PENTOSE PHOSPHATE PATHWAY

- In most animal tissues, the major catabolic fate of glucose 6-phosphate is glycolytic breakdown to pyruvate, much of which is then oxidized via the citric acid cycle, ultimately leading to the formation of ATP.

Other fate of Glucose-6-phosphate:

- Oxidation of glucose 6-phosphate to pentose phosphates by the **pentose phosphate pathway** (also called the **phosphogluconate pathway** or the **hexose monophosphate pathway/shunt**).
- Enzymes for **HMP** are located in Cytosol.
- Primary functions of the pathway:
  1. To provide NADPH for reductive biosynthesis.
  2. To provide ribose-5-phosphate for nucleotide and nucleic acid biosynthesis.
  3. Intermediates may be used to produce ATP.

- Rapidly dividing cells, such as those of bone marrow, skin, and intestinal mucosa, and those of tumors, use the pentose ribose 5-phosphate to make RNA, DNA, and such coenzymes as ATP, NADH, FADH2, and coenzyme A.

- ✓ In other tissues, the essential product of the pentose phosphate pathway is not the pentoses but the electron donor NADPH, needed for reductive biosynthesis or to counter the damaging effects of oxygen radicals.

- ✓ Tissues that carry out extensive fatty acid synthesis (liver, adipose, lactating mammary gland) or very active synthesis of cholesterol and steroid hormones (liver, adrenal glands, gonads) require the NADPH provided by this pathway.

- ✓ Erythrocytes and the cells of the lens and cornea are directly exposed to oxygen and thus to the damaging free radicals generated by oxygen. By maintaining a reducing atmosphere (a high ratio of NADPH to NADP and a high ratio of reduced to oxidized glutathione), such cells can prevent or undo oxidative damage to proteins, lipids, and other sensitive molecules.

Pentose Phosphate Pathway can be divided into two Phases:

1.Oxidative Phase

2. Non-oxidative Phase

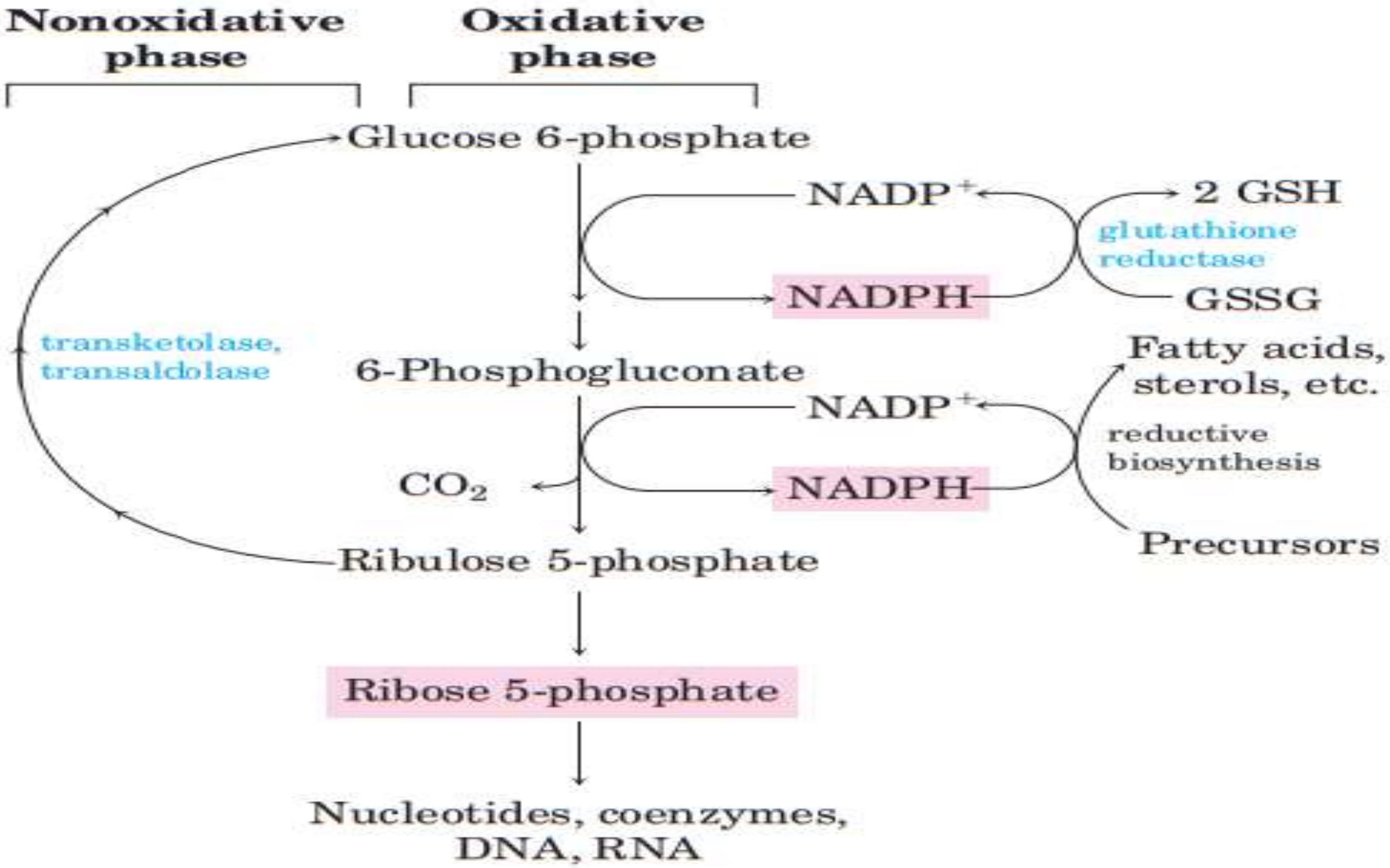


FIGURE 14–20 General scheme of the pentose phosphate pathway. NADPH formed in the oxidative phase is used to reduce glutathione, GSSG (see Box 14–4) and to support reductive biosynthesis. The other product of the oxidative phase is ribose 5-phosphate, which serves as a precursor for nucleotides, coenzymes, and nucleic acids. In cells that are not using ribose 5-phosphate for biosynthesis, the nonoxidative phase recycles six molecules of the pentose into five molecules of the hexose glucose 6-phosphate, allowing continued production of NADPH and converting glucose 6-phosphate (in six cycles) to CO_2.

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

- The first reaction of the pentose phosphate pathway , is the oxidation of glucose 6-phosphate by glucose 6-phosphate dehydrogenase (G6PD) to form 6-phosphoglucono--lactone, an intramolecular ester.

- NADP is the electron acceptor.

- The lactone is hydrolyzed to the free acid 6-phosphogluconate by a specific lactonase, then 6-phosphogluconate undergoes oxidation and decarboxylation by 6-phosphogluconate dehydrogenase to form the ketopentose ribulose 5-phosphate; the reaction generates a second molecule of NADPH.

- Phosphopentose isomerase converts ribulose 5-phosphate to its aldose isomer, ribose 5-phosphate. In some tissues, the pentose phosphate pathway ends at this point, and its overall equation is

$$\text{Glucose 6-phosphate} + 2\text{NADP}^+ + H_2O \longrightarrow \text{ribose 5-phosphate} + CO_2 + 2\text{NADPH} + 2H^+$$

- The net result is the production of NADPH, a reductant for biosynthetic reactions, and ribose 5-phosphate, a precursor for nucleotide synthesis.

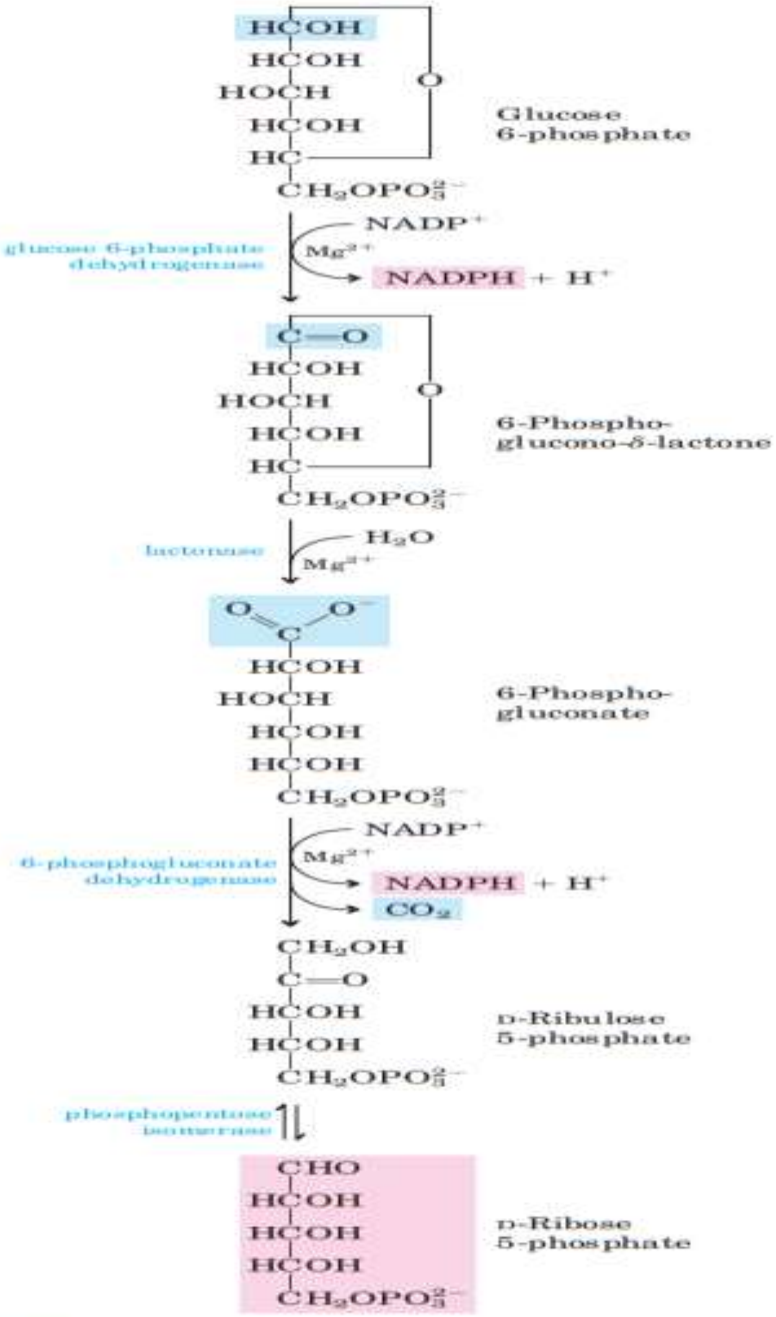


FIGURE 14–21 Oxidative reactions of the pentose phosphate pathway. The end products are ribose 5-phosphate, CO_2, and NADPH.

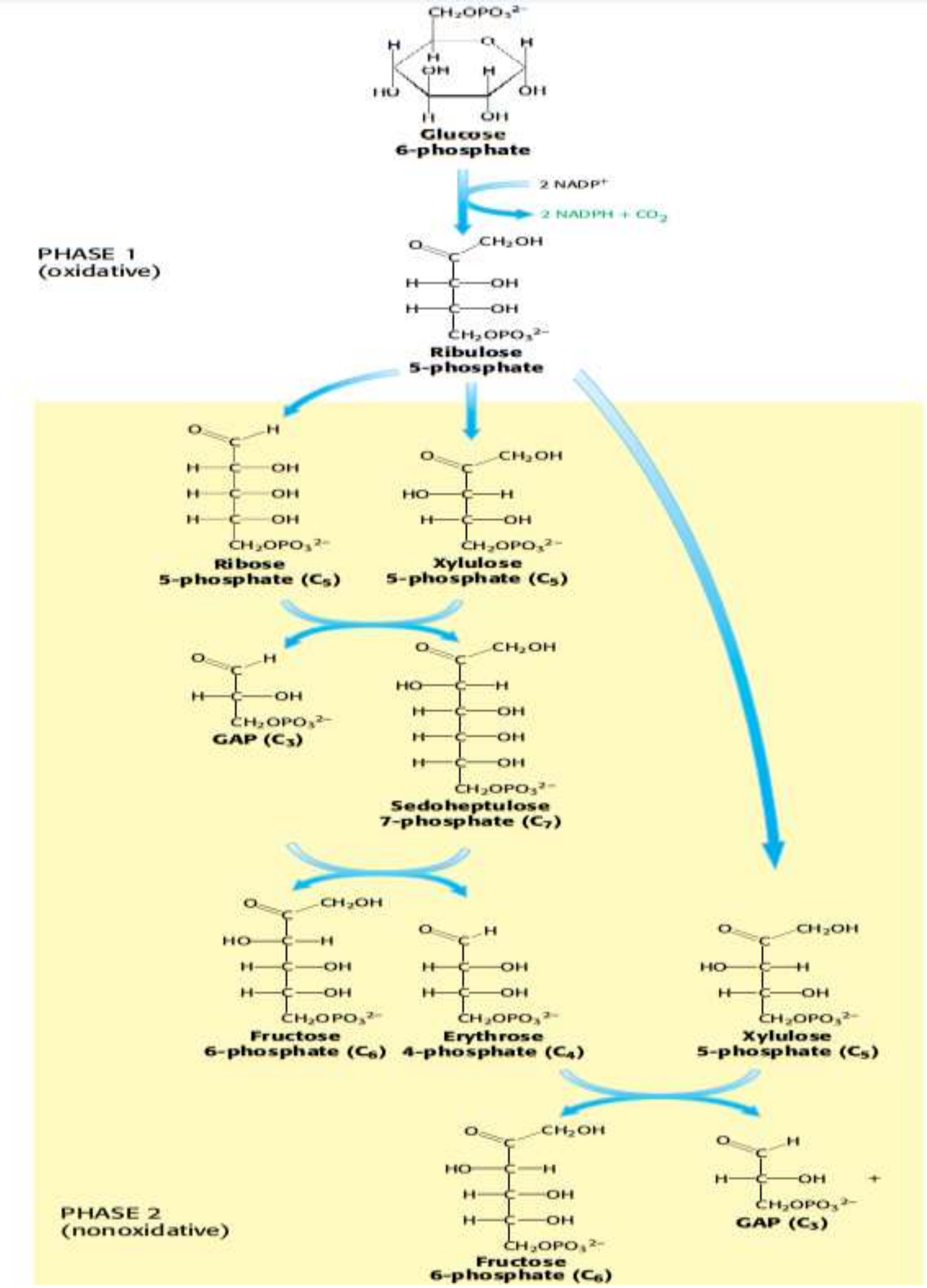


FIGURE 20.18 Pentose phosphate pathway. The pathway consists of (1) an oxidative phase that generates NADPH and (2) a nonoxidative phase that interconverts phosphorylated sugars.

THE NON-OXIDATIVE PHASE

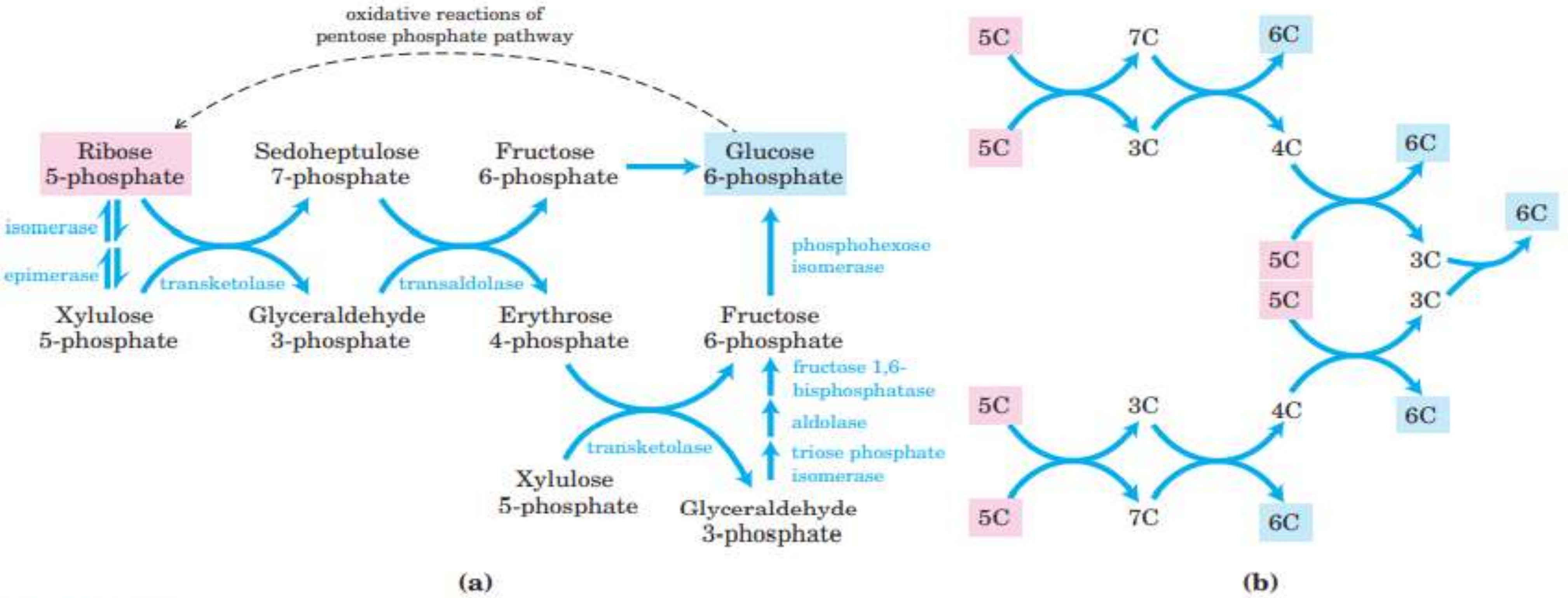
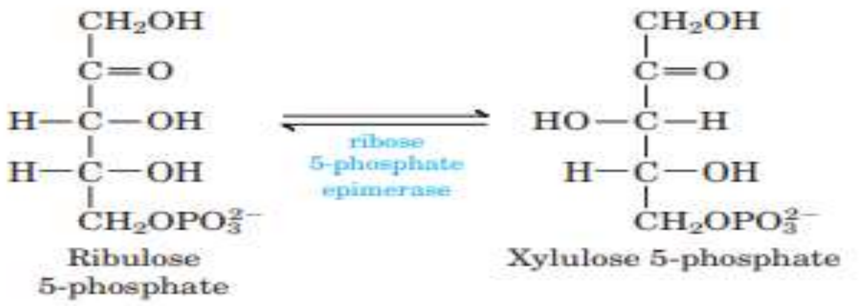


FIGURE 14–22 Nonoxidative reactions of the pentose phosphate pathway. (a) These reactions convert pentose phosphates to hexose phosphates, allowing the oxidative reactions (see Fig. 14–21) to continue. Transketolase and transaldolase are specific to this pathway; the other enzymes also serve in the glycolytic or gluconeogenic pathways. **(b)** A schematic diagram showing the pathway from six pentoses (5C) to five hexoses (6C). Note that this involves two sets of the interconversions shown in **(a)**. Every reaction shown here is reversible; unidirectional arrows are used only to make clear the direction of the reactions during continuous oxidation of glucose 6-phosphate. In the light-independent reactions of photosynthesis, the direction of these reactions is reversed (see Fig. 20–10).

- The **Nonoxidative Phase Recycles Pentose Phosphates to Glucose 6-Phosphate.**
- In tissues that require primarily NADPH, the pentose phosphates produced in the oxidative phase of the pathway are recycled into glucose 6-phosphate.
- In this nonoxidative phase, ribulose 5-phosphate is first epimerized to xylulose 5-phosphate:



- Then, in a series of rearrangements of the carbon skeletons, six five-carbon sugar phosphates are converted to five six-carbon sugar phosphates, completing the cycle and allowing continued oxidation of glucose 6-phosphate with production of NADPH.

- Continued recycling leads ultimately to the conversion of glucose 6-phosphate to six CO2.

- Two enzymes unique to the pentose phosphate pathway act in these interconversions of sugars: transketolase and transaldolase.

- Transketolase catalyzes the transfer of a two-carbon fragment from a ketose donor to an aldose acceptor.

- In its first appearance in the pentose phosphate pathway, transketolase transfers C-1 and C-2 of xylulose 5-phosphate to ribose 5-phosphate, forming the seven-carbon product sedoheptulose 7-phosphate. The remaining three-carbon fragment from xylulose is glyceraldehyde 3-phosphate.

- Next, transaldolase catalyzes a reaction similar to the aldolase reaction of glycolysis: a three-carbon fragment is removed from sedoheptulose 7-phosphate and condensed with glyceraldehyde 3-phosphate, forming fructose 6-phosphate and the tetrose erythrose 4-phosphate.

- Now transketolase acts again, forming fructose 6-phosphate and glyceraldehyde 3-phosphate from erythrose 4-phosphate and xylulose 5-phosphate.

- Two molecules of glyceraldehyde 3-phosphate formed by two iterations of these reactions can be converted to a molecule of fructose 1,6- bisphosphate as in gluconeogenesis, and finally FBPase-1 and phosphohexose isomerase convert fructose 1,6-bisphosphate to glucose 6-phosphate.

- Overall, six pentose phosphates have been converted to five hexose phosphate.

Summary of Pentose Phosphate Pathway of Glucose Oxidation:

■ The oxidative pentose phosphate pathway (phosphogluconate pathway, or hexose monophosphate pathway) brings about oxidation and decarboxylation at C-1 of glucose 6-phosphate, reducing NADP to NADPH and producing pentose phosphates.

■ NADPH provides reducing power for biosynthetic reactions, and ribose 5-phosphate is a precursor for nucleotide and nucleic acid synthesis. Rapidly growing tissues and tissues carrying out active biosynthesis of fatty acids, cholesterol, or steroid hormones send more glucose 6-phosphate through the pentose phosphate pathway than do tissues with less demand for pentose phosphates and reducing power.

■ The first phase of the pentose phosphate pathway consists of two oxidations that convert glucose 6-phosphate to ribulose 5-phosphate and reduce NADP to NADPH. The second phase comprises nonoxidative steps that convert pentose phosphates to glucose 6-phosphate, which begins the cycle again.

■ In the second phase, transketolase and transaldolase catalyze the interconversion of three-, four-, five-, six-, and seven-carbon sugars, with the reversible conversion of six pentose phosphates to five hexose phosphates. In the carbon-assimilating reactions of photosynthesis, the same enzymes catalyze the reverse process, the reductive pentose phosphate pathway: conversion of five hexose phosphates to six pentose phosphates.

■ 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.