Pentose Phosphate Pathway (PPP)
Hexose Monophosphate (Shunt)

- It is an alternative pathway for the metabolism of glucose that can be divided into two phases.
  i. An oxidative nonreversible phase, in which glucose 6-phosphate undergoes dehydrogenation and decarboxylation to yield ribulose 5-phosphate.
  ii. A non-oxidative reversible phase, in which ribulose 5-phosphate is converted back to glucose 6-phosphate by a series of reactions involving mainly two enzymes: transketolase and transaldolase.

- Carbon 1 of glucose 6-phosphate is released as CO₂, and two NADPH are produced for each glucose 6-phosphate entering the oxidative part of the pathway.
- No ATP is directly consumed or produced in the reactions.
- The pentose phosphate pathway occurs in the cytosol.

Metabolic functions of PPP:
1. The pathway provides a major portion of the body’s NADPH, which functions as a biochemical reductant for synthesis of fatty acids and steroids.
2. It also produces ribose 5-phosphate, required for the biosynthesis of nucleotides, and provides a mechanism for the metabolic use of five-carbon sugars obtained from the diet or the degradation of structural carbohydrates in the body.

Reactions of HMP Shunt

A) Irreversible Oxidative Reactions
The oxidative portion of the pentose phosphate pathway consists of three reactions that lead to the formation of ribulose 5-phosphate, CO₂, and two molecules of NADPH for each molecule of glucose 6-phosphate oxidized. This portion of the pathway is particularly important in the
  i. liver, lactating mammary glands, and adipose, which are active in the NADPH-dependent biosynthesis of fatty acids
  ii. testes, ovaries, placenta and adrenal cortex, which are active in the NADPH-dependent biosynthesis of steroid hormones
  iii. erythrocytes, which require NADPH to keep glutathione reduced.
Figure 20-2. The pentose phosphate pathway.

The pentose phosphate pathway. (\(\text{PO}_4^{3-}\); PRPP, 5-phosphoribosyl 1-pyrophosphate.)
1. **Dehydrogenation of glucose 6-phosphate**

   The pathway is regulated primarily at the G6PD reaction.

   **a. NADPH** is a potent competitive inhibitor of the enzyme
   
   - Under most metabolic conditions, the ratio of NADPH/NADP⁺ is sufficiently high to substantially inhibit enzyme activity.
   - However, increased demand for NADPH decreases the ratio of NADPH/NADP⁺ and flux through the cycle increases in response to the enhanced activity of G6PD.

   **b. Insulin** upregulates expression of the gene for G6PD, and flux through the pathway increases in the well-fed state.

2. **Formation of ribulose 5-phosphate**

   6-Phosphogluconolactone is hydrolyzed by 6-phosphogluconolactone hydrolase. The **oxidative decarboxylation** of 6-phosphogluconate is catalyzed by 6-phosphogluconate dehydrogenase and produces ribulose 5-phosphate, CO₂ (from carbon 1 of glucose), and a second molecule of NADPH.

**B. Reversible Non-oxidative Reactions**

   - These reactions occur in all cells synthesizing nucleotides and nucleic acids.
   - These reactions catalyze the interconversion of sugars containing three to seven carbons. These reversible reactions permit ribulose 5-phosphate (produced by the oxidative portion of the pathway) to be converted either to ribose 5-phosphate (needed for nucleotide synthesis) or to intermediates of glycolysis—fructose 6-phosphate and glyceraldehyde 3-phosphate.
   - Therefore, PPP is not an isolated cycle; but is integrated with glycolysis.

**Relationship between glycolysis and PPP**

   **a. Conversion of pentose phosphate to intermediates of glycolysis**
   
   - Cells that carry out reductive biosynthetic reactions have a greater need for NADPH than for ribose 5-phosphate.
   - In this case, *transketolase* (which transfers two-carbon units in a TPP-requiring reaction) and *transaldolase* (which transfers three-carbon units) convert the ribulose 5-P produced as an end product of the oxidative reactions to glyceraldehyde 3-P and fructose 6-P that are intermediates of glycolysis.

   **b. Conversion of glycolysis intermediates to pentose phosphate**

   - In contrast, under conditions in which the demand for ribose for incorporation into nucleotides and nucleic acids is greater than the need for NADPH, the non-oxidative reactions can provide the biosynthesis of ribose 5-phosphate from glyceraldehyde 3-phosphate and fructose 6-phosphate in the absence of the oxidative steps.
The PPP compared with glycolysis
Although glucose 6-phosphate is common to both pathways, the pentose phosphate pathway is markedly different from glycolysis.
1. PPP oxidation utilizes NADP rather than NAD
2. CO2, which is not produced in glycolysis, is a characteristic product of PPP.
3. No ATP is generated in the PPP, whereas ATP is a major product of glycolysis

Metabolic Uses of NADPH
A. Reductive biosynthesis
   ▪ Like NADH, NADPH can be considered as a high-energy molecule. However, the electrons of NADPH are destined for use in reductive biosynthesis, rather than for transfer to oxygen as is the case with NADH.
   ▪ Thus, in the metabolic transformations of the PPP, part of the energy of glucose 6-P is conserved in NADPH that can be used as a source of electrons for the biosynthesis of fatty acids, cholesterol and steroidal hormones.

B. Reduction of hydrogen peroxide
   ▪ Hydrogen peroxide is one of a family of reactive oxygen species (ROS) that are formed from the partial reduction of molecular oxygen.
   ▪ These compounds are formed continuously as by-products of aerobic metabolism as well as through reactions with drugs and environmental toxins.
   ▪ These highly reactive oxygen intermediates can cause serious damage to DNA, proteins, and unsaturated lipids, and can lead to cell death.
   ▪ ROS have been implicated in a number of pathologic processes, including cancer, inflammatory disease, and aging.

The cell has several protective mechanisms that minimize the toxic potential of these compounds.

i- Enzymes that catalyze antioxidant reactions
   ▪ Reduced glutathione, a tripeptide-thiol (γ-glutamylcysteinylglycine) present in most cells, can detoxify hydrogen peroxide in a reaction, catalyzed by glutathione peroxidase, forming oxidized glutathione, which no longer has protective properties.
   ▪ Cells regenerate reduced glutathione in a reaction catalyzed by glutathione reductase, using NADPH as a source of reducing equivalents.
Thus, NADPH indirectly provides electrons for the reduction of hydrogen peroxide. [Note: Erythrocytes are totally dependent on the pentose phosphate pathway for their supply of NADPH because, unlike other cell types, erythrocytes do not have an alternate source for this essential coenzyme].

- Additional enzymes, such as superoxide dismutase and catalase, catalyze the conversion of other toxic oxygen intermediates to harmless products.

**ii- Antioxidant chemicals**

- A number of intracellular reducing agents, such as ascorbate, vitamin E, and β-carotene, can reduce and, thus, detoxify oxygen intermediates.
- Consumption of foods rich in these antioxidant compounds has been correlated with a reduced risk for certain types of cancers, as well as decreased frequency of certain other chronic health problems.

**C. Cytochrome P450 monooxygenase system**

- Monooxygenases (mixed function oxidases) incorporate one atom from molecular oxygen into a substrate (creating a hydroxyl group), with the other atom being reduced to water.
- The cytochrome P450 monooxygenase system uses NADPH to provide the required reducing equivalents.
- The overall reaction catalyzed by a cytochrome P450 enzyme is:
  \[ \text{R-H + O}_2 + \text{NADPH + H}^+ \rightarrow \text{R-OH + H}_2\text{O + NADP}^+ \]
  where R may be a steroid, drug, or other chemical.

**D. Synthesis of nitric oxide (NO)**

- NO is a mediator in a broad array of biologic systems.
- NO is the endothelium-derived relaxing factor, which causes vasodilation by relaxing vascular smooth muscle.
- NO also acts as a neurotransmitter, prevents platelet aggregation, and plays an essential role in macrophage function.

**Glucose 6-P Dehydrogenase Deficiency**

- G6PD deficiency is an X-linked inherited disease characterized by hemolytic anemia caused by the inability to detoxify oxidizing agents.
- G6PD deficiency has the highest prevalence in the Middle East, tropical Africa and Asia, and parts of the Mediterranean.
- Note: G6PD deficiency also can induce neonatal jaundice appearing 1–4 days after birth that results from increased production of unconjugated bilirubin.
- The life span of individuals with a severe form of G6PD deficiency may be somewhat shortened as a result of complications arising from chronic hemolysis.
This negative effect of G6PD deficiency has been balanced in evolution by an advantage in survival—an increased resistance to falciparum malaria shown by female carriers of the mutation.

A. Role of G6PD in red blood cells
- Diminished G6PD activity impairs the ability of the cell to form the NADPH that is essential for detoxification of free radicals and peroxides formed within the cell.
- Glutathione also helps maintain the reduced states of sulfhydryl groups in proteins, including hemoglobin. Oxidation of those sulfhydryl groups leads to the formation of denatured proteins that form insoluble masses (called Heinz bodies) that attach to the red cell membranes.
- Although G6PD deficiency occurs in all cells, it is most severe in erythrocytes, where the PPP provides the only source for NADPH.
- Other tissues have alternative sources for NADPH production (such as NADP+-dependent malate dehydrogenases), that can keep glutathione reduced.
- The erythrocyte has no nucleus or ribosomes and cannot renew its supply of the enzyme. Thus, red blood cells are particularly vulnerable to enzyme variants with diminished stability.

B. Precipitating factors in G6PD deficiency
Most individuals who have inherited one of the many G6PD mutations do not show clinical manifestations, that is, they are asymptomatic. However, some patients with G6PD deficiency develop hemolytic anemia if they are treated with an oxidant drug, ingest fava beans, or contract a severe infection.

1. Oxidant drugs: Commonly used drugs that produce hemolytic anemia in patients with G6PD deficiency are best remembered from the reminder AAA—Antibiotics (for example, sulfamethoxazole and chloramphenicol), Antimalarials (for example, primaquine but not quinine), and Antipyretics (for example, acetanilide but not acetaminophen).
2. **Favism:** Some forms of G6PD deficiency, for example the Mediterranean variant, are particularly susceptible to the hemolytic effect of the fava (broad) bean, a dietary staple in the Mediterranean region. Favism, the hemolytic effect of ingesting fava beans, is not observed in all individuals with G6PD deficiency, but all patients with favism have G6PD deficiency.

3. **Infection:** Infection is the most common precipitating factor of hemolysis in G6PD deficiency. The inflammatory response to infection results in the generation of free radicals in macrophages, which can diffuse into the red blood cells and cause oxidative damage.