WELCOME

CARBOHYDRATE DIGESTION, METABOLISM AND GLUCOSE TOLERANCE TEST

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Carbohydrate digestion

- Carbohydrates are a class of natural organic substances that includes **sugars**, **starch** and **cellulose** (indigestible plant fiber). The **digestion of a particular carbohydrate in the gastrointestinal tract** depends upon the complexity of the **carb's molecular structure** -

- In simple terms, carbs divide into 4 types: (1) **monosaccharides**, like glucose (dextrose or corn sugar), fructose (fruit sugar) and galactose, which are digested rapidly; (2) **disaccharides**, like sucrose (table sugar), lactose (milk sugar) and maltose, which are digested quite quickly; (3) **polysaccharides**, like starch, which take longer to digest; and (4) **very complex carbs**, like cellulose (indigestible plant fiber) which cannot be digested at all.

How We Digest Carbohydrate

- In simple terms, our digestion system - from the mouth to the small intestine - is designed to break down disaccharides and polysaccharides into monosaccharides. This metabolism of carbohydrates is achieved through the secretion of a number of **digestive enzymes** into the gastrointestinal tract where they attack carbohydrates and gradually convert them into **simple sugars like glucose** so they can be absorbed into the blood.

In the Mouth

- The process of digesting carbohydrates begins in the mouth. Our saliva contains an enzyme called **amylase(ptyalin)** that starts breaking down the more complex carbs into simpler types.

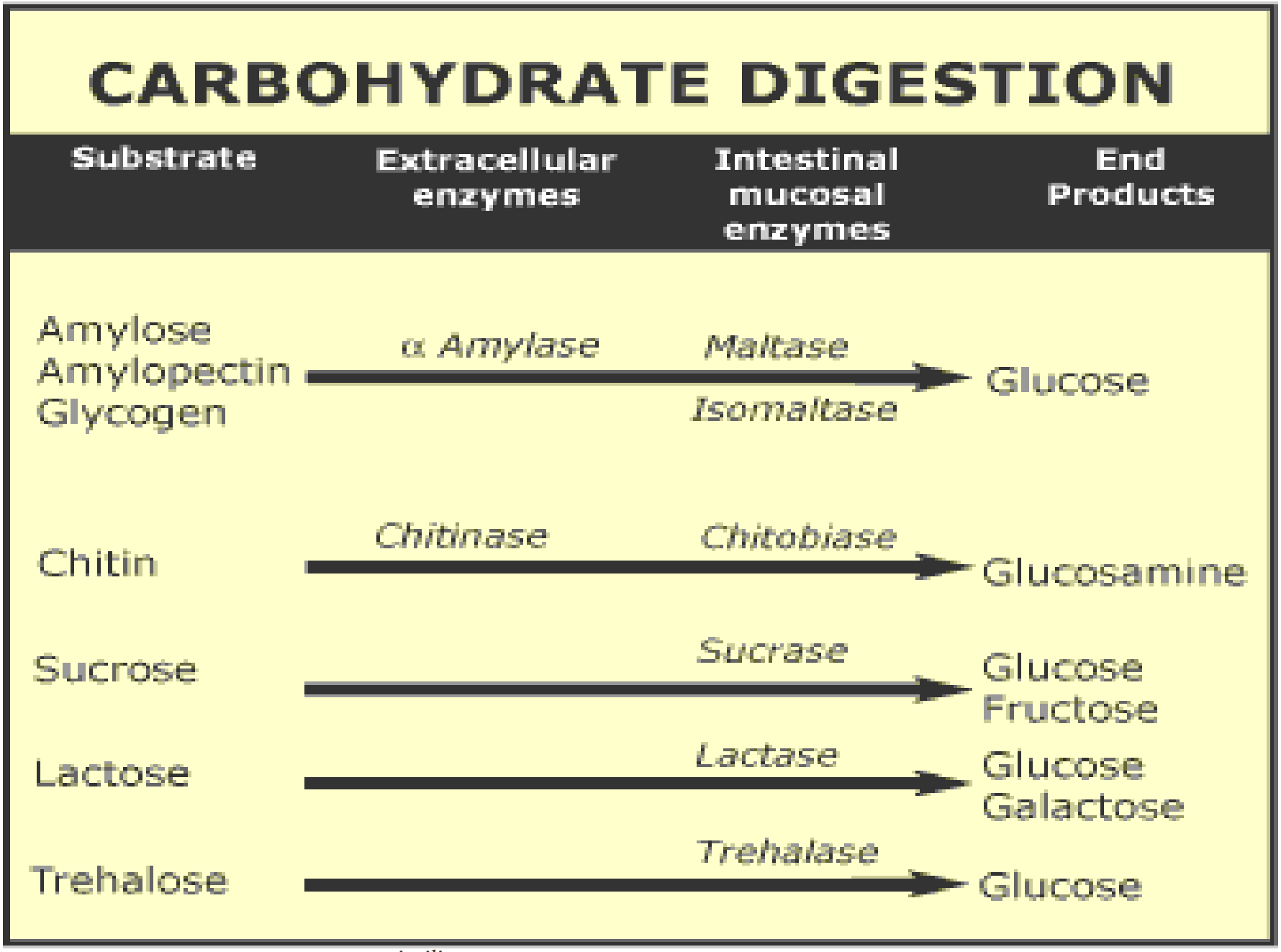
In the Stomach

- Enzyme activity continues in the stomach, but slows down significantly as **digestive acids** are released into the stomach by the glands.

In the Small Intestine

- Another version of amylase is secreted by the **pancreas** into the duodenum (first section of small intestine). This cuts down carbohydrates into simple sugars - **maltose**, **lactose** and **sucrose**. As the carbohydrate passes further into the intestine, the enzymes **maltase**, **lactase** and **sucrase** chop maltose, lactose and sucrose into smaller bits, more easily absorbed, which are eventually converted to glucose and absorbed through the intestinal walls into the bloodstream.

CARBOHYDRATE DIGESTION



G.I Tract Region	Enzyme (or secretio)	Substrate	End Product	pH
Mouth	Saliva	Lubricates and softens food		
	Amylase (ptyalin)	Starch Dextrin	Dextrin Glucose	
Crop	Mucus	Lubricates and softens food		4.5
Stomach	HCl	Lower stomach pH		2.5
Duodenum	Amylase (amylopsin)	Starch Dextrin	Maltose Glucose	2.5

ABSORPTION OF CHO

- Essentially all the carbohydrates in the food are
- absorbed in the form of monosaccharides; only a small fraction are absorbed as disaccharides and almost none as larger carbohydrate compounds.

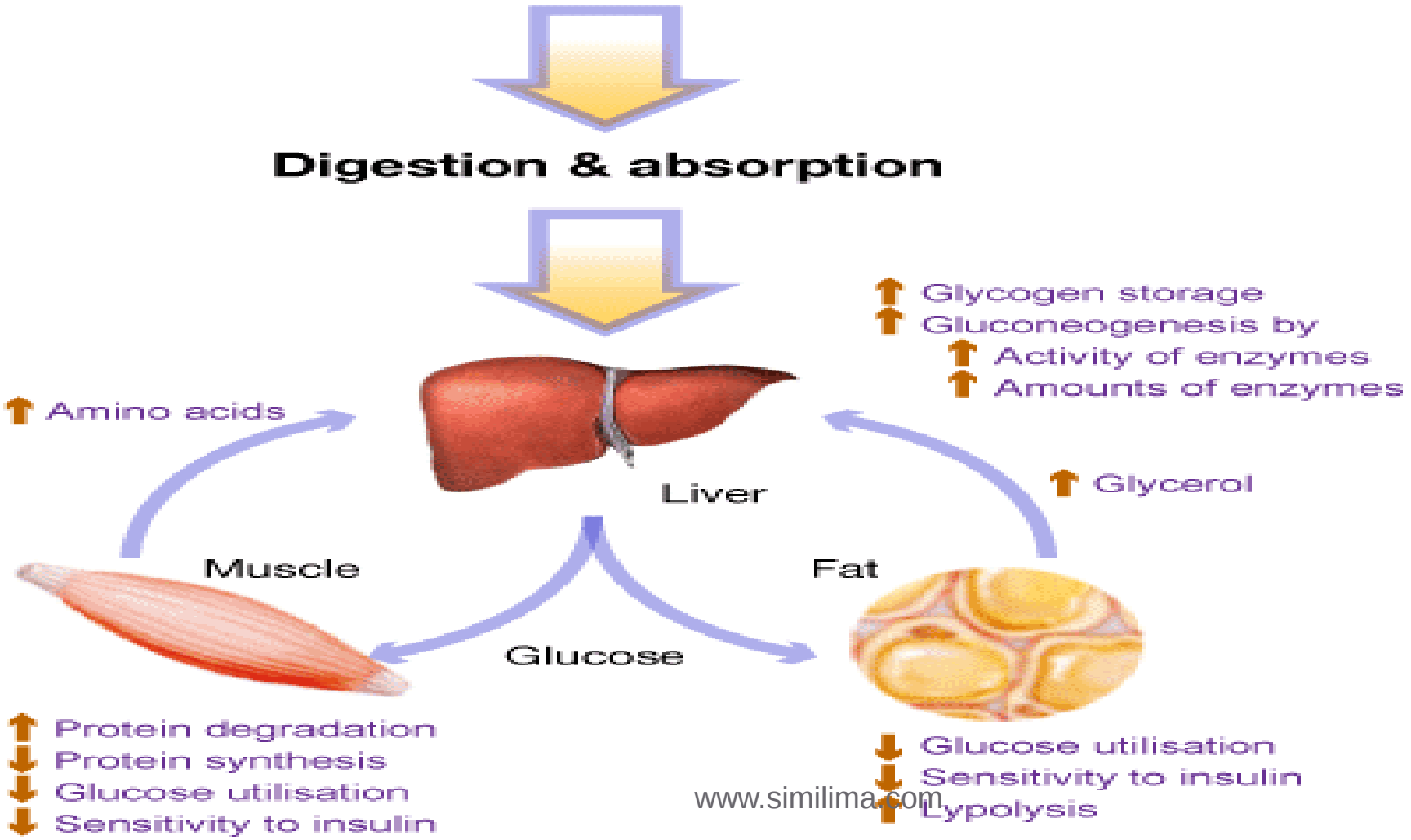
- All the monosaccharides are absorbed by an active transport process.

- **Glucose Is Transported by a Sodium Co-Transport Mechanism** with the help of **sodium dependant glucose transporter (SGluT)**
- Galactose is transported by almost exactly the same mechanism as glucose
- Fructose is transported by facilitated diffusion

- After carbohydrates are duly broken down into glucose, in the duodenum and jejunum of the small intestine, the glucose is absorbed into the bloodstream and taken to the liver, where it is stored or distributed to cells throughout the body for energy. In this way, the **liver regulates blood glucose levels** to provide sufficient energy for the body. For example, excess glucose is converted in the liver to **glycogen** (glycogenesis) in response to the **hormone insulin**, and stored.

Glucose Metabolism By The Liver

Carbohydrates in food

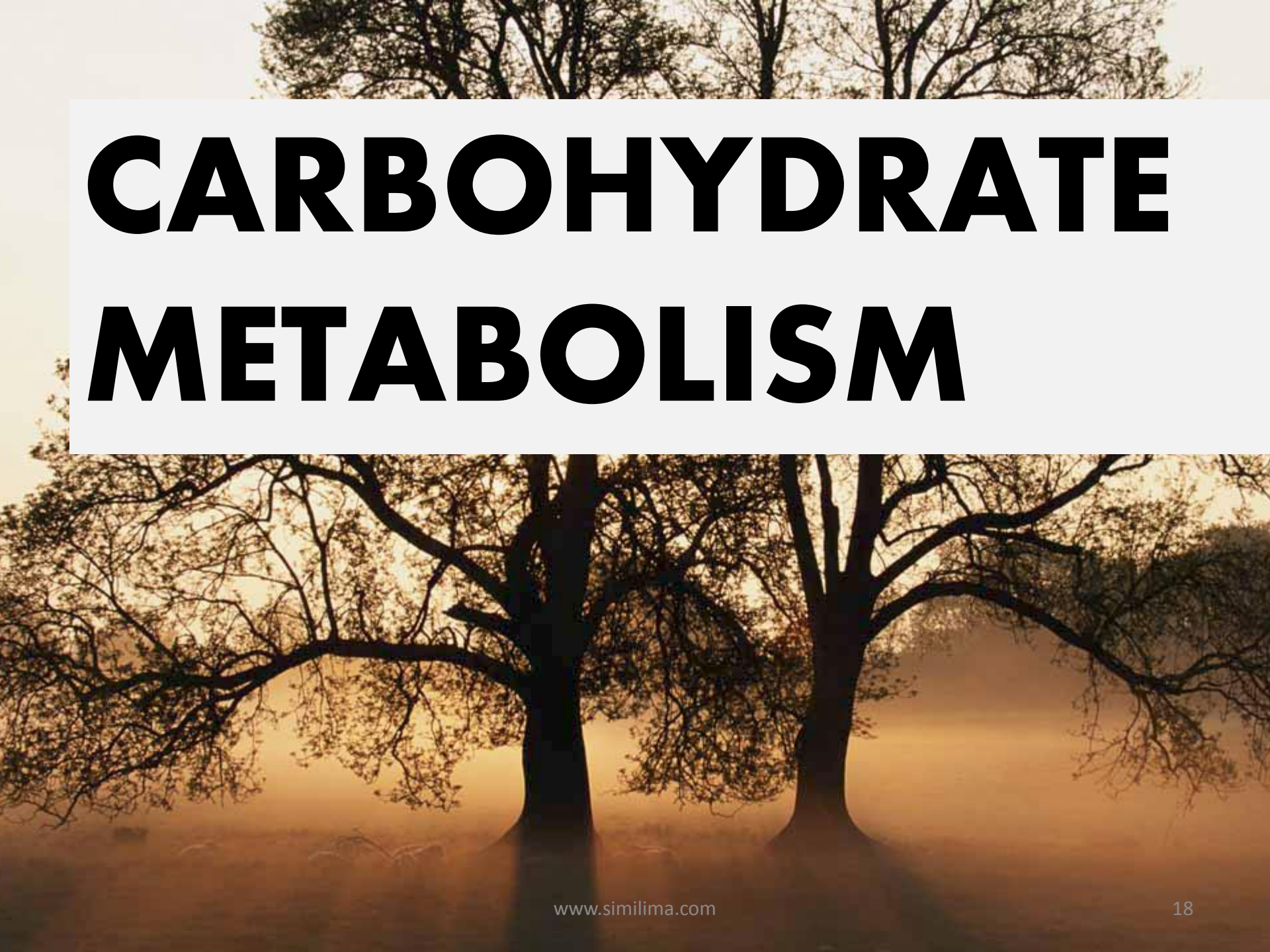


The Glycemic Index

- The blood glucose responses of carbohydrate foods can be classified by the glycemic index (GI). It is defined as the glycemic response elicited by a 50g carbohydrate portion of a food expressed as a percent of that elicited by a 50g carbohydrate portion of a standard food .The standard food has been glucose or white bread. If glucose is the standard, (ie. GI of glucose = 100) the GI values of foods are lower than if white bread is the standard by a factor of 1.38 because the glycemic response of glucose is 1.38 times that of white bread.

Implications of the Glycemic Index

- There are a number of long-term implications of altering the rate of absorption, or GI, of dietary carbohydrate. There is good evidence that reducing diet GI improves overall blood glucose control in subjects with diabetes and reduces serum triglycerides in subjects with hypertriglyceridemia .



CARBOHYDRATE METABOLISM

- **Carbohydrate metabolism** denotes the various biochemical processes responsible for the formation, breakdown and interconversion of carbohydrates in living organisms.

Metabolic pathways

- Carbon fixation, or photosynthesis, in which CO_2 is reduced to carbohydrate.
- Glycolysis - the oxidation metabolism of glucose molecules to obtain ATP and pyruvate
  - Pyruvate from glycolysis enters the Krebs cycle, also known as the citric acid cycle, in aerobic organisms after moving through pyruvate dehydrogenase complex.

- Glycogenesis - the conversion of excess glucose into glycogen as a cellular storage mechanism.
- Glycogenolysis - the breakdown of glycogen into glucose, which provides a glucose supply for glucose-dependent tissues.
  Gluconeogenesis - *de novo* synthesis of glucose molecules from simple organic compounds. an example in humans is the conversion of a few amino acids

Glucoregulation

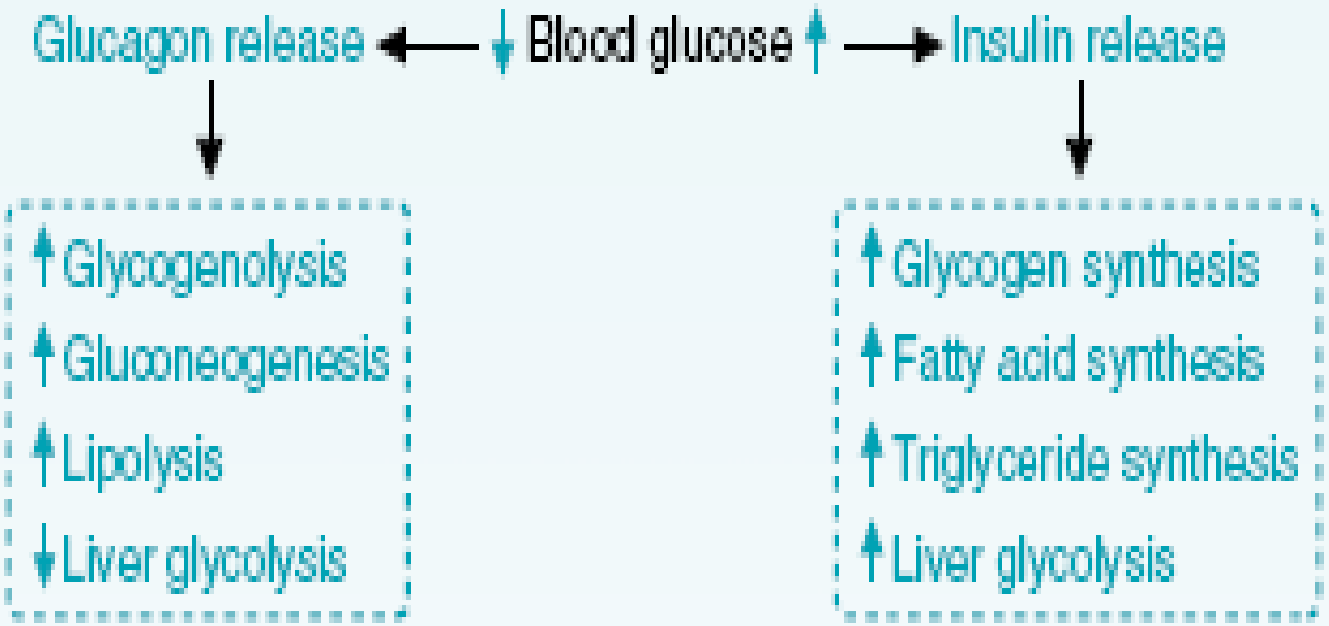
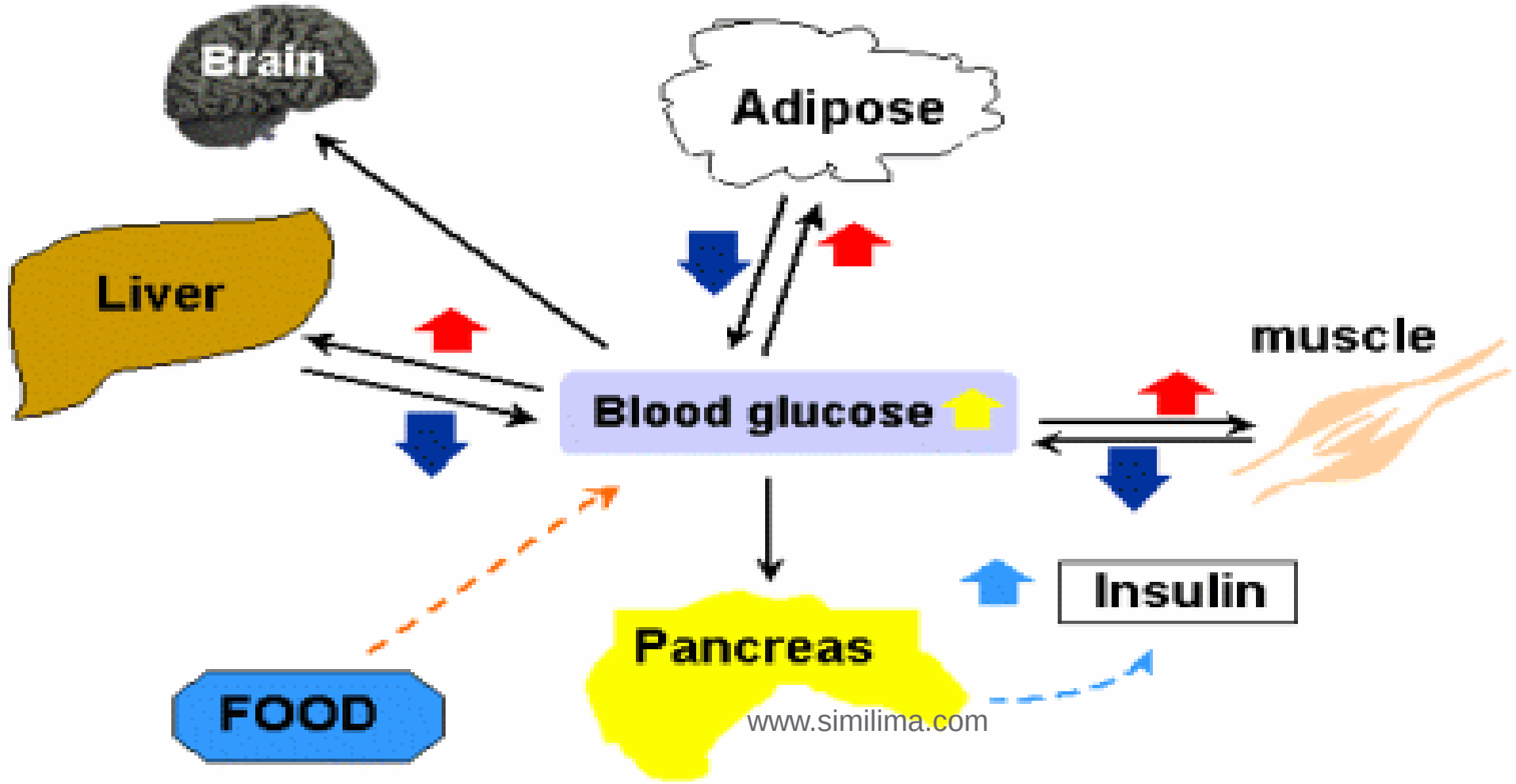


Fig 10. Pathways regulated by the release of glucagon (in response to a lowering of blood glucose levels) and insulin (released in response to an elevation of blood glucose levels). Tissue-specific differences occur in the response to these hormones, as detailed in the subsequent chapters of this section.

GLYCOLYSIS


Brain
Adipose
Liver
muscle
Blood glucose
Insulin
Pancreas
FOOD
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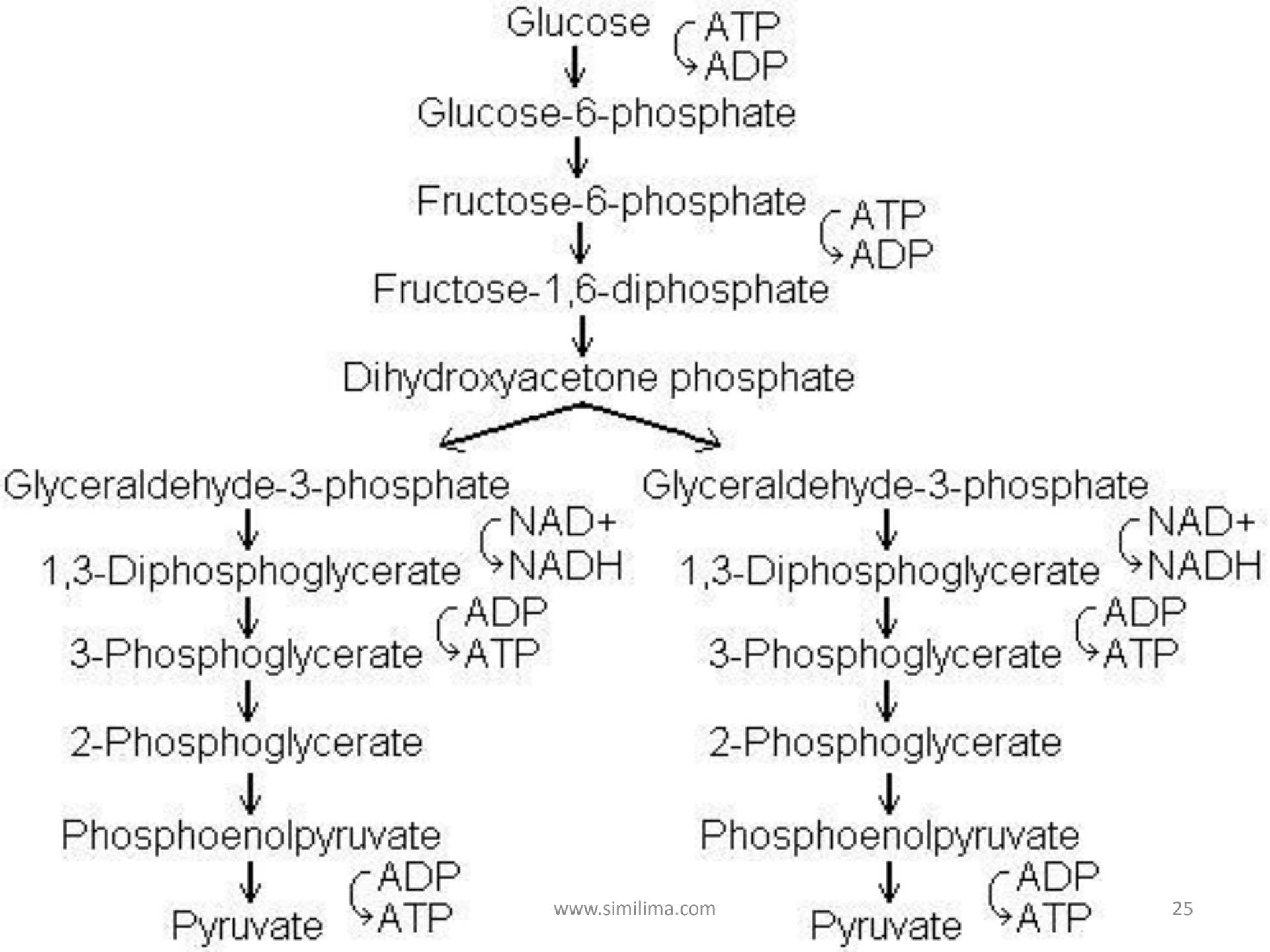
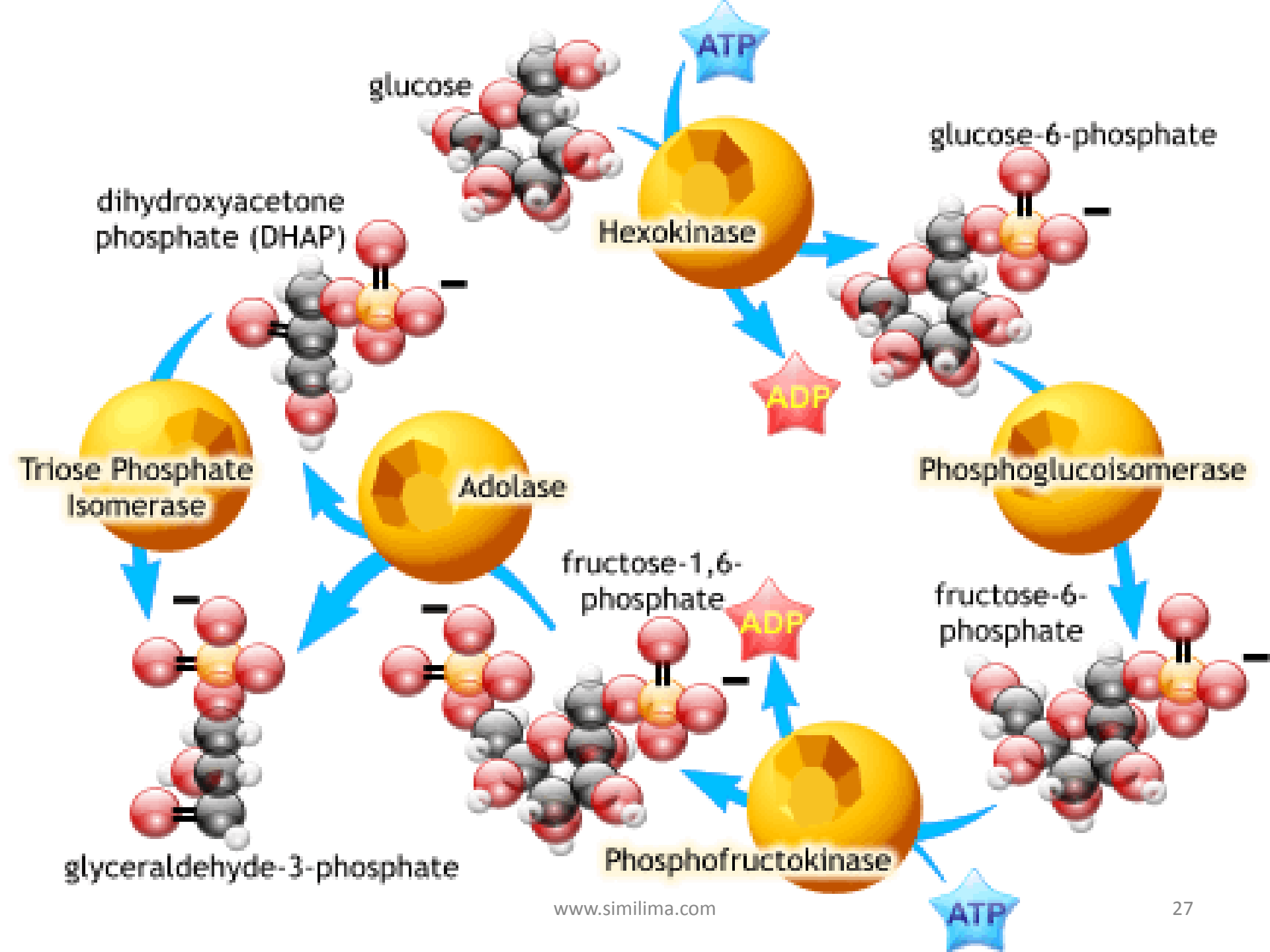
- **Glycolysis** is the metabolic pathway that converts glucose $C_6H_{12}O_6$, into pyruvate. The free energy released in this process is used to form the high-energy compounds ATP and NADH
- The most common type of glycolysis is the ***Embden-Meyerhof-Parnas pathway*** *(EMP pathway)*, which was first discovered by Gustav Embden, Otto Meyerhof and Jakub Karol Parnas

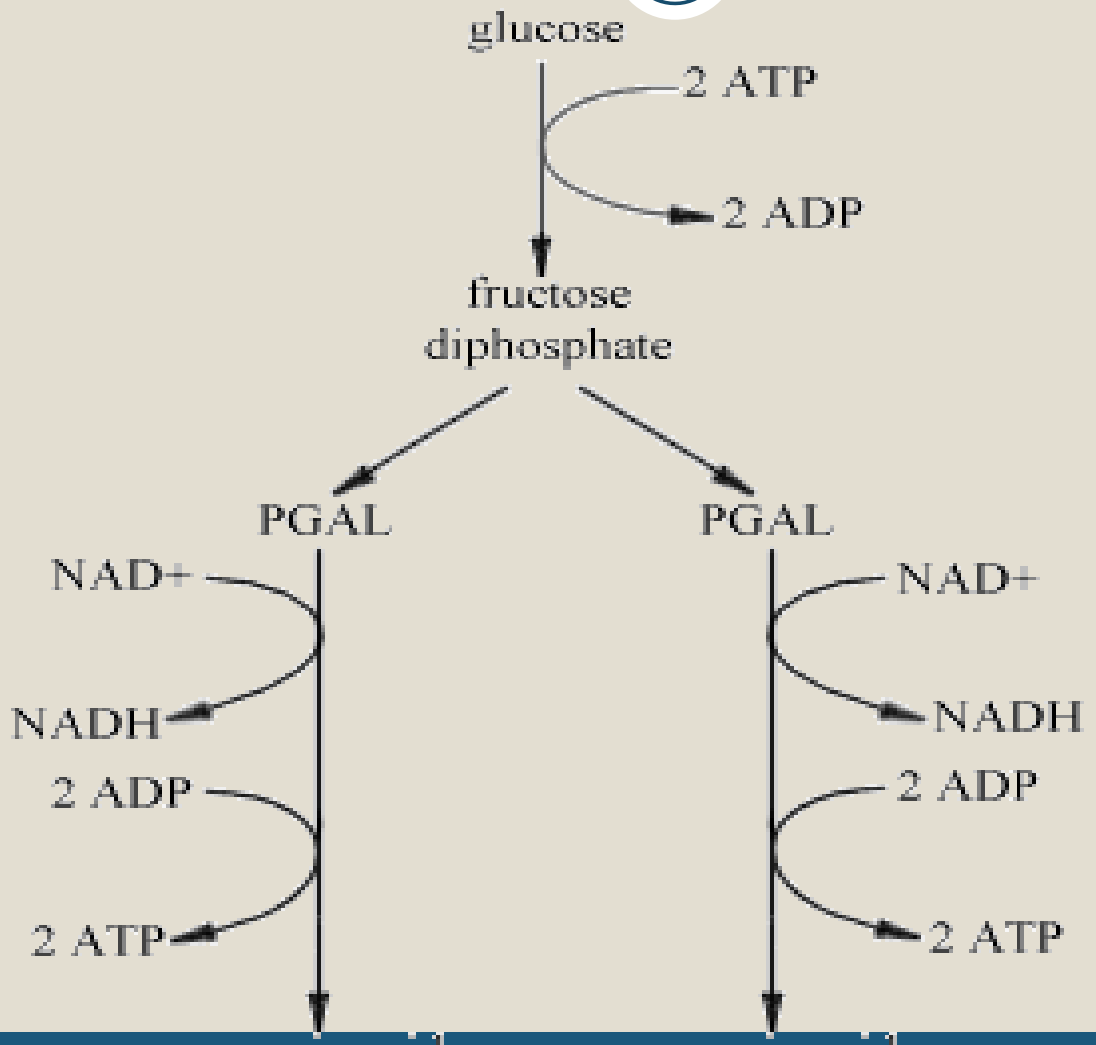

Glucose
ATP
ADP
Glucose-6-phosphate
Fructose-6-phosphate
ATP
ADP
Fructose-1,6-diphosphate
Dihydroxyacetone phosphate
Glyceraldehyde-3-phosphate
Glyceraldehyde-3-phosphate
NAD+
NADH
1,3-Diphosphoglycerate
1,3-Diphosphoglycerate
NAD+
NADH
ADP
ATP
3-Phosphoglycerate
3-Phosphoglycerate
ADP
ATP
2-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
Phosphoenolpyruvate
ADP
ATP
Pyruvate
Pyruvate
ADP
ATP

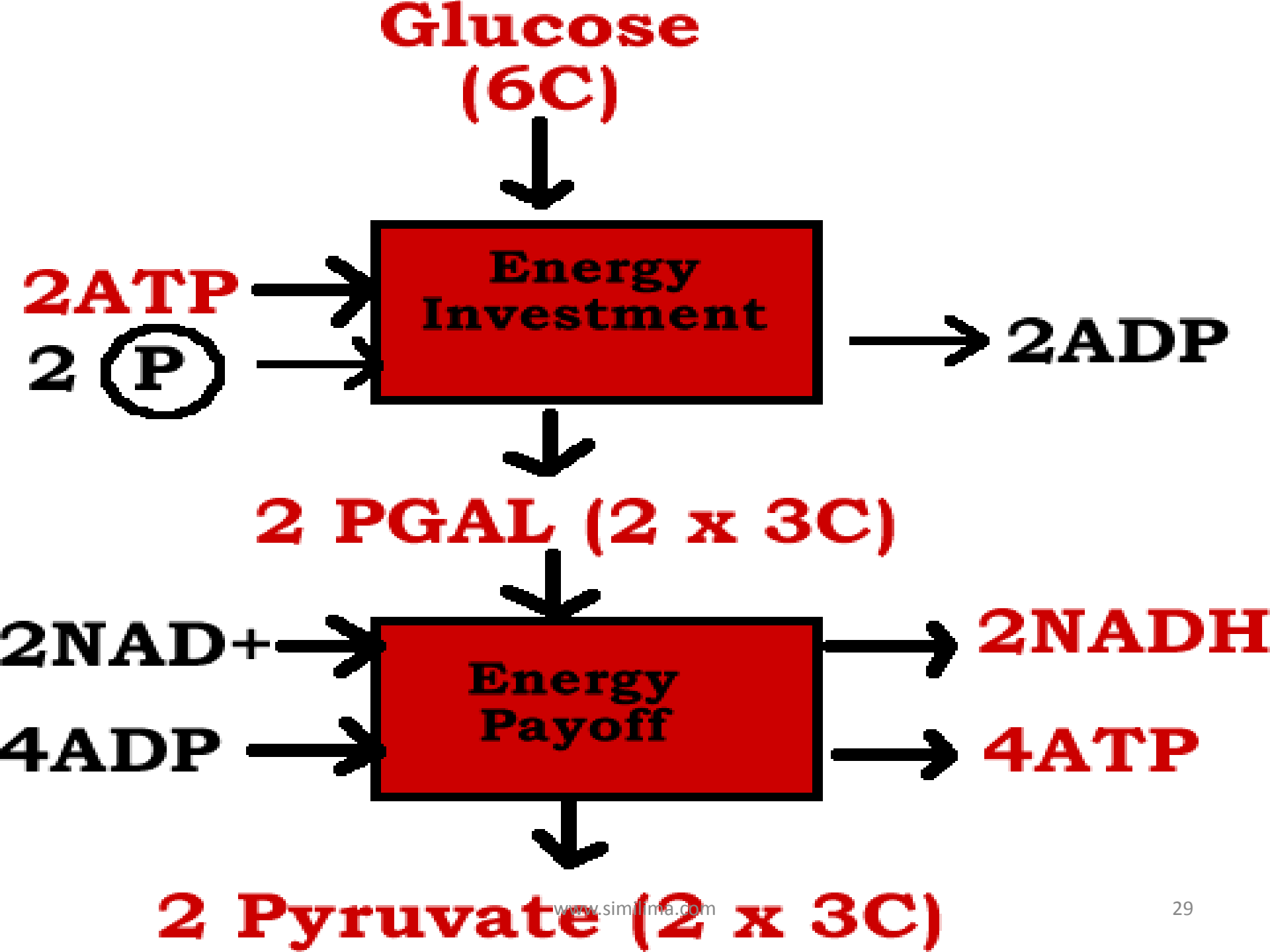
Pay-off phase

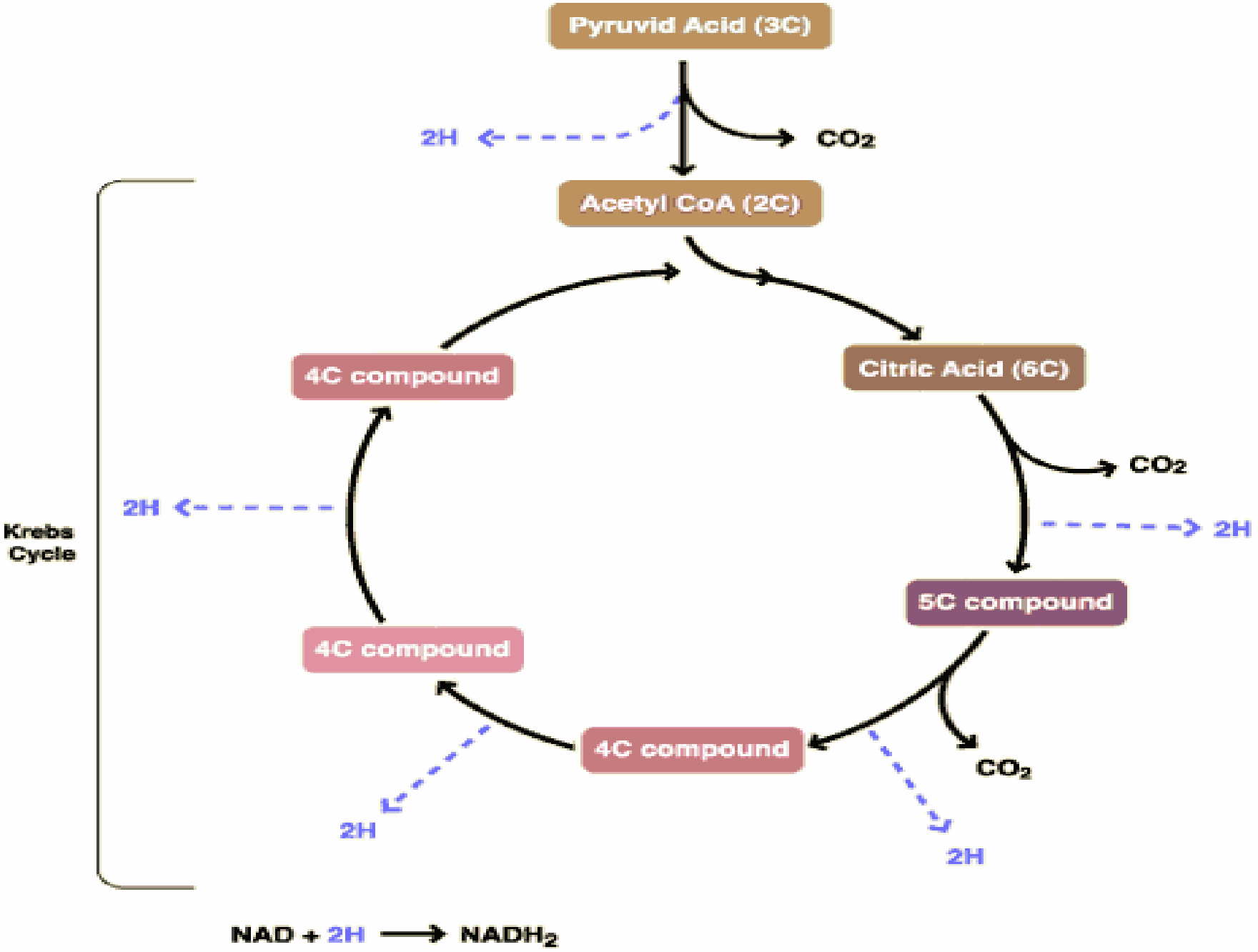
- The second half of glycolysis is known as the pay-off phase, characterised by a net gain of the energy-rich molecules ATP and NADH. Since glucose leads to two triose sugars in the preparatory phase, each reaction in the pay-off phase occurs twice per glucose molecule. This yields 2 NADH molecules and 4 ATP molecules, leading to a net gain of 2 NADH molecules and 2 ATP molecules from the glycolytic pathway per glucose.


glucose
ATP
Hexokinase
glucose-6-phosphate
dihydroxyacetone
phosphate (DHAP)
ADP
Triose Phosphate
Isomerase
Adolase
Phosphoglucoisomerase
fructose-1,6-
phosphate
ADP
fructose-6-
phosphate
glyceraldehyde-3-phosphate
Phosphofructokinase
ATP

Glycolysis


glucose
2 ATP
2 ADP
fructose diphosphate
PGAL
PGAL
NAD+
NAD+
NADH
NADH
2 ADP
2 ADP
2 ATP
2 ATP
pyruvic acid
pyruvic acid


Glucose
(6C)
2ATP
2 P
Energy
Investment
2ADP
2 PGAL (2 x 3C)
2NAD+
4ADP
Energy
Payoff
2NADH
4ATP
2 Pyruvate (2 x 3C)



The Cori cycle

- The **Cori cycle** refers to the metabolic pathway in which lactate, produced by anaerobic glycolysis in the muscle, moves to the liver and is converted to glucose, through gluconeogenesis; glucose can then return to supply the muscle.

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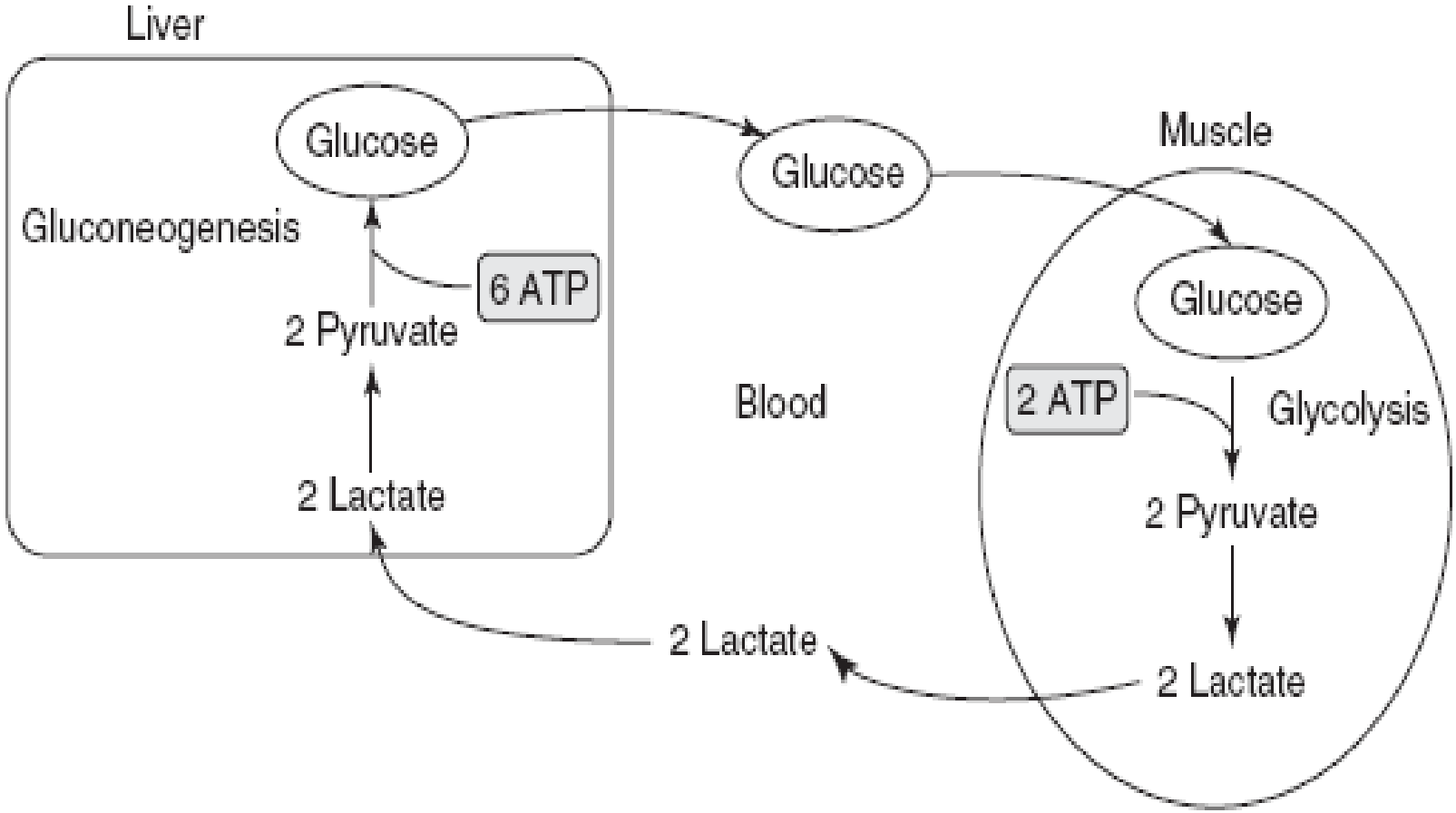


RAPAPORT LEUBERING SHUNT

- **B P G Shunt**

  Occurs in erythrocytes.

  No ATP is generated in this step.

2,3 BPG- when combines with Hb – **reduces the affinity towards 02.**

1,3 bisphospho glycerate

2,3 bisphospho glycerate

3,phospho glycerate

Regulation

- Glycolysis is regulated by slowing down or speeding up certain steps in the glycolysis pathway. This is accomplished by inhibiting or activating the enzymes that are involved.

Deficiency of glycolytic enzymes

- Deficiency of pyruvate kinase& hexokinase are most the common.
- Important manifestation is hemolytic anemia

Gluconeogenesis

- Gluconeogenesis is the generation of glucose from organic molecules such as pyruvate, lactate, glycerol and amino acids (primarily alanine and glutamine)
- Gluconeogenesis takes place in the liver, and to a lesser extent in the kidneys.
- The process occurs during periods of starvation or intense exercise.

- Most steps in gluconeogenesis are the reverse of those found in glycolysis, the three regulated and strongly exergonic reactions of glycolysis are replaced with more energetically favourable reactions

- Pyruvate, the first designated substrate of the gluconeogenic pathway, can then be used to generate glucose.All citric acid cycle intermediates, through conversion to oxaloacetate, amino acids other than lysine or leucine, and glycerol can also function as substrates for gluconeogenesis. Transamination or deamination of amino acids facilitates entering of their carbon skeleton into the cycle directly (as pyruvate or oxaloacetate), or indirectly via the citric acid cycle.

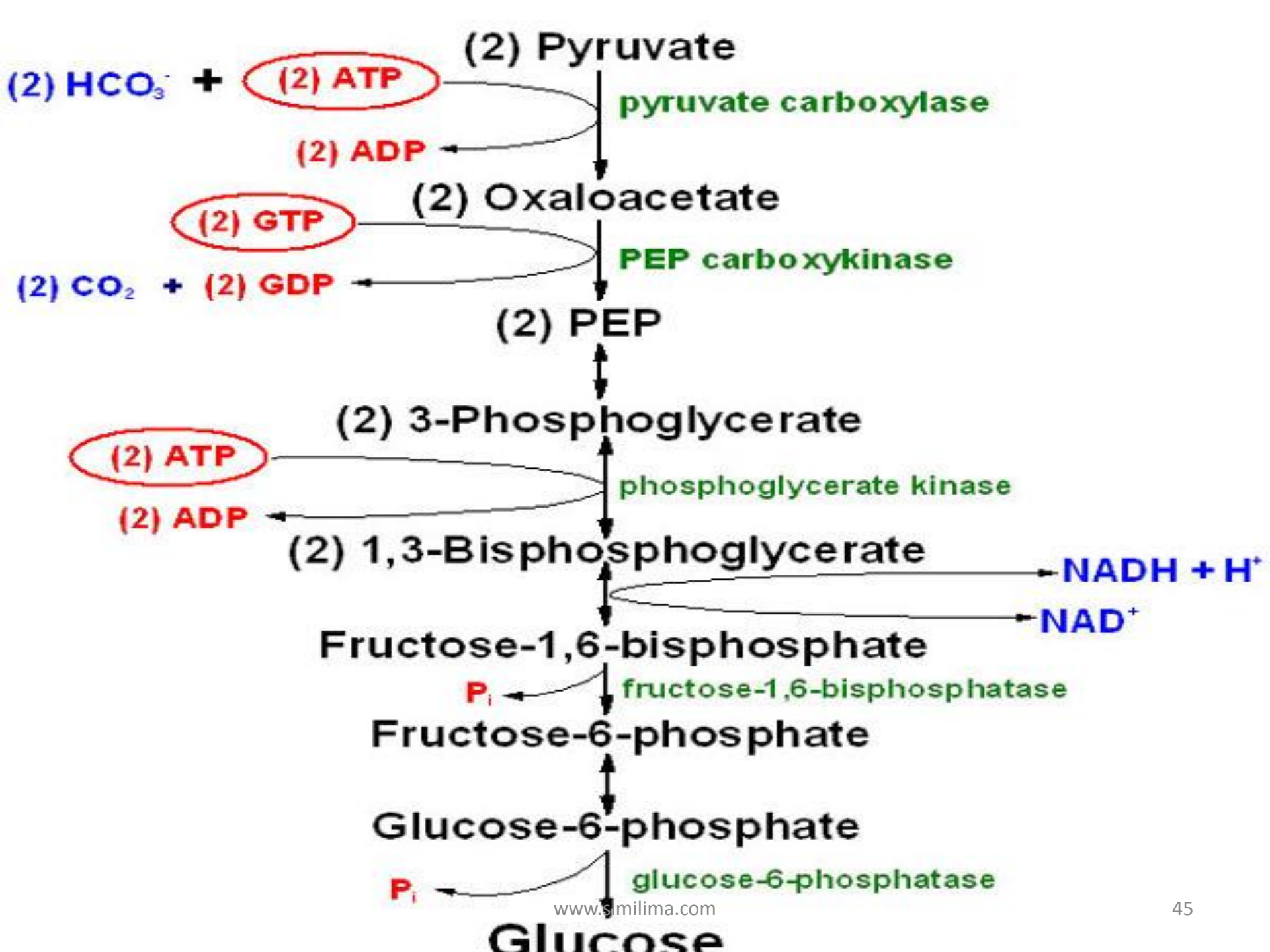
Pathway

- Gluconeogenesis begins in the mitochondria with the formation of oxaloacetate through carboxylation of pyruvate. This reaction also requires one molecule of ATP, and is catalyzed by pyruvate carboxylase. This enzyme is stimulated by high levels of acetyl-CoA (produced in β-oxidation in the liver) and inhibited by high levels of ADP.

- Oxaloacetate is reduced to malate using NADH, a step required for transport out of the mitochondria.
- Malate is oxidized to oxaloacetate using NAD^+ in the cytoplasm, where the remaining steps of gluconeogenesis occur.
- Oxaloacetate is decarboxylated and phosphorylated to produce phosphoenolpyruvate by phosphoenolpyruvate carboxykinase. One molecule of GTP is hydrolyzed to GDP during this reaction.

- The next steps in the reaction are the same as reversed glycolysis. However, fructose-1,6-bisphosphatase converts fructose-1,6-bisphosphate to fructose 6-phosphate, requiring one water molecule and releasing one phosphate. This is also the rate-limiting step of gluconeogenesis.


Glucose
Glucose-6-Phosphatase
Glucose-6-Phosphate
Fructose-6-Phosphate
Fructose-1,6-bisphosphatase
Fructose-1,6-bisphosphate
Dihydroxyacetone-Phosphate
Glyceraldehyde-3-Phosphate
Glycerol
1,3-Bisphosphoglycerate
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
PEP Carboxykinase
Oxaloacetate
Pyruvate carboxylase
Pyruvate


(2) Pyruvate
(2) HCO_3^- + (2) ATP
pyruvate carboxylase
(2) ADP
(2) Oxaloacetate
(2) GTP
PEP carboxykinase
(2) CO_2 + (2) GDP
(2) PEP
(2) 3-Phosphoglycerate
(2) ATP
phosphoglycerate kinase
(2) ADP
(2) 1,3-Bisphosphoglycerate
NADH + H^+
NAD^+
Fructose-1,6-bisphosphate
P_i
fructose-1,6-bisphosphatase
Fructose-6-phosphate
Glucose-6-phosphate
P_i
glucose-6-phosphatase
Glucose

- Glucose-6-phosphate is formed from fructose 6-phosphate by phosphoglucoisomerase. Glucose-6-phosphate can be used in other metabolic pathways or dephosphorylated to free glucose. Whereas free glucose can easily diffuse in and out of the cell, the phosphorylated form (glucose-6-phosphate) is locked in the cell, a mechanism by which intracellular glucose levels are controlled by cells.

- The final reaction of gluconeogenesis, the formation of glucose, occurs in the lumen of the endoplasmic reticulum, where glucose-6-phosphate is hydrolyzed by glucose-6-phosphatase to produce glucose. Glucose is shuttled into the cytosol by glucose transporters located in the membrane of the endoplasmic reticulum.
-

Regulation

- The rate of gluconeogenesis is ultimately controlled by the action of a key enzyme, fructose-1,6-bisphosphatase, which is also regulated through signal tranduction by cAMPand its phosphorylation.
- Most factors that regulate the activity of the gluconeogenesis pathway do so by inhibiting the activity or expression of key enzymes. However, both acetyl CoA and citrate activate gluconeogenesis enzymes (pyruvate carboxylase and fructose-1,6-bisphosphatase, respectively). Due to the reciprocal control of the cycle, acetyl-CoA and citrate also have inhibitory roles in the activity of pyruvate kinase.

Glycogenesis

- It is the process of glycogen synthesis, in which glucose molecules are added to chains of glycogen for storage. This process is activated during rest periods following the Cori cycle, in the liver, and also activated by insulin in response to high glucose levels, for example after a carbohydrate-containing meal.

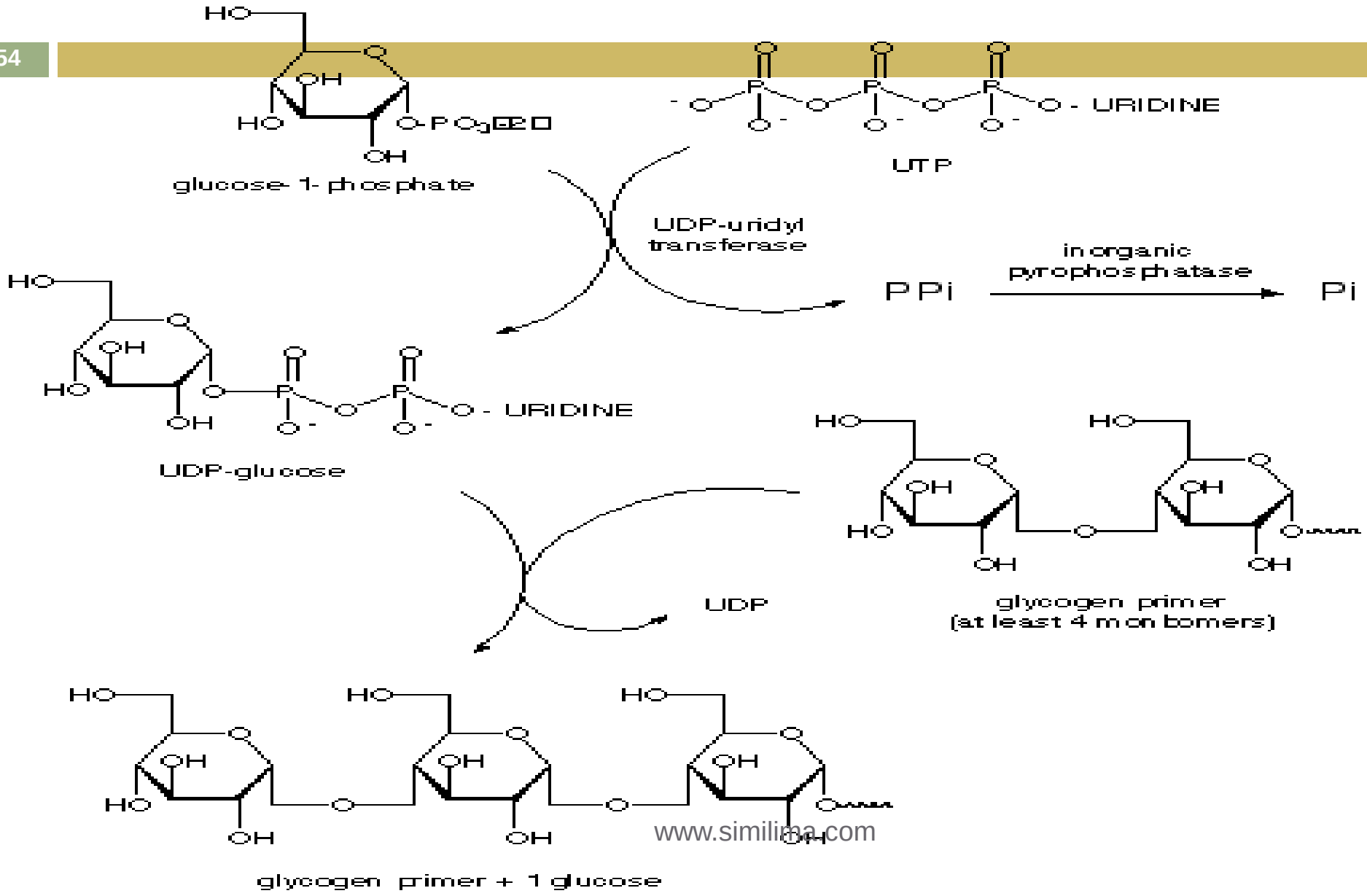
Glycogenesis

Steps

- Glucose is converted into glucose-6-phosphate by the action of glucokinase or hexokinase.
- Glucose-6-phosphate is converted into glucose-1-phosphate by the action of Phosphoglucomutase, passing through an obligatory intermediate step of glucose-1,6-bisphosphate
- Glucose-1-phosphate is converted into UDP-glucose by the action of Uridyl Transferase (also called UDP-glucose pyrophosphorylase) and pyrophosphate is formed, which is hydrolyzed by pyrophosphatase into 2 molecules of Pi.

- Glucose molecules are assembled in a chain by glycogen synthase, which must act on a pre-existing glycogen primer or glycogenin (small protein that forms the primer). The mechanism for joining glucose units is that glycogen synthase binds to UDPG, causing it to break down into an oxonium ion, also formed in glycogenolysis. This oxonium ion can readily add to the 4-hydroxyl group of a glucosyl residue on the 4 end of the glycogen chain.

- Branches are made by branching enzyme (also known as amylo-α(1:4)->α(1:6)transglycosylase), which transfers the end of the chain onto an earlier part via α-1:6 glucosidic bond, forming branches, which further grow by addition of more α-1:4 glucosidic units.



Control and regulation

- Epinephrine not only activates glycogen phosphorylase but also inhibits glycogen synthase. This amplifies the effect of activating glycogen phosphorylase.
- Insulin has an antagonistic effect to adrenaline
- The calcium ions activate phosphorylase kinase. This activates glycogen phosphorylase and inhibits glycogen synthase.

GLYCOGENOLYSIS

Glycogenolysis

- Glycogenolysis takes place in the muscle and liver tissues, where glycogen is stored, as a hormonal response to epinephrine (e.g., adrenergic stimulation) and/or glucagon, a pancreatic peptide triggered by low blood glucose concentrations, and produced in the alpha cells of the islets of Langerhans

- Liver (hepatic) cells can consume the glucose-6-phosphate in glycolysis or remove the phosphate group using the enzyme glucose-6-phosphatase and release the free glucose into the bloodstream for uptake by other cells.
  Muscle cells in humans do not possess glucose-6-phosphatase and, hence, will not release glucose, but instead use the glucose-6-phosphate in glycolysis.
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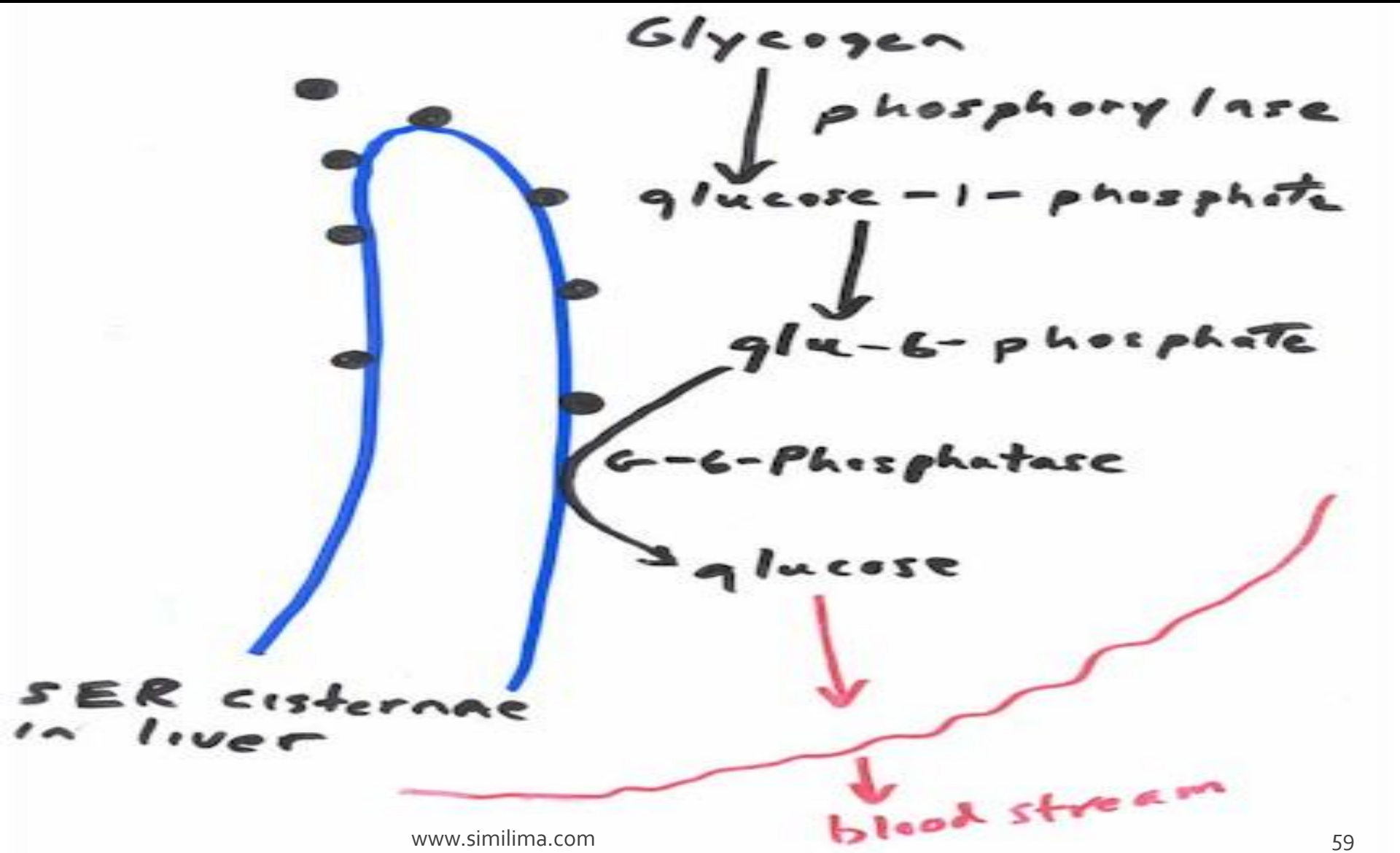
GLYCOGENOLYSIS



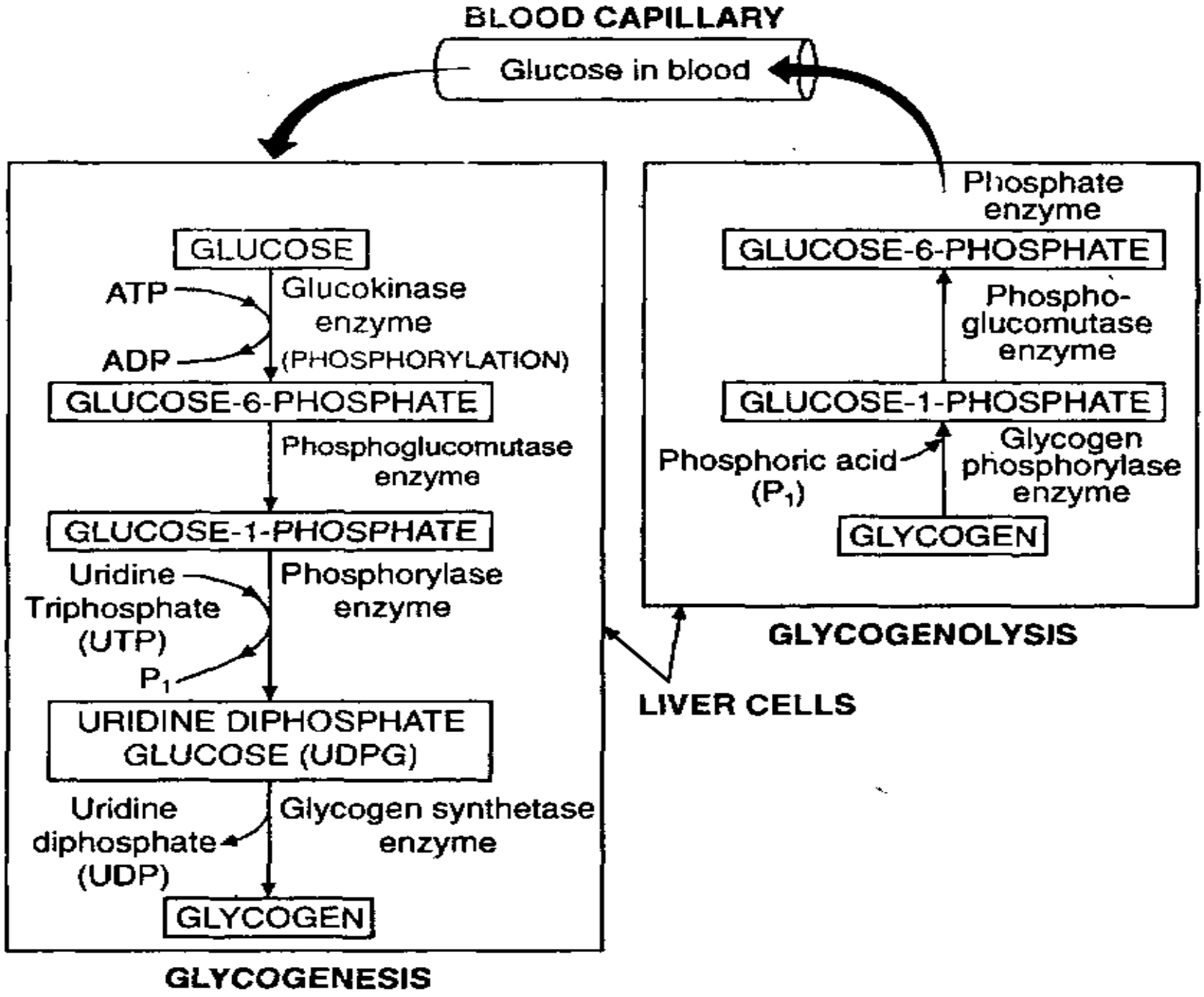
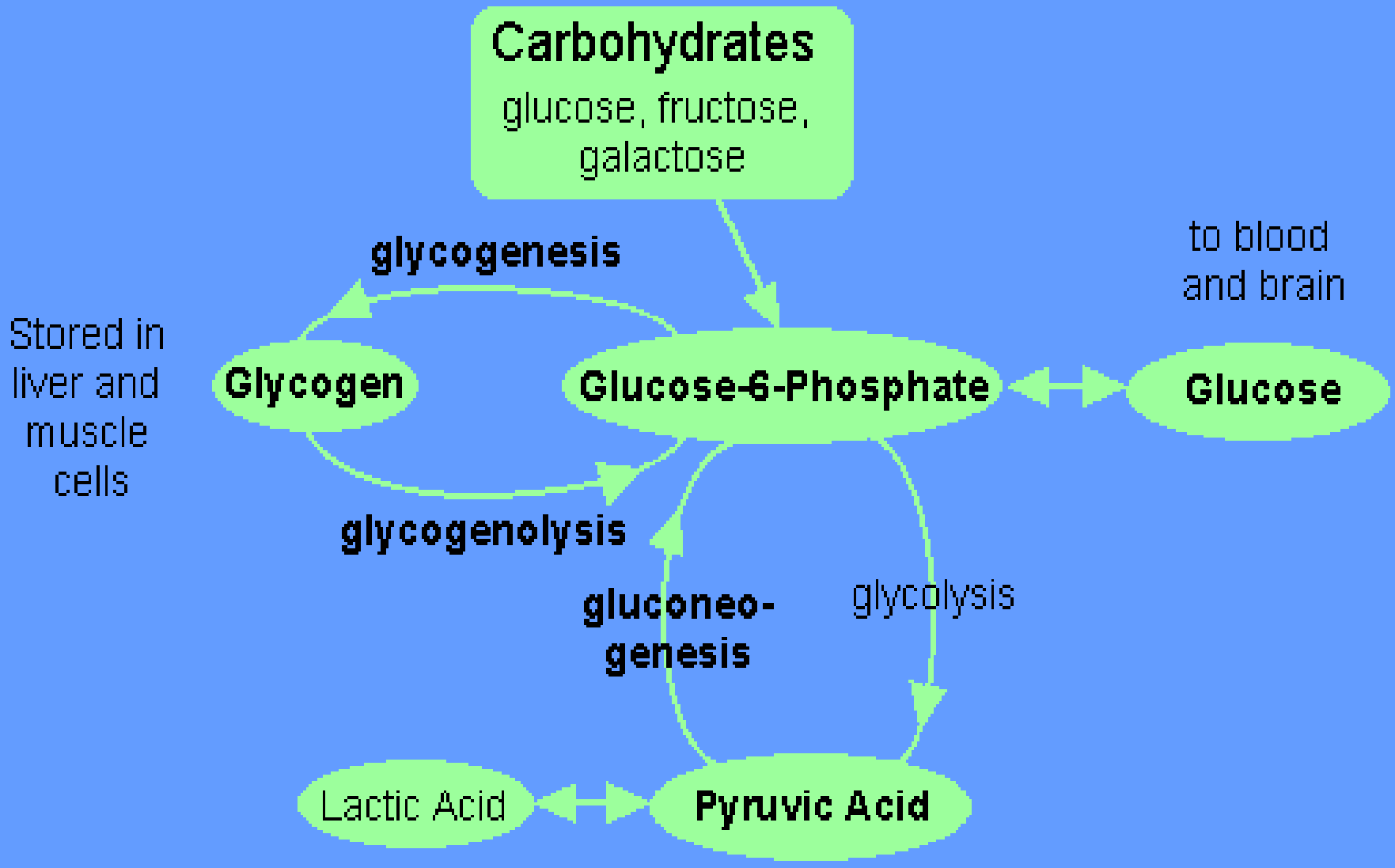


Fig. 6.11 Reaction sequences of glycogenesis and glycogenolysis

Carbohydrate Summary



Glucose tolerance test

- A **glucose tolerance test** is a medical test in which glucose is given and blood samples taken afterward to determine how quickly it is cleared from the blood
- The test is usually used to test for diabetes, insulin resistance, and sometimes reactive hypoglycemia or rarer disorders of carbohydrate metabolism.

- In the most commonly performed version of the test, an *oral glucose tolerance test* (OGTT), a standard dose of glucose is ingested by mouth and blood levels are checked two hours later.

Preparation

- The patient is instructed not to restrict carbohydrate intake in the days or weeks before the test. The test should not be done during an illness, as results may not reflect the patient's glucose metabolism when healthy.
- Usually the OGTT is performed in the morning as glucose tolerance can exhibit a diurnal rhythm with a significant decrease in the afternoon.
- The patient is instructed to fast (water is allowed) for 8–12 hours prior to the tests.

Oral Glucose Tolerance Test

No food or drink 8 to 12 hours prior to test

Drink glucose

Blood is tested two hours later

High glucose level = potential diabetes

Procedure

- A blood sample is drawn.
- The patient is then given a measured dose of glucose solution to drink within a 5 minute time frame.
- Blood is drawn at intervals for measurement of glucose (blood sugar), and sometimes insulin levels. The intervals and number of samples vary according to the purpose of the test. For simple diabetes screening, the most important sample is the 2 hour sample and the 0 and 2 hour samples may be the only ones collected.

Dose of glucose and variations

- The WHO recommendation is for a 75g oral dose in all adults: the dose is adjusted for weight only in children. The dose should be drunk within 5 minutes.
- A variant is often used in pregnancy to screen for gestational diabetes, with a screening test of 50 grams over one hour. If elevated, this is followed with a test of 100 grams over three hours.

Substances measured and variations

- If renal glycosuria (sugar excreted in the urine despite normal levels in the blood) is suspected, urine samples may also be collected for testing along with the fasting and 2 hour blood tests.

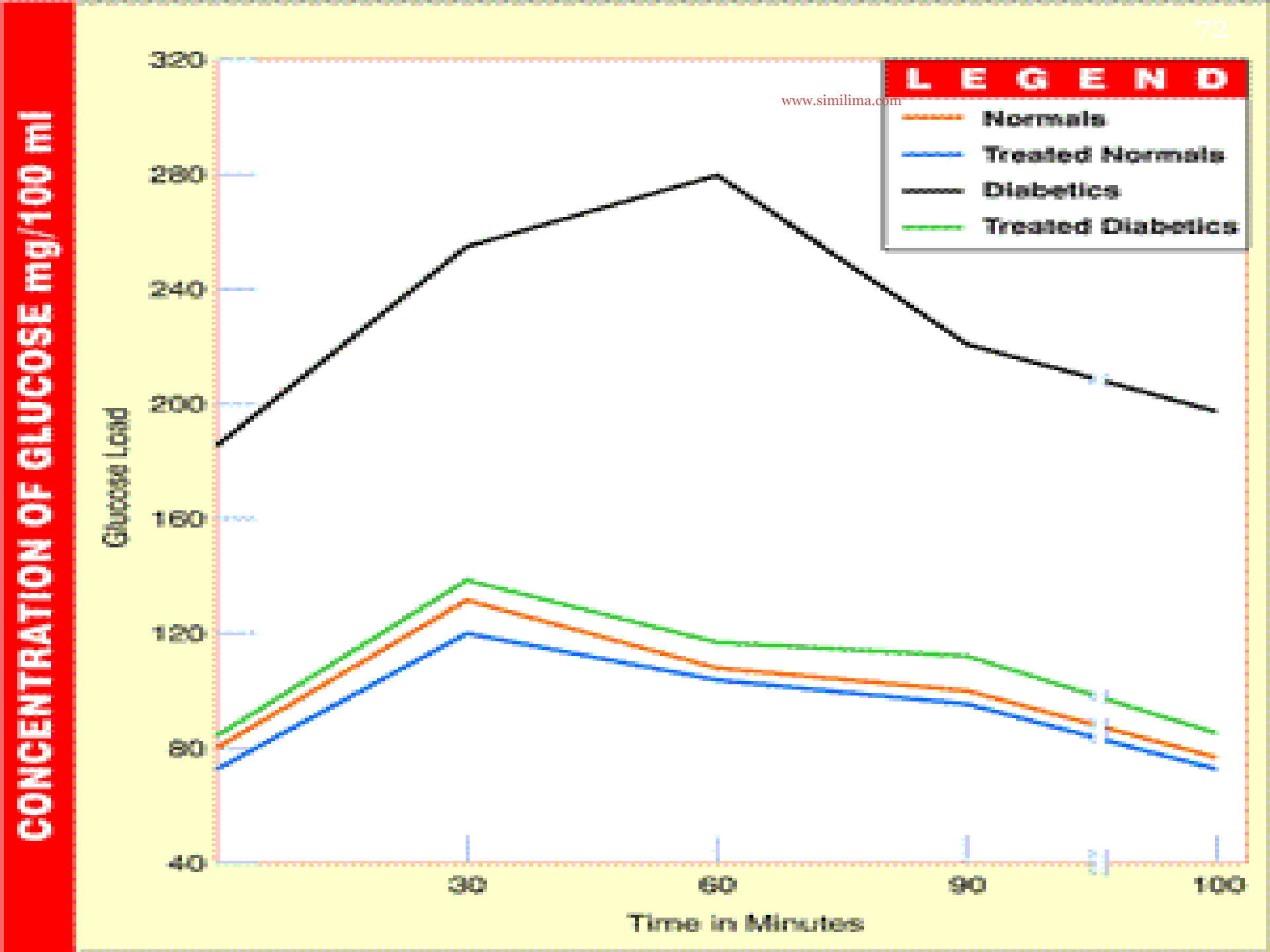
Interpretation of OGTT results

- **Fasting plasma glucose** (measured before the OGTT begins) should be below 6.1 mmol/l (110 mg/dl). Fasting levels between 6.1 and 7.0 mmol/l (110 and 125 mg/dl) are borderline ("impaired fasting glycaemia"), and fasting levels repeatedly at or above 7.0 mmol/l (**126** mg/dl) are diagnostic of diabetes.

- The **2 hour OGTT** glucose level should be below 7.8 mmol/l (140 mg/dl). Levels between this and 11.1 mmol/l (200 mg/dl) indicate "impaired glucose tolerance". Glucose levels above 11.1 mmol/l (**200** mg/dl) at 2 hours confirms a diagnosis of diabetes.

1999 WHO Diabetes criteria - Interpretation of Oral Glucose Tolerance Test

Glucose levels	NORMAL		impaired fasting glycaemia (IFG)		impaired glucose tolerance (IGT)		Diabetes Mellitus (DM)	
Venous Plasma	Fasting	2hrs	Fasting	2hrs	Fasting	2hrs	Fasting	2hrs
(mmol/l)	<6.1	<7.8	≥ 6.1 & <7.0	<7.8	<7.0	≥7.8	≥7.0	≥11.1
(mg/dl)	<110	<140	≥110 & <126	<140	<126	≥140	≥126	≥200



Glycogen storage disease

NUMBER	ENZYME DEFICIENCY	EPONYM	SYMPTOMS
GSD type I	glucose-6-phosphatase	**von Gierke's disease**	**Hypo-glycemia,** Growth failure, Lactic acidosis, hyperuricemia
GSD type II	acid maltase	Pompe's disease	Death by age ~2 years , Muscle weakness, heart failure

NUMBER	ENZYME DEFICIENCY	EPONYM	SYMPTOMS
GSD type III	Glycogen debrancher	Cori's disease or Forbes' disease	Myopathy
GSD type IV	glycogen branching enzyme	Andersen disease	Failure to thrive, death at age ~5 years

NUMBER	ENZYME DEFICIENCY	EPONYM	SYMPTOMS
GSD type V	muscle glycogen phosphorylase	McArdle disease	Exercise-induced cramps, Rhabdomyolysis, Renal failure
GSD type VI	liver glycogen phosphorylase	Hers' disease	**Hypoglycemia,**

NUMBER	ENZYME DEFICIENCY	EPONYM	SYMPTOMS
GSD type VII	muscle phosphofructokinase	Tarui's disease	Exercise-induced muscle cramps and weakness, growth retardation, Haemolytic anaemia
GSD type IX	phosphorylase kinase		Delayed motor development, Growth retardation

NUMBER	ENZYME DEFICIENCY	EPONYM	SYMPTOMS
GSD type XI	glucose transporter, GLUT2	Fanconi-Bickel syndrome	
GSD type XII	Aldolase A	Red cell aldolase deficiency	Exercise intolerance, cramps

NUMBER	ENZYME DEFICIENCY	EPONYM	SYMPTOMS
GSD type 0	glycogen synthase		Occasional muscle cramping


THANK U…