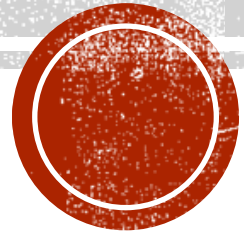
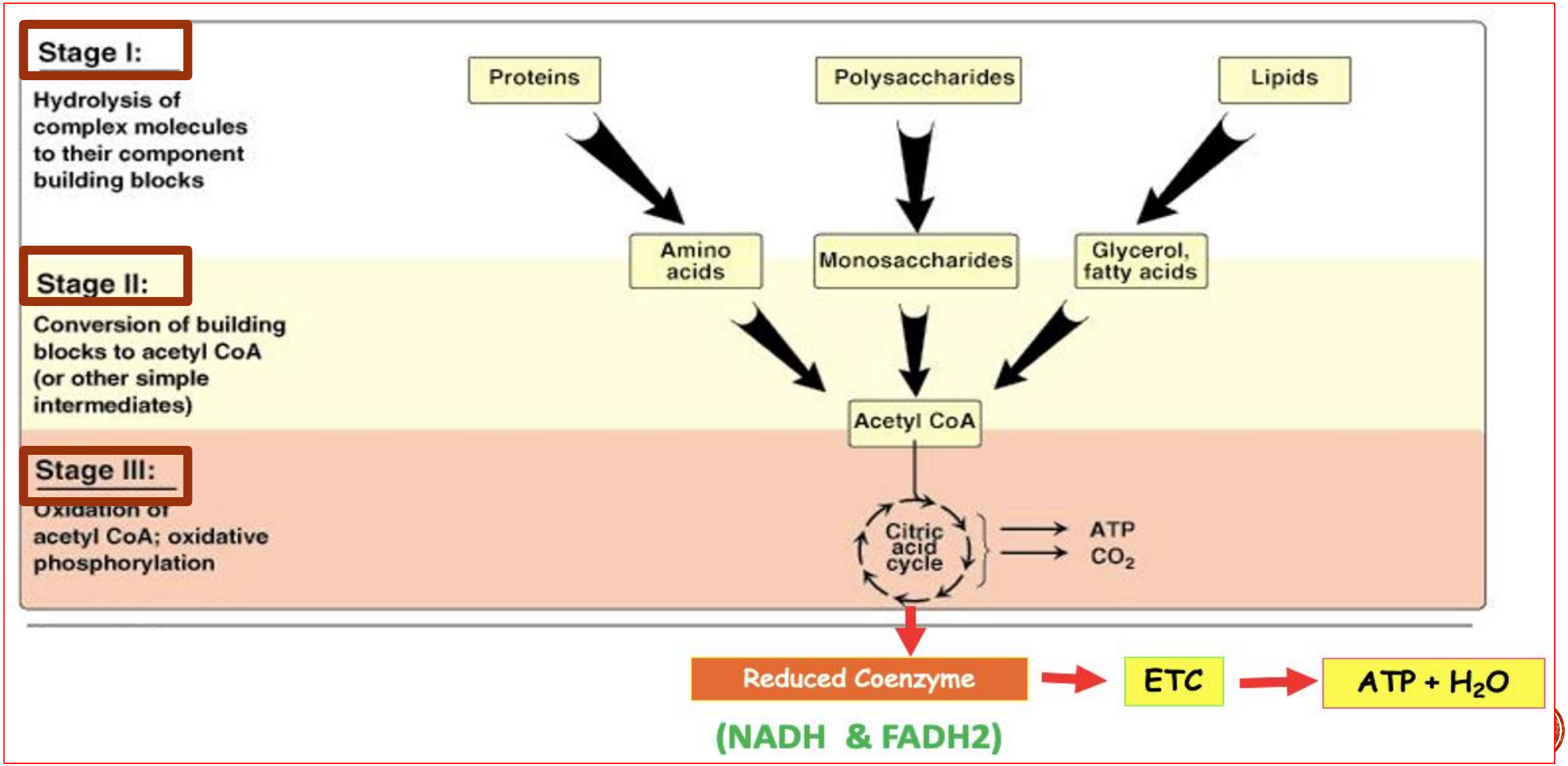
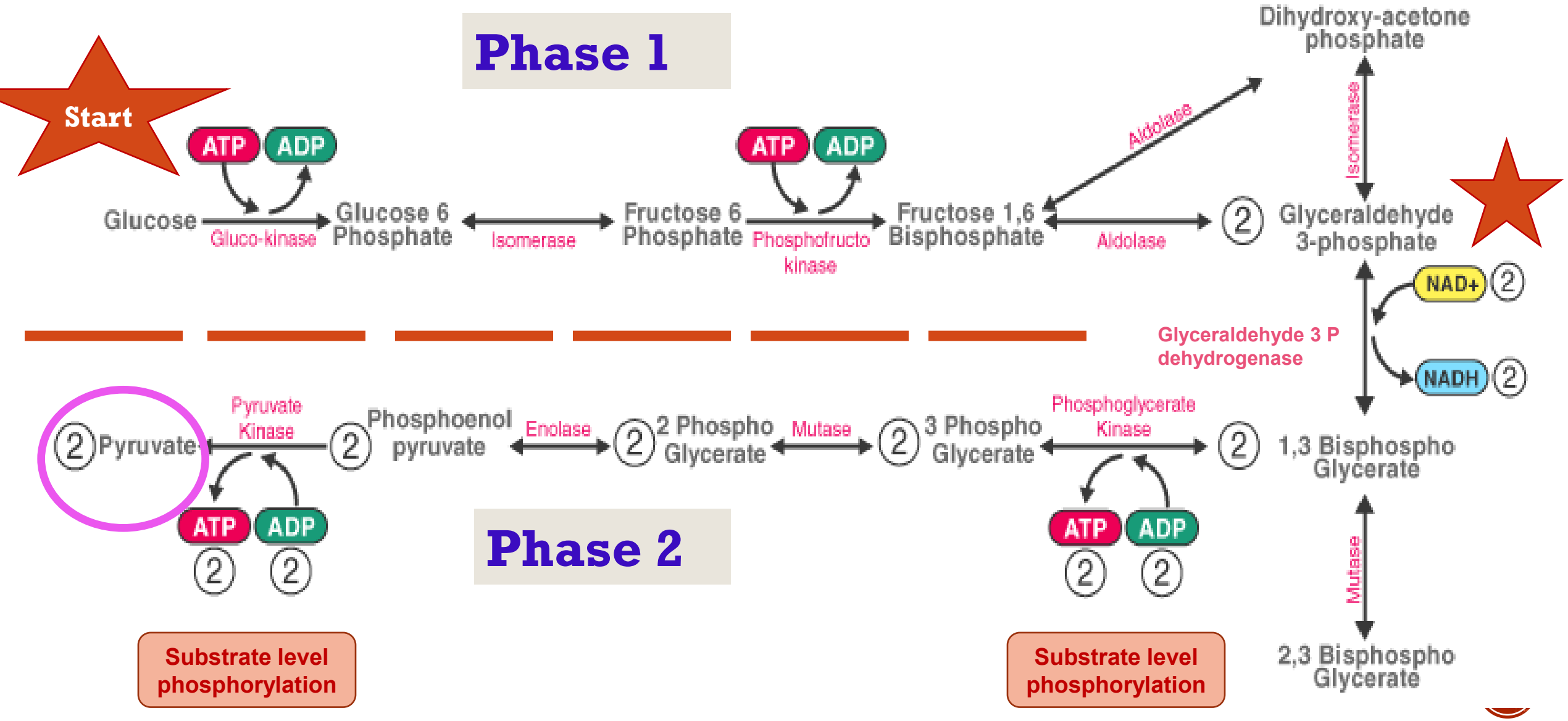
Glucose Oxidation (II. Krebs's cycle)



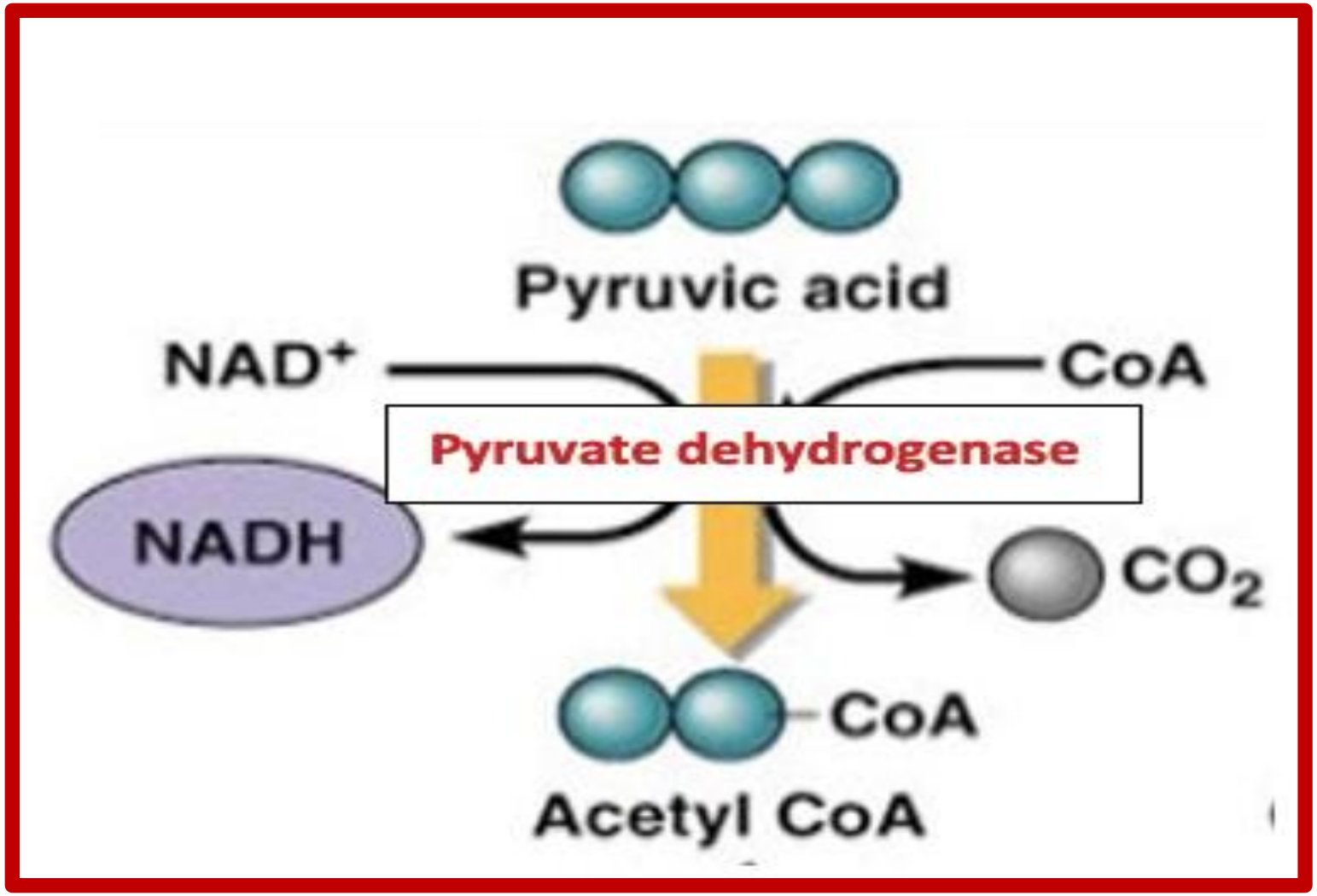
Fate of food staff & stages of metabolism



2 Phases of glycolysis (10 enzymatic reactions)



Oxidative decarboxylation of pyruvate



Krebs cycle (TCA)

1. Definition
2. Site
3. Phases (Steps)
4. Products
5. Importance
6. Regulation

Krebs cycle / Tricarboxylic acid cycle (TCA)

Definition:

It is a series of biochemical reactions that are responsible for complete oxidation of acetyl CoA to 2 CO_2, with production of ATP and reducing equivalents (NADH & $FADH_2$)

Site:

Mitochondria of all cells except RBCs (no mitochondria)

Products of 1 acetyl CoA in Krebs cycle

2 CO_2

1 ATP
(substrate level phosphorylation)

3 NADH+H

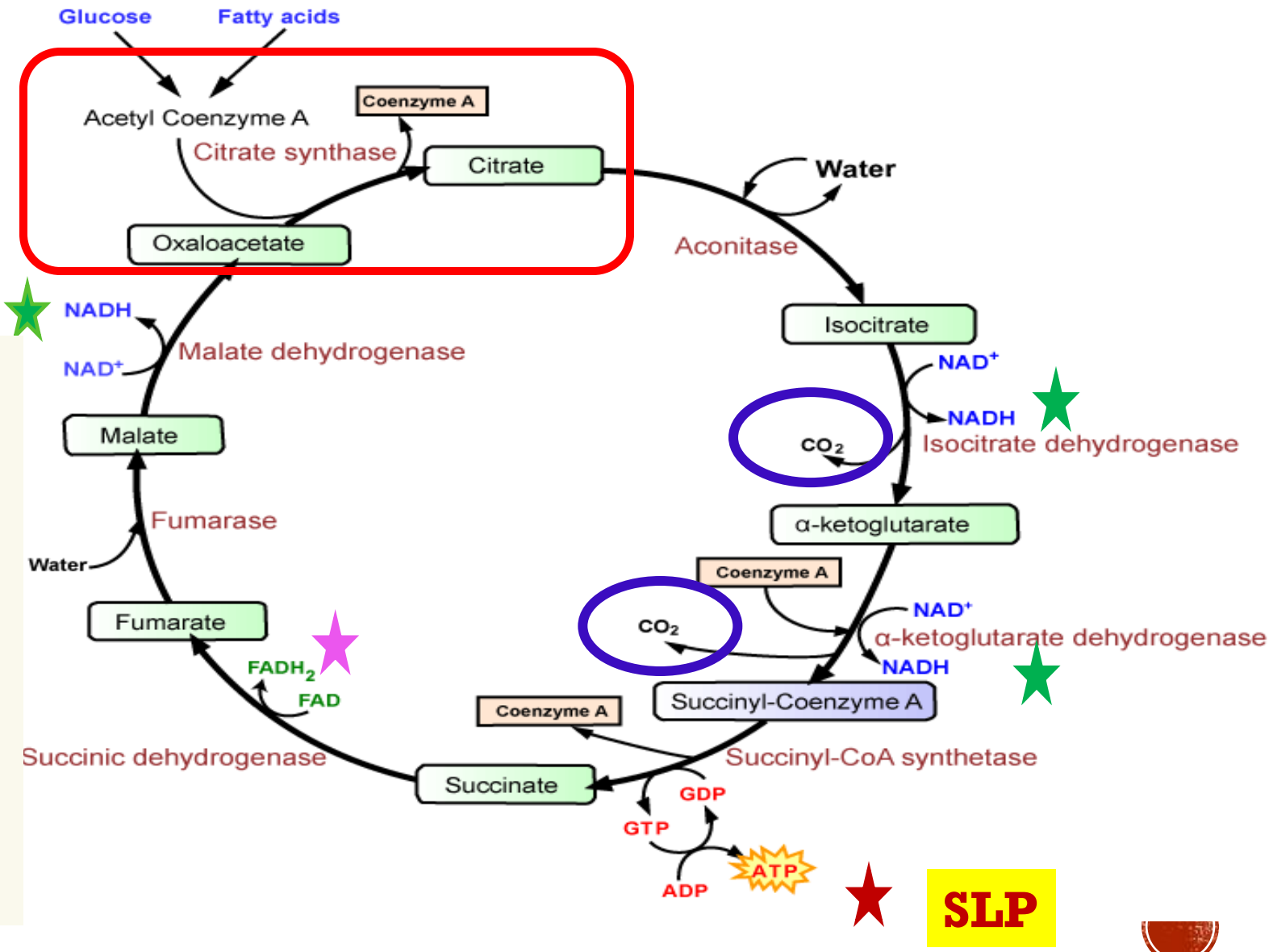
1 $FADH_2$

Steps of Krebs cycle

I) Condensation of Acetyl CoA (2C) + Oxoacetate (4C) to form **Citrate (6C)**

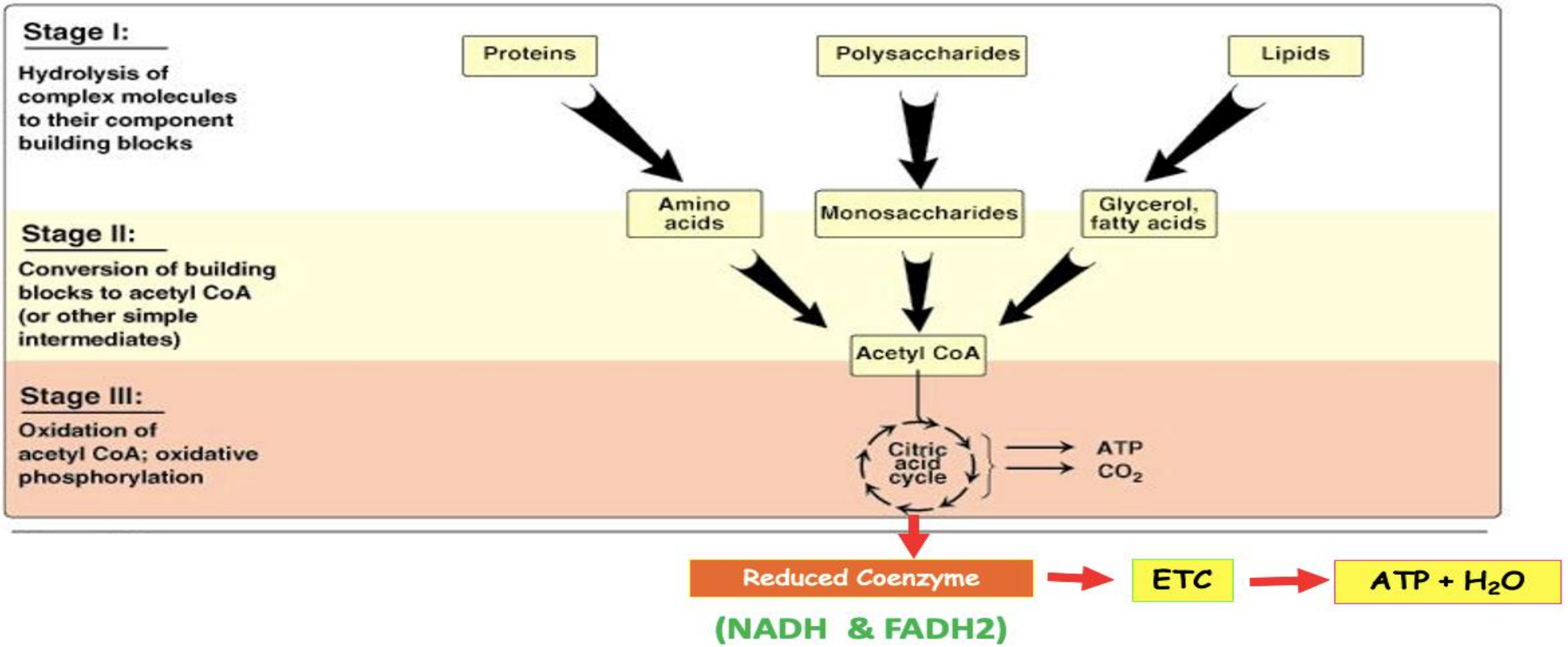
II) Oxidation: series of oxidation reactions to regenerate Oxalacetate. with the release of:

- ✓ **2 CO2**→ then regeneration of Oxalacetate.
- ✓ **1 ATP** is formed at SLP
- ✓ all energy is captured as **3 NADH+H & 1 FADH2**



Importance of Krebs cycle

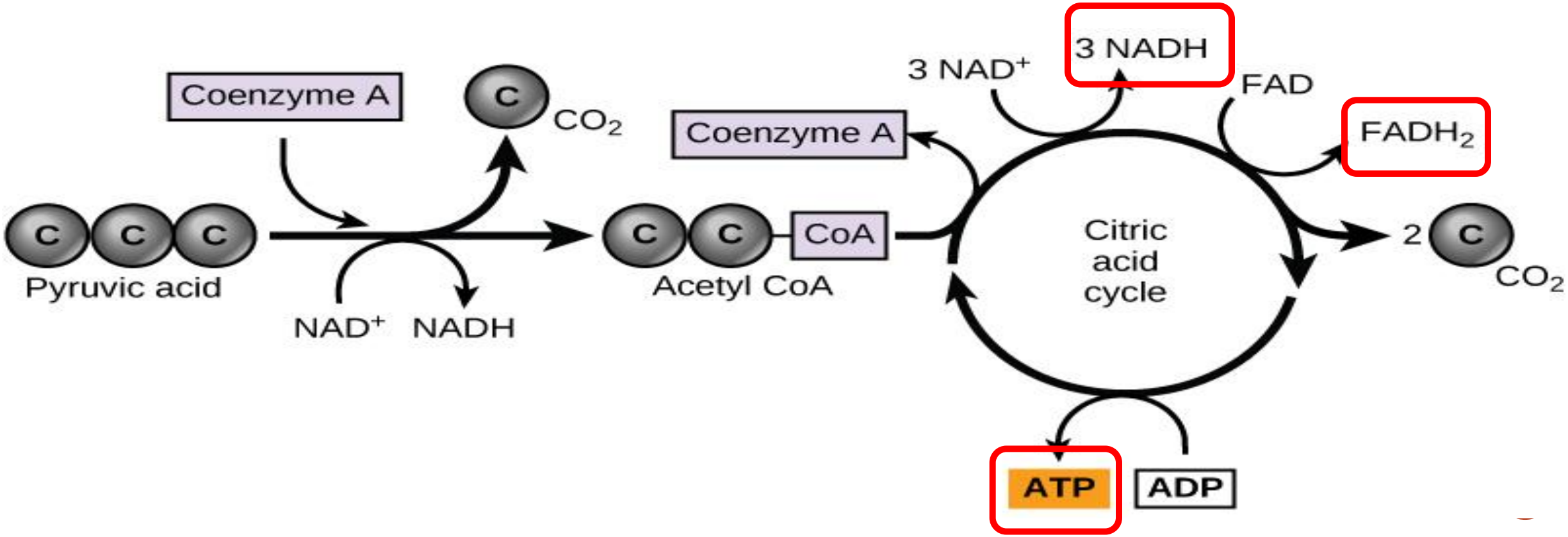
1) **Final common metabolic pathway** for oxidation of carbohydrates, fats & proteins



Importance of Krebs cycle (cont.)

2) Energy production / 1 molecule acetyl CoA. (**12 ATP**)

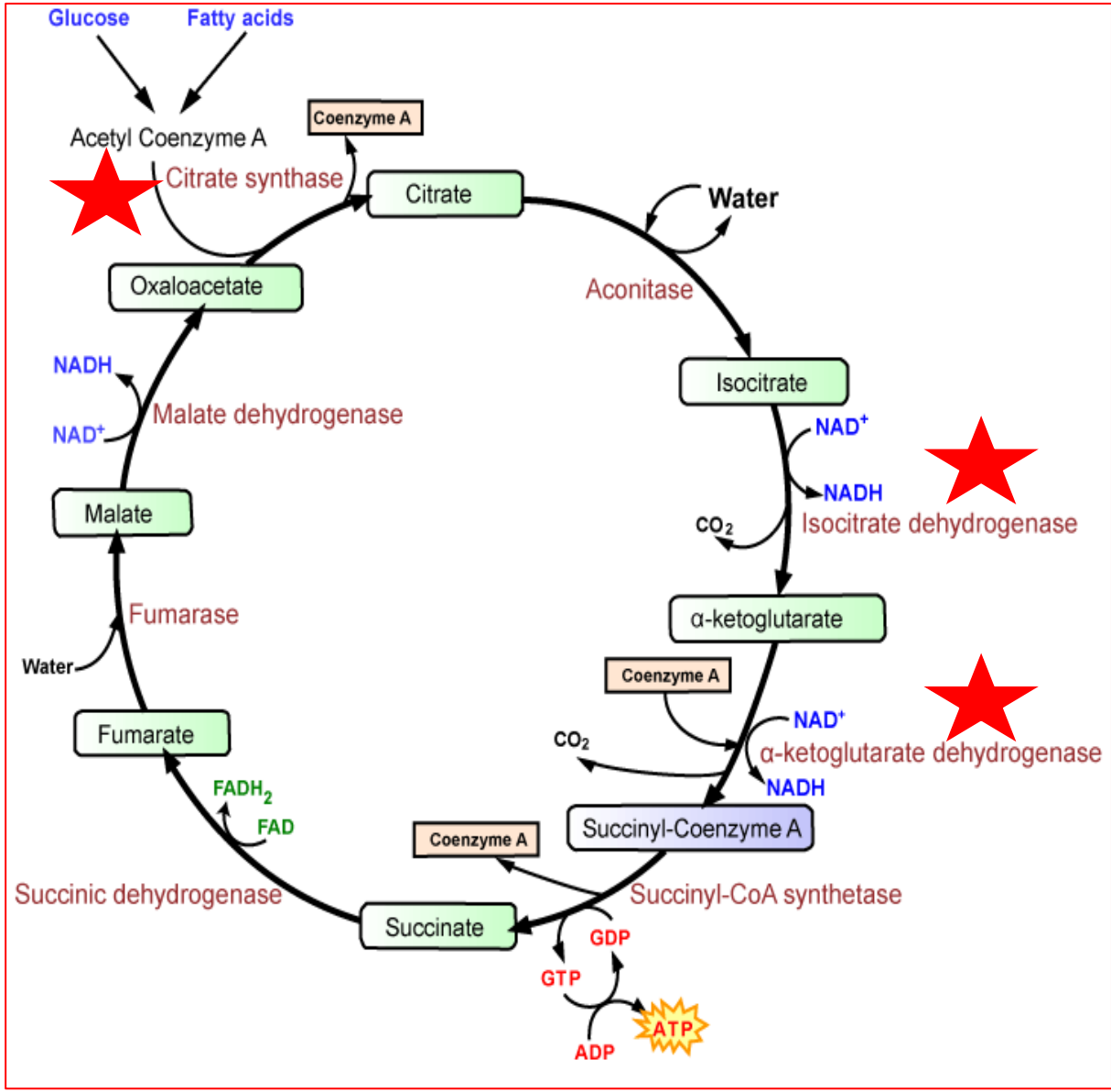
- **1 ATP : at substrate level phosphorylation**
- **1 FADH2→ ETC→ (1x2) → 2 ATP**
- **3 NADH → ETC→ (3x3) → 9 ATP**



Regulation of Krebs cycle (Regulatory enzymes of TCA)

- **Krebs cycle is regulated at the 3 irreversible steps catalyzed by:**

1. Citrate synthase
2. Isocitrate dehydrogenase
3. α-ketoglutarate dehydrogenase

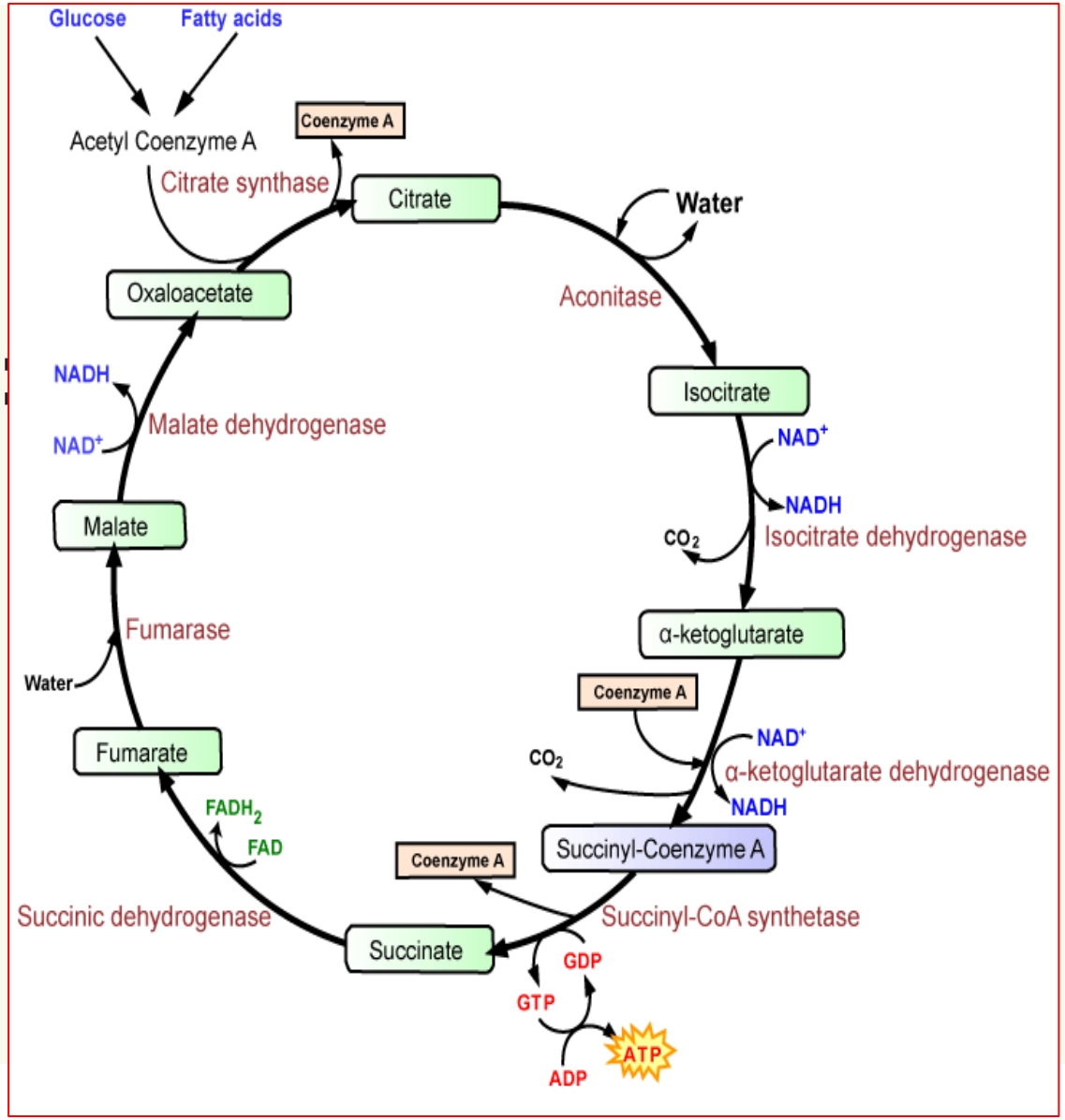


Regulation of Krebs cycle (energy level of the cell)

❖ **Krebs cycle is regulated according to the energy level:**

1. **High ATP or NADH →**
   Down regulate these 3 enzymes

2. **High ADP or NAD→**
   upregulate of these 3 enzymes



Regulation of Krebs cycle (activators and inhibitors)

❖ Krebs cycle is activated and inhibited by other molecules:

Activator of Krebs

1. Ca : Activates **Citrate synthase enzyme**:

Ca2+ which increases in concentration during muscular contraction (there is increased energy demand).

Inhibitors of TCA cycle:

1. **Fluoroacetate**: inhibits **aconitase**
2. **Arsenate:** inhibits **α ketoglutarate dehydrogenase**
3. **Malonyl COA**: inhibits **succinate dehydrogenase**

Complete oxidation of 1 Glucose

Pathway	Energy production
Aerobic Glycolysis **(Glucose→2 pyruvate)**	2 ATP 2 NADH+H→ 6 ATP
Oxidative decarboxylation **(pyruvate →acetyl CoA)**	1 NADH+H → 3 ATP **(2 pyruvate → 2 acetyl CoA→ 2 NADH= 6 ATP)**
Krebs Cycle **(Acetyl CoA→ 2 CO2, H2O)**	1 ATP 1 FADH2 → 2 ATP 3 NADH+H → 9 ATP = 12 ATP **(2 acetyl CoA in Krebs cycle (2X 12= 24 ATP)**
Total ATPs / 1 glucose	38 ATPs

1 NADH→ 3 ATP in ETC

1 FADH2→ 2 ATP in ETC

- ✓ **Complete oxidation of 1 glucose by aerobic respiration produces: 38 ATP + 6 CO2**
- ✓ **NB: anerobic glycolysis produces only 2 ATPs (no O2 →so, Krebs cycle, ETC are not working)**
- ✓ **Each ATP = 10,000 calories.**

Summary

MCQs

Which one of the following Krebs cycle enzymes is activated by Ca ?

a) Fumarase
b) Citrate synthase enzyme
c) Aconitase
d) Succinate dehydrogenase
e) α ketoglutarate dehydrogenase

MCQs

The enzyme of TCA cycle is located in:

a) Lysosome
b) Plasma membrane
c) Nucleus
d) Cytoplasm
e) Mitochondria

MCQs

The end product of glycolysis (pyruvate) enter TCA as :

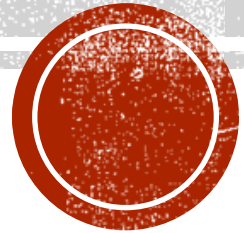
a) Acetyl CoA
b) Pyruvate
c) NADH
d) Glucose
e) Oxalacetate

MCQs

How many ATPs are produced during oxidation of 1 acetyl CoA molecule in TCA?

a) 10
b) 13
c) 8
d) 12
e) 6

Glucose Oxidation
III. Pentose shunt



Hexose Monophosphate Pathway (HMP). (Pentose Shunt)

It is an alternate pathway for oxidation of glucose

Definition:

- It is an alternative pathway for glucose oxidation.
- In which Glucose as (**G6P**) is oxidized and produces:

1- Pentose-5- phosphate, and

2- NADPH for biosynthetic reactions.

No energy is produced from glucose oxidation in HMP

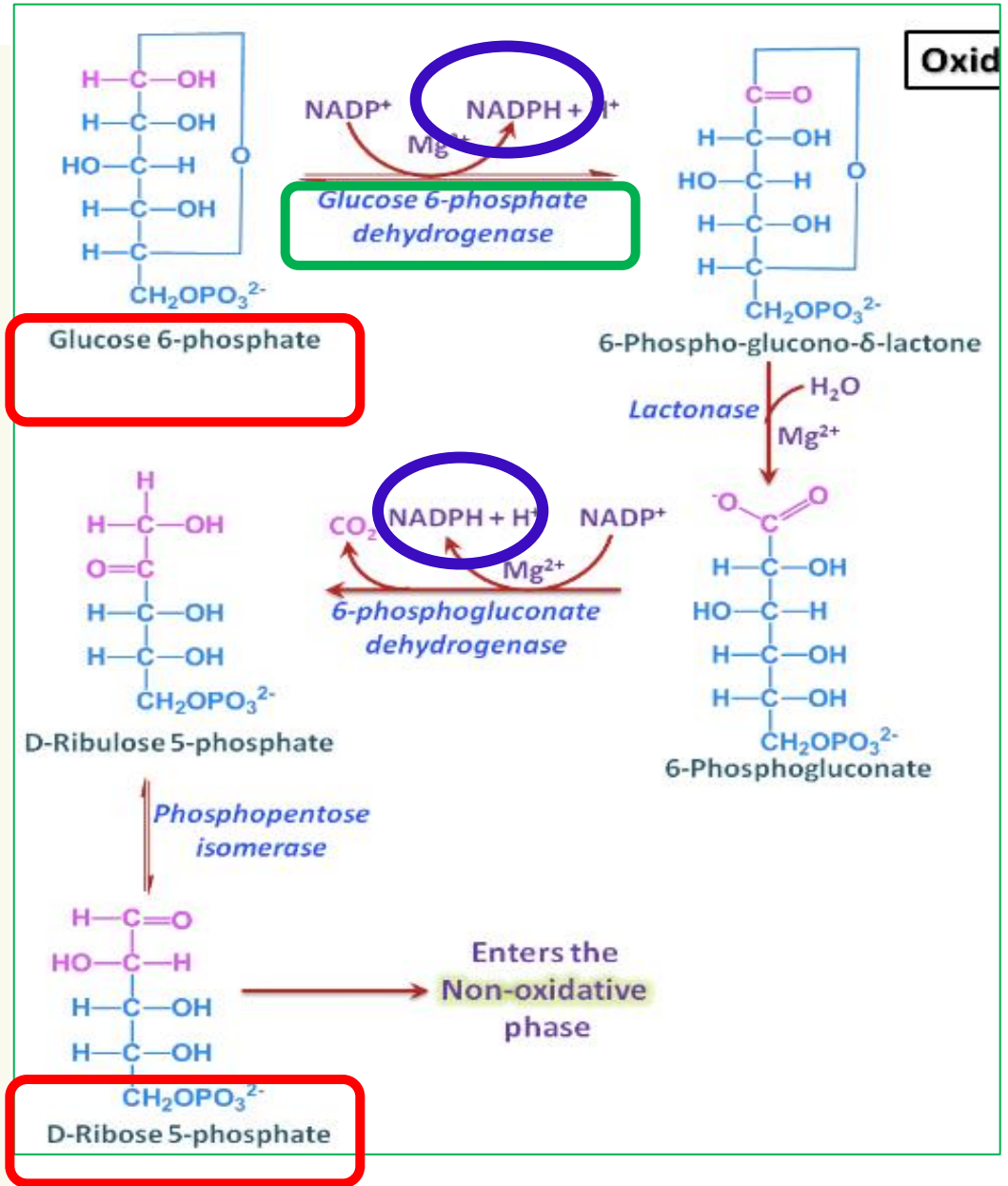
Hexose Monophosphate Pathway (HMP). (Pentose Shunt)

Site:

- ✓ **Cytosol** of many cells especially the followings:
  - ➢ **Liver→ cholesterol & FAs synthesis**
  - ➢ **mammary gland, adipose tissue→ FAs synthesis**
  - ➢ **Testes & ovaries→ male and female sex hormone synthesis**
  - ➢ **Adrenal gland cortex → steroid hormone synthesis**
  - ➢ **Red blood cells→ maintenance of reduced glutathione ******
- ✓ As all these sites undergo **synthetic reactions** that require the presence of **NADPH**

Phases of HMP

- ✓ **Irreversible**
- ✓ **Start by**: Glucose 6 phosphate (G6P)
- ✓ **End by formation of** : **Ribose 5 P** → enter nonoxidative step
- ✓ **Produce: 2 NADPH**
- ✓ Imp enzyme: **G-6-P dehydrogenase** (G6PD)
- ✓ The 1st reaction catalysed by **G-6-P dehydrogenase (G6PD) = (key regulatory enzyme)**

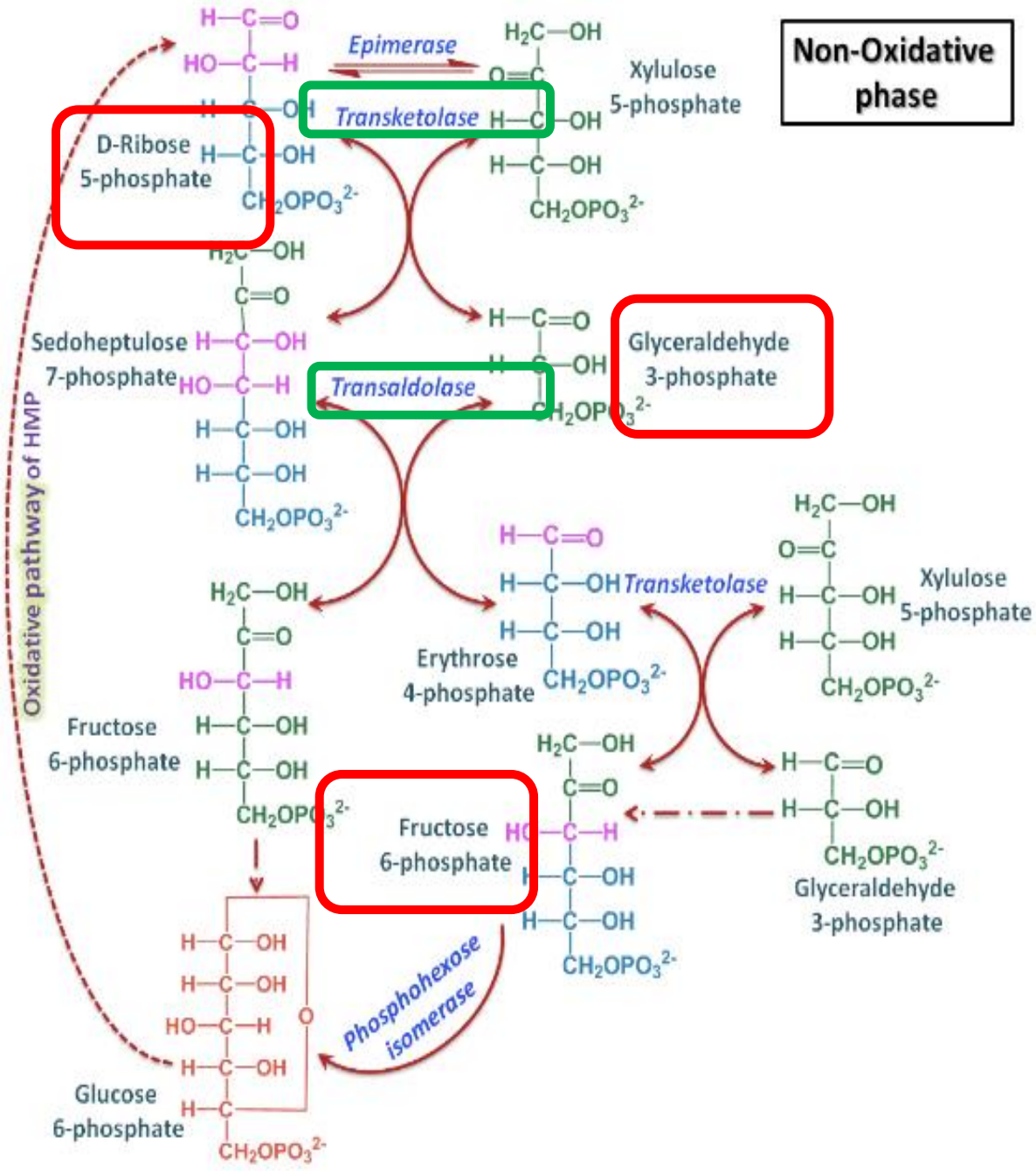


II. Non-Oxidative phase

- ✓ **Reversible steps**
- ✓ **Start by:** **Ribose-5-P.**

  (for nucleotide synthesis)
- ✓ **Produce :**
  - **Fructose 6-phosphate**
  - **Glyceraldehyde 3-phosphate**

  (both may enter glycolysis)
- ✓ **Imp enzymes:**
  - **Transketolase → transfer 2-C**
  - **Transaldolase → transfer 3-C**



Importance, Function (Products) of HMP

Products of HMP

- **NADPH**
  - **1- Reductive synthesis** (FAs, cholesterol & steroids synthesis)
  - **2- Reduction of oxidized glutathione** (Important for RBCs)
- **Pentoses (Ribose 5 P)**
  - **1-Nucleic acids :** (DNA & RNA)
  - **2-Nucleotides:** (ATP, GTP, UTP, CTP)
  - **3 Coenzymes:** (NAD ,FAD ,CoA-SH).

Importance of HMP in RBCs (Glutathione)

A). In RBC

- ✓ RBC function is to carry Hemoglobin that carry O2 to the tissue and CO2 out of the tissue.
- ✓ So, RBCs is exposed heavily to **oxidative stress like H2O2** that is a powerful oxidant that produces damage of its DNA, proteins & phospholipids → **decrease life span of RBCS.**
- ✓ **Reduced Glutathione** (GSH) helps RBCs to get rid of accumulated H2O2

  2 Reduced glutathione**(GSH)** + H2O2 ⟶ oxidized glutathione **(GSSG)** +2 H2O

- ✓ As a result, the reduced glutathione will be converted to oxidized glutathione and must be regenerated.

B) Importance of NADPH produced by HMP in RBCs

1- it is used to regenerate back the **reduced glutathione** from the oxidized one.

✓ **if no NADPH**→ no reduced glutathione → accumulation of H2O2 inside RBCs→ → decrease life span of RBCS (RBCs hemolysis).

2-it is needed for synthesis of **FA & cholesterol** in RBCs membrane.

✓ **If no NADPH**→ inhibit F.A. and cholesterol synthesis in cell membrane of RBCs → increase fragility of RBCs and haemolysis→ decrease life span of RBCS.

Clinical Relevance of HMP (G6PD deficiency, Favism)

Characters

- ✓ X linked recessive disorder characterized by **haemolytic anaemia** due to genetic deficiency of **G6PD enzyme .**
- ✓ Affects more than 200 million individuals worldwide.
- ✓ **Deficiency of G6PD→ decrease NADPH→**RBCs cannot deal with the increased **oxidative stress (H2O2)→** Increasing **fragility and haemolysis.**

Clinical Relevance of HMP
Favism (G6PD deficiency)

Precipitating factors of haemolysis

- ✓ **Not all** patients with G6PD deficiency develop favism and haemolytic anaemia
- ✓ **Some** individual when exposed to factors that increases oxidative stress(like H2O2) in RBCS will show haemolysis.
- ✓ **These factors like:**
  1) **Oxidizing drugs e**.g. **aspirin** , **primaquine** (anti-malarial drugs) , **sulphonamides (** antibiotics) : all stimulate production of H2O2.
  2) **Favism: eating fava beans:** contain oxidizing agents (divicine).
  3) **Infection:** It is the most common precipitating factors of hemolysis in G6PD deficiency due to generation of more ROS.

Clinical Relevance of HMP
Favism (G6PD deficiency)

Mechanism of haemolysis

- G6PD deficiency → decrease in NADPH → deficiency in reduced glutathione→ accumulation of ROS (H_2O_2) that leads to:

  oxidation of polyunsaturated fatty acids present in the cell membrane phospholipids of RBCs→ its fragility & hemolysis.

Treatment

1. **Avoidance** of the above factors
2. **Blood transfusion** during the attack of homolysis


Life
isn't about
finding yourself.
...
Life
is about
creating yourself.