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Pentose phosphate pathway

Pentose phosphate pathway

The pentose phosphate pathway or Hmp shunt or Worburg-Lipman pathway or Phosphogluconate pathway is a **semi-independent alternative pathway that parallels glycolysis.**

It **generates the reducing agent reduced nicotinamide adenine dinucleotide phosphate (NADPH),** which is independent of the NADH of oxidative phosphorylation, and pentoses.

There are **two distinct phases** in the pentose phosphate shunt.

The first is the **oxidative phase**, in which NADPH is generated, and the **second is the synthesis of 5-carbon sugars.**

The primary purpose of this alternative pathway is the **generation of reducing equivalents, in the form of NADPH, used in reductive biosynthesis within cells, such as fatty acid synthesis.**

Production of **ribose-5-phosphate used** in the **synthesis of nucleotides or RNA and production** of **erythrose-4-phosphate** are used in the **synthesis of aromatic amino acids.**

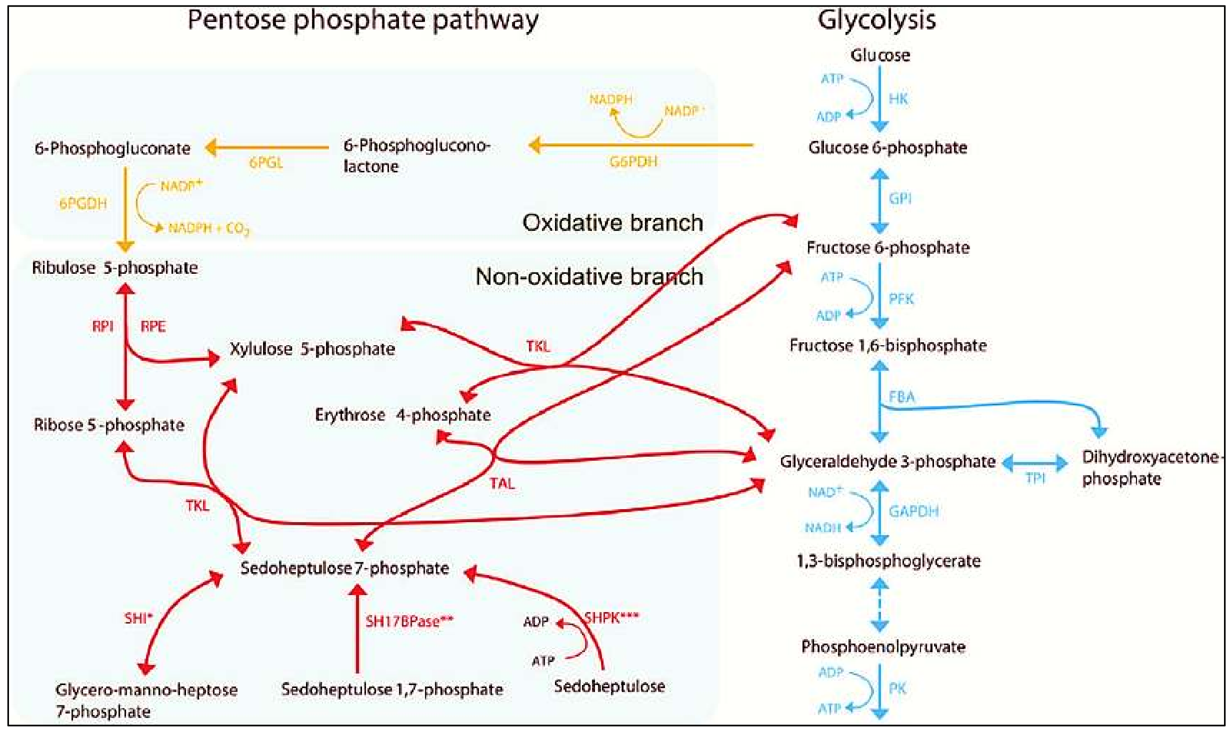
In humans and mammals, the pentose phosphate shunt occurs exclusively **in the cytoplasm of cells, and is found to be most active in the liver, mammary gland, and adrenal cortex.**

Occurrences

It occurs in **adrenal cortex, testes, liver, adipose tissues, lactating mammary glands, leucocytes and in mature RBCs.** The reaction occurs in **cytosol** of cells.

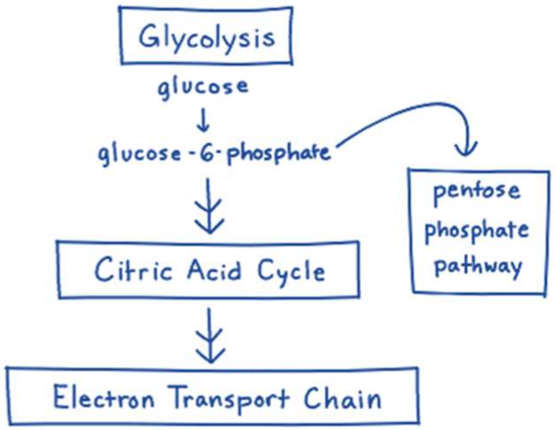
Discovery

The discovery in 1931-1935 by the German biochemist, **Otto Warburg, of the oxidative division of the pathway** and of the chemistry and role of a new pyridine nucleotide co-enzyme in its reactions is delineated.



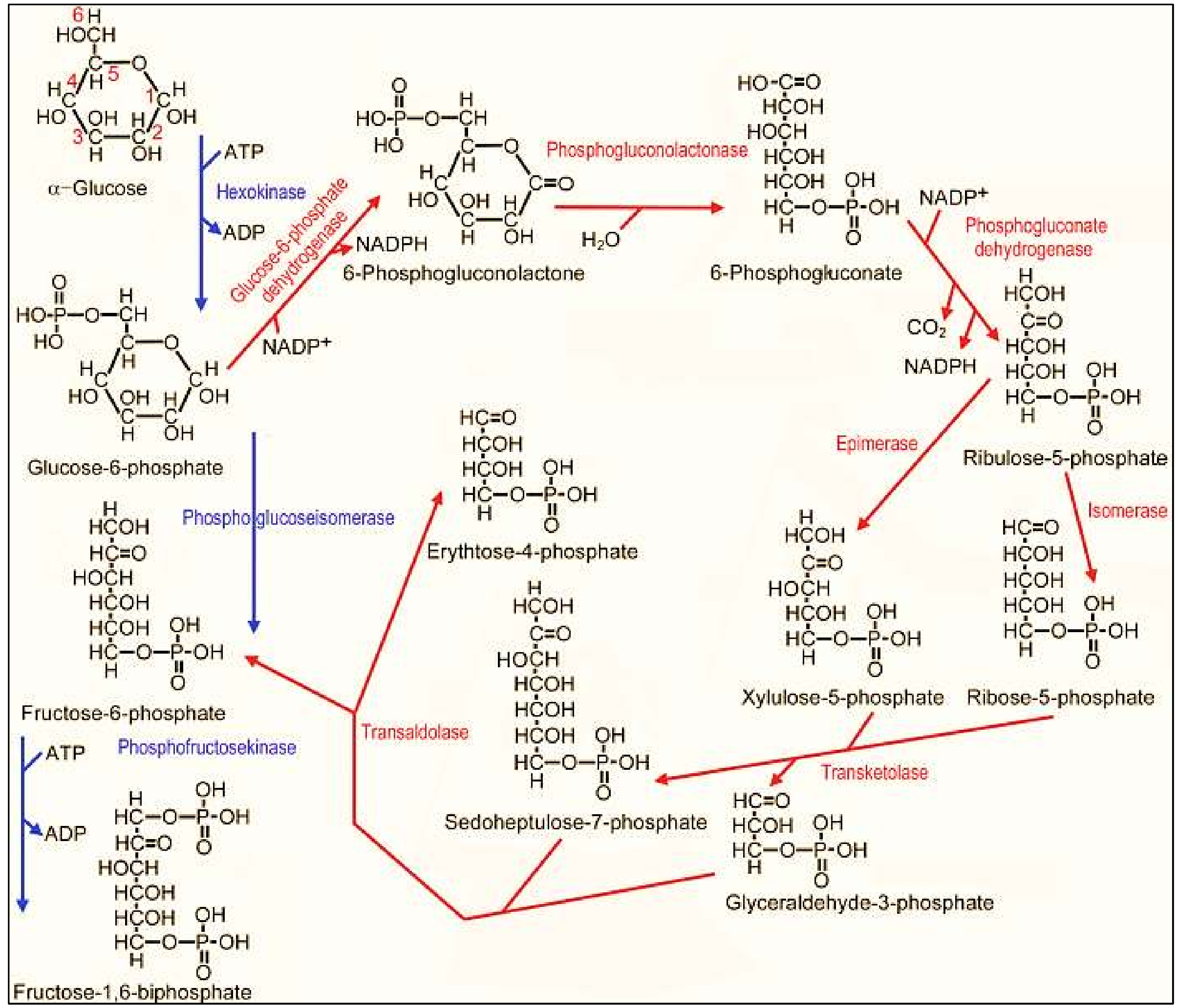
Why it is known as HMP Shunt?

- The HMP shunt is an **alternative pathway to glycolysis and is used to produce ribose-5-phosphate and nicotinamide adenine dinucleotide phosphate (NADPH).**
- It is called shunt because the **pathway allows for carbon atoms from glucose 6-phosphate to take a brief detour (a shunt) before they proceed down the Embden–Meyerhof (glycolytic) pathway.**
- A 6-carbon sugar, glucose, may enter the glycolytic pathway or enter the alternative HMP shunt **depending on the cell's individual needs at the time.**
- The HMP shunt pathway is **under the regulation of the demands of NADPH in the respective tissue.**
- The **rate-limiting enzyme is G6PD** and has **allosteric inhibition directed by the presence of NADPH and allosteric activation via the presence of NADP+.**
- Consequently, the **activity of G6PD activity also increases in a fed state** with a high carbohydrate diet, and conversely, **decreases in a starving or a diabetic state.**

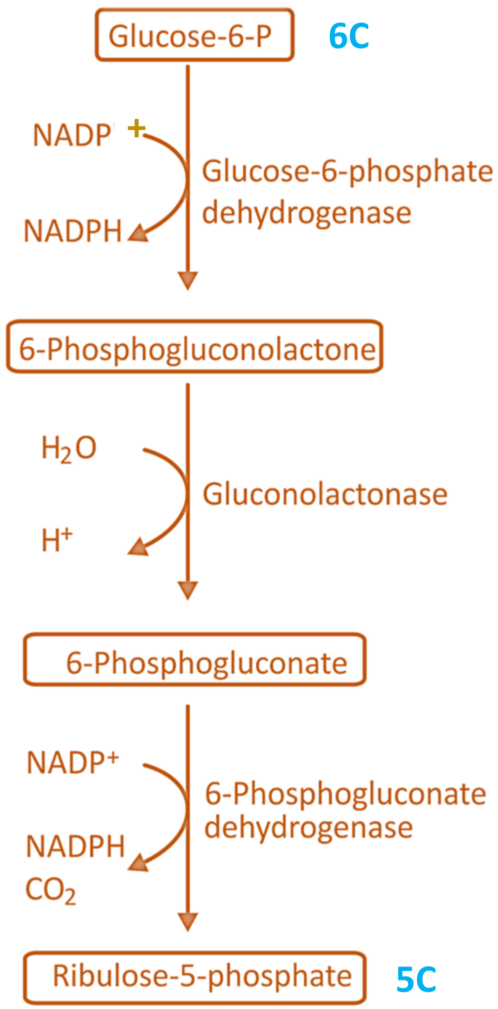


Overall reaction

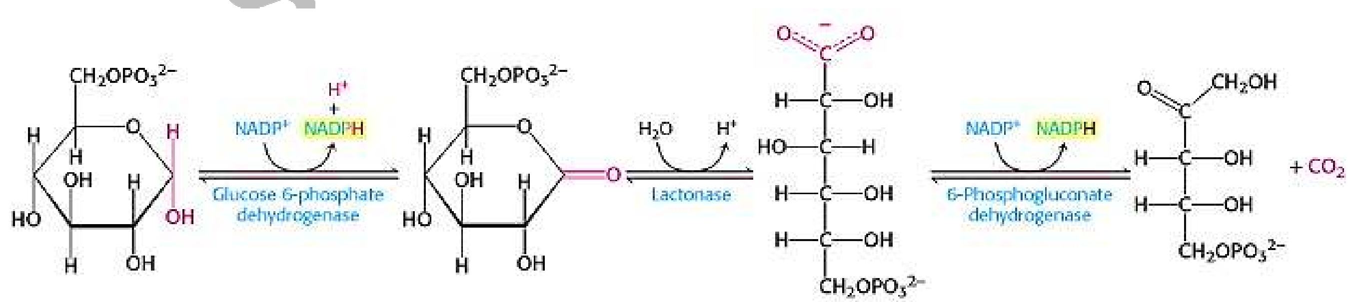
- A series of reactions, broken down into the **oxidative (irreversible) and non-oxidative phases (reversible).**
- The **oxidative phase** is responsible for **converting the intermediate glucose-6-phosphate to 6-phosphogluconate, using the glucose-6-phosphate dehydrogenase (G6PD) enzyme.** The **by-product** of this reaction is the important molecule **NADPH.** 6-phosphogluconate then converts **into ribulose-5-phosphate,** and NADPH gets produced again as a by-product.
- The **non-oxidative phase** of the HMP shunt involves the **conversion of ribulose-5-phosphate to ribose-5-phosphate (R-5-P) through a series of independent reactions. R-5-P** in this reaction can be **returned to the glycolytic pathway as fructose-6-phosphate**



Oxidative Phase (irreversible)



- **Glucose-6-phosphate is oxidized** to form 6 phospho gluconolactone with the help of G6PD.
- NADPH is produced as a byproduct of this reaction as **NADP+ is reduced as glucose-6-phosphate is oxidized.**
- Following the oxidation of glucose-6-phosphate, another reaction, **catalyzed by a gluconolactonase, uses water to form 6-phosphogluconate.**
- Next, 6-phosphogluconate converts into ribulose-5-phosphate with the help of 6-phosphogluconate dehydrogenase. In t his reaction, a **carbon is removed (cleaved) and CO2 is released.**
- Once again, **the electrons released from this cleavage is used to reduce NADP+ to NADPH.**



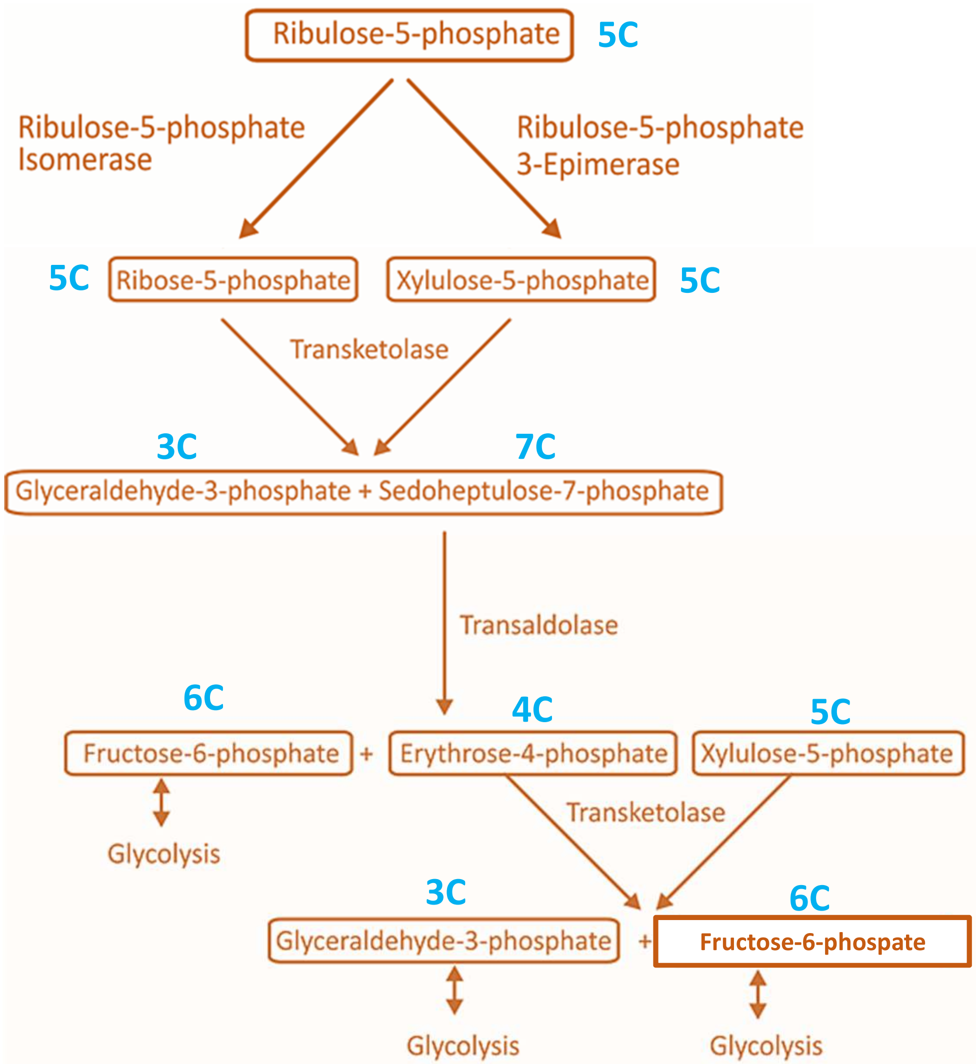
Glucose 6-phosphate

6-Phosphoglucono-δ-lactone

6-Phospho-gluconate

Ribulose 5-phosphate

Non-oxidative phase



- In the **nonoxidative phase**, the pathway catalyzes the interconversion of **three-, four-, five-, six-, and seven-carbon sugars** in a series of nonoxidative reactions that can result in the **synthesis of five-carbon sugars for nucleotide biosynthesis or the conversion of excess five-carbon sugars into intermediates of the glycolytic pathway.**
- All these reactions take place in the **cytosol.**

The Pentose Phosphate Pathway and Glycolysis Are Linked by Transketolase and Transaldolase

In these cases, ribose 5-phosphate is converted into glyceraldehyde 3-phosphate and fructose 6-phosphate by transketolase and transaldolase.

These enzymes create a **reversible link** between the pentose phosphate pathway and glycolysis by catalyzing these three successive reactions.

$$C_5 + C_5 \xrightleftharpoons{\text{Transketolase}} C_3 + C_7$$

$$C_3 + C_7 \xrightleftharpoons{\text{Transketolase}} C_6 + C_4$$

$$C_4 + C_5 \xrightleftharpoons{\text{Transketolase}} C_6 + C_3$$

The net result is the formation of two hexoses and one triose from three pentoses:

$$3\,C_5 \rightleftharpoons 2\,C_6 + C_3$$

Steps involved in non-oxidative phase

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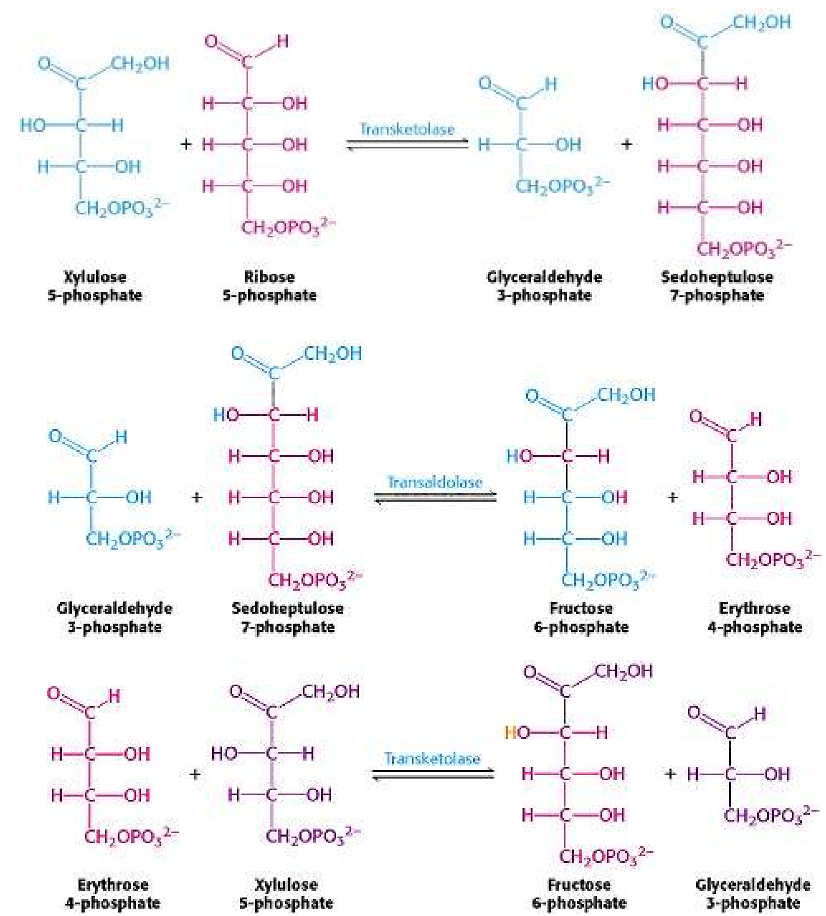
Ribulose-5-phosphate converts into ribose-5-phosphate with the help of ribulose-5-phosphate or Ribulose-5-phosphate converts into Xylulose-5-phosphate with the help of Ribulose-5-phosphate epimerase.

- The first reaction linking the pentose phosphate pathway and glycolysis is the **formation of glyceraldehyde 3-phosphate and sedoheptulose 7-phosphate from two pentoses with the help of transketolase.**
- Glyceraldehyde 3-phosphate and sedoheptulose 7-phosphate react **to form fructose 6-phosphate and erythrose 4-phosphate with the help of transaldolase.**
- Next, **transketolase catalyzes the synthesis of fructose 6-phosphate and glyceraldehyde 3-phosphate from erythrose 4-phosphate and xylulose 5-phosphate.**
- Both transketolase and transaldolase needs **Mg++ and TPP.**



Reactions of Pentose phosphate pathway

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Reaction	Enzyme
Oxidative phase	
Glucose 6-phosphate + NADP$^+$ → 6-phosphoglucono-δ-lactone + NADPH + H^+	Glucose 6-phosphate dehydrogenase
6-Phosphoglucono-δ-lactone + H_2O → 6-phosphogluconate + H^+	Lactonase
6-Phosphogluconate + NADP$^+$ → ribulose 5-phosphate + CO_2 + NADPH	6-Phosphogluconate dehydrogenase
Nonoxidative Phase	
Ribulose 5-phosphate ⇌ ribose 5-phosphate	Phosphopentose isomerase
Ribulose 5-phosphate ⇌ xylulose 5-phosphate	Phosphopentose epimerase
Xylulose 5-phosphate + ribose 5-phosphate ⇌ sedoheptulose 7-phosphate + glyceraldehyde 3-phosphate	Transketolase
Sedoheptulose 7-phosphate + glyceraldehyde 3-phosphate ⇌ fructose 6-phosphate + erythrose 4-phosphate	Transaldolase
Xylulose 5-phosphate + erythrose 4-phosphate ⇌ fructose 6-phosphate + glyceraldehyde 3-phosphate	Transketolase

Importance of pentose phosphate pathway

- Alternative pathway of carbohydrate metabolism which is **independent of glycolysis and TCA cycle.**
- The importance of the HMP shunt is **R-5-P and NADPH molecules** that generated in the reaction.
- **R-5-P undergoes a series of reactions to create the different ribose sugars that comprise the DNA and RNA molecules**, required to carry genetic information.
- Moreover, **R-5-P also converts into erythrose-4-phosphate for the synthesis of aromatic amino acids**. As such, this pathway is an essential source of these ribose sugars.
- **NADPH** is also an important molecule as it has a plethora of functions throughout the body. It **takes part in anabolism processes such as that of synthesis steroids and fatty acids.**
- NADPH is also important in the **respiratory burst process**, an essential component of the immune response within phagolysosomes. The NADPH is **used to reduce oxygen into an oxygen radical that converts into hydrogen peroxide**, which in turn, transforms into bleach. Bleach in the phagolysosomes is introduced to offending pathogens to cause death.
- **NADPH is also required to reduce the molecule glutathione**. Using glutathione reductase and NAPDH, oxidized glutathione is converted into its reduced form, and can detoxify free radicals and peroxides; this limits the possibility of any free radical injury in tissues with NADPH present, namely that the red blood cells.
- **In leucocytes**, during phagocytosis the NADPH produced is utilized by NADPH oxidase in **producing superoxide anions (O_2^-) for destroying phagocytosed materials.**
- NADPs obtained from this pathway **produce ATP which amount is comparable to that obtained from Glycolysis-TCA cycle.** Formation of **12 molecules of reduced NADP** from 6 molecules of Glucose 6 phosphate via hexose monophosphate shunt ultimately can lead to **synthesis of 36 molecules of ATP.** Thus, capture of energy released in oxidation of glucose via this pathway (hexose monophosphate shunt) is as effective as that of glycolytic-Krebs cycle pathway.