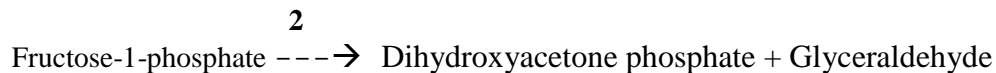
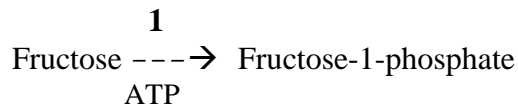


## Fructose and Galactose metabolism

### Fructose

Fructose is important in humans since it represents 50% of the carbohydrate in sucrose.



Reaction #1: Fructokinase

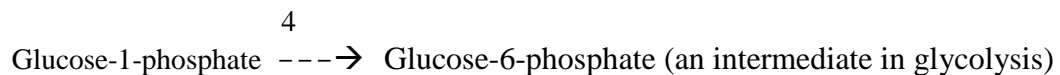
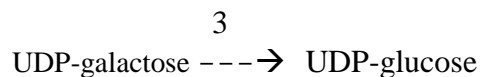
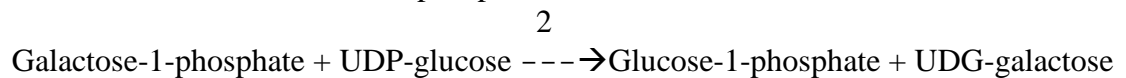
Reaction #2: Fructose-1-phosphate aldolase

Reaction #3: Triose kinase

Dihydroxyacetone phosphate and glyceraldehyde-3-phosphate are intermediates in glycolysis.

### Galactose

Galactose is a component of lactose (milk sugar).



Reaction #1: Galactokinase  
Reaction #2: Galactose-1-phosphate uridyl transferase  
Reaction #3: UDP-galactose 4-epimerase  
Reaction #4: Phosphoglucomutase

### **Hereditary fructose intolerance**

1. Genetic disease associated with a deficiency in liver fructose 1-phosphate aldolase.
2. Ingestion of fructose results in the accumulation of fructose 1-phosphate.
3. This depletes the Pi and ATP in the liver.
4. Fructose 1-phosphate stimulates glucokinase in liver and pancreatic  $\beta$  cells by removing the inhibitory protein. This causes increased uptake of glucose by these tissues and also increased insulin secretion by  $\beta$  cells. The result is hypoglycemia.
5. The disease is also associated with liver disease (jaundice) and renal tubular damage (Fanconi syndrome).
6. Decreased Pi levels leads to increased breakdown of adenine nucleotides (AMP, ADP), causing hyperuricemia (gout).
7. No cataract (Fructose, being a ketose, is not a substrate for aldose reductase).
8. Treated by restricting dietary intake of fructose, sucrose, fruit juices and honey.

### **Galactosemia**

1. Inability to transform galactose into glucose.
2. Genetic disease with two forms:
  - a. Deficiency of galactokinase: Mild form; this can cause cataract but only at late in life.
  - b. Deficiency of galactose-1-phosphate uridyl transferase: Severe form.
3. The severe form results in cataract formation even during childhood, growth failure, mental retardation and eventually death due to liver damage (jaundice).
  - a. Galactose is reduced to galactitol by aldose reductase, which initiates cataract formation and may play a role in the CNS effects. Aldose reductase inhibitors are in clinical use for cataract treatment.
4. Restriction of galactose and lactose (no breast feeding) in the diet causes a reversal of the clinical symptoms (except for the mental retardation). Initiation of dietary treatment at infancy will prevent the disease.

## HEXOSE MONOPHOSPHATE PATHWAY [Pentose Phosphate Pathway]

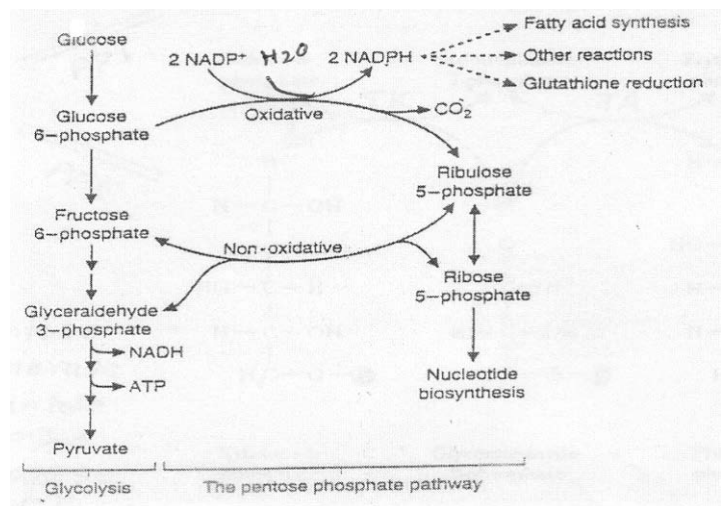
This pathway provides another way to metabolize glucose; the two major products of the pathway are **reduced nicotinamide adenine dinucleotide phosphate (NADPH)** and **ribose-5-phosphate**. The entire pathway occurs in the cytoplasm.

NADPH is required for many reductive biosynthetic reactions where it serves as a donor of protons and electrons. Examples of such syntheses would be that of fatty acids, cholesterol, bile acids and steroid hormones. The pathway is very active in liver, adipose tissue, lactating mammary gland, adrenal cortex, testes, and ovary. NADPH is also utilized for detoxification of drugs by monooxygenases and the glutathione defense system against injury by reactive oxygen species (ROS). Therefore, the hexose monophosphate pathway is active in erythrocytes where the glutathione defense system involving NADPH protects the cell from oxidative damage. The pathway is also active in activated phagocytes where NADPH serves as the electron donor for the production of ROS involved in the killing of phagocytosed microorganisms. The ribose-5-phosphate and its derivatives are found in such molecules as ATP, CoA, NAD, FAD, RNA and DNA.

For some cells (e.g. red blood cells), this is the only mechanism to generate NADPH, while in others, malic enzyme also generates NADPH [ $\text{Malate} + \text{NADP}^+ \rightarrow \text{pyruvate} + \text{CO}_2 + \text{NADPH}$ ]

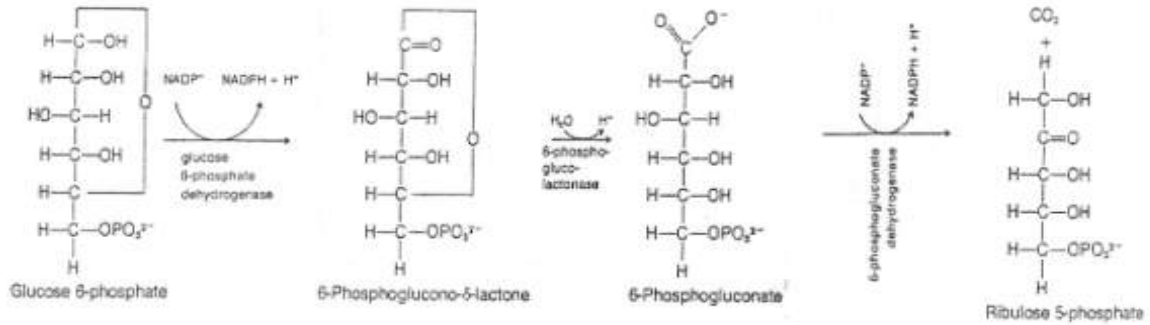
The reactions of the pathway can be grouped into two steps:

- The oxidative stage converts glucose 6-P into ribulose 5-P generating 2 NADPH molecules. This stage is irreversible.
- The nonoxidative stage consists of a series of reversible reactions that permit the conversion of ribulose 5-P to ribose 5-P which can be either used for the biosynthesis of RNA, DNA, ATP and several coenzymes or converted to glyceraldehyde 3-P and fructose 6-P which are intermediates in the glycolytic pathway.

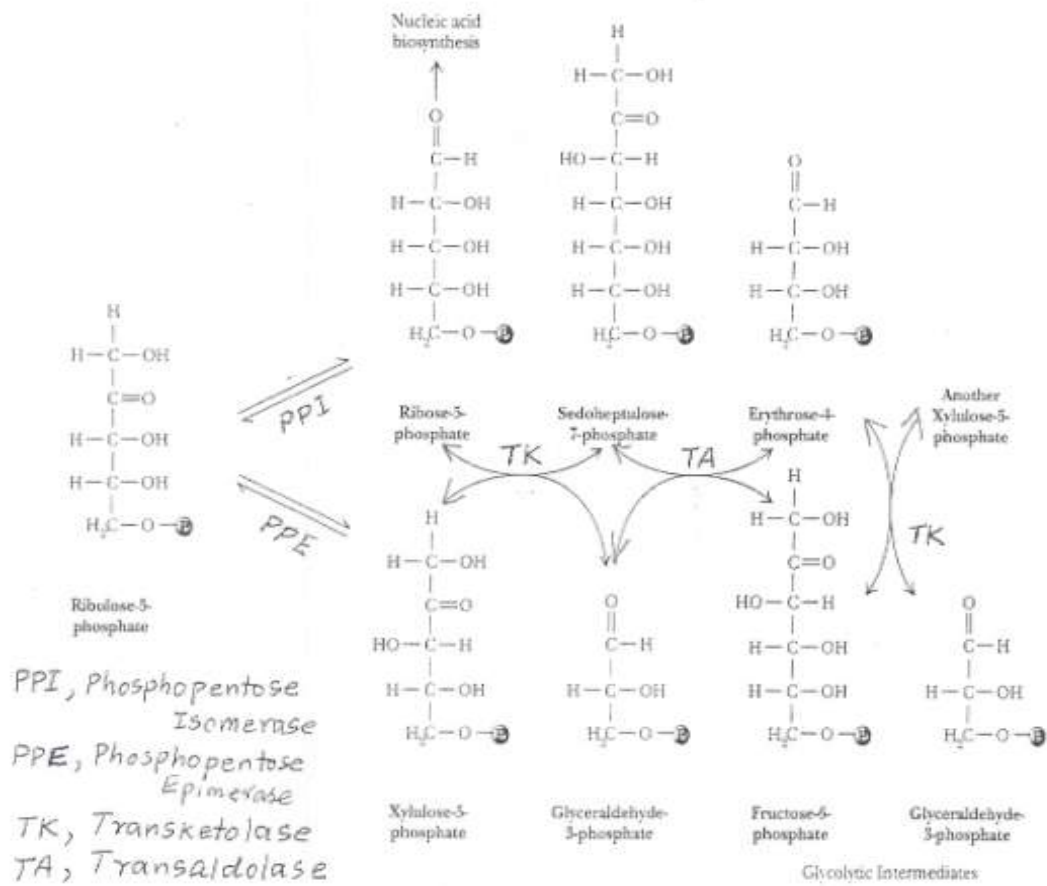




## Oxidative phase



## Nonoxidative phase



## **The Oxidative Stage**

**Two NADPH are generated in the conversion of glucose-6-phosphate into ribulose-5-phosphate and CO<sub>2</sub>.**

The pathway begins with the dehydrogenation of glucose-6-phosphate at C-1, a reaction catalyzed by glucose-6-phosphate dehydrogenase and NADP<sup>+</sup>; the products are 6-phosphogluconolactone and NADPH + H<sup>+</sup>.

The next step is the hydrolysis of the lactone by a specific gluconolactone hydrolase to give 6-phosphogluconate. 6-Phosphogluconate is then decarboxylated by 6-phosphogluconate dehydrogenase to give CO<sub>2</sub> and ribulose-5-phosphate and another NADPH + H<sup>+</sup>.

## **The Nonoxidative Stage**

Ribulose-5-phosphate is reversibly transformed into D-ribose-5-phosphate by phosphopentose isomerase.

Under many metabolic conditions the phosphogluconate pathway ends at this point.

The net result is the production of NADPH for reductive synthesis and the production of D-ribose-5-phosphate for nucleotide synthesis.

However, many cells need more NADPH than ribose-5-phosphate or they may not need ribose-5-phosphate at all. Under these conditions ribose-5-phosphate is converted into glyceraldehyde-3-phosphate and fructose-6-phosphate.

To carry out that conversion, i.e. to convert pentose phosphate pathway intermediates to glycolytic intermediates, we need additional enzymes, namely:

phosphopentose epimerase  
transketolase  
transaldolase

Phosphopentose epimerase is required to convert ribulose-5-phosphate to xylulose-5-phosphate

Transketolase catalyzes the transfer of a two carbon unit from a ketose to an aldose.

Transaldolase catalyzes the transfer of a three carbon unit from a ketose to an aldose.

Thiamine, a B-complex vitamin (also known as vitamin B1), is absolutely essential for the catalytic activity of transketolase. Thiamine pyrophosphate is the cofactor form of this vitamin which is needed for transketolase function.

### **Wernicke-Korsakoff syndrome, Wernicke encephalopathy, Korsakoff psychosis**

All these three clinical conditions are related and the condition is associated with thiamine deficiency in genetically susceptible individuals. This is seen mostly in chronic alcoholics. The disease is characterized by ophthalmoplegia, ataxia, loss of recent memory, and confusion. Patients are disoriented, indifferent, and inattentive. Thiamine deficiency underlies the disease and treatment with thiamine effectively reverses the clinical symptoms. Alcohol use causes thiamine deficiency by several mechanisms. This includes poor nutrition, impaired intestinal absorption, and impaired conversion of thiamine into its coenzyme form thiamine pyrophosphate. Activities of all four thiamine pyrophosphate-dependent enzymes, namely transketolase, pyruvate dehydrogenase,  $\alpha$ -ketoglutarate dehydrogenase, and branched chain keto acid dehydrogenase, are reduced in thiamine deficiency. This leads to defective glucose utilization and glutamate-induced excitotoxicity in the brain.

### **Beriberi**

This clinical condition is also caused by thiamine deficiency, but this occurs mostly due to nutritional deficiency and has nothing to do with alcohol use. There are two types of beriberi. **Wet beriberi** is characterized mostly by problems with the cardiovascular system: poor heart function, decreased perfusion of organs, edema, and poor skeletal muscle function. **Dry beriberi** is characterized mostly by neurological involvement including polyneuropathy.

### Control of the pathway

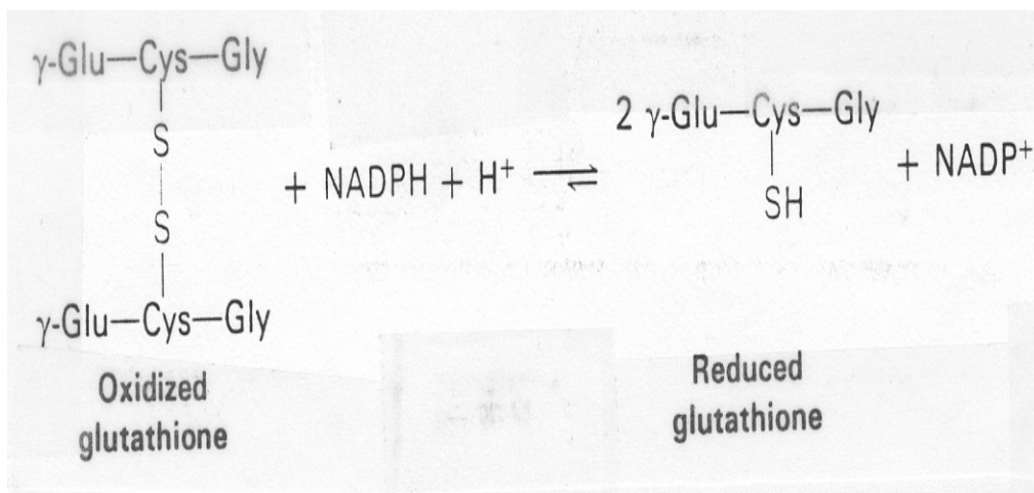
The rate of the pentose pathway is controlled by the level of  $\text{NADP}^+$ .

The first reaction of the oxidative branch is essentially irreversible. It is the rate limiting step and the level of  $\text{NADP}^+$  is the most important regulatory factor.

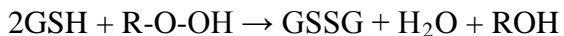
## THE RED CELL, GLUTATHIONE, AND THE HMS PATHWAY

The HMS is the only source of NADPH in the red cell, and so the production of NADPH is diminished in glucose 6-phosphate dehydrogenase deficiency.

The major role of NADPH in red cells is to reduce the disulfide form of glutathione to the sulfhydryl form. This reaction is catalyzed by glutathione reductase.



The reduced form of glutathione, a tripeptide with a free sulfhydryl group serves as a sulfhydryl buffer that maintains the cysteine residues of hemoglobin and other red cell proteins in the reduced state. The ratio of the reduced form of glutathione (GSH) to the oxidized form (GSSG) is normally about 500. The reduced form also plays a role in detoxification by reacting with hydrogen peroxide and organic peroxides.



Reduced glutathione appears to be essential for maintaining normal red cell structure and for keeping hemoglobin in the ferrous state. Cells with lowered levels of GSH are more susceptible to hemolysis.

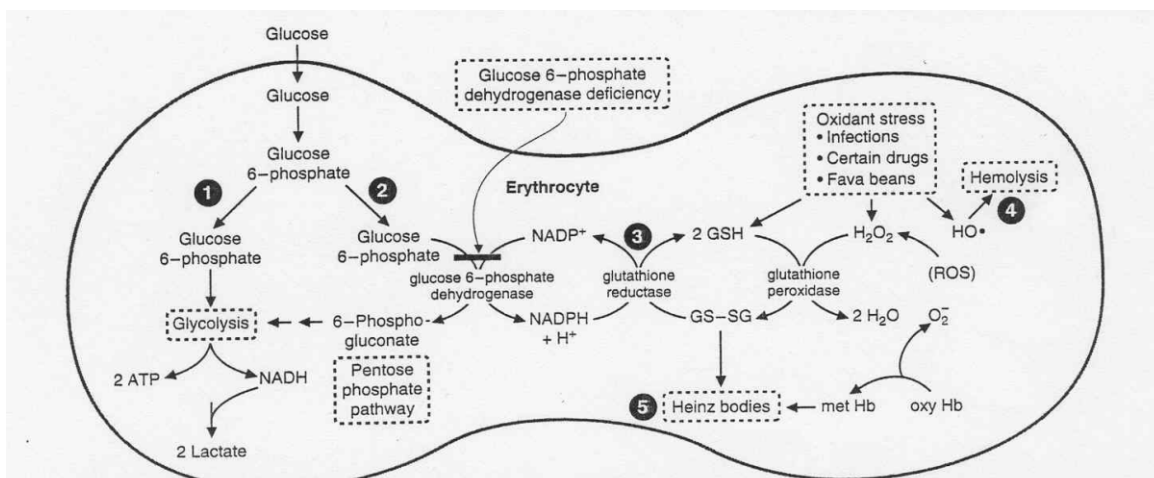


Fig. 28.7. Hemolysis caused by reactive oxygen species. 1. Maintenance of the integrity of the erythrocyte membrane depends on its ability to generate ATP and NADH from glycolysis. 2. NADPH is generated by the pentose phosphate pathway. 3. NADPH is utilized for the reduction of oxidized glutathione to reduced glutathione. Glutathione is necessary for the removal of  $\text{H}_2\text{O}_2$  and lipid peroxides generated by reactive oxygen species (ROS). 4. In the erythrocytes of healthy individuals, the continuous generation of superoxide ion from the nonenzymatic

oxidation of hemoglobin provides a source of reactive oxygen species. The glutathione defense system is compromised by glucose 6-phosphate dehydrogenase deficiency, infections, certain drugs, and the purine glycosides of fava beans. 5. As a consequence, Heinz bodies, aggregates of cross-linked hemoglobin, form on the cell membranes and subject the cell to mechanical stress as it tries to go through small capillaries. The action of the ROS on the cell membrane as well as mechanical stress from the lack of deformability result in hemolysis.

Certain drugs, many of which are also strong oxidizing agents, distort the surface of red cells in the absence of reduced glutathione and this makes them more susceptible to destruction and removal by the spleen. These drugs also increase the rate of formation of toxic peroxides which are normally eliminated by reaction with GSH. The involvement of glutathione in maintaining the integrity of the red cell membrane was elucidated as a result of treating a drug-induced hemolytic anemia. The ingestion of primaquine, an antimalarial drug, led to hemolytic anemia in certain patients. The primary underlying cause was a deficiency of glucose 6-phosphate dehydrogenase; this leads to decreased levels of NADPH, which leads to decreased levels of reduced glutathione, accelerated destruction of red cells and Heinz body formation in the circulating red cells.

**Oxidative drugs:** chloramphenicol, nitrofurantoin, dapsone, primaquine, quinine, malaroprol, sulfa drugs. These drugs may cause hemolytic anemia in individuals with glucose-6-phosphate dehydrogenase deficiency. This enzyme deficiency is X-linked and occurs mostly in males (prevalence: 1% in Middle Eastern males, 5% in Chinese males, and 10% in African American males).

Severe cases of glucose-6-phosphate deficiency due to genetic defects can cause phagocyte dysfunction. Apart from hemolytic anemia, the clinical presentation is similar to that of chronic granulomatous disease. The genetic presentation is also similar to that of  $\text{gp91}^{\text{phos}}$  deficiency. Neutrophil dysfunction does not occur in African Americans with glucose-6-phosphate deficiency (but hemolytic anemia occurs when exposed oxidative stress) because the enzyme defect in this population is primarily due to an unstable enzyme. The enzyme defect is seen only in aging erythrocytes.