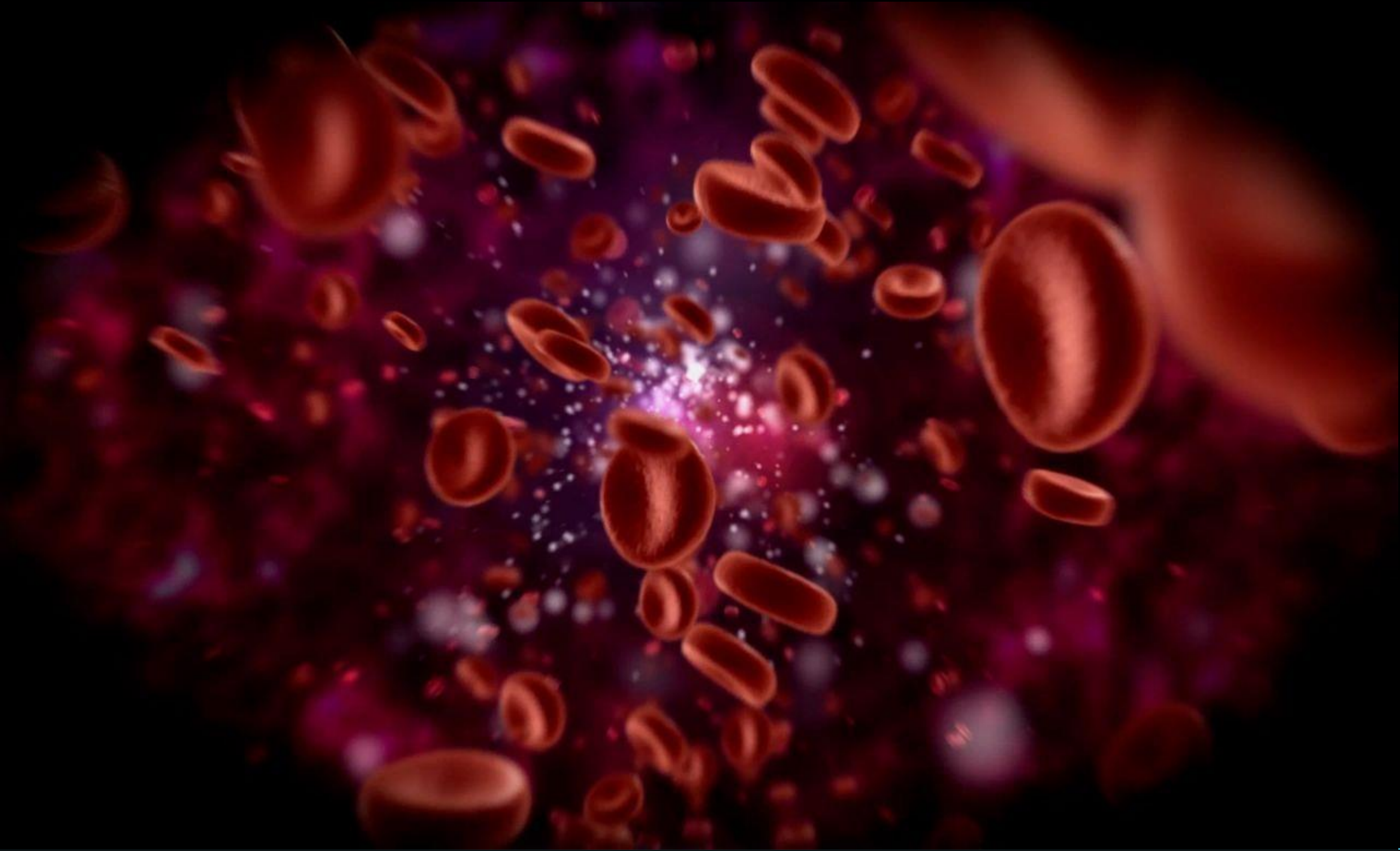

ATHAR BATCH

BIOCHEMISTRY

lecture : 1

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النادي الطبي

Erythrocytes Metabolism

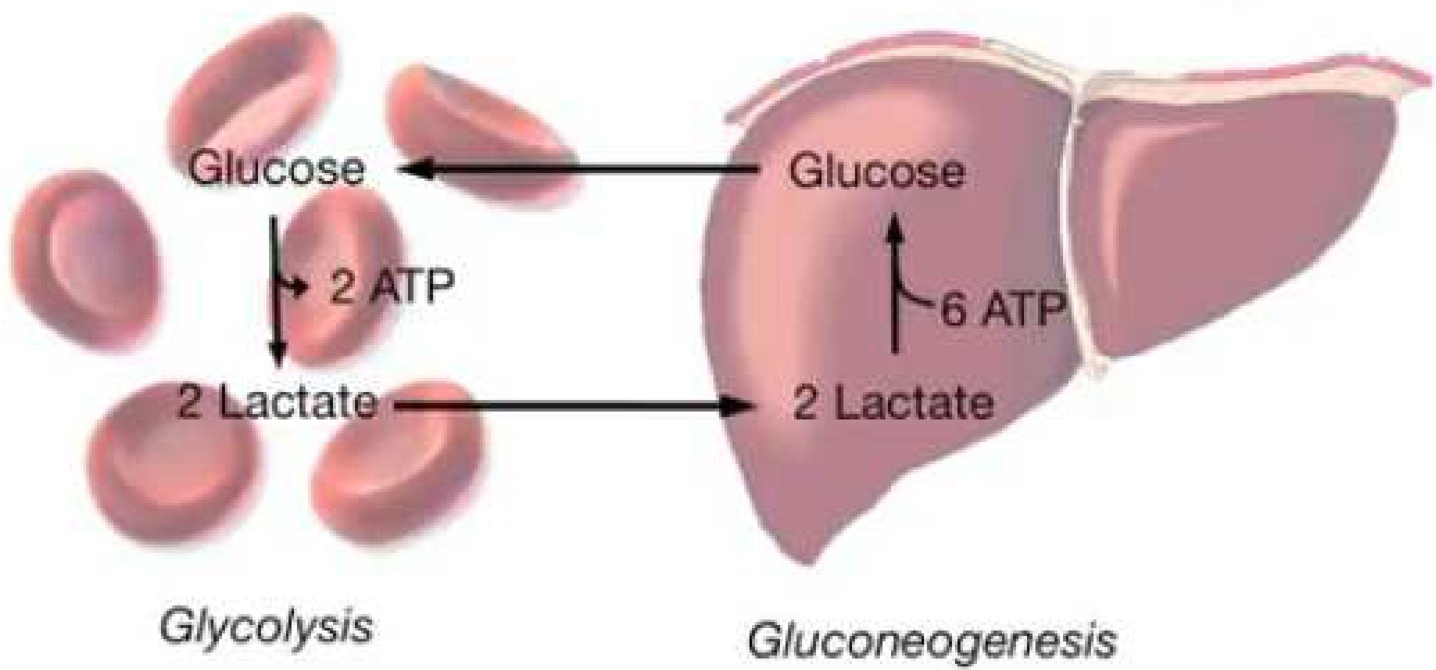
By

Dr. Walaa Bayoumie El Gazzar

Glycolysis in red blood cells

Pentose phosphate pathway

Cori Cycle


Glucose
2 ATP
2 Lactate
Glucose
6 ATP
2 Lactate
Glycolysis
Gluconeogenesis

* We all know that the function of RBCs is to transfer O_2 to the Body tissues. if the RBCs contain mitochondria, it will consume the O_2 in glycolysis. that is why it is unfavorable for RBCs to contain Mitochondia

* the erythrocytes are dependent on glycolysis alone to produce ATP.
* Glycolysis → Aerobic ⇒ Results in the formation of pyruvate.
  → Anaerobic ⇒ Results in the formation of Lactic acid
* Aerobic glycolysis → in the presence of Mitochondria & O_2.
* Anaerobic glycolysis → in the absence of Mitochondria or O_2
* The amount of ATP that results from aerobic g. is larger than that from anaerobic glycolysis.
* accumulation of lactate leads to acidosis, thus affecting RBCs function.

function of RBCs.

* Lactate must be eleminated by gluconeogenesis in the Liver.
* Cori cycle : is the metabolic loop that occur between RBCs & the liver (glycolysis → Formation of Lactate → Transfer of Lactate to the Liver → gluconeogenesis → formation of glucose → utilized in glycolysis)
* gluconeogenesis process has a high energy cost. (we need 6 ATP to convert 2 molecules of lactic acid to one molecule of glucose).

Glycolysis
(Embden-meyerhof pathway)

- **Definition:**

  - It is oxidation of glucose or glycogen to pyruvic acid (in presence of O_2) or lactic acid (in absence of O_2).

- **Site:**

  - It occurs in the cytosol of every cell. Glucose can only give lactic acid in:

- RBCs (no mitochondria).
- Exercising muscles (O_2 lack).

- **Steps:** The steps of glycolysis can be classified into two phases:

PHASE ONE:

In this phase glucose is converted into two molecules of glyceraldehydes-3-phosphate.

PHASE TWO:

In this phase the 2 molecules of glyceraldehydes-3-phospshate are converted into two molecules of pyruvate (aerobic) or lactate (anaerobic).

* Pase one ⇒ investment stage

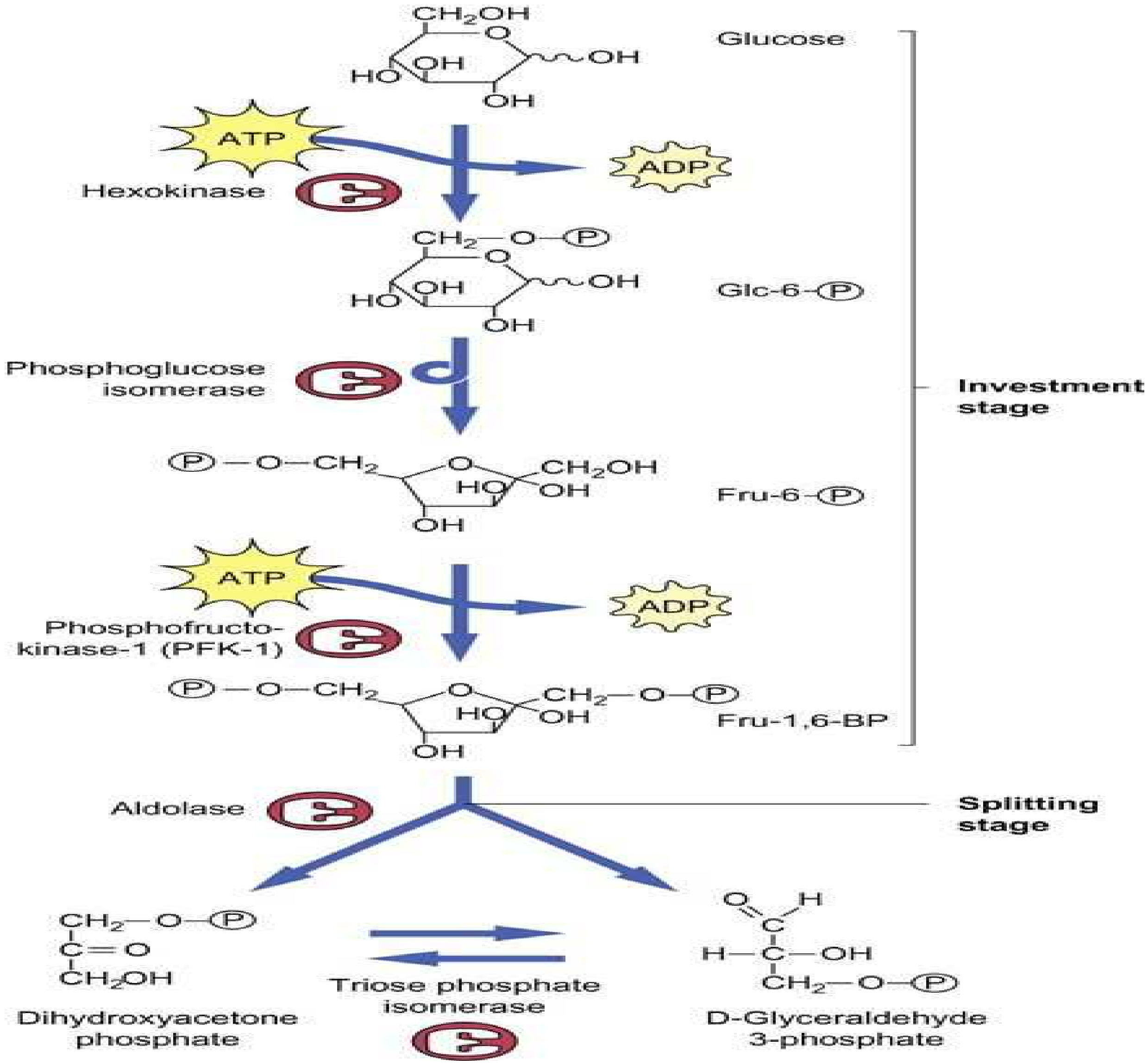
this phase require 2ATP to prime the glycolysis process.

* Phase two ⇒ yield stage

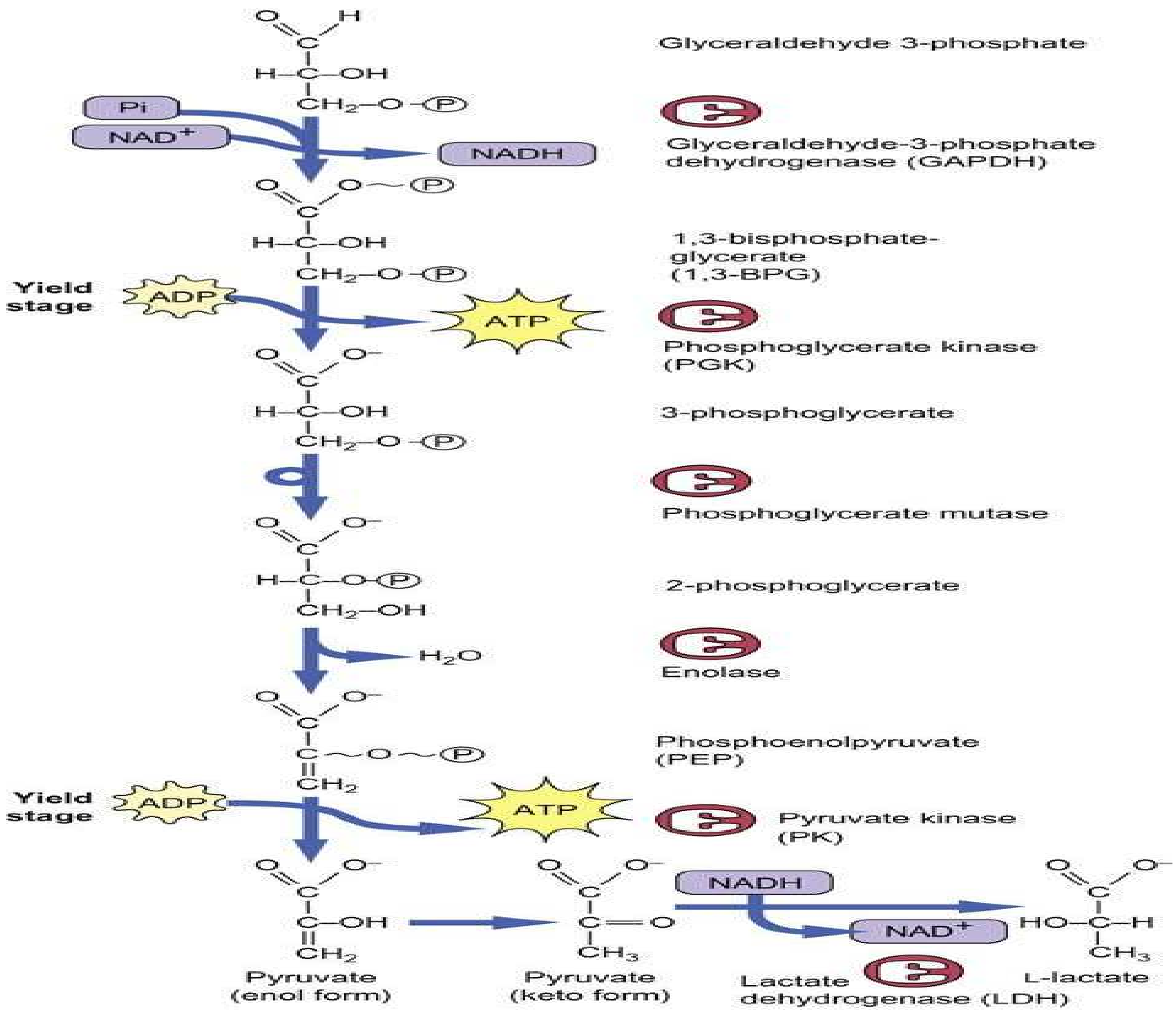
Results in formation of Lactic acid

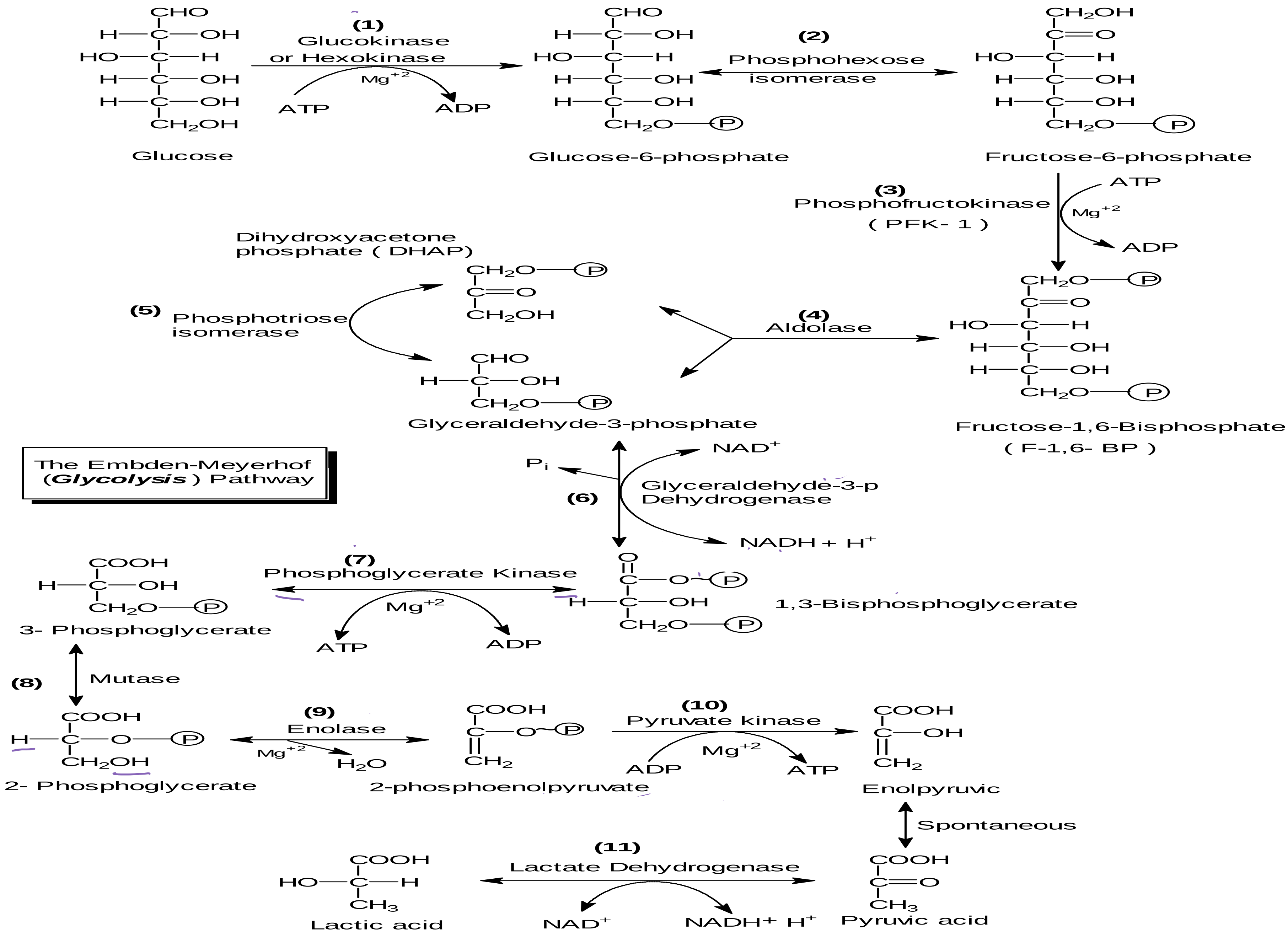
The investment stage of glycolysis

***2 ATP** are invested to prime the metabolism of glucose by glycolysis*



The yield stage of glycolysis:





The Embden-Meyerhof (*Glycolysis*) Pathway
Glucose
(1) Glucokinase or Hexokinase
Mg+2
ATP
ADP
Glucose-6-phosphate
(2) Phosphohexose isomerase
Fructose-6-phosphate
(3) Phosphofructokinase (PFK- 1)
Fructose-1,6-Bisphosphate (F-1,6- BP)
(4) Aldolase
Dihydroxyacetone phosphate (DHAP)
(5) Phosphotriose isomerase
Glyceraldehyde-3-phosphate
(6) Glyceraldehyde-3-p Dehydrogenase
Pi
NAD+
NADH + H+
1,3-Bisphosphoglycerate
(7) Phosphoglycerate Kinase
3- Phosphoglycerate
(8) Mutase
2- Phosphoglycerate
(9) Enolase
H2O
2-phosphoenolpyruvate
(10) Pyruvate kinase
Enolpyruvic
Spontaneous
Pyruvic acid
(11) Lactate Dehydrogenase
NADH+ H+
Lactic acid

1) Glucose is phosphorylated to form Glucose-6-phosphate by the enzyme Glucokinase or Hexokinase, with utilization of ATP.

* the phosphate group attached to glucose is Low energy phosphate.

2) Isomerase enzyme then rearrange the glucose-6-phosphate molecule to get Fructose-6-phosphate.

* the phosphate group is low energy phosphate

3) phosphofructokinase-1 adds a phosphate group on C_1 of Fructose-6-phosphate to form Fructose-1,6-Bisphosphate with utilization of ATP

4) Formation of ① Dihydroxyacetone phosphate & ② glyceraldehyde-3-phosphate by Aldolase enzyme.

5) Dihydroxyacetone phosphate (DHAP) is converted to Glyceraldehyde-3-phosphate by isomerase enzyme.

6) Glyceraldehyde-3-phosphate Dehydrogenase ⇒ converts Glyceraldehyde-3-phosphate to 1,3-Bisphosphoglycerate by utilization of NAD^+.

* the carboxylic phosphate (COOH + Ⓟ) is a high↑energy phosphate.
* NADH when enter the Mitochondria Produce 3 ATP.

7) phosphoglycerate kinase enzyme utilizes the high energy phosphate in 1,3-Bisphosphoglycerate to produce ATP and form 3-phosphoglycerate.

* the phosphate group is low energy phosphate.

8) Mutase enzymes ⇒ Rearrangement of 3-phosphoglycerate to form 2-phosphoglycerate.

* Note :
Carboxylic phosphate is a high energy phosphate, while ester Bond phosphate is a Low energy phosphate.
- enol phosphate → high energy phosphate

9) Enolase enzyme (Needs Mg^{+2}) ⇒ forms 2-phosphoenolpyruvate.

* enol phosphate is high energy phosphate
* enol : 2 carbons bound to each other by a double Bond, one of the carbons pairing with a hydroxyl group

10) Pyruvate kinase utilizes the high energy phosphate to produce ATP. and forms Enolpyruvic.

11) enolpyruvate is converted spontaneously to pyruvic acid.

12) Lactate dehydrogenase ⇒ Converts pyruvic acid to lactic acid By utilization of [redacted] NADH + H^+ (this reaction is reverse

Energy gain of glycolysis:

- **Energy consumed:**

Step (1) by glucokinase: One ATP is lost (spared if we start with glycogen).

Step (3) by phosphofructokinase: One ATP is lost. So, the total lost 2 ATPs

- **Energy gained:**

Step (6) by glyceraldehyde -3 P dehydrogenase: 2 NADH+H^+ (6 ATPs) gained only in the presence of O_2.

Step (7) by phosphoglycerokinase: 2 ATPs gained.

Step (10) by pyruvate kinase: 2 ATPs gained. So, the total gains 10 ATPs.

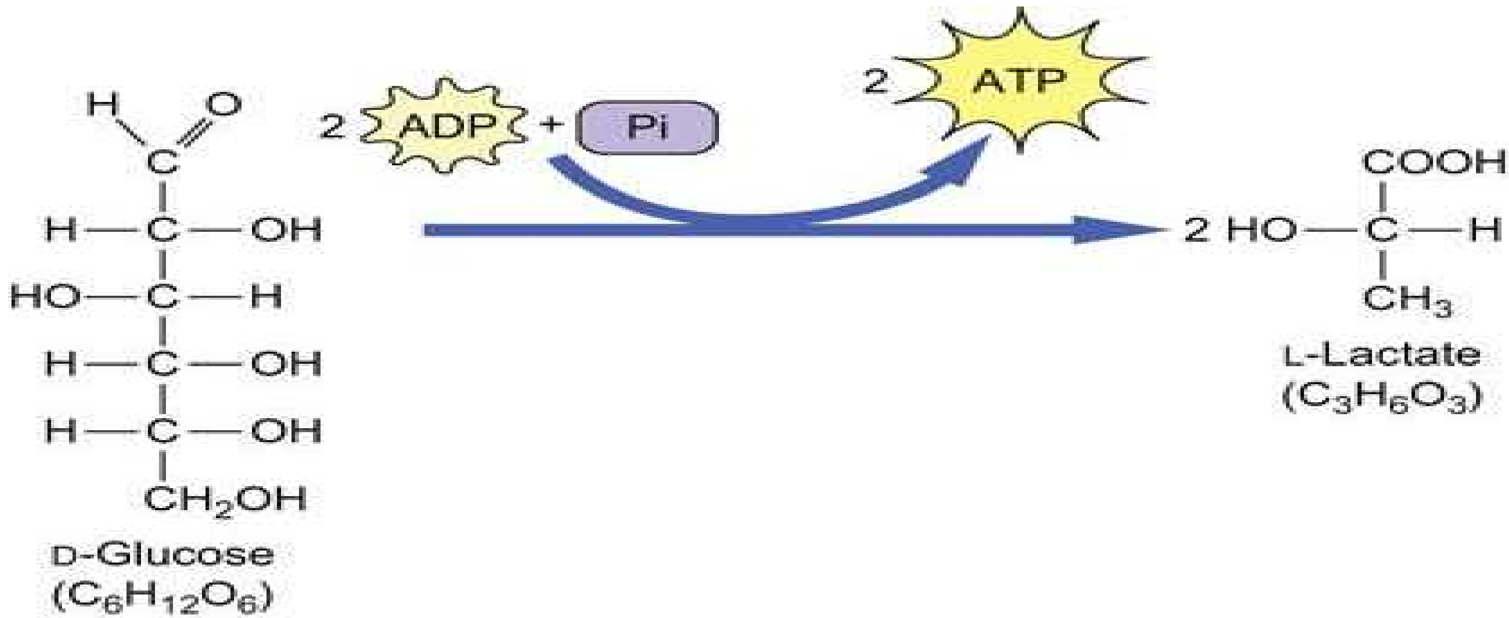
So, Energy gained under anaerobic condition (i.e.) Glucose to 2 molecules of lactic acid is 2 ATPs and 3 ATPs if we start with glycogen.

Energy gained under aerobic condition (i.e.) Glucose to 2 molecules of pyruvic acid and 2 NADH +H+

= 2 ATPs + 6 ATPs (from 2 NADH+H^+) = **8 ATPs** and 9 ATPs if we start with glycogen.

Glycolysis in red blood cells

- RBCs have no mitochondria so, glucose oxidation by Glycolysis gives **2 lactic acids** and only **2 ATPs.**

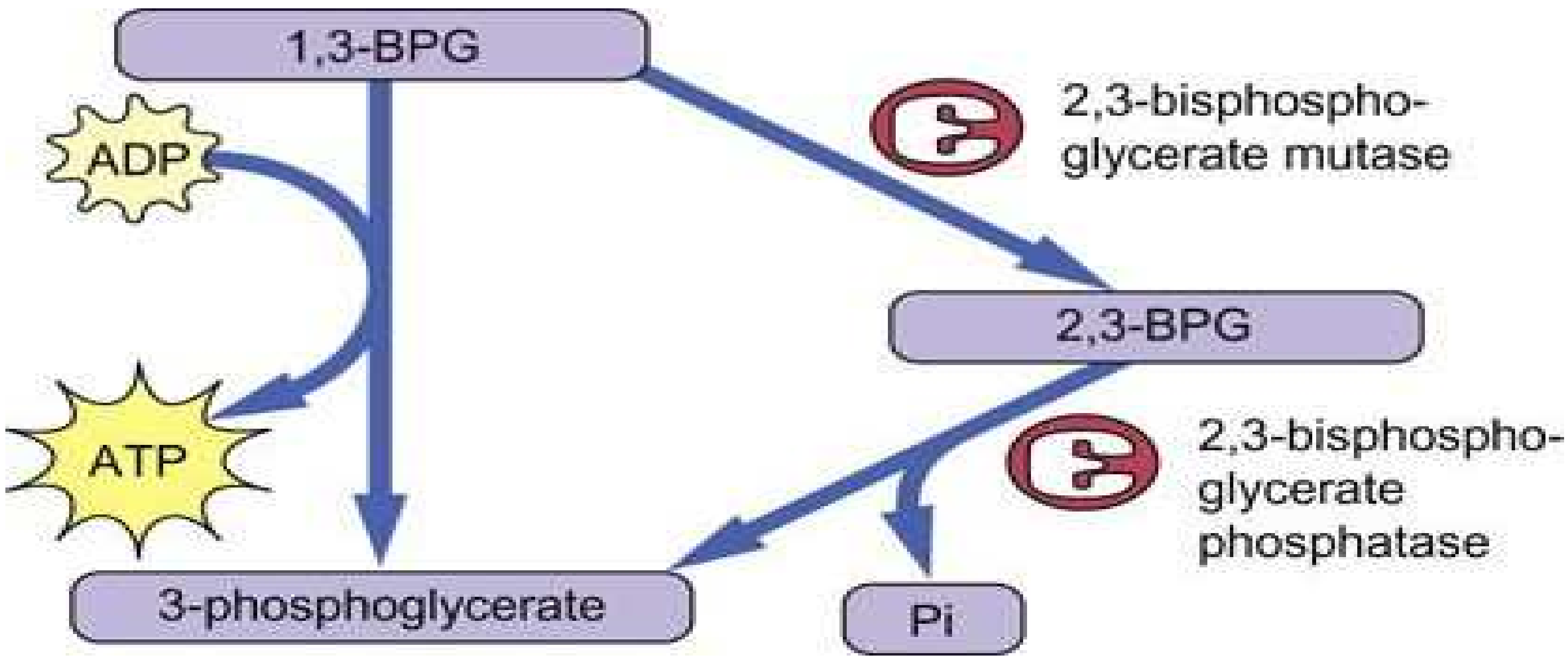


Sometimes Glycolysis in RBCs gives NO ATP !!!!!!!!!!!!!!!!!!!!!!!!!

Remember

- The 2,3-bisphosphoglycerate (BPG) molecule carries 5 negative charges and is derived from oxidation of glucose (glycolysis) in red cells.
- It binds to a positively charged pocket in Hb between the 2 β chains (small cavity in the center of the four Hb subunits)
- Binding favors the T- form of Hb, reducing affinity for oxygen and helping delivery of oxygen to tissues.
- BPG increases in red blood cells in cases of chronic anemia and in hypoxia. This helps delivery of oxygen to tissues.

Pathway for biosynthesis and degradation of 2,3-bisphosphoglycerate.



- **This pathway discovered by Rapoport-Lubring and called Rapoport-Lubring cycle.**
- **About 15 to 25% of the glucose utilized in red cells is utilized through BPG shunt.**

* Anaerobic glycolysis may not produce any ATP, and this occur when 2,3 Bisphosphoglycerate is formed.

* 1,3 Bisphosphoglycerate is converted by 2,3-Bisphosphoglycerate mutase enzume

- So RBCs need 2, 3 bisphosphoglycerate as its increase will decrease the oxygen affinity for hemoglobin to oxygen and helping oxygen delivery to tissues.
- RBCs 1, 3 diphosphoglycerate is changed by mutase to 2, 3 diphosphoglycerate which by phosphatase is changed to 3-phosphoglycerate to continue glycolysis till pyruvic acid.

•Importance of glycolysis in Red cells:

- **Energy production**: the only pathway that supplies the red cells with ATP.
- **Bisphosphoglycerate shunt** (BPG shunt).
- **Reduction of methemoglobin**: glycolysis provides NADH for reduction of met-Hb in red cells by the **NADH-cyt.b5-methemoglobin reductase system.**

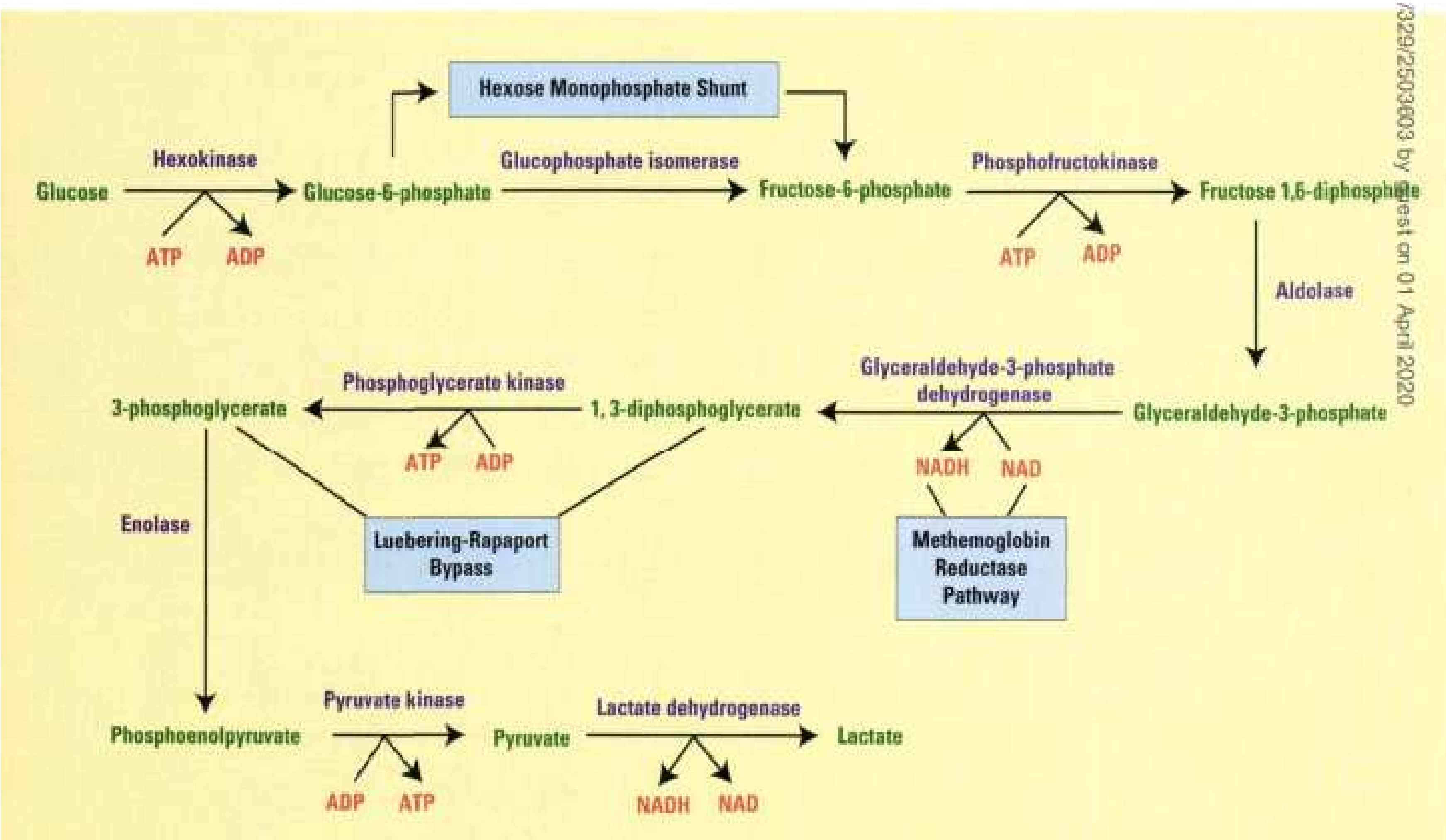
- The **ferrous iron of hemoglobin** is susceptible to oxidation by superoxide and other oxidizing agents, forming **methemoglobin**, **which cannot transport oxygen.**
- Only a very small amount of methemoglobin is present in normal blood, as the red blood cell possesses an effective system **(the NADH-cytochrome b5 methemoglobin reductase system)** for reducing heme Fe^{3+} back to the Fe^{2+} state.

* when ferrous iron is oxidized, it is converted to ferric iron.
* Hemoglobin that carries the ferric iron is called methemoglobin
* Methemoglobin cannot transport oxygen becaus ferric iron cannot carry O_2.
* NADH cytochrome b5 methemoglobin reductase system reduces Fe^{+3} back to Fe^{+2}

- This system consists of **NADH (generated by glycolysis)**, a **flavoprotein named cytochrome b5 reductase** (also known as methemoglobin reductase), and **cytochrome b_5** (electron transport hemoprotein).
- The Fe^{3+} of methemoglobin is reduced back to the Fe^{2+} state by the action of **reduced cytochrome b_5**:

$$\text{Hb-}Fe^{3+} + \text{cyt } b_{5\ red} \longrightarrow \text{Hb-}Fe^{2+} + \text{cyt } b_{5\ ox}$$

- Reduced cytochrome b_5 is then regenerated by the action of cytochrome b_5 reductase (NADH-dependent enzyme):


Hexose Monophosphate Shunt
Hexokinase
Glucose
Glucose-6-phosphate
ATP
ADP
Glucophosphate isomerase
Fructose-6-phosphate
Phosphofructokinase
ATP
ADP
Aldolase
Glyceraldehyde-3-phosphate
dehydrogenase
Glyceraldehyde-3-phosphate
NADH
NAD
Methemoglobin
Reductase
Pathway
Phosphoglycerate kinase
3-phosphoglycerate
1, 3-diphosphoglycerate
ATP
ADP
Luebering-Rapaport
Bypass
Enolase
Phosphoenolpyruvate
Pyruvate kinase
ADP
ATP
Pyruvate
Lactate dehydrogenase
NADH
NAD
Lactate

Hemolytic anemia due to deficiency of glycolytic enzymes:

- Inherited deficiency of glycolytic enzymes produces hemolytic anemia because red cells are dependent on glycolysis for production of ATP.
- About 95% of these patients have deficiency of **pyruvate kinase** and 4% have deficiency of **phosphohexose isomerase**.