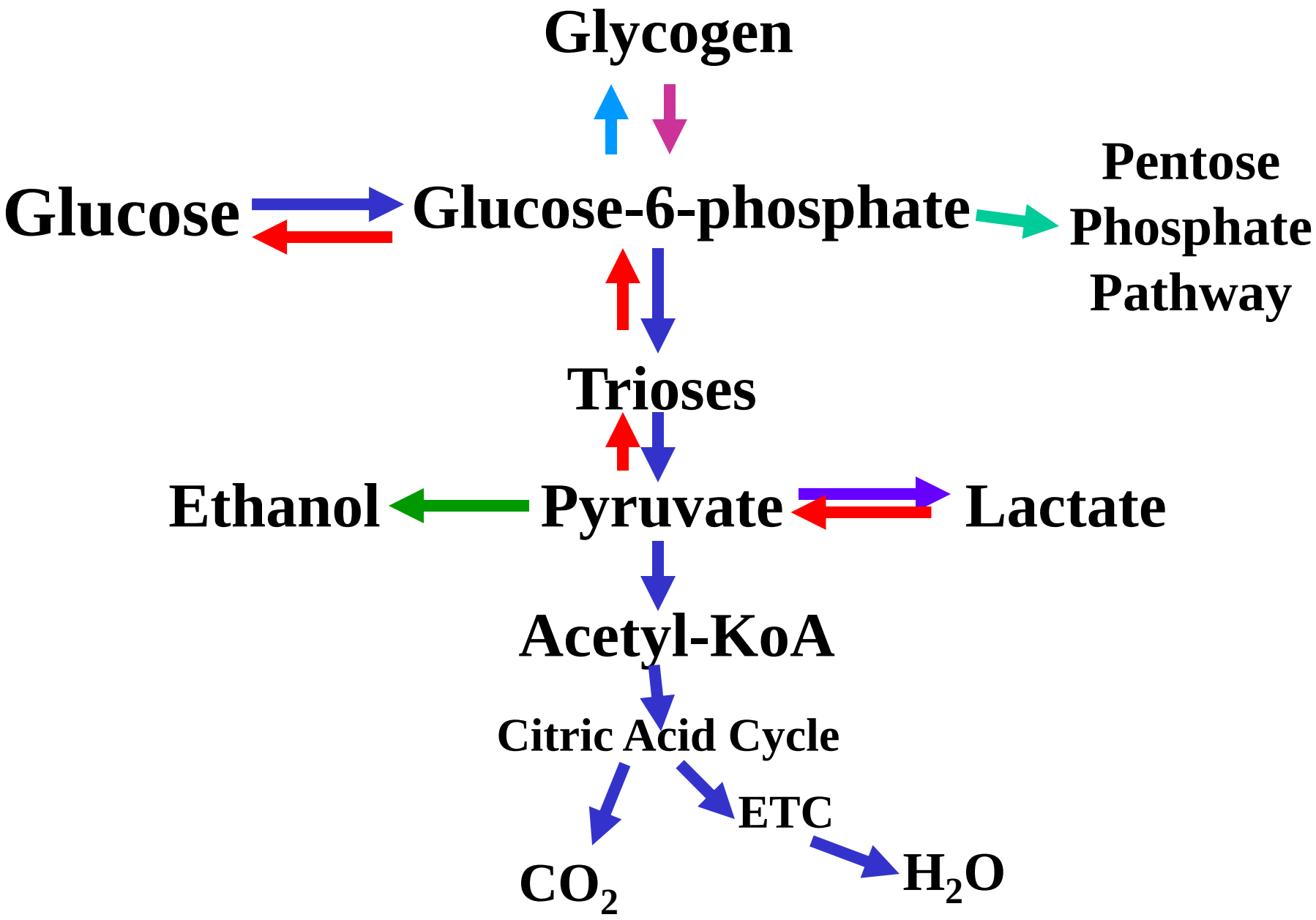
METABOLISM OF CARBOHYDRATES

Lecture II

The general scheme of glucose metabolism



The general scheme of glucose metabolism (cont.)

- Glycolysis
  - in aerobic conditions
  - in anaerobic conditions
- Gluconeogenesis
- Alcohol fermentation
- Pentose Phosphate Pathway
- Glycogen biosynthesis (glycogenesis)
- Glycogenolysis (mobilisation of glycogen)

Glycolysis, the major pathway for glucose metabolism, occurs in the cytosol of all cells.

It can function either aerobically or anaerobically, depending on the availability of oxygen and the ETC.

Glycolysis is also the main pathway for the metabolism of fructose, galactose and other carbohydrates.

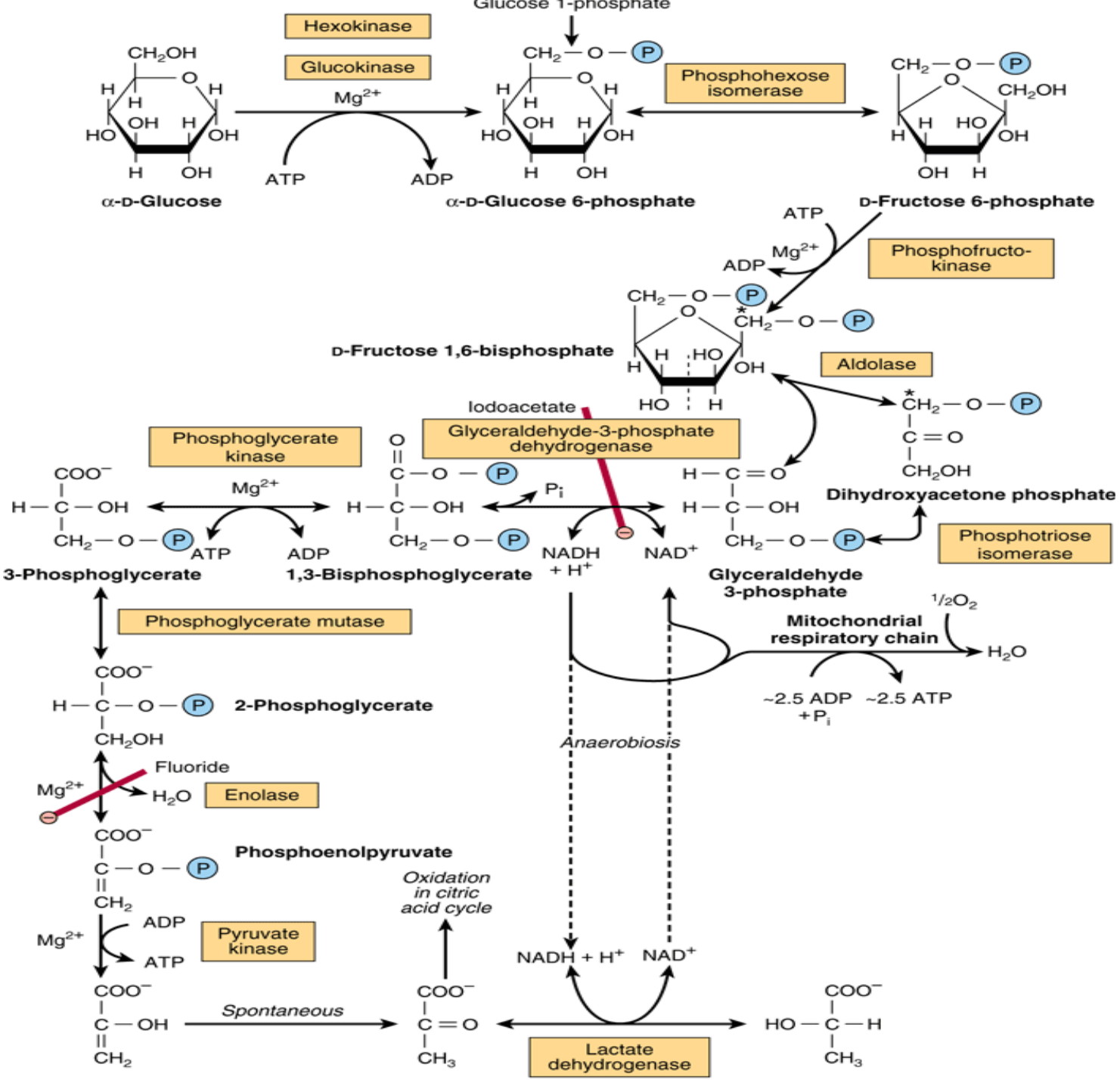
The roles of glycolysis:

- **to produce energy**

- **to produce intermediates for biosynthetic pathways**

Reactions of Glycolysis

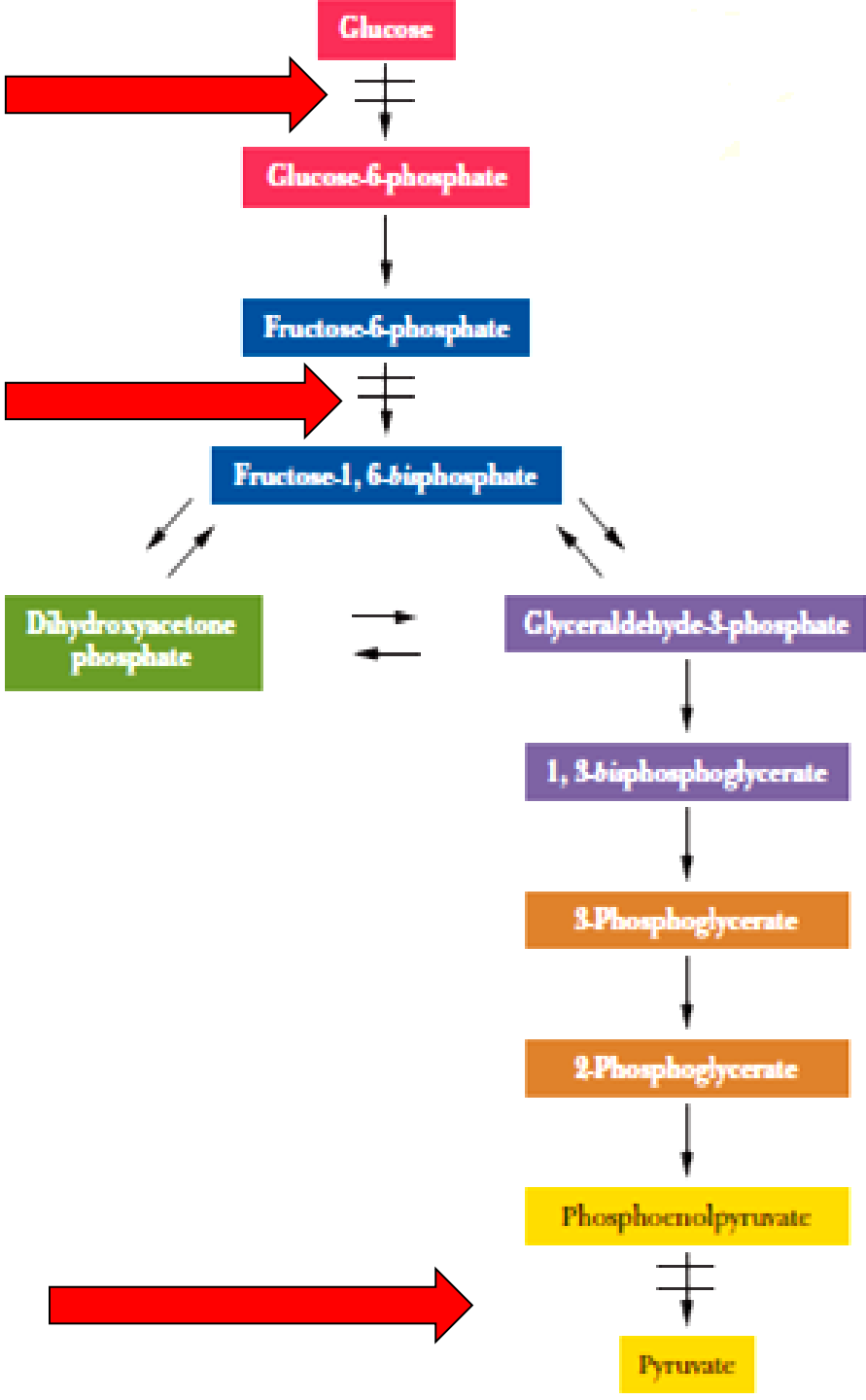
Harper's Illustrated Biochemistry


Glucose 1-phosphate
Hexokinase
Glucokinase
Mg2+
ATP
ADP
α-D-Glucose
α-D-Glucose 6-phosphate
Phosphohexose isomerase
D-Fructose 6-phosphate
ATP
Mg2+
ADP
Phosphofructo-kinase
D-Fructose 1,6-bisphosphate
Aldolase
Iodoacetate
Glyceraldehyde-3-phosphate dehydrogenase
Phosphoglycerate kinase
Mg2+
Pi
ATP
ADP
NADH + H+
NAD+
3-Phosphoglycerate
1,3-Bisphosphoglycerate
Dihydroxyacetone phosphate
Glyceraldehyde 3-phosphate
Phosphotriose isomerase
Phosphoglycerate mutase
1/2O2
Mitochondrial respiratory chain
H2O
~2.5 ADP +Pi
~2.5 ATP
2-Phosphoglycerate
Anaerobiosis
Fluoride
Mg2+
H2O
Enolase
Phosphoenolpyruvate
Oxidation in citric acid cycle
Mg2+
ADP
ATP
Pyruvate kinase
NADH + H+
NAD+
Spontaneous
Lactate dehydrogenase

REGULATION OF GLYCOLISIS

Irreversible steps are regulated

- Hexokinase/Glucokinase
- Phosphofructokinase
- Pyruvate kinase



Regulation of Glycolysis

Major sites for regulation:

- **hexokinase**

I: glucose-6-P

- **glucokinase**

A: Insulin

High concentrations of glucose

I: glucagon

Regulation of Glycolysis

Major sites for regulation:

- **phosphofructokinase**

A: Insulin, AMP, fructose 6-P

fructose 2,6-bisphosphate

I: ATP, citrate, glucagon

Regulation of Glycolysis

Major sites for regulation:

- **pyruvate kinase**

A: Insulin, fructose 1,6-bisphosphate

I: ATP, alanine, glucagon

OXIDATIVE DECARBOXYLATION of PYRUVATE by PYRUVATE DEHYDROGENASE COMPLEX

$$\text{Pyruvate} + NAD^+ + CoA \rightarrow$$

$$\text{Acetyl-CoA} + NADH + H^+ + CO_2$$

Enzymes of complex:

E_1 - pyruvate dehydrogenase

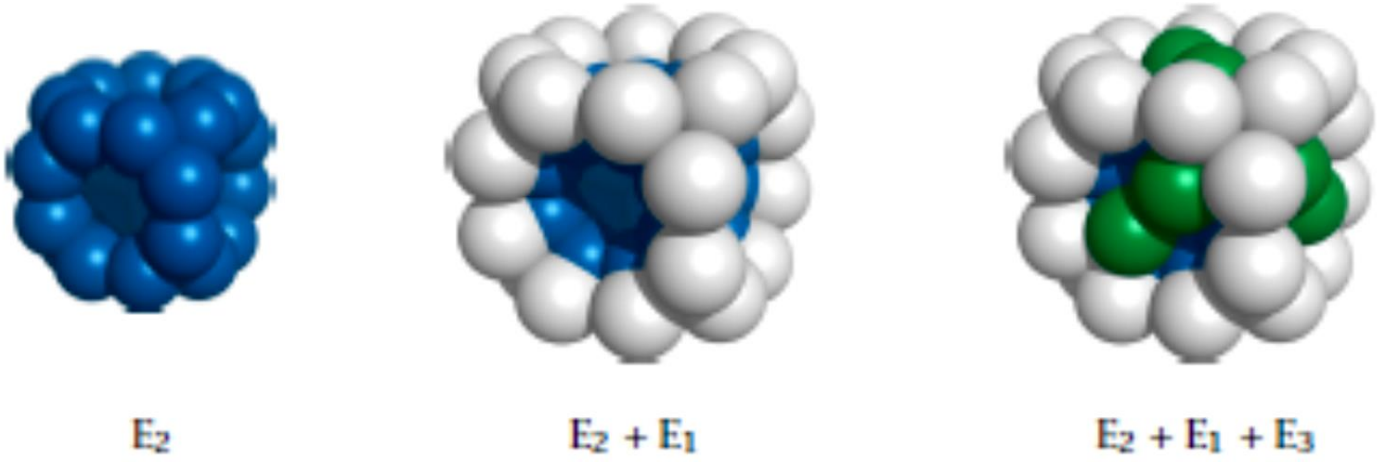
E_2 - dihydrolipoyl transacetylase

E_3 - dihydrolipoyl dehydrogenase

Coenzymes:

thiamin diphosphate, lipoic acid,

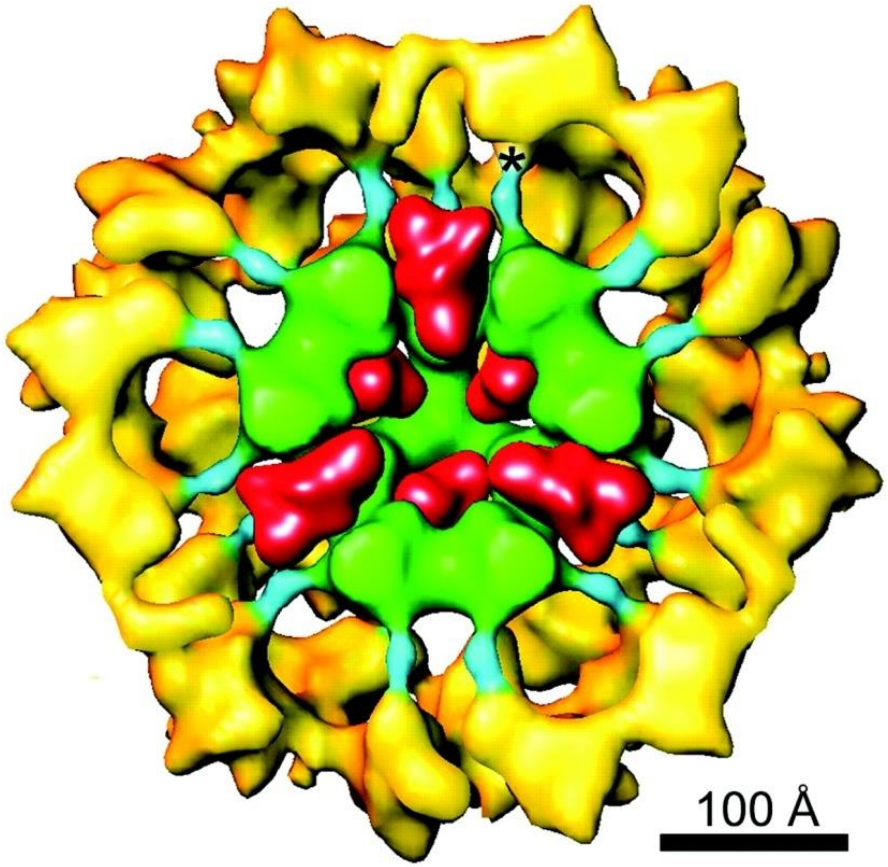
CoA-SH, FAD, NAD^+

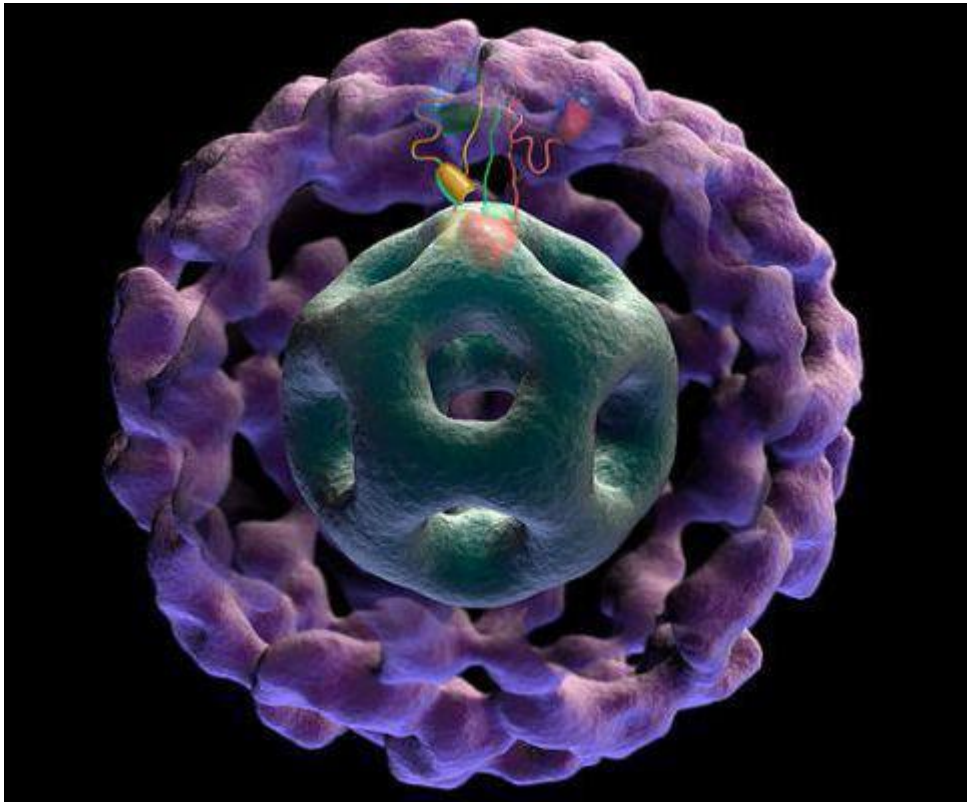


Each pyruvate dehydrogenase complex contains multiple copies of each of the three enzyme subunits. E_1 and E_2 are present in 24 copies each.

The *E. coli* enzyme contains 12 copies of E_3, as shown in this illustration, whereas 24 copies are found in the mammalian enzyme.
In addition, the complex also contains regulatory kinase and phosphatase subunits

PYRUVATE DEHYDROGENASE COMPLEX

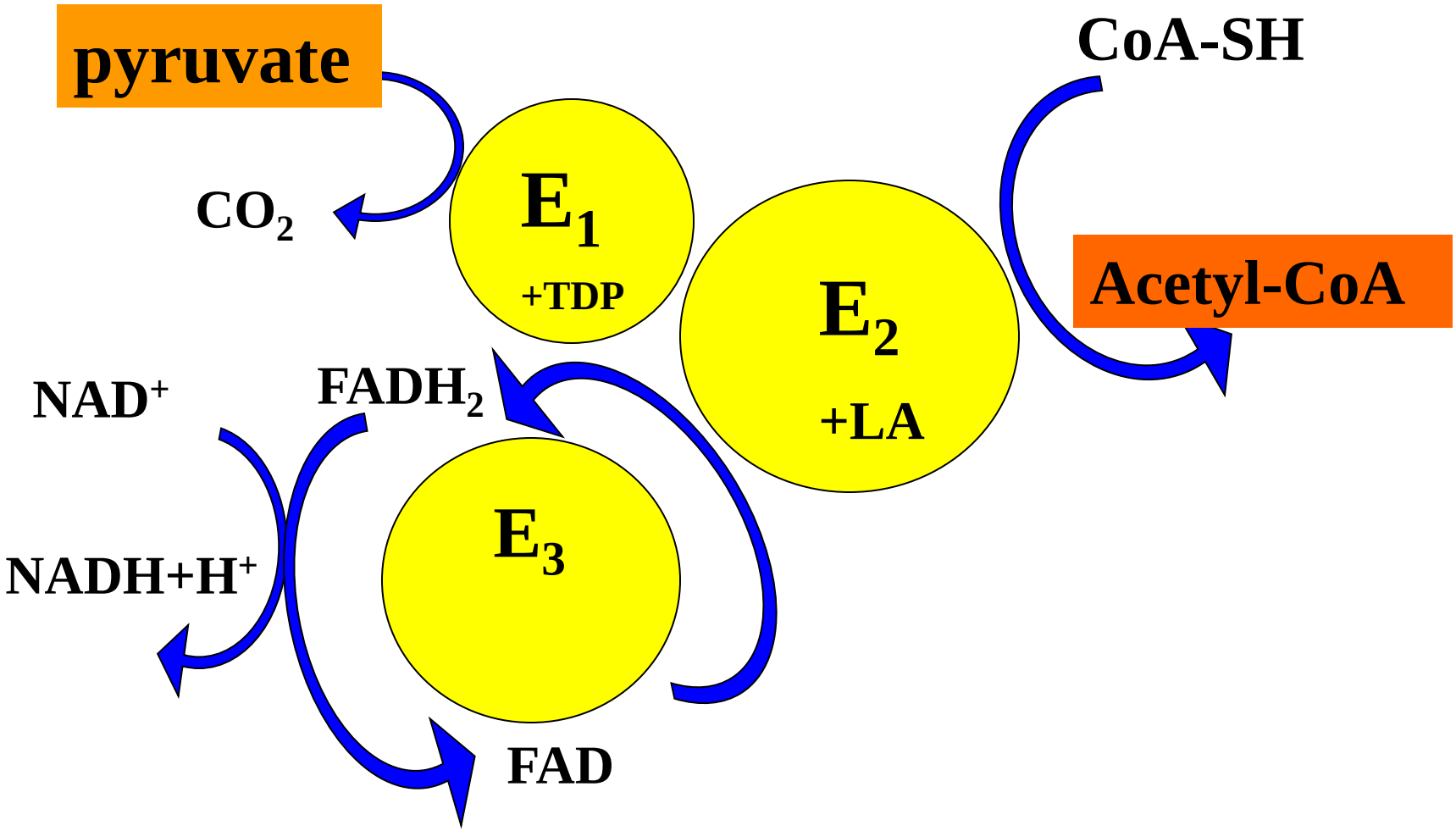


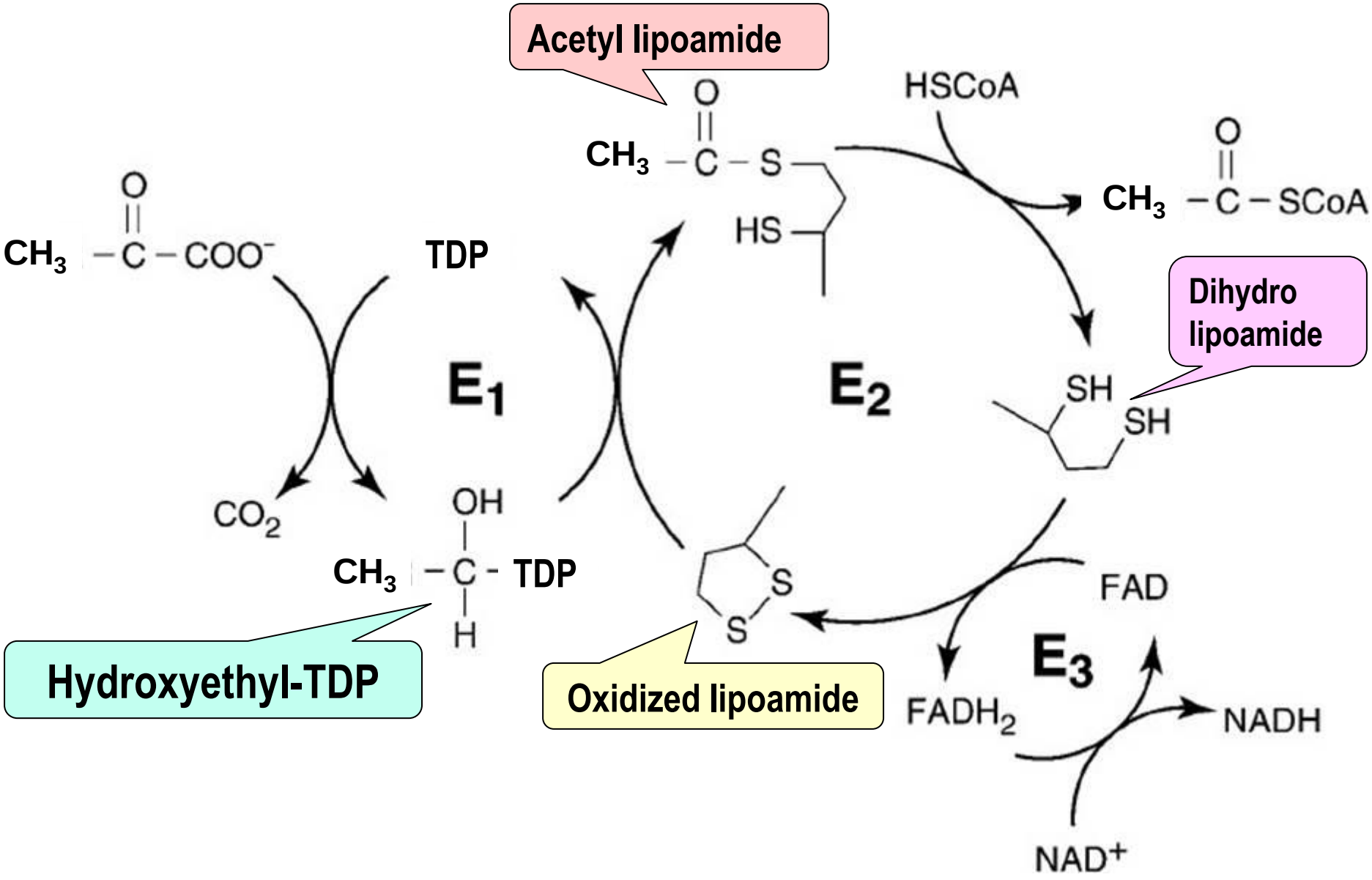


The reaction intermediates thus need to travel only a short distance from one active site to the next, which increases the overall catalytic efficiency.

This is the key advantage of multi-enzyme complexes over a series of individual enzymes.

OXIDATIVE DECARBOXYLATION of PYRUVATE by PYRUVATE DEHYDROGENASE COMPLEX




Acetyl lipoamide
HSCoA
CH3 – C – SCoA
Dihydro lipoamide
CH3 – C – COO⁻
TDP
E1
E2
CO2
OH
CH3 – C – TDP
H
Hydroxyethyl-TDP
Oxidized lipoamide
FAD
E3
FADH2
NADH
NAD+

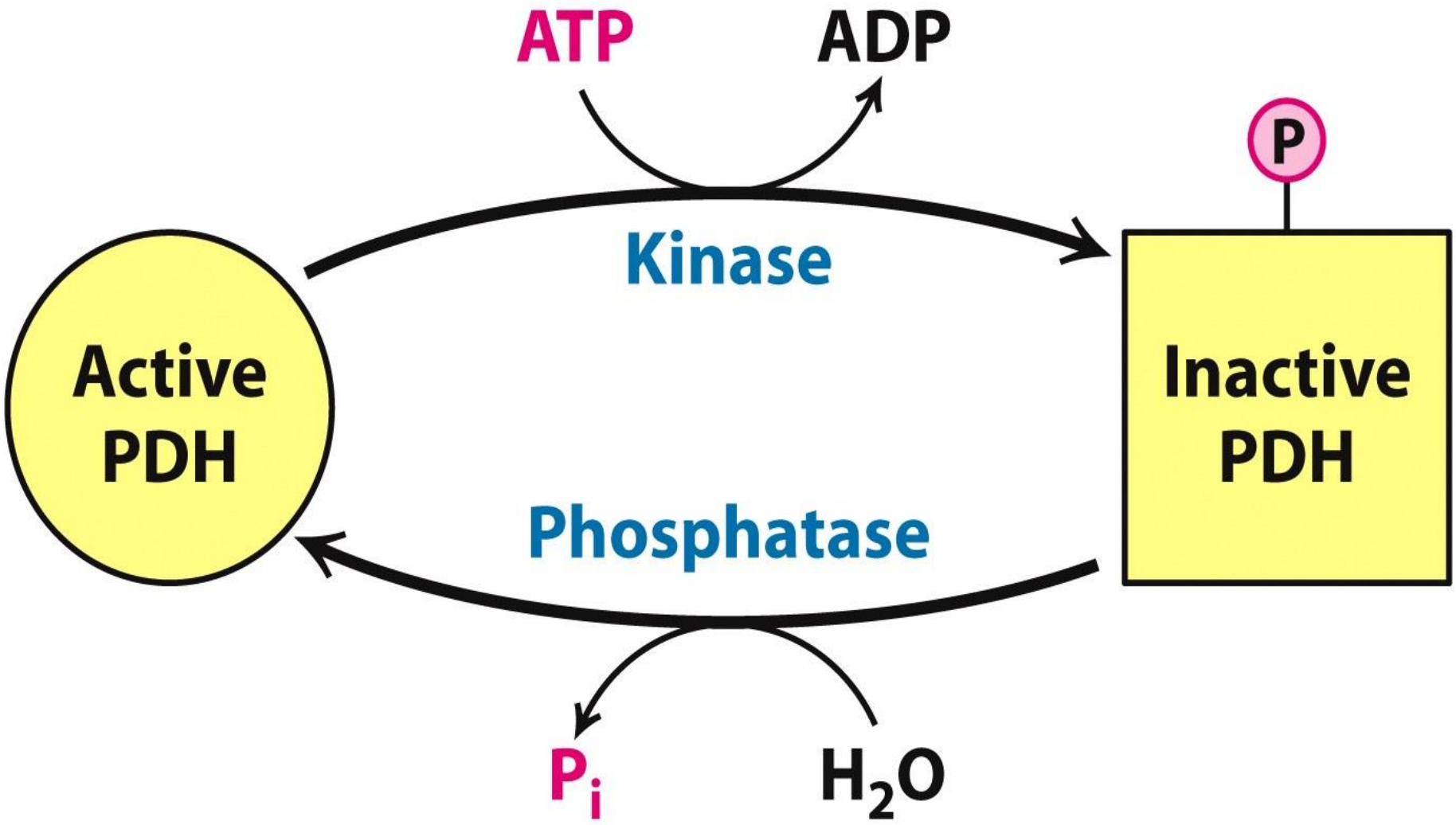
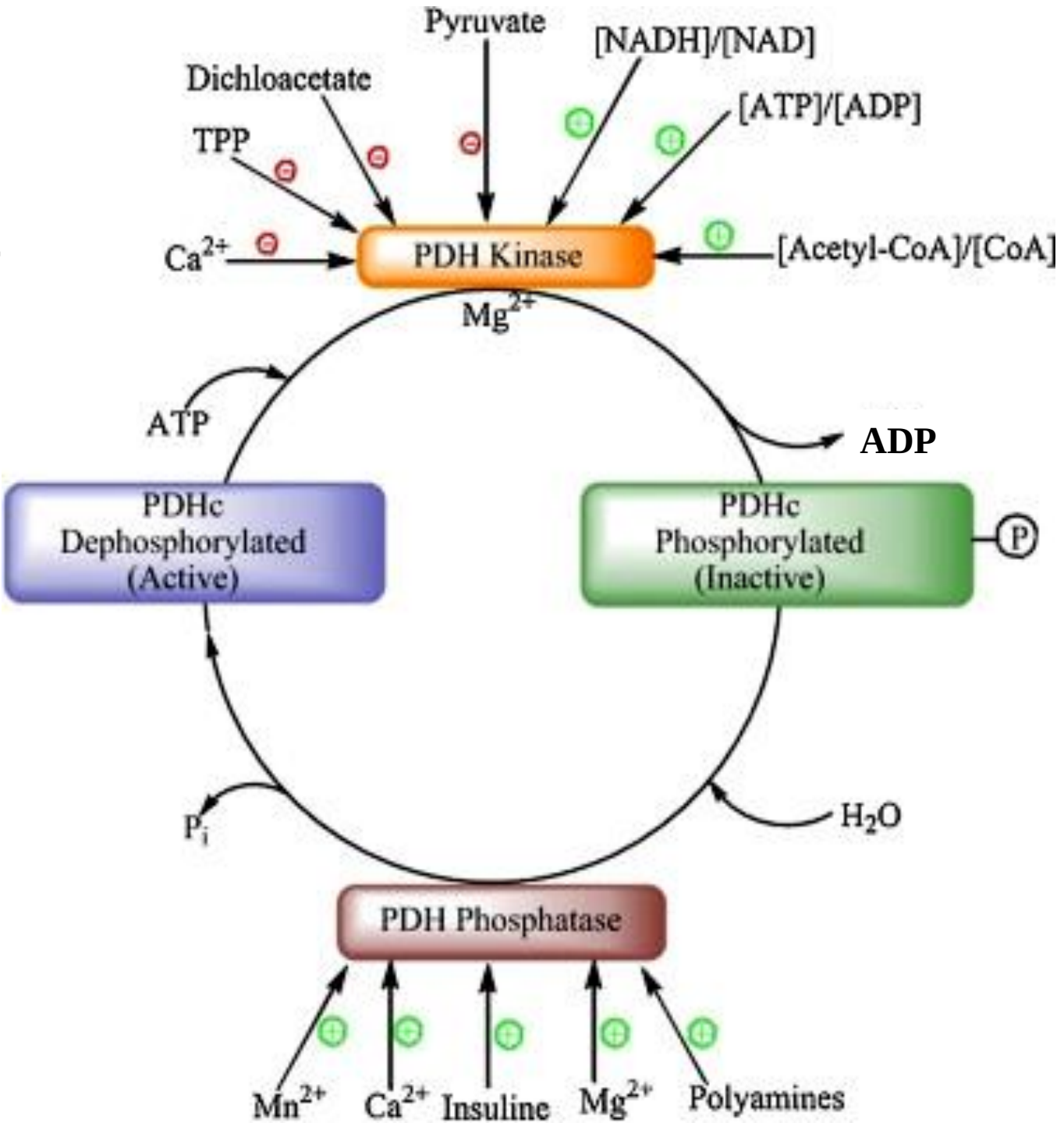
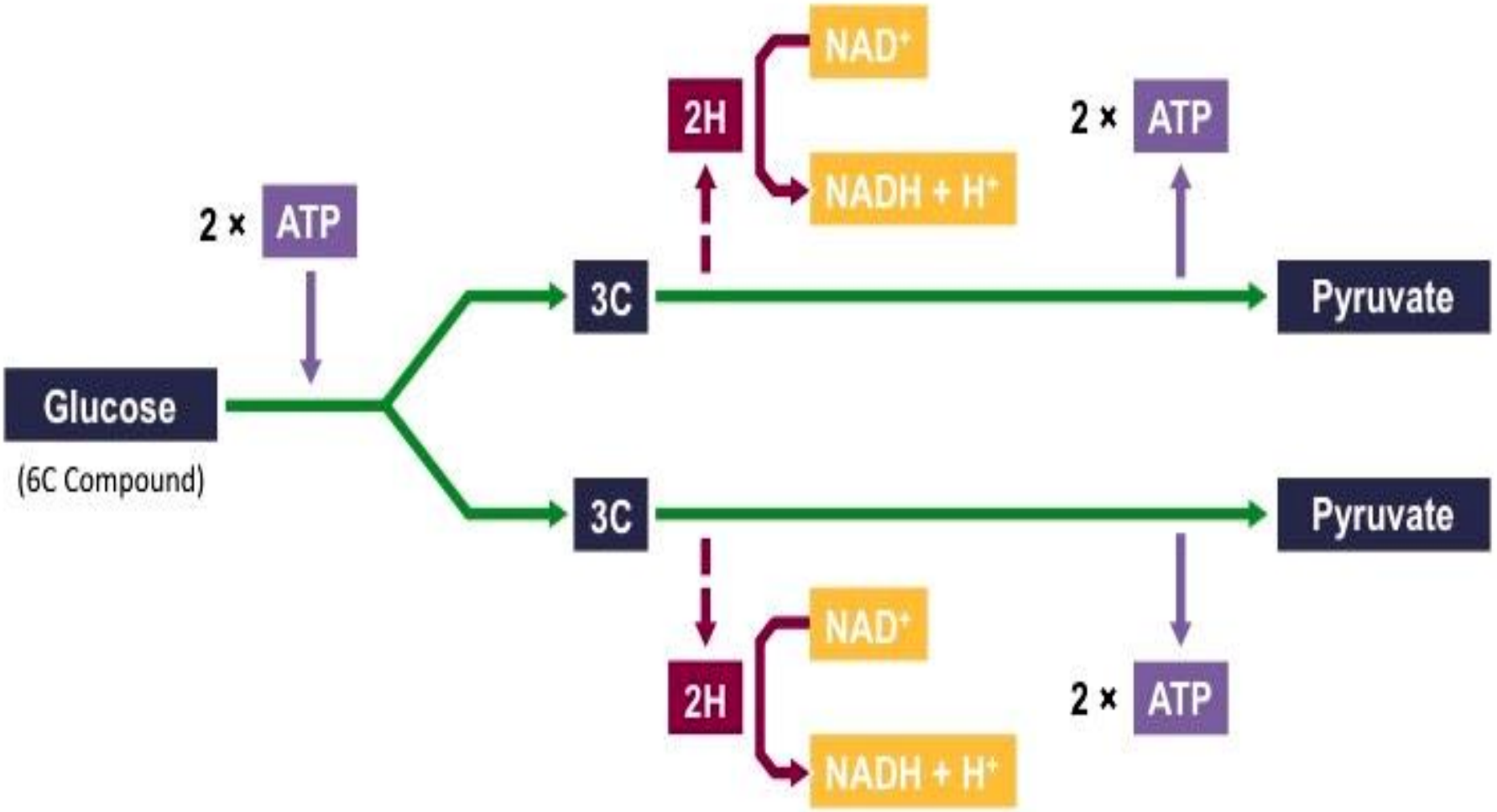


Figure 17.17
***Biochemistry*, Seventh Edition**

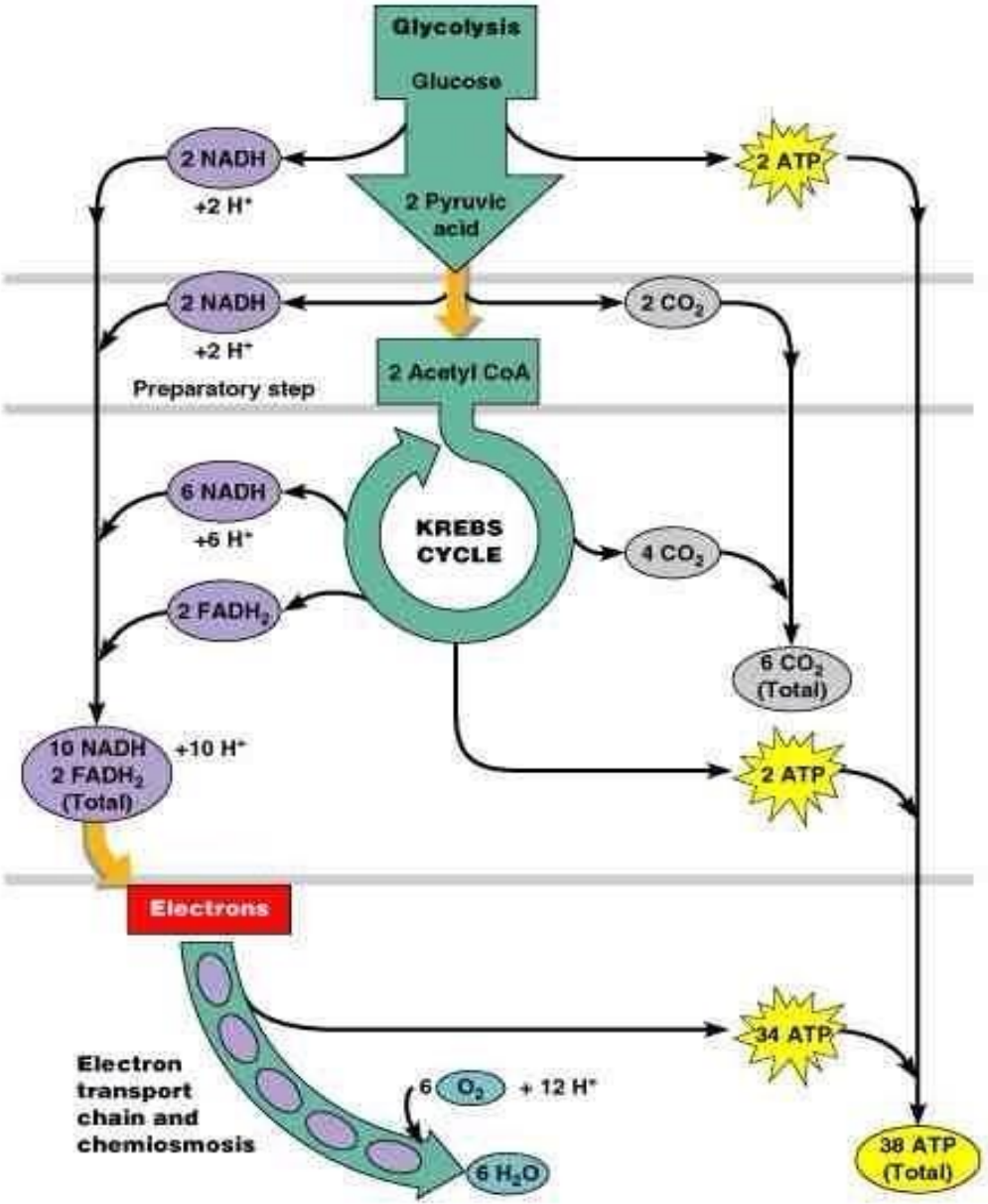
REGULATION OF PYRUVATE DEHYDROGENASE COMPLEX





Net Gain: 2 × ATP ; 2 × NADH + H+ (+ 2 × pyruvate)

ATP Formation in the Catabolism of Glucose



ATP Formation in the Catabolism of Glucose

Glyceraldehyde 3-Phosphate DH	**2 NADH**	**6 (5)**
Phosphoglycerate kinase	***substrate level phosphorylation***	**2**
Pyruvate kinase	***substrate level phosphorylation***	**2**
Consumption of ATP		**- 2**
Pyruvate DH	**2 NADH**	**6 (5)**
Isocitrate DH	**2 NADH**	**6 (5)**
α-Ketoglutarate DH	**2 NADH**	**6 (5)**
Succinate thiokinase	***substrate level phosphorylation***	**2**
Succinate DH	**2 $FADH_2$**	**4 (3)**
Malate DH	**2 NADH**	**6 (5)**
TOTAL (aerob.)		**38 (32)**
TOTAL (anaerob.)		**2**

Gluconeogenesis

The process of synthesizing glucose from noncarbohydrate precursors

The major substrates: glucogenic amino acids, lactate, glycerol, propionate

Tissues: liver, kidney, small intestine

Importance of gluconeogenesis

- **Gluconeogenesis meets the needs of the body for glucose when insufficient carbohydrate is available from the diet or glycogen reserves.**

- **Gluconeogenesis clears lactate produced by muscle and erythrocytes and glycerol produced by adipose tissue.**

Obligate glucose users

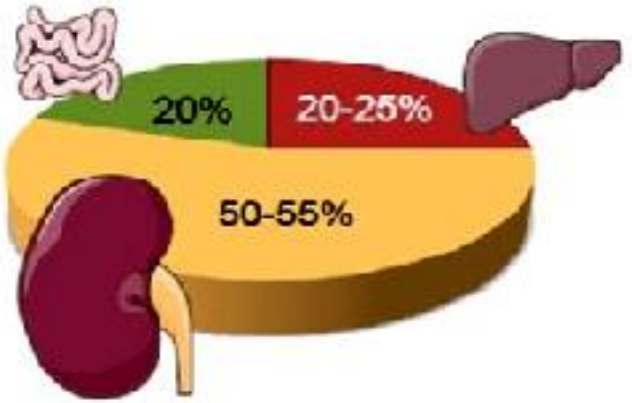
- Red blood cells
- Medulla cells of the kidney
- Activated T-cells of the immune system
- Sertoli cells of the testis

Not obligate users (preferring glucose)

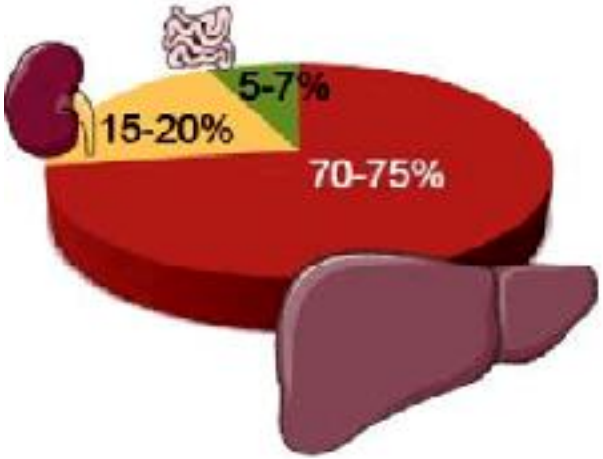
- Retinal cells
- Neurons
- Fibroblasts
- Smooth muscle cells of vascular system

The liver, kidney and intestines all contribute more or less to GNG. This depends on whether or not you're eating and what you're eating.

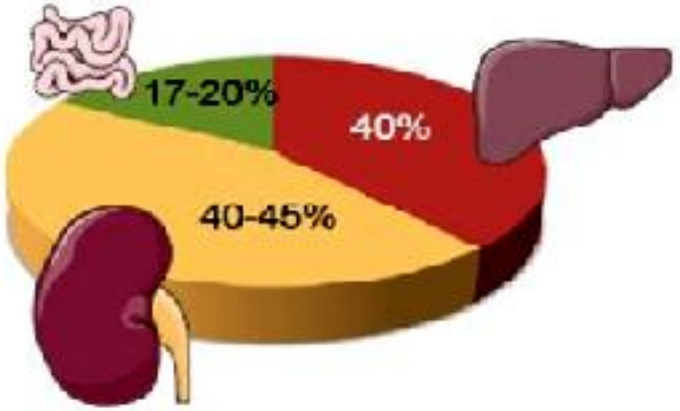
Fasting (24-48h)



Post-absorptive state
Standard (starch) diet

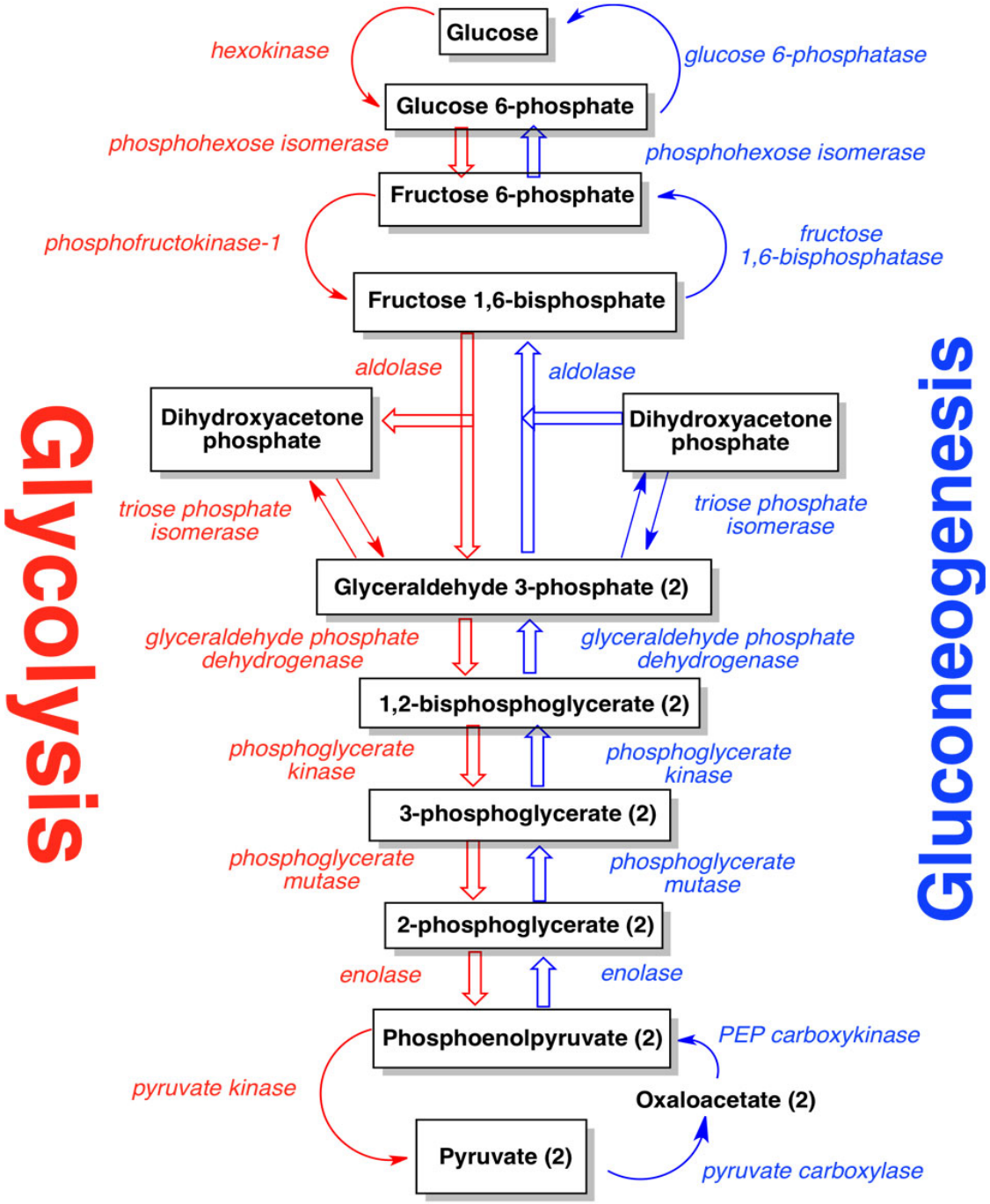


Post-absorptive state
Protein-enriched diet



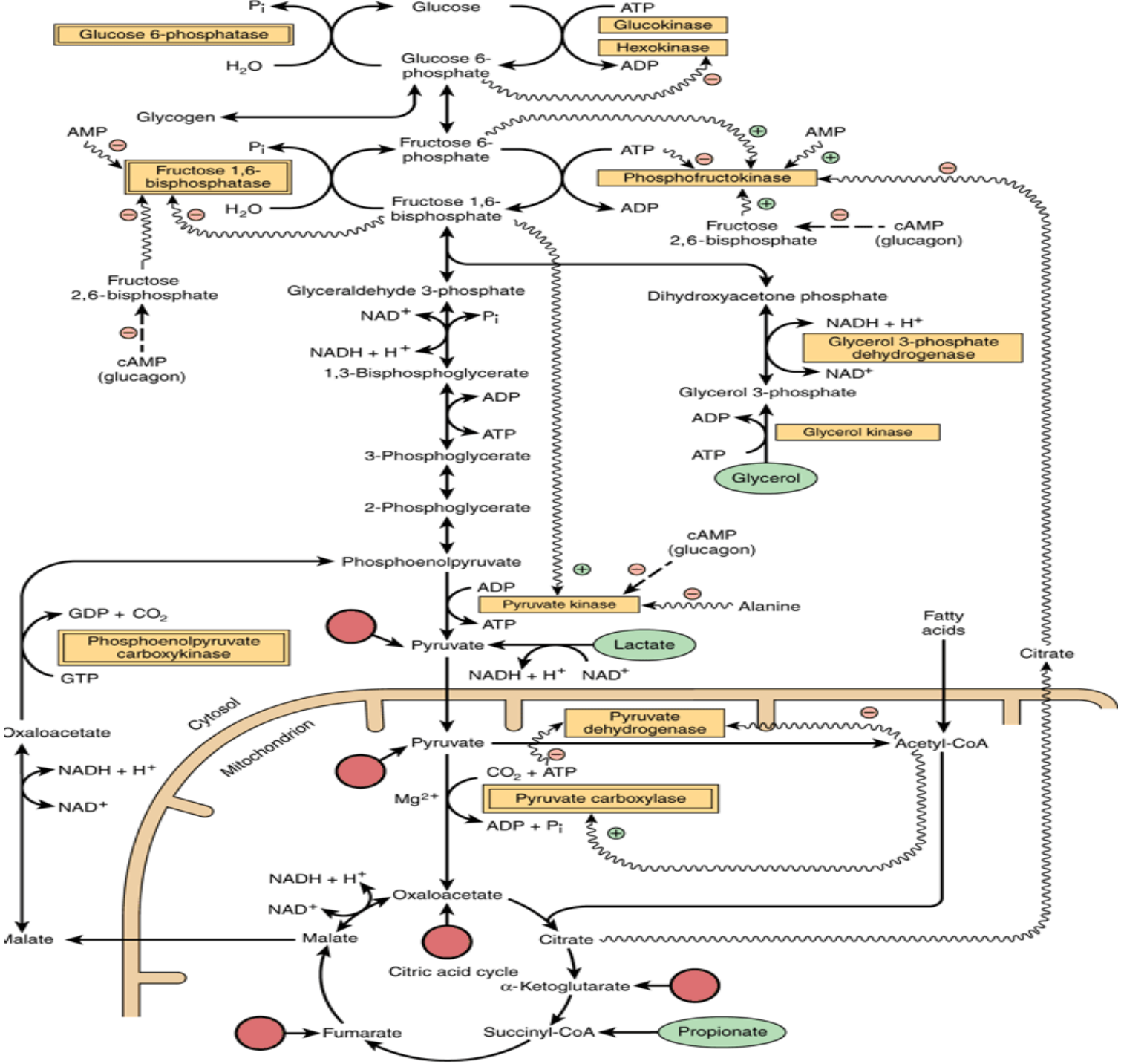
Many of the reaction steps involved in gluconeogenesis are catalyzed by the same enzymes that are used in glycolysis.

The non-reversible steps are bypassed with participation of specific to gluconeogenesis enzymes


Glycolysis
Gluconeogenesis
Glucose
hexokinase
glucose 6-phosphatase
Glucose 6-phosphate
phosphohexose isomerase
phosphohexose isomerase
Fructose 6-phosphate
phosphofructokinase-1
fructose 1,6-bisphosphatase
Fructose 1,6-bisphosphate
aldolase
aldolase
Dihydroxyacetone phosphate
Dihydroxyacetone phosphate
triose phosphate isomerase
triose phosphate isomerase
Glyceraldehyde 3-phosphate (2)
glyceraldehyde phosphate dehydrogenase
glyceraldehyde phosphate dehydrogenase
1,2-bisphosphoglycerate (2)
phosphoglycerate kinase
phosphoglycerate kinase
3-phosphoglycerate (2)
phosphoglycerate mutase
phosphoglycerate mutase
2-phosphoglycerate (2)
enolase
enolase
Phosphoenolpyruvate (2)
PEP carboxykinase
pyruvate kinase
Oxaloacetate (2)
Pyruvate (2)
pyruvate carboxylase

Scheme of Glyconeogenesis

Harper's Illustrated Biochemistry


Glucose
Glucose 6-phosphatase
P_i
H_2O
Glucokinase
Hexokinase
ATP
ADP
Glucose 6-phosphate
Glycogen
AMP
Fructose 1,6-bisphosphatase
Fructose 6-phosphate
Phosphofructokinase
Fructose 1,6-bisphosphate
Fructose 2,6-bisphosphate
cAMP (glucagon)
Glyceraldehyde 3-phosphate
Dihydroxyacetone phosphate
NAD^+
$NADH + H^+$
Glycerol 3-phosphate dehydrogenase
1,3-Bisphosphoglycerate
Glycerol 3-phosphate
Glycerol kinase
Glycerol
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
Pyruvate kinase
Alanine
$GDP + CO_2$
GTP
Phosphoenolpyruvate carboxykinase
Pyruvate
Lactate
Fatty acids
Citrate
Cytosol
Mitochondrion
Oxaloacetate
Pyruvate dehydrogenase
Acetyl-CoA
$CO_2 + ATP$
Mg^{2+}
Pyruvate carboxylase
$ADP + P_i$
Malate
Citric acid cycle
α-Ketoglutarate
Fumarate
Succinyl-CoA
Propionate

Key Reactions of Glyconeogenesis

Pyruvate → Oxaloacetate

a biotin-dependent reaction catalyzed by

pyruvate carboxylase

take place in the mitochondria

Oxaloacetate → Phosphoenolpyruvate

GTP-dependent ***PEP carboxykinase***

take place in the cytoplasm

Key Reactions of Glyconeogenesis

Fructose 1,6-bisphosphate →

Fructose 6-phosphate

fructose 1,6-bisphosphatase

is an important regulation point in gluconeogenesis

I:Fructose 2,6-bisphosphate

Glucose 6-phosphate → Glucose

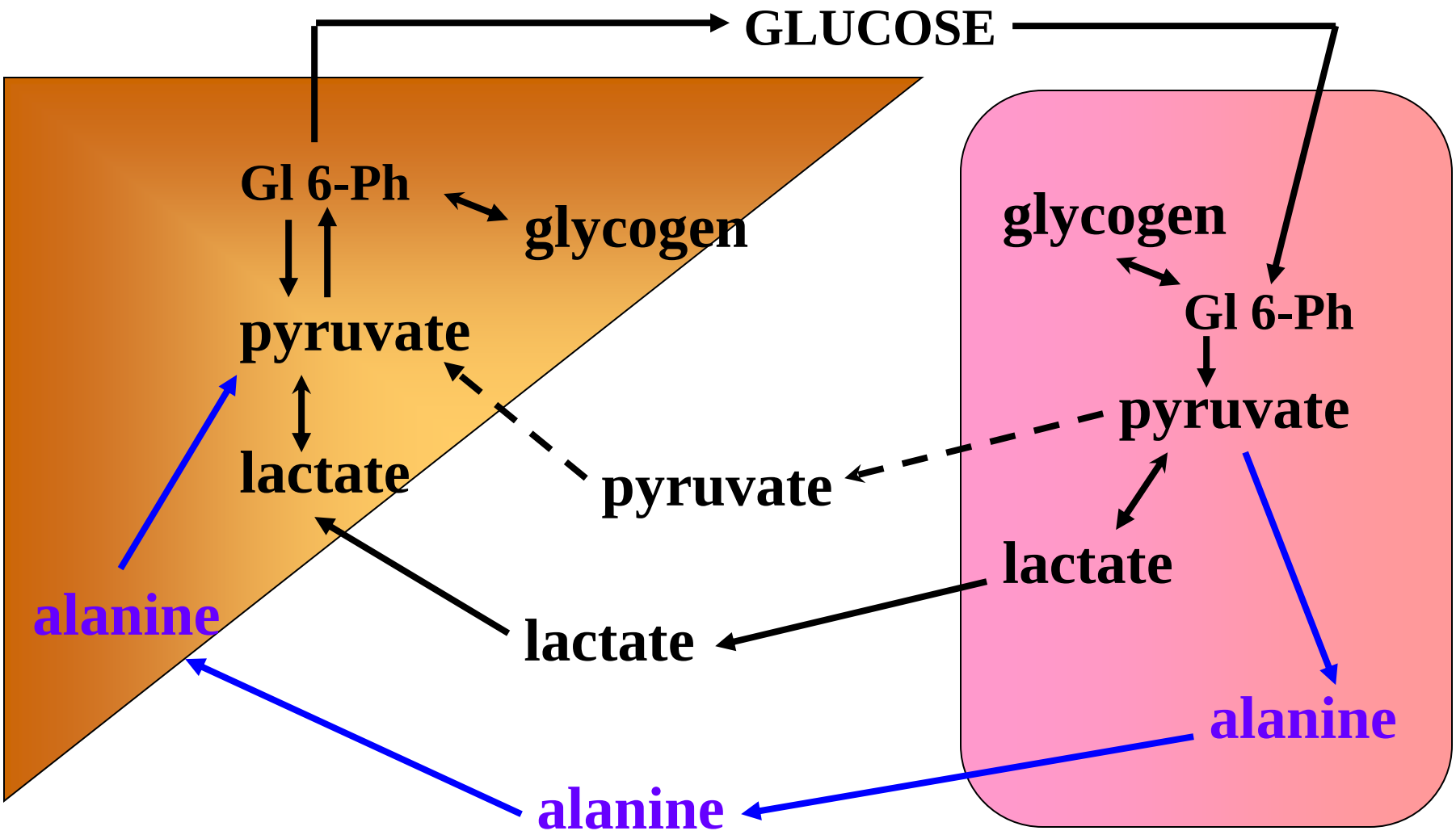
glucose 6-phosphatase

Cori cycle

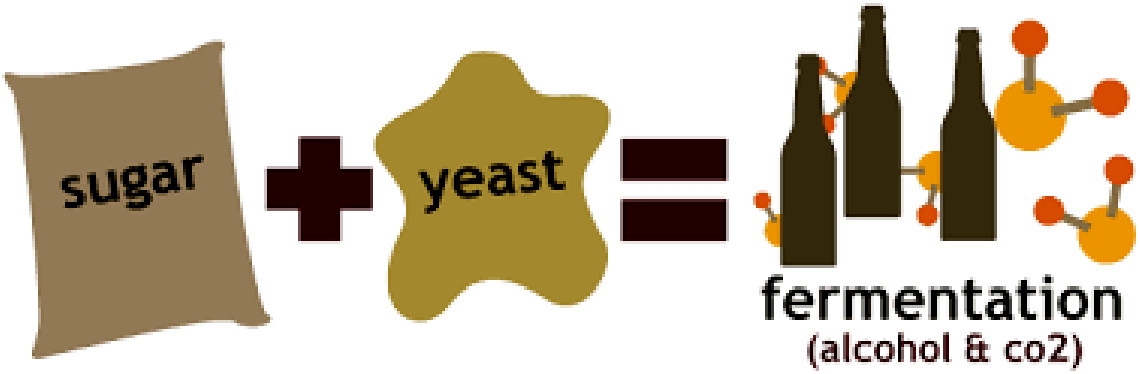
Lactate can be further metabolised only by its reconversion to pyruvate. Lactate and pyruvate can readily diffuse out from the cells in which they are produced and pass into the circulation. From circulation, they are removed by the liver and in liver cells they are reconverted to form glucose and glycogen by gluconeogenesis.

This cycle is referred to as Cori cycle.

Cori cycle

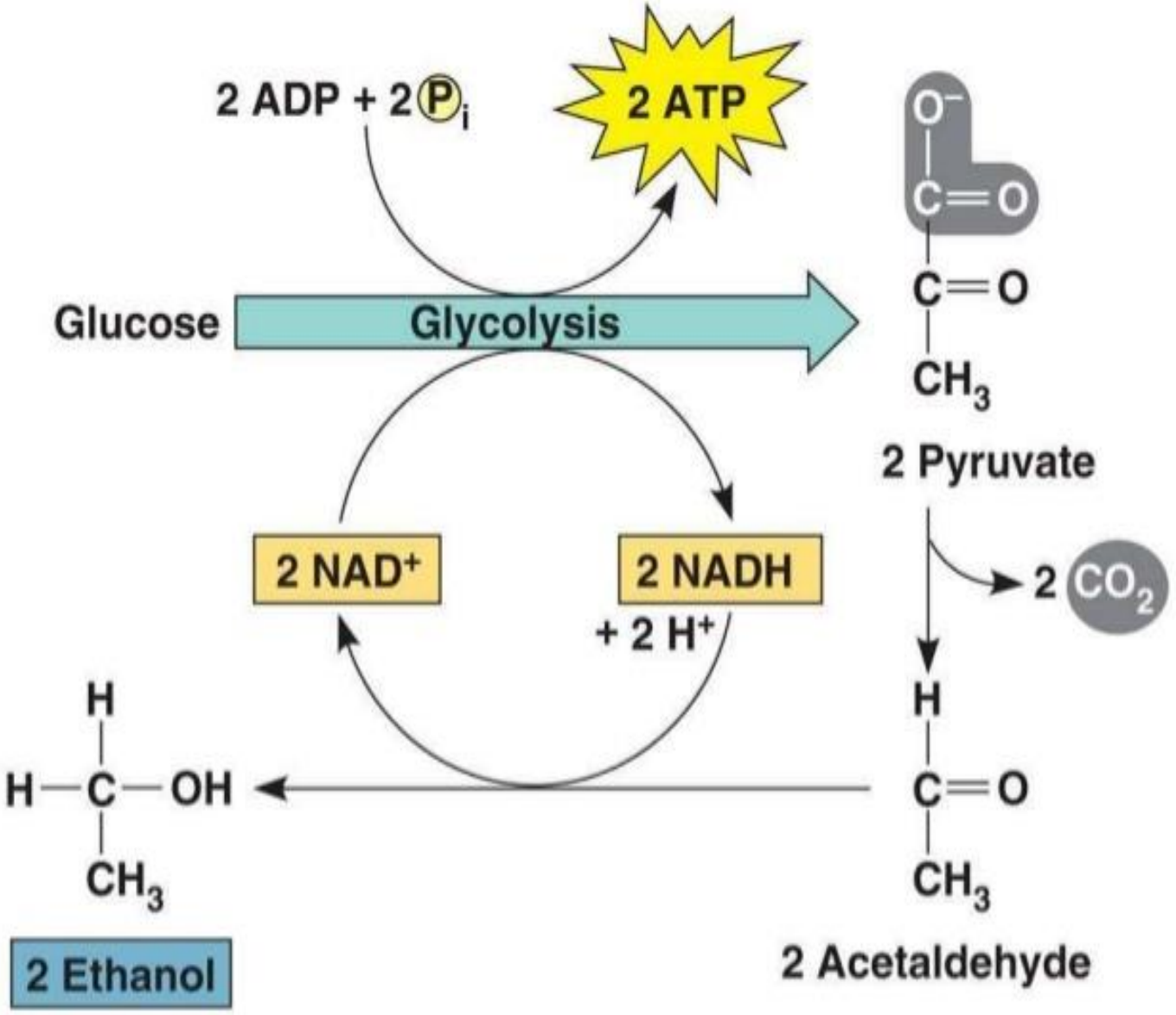

GLUCOSE
Gl 6-Ph
glycogen
pyruvate
lactate
alanine
pyruvate
lactate
alanine
glycogen
Gl 6-Ph
pyruvate
lactate
alanine

Alcohol fermentation



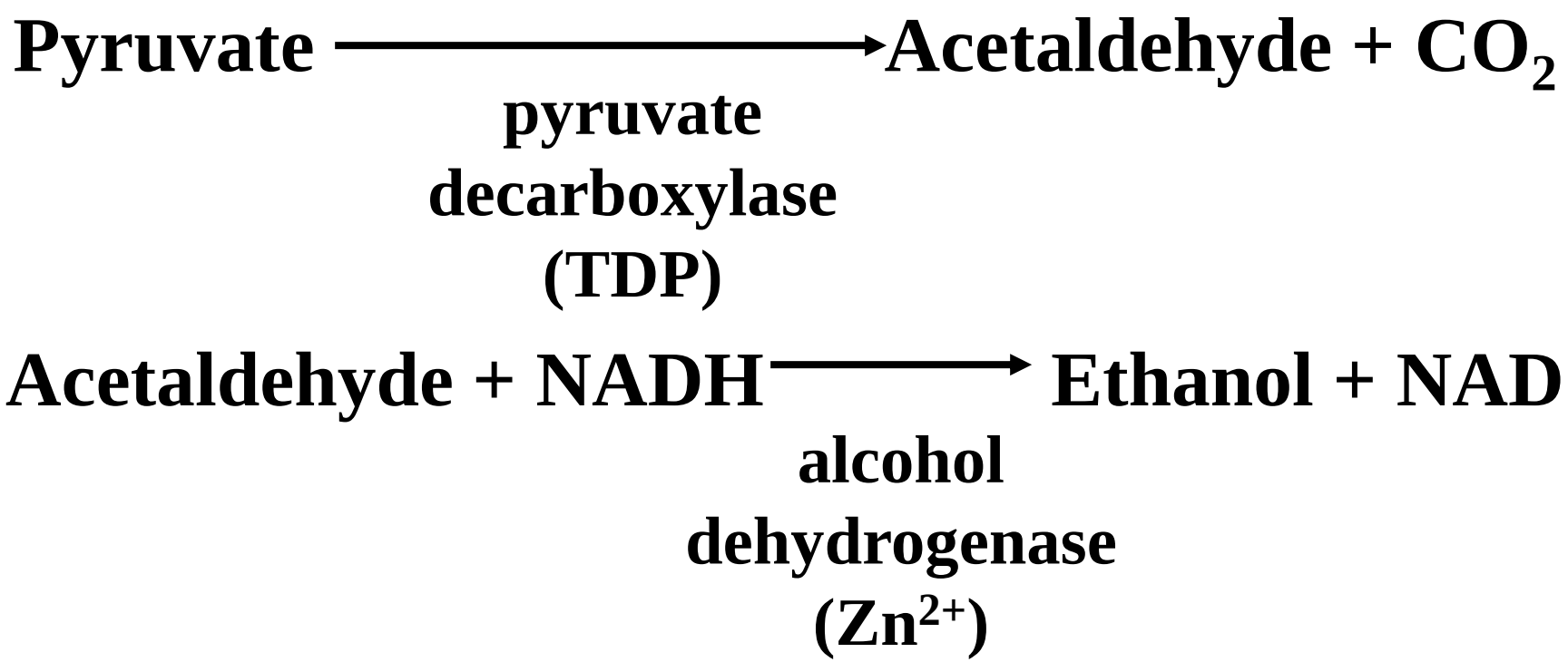
- **Yeast and a few other microorganisms use alcohol fermentation that produces ethyl alcohol and carbon dioxide.**
- **This process is used to produce alcoholic beverages and causes bread dough to rise**

Alcohol fermentation



(a) Alcohol fermentation

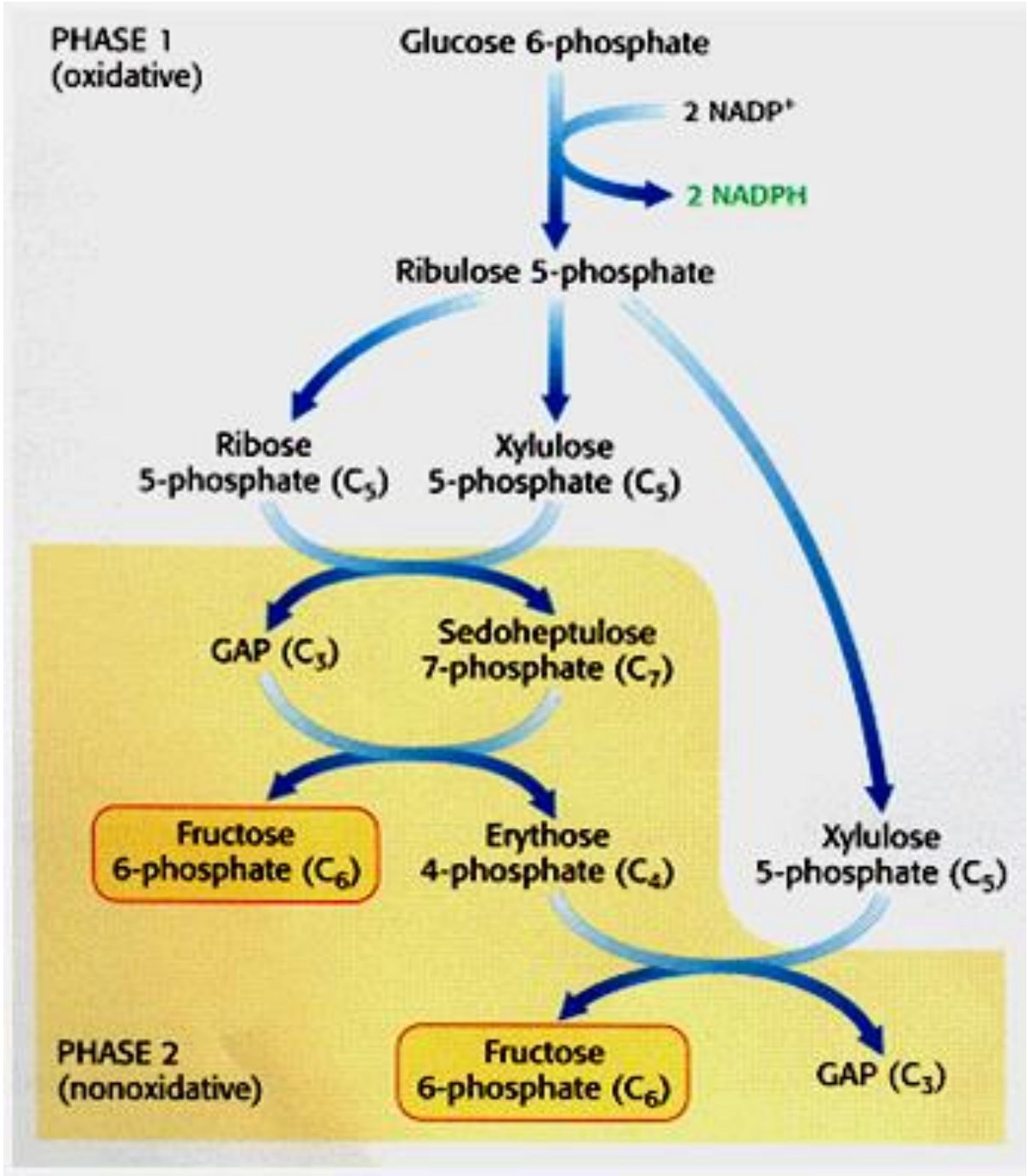
Alcohol fermentation



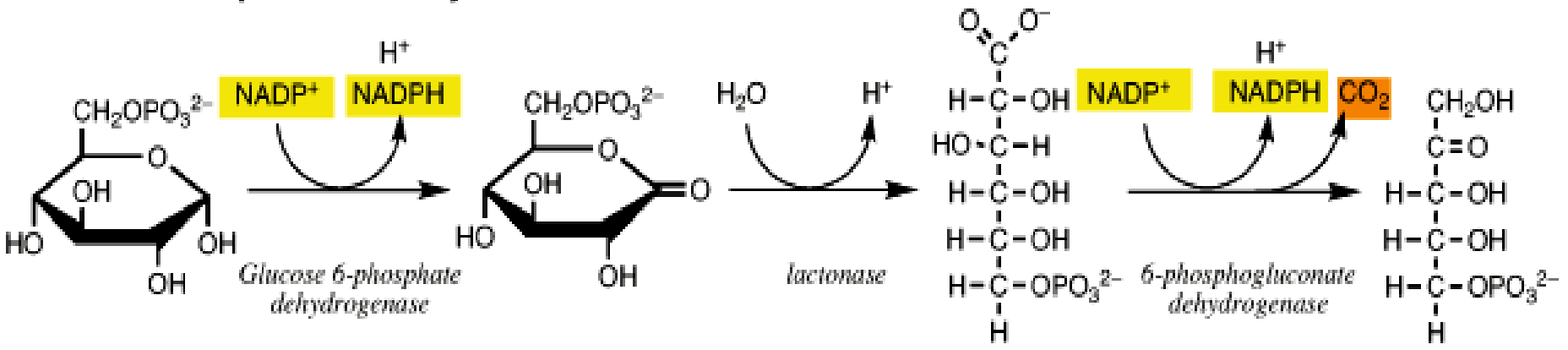
Pentose Phosphate Pathway

- **formation of NADPH for synthesis of fatty acids and steroids**

- **the synthesis of ribose for nucleotide biosynthesis**

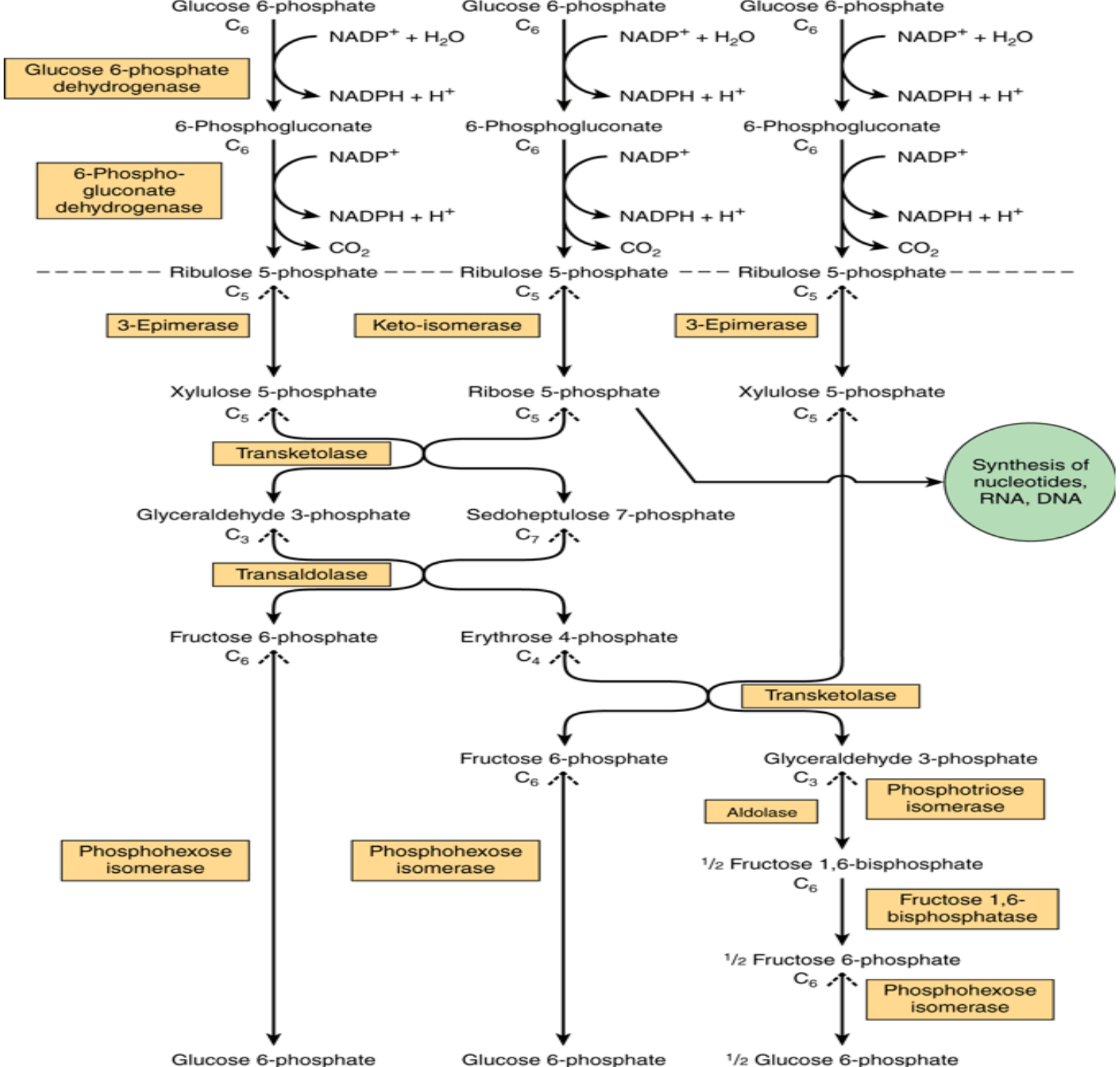

PHASE 1
(oxidative)
Glucose 6-phosphate
2 NADP+
2 NADPH
Ribulose 5-phosphate
Ribose
5-phosphate (C5)
Xylulose
5-phosphate (C5)
GAP (C3)
Sedoheptulose
7-phosphate (C7)
Fructose
6-phosphate (C6)
Erythose
4-phosphate (C4)
Xylulose
5-phosphate (C5)
PHASE 2
(nonoxidative)
Fructose
6-phosphate (C6)
GAP (C3)

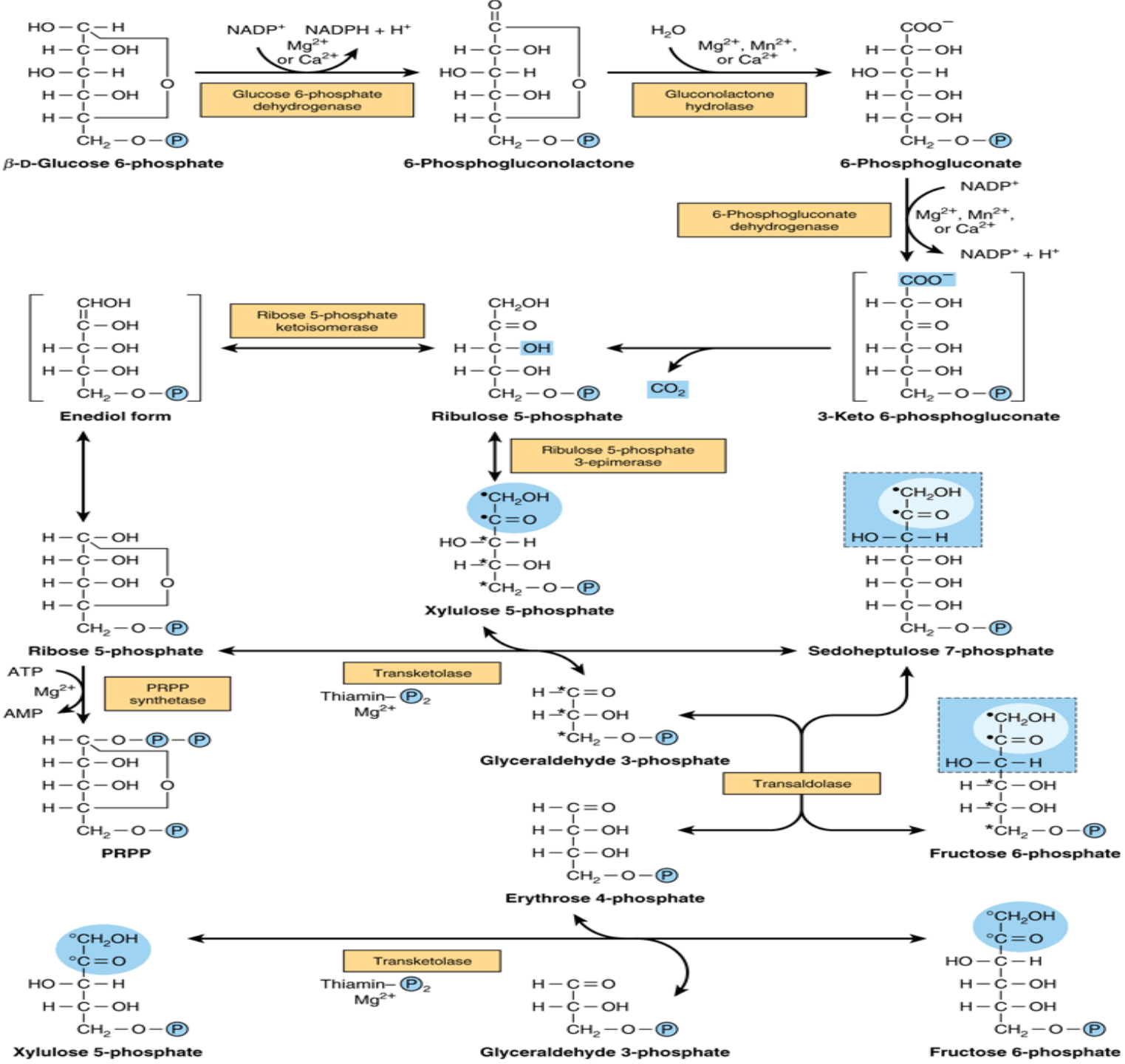
1. Pentose Phosphate Pathway: Oxidative Phase



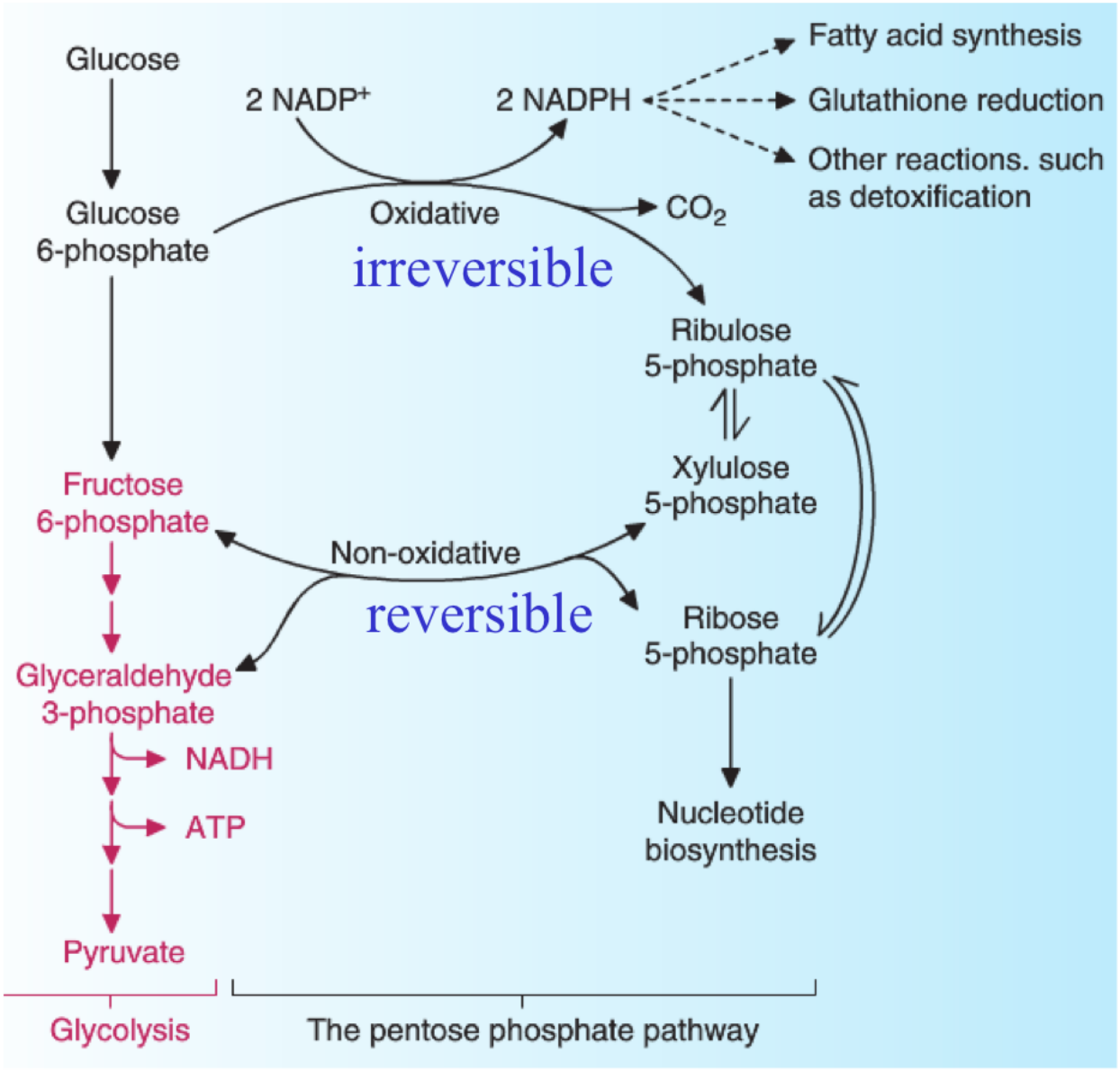
Reactions of Pentose Phosphate Pathway

Harper's Illustrated Biochemistry


Glucose 6-phosphate
C6
NADP+ + H2O
NADPH + H+
Glucose 6-phosphate dehydrogenase
6-Phosphogluconate
C6
NADP+
NADPH + H+
CO2
6-Phospho-gluconate dehydrogenase
Ribulose 5-phosphate
C5
3-Epimerase
Keto-isomerase
Xylulose 5-phosphate
Ribose 5-phosphate
Transketolase
Glyceraldehyde 3-phosphate
C3
Sedoheptulose 7-phosphate
C7
Transaldolase
Fructose 6-phosphate
C6
Erythrose 4-phosphate
C4
Synthesis of nucleotides, RNA, DNA
Aldolase
Phosphotriose isomerase
Phosphohexose isomerase
1/2 Fructose 1,6-bisphosphate
Fructose 1,6-bisphosphatase
1/2 Fructose 6-phosphate
1/2 Glucose 6-phosphate


β-D-Glucose 6-phosphate
NADP+ NADPH + H+
Mg2+ or Ca2+
Glucose 6-phosphate dehydrogenase
6-Phosphogluconolactone
H2O
Mg2+, Mn2+, or Ca2+
Gluconolactone hydrolase
6-Phosphogluconate
6-Phosphogluconate dehydrogenase
NADP+
Mg2+, Mn2+, or Ca2+
NADP+ + H+
3-Keto 6-phosphogluconate
CO2
Ribose 5-phosphate ketoisomerase
Enediol form
Ribulose 5-phosphate
Ribulose 5-phosphate 3-epimerase
Xylulose 5-phosphate
Ribose 5-phosphate
Sedoheptulose 7-phosphate
ATP
Mg2+
AMP
PRPP synthetase
PRPP
Transketolase
Thiamin–P2
Mg2+
Glyceraldehyde 3-phosphate
Transaldolase
Fructose 6-phosphate
Erythrose 4-phosphate
Xylulose 5-phosphate
Transketolase
Thiamin–P2
Mg2+
Glyceraldehyde 3-phosphate
Fructose 6-phosphate

Pentose phosphate pathway and its link to glycolysis



- NADPH
- Ribose 5-P
- Glucose 6-P dehydrogenase deficiency

REGULATION OF PENTOSE PHOSPHATE PATHWAY

- **The entry of glucose 6-phosphate into the pentose phosphate pathway is controlled by the cellular concentration of NADPH**
- **NADPH is a strong inhibitor of glucose 6-phosphate dehydrogenase**
- **As NADPH is used in various pathways, inhibition is relieved, and the enzyme is accelerated to produce more NADPH**

- G6PD deficiency is an allelic abnormality which is inherited in an X-linked recessive fashion.
- G6PD deficiency is also known as "favism" since G6PD deficient individuals are also sometimes allergic to fava beans.
- Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency is the most common human enzyme deficiency in the world; it affects an estimated 400 million people.

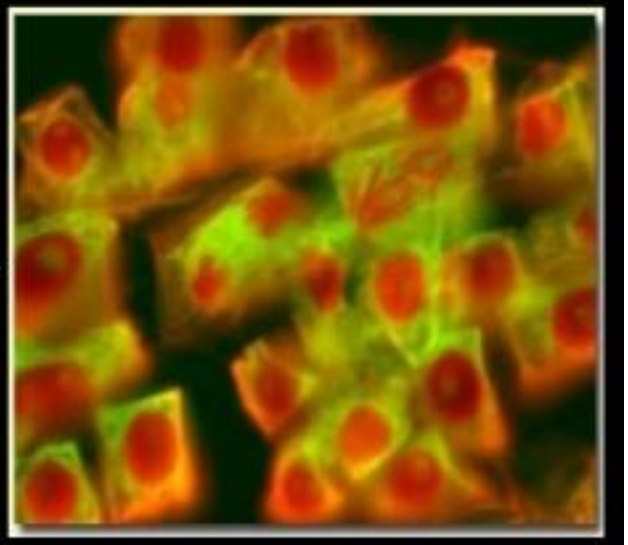
Manifestation after:
- foods (beans)
- drugs
- infection

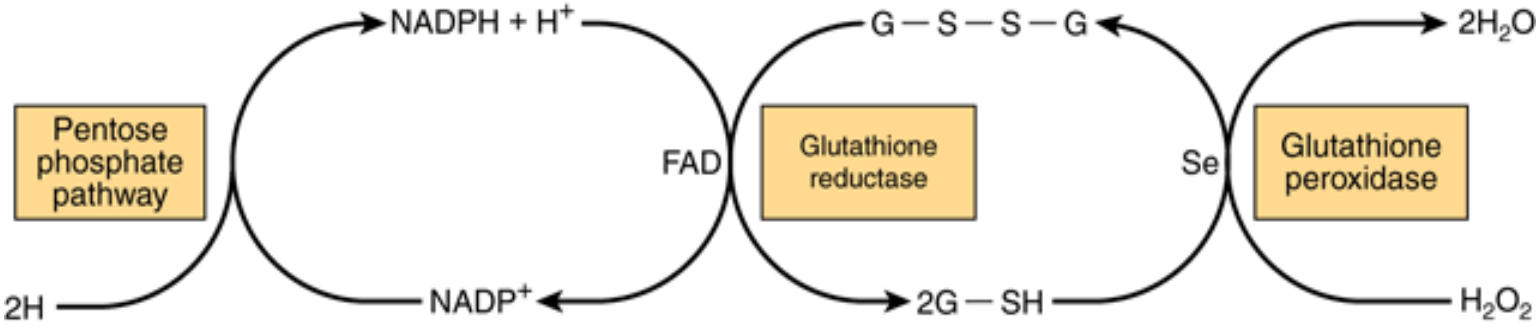
Effect
- oxidative stress → haemolysis

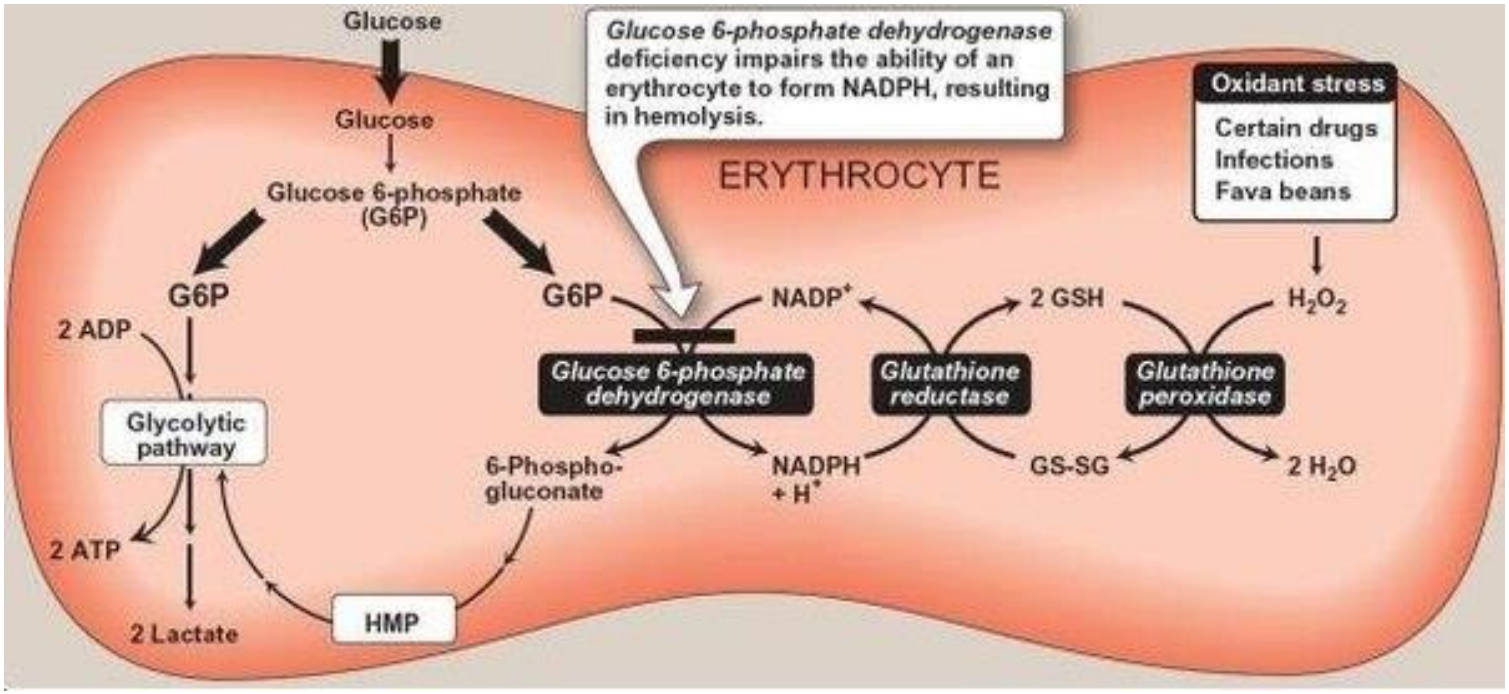
WHAT IS FAVISM ?

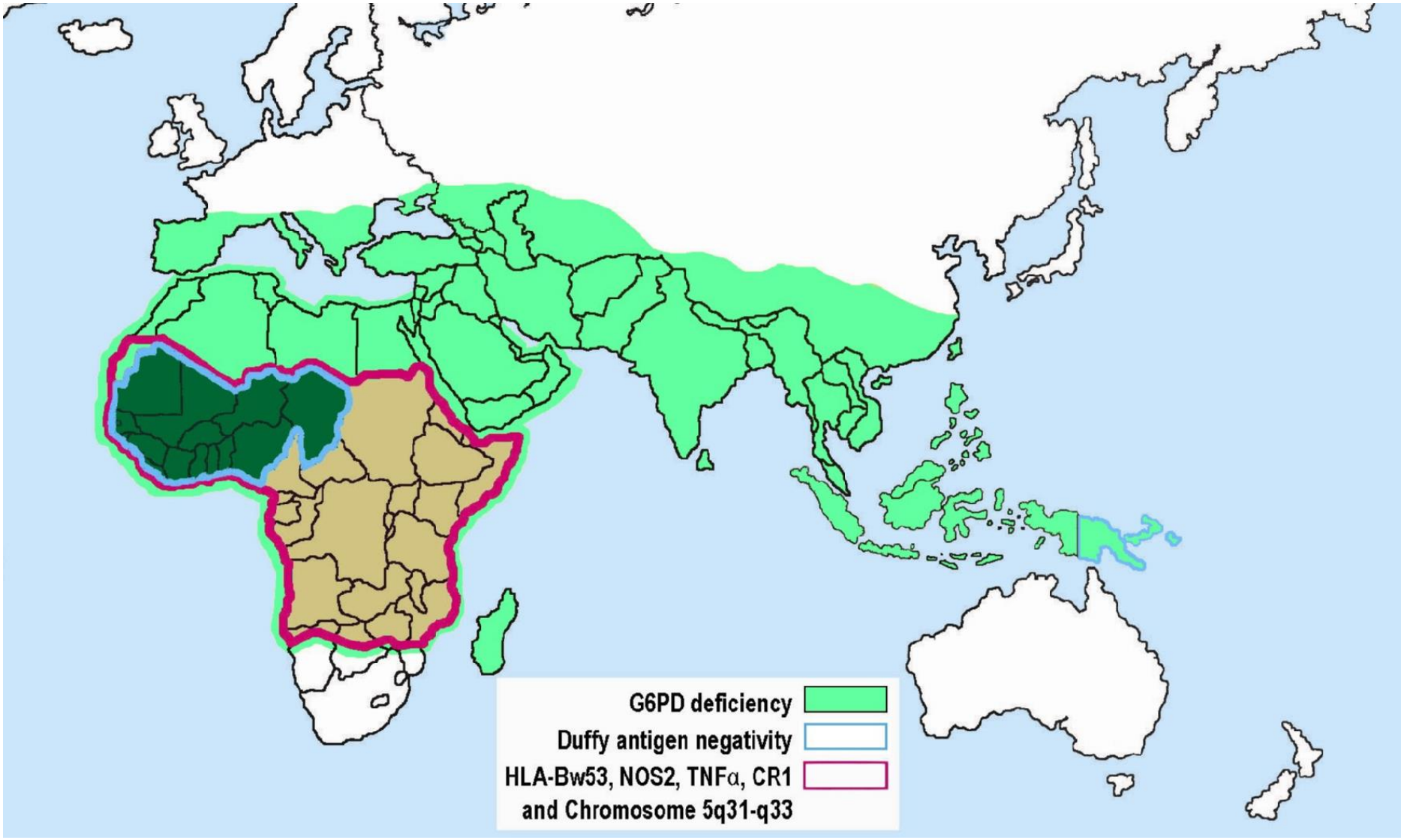
- Favism is formally defined as hemolytic response to the consumption of broad beans
- Favism is disorder characterized by hemolytic reaction to the consumption of broad beans
- All individual with favism show G6PD deficiency
- However not all individuals with G6PD deficiency

Show favism




NADPH + H+
G — S — S — G
2H2O
Pentose phosphate pathway
FAD
Glutathione reductase
Se
Glutathione peroxidase
2H
NADP+
2G — SH
H2O2


Glucose
Glucose
Glucose 6-phosphate (G6P)
Glucose 6-phosphate dehydrogenase deficiency impairs the ability of an erythrocyte to form NADPH, resulting in hemolysis.
ERYTHROCYTE
Oxidant stress
Certain drugs
Infections
Fava beans
G6P
2 ADP
Glycolytic pathway
2 ATP
2 Lactate
HMP
6-Phospho-gluconate
G6P
NADP+
Glucose 6-phosphate dehydrogenase
NADPH + H+
2 GSH
Glutathione reductase
GS-SG
H2O2
Glutathione peroxidase
2 H2O


G6PD deficiency
Duffy antigen negativity
HLA-Bw53, NOS2, TNFα, CR1
and Chromosome 5q31-q33