A study material for M.Sc. Biochemistry (Semester: II) Students on the topic

(CC-06; Unit II)

Pentose Phosphate Pathway (PPP)

Or

Hexose Monophosphate (HMP) Shunt Pathway

An alternate pathway of Glucose Breakdown

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Glycolysis is the most common pathway for catalysis of Glucose. Glucose converts into pyruvate through this pathway and then the pyruvate may have different fate according to the cell type and availability of Oxygen in the cell. It may convert into Acetyl coenzyme A and then may enter into Citric Acid Cycle in eukaryotic cells in the presence of oxygen. This is the central pathway of Glucose Catabolism. The aims of this central pathway is

1. To produce energy in the form of ATP by producing direct ATP (Substrate level Phosphorylation) and $NADPH+H^+$ and $FADH_2$ (Oxidative Phosphorylation through Electron Transport System).
2. To produce different other required compounds in the cell according to the need (such as Amino Acids, Lipids etc.) as different intermediates of this pathway serves as precursor of different other pathways and helps in the synthesis of other secondary metabolites too.
3. To catabolise Glucose into CO_2 molecules (for the cycling of material).

Now, due to different situations arise in the cells:

1. Cells need continuous supply of Nucleotides for the synthesis of Nucleic acids (DNA and RNA). These Nucleic acids are in high demand during Cell Division and in metabolically active cells (such as Liver cells) and for the synthesis of these Nucleic acid, nucleotides are needed and for the synthesis of nucleotides, pentose sugar (Ribose) acts as precursor. Hence pentose sugars are needed.
2. The rapidly dividing cells (such as Bone marrow, internal mucosa, skin cells etc.) and metabolically active cells also need high amount of energy and hence they need high amount of nucleotides for this purpose and hence high amount of pentose is needed.

3. Oxygen is life for living organisms (aerobic) but direct oxygen and excess oxygen is toxic. Oxygen binds with different biomolecule and makes them inert. Several Biomolecules loses their character due to oxidative damage. Hence, the cells which are constantly in the exposure of oxygen (such as skin cells) are in great stress. They need a reducing atmosphere for the protection of their biomolecules. High concentration of reducing agents such as $NADPH+H^+$ and $FADH_2$ serves this purpose.
4. As the need of energy is high in dividing cells and metabolically active cells, the pace of Glycolysis and other primary pathway increases, due to this, their arises a condition of Enzyme overload (much number of substrate molecules available per second per enzyme molecule).

   In these conditions there is a strong need of Alternate pathway of Glucose catabolism. Pentose Phosphate Pathway (PPP) or Hexose Monophosphate Shunt pathway serves these purposes.

- This pathway produces Pentose (Ribose) Sugars from Hexose (Glucose) associated with phosphate, Hence its name is Pentose Phosphate Pathway.
- You may remember the term Shunt from physics (a short resistance in parallel). This pathway is also parallel and short pathway then the mainstream pathway. Hence it has another name Hexose Monophosphate (HMP) Shunt pathway.

The Pentose Phosphate Pathway is divided into two phases:

1. Oxidative Phase
2. Non- Oxidative Phase.

Glucose converts into Ribose (Pentose) in the Oxidative Phase while Ribose reconverts into Glucose in the Non-Oxidative Phase. In the meanwhile, one CO_2 molecule per cycle is lost during oxidative phase and 2 molecules of $NADPH+H^+$ are produced. These $NADPH+H^+$ helps in ATP production with the help of electron transport system.

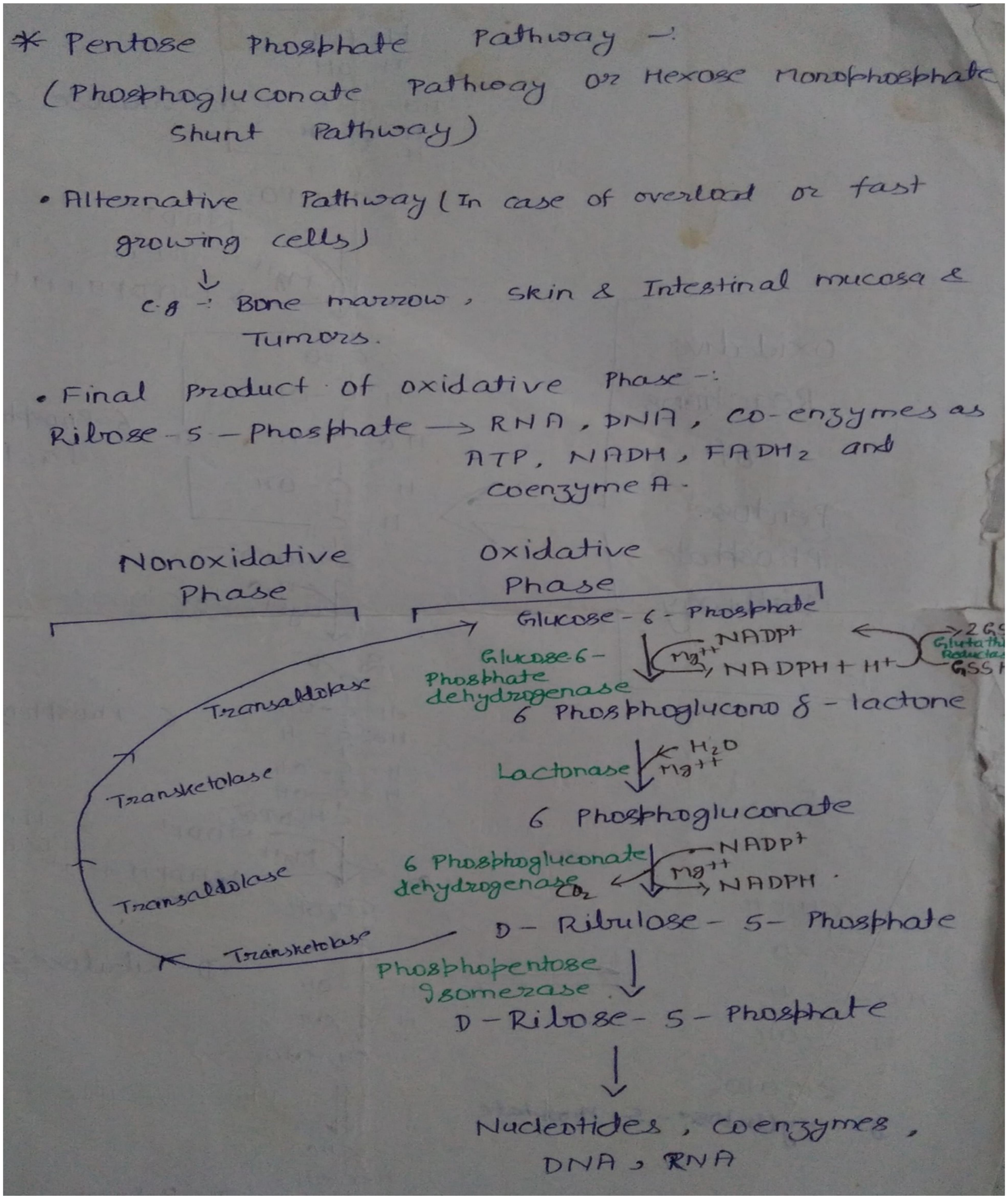
For the sake of convenience of understanding we take 6 molecules of Glucose as our input. Hence, It can be visualized as follows:

1. 6 Molecules Glucose (6 carbon) = 36 Carbons + 12 $NADP^+$ ---- **Oxidative Phase** ------→ 6 Molecules Ribose (5 carbon) = 30 Carbons + 6 CO_2 + 12 $NADPH+H^+$

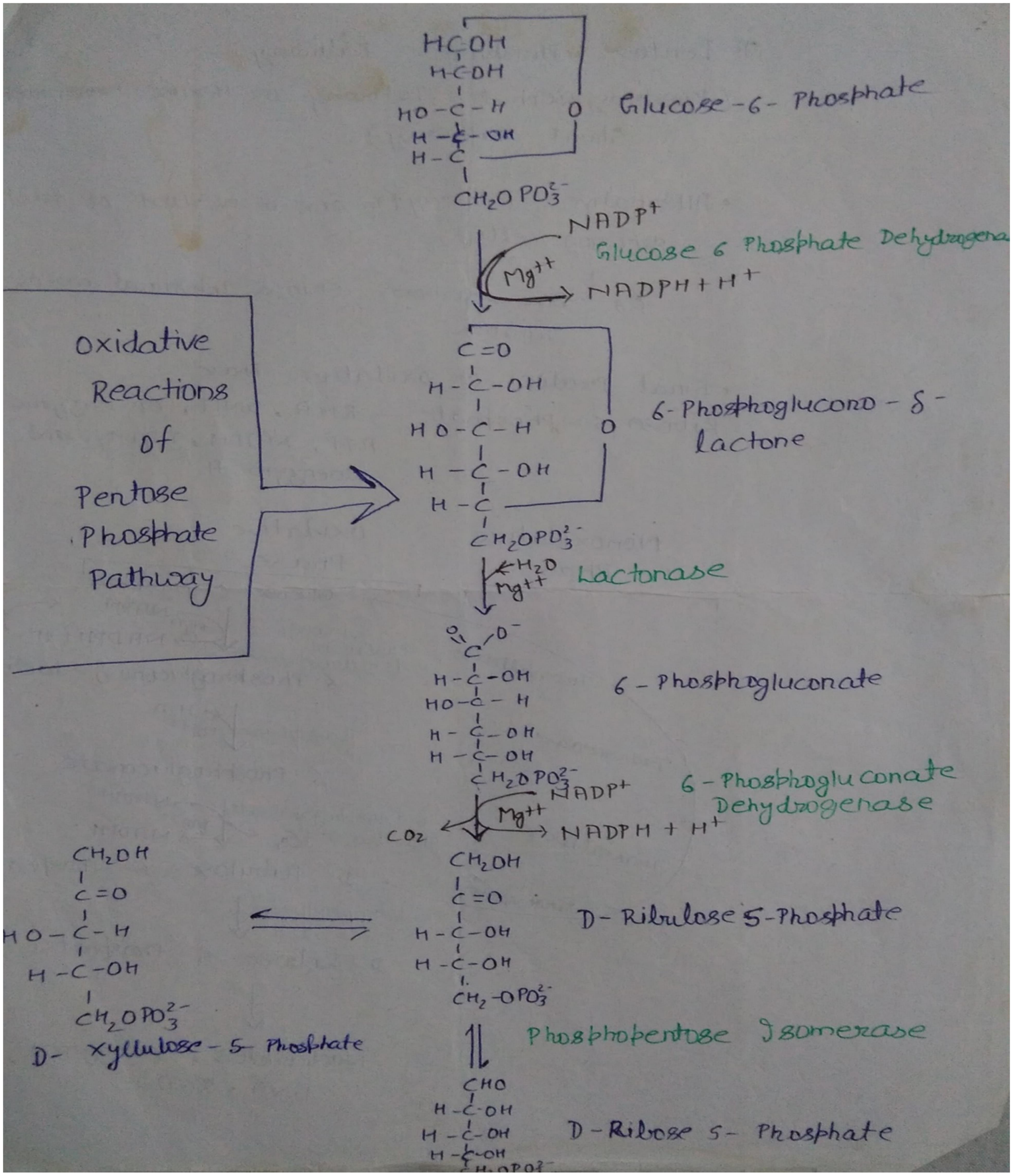
2. 6 Molecules Ribose/Pentose (5 carbon) = 30 Carbons ---- **Non- Oxidative Phase** ------→ 5 Molecules Glucose (5 carbon) = 30 Carbons

3. 12 $NADPH+H^+$ = 30 ATP approx.. (Considering 1 $NADPH+H^+$ = 2.5 ATP according to Lehninger)
4. The cells which needs only Ribose for the synthesis of Nucleotides may have absence of Non-Oxidative phase. While the cells which requires $NADPH+H^+$ in high amount (either

for creation of a reduced environment or for the production of High amount of ATP), must have to undergo both the phases, so that complete oxidation of substrate takes place.



Phase I. Oxidative phase: This is the main part of Hexose Monophosphate Shunt pathway. In this Glucose 6-phosphate, a six-carbon phosphorylated sugar, is converted to Ribulose 5-phosphate, a five-carbon phosphorylated sugar, with the concomitant formation of two molecules of NADPH and the release of C-1 of glucose as CO_2. The Ribulose 5-phosphate further converts into Ribose 5-phosphate. The steps are as follows:

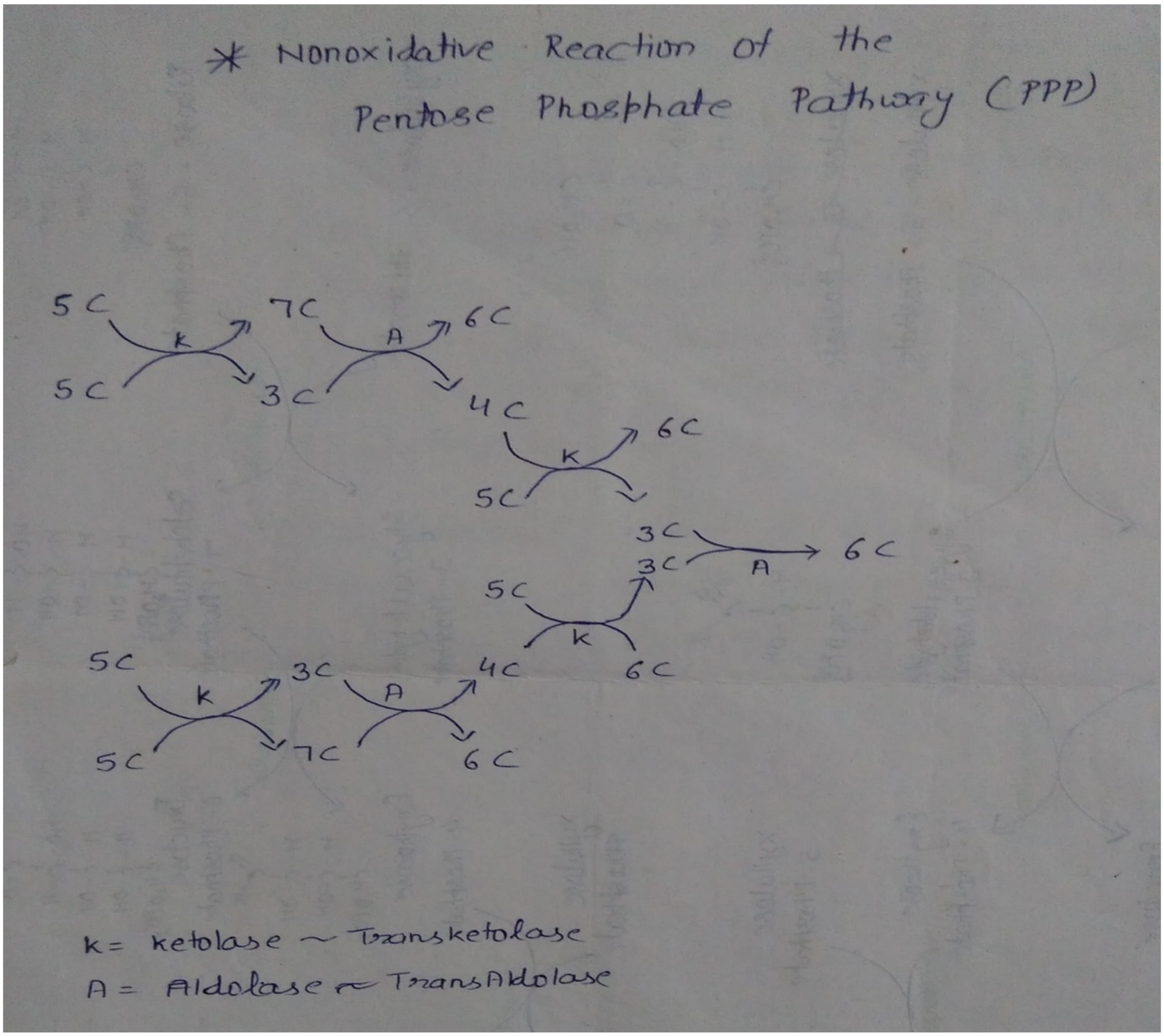


Phase II. Non- Oxidative phase: This phase is actually the recovery of Glucose molecules from pentose, so that the complete oxidation of Glucose takes place. It includes only two main enzymes:

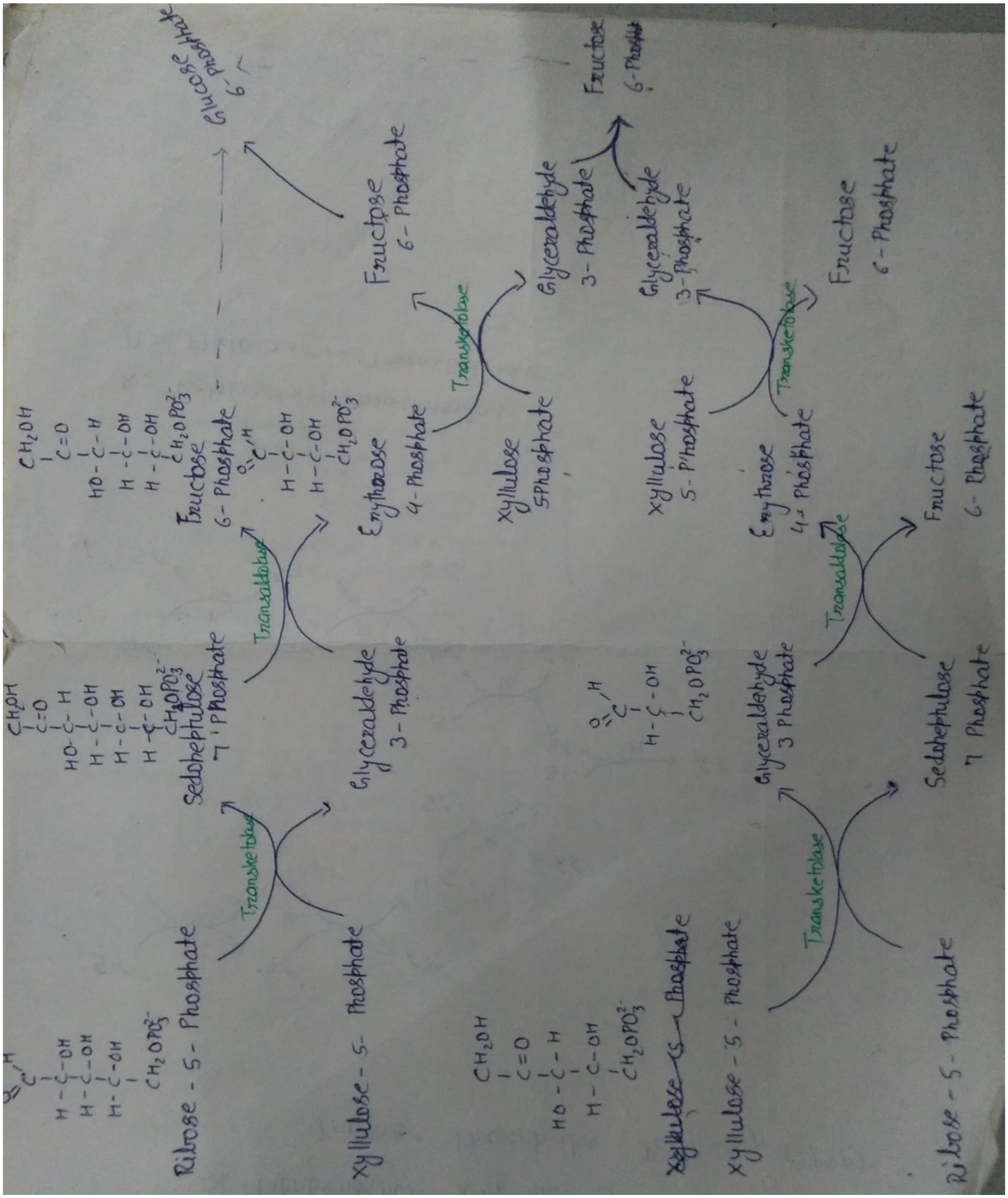
a. Transketolase: It transfer Carbon atoms from Ketone groups (Ketoses)

b. Trans aldolase: It transfer Carbon atoms from Aldehyde groups (Aldoses)
These matters have already been discussed in the earlier classes.

One thing, you can see here is that, these enzymes are used in alternate fashion in the Non- Oxidative phase of PPP. You can remember the sequence by the word "KAKA" (used in countryside to call Uncle). Here K stands for Ketolase and A for Aldolase.



Detailed Non-Oxidative Phase:



Now,

Can we justify that Pentose phosphate pathway is actually an alternate pathway ?

It can only be justified by ATP balance sheet. Let us compare:

ATP Balance Sheet for Catalysis of Glucose

A. Glycolysis —: (Per Glucose molecule) —:

I. Glucose ⟶ Glucose·6P ⟶ (−1 ATP) ⟶ (−1 ATP)

II F-6-P ⟶ F 1 6 BP ⟶ (−1 ATP) ⟶ (−1 ATP)

III 2(3 PGAl) ⟶ 2(1,3 BPG) ⟶ (1×2 NADH+H^+) ⟶ (+5 ATP)

IV 2(1,3 BPG) ⟶ 2(3 PG) ⟶ 1×2 ATP ⟶ (+2 ATP)

V PEP ⟶ Pyruvate ⟶ 1×2 ATP ⟶ (+2 ATP)

Total ⟶ +7 ATP

(B) Link reaction —: (Per Pyruvate molecule)

I. Lipoamide (Red) ⟶ Lipoamide (oxi) ⟶ NADH+H^+ ⟶ 2.5 ATP

Total ⟶ 2.5 ATP

(C) Kreb's cycle —: (Per Acetyl Co-A molecule)

1. Isocitrate ⟶ oxalosuccinate ⟶ 1 NADH + H^+ ⟶ 2.5 ATP
2. α-k Glutarate ⟶ Succinyl co-A ⟶ NADH+ H^+ ⟶ 2.5 ATP
3. Succinyl co-A ⟶ succinate ⟶ 1 ATP ⟶ 1 ATP
4. Succinate ⟶ Fumarate ⟶ 1 $FADH_2$ ⟶ 1.5 ATP
5. Malate ⟶ OAA ⟶ 1 NADH + H^+ ⟶ 2.5 ATP

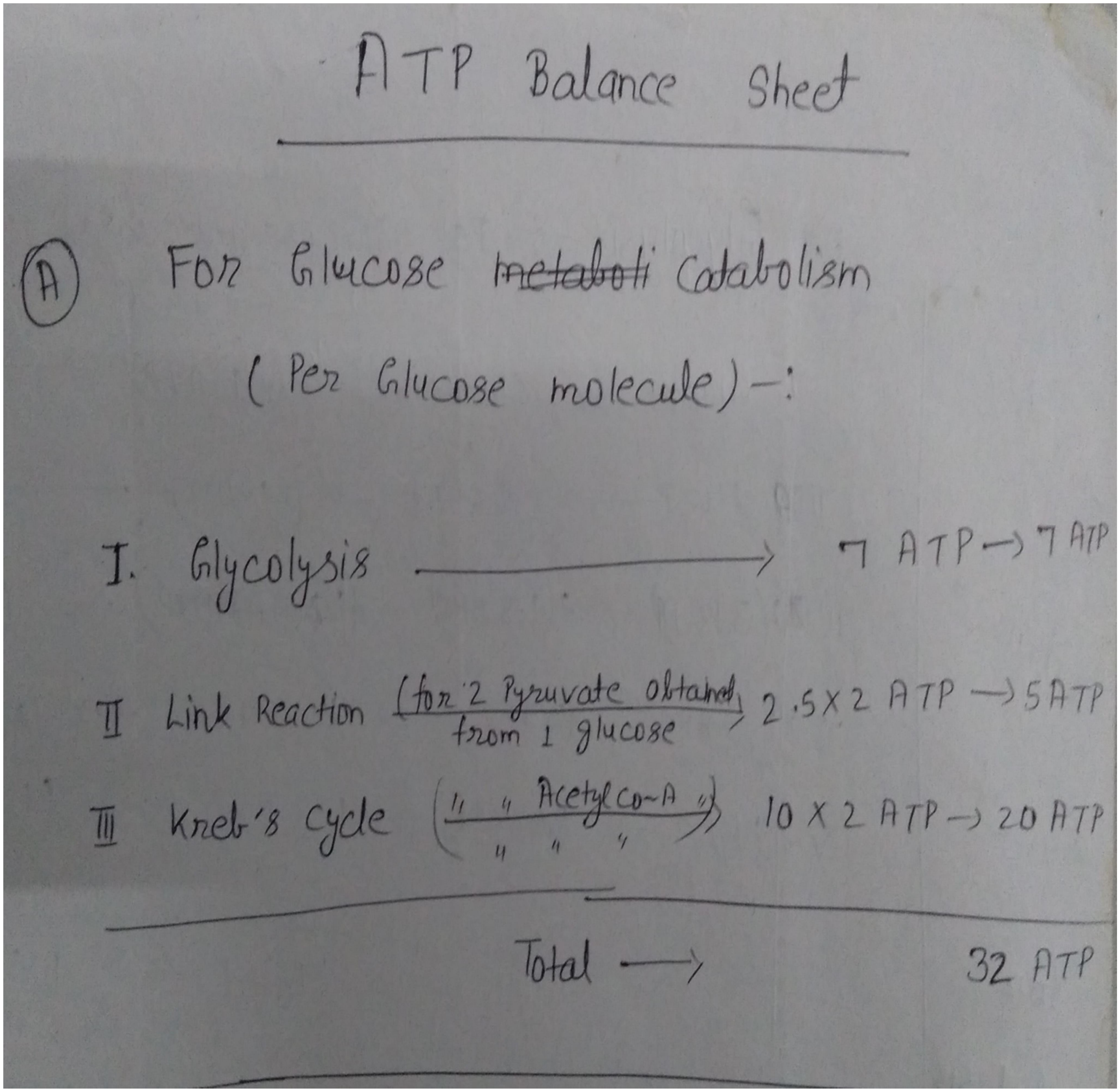
Total ⟶ 10 ATP

* Calculation Assumption —:

1 NADH + H^+ = 2.5 ATP

1 $FADH_2$ = 1.5 ATP

(Standard no. of ATP according to Lehninger)



ATP Balance Sheet

Ⓐ For Glucose ~~metaboli~~ Catabolism

(Per Glucose molecule) –:

I. Glycolysis ⟶ 7 ATP → 7 ATP

II Link Reaction (for 2 Pyruvate obtained from 1 glucose) → 2.5 X 2 ATP → 5 ATP

III Kreb's cycle (" " Acetyl Co~A " / " " ") → 10 X 2 ATP → 20 ATP

Total ⟶ 32 ATP

Hence, we can see that 32 ATP are obtained from the catalysis of Glucose through main pathway Taking into consideration that:

$1\ NADPH+H^+ = 2.5\ ATP$

& $1\ FADH_2 = 1.5\ ATP$ (according to Lehninger)

Now we have to calculate the number of ATP produced through Pentose Phosphate Pathway and then we have to compare both.

ATP Balance sheet (for oxidation of one Glucose molecule) –: 6 CO_2 Production

→ As in one Pathway (oxidative) ~~are~~ one Glucose molecule is converted into one Pentose (Ribose) and one CO_2 is produced.

→ We have to consider six such Pathways for the catalysis of one Glucose molecule (6 CO_2 Production)

In one Pathway –: (one CO_2 Production)

1. Glucose-6-P → 6-Phosphogluconolactone ⇒ 1 $NADPH + H^+$ → 2.5 ATP
2. 6-Phosphogluconate → Ribulose-5-P ⇒ 1 $NADP + H^+$ → 2.5 ATP

Total ⇒ 5.0 ATP

For one Glucose Molecule ⇒ 6 CO_2 Producton

6 × 5.00 ATP ⇒ **30 ATP**

Now –:

Catalysis of one Glucose molecule Produces:

Through Main Pathway ⇒ 32 ATP
Through PPP (alternate Pathway) ⇒ 30 ATP

} Comparisible Values.

Hence on the basis of ATP balance sheets we can conclude that, Pentose Phosphate Pathway is an alternate pathway for the catabolism of Glucose. It is also shorter than the main pathway, hence, it can also be termed as Shunt Pathway.

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