GLUCONEOGENESIS

- **The synthesis of glucose from noncarbohydrate compounds is known as gluconeogenesis.**
- **The major substrates/precursors for gluconeogenesis are lactate, pyruvate, glucogenic amino acids, propionate and glycerol.**

When Gluconeogenesis Occurs

Gluconeogenesis is a metabolic process that occurs in the liver and kidneys to produce glucose when the body's needs aren't met by its normal sources of glucose. This happens when:

- **Starvation:** When the body's glycogen stores are depleted, gluconeogenesis takes over to produce glucose.
- **Intense exercise:** When the body's normal sources of glucose aren't enough to meet its needs.
- **Meals high in fat and protein:** After a meal high in fat and protein but no carbohydrate, gluconeogenesis occurs.
- **Between meals:** Gluconeogenesis helps meet the body's needs between meals.

Gluconeogenesis uses substrates like glycerol, lactate, and certain amino acids to produce glucose.

Location of gluconeogenesis

- Gluconeogenesis occurs mainly in the cytosol, although some precursors are produced in the mitochondria.
- Gluconeogenesis mostly takes place in liver (about 1 kg glucose synthesized everyday) and, to some extent, in kidney matrix (about one-tenth of liver capacity)
- **Importance of Gluconeogenesis :**
- Glucose occupies a key position in the metabolism and its continuous supply is absolutely essential to the body for a variety of functions

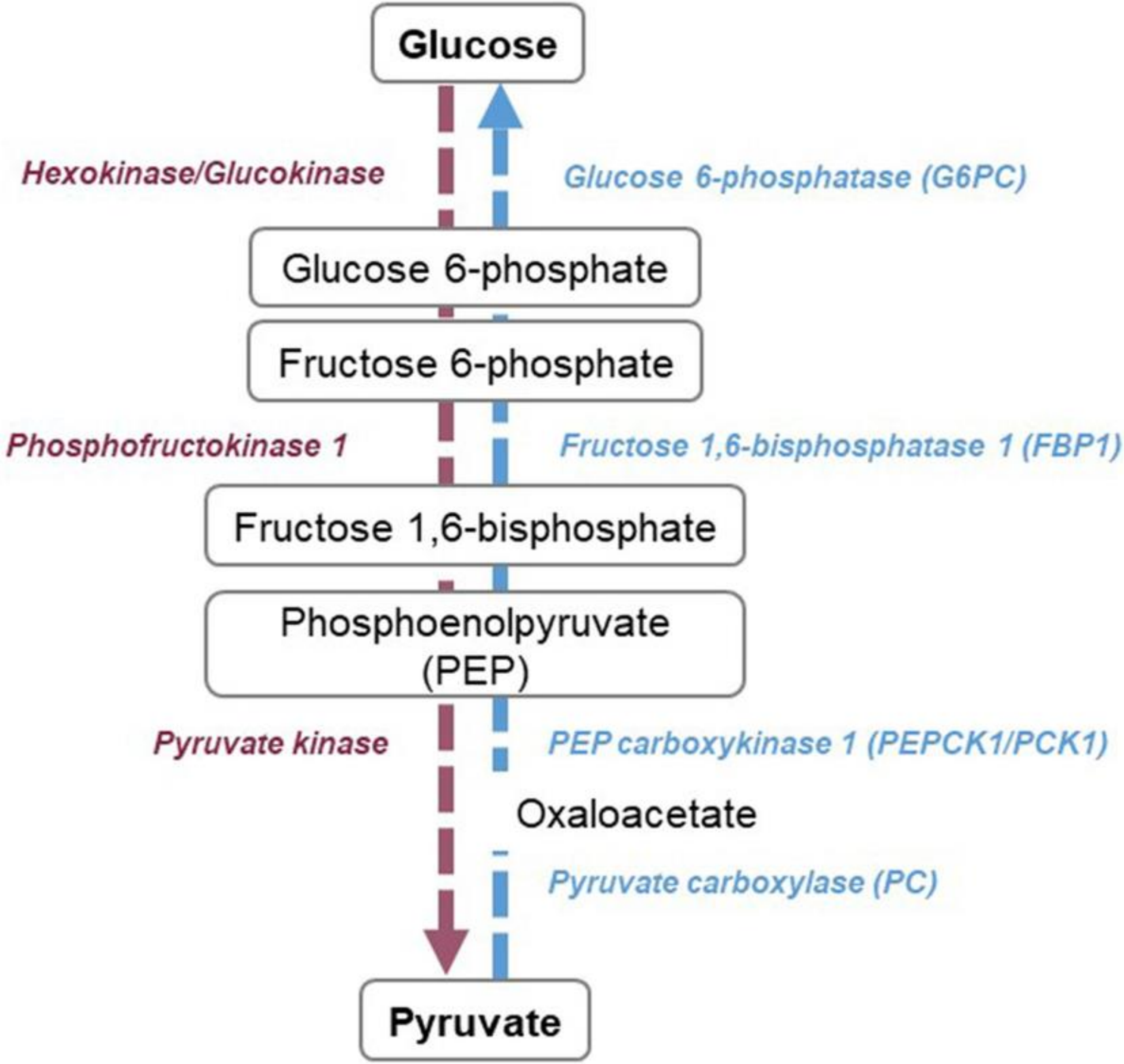
1. **Brain and central nervous system/ erythrocytes, testes and kidney medulla are dependent on glucose for continuous supply of energy.**

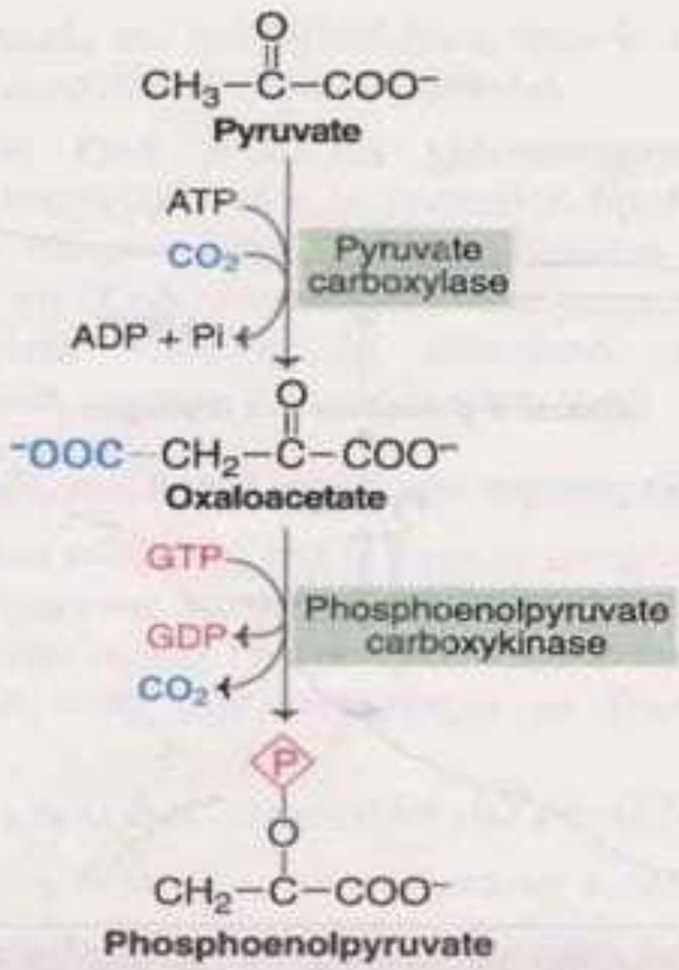
- Human brain alone requires about 120 g of glucose per day, out of about 160 g needed by the entire body.

2. **Glucose is the only source that supplies energy to the skeletal muscle, under anaerobic conditions.**

3. In fasting even more than a day, **gluconeogenesis must occur to meet the basic requirements of the body for glucose** and to maintain the intermediates of citric acid cycle. This is essential for the **survival** of humans and other animals.

4. Certain metabolites produced in the tissues **accumulate in the blood**, e.g. lactate, glycerol, propionate etc. Gluconeogenesis effectively **clears them from the blood.**


Glucose
Hexokinase/Glucokinase
Glucose 6-phosphatase (G6PC)
Glucose 6-phosphate
Fructose 6-phosphate
Phosphofructokinase 1
Fructose 1,6-bisphosphatase 1 (FBP1)
Fructose 1,6-bisphosphate
Phosphoenolpyruvate (PEP)
Pyruvate kinase
PEP carboxykinase 1 (PEPCK1/PCK1)
Oxaloacetate
Pyruvate carboxylase (PC)
Pyruvate



CH3–C–COO–
Pyruvate
ATP
CO2
Pyruvate carboxylase
ADP + Pi
–OOC–CH2–C–COO–
Oxaloacetate
GTP
GDP
CO2
Phosphoenolpyruvate carboxykinase
P
CH2–C–COO–
Phosphoenolpyruvate

Reactions of gluconeogenesis

- Gluconeogenesis closely resembles the reversed pathway of glycolysis, although it is not the complete reversal of glycolysis.
- Essentially, 3 (out of 10) reactions of glycolysis are irreversible.
- The **seven reactions** are **common** for both glycolysis and gluconeogenesis.
- The **three irreversible steps** of glycolysis are catalyzed by the enzymes, namely hexokinase, phosphofructokinase and pyruvate kinase.
- These three stages-bypassed by alternate enzymes specific to gluconeogenesis-are discussed.

1. Conversion of pyruvate to phosphoenolpyruvate : This takes place in two steps.

- Pyruvate carboxylase is a biotin dependent **mitochondrial** enzyme that converts pyruvate to oxaloacetate in presence of ATP and CO_2. This enzyme regulates gluconeogenesis and requires acetyl CoA for its activity.
- Oxaloacetate is synthesized in the **mitochondrial matrix**. It has to be transported to the cytosol to be used in gluconeogenesis, where the rest of the pathway occurs. Due to membrane impermeability, oxaloacetate cannot diffuse out of the mitochondria. It is **converted to malate** and then transported to the cytosol. **Within the cytosol, oxaloacetate is regenerated.**
- The reversible conversion of oxaloacetate and malate is catalysed by malate dehydrogenase, an enzyme present in both mitochondria and cytosol.
- In the cytosol, phosphoenolpyruvate carboxykinase converts oxaloacetate to phosphoenolpyruvate. **GTP or ITP** (not ATP) is used in this reaction and the CO_2 (fixed by carboxylase) is liberated. For the conversion of pyruvate to phosphoenol pyruvate, 2 ATP equivalents are utilized.

2. Conversion of fructose 1,6-bisphosphate to fructose 6-phosphate :

- Phosphoenolpyruvate undergoes the reversal of glycolysis until fructose 1,6-bisphosphate is produced.
- **The enzyme fructose 1,6-bisphosphatase converts fructose 1,6-bisphosphate to fructose 6-phosphate.**
- This enzyme requires Mg^{+2} ions.
- Fructose 1,6 - bisphosphatase is absent in smooth muscle and heart muscle. This enzyme is also regulatory in gluconeogenesis.

3. Conversion of glucose 6-phosphate to glucose :

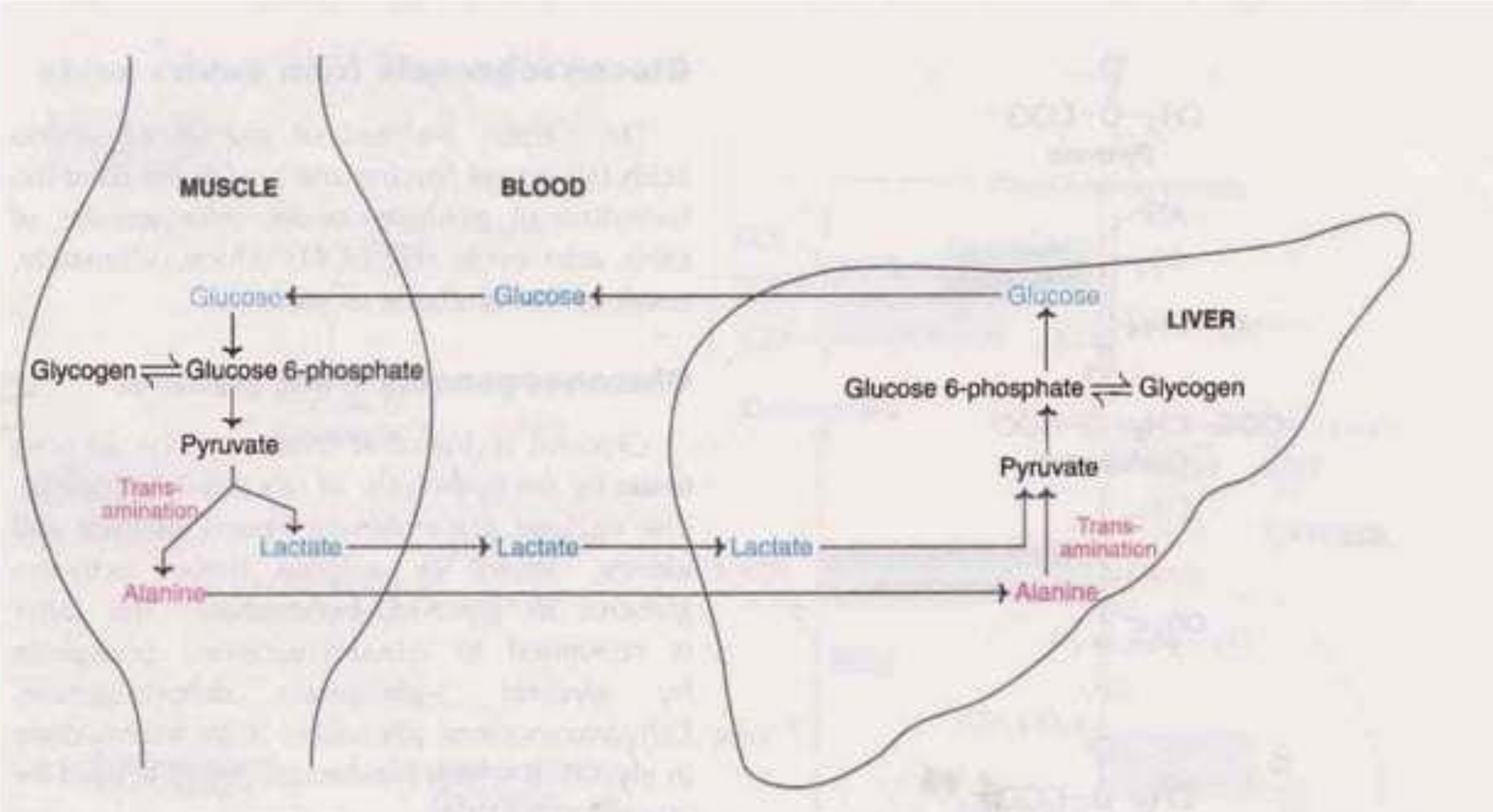
- Glucose-5-phosphatase catalyzes the conversion of **glucose 6-phosphate to glucose.**
- The presence or absence of this enzyme in a tissue determines whether the tissue is capable of contributing glucose to the blood or not.
- **It is mostly present in liver and kidney but absent in muscle, brain and adipose tissue.**
- The overall summary of gluconeogenesis for the conversion of pyruvate to glucose is shown below -
- 2 Pyruvate + 4ATP + 2GTP + 2NADH + $2H^+$ + $6H_2O$ $\longrightarrow$ Glucose + $2NAD^+$ + 4ADP + 2GDP + 6Pi + $6H^+$

- **Gluconeogenesis from amino acids**
- The carbon skeleton of glucogenic amino acids (all except leucine and lysine) results in the formation of pyruvate or the intermediates of citric acid cycle which, ultimately, result in the synthesis of glucose.
- **Gluconeogenesis from glycerol**
- Glycerol is liberated mostly in the adipose tissue by the hydrolysis of fats (triacylglycerols).
- The enzyme glycerokinase (found in liver and kidney, absent in adipose tissue) activates glycerol to glycerol 3-phosphate.
- The latter is converted to dihydroxyacetone phosphate by glycerol 3-phosphate dehydrogenase.
- Dihydroxyacetone phosphate is an intermediate in glycolysis which can be conveniently used for glucose production.

- **Gluconeogenesis from propionate**
- Oxidation of odd chain fatty acids and the breakdown of some amino acids (methionine, isoleucine) yields a three carbon propionyl CoA.
- Propionyl CoA carboxylase acts on this in presence of ATP and biotin and converts to **methyl malonyl CoA** which is then converted to **succinyl CoA** in presence of 812 coenzyme.
- Succinyl CoA formed from propionyl CoA enters gluconeogenesis via citric acid cycle.
- **Glucose alanine cycle :**
- There is a continuous transport of amino acids from muscle to liver, which predominantly occurs during starvation.
- Alanine dominates among the transported amino acids.
- It is estimated that **pyruvate in skeletal muscle undergoes transamination to produce alanine.**
- Alanine is transported to liver and used for gluconeogenesis.
- This cycle is referred to as **glucose-alanine cycle.**

Gluconeogenesis from lactate (Cori Cycle) :

- Lactate produced by active skeletal muscle is a major precursor for gluconeogenesis. Under anaerobic conditions, pyruvate is reduced to lactate by lactate dehydrogenase (LDH).
- Pyruvate + NADH $+H^+ \longleftrightarrow$ Lactate + NAD^+
- Lactate is a dead end in glycolysis, since it must be reconverted to pyruvate for its further metabolism.
- **Lactate or pyruvate produced in the muscle cannot be utilized for the synthesis of glucose due to the absence of the key enzymes of gluconeogenesis (glucose 6-phosphatase and fructose 1,6-bisphosphatase).**
- The plasma membrane is **freely permeable to lactate.**
- **Lactate is carried from the skeletal muscle through blood and handed over to liver, where it is oxidized to pyruvate.**
- Pyruvate, so produced, is converted to glucose by gluconeogenesis, which is then transported to the skeletal muscle. The cycle involving the **synthesis of glucose in liver from the skeletal muscle lactate and the reuse of glucose** thus synthesized by the muscle for energy purpose is known as **Cori cycle.**


MUSCLE
BLOOD
LIVER
Glucose
Glucose
Glucose
Glycogen
Glucose 6-phosphate
Glucose 6-phosphate
Glycogen
Pyruvate
Pyruvate
Trans-amination
Trans-amination
Lactate
Lactate
Lactate
Alanine
Alanine

Regulation of gluconeogenesis

- The hormone glucagon and the availability of substrates mainly regulate gluconeogenesis.
- **Influence of glucagon :**
- This is a hormone, secreted by α-cells of the pancreatic islets. Glucagon stimulates gluconeogenesis by two mechanisms
- 1. **Active form of pyruvate kinase is converted to inactive form.** Decreased pyruvate kinase results in the **reduced conversion of phosphoenol pyruvate to pyruvate** and the former is diverted for the synthesis of glucose.
- 2. Glucagon reduces the concentration of fructose 2,6-bisphosphate in the liver, which stimulates gluconeogenesis. This is because glucagon:
    - ✓ Reduces the activity of PFK-2: Glucagon causes phosphorylation of PFK2-ser-32, which reduces the activity of PFK-2.
    - ✓ Increases the activity of FBPase-2: Glucagon increases the activity of FBPase-2

- **Availability of substrates :**
- Among the various substrates, **glucogenic amino acids** (Alanine, glycine, serine, cysteine, threonine and tryptophan) have stimulating influence on gluconeogenesis.
- **Acetyl CoA promotes gluconeogenesis :**
- During starvation - due to excessive lipolysis in adipose tissue - acetyl CoA accumulates in the liver.
- **Acetyl CoA activates pyruvate carboxylase** resulting in enhanced glucose production

Gluconeogenesis from fat ?

- It is often stated that glucose cannot be synthesized from fat.
- **since the fatty acids (most of them being even chain), on oxidation, produce acetyl CoA which cannot be converted to pyruvate.**
- Further, the two carbons of acetyl CoA disappear as 2 moles of CO_2 in TCA cycle.
- Therefore, **even chain fatty acids cannot serve as precursors for glucose formation.**
- The prime reason why animals cannot convert fat to glucose is the **absence of glyoxylate cycle.**
- However, the **glycerol** released from lipolysis and the **propionate** obtained from the oxidation of odd chain fatty acids are good substrates for gluconeogenesis.