UNIT-II

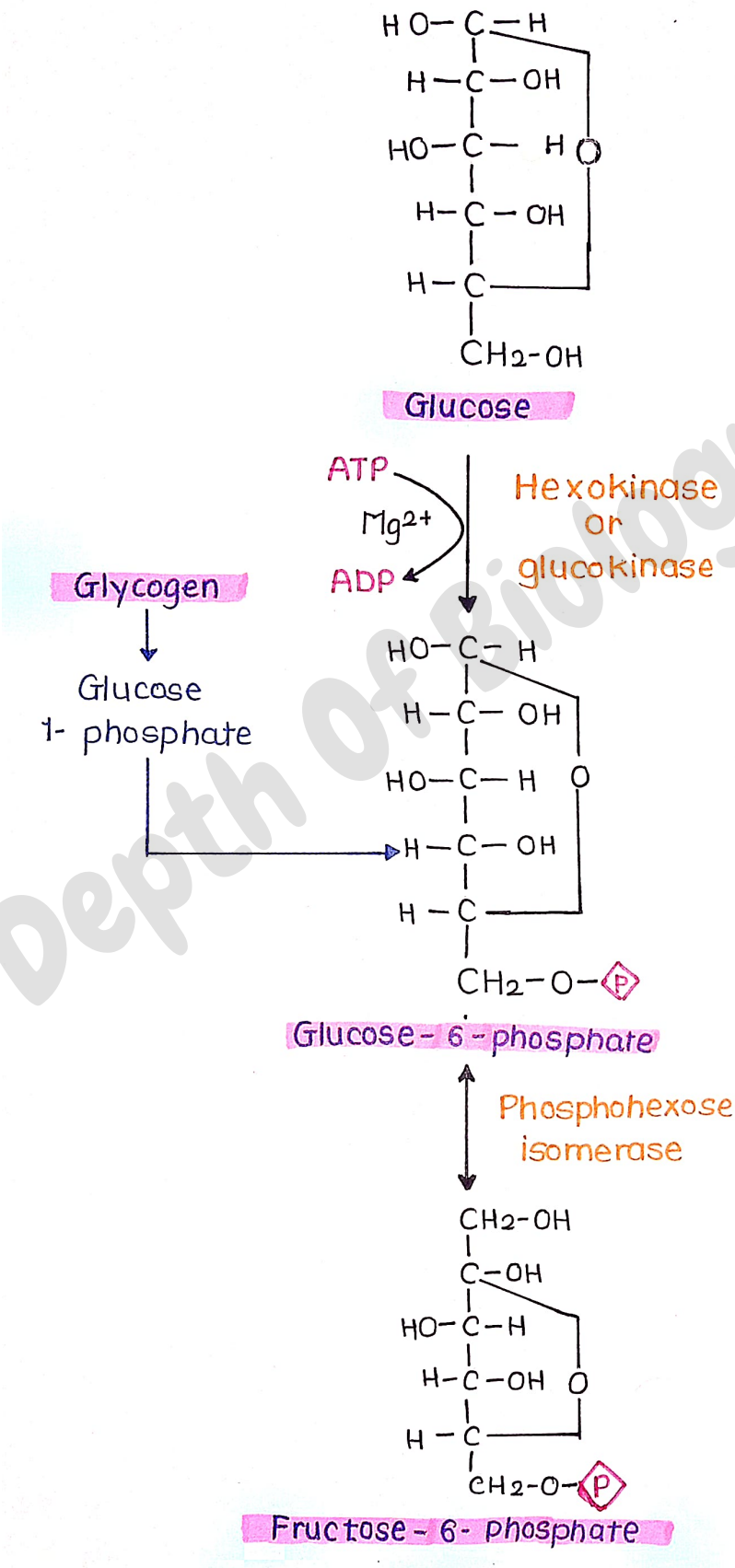
· 10/15 Marks Question

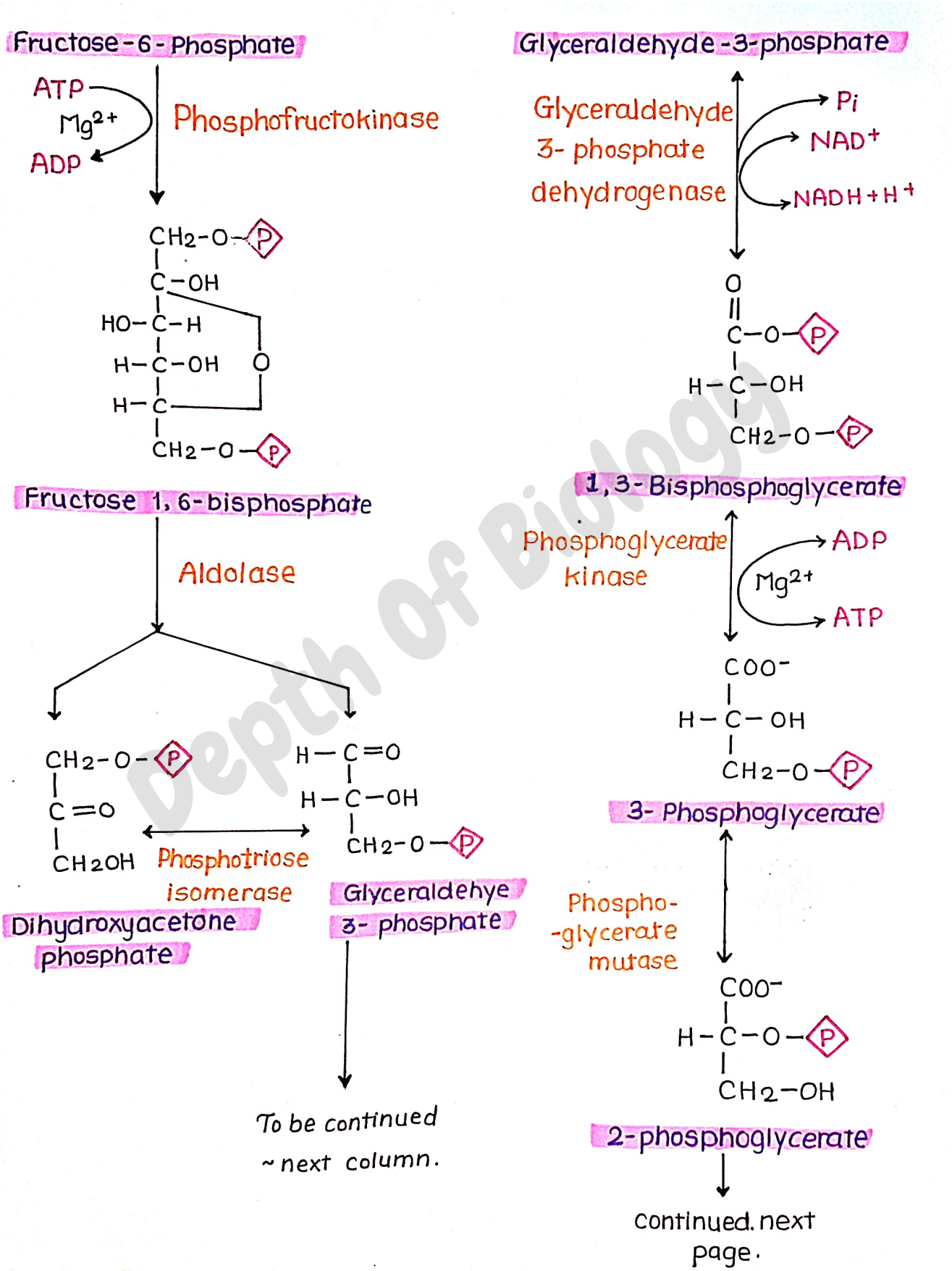
Q.1 Explain glycolysis, its pathway, energetics & significance.

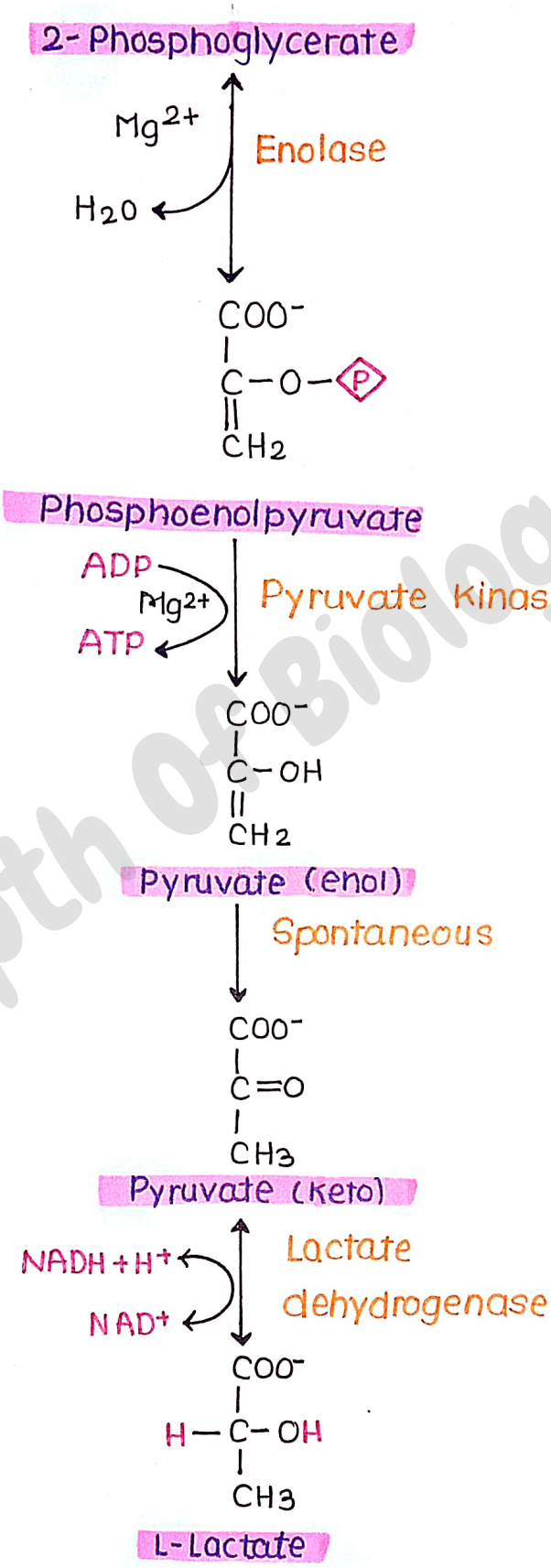
⇨ **ANSWER: GLYCOLYSIS**

- Glycolysis is the first step of glucose metabolism.
- It is the enzymatic breakdown of one glucose (6C) into two pyruvate (3C) molecules.
- It occurs in the cytoplasm of all cells.
- It is an anaerobic pathway (does not require oxygen), but its products are further processed under aerobic or anaerobic conditions.
- Also called the Embden-Meyerhof-Parnas (EMP) pathway.
- **Definition**: Glycolysis is the enzymatic breakdown of glucose into pyruvate, producing energy in the form of ATP and NADH. It occurs in the cytoplasm and is the first step of cellular respiration.
- **Glycolysis Pathway Steps**:
- Glycosis consists of 10 steps, divided into 2 phases

1. Preparatory Phase (Energy Investment Phase)
2. Pay-off Phase (Energy Generation Phase)







Glycolysis

Preparatory Phase

- **Step1 : Phosphorylation of glucose.**
- Glucose $\xrightarrow[Mg^{2+}]{\text{Hexokinase or glucokinase}}$ Glucose-6-Phosphate
  (ATP → ADP)
- **Enzyme** : **Hexokinase** [in most tissues) or **Glucokinase** [in liver & β-cells].
- **Co-factor** : Mg^{2+}
- **Reaction** : ATP donates phosphate → ADP formed.
- **Purpose** : Traps glucose inside the cell, makes it more reactive.

- **Step 2** : **Isomerization**
- Glucose-6-phosphate $\xrightarrow{\text{Phosphohexose isomerase.}}$ Fructose-6-phosphate
- **Enzyme** : **Phosphohexose isomerase**
- Changes aldose (glucose) to ketose (fructose).
- Makes the molecule symmetrical for later splitting.

- **Step 3 : Second phosphorylation**
- Fructose-6-Phosphate $\xrightarrow[Mg^{2+}]{\text{Phosphofructokinase}}$ Fructose 1,6-Bisphosphate.
  (ATP → ADP)
- **Enzyme** : **Phosphofructokinase**

- **Reaction** : Uses 1 ATP → ADP
- Key regulatory step : Rate-limiting, highly regulated by energy status (ATP/AMP).
- Adds second phosphate.

Step 4 : Cleavage

- Fructose 1,6-bisphosphate —(Aldolase)→ Dihydroxyacetone phosphate. + Glyceraldehye 3-phosphate.
- **Enzyme** : Aldolase
- Breaks the 6C sugar into two 3C sugars.

Step 5 : Isomerization of Dihydroxyacetone phosphate [DHAP].

- Dihydroxyacetone phosphate [DHAP] ⟷ (Phosphotriose) Glyceraldehyde 3-phosphate.
- **Enzyme** : Phosphotriose
- Only Glyceraldehyde-3-phosphate (G3P) continues in glycolysis, so Dihydroxyacetone phosphate (DHAP) is converted to (G3P) Glyceraldehyde-3-phosphate.
- At the end of this phase, two molecules of G3P are formed from one glucose.

✧ Pay- off Phase (steps 6-10).

- Each reaction now happens twice.
  (Once per G3P = Glyceraldehye)

- **Step 6 : Oxidation and phosphorylation**

- Glyceraldehyde-3-Phosphate ⟷ 1,3-Bisphospho-glycerate
  (NADH+H⁺, NAD⁺, Pi; Glyceraldehyde 3-phosphate dehydrogenase.)

- Enzyme : Glyceraldhyde-3-phosphate dehydrogenase
- Adds inorganic phosphate (no ATP used).
- Produces 2 NADH per glucose.
- It is reversible reaction.

- **Step 7 : Substrate-level phosphorylation.**

- 1-3-Bisphosphoglycerate ⟷ 3-Phosphoglycerate
  (Phosphoglycerate kinase. ADP, Mg^{2+}, ATP)

- Enzyme : Phosphoglycerate kinase
- Transfers high-energy phosphate to ADP → ATP
- Produces 2 ATP per glucose.
- It is reversible reaction.

- **Step 8 : Isomerization**

- 3 Phosphoglycerate $\xleftrightarrow[\text{mutase}]{\text{Phosphoglycerate}}$ 2-phosphoglycerate

- **Enzyme : Phosphoglycerate mutase**
- Moves phosphate from 3rd to 2nd carbon.
- Reaction is reversible.

- **Step 9 : Dehydration**

- 2-phosphoglycerate $\xrightarrow[Mg^{2+}]{\text{Enolase}}$ Phosphoenol-pyruvate. (PEP) + H_2O

- **Enzyme : Enolase**
- Removes water (dehydration), creates high-energy enol phosphate.

Step 10 : Substrate-level - phosphorylation

- (PEP) Phosphoenol-pyruvate $\xrightarrow[Mg^{2+}]{\text{Pyruvate Kinase}}$ Pyruvate [enol] + ADP → ATP

- Enzyme : Pyruvate kinase
- Transfers phosphate from PEP to ADP → ATP.
- Produces 2 ATP per glucose.

- At the end Pyruvate (enol) is converted to Pyruvate (keto) Spontaneously.
- And Pyruvate (keto) is converted to L-Lactate as product in presence of $NAD^+ \longrightarrow NADH + H^+$ and enzyme Lactate dehydrogenase.

Energetics of Glycolysis

Step	ATP used	ATP formed	NADH formed
Glucose ⟶ Glucose -6- Phosphate Enzyme : Hexokinase	-1		
Fructose-6- phosphate ↓ Fructose 1,6- bisphosphate Enzyme : Phosphofructo- -kinase	-1		
Glyceraldehyde-3- Phosphate ↓ 1,3- Bisphosphoglycerate Enzyme : Glyceraldehyde -3- phosphate dehydrogen.			+2
1,3- Bisphosphoglycerate ↓ 3- Phosphoglycerate Enzyme : Phosphoglycerate kinase.		+2	
Phosphoenolpyruvate ↓ Pyruvate Enzyme : Pyruvate kinase		+2	
TOTAL :	-2	+4	+2

- Net ATP directly : +4 −2 = +2 ATP
- NADH : 2 NADH × 3 ATP (oxidative phosphorylation)
  = 6 ATP.
- Total ATP (aerobic) : 8 ATP per glucose.

Significance of Glycolysis

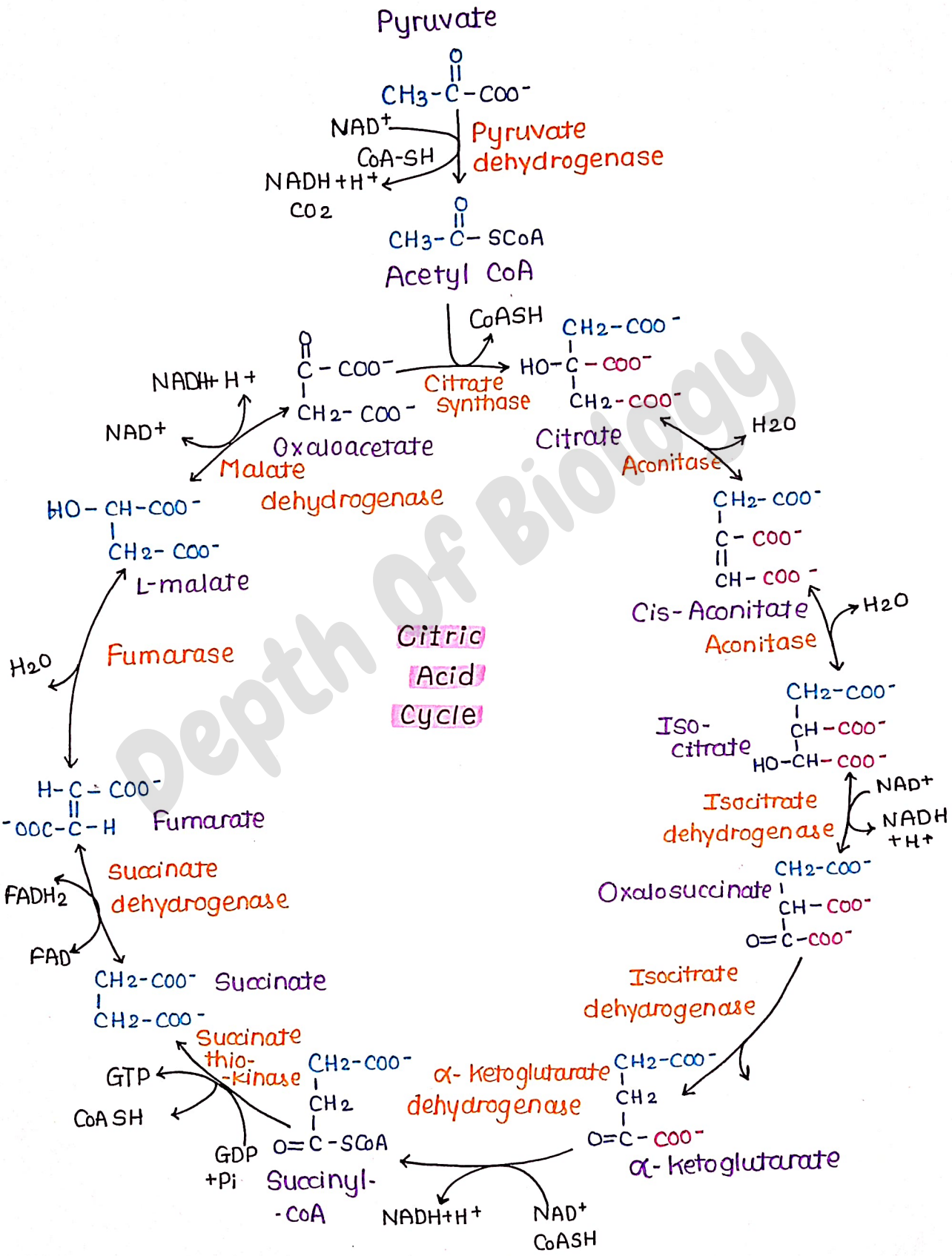
- Major pathway for ATP production in tissues like RBCs (which lack mitochondria).
- Provides intermediates for biosynthetic pathways (eg. 3-Phosphoglycerate for serine synthesis).
- Produces pyruvate, which can be converted to :
  - Acetyl-CoA ⟶ enters TCA cycle (aerobic)
  - Lactate ⟶ under anaerobic conditions.
- Important in muscle during exercise when oxygen is limited.
- Helps in metabolism of dietary carbohydrates.

Q.2. Give a detail note on citric acid Cycle.

ANSWER: CITRIC ACID CYCLE (KREBS CYCLE / TCA CYCLE).

- The citric acid Cycle (CAC), also called the Kreb's cycle or Tricarboxylic Acid Cycle (TCA Cycle), is a central metabolic pathway that takes place in the mitochondrial matrix.
- It plays a major role in the oxidation of carbohydrates, fats and proteins releasing energy in the form of ATP, NADH and $FADH_2$.
- Location: occurs in → mitochondrial matrix (in all aerobic organisms).
- Acetyl-CoA is the starting molecule.
- It is formed by the oxidative decarboxylation of pyruvate (the end product of glycolysis) by the pyruvate dehydrogenase complex.
- Overall Reaction of the Cycle:

$$\text{Acetyl CoA} + 3\,NAD^+ + FAD + GDP + P_i + 2H_2O \longrightarrow 2CO_2 + 3NADH + 3H^+ + FADH_2 + GTP + CoA - SH$$



- **Steps of Citric acid Cycle**:

1. **Condensation**:
   - Acetyl CoA (2C) + Oxaloacetate (4C)
     ↓
     Citrate (6C)
   - **Enzyme**: Citrate synthase

2. **Isomerization**:
   - Citrate ⟶ Isocitrate
   - **Enzyme**: Aconitase (via intermediate cis-aconitate).

3. **First Oxidative Decarboxylation**:
   - Isocitrate ⟶ α-Ketoglutarate (5C) + CO_2
   - **Enzyme**: Isocitrate dehydrogenase.
   - NAD^+ is reduced to NADH

4. **Second Oxidative Decarboxylation**:
   - α-Ketoglutarate ⟶ Succinyl-CoA (4C) + CO_2
   - **Enzyme**: α-Ketoglutarate dehydrogenase complex.
   - NAD^+ is reduced to NADH.

5. **Substrate-Level Phosphorylation**:
   - Succinyl-CoA ⟶ Succinate
   - **Enzyme**: Succinyl-CoA synthetase.
   - GTP (or ATP) is formed.

6. **Oxidation**:
   - Succinate ⟶ Fumarate
   - Enzyme: Succinate dehydrogenase
   - FAD is reduced to $FADH_2$.

7. **Hydration**:
   - Fumarate ⟶ Malate
   - Enzyme: Fumarase

8. **Final Oxidation**:
   - Malate → Oxaloacetate
   - Enzyme: Malate dehydrogenase.
   - NAD^+ is reduced to NADH

- **Energetics**

- Energy Yield per Acetyl-CoA

Product	Number	ATP Equivalent
3 NADH	3	9 ATP
1 $FADH_2$	1	2 ATP
1 GTP	1	1 ATP
Total	–	12 ATP

- Since 1 glucose ⟶ 2 Acetyl-CoA ⟶ 2 turns of cycle, total 24 ATP generated from TCA cycle per glucose.

- **Regulation of TCA cycle:**
- The cycle is regulated at 3 enzymes:

1. Citrate synthase
2. Isocitrate dehydrogenase
3. α-ketoglutarate dehydrogenase.

- These are regulated by availability of substrates, ATP/ADP ratio, and feedback inhibition by NADH and succinyl-CoA.

- **Significance of TCA cycle:**

1. **Central pathway**: Final common pathway for oxidation of carbohydrates, fats and proteins.
2. **Energy production**: Major source of NADH and $FADH_2$ for ATP generation via oxidative phosphorylation.
3. **Amphibolic nature**: Both catabolic and anabolic functions.
4. **Intermediates used in biosynthesis of**:
   - Amino acids
   - Glucose (via gluconeogenesis)
   - Porphyrins, purines and pyrimidines.
5. **Maintains oxaloacetate pool** for continued cycling.

- **Anaplerotic Reactions** [Refilling reactions]
- Reactions that helps to recharge the citric acid cycle.
  - Pyruvate ⟶ Oxaloacetate [By pyruvate carboxylase].
  - Asparate ⟶ Oxaloacetate
  - Glutamate ⟶ α-Ketoglutarate.

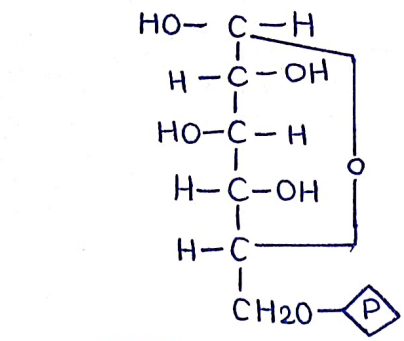
- The citric acid cycle is essential for life.
- It not only produces energy-rich molecules but also provides precursors for biosynthetic processes.
- Its tight regulation ensures energy balance and metabolic flexibility in cells.

Q.3. Explain HMP Shunt or Pentose Phosphate pathway (PPP).

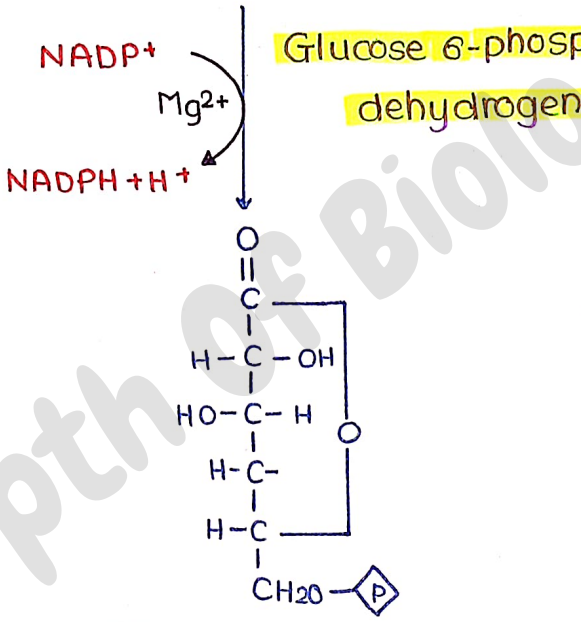
ANSWER : HMP Shunt or Pentose Phosphate Pathway

- Hexose Monophosphate Shunt (HMP Shunt).
- also called as Pentose Phosphate Pathway (PPP) or Phosphogluconate.
- The HMP Shunt is an alternative pathway for breakdown of glucose-6-phosphate.
- Unlike glycolysis, it does not produce ATP, but instead plays important roles in :
  - Producing NADPH for biosynthesis and antioxidant defense.
  - Producing Ribose-5-phosphate for the synthesis of DNA, RNA and nucleotides.
  - Providing intermediates for glycolysis.
- Occurs in the cytoplasm of cells
- Highly active in :
  - liver
  - Adipose tissue
  - RBCs
  - Adrenal cortex
  - Lactating mammary gland.

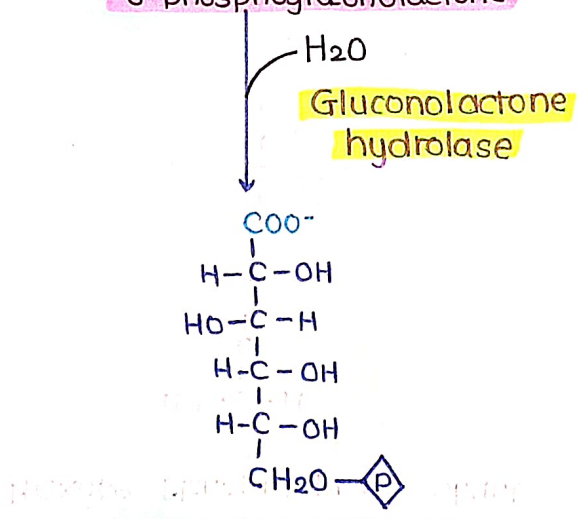
Hexose Monophosphate Shunt



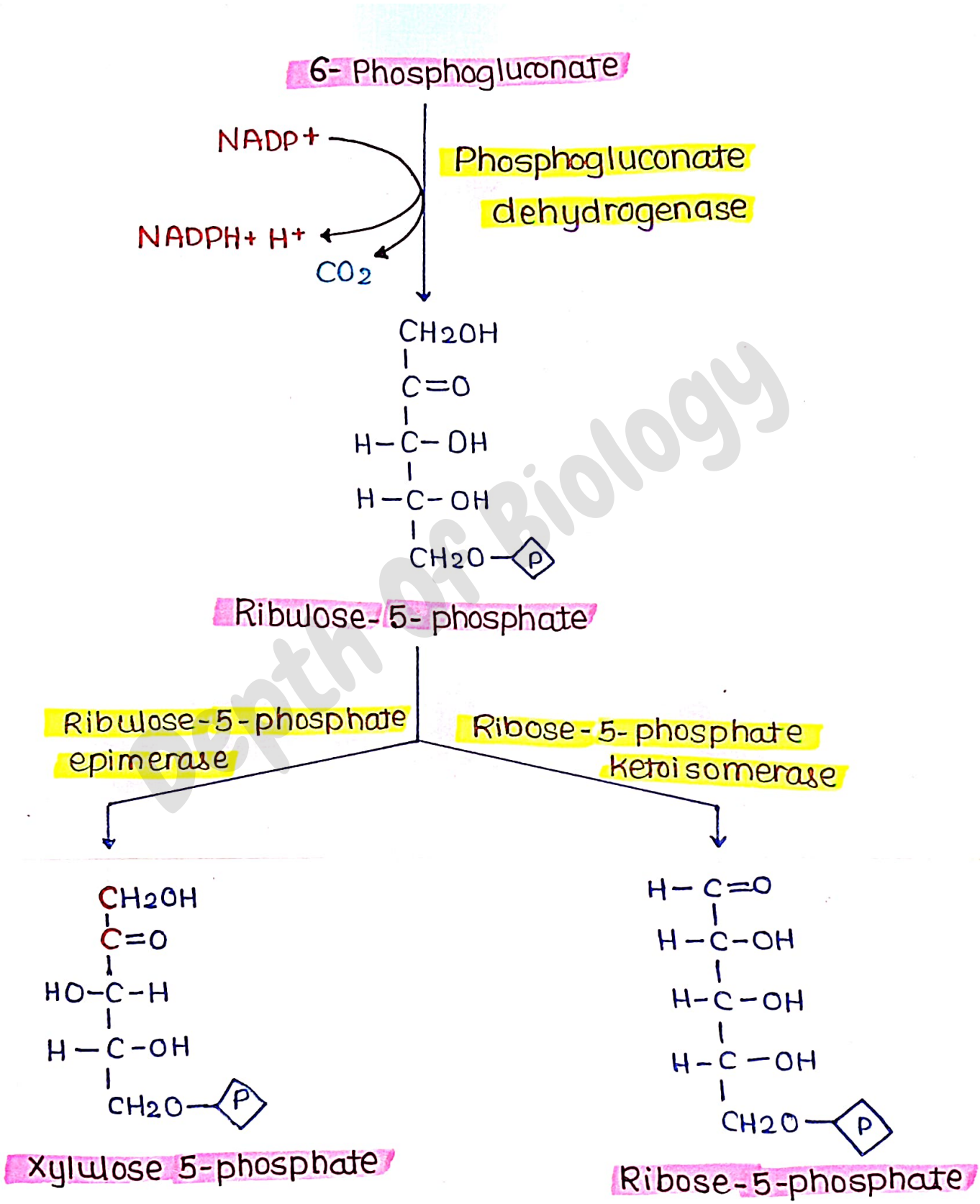
Glucose-6-phosphate

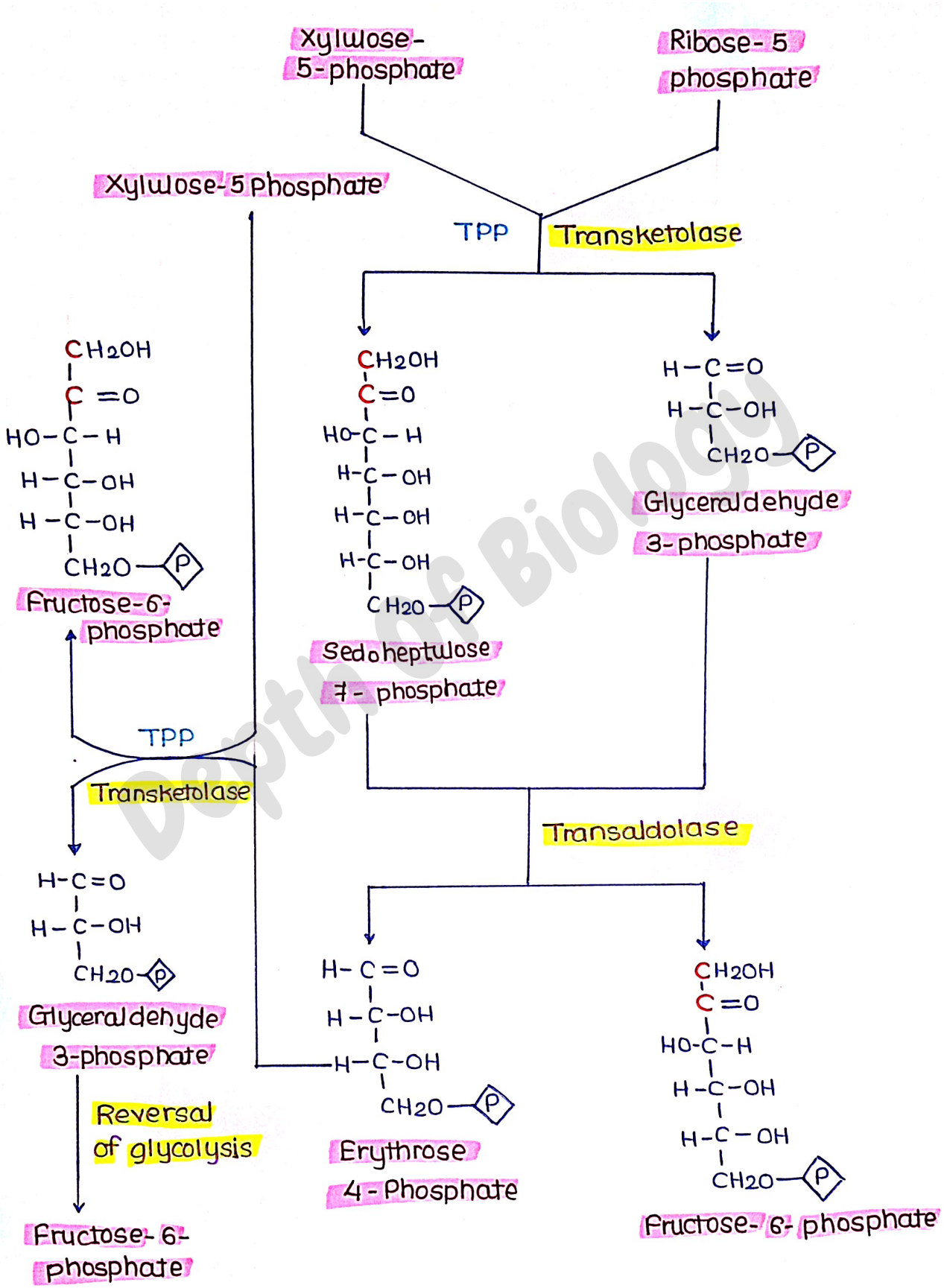


6-phosphogluconolactone



6-Phosphogluconate





HMP Shunt Pathway

- The pathway has two phases :
  1. Oxidative Phase - irreversible.
  2. Non-oxidative Phase - reversible.

1. Oxidative Phase (Irreversible)

Main function : Produce NADPH and Ribulose-5-phosphate

Step	Reaction	Enzyme	Products
1.	Glucose-6-phosphate ↓ 6-phosphogluconolactone	Glucose-6-phosphate dehydrogenase (G6PD)	1 NADPH
2.	6-phosphogluconolactone ↓ 6-phosphogluconate	Lactonase	-
3.	6-phosphogluconate ↓ Ribulose-5-phosphate + CO_2	6-phosphogluconate dehydrogenase	1 NADPH

- Total NADPH produced = 2 per glucose-6-phosphate.
- Ribulose-5-phosphate enters the non-oxidative phase.

2. Non-oxidative Phase (Reversible)

- Main function: Convert 5- carbon sugars to 3- & 6-carbon sugars or form Ribose-5-phosphate for nucleotide synthesis.

- For nucleotide synthesis
  - Ribulose-5-phosphate ⟶ Ribose-5-phosphate
  - Enzyme: Isomerase

- For glycolysis or sugar rearrangement

Reaction	Enzyme	Outcome
Ribulose-5-Phosphate ↓ Xylulose-5-Phosphate	Epimerase	Isomer conversion
Ribose-5-phosphate + Xylulose-5-phosphate ⟶ Glyceraldehyde-3 phosphate + Sedoheptulose-7-P	Transketolase	Carbon shuffling
Sedoheptulose-7-phosphate + Glyceraldehyde-3-phosphate ↓ Fructose-6-Phosphate + Erythrose-4-Phosphate	Transaldolase	Enters glycolysis.
Erythrose-4-Phosphate + Xylulose-5 phosphate ⟶ Fructose-6-Phosphate + Glyceraldehyde-3-Phosphate	Transketolase	More glycolysis intermediates.

- These products (Fructose-6-phosphate & Glyceraldehyde-3-phosphate) re-enter glycolysis.

- **Significance of HMP Shunt**

1. **Production of NADPH**

- The HMP Shunt is a major source of NADPH.
- NADPH is essential for:
  - Fatty acid synthesis
  - Cholesterol synthesis
  - Steroid hormone synthesis
  - Detoxification in liver (via cytochrome p450 system)
  - Protecting red blood cells from oxidative stress (by maintaining reduced glutathione).

2. **Formation of Ribose-5-phosphate**

- Used in the synthesis of:
  - DNA and RNA
  - Nucleotides like ATP, NAD^+, FAD, and CoA.
- Important for rapidly dividing cells (bone marrow, skin, cancer cells).

3. **Interconversion of Sugars**

- Converts - 5- carbonsugars into glycolysis intermediates like :
- Fructose - 6- phosphate
- Glyceraldehyde - 3- phosphate
- Helps maintain balance between carbohydrate metabolism and nucleotide needs.

4. **Active in Tissues with High NADPH Demand**

- Liver (for fat and cholesterol) synthesis
- Adipose tissue (for fatty acids)
- Adrenal glands (for steroid hormones)
- Red blood cells (for antioxidant protection)

5. **Role in disease - G6PD Deficiency**

- If the enzyme G6PD is deficient :
- NADPH is not produced properly
- RBCs are damaged by oxidative stress.
- Leads to hemolytic anemia.

Q.4. Explain Diabetes Mellitus.

⇨ **ANSWER** : · **Diabetes Mellitus.**

- Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia (increased blood glucose level) due to defective insulin secretion, insulin action, or both.
- It is associated with disturbances in the metabolism of carbohydrates, fats and proteins.

- **TYPES OF DIABETES**

1. **Type 1 diabetes mellitus (Insulin-dependent or IDDM):**

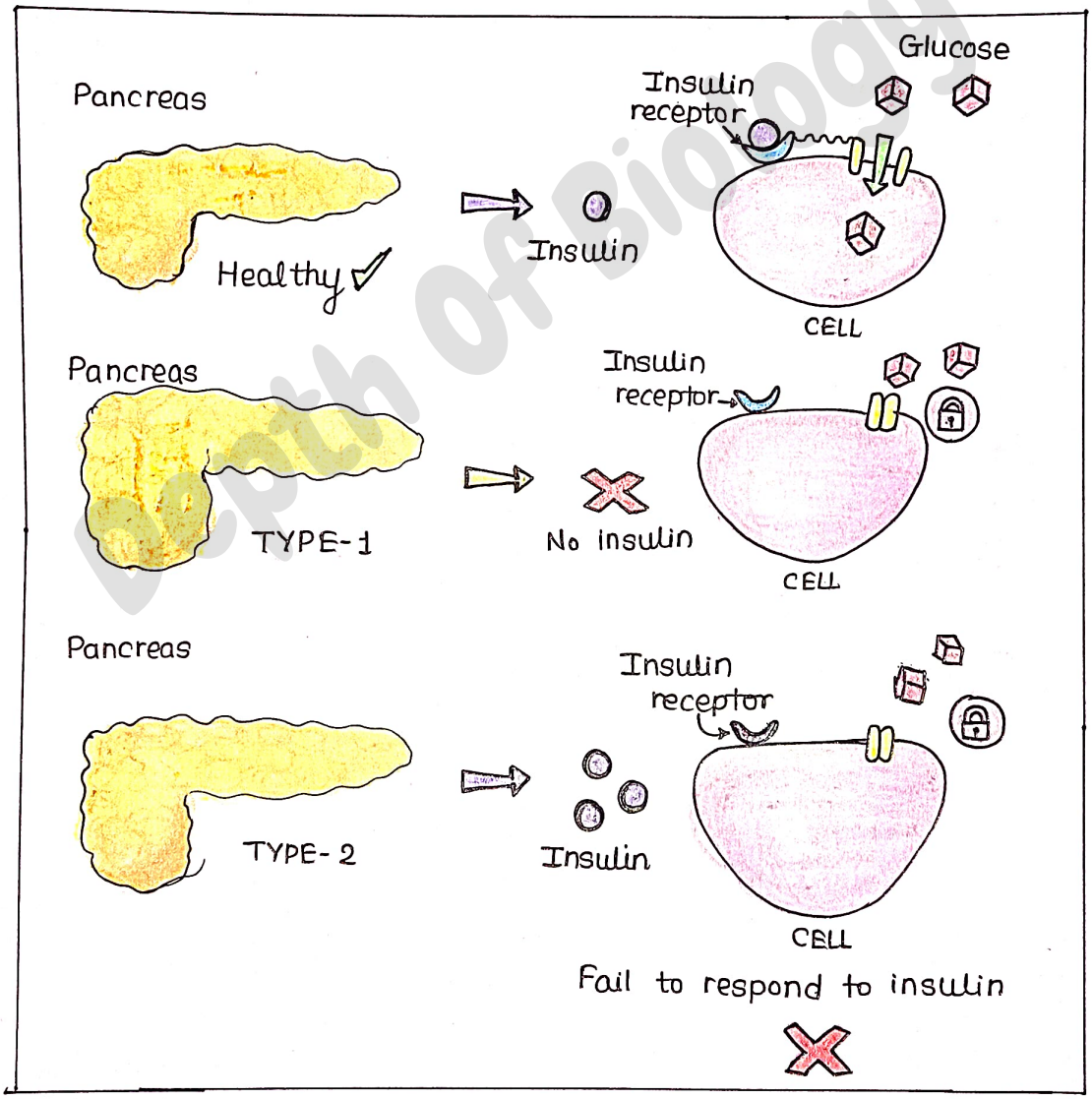
- Caused by autoimmune destruction of pancreatic β-cells.
- Results in complete deficiency of insulin.
- Common in children and adolescents.
- Requires lifelong insulin therapy.

2. **Type 2 Diabetes Mellitus (Non-insulin dependent or NIDDM):**

- Caused by insulin resistance and relative insulin deficiency.
- Associated with obesity, sedentary lifestyle, and genetic factors.
- More common in adults.
- Treated with oral hypoglycemic agents, diet, exercise and sometimes insulin.

3. Gestational Diabetes Mellitus

- Occurs during pregnancy.
- Due to hormonal imbalance affecting insulin action.
- May lead to fetal complications and future risk of type 2 diabetes in mother.



Mechanism of Type 1

- Type 1 Diabetes Mellitus (T1DM)
  Insulin-Dependent Diabetes Mellitus (IDDM)
- Autoimmune destruction of β-cells in Islets of Langerhans (pancreas)
- This leads to absolute insulin deficiency.
- The immune system produces autoantibodies (like anti-GAD) that attack β-cells.
- No insulin means:
  - Glucose cannot enter cells.
  - The liver continues gluconeogenesis and glycogenolysis unchecked.
  - Result: Hyperglycemia (high blood sugar).
- ↑ Blood glucose → Glycosuria → Polyuria, Polydipsia.
- Lack of insulin → Lipolysis → free fatty acids
  ↓
  Ketone body formation
  ↓
  Ketoacidosis.
- Proteolysis occurs → Muscle wasting and weight loss.

Mechanism of Type 2

- Type 2 Diabetes Mellitus (T2DM) - Non-Insulin Dependent Diabetes Mellitus (NIDDM).
- Insulin resistance in target tissues (like muscle, liver, fat).

- β-cells initially secrete more insulin to compensate → Hyperinsulinemia.
- Over time, β-cell dysfunction occurs → Relative insulin deficiency.
- Cells fail to respond to insulin → Glucose uptake decreases → Hyperglycemia.
- Liver ↑ glucose production → Worsens hyperglycemia.
- Adipose tissue shows increased lipolysis, but no ketoacidosis (as some insulin is present).
- Hyperglycemia with normal or high insulin in early stages.
- Long-term: β-cell failure, may require insulin therapy.

- **Biochemical Changes in Diabetes Mellitus:**

1. **Carbohydrate Metabolism:**

- Decreased glucose uptake by cells due to insulin deficiency.
- Increased gluconeogenesis and glycogenolysis in liver.

2. **Lipid Metabolism:**

- Increased lipolysis in adipose tissue → releases free fatty acids (FFAs).

- FFAs are converted to ketone bodies in liver → causes ketosis and ketoacidosis (mainly in Type 1).
- Increased plasma cholesterol and triglycerides.

- **Protein Metabolism**:
- Increased proteolysis → muscle wasting.
- Amino acids are used for gluconeogenesis, worsening hyperglycemia.
- Negative nitrogen balance and poor wound healing.

- **Symptoms** [Clinical Features]
  - **Polyuria**: Excess urination
  - **Polydipsia**: Excess thirst
  - **Polyphagia**: Excess hunger
  - **Weight loss** (in Type 1)
  - **Fatigue**, blurred vision, infections
  - **Ketone breath** (in diabetic ketoacidosis).

- **Diagnosis**:
  According to WHO and ADA
- Fasting blood glucose > 126 mg/dL
- Postprandial blood glucose > 200 mg/dL
- HbA1c ≥ 6.5%
- Urine test for glucose and ketones.
- Oral Glucose Tolerance Test (OGTT).

- **Complications**
- **Acute** :
- Diabetic ketoacidosis (Type 1)
- Hyperosmolar coma (Type 2)
- **Chronic** :
- Microvascular : Retinopathy, nephropathy, neuropathy
- Macrovascular : Atherosclerosis, heart disease, stroke.
- Others : Diabetic foot, infections, delayed wound healing.
- **Treatment and Management** :
- **Type 1**
- Insulin therapy is essential.
- Diet and lifestyle regulation.
- Monitoring of blood glucose.
- **Type 2**
- Weight reduction, physical activity.
- Oral hypoglycemic drugs (e.g. Metformin, Sulfonylureas).
- Insulin if needed.
- **Prevention and Lifestyle Management** :
- Healthy diet, regular exercise.
- Avoid obesity
- Regular health check-ups
- Stress management.

- Diabetes mellitus is a growing global health concern. Early diagnosis, lifestyle changes and proper medical care can prevent complications and improve quality of life.
- Understanding the biochemical basis helps in better diagnosis and treatment planning.

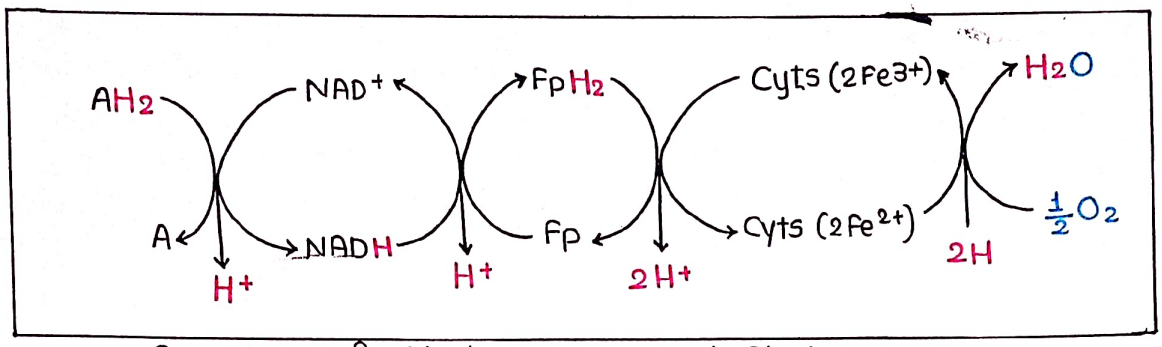
Q.5. Explain ETC & Oxidative phosphorylation

⇨ **ANSWER**:

- The Electron Transport Chain (ETC) and Oxidative Phosphorlyation together form the final stage of cellular respiration.
- They occur in the inner mitochondrial membrane and are responsible for producing the maximum ATP from the energy source stored in NADH and $FADH_2$.

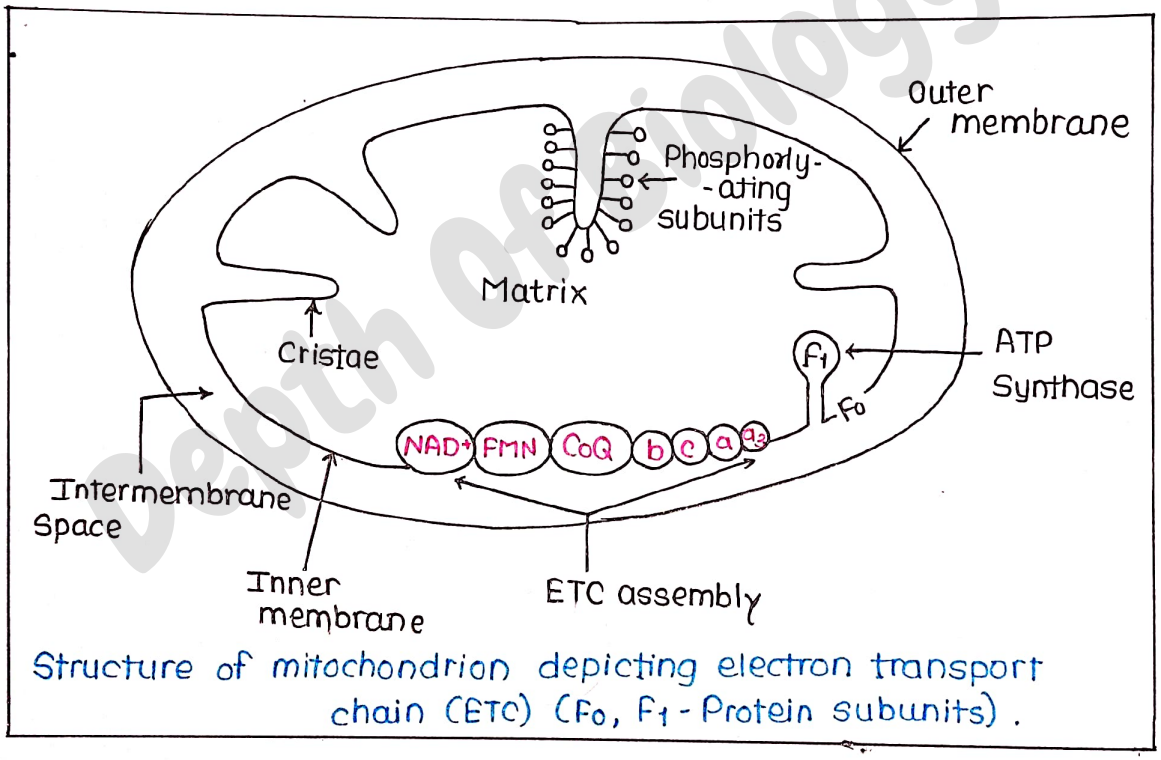
1. **Electron Transport Chain (ETC)**

- **Location**: Inner membrane of mitochondria.
- **Main Role**: Transfers electrons from NADH and $FADH_2$ to oxygen (O_2).
- This transfer releases energy, which is used to pump proton (H^+) across the membrane.



Overview of Electron Transport Chain

[A - Substrate ; F_p - Flavoprotein ; Cyts - Cytochrome]



Structure of mitochondrion depicting electron transport chain (ETC) (F_o, F_1 - Protein subunits).

· **ETC Complexes** :

There are 5 complexes in Electron Transport Chain (ETC) as given below in the table:

Complex	Name	Function
I	NADH dehydrogenase	• Transfers e^- from NADH to ubiquinone (Q), pumps H^+.
II	Succinate dehydrogenase	• Transfers e^- from $FADH_2$ to Q (no H^+ pumping).
III	Cytochrome bc_1 complex	• Transfer e^- from Q to cytochrome c_1 pumps H^+.
IV	Cytochrome c oxidase	• Transfers e^- to O_2 forming water (H_2O), pumps H^+
V	ATP Synthase (used in phosphorylation)	• Synthesizes ATP using the proton gradient.

- **Mobile Electron Carriers:**
- **Ubiquinone (CoQ)** - transfers electrons from Complex I/II to III.
- **Cytochrome c** - carries electrons from Complex III to IV.

- **End Result of ETC:**
- Oxygen is the final electron acceptor → forms H_2O.
- Proton gradient is created across the membrane (high in intermembrane space, low in matrix).

2. Oxidative Phosphorylation

- **Definition** : The process of ATP formation using the energy of proton gradient created by the ETC is called oxidative phosphorylation.

- **Mechanism** :
  - Due to the proton gradient, protons flow back into the mitochondrial matrix via ATP synthase (complex V).
  - This flow of H^+ provides energy for ADP + Pi ⟶ ATP synthesis.

- **Energy Yield** :

Molecule	ATP Produced
1 NADH	2.5 to 3 ATP
1 $FADH_2$	1.5 to 2 ATP

- **Uncouplers of Oxidative Phosphorylation:**
  - Substances like DNP (2,4- dinitrophenol) disconnect ETC from ATP synthesis ⟶ energy released as heat.

- **Significance** :
  - Produces ~ 34 ATP out of total 38 ATP per glucose molecules.
  - Essential for energy production in aerobic organisms.
  - Maintains cell survival and function.

- ETC transfers electrons from NADH / $FADH_2$ to O_2 through a series of complexes.
- This builds a proton gradient.
- Oxidative phosphorylation uses this gradient to synthesize ATP.
- Occurs in mitochondria, requires oxygen and forms water + energy.

Q.6. Explain Gluconeogenesis.

⇨ **ANSWER** : GLUCONEOGENESIS

- Gluconeogenesis is the metabolic process by which glucose is synthesized from non-carbohydrate sources.
- It is essential during fasting, starvation or intense exercise when blood glucose levels fall.
- Occurs mainly in the liver and kidney cortex.

- **Definition** :
- Gluconeogenesis is the formation of new glucose molecules from non-carbohydrate precursors like:
  - Lactate
  - Amino acids (especially alanine)
  - Glycerol
  - Propionate

- **Site of Gluconeogenesis:**
- Liver (major site)
- Kidney cortex (minor site, during prolonged fasting).
- Occurs in mitochondria and cytosol of liver cells.
- **Pathway of Gluconeogenesis:**
- Gluconeogenesis is not just reverse glycolysis because 3 steps of glycolysis are irreversible.
- So, alternative enzymes are used at these steps:

1. **Pyruvate to Phosphoenolpyruvate (PEP):**

- Step 1:

  Pyruvate ⟶ Oxaloacetate

  (Enzyme: Pyruvate carboxylase, requires biotin).

- Step 2: Oxaloacetate

  ↓

  Phosphoenolpyruvate (PEP)

  (Enzyme: Phosphoenolpyruvate (PEP) carboxykinase).

2. **Fructose-1,6-bisphosphate to Fructose-6-phosphate.**
   (Enzyme: Fructose-1,6-bisphosphatase).

3. **Glucose-6-phosphate to Glucose**
   (Enzyme: Glucose-6-phosphatase).

- Occurs in endoplasmic reticulum of liver and kidney (not present in muscle).

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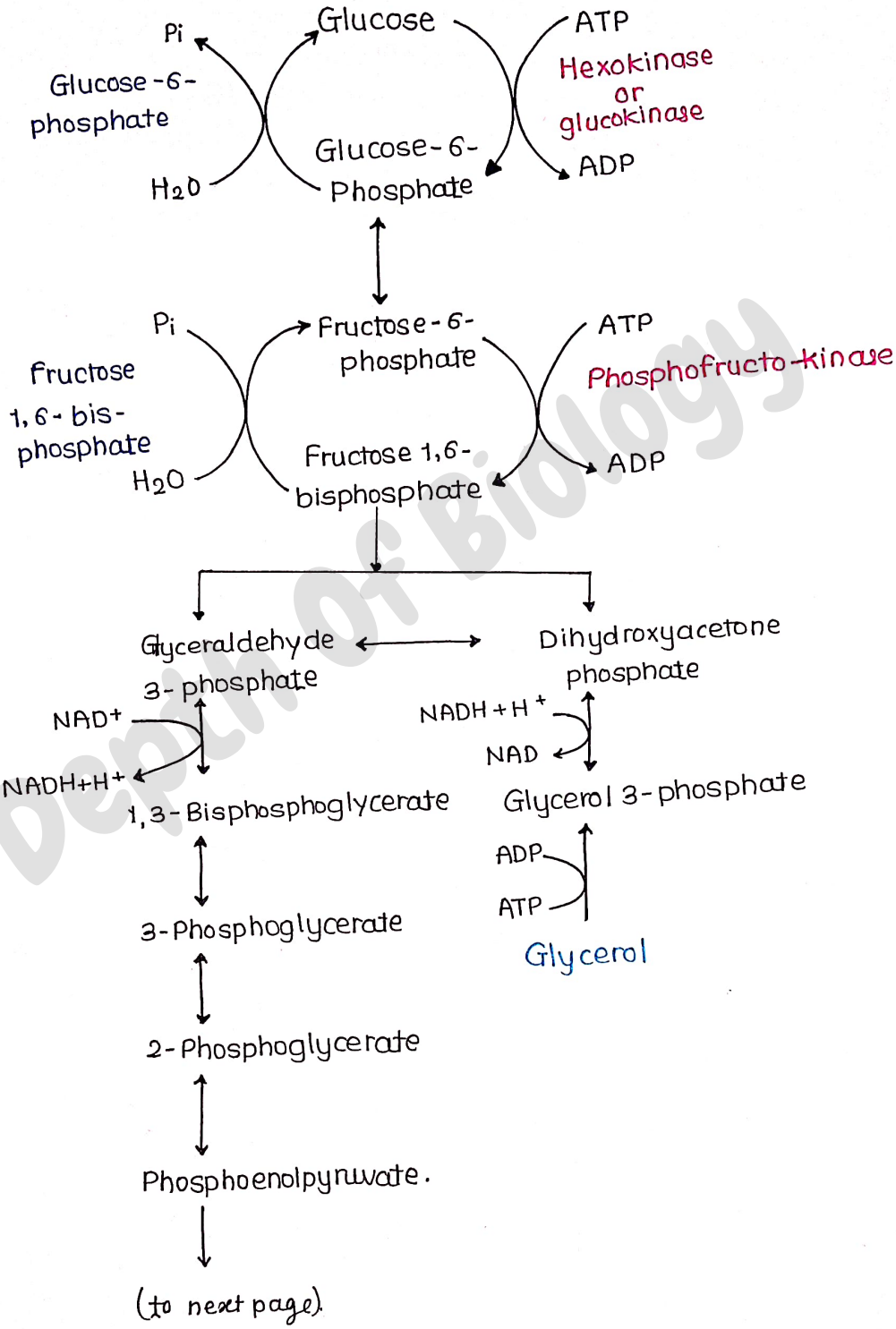
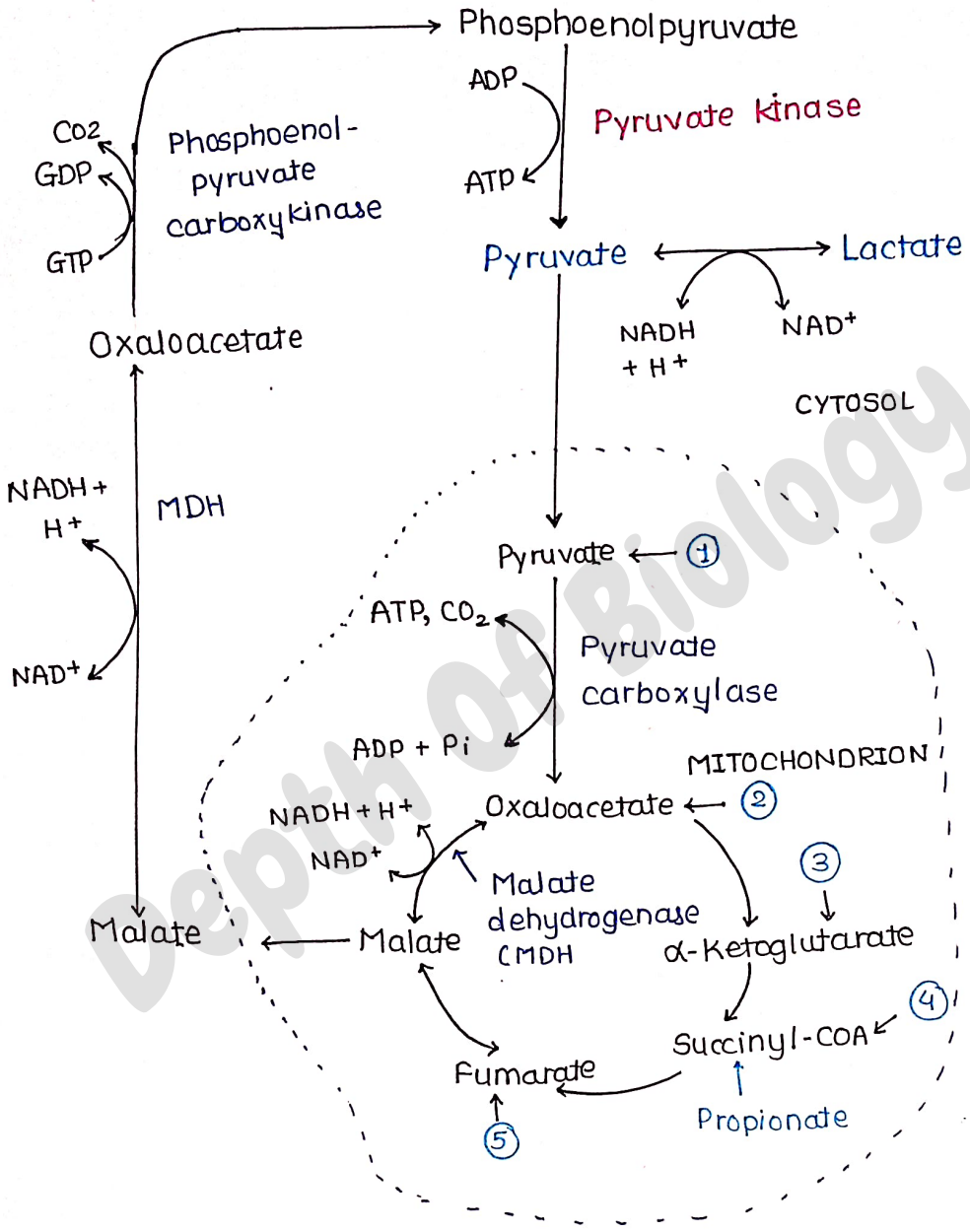




- **Overall conversion :**

2 Pyruvate ⟶ Glucose

Occurs in mitochondria and cytosol of liver and kidney cells.

- **Pathway**
- Step 1: Pyruvate ⟶ Oxaloacetate (OAA)
- Enzyme : Pyruvate carboxylase
- Location : Mitochondria
- Cofactor : Biotin
- Energy used : 1 ATP.
- OAA is formed in mitochondria and transported as malate to cytosol.

- Step 2 : Oxaloacetate ⟶ Phosphoenolpyruvate (PEP)
- Enzyme : PEP carboxykinase (PEPCK)
- Location : Cytosol
- Energy used : 1 GTP

- Step 3 to 7 :
- PEP is converted back through glycolysis in reverse, using the same enzymes until it reaches :
- Fructose-1,6-bisphosphate.

- Step 8 (Bypasses irreversible Phosphofructose kinase-1 step of glycolysis) :
  - Fructose-1,6-bisphosphate → Fructose-6-phosphate
  - Enzyme : Fructose-1,6-bisphosphate.
  - Important regulatory step.

- Step 9 : Fructose-6- phosphate ↔ Glucose-6-phosphate
- Enzyme : Phosphoglucose isomerase. (reversible)
- Step 10 : Final step, unique to liver/kidney.
- Glucose-6-phosphate ⟶ Glucose
- Enzyme : Glucose-6-phosphate
- Location : Endoplasmic reticulum
- Absent in muscle and brain, hence they can't release free glucose.
- Net Reaction:

$$2 \text{ pyruvate} + 4 \text{ ATP} + 2 \text{ GTP} + 2 \text{ NADH} + 6 H_2O \rightarrow \text{Glucose} + 4 \text{ ADP} + 2 \text{GDP} + 6 \text{pi} + 2 NAD^+ + 2H^+$$

- Significance of Gluconeogenesis
- Gluconeogenesis plays a vital role in maintaining glucose homeostasis, especially during fasting, starvation, or prolonged exercise.
- Its important can be explained through the following points :

1. Maintains Blood Glucose levels
- During fasting or starvation, glycogen stores are depleted within 12-18 hours.

- Gluconeogenesis becomes the only source of glucose, especially for glucose-dependent tissues.

2. Supplies Glucose to Essential Organs

- Organs like
  Brain, Red Blood cells (RBCs), Renal medulla, Lens and cornea of eye, Testes rely exclusively on glucose for energy.
- Gluconeogenesis ensures a continuous supply of glucose to these tissues.

3. Prevents Hypoglycemia

- By producing glucose when dietary intake is low, it helps prevent dangerously low blood sugar levels, especially between meals or overnight.

4. Removes Metabolic By-products

- Lactate (from anaerobic glycolysis in muscle) and glycerol (from fat breakdown) are converted into glucose.
- This helps detoxify and recycle metabolic intermediates (Cori cycle, glucose-alanine cycle).

5. Supports Metabolic Needs During Stress or Illness.

- During infections, trauma or burns, energy demand increases.
- Gluconeogenesis supports increased glucose demand for immune cells and healing tissues.

6. Helps in Nitrogen Waste Disposal

- Converts alanine to glucose in the glucose-alanine cycle, removing excess nitrogen from muscle.

7. In Diabetes Mellitus

- In uncontrolled diabetes, gluconeogenesis is abnormally increased, contributing to hyperglycemia.

8. Critical in fasting Adaptation

- In prolonged fasting or starvation, body switches to fat metabolism, but brain still needs glucose.
- Gluconeogenesis helps preserve brain function.

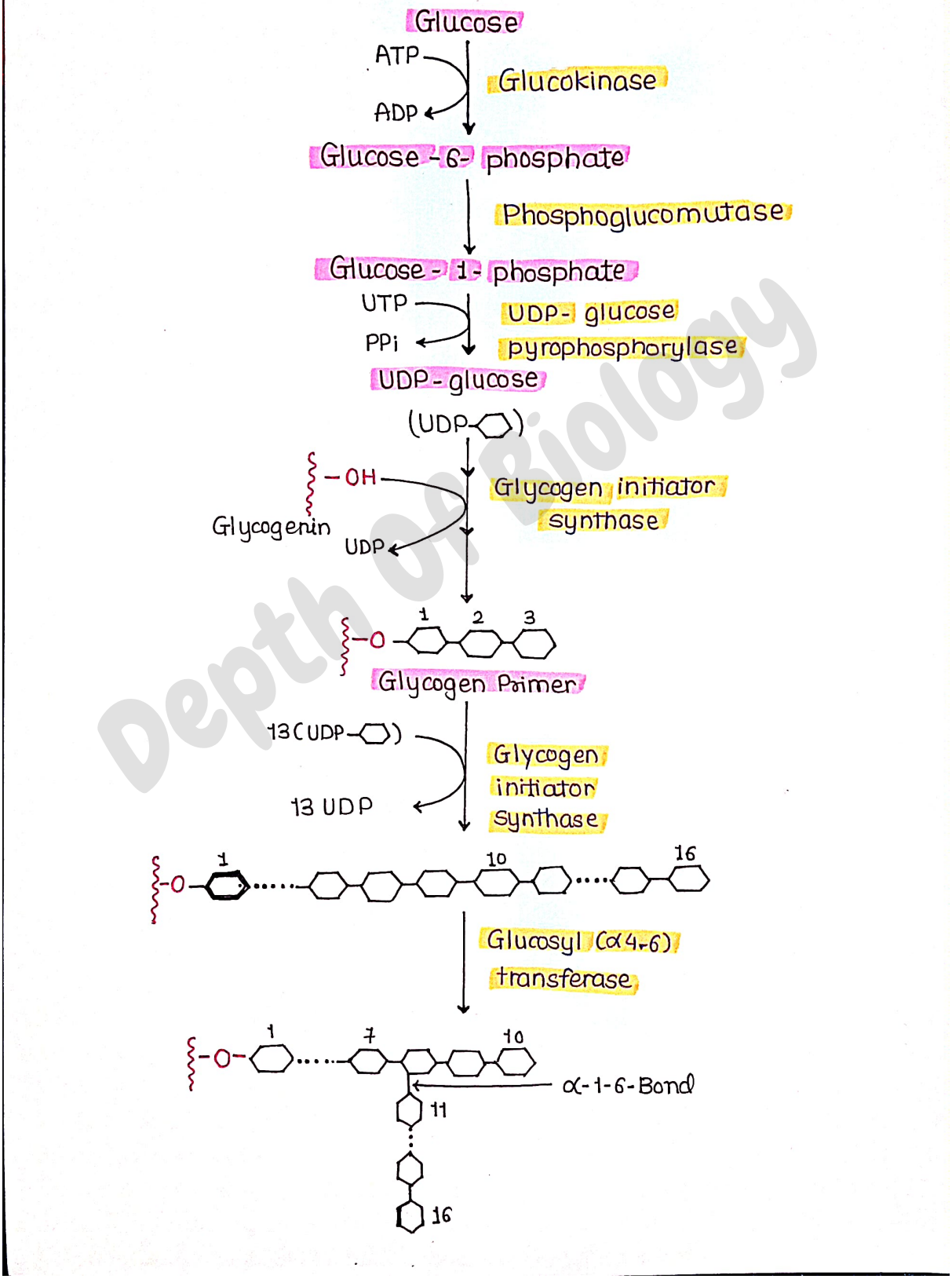
- Gluconeogenesis is a life-sustaining process that maintains energy balance, prevents hypoglycemia. and recycles metabolic waste.
- It is essential for survival during periods of low carbohydrate intake or increased energy demand.

Q.7. Glycogen Metabolism Pathway

ANSWER : INTRODUCTION

- Glycogen is the storage form of glucose in animals.
- It is a highly branched polysaccharide made of glucose units linked by α-1,4 and α-1,6 glycosidic bonds.
- Stored mainly in :
  - Liver - to maintain blood glucose
  - Muscle - for energy during muscle activity.
- Glycogen metabolism includes :
  - Glycogenesis (synthesis of glycogen)
  - Glycogenolysis (breakdown of glycogen).

- **Glycogenesis : Synthesis of glycogen**
- Glycogenesis is the anabolic (biosynthetic) pathway by which glucose molecules are converted into glycogen for storage.
- It is important for maintaining glucose homeostasis and storing energy for later use.



Elongation by
glucose synthase
(forming α 1,4-bonds)

Branching by
glucosyl 4-6 transferase
(α-1,6-bonds)

GLYCOGEN

- **Steps of Glycogenesis :**

1. Glucose ⟶ Glucose-6-Phosphate
   - Enzyme : Hexokinase / Glucokinase (liver) (muscle).
   - Energy used : 1 ATP
2. Glucose-6-Phosphate ⟶ Glucose-1-Phosphate
   - Enzyme : Phosphoglucomutase
3. Glucose-1-phosphate + UTP ⟶ UDP-glucose + PPi
   - Enzyme : UDP-glucose pyrophosphorylase
4. UDP-glucose + Glycogen primer ⟶ Extended glycogen
   - Enzyme : Glycogen synthase
   - Adds glucose in α-1,4 linkages.

5. Branching of glycogen (α-1,6 bonds)

- Enzyme : Branching enzyme.
- Increases solubility and availability of glycogen.

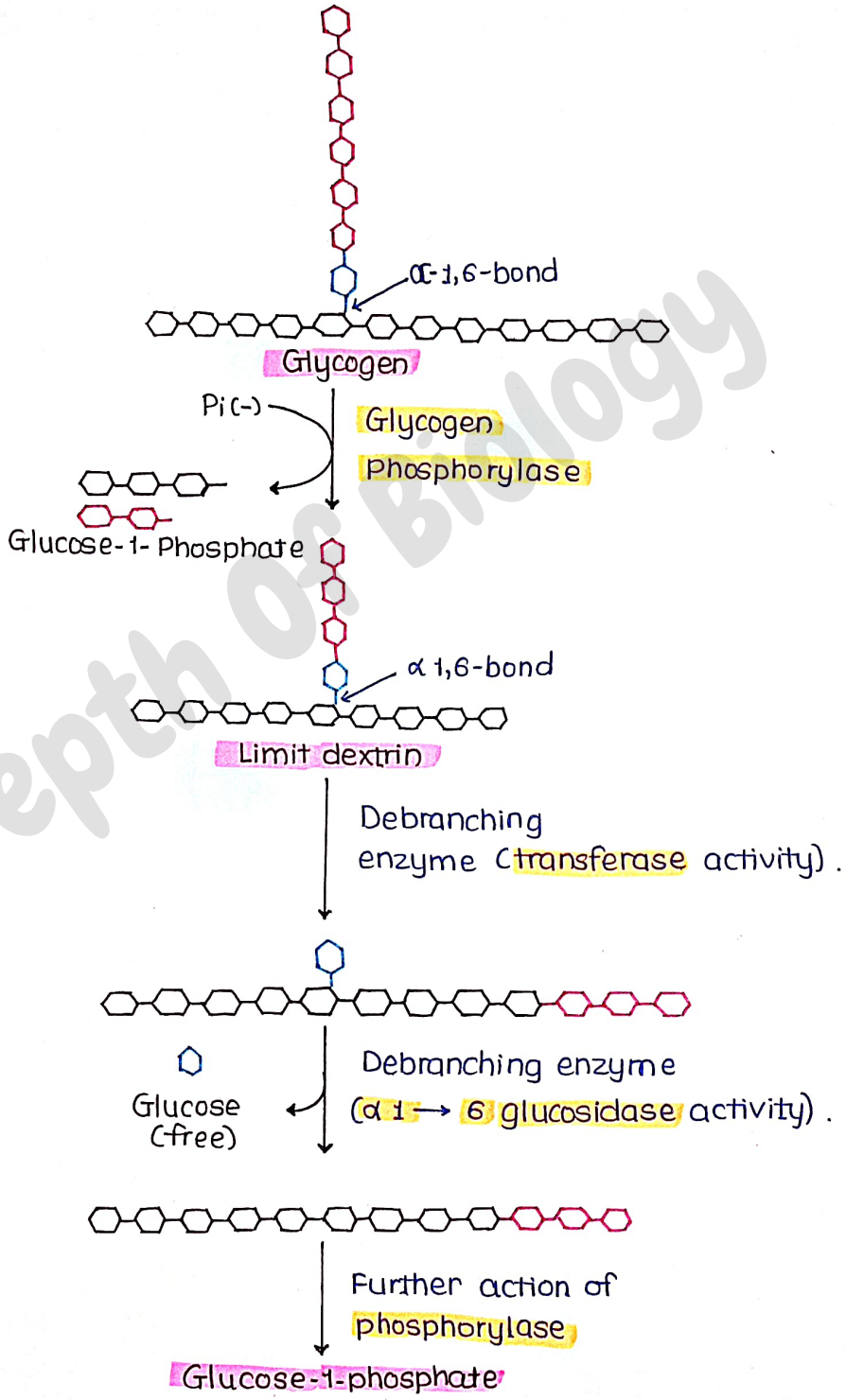
- **Energetics of Glycogenesis**

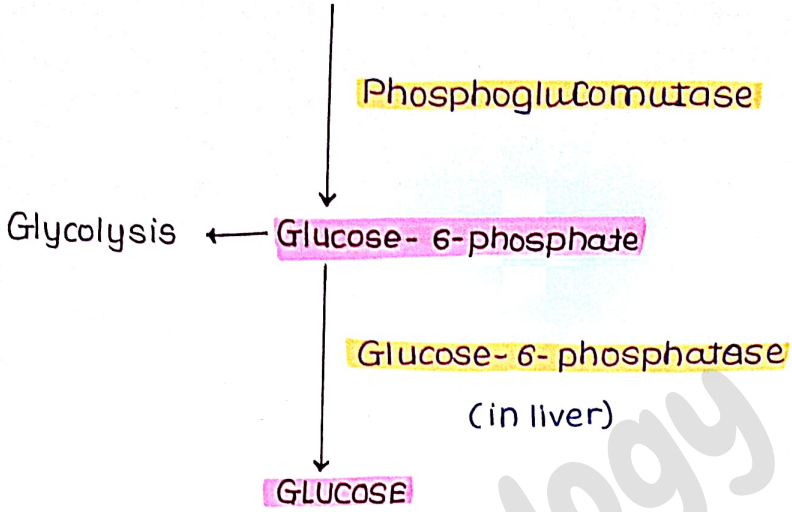
- For each glucose stored as glycogen :
  - 1 ATP (used during glucose phosphorylation).
  - 1 UTP (used to activate glucose → UDP-glucose).
- So, storing 1 glucose molecule in glycogen requires ~ 2 high-energy phosphate bonds.

- **GLYCOGENOLYSIS**

- Glycogenolysis is the catabolic (breakdown) pathway by which glycogen is broken down into glucose-1-phosphate and free glucose.
- The process is activated during fasting, exercise or stress when the body needs additional glucose.
- It helps in maintaining blood glucose levels and providing energy rapidly during demand.

GLYCOGENOLYSIS PATHWAY





- **Glycogenolysis : Breakdown of Glycogen**

- **Steps of Glycogenolysis :**

1. Glycogen → Glucose-1-phosphate
   - Enzyme : **Glycogen phosphorylase**
   - Cleaves α-1,4 bonds
2. Debranching of glycogen :
   - Enzyme : Debranching enzyme (bifunctional)
   - Transferase activity- transfers 3 glucose units.
   - Glucosidase activity- removes branch point glucose (α-1,6).
3. Glucose-1-phosphate → Glucose-6-phosphate
   - Enzyme : **Phosphoglucomutase**

4. Glucose-6-phosphate → Free glucose (in liver only)

- Enzyme : Glucose-6-phosphatase
- Not present in muscle (muscle uses glucose for itself).

- **Energetics of Glycogenolysis :**

- Glucose-1-phosphate is produced without using ATP.
- Saves energy compared to taking glucose from blood.
- In muscle : Glycogen → G-6-P (Glucose-6-phosphate) directly enters glycolysis = energy-efficient.

- **Significance of Glycogen Metabolism**

1. Maintains blood glucose
- Liver glycogen releases glucose between meals and during fasting.
2. Provides quick energy
- Muscle glycogen gives glucose for rapid energy during exercise.
3. Prevents hypoglycemia
- Especially important for brain and RBCs which need constant glucose.
4. Reversible and regulated
- Glycogen can be synthesized or broken down rapidly depending on body needs.
5. Buffer system.
- Acts as a short term energy reserve.

- **Regulation of Glycogen metabolism**

Hormone	Effect on Glycogenesis	Effect on Glycogenolysis
Insulin	Stimulates	Inhibits
Glucagon	Inhibits (liver)	Stimulates (liver)
Epinephrine	Inhibits (muscle & liver)	Stimulates (muscle and liver)

- Controlled by cAMP signaling and phosphorylation / dephosphorylation of enzymes.

- **Clinical Significance**

- **Glycogen Storage Diseases (GSDs):**
- Caused by defects in enzymes.
- Examples:
  - **Von Gierke's Disease** - glucose-6-phosphatase deficiency.
  - **McArdle's disease** - muscle phosphorylase deficiency.

Conclusion:

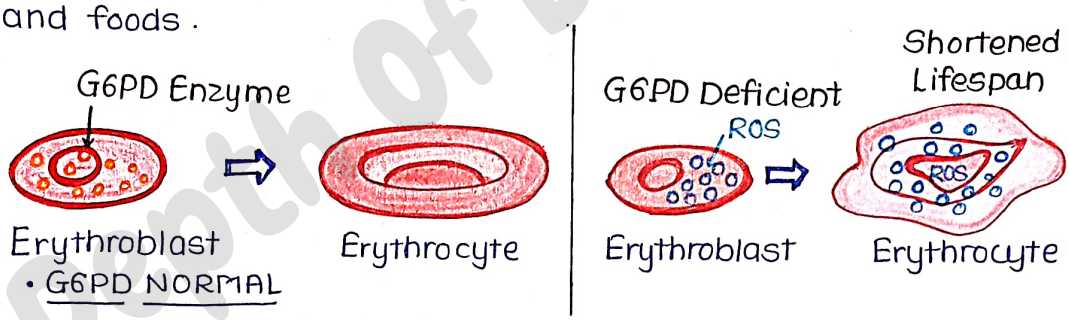
- Glycogen metabolism is essential for maintaining glucose homeostasis, supporting physical activity and protecting against hypoglycemia.
- Its precise hormonal regulation ensures a balance between energy storage and energy release based on the body's need.

2/3/MCQ

Q.1 Define G-6PD deficiency

⇨ **ANSWER**: G-6PD deficiency

- G-6PD Deficiency (Glucose-6-phosphate dehydrogenase deficiency) is an inherited genetic disorder where the body has low levels of the enzyme G-6PD.
- This enzyme protects red blood cells from damage by reactive oxygen species.
- Lack of it can cause the breakdown of red blood cells (Hemolysis), especially after infections or certain drugs and foods.



- It is one of the most common enzyme deficiencies worldwide.

Q.2 Define Glycogen storage disorders

⇨ **ANSWER**: Glycogen storage disease (GSD).

Definition: • Glycogen storage diseases (GSDs) are a group of inherited metabolic disorders caused by enzyme defects in glycogen metabolism (synthesis of breakdown).

- These defects lead to abnormal storage and structure of glycogen in tissues like liver and muscles.
- As a result, patients may experience low blood sugar (hypoglycemia), enlarged liver, muscle weakness or cramps.

Q.3 Explain ETC inhibitors

⇨ **ANSWER** : ETC Inhibitors

- ETC inhibitors are chemical substances that block the normal flow of electrons in the electron transport chain (ETC) located in mitochondria.
- By blocking electron flow, they prevent ATP production, reduce cellular energy and may cause cell damage.
- Example includes:
- Rotenone (inhibits complex I)
- Antimycin A (inhibits complex III)
- Cyanide and carbon monoxide (inhibit complex IV).

Q.4 Explain Uncouplers with example

⇨ **ANSWER**: UNCOUPLERS

Definition: Uncouplers are substances that disconnect (uncouple) oxidation (electron transport) from phosphorylation (ATP synthesis) in mitochondria.

- They allow protons to leak across the mitochondrial membrane without producing ATP, so energy is released as heat.
- **Example**: 2,4-Dinitrophenol (DNP), which carries protons across the membrane, increasing heat production but decreasing ATP.