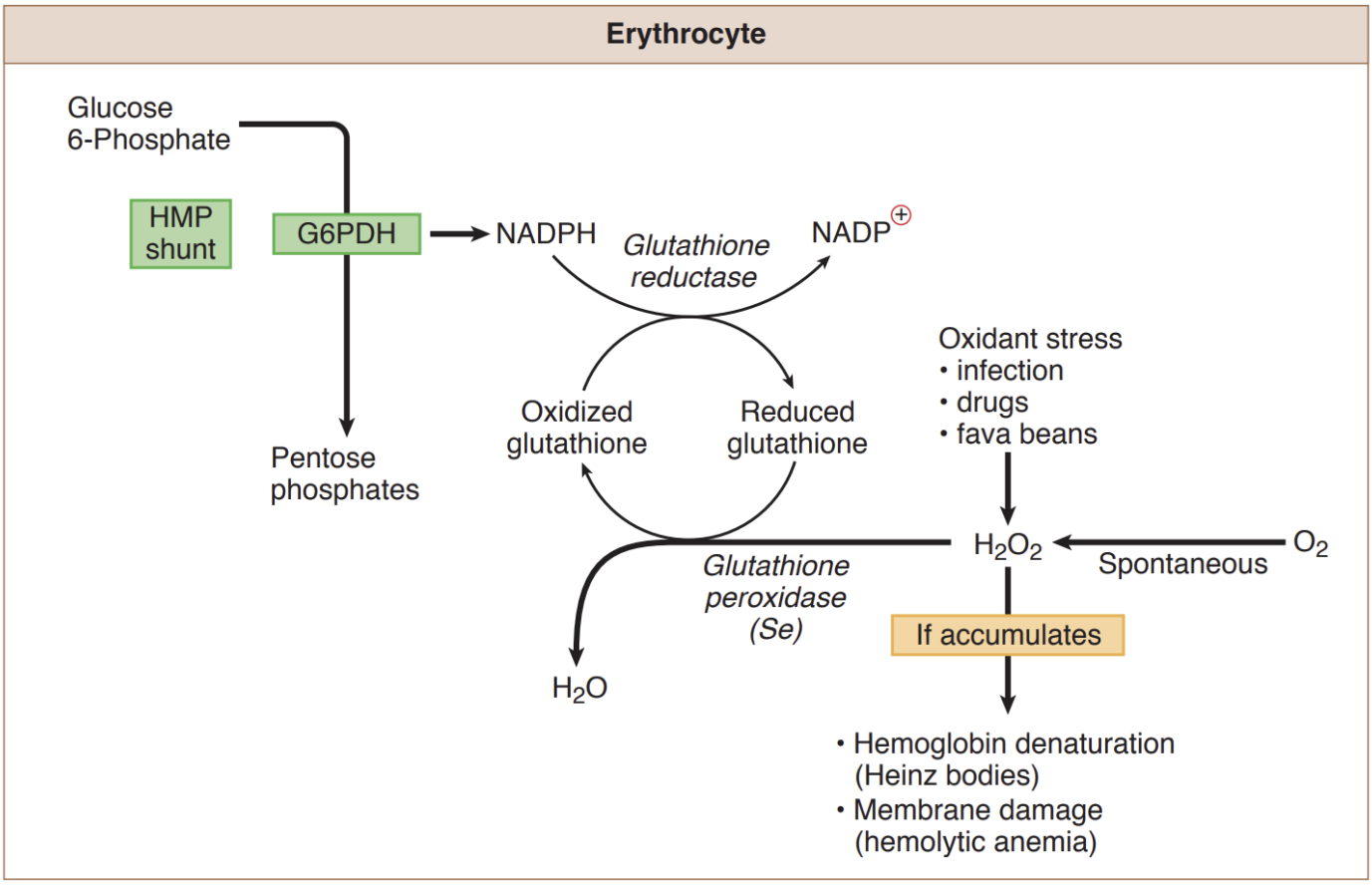
2- Generation of NADPH:

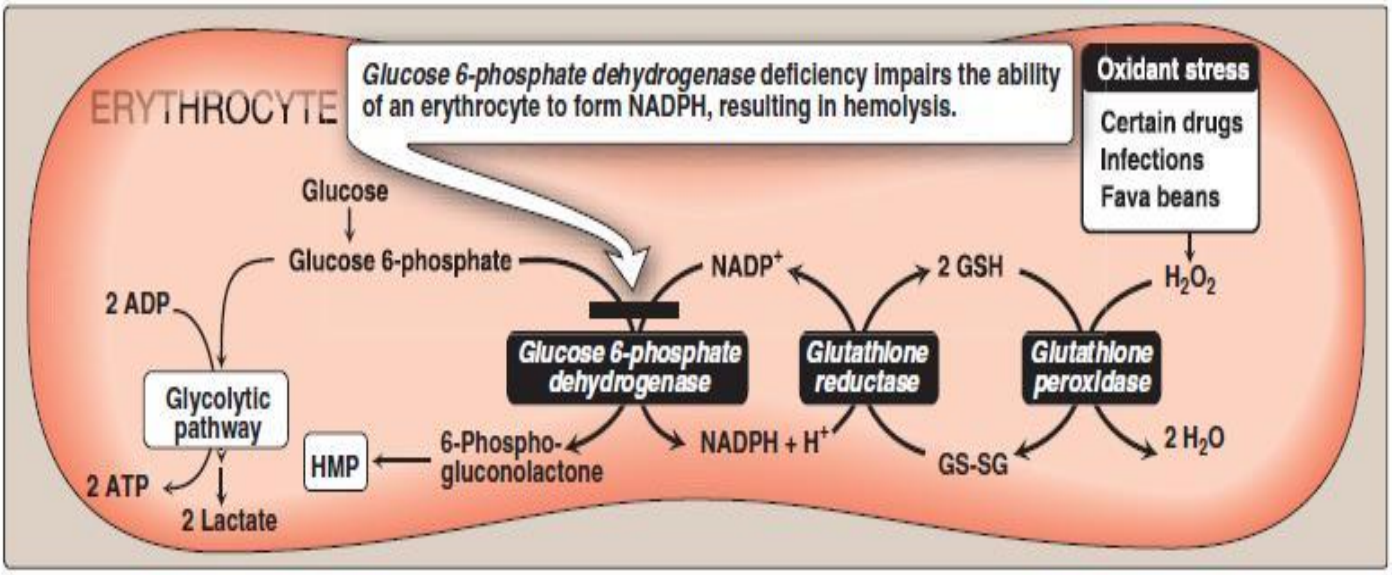
- ***NADPH** is required for many reduction and hydroxylation reactions.*
- ***Examples of such reactions where NADPH is used (fates):***
  1. *Cytoplasmic de novo **fatty acid** synthesis.*
  2. *Synthesis of **cholesterol.***
  3. *Synthesis of **steroids.***
  4. *Synthesis of **malate** from pyruvate by malic enzyme.*
  5. *Conversion of oxidized glutathione (G-S-S-G) to **reduced glutathione (G-SH).***

3- This pathway serves as an entry into glycolysis (non-oxidative phase).

▪ Role of HMP shunt in red blood cells:

- *Generation of NADPH which is required for **reduction** of oxidized glutathione (G-S-S-G) to reduced glutathione (2 G-SH) in a reaction catalyzed by **glutathione reductase** enzyme to protect the cells against H2O2.* **MCQ**





- ***Effect of H2O2 on RBCs:***

*1) H2O2 causes **peroxidation of fatty acids** present in cell membrane → Hemolysis*

*2) H2O2 causes conversion of **hemoglobin into met-hemoglobin** → ↑ RBCs fragility*

Favism (G6PD Deficiency)

Def:	• *It is due to genetic deficiency of Glucose 6-P dehydrogenase (G6PD) resulting in hemolytic anemia.* **MCQ** • ***X-linked recessive disorder** (so, it is more common in **males**).*
Mechanism:	• *G6PD deficiency → ↓ NADPH formation → ↓ reduced glutathione → impairs the ability of RBCs to protect itself from **oxidative damage** → accumulation of H2O2 → **Hemolysis.***
Precipitating factors:	***a)** **Certain drugs e.g.** aspirin, antimalarial drugs (primaquine), sulfonamides (stimulate production of H2O2).* ***b)** **Eating fava beans** (contain oxidizing agents).*
Treatment	• *The only treatment is to **avoid the above factors.*** • ***Blood transfusion** during the attack of hemolysis.*