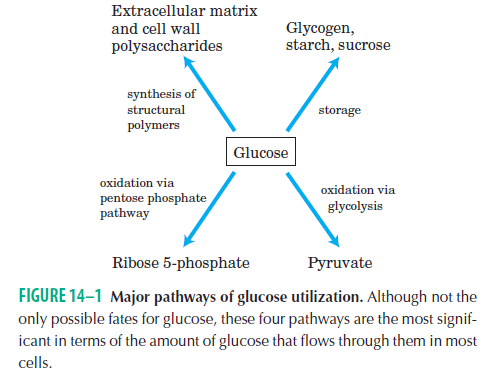
**Chapter 14** **Glycolysis, Gluconeogenesis and the Pentose Phosphate Pathway**

* In animals and higher plants, glucose has four major fates; it may be
* used in the synthesis of complex polysaccharides destined for the extracellular space
* stored in cells (as a polysaccharide or as sucrose)
* oxidized to a three-carbon compound (pyruvate) via glycolysis to provide ATP and metabolic intermediates
* oxidized via the pentose phosphate pathway to yield ribose 5-phosphate for nucleic acid synthesis and NADPH for reductive biosynthetic processes (**Fig. 14-1)**.



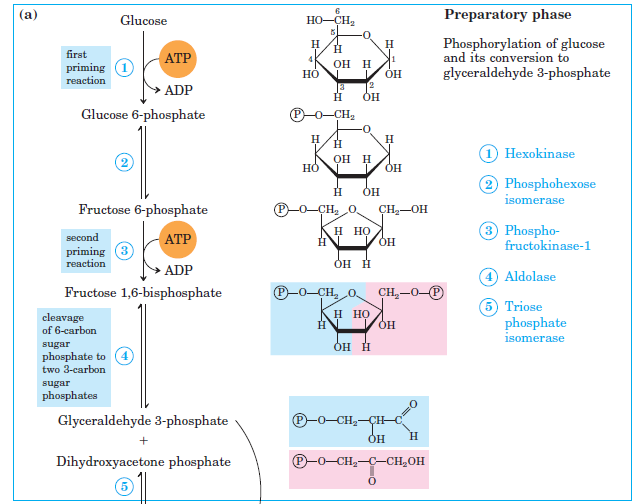
**14.1 Glycolysis**

* Glycolysis occurs in the cytosol.
* In glycolysis,
* a molecule of glucose is degraded in a series of enzyme-catalyzed reactions to yield two molecules of the three-carbon compound pyruvate.
* some of the free energy released from glucose is conserved in the form of ATP and NADH.
* **Fermentation** is a general term for the anaerobic degradation of glucose or other organic nutrients to obtain energy, conserved as ATP.

**Glycolysis Has Two Phases**

* The breakdown of the six-carbon glucose into two molecules of the three-carbon pyruvate occurs in 10 steps.
* The first 5 of them constitute the preparatory phase **(Fig. 14-2a).**

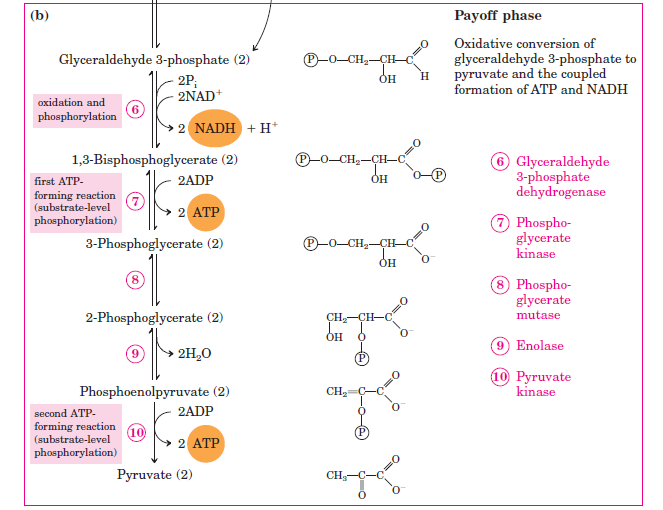
1. Phosphorylation of glucose (1 ATP is used)
2. Conversion of glucose 6-phosphate

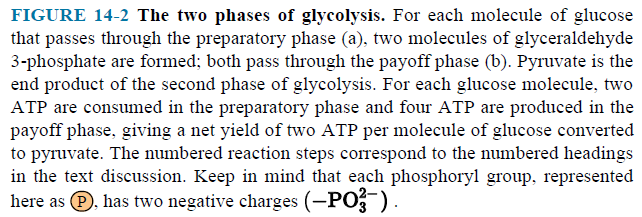


1. Phosphorylation of fructose 6-phosphate (1 ATP is used)
2. Cleavage of fructose 1,6-bisphosphate
3. Interconversion of the triose phosphates

(1 Glucose and 2 ATP are used) (2 glyceraldehyde 3-phosphate are produced)

* The last 5 of them constitute the payoff phase **(Fig. 14-2b).**





1. Oxidation and phosphorylation of glyceraldehyde 3-phosphate
2. Phosphoryl transfer from 1,3-bisphosphoglycerate

The formation of ATP by phosphoryl group transfer from a substrate such as1,3-bisphosphoglycerate is referred to as a **substrate-level phosphorylation**.

1. Conversion of 3-phosphoglycerate
2. Dehydration of 2-phosphoglycerate
3. Transfer of the phosphoryl group from phosphoenolpyruvate

A substrate-level phosphorylation occurs.

* The overall equation for glycolysis under aerobic conditions :

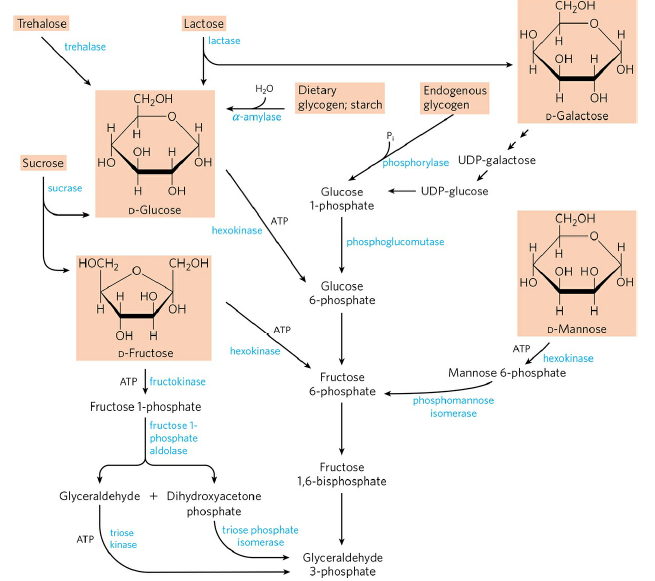
Glucose + 2NAD+ + 2ADP + 2Pi  2pyruvate + 2NADH + 2H+ + 2ATP + 2H2O

2 NADH (four electrons) will be used for synthesis of ATP.

* Glycolysis releases only a small fraction of the total available energy of the glucose molecule
* The two molecules of pyruvate still contain most of the chemical potential energy of glucose.
* Energy can be extracted by oxidative reactions in the citric acid cycle and oxidative phosphorylation.

**14. 2 Feeder Pathways for Glycolysis**

* The most significant are
* the storage polysaccharides : glycogen and starch
* the disaccharides : maltose, lactose and sucrose
* the monosaccharides : fructose, galactose and mannose
* Dietary polysaccharides and disaccharides undergo hydrolysis to monosaccharides.
* Endogenous glycogen and starch are degraded by phosphorolysis.
* Other monosaccharides enter the glycolytic pathway at several points (**Fig. 14-11)**.

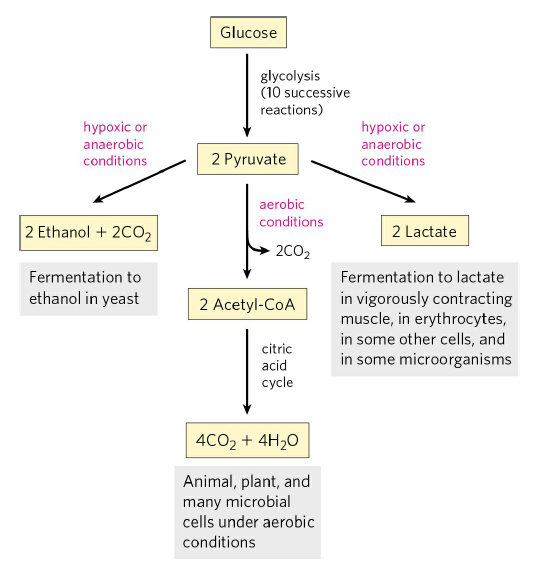


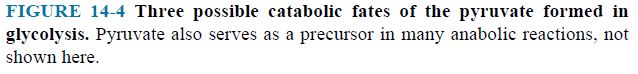


* The liver enzyme fructokinase catalyzes the phosphorylation of fructose at C-1 rather than C-6.

**14.3. Fates of Pyruvate under Anaerobic Conditions: Fermentation**

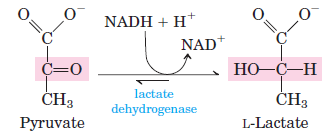
* There are three possible catabolic fates of the pyruvate formed in glycolysis **(Fig. 14-4)**.
* Under aerobic conditions, the pyruvate is oxidized to acetyl-CoA.
* Acetyl-CoA enters the citric acid cycle and is oxidized to CO2 and H2O.





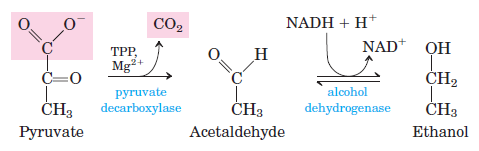
* Under hypoxic (low-oxygen) conditions,

1. Pyruvate is the terminal electron acceptor in lactic acid fermentation **(p. 563)**.



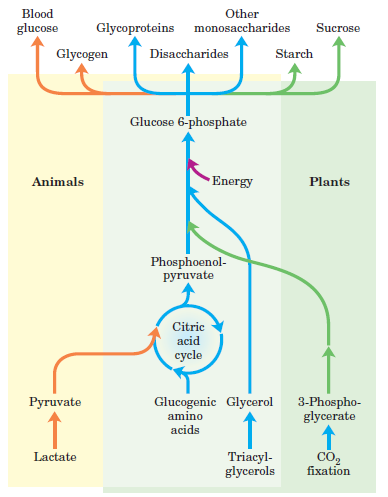
* Fermentation is the general term, which extracts energy (as ATP) but do not consume oxygen or change the concentrations of NAD+ or NADH.

1. Pyruvate is converted to ethanol and CO2 in a two-step process. Ethanol is the reduced product in alcohol fermentation.



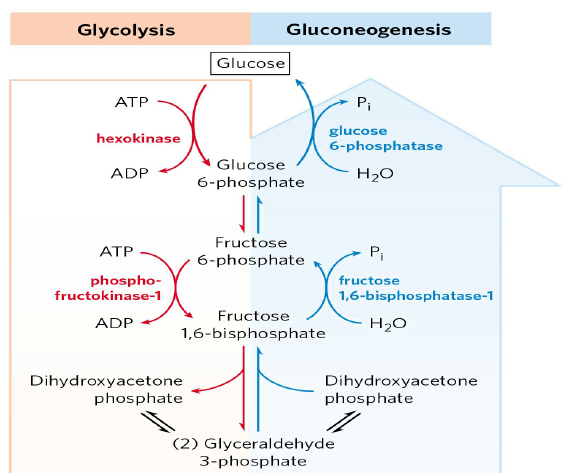
**14.4 Gluconeogenesis**

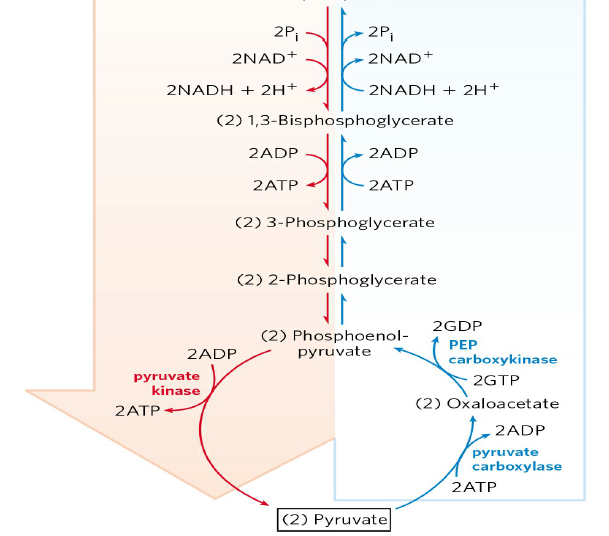
* The human brain alone requires over 120 g of glucose each day - more than half of all the glucose stored as glycogen in muscle and liver.
* Gluconeogenesis is the pathway for synthesis of glucose from simpler precursors **(Fig. 14–16)**.
* Gluconeogenesis occurs in all animals, plants, fungi and microorganisms.
* In mammals, gluconeogenesis takes place mainly in the liver.





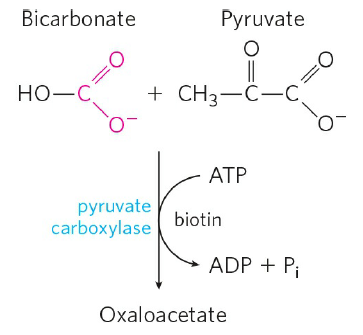
* The glucose produced passes into the blood to supply other tissues.
* Gluconeogenesis and glycolysis are not identical pathways running in opposite directions, although they do share several steps (**Fig. 14–17)**.
* 7 of the 10 enzymatic reactions of gluconeogenesis are the reverse of glycolytic reactions.
* Three reactions of glycolysis are essentially irreversible in vivo and cannot be used in gluconeogenesis.
* In gluconeogenesis, the three irreversible steps are bypassed by a separate set of enzymes.

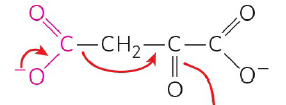






* In animals, both pathways occur largely in the cytosol.
* Conversion of pyruvate to phosphoenolpyruvate (PEP) requires enzymes in both the cytosol and mitochondria.
* Pyruvate is first transported from the cytosol into mitochondria or is generated from alanine within mitochondria.
* Then, **pyruvate carboxylase**, a mitochondrial enzyme that requires the coenzyme **biotin**, converts the pyruvate to oxaloacetate (**Fig. 14–18a)**.

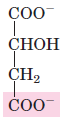




**FIGURE 14–18 a Synthesis of oxaloacetate from pyruvate.**

* Because the mitochondrial membrane has no transporter for oxaloacetate, before export to the cytosol the oxaloacetate must be reduced to malate by mitochondrial **malate dehydrogenase**.

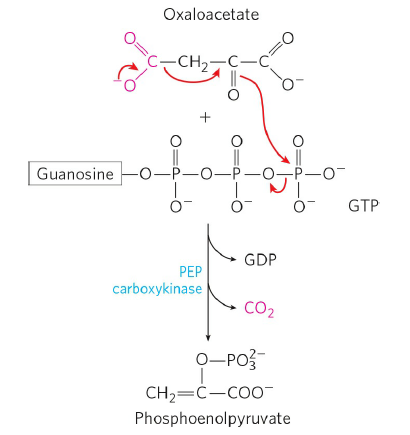
Oxaloacetate + NADH + H+ Malate + NAD+



* Malate leaves the mitochondrion through a specific transporter in the inner mitochondrial membrane and in the cytosol it is reoxidized to oxaloacetate.

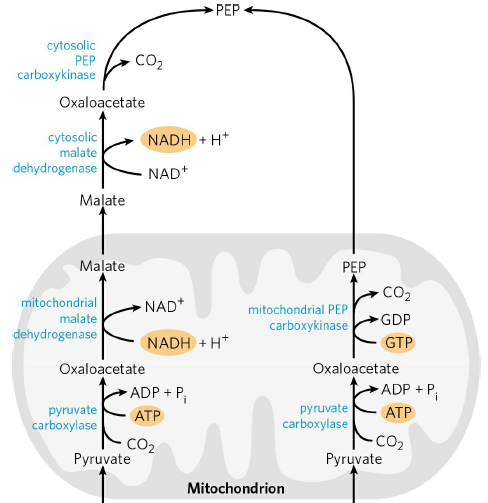
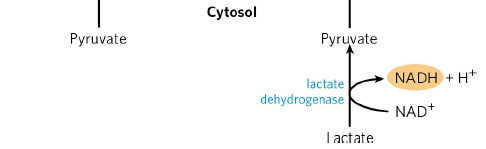
Malate + NAD+ Oxaloacetate + NADH + H+

* The oxaloacetate is then converted to PEP by **phosphoenolpyruvate carboxykinase (Fig. 14–18b)**.



**FIGURE 14–18 b Synthesis of phosphoenolpyruvate from oxaloacetate.**

* A second pyruvate PEP bypass predominates when lactate is the glucogenic precursor (**Fig. 14-20)**. This pathway makes use of lactate produced by glycolysis in erythrocytes or anaerobic muscle.



* After the pyruvate produced by the lactate dehydrogenase is transported into the mitochondrion, it is converted to oxaloacetate by pyruvate carboxylase.
* This oxaloacetate is converted directly to PEP by a mitochondrial isozyme of PEP carboxykinase, and the PEP is transported out of the mitochondrion to continue on the gluconeogenic path.
* Conversion of fructose 1,6-bisphosphate to fructose 6-phosphate is the second bypass.
* This reaction is catalyzed by **fructose 1,6-bisphosphatase (FBPase-1)**.

Fructose 1,6-bisphosphate + H2O fructose 6-phosphate + Pi

* Conversion of glucose 6-phosphate to glucose is the third bypass.
* This reaction is catalyzed by **glucose 6-phosphatase**.

Glucose 6-phosphate + H2O glucose + Pi

**Gluconeogenesis Is Energetically Expensive, but Essential**

* The sum of the biosynthetic reactions leading from pyruvate to free blood glucose is

2 Pyruvate + **4ATP** + **2GTP** + 2NADH + 2H+ + 4H2O

Glucose + 4ADP + 2GDP + 6Pi + 2NAD+

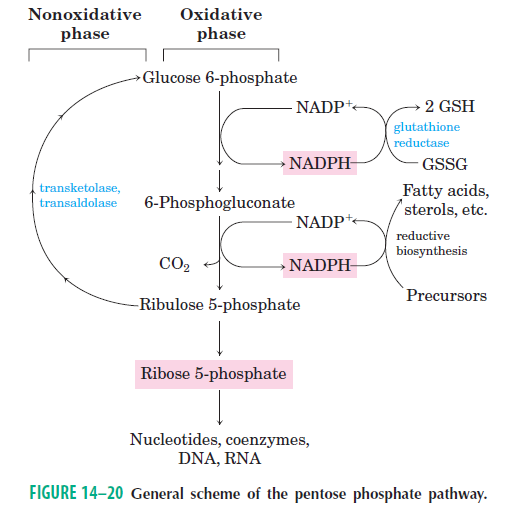
* Clearly, this equation is not simply the reverse of the equation for conversion of glucose to pyruvate by glycolysis. Remember

Glucose + 2ADP + 2Pi + 2NAD+ 2 pyruvate + **2ATP** + 2NADH + 2H+ + 2H2O

* Gluconeogenesis requires additional **2 ATP** and **2 GTP** molecules.

**14.5 Pentose Phosphate Pathway of Glucose Oxidation**

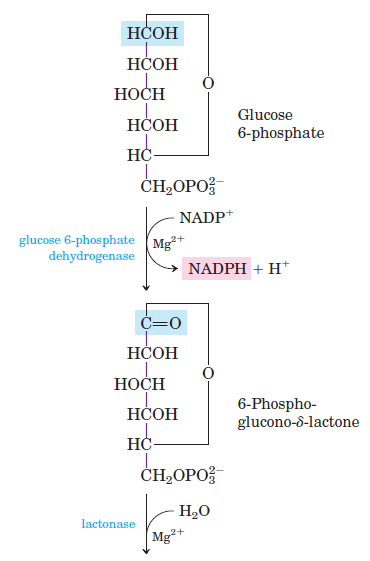
* Glucose 6-phosphate does have other catabolic fates.
* Oxidation of glucose 6-phosphate to pentose phosphates is occurred by the pentose phosphate pathway.
* In this oxidative pathway, NADP+ is the electron acceptor, yielding NADPH.
* Pentose phosphate and NADPH products are needed by the cell (**Fig. 14-20)**.

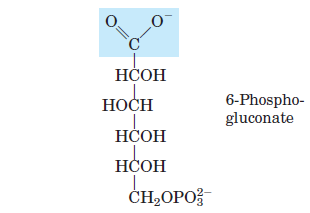


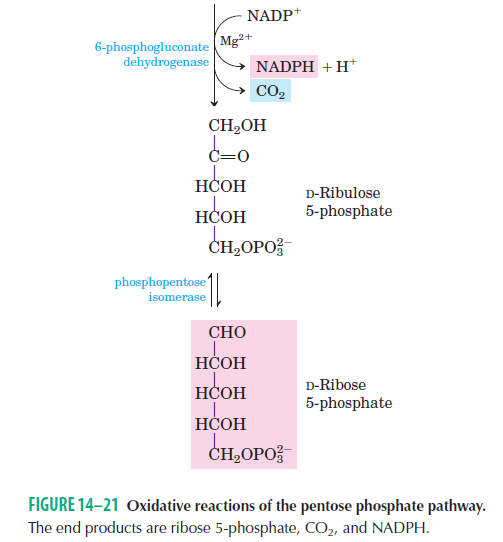
* All the enzymes in the pentose phosphate pathway are located in the cytosol.

**The Oxidative Phase Produces Pentose Phosphates and NADPH**

* The first reaction is the oxidation of glucose 6-phosphate to form 6-phosphoglucono-lactone **(Fig. 14–21)**.
* The lactone is hydrolyzed to 6-phosphogluconate.
* 6-phosphogluconate undergoes oxidation and decarboxylation to form ribulose 5-phosphate.
* Ribulose 5-phosphate is converted to ribose 5-phosphate.





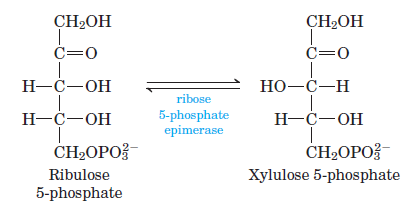


* Its overall equation is

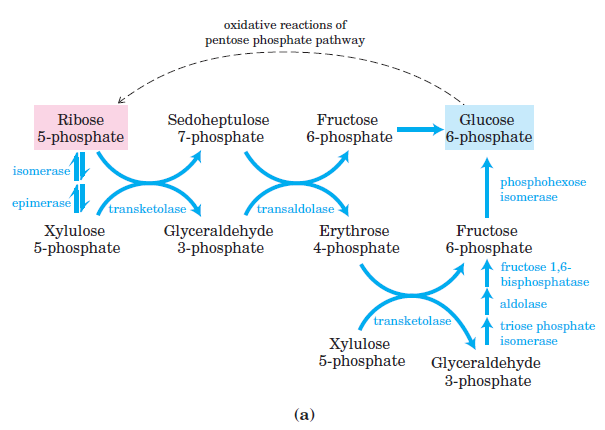
Glucose 6-phosphate + 2NADP+ + H2O ribose 5-phosphate + CO2 + 2NADPH + 2H+

**The Nonoxidative Phase Recycles Pentose Phosphates to Glucose 6-Phosphate**

* Ribulose 5-phosphate is epimerized to xylulose 5-phosphate.

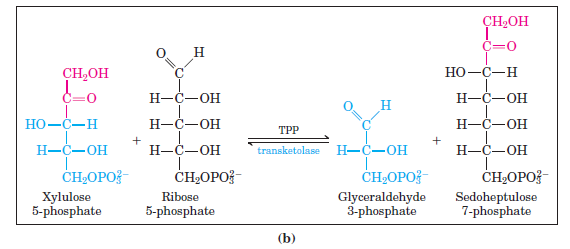


* Nonoxidative reactions are shown in **(Fig. 14-23a)**.



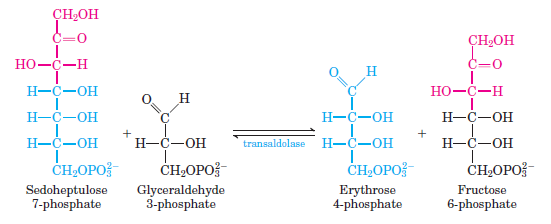


* Two pentose phosphates are converted to a triose phosphate and a seven-carbon sugar phosphate **(Fig. 14-24b)**.



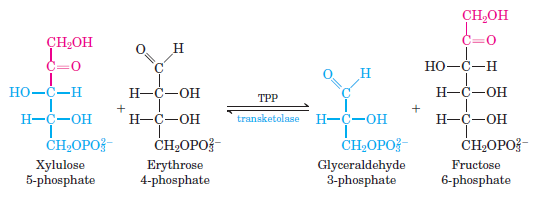


* Sedoheptulose 7-phosphate and glyceraldehyde 3-phosphate are converted to fructose 6-phosphate and erythrose 4-phosphate **(Fig. 14-25)**.





* Erythrose 4-phosphate and xylulose 5-phosphate are converted to fructose 6-phosphate and glyceraldehyde 3-phosphate **(Fig. 14-26)**.





**Glucose 6-Phosphate Is Partitioned between Glycolysis and the Pentose Phosphate Pathway**

* Entry of glucose 6-phosphate either into glycolysis or into the pentose phosphate pathway is largely determined by the relative concentrations of NADP+ and NADPH.
* Without this electron acceptor, the first reaction of the pentose phosphate pathway cannot proceed **(Fig. 14-27)**.

