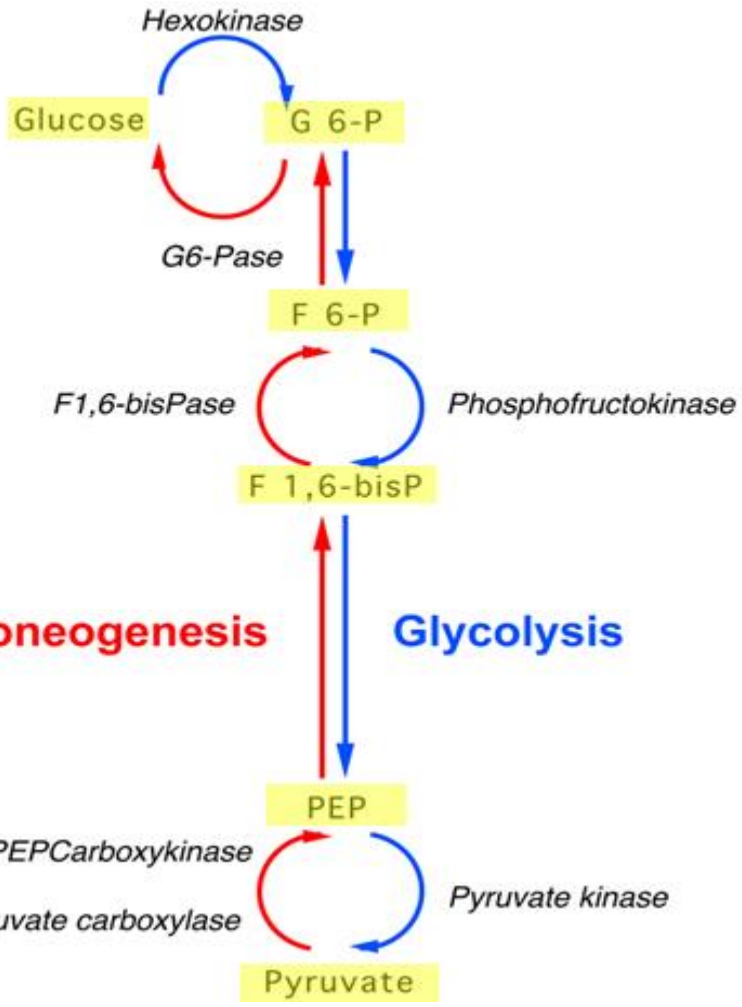
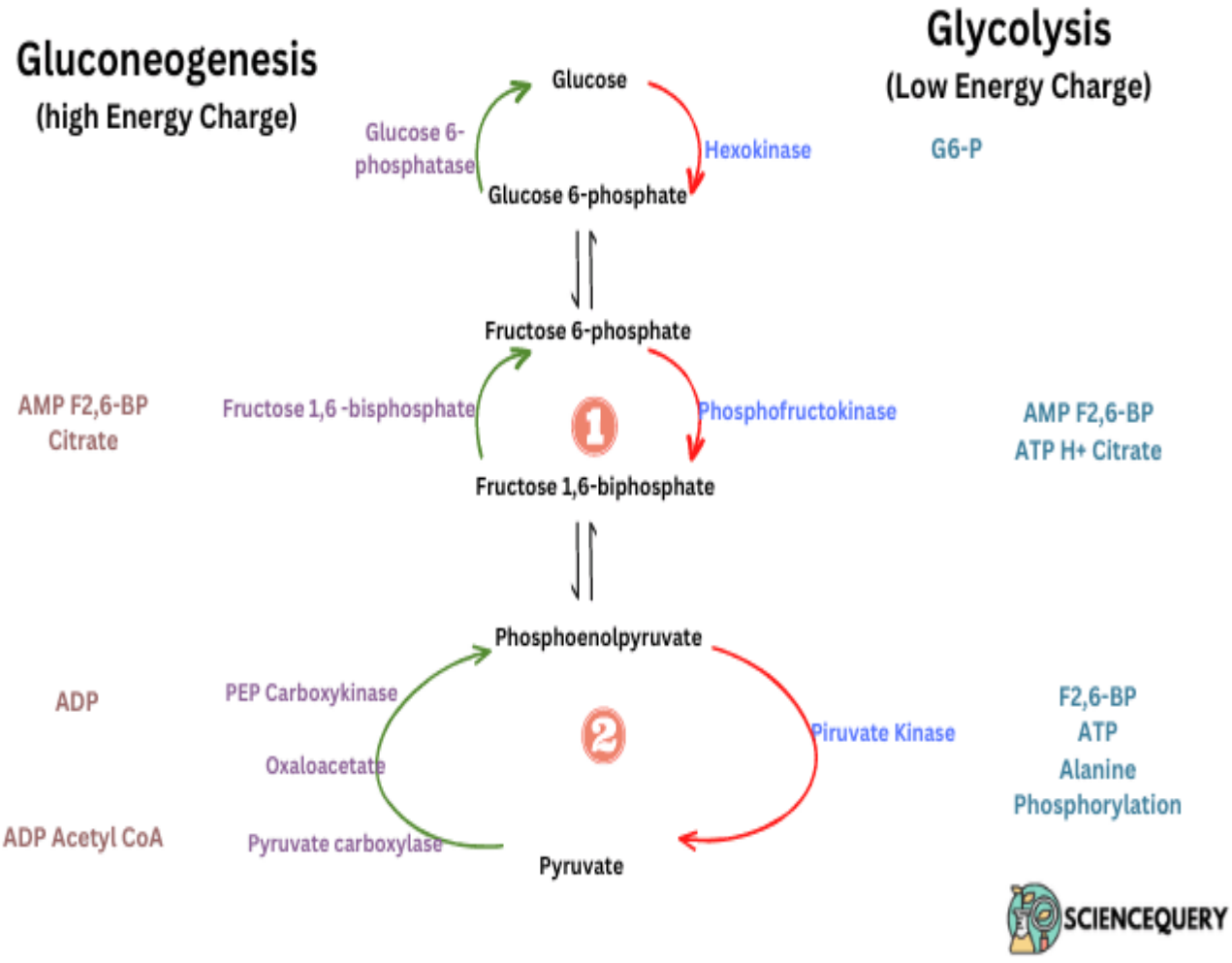
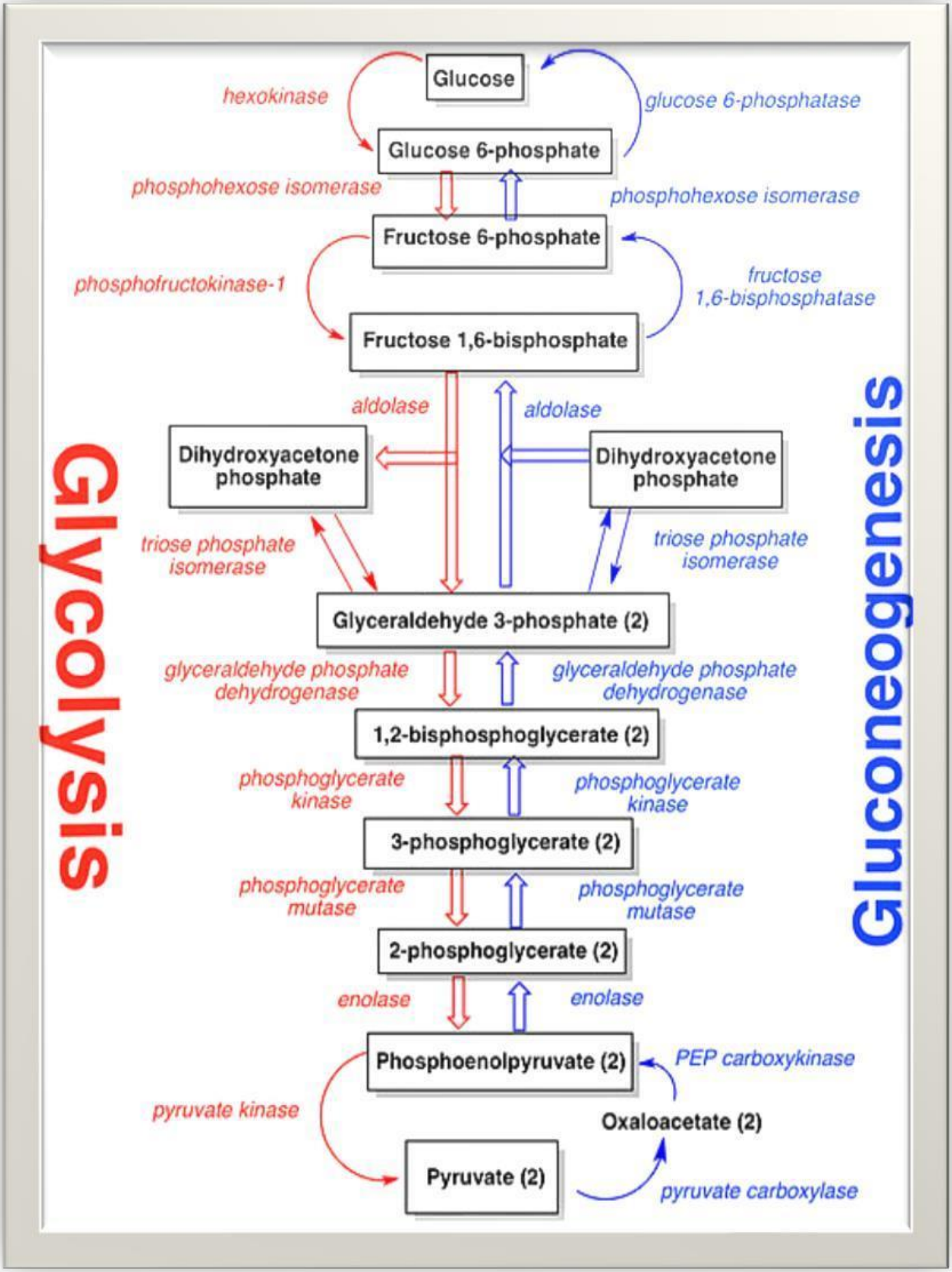
Gluconeogenesis

Def:	• *Synthesis of **glucose** from **non-carbohydrate precursors**.*
Site:	• ***Cytosol and mitochondria** of **Liver** (primary gluconeogenic organ) and **kidney**.* **MCQ** • *Occurs in small amount in **intestine**.*
Importance:	• ***It meets the body's needs for glucose** in cases of carbohydrate deficiency as fasting and starvation.* • ***it is important for tissues requiring continuous supply of glucose** as brain , RBCs , kidney, lense , cornea , testis , exercising ms.*
Steps:	***Is gluconeogenesis the simple reversal of glycolysis?*** • *The main pathway of gluconeogenesis is **a reversal of glycolysis**, but thermodynamic barriers prevent the **simple reversal**.* • ***Seven** of the reactions of glycolysis are **reversible** & are shared between glycolysis and gluconeogenesis.* • ***Three** of the reactions of glycolysis are **irreversible**.* ***So, bypassed by special reactions that are unique to gluconeogenesis.***


Hexokinase
Glucose
G 6-P
G6-Pase
F 6-P
F1,6-bisPase
Phosphofructokinase
F 1,6-bisP
Gluconeogenesis
Glycolysis
PEP
PEPCarboxykinase
Pyruvate carboxylase
Pyruvate kinase
Pyruvate

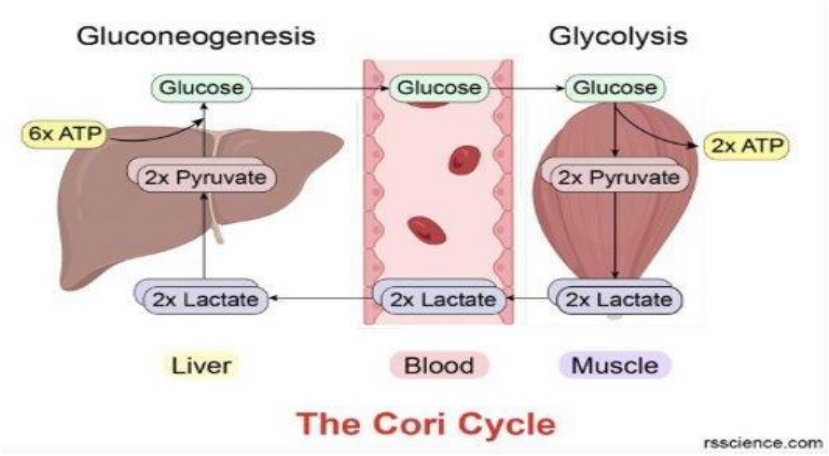

Gluconeogenesis
(high Energy Charge)
Glycolysis
(Low Energy Charge)
Glucose
Glucose 6-phosphatase
Hexokinase
G6-P
Glucose 6-phosphate
Fructose 6-phosphate
AMP F2,6-BP
Citrate
Fructose 1,6 -bisphosphate
1
Phosphofructokinase
AMP F2,6-BP
ATP H+ Citrate
Fructose 1,6-biphosphate
Phosphoenolpyruvate
ADP
PEP Carboxykinase
2
Piruvate Kinase
F2,6-BP
ATP
Alanine
Phosphorylation
Oxaloacetate
ADP Acetyl CoA
Pyruvate carboxylase
Pyruvate
SCIENCEQUERY


Glycolysis
Gluconeogenesis
Glucose
hexokinase
glucose 6-phosphatase
Glucose 6-phosphate
phosphohexose isomerase
phosphohexose isomerase
Fructose 6-phosphate
phosphofructokinase-1
fructose 1,6-bisphosphatase
Fructose 1,6-bisphosphate
aldolase
aldolase
Dihydroxyacetone phosphate
Dihydroxyacetone phosphate
triose phosphate isomerase
triose phosphate isomerase
Glyceraldehyde 3-phosphate (2)
glyceraldehyde phosphate dehydrogenase
glyceraldehyde phosphate dehydrogenase
1,2-bisphosphoglycerate (2)
phosphoglycerate kinase
phosphoglycerate kinase
3-phosphoglycerate (2)
phosphoglycerate mutase
phosphoglycerate mutase
2-phosphoglycerate (2)
enolase
enolase
Phosphoenolpyruvate (2)
PEP carboxykinase
pyruvate kinase
Oxaloacetate (2)
Pyruvate (2)
pyruvate carboxylase

Reactions Unique to Gluconeogenesis مهم جدا

1	• **Carboxylation of pyruvate to → oxaloacetate** ➢ **Site**: *in the mitochondria* ➢ **Enzyme**: *pyruvate carboxylase.* **MCQ** ➢ **Needs :** *ATP* ➢ **Coenzyme**: *Biotin* **MCQ**
2	• **Conversion of oxaloacetate to → phosphoenolpyruvate (PEP):** ➢ *Oxaloacetate is* ***transported outside*** *mitochondria.* ➢ **Site**: *chiefly in* ***cytoplasm.*** ➢ **Enzyme**: *phosphoenolpyruvate (PEP)-carboxykinase.* ➢ **Needs :** *GTP.*
3	• **Dephosphorylation of fructose 1,6-bisphosphate to → Fructose 6-phosphate:** ➢ **Enzyme:** *fructose 1,6-bisphosphatase.* ➢ **bypasses** *the irreversible phosphofructokinase-1 (PFK-1) reaction.*
4	• **Dephosphorylation of glucose 6-phosphate to → Glucose:** ➢ **Enzyme:** *glucose 6-phosphatase* ➢ **bypasses** *the irreversible hexokinase/glucokinase reaction*

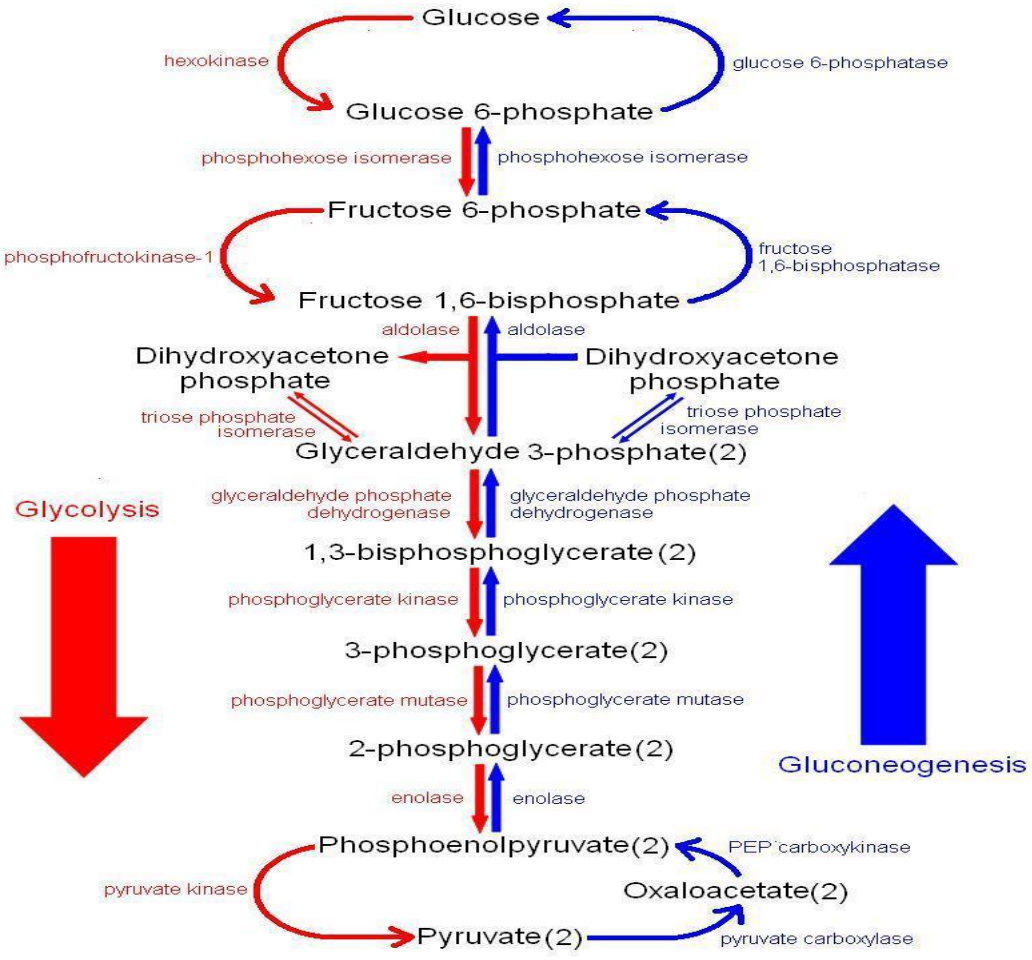
Substrates for Gluconeogenesis مهم جدا

1. Glycerol:	• *Glycerol is released during the **hydrolysis of triacylglycerols** in adipose tissue.* • *Glycerol → glycerol 3 phosphate → DHAP → glucose.*
2. Lactate:	• ***Lactate is released into the blood by:*** ➢ ***Exercising muscle.*** ➢ *Cells that lack mitochondria as **RBC.*** • ***The Cori cycle:*** ➢ ***glucose** is converted by exercising muscle to **lactate**, which diffuses into the **blood.*** ➢ *This lactate is taken up by the **liver** and reconverted to **glucose**, which is released back into the **circulation.*** 
3. Glucogenic Amino Acids:	• *They are derived from hydrolysis of **tissue proteins**, are major source of glucose during **fasting.*** • *Glucogenic amino acid → **α-Keto acids** such as oxaloacetate & α-KG.* • *These substrates can enter the **TCA** cycle and form oxaloacetate, a direct precursor of PEP.*
4. Propionyl CoA:	• *Fatty acids with an odd number of carbons produce **propoinyl-CoA.*** • *Propionyle COA → Methyle Malonyle CoA → Succinyle COA → → PEP → glucose.*

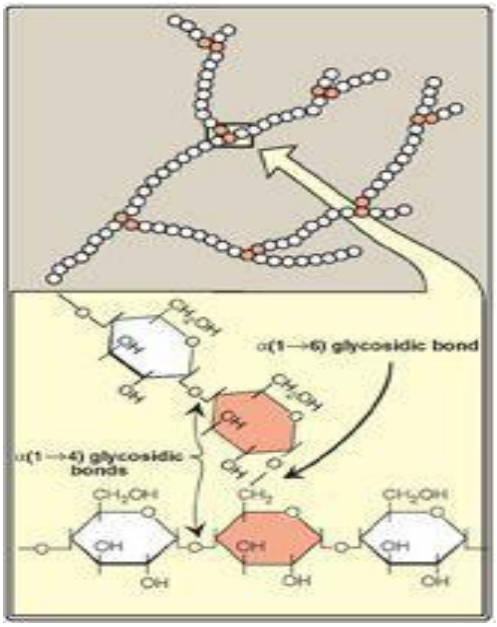
Regulation of gluconeogenesis:

- *Glycolysis & Gluconeogenesis are* ***reciprocally regulated.***
- ***Key enzymes which regulate gluconeogenesis are:*** **MCQ**
  1. *Pyruvate carboxylase*
  2. *Phosphoenolpyruvate carboxykinase*
  3. *Fructose 1,6-biphosphatase*
  4. *Glucose 6- phosphatase*

Hormonal regulation	**Insulin**	**Glucagon**
	• ***Inhibits*** *gluconeogenesis*	• ***Stimulates*** *gluconeogenesis*
Fructose 2,6-biphosphate: MCQ	• ***Inhibits*** *gluconeogenesis* • ***Stimulates*** *glycolysis.*	



Glycogen Metabolism

Structure and Function:	• *Glycogen is the **storage form** of glucose in animals* • *It is stored mainly in **liver** and **muscles**.* **MCQ**
Importance:	• ***Muscle glycogen:*** *serves as a fuel reserve during muscle contraction.* • ***Liver glycogen:*** ➢ *maintains the blood glucose concentration during early stages of fasting.* ➢ *Liver glycogen stores are depleted in **12-18 hour***
Structure of glycogen:	• *Glycogen is a **branched-chain polysaccharide made from α-D-glucose.*** **MCQ** • *The primary glycosidic bond is an **α (1→ 4) linkage.*** • *After an average of 8-10 glucosyl residues, there is a branch containing an **α (1→ 6) linkage.*** 
Metabolism of glycogen includes:	A. ***Synthetic phase (glycogenesis):*** *Formation of glycogen* B. ***Catabolic phase (glycogenolysis):*** *Breakdown of glycogen*

A) Glycogenesis

- ***Definition:***
  - *formation of **glycogen** from **glucose.***
- ***Sites:***
  - *In the **cytosol of liver and muscle.** **MCQ***

> ***NB:** The process requires **ATP** and **Uridine triphosphate (UTP).** **MCQ***

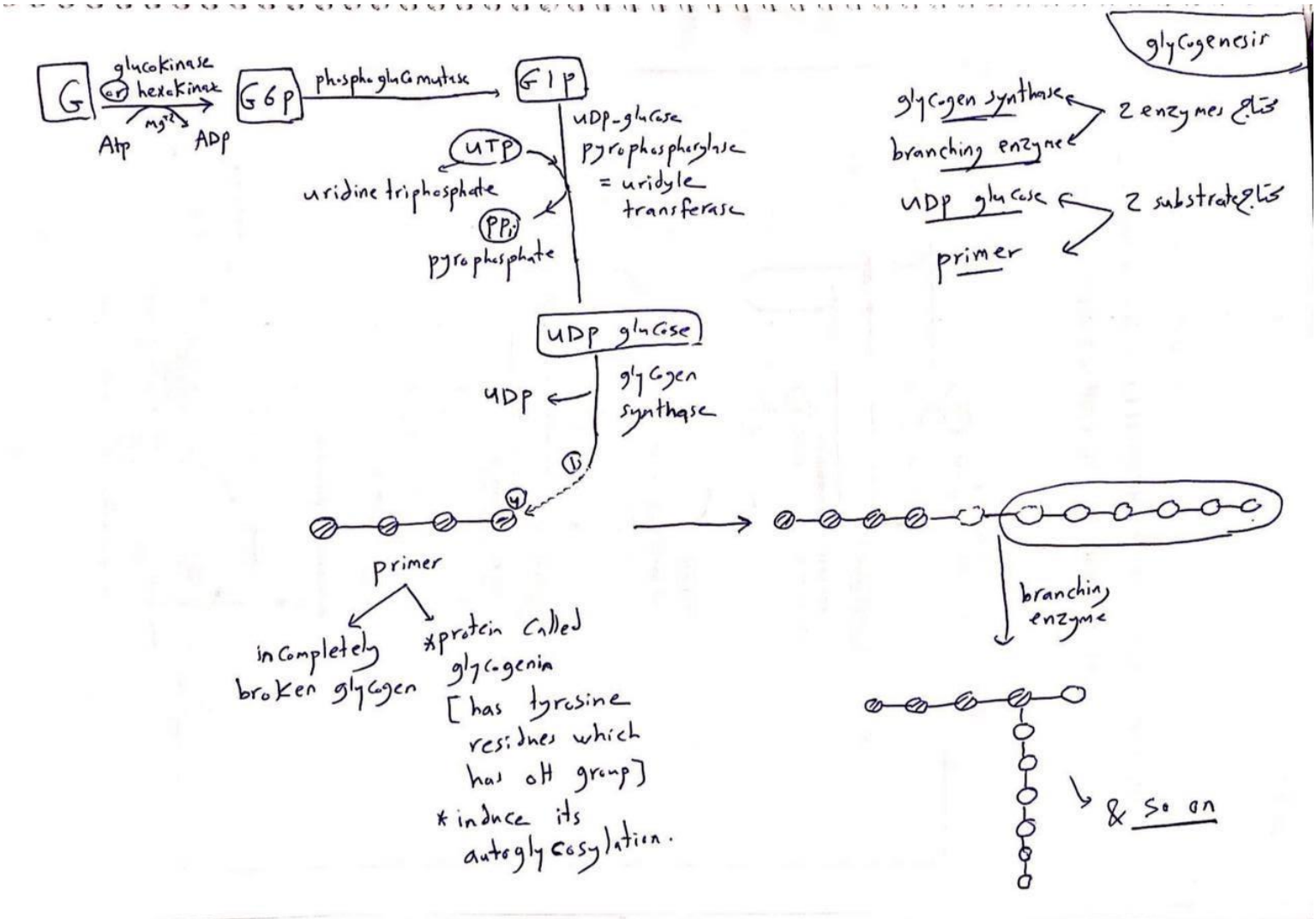
- ***Reactions of Glycogenesis:***

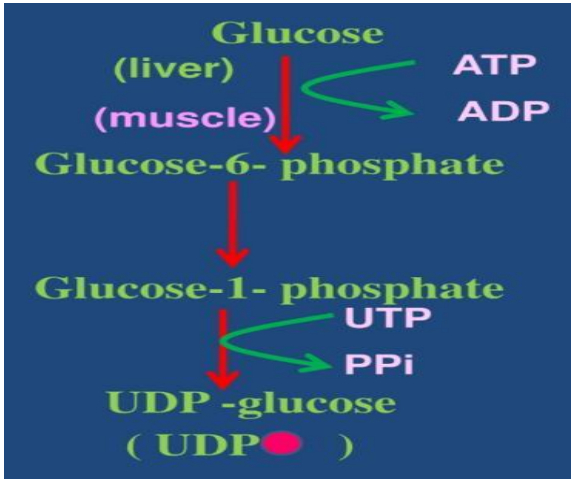
*A. Synthesis of **uridine diphosphate glucose.***

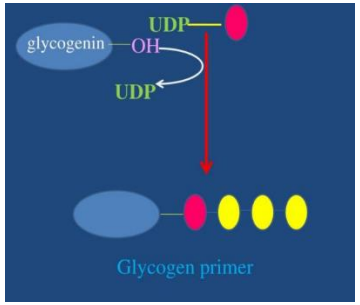
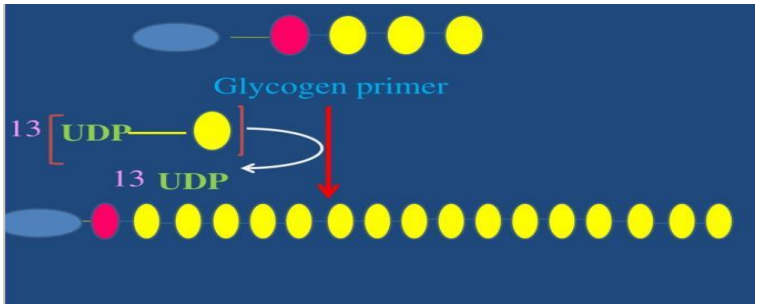
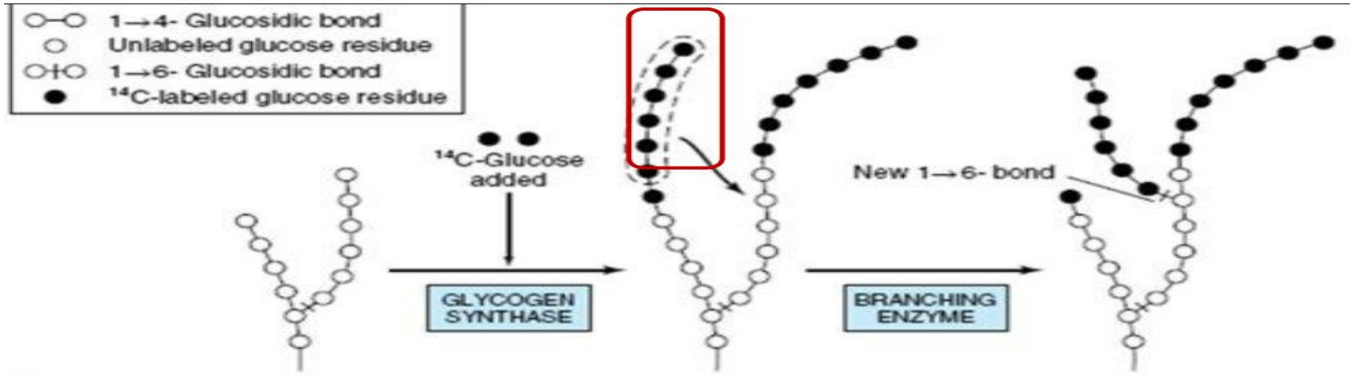
*B. Synthesis of **a primer** to initiate glycogen synthesis.*

*C. Elongation of glycogen chains by **glycogen synthase.***

*D. Formation of **branches** in glycogen.*



Step	Enzyme	Mechanism
1) Synthesis of UDP-glucose	***UDP-glucose pyrophosphorylase***	• *Glucose 6-phosphate is converted to glucose 1-P by Phosphoglucomutase enzyme* • *Glucose 1-P + uridine triphosphate (UTP) → UDP- glucose + pyrophosphate.* 
2) Elongation of glycogen chains	***Glycogen synthase enzyme***	• *Transfer **Glucose** from UDP-glucose to the **non-reducing end** of the glycogen primer.* • *Makes **α (1→4) linkages.*** • ***Cannot initiate** chain synthesis, require glycogen primer.* **MCQ**

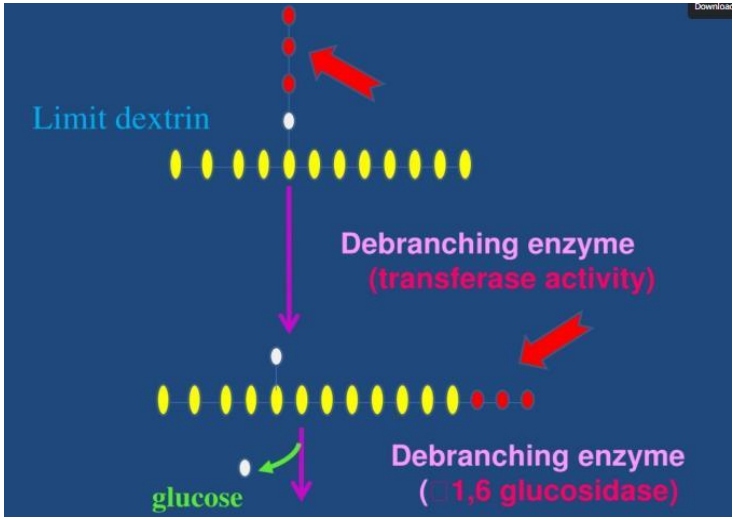
3) Synthesis of a primer	***Glycogen synthase***	• *If glycogen is depleted a protein called* ***Glycogenin****, gets glycosylated forming short α (1→4) glucosyl chain that serves as primer (The reaction is catalyzed by glycogenin itself,* ***auto-glucosylation****).*  
4) Formation of branches	***Branching enzyme***	• *Amylo-α (1→ 4) → α (1→ 6) transglucosidase.* • *Transfer a chain of* ***6-8 glucosyl residues*** *from the end of the glycogen chain → To nearby non-terminal glucosyl residue by an* ***α 1→ 6 linkage****.*  ***Figure 18–3.*** The biosynthesis of glycogen. The mechanism of branching as revealed by adding ^{14}C-labeled glucose to the diet in the living animal and examining the liver glycogen at further intervals.

B) Glycogenolysis

- ***Definition:*** *The processes of glycogen degradation.*
- ***Steps:***

Step	Enzyme	Mechanism
a) Shortening of chains	***Glycogen phosphorylase enzyme***	• *Cleaves the terminal α (1 → 4) glycoside bond By simple phosphorolysis producing glucose 1 - P* **MCQ** • *Until **last four glucosyl units** before a branch point* • *Coenzyme: **Pyridoxal phosphate (PLP).***
b) Removal of branches by Debranching enzyme	***Debranching enzyme*** *(single protein with two enzymatic activities).* **MCQ**	***1- Oligo-α (1→ 4) → α (1→ 4) - glucan transferase:*** ➢ *Removes the outer three of the four glucosyl residues and transfers them to the nonreducing end of another chain.* ***2- Amylo-α (1→6)- glucosidase activity:*** ➢ *Remove the remaining single glucose residue (attached by α(1→6) linkage) by hydrolysis releasing free glucose.*

<table>
<tr>
<td>c) Conversion of glucose 1-P to glucose 6-P</td>
<td>Phospho-glucomutase enzyme</td>
<td>
Glucose 1-P (produced by glycogen phosphorylase):
<table>
<tr><td>Liver:</td><td>G-6P transported into the ER by glucose 6-phosphate translocase.
Then converted to glucose by glucose 6-phosphatase.</td></tr>
<tr><td>Muscle:</td><td>G-6P enters glycolysis (as muscle lacks glucose 6-phosphatase enzyme). MCQQ</td></tr>
</table>
</td>
</tr>
<tr>
<td>d) Lysosomal degradation of glycogen</td>
<td></td>
<td>Small amount (1–3%) of glycogen is continuously degraded by the lysosomal enzyme, α (1→4)-glucosidase (acid maltase).</td>
</tr>
</table>



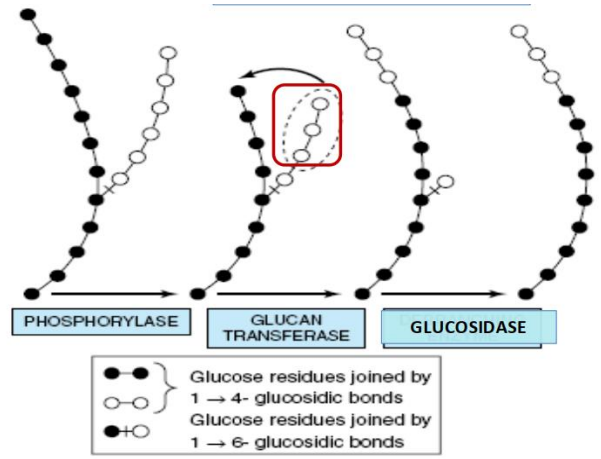


Figure 18–4. Steps in glycogenolysis.

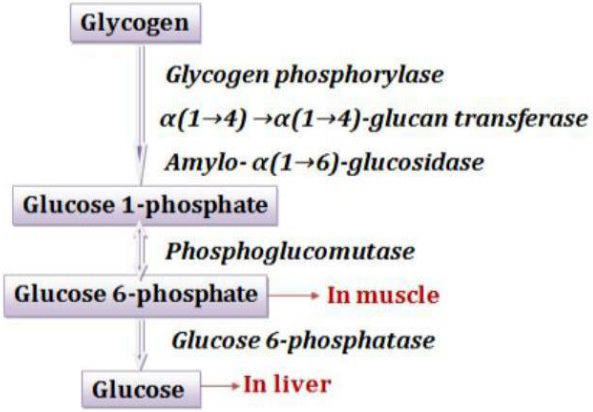


Diagram: Steps of glycogenolysis

glycogenolysis

① glycogen phosphorylase

* يحتفل بـ α 1-4 bond

* يكسر باضافة فوسفات

* هينفصل جزئ جلوكوز متصل به فوسفات على الكربونة الأولى [G1P]

phosphoglucomutase

G6P

liver

translocase

ER

G6P

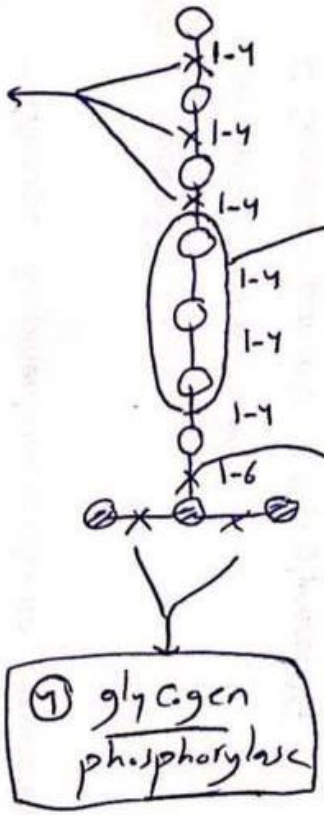
glucose

glucose 6 phosphatase

MS

absence of glucose 6 phosphatase enzyme

So G6P is Converted into Lactic acid.



② glucan transferase

* transfer 3 glucose units from on branch to another

the same enzyme (bifunctional enzyme)

③ debranching enzyme

* يحتفل بـ α 1-6 bond

* يحتفل باضافة H_2O

* ينفصل free glucose

① glycogen phosphorylase

⑤ 1-3% of glycogen degraded by lysosomal enzymes

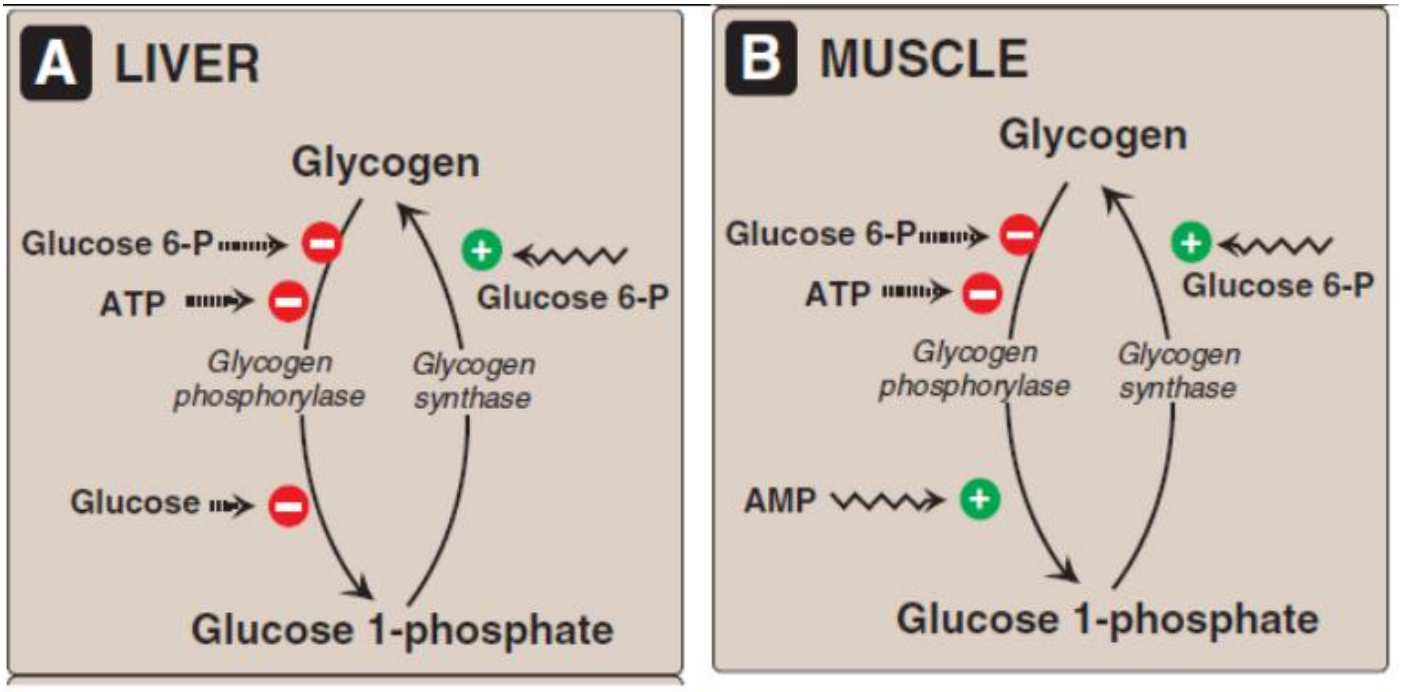
Regulation of glycogen metabolism:

- **Control (Key rate limiting) enzymes:**
  - *Glycogen synthase & Glycogen phosphorylase.* **MCQ**

***1) Allosterically** controlled to meet the needs of a particular tissue.*

***2) Hormonally** regulated to meet the needs of the body as a whole.*

1- Allosteric regulation:	• ***Glycogen synthase** is **activated** by G-6-phosphate (in fed state)* • ***Glycogen phosphorylase** is **inhibited** by G-6-phosphate, ATP and glucose itself (in the liver).* • ***Glycogen phosphorylase** is activated by Ca++ and AMP (in ms).*
2- Hormonal regulation: **MCQ**	• ***Insulin:** stimulates glycogen synthesis (glycogenesis) and inhibits its breakdown.* • ***Glucagon (liver) and Epinephrine (muscle and liver):** stimulate glycogenolysis & inhibit glycogenesis.*



Glycogen Storage Disease (Glycogenoses)

- *Group of inherited disorders characterized by deficient mobilization of glycogen OR deposition of abnormal forms of glycogen → (GSD).*
- *Result from **a defect in an enzyme** required for glycogen synthesis or degradation*

- ***Severity:***
  - *The severity ranges from **mild to severe and fatal.***

- ***May affect:***
  - ***Single tissue**: liver (hypoglycemia) or muscle (muscle weakness).*
  - ***may be more generalized.***

	Type Ia	Type II	Type IIIa	Type IV	Type V	Type VI
Other name	**Von gierke's disease**	**Pompe's disease**	**Limit Dextrinosis (Cori's disease)**	**Amylopectinosis**	**Mc Ardle's syndrome**	**Her's disease**
Enzyme deficiency	**Glucose 6 Phosphatase** **MCQ**	*Lysosomal α-(1-4) & α-(1- 6) glucosidase* **(Acid maltase)**	**Debranching enzyme (liver & Muscle)**	**Branching enzyme**	**Muscle Phosphorylase** **MCQ**	**Liver phosphorylase**
C/P	• *Affects liver & kidney (**high glycogen** in liver & renal tubules)* • **Hypoglycemia.** • **Lactic acidemia.** • **Hyperlipemia.**	• **Accumulation of glycogen** *in lysosome*	• **Fasting hypoglycemia.** • **Muscle weakness.** • **Accumulation of** *characteristic branched polysaccharide (Limit Dextrin).*	• **Accumulation of polysaccharide with few branches.** • **Early death** *from heart or liver failure.*	• **High glycogen** *in muscle.* • **Poor exercise tolerance**	• **Hepatomegaly,** *accumulation of glycogen in liver.* • **Mild hypoglycemia.** • **Generally, good prognosis**