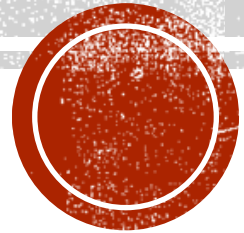
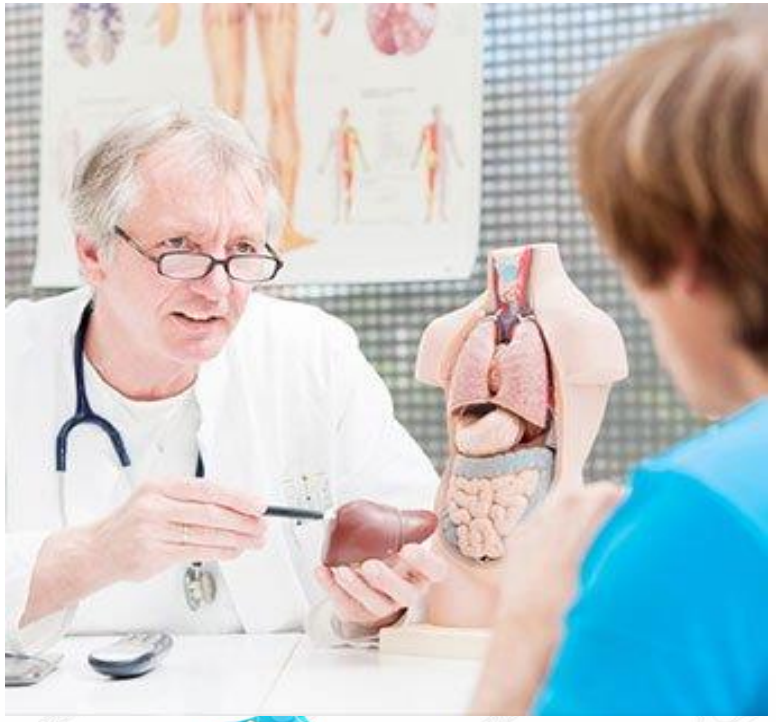
Regulation of enzyme action
+Clinical enzymology



Case scenario

A 54 years old woman presented with vague complaints of fatigue. She also complained of some loss of appetite and vague pain especially towards the right side of the abdomen. Her abdomen examination revealed a borderline enlargement of the liver.



- **Suggest suitable biochemical investigations to help diagnosis.**

Students Learning Outcomes

By the end of this lecture, the students should be able to:

1. Identify causes of changing enzyme amount and activity.
2. Discuss enzyme: induction, repression
3. Explain allosteric regulation, feedback regulation, covalent modification and regulation by cleavage.
4. Identify different types of plasma enzymes and their biomedical importance .

Contents

- **Regulation of enzyme action**
  - **I. Control of enzyme quantity**
    1. Induction
    2. Repression
  - **II. Altering the enzyme catalytic efficiency**
    1. Allosteric regulation
    2. Feedback inhibition
    3. Covalent modification.
    4. Proenzyme (zymogen).
    5. Protein-protein interaction.
- **(Clinical enzymology) Plasma enzymes**

1. Regulation of enzyme action

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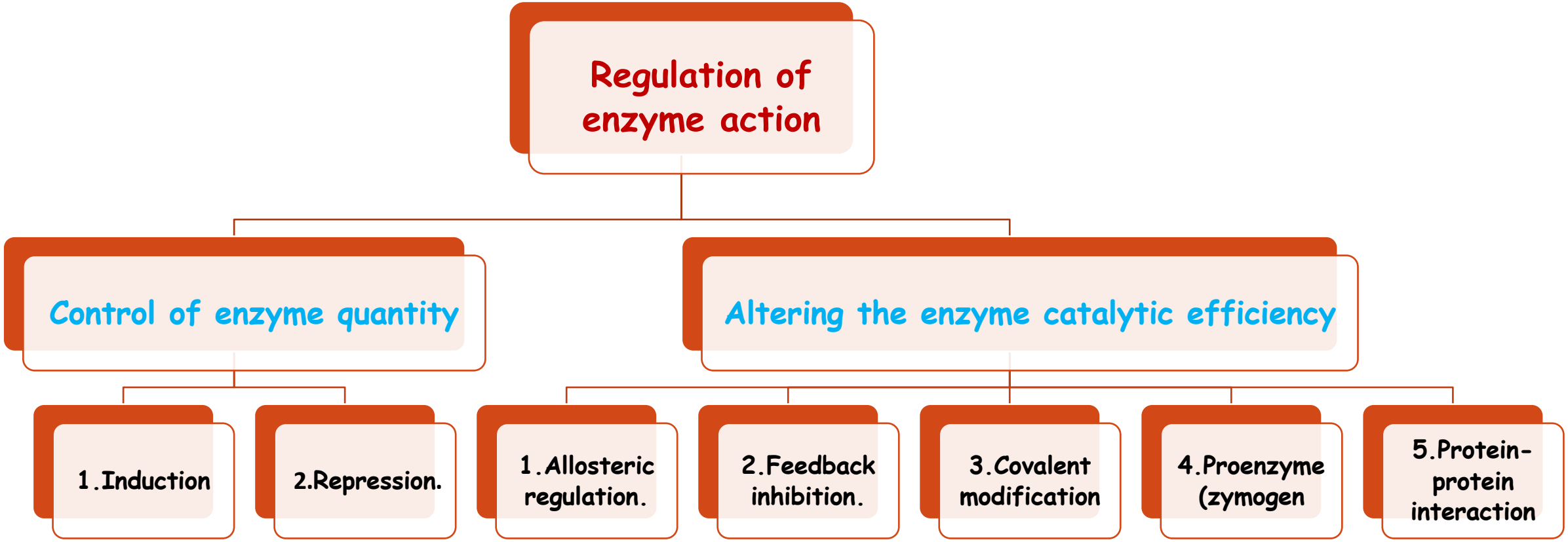


Control of enzyme quantity

1. Induction
2. Repression

I. Control of enzyme quantity

- ✓ Change in **Enzyme amount** (Increase or decrease the amount)
- ✓ **Long term** regulation (at the level of gene expression)
- ✓ **Slow** (hrs., days)
- ✓ It work by controlling **the rate of Enzyme synthesis by either**: Induction or Repression

1- Induction	2- Repression
↑ **rate** of enzyme synthesis by substances called **inducers**	↓ **rate of enzyme synthesis by substances called repressors**
Inducers substances that increase the rate of enzyme **synthesis** at the level of **gene expression**	**Repressors** • substances that decrease the rate of enzyme **synthesis** at the level of **gene expression** • are usually **end products** the reaction, so repression is sometimes called **feedback regulation.**

Control of enzyme catalytic efficacy

1. Allosteric regulation
2. Feedback inhibition
3. Covalent modification.
4. Proenzyme (zymogen).
5. Protein-protein interaction.

II. Control of enzyme catalytic efficacy

- ✓ Change in Enzyme **activity** (by increase or decreasing the activity)
- ✓ **Short** term regulation
- ✓ **Rapid** (secs, mins)
- ✓ It work through :

1. Allosteric regulation
2. Feedback inhibition
3. Covalent modification.
4. Proenzyme (zymogen).
5. Protein-protein interaction.

1. Allosteric regulation

✓ **Some Enzyme has two sites;**

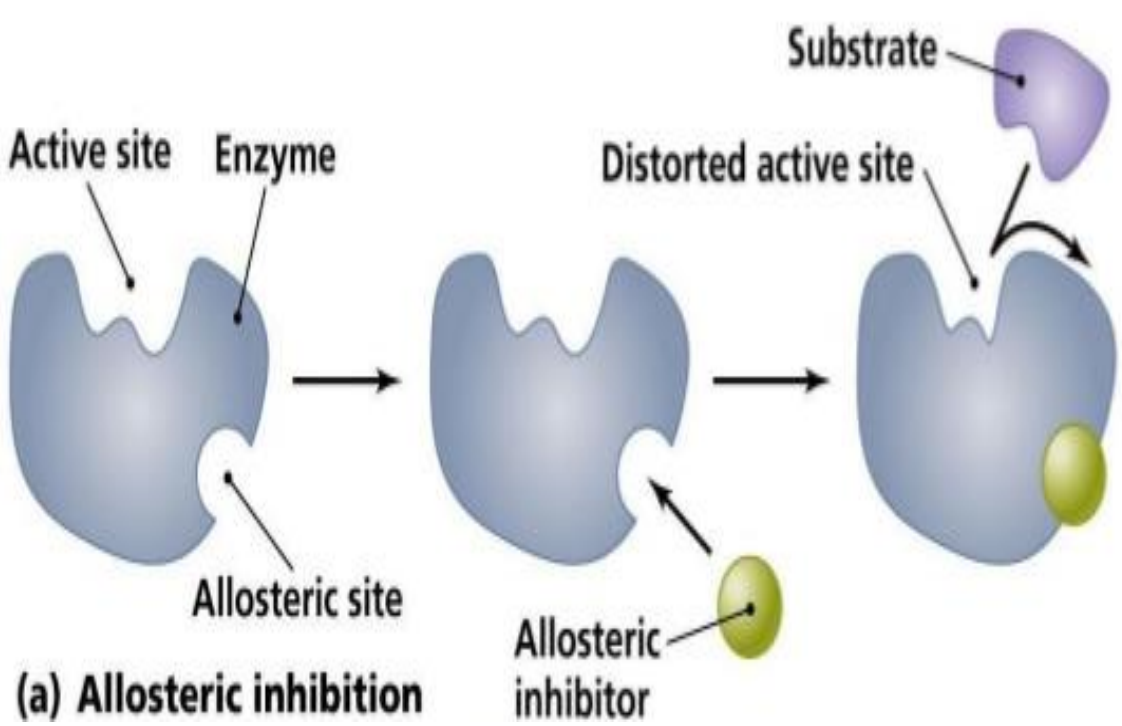
1- Active site for **substrate binding** → for catalysis

2- Allosteric site (another site) for **effector (regulator) binding** → for regulation of the E activity

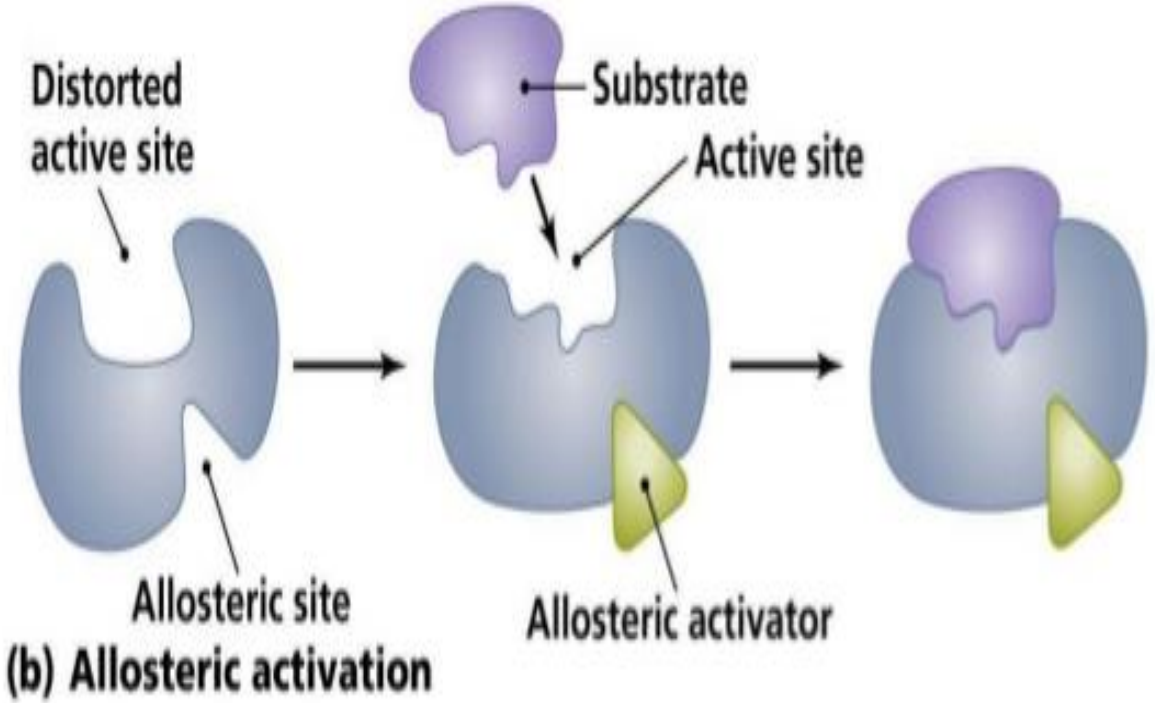
✓ **Binding of the allosteric effector to the regulatory site → conformational** changes in the catalytic site→ becomes either:

1. **More fit for substrate binding**→ ↑ Enz. activity → so called **+Ve** effector (allosteric **activator**).
2. **Unfit for substrate binding** → ↓ Enz. activity → so called **-Ve** effector (allosteric **inhibitor**)

Effector as an inhibitor



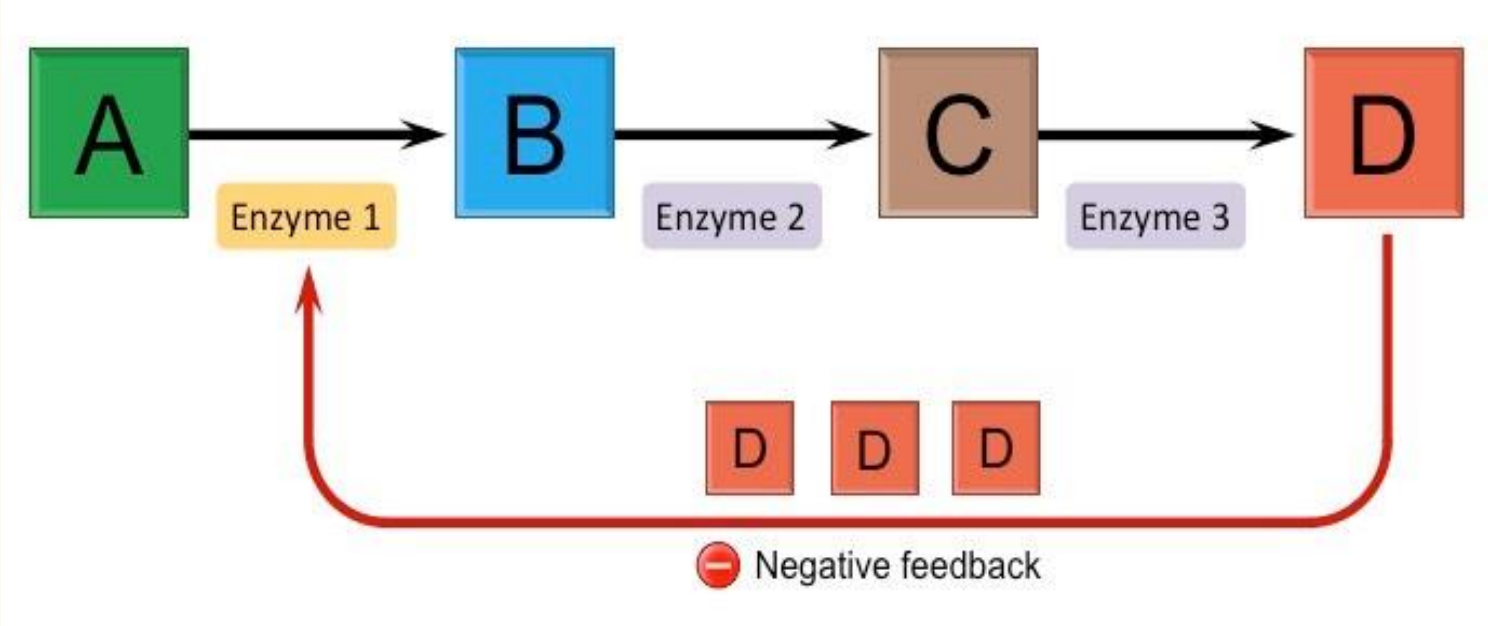
Effector as an activator



2. Feedback Inhibition

✓ In biosynthetic pathways, **an end product** may directly inhibit an enzyme early in the pathway.

✓ This inhibited enzyme usually catalyzes the **early** functionally **irreversible** step in the **pathway**

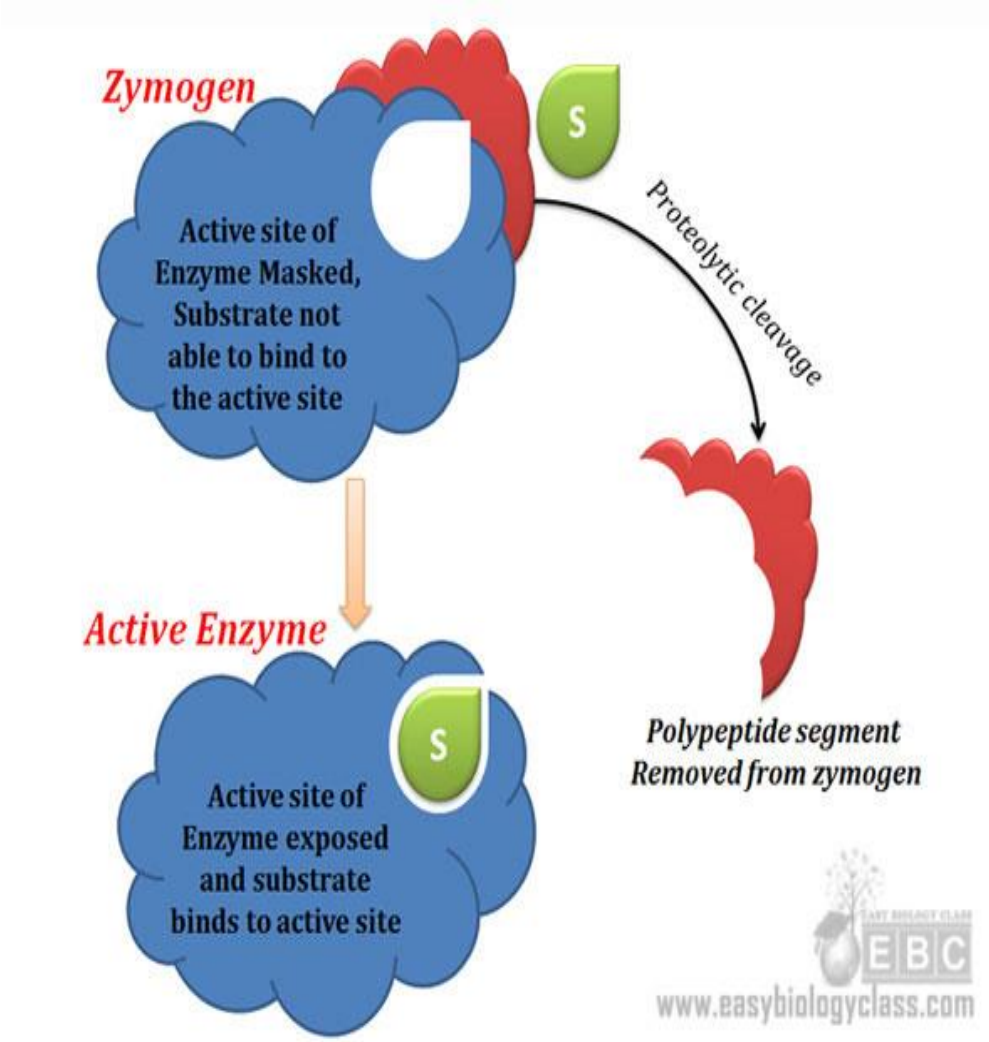


A: **Initial reactant**
B, C : **Intermediates**
D: **End (Final) product**

Accumulation of end product (D)→ back signal (-Ve feedback) → ↓↓ of Enzyme1→ slow the pathway

3. Pro-enzymes (Zymogens)

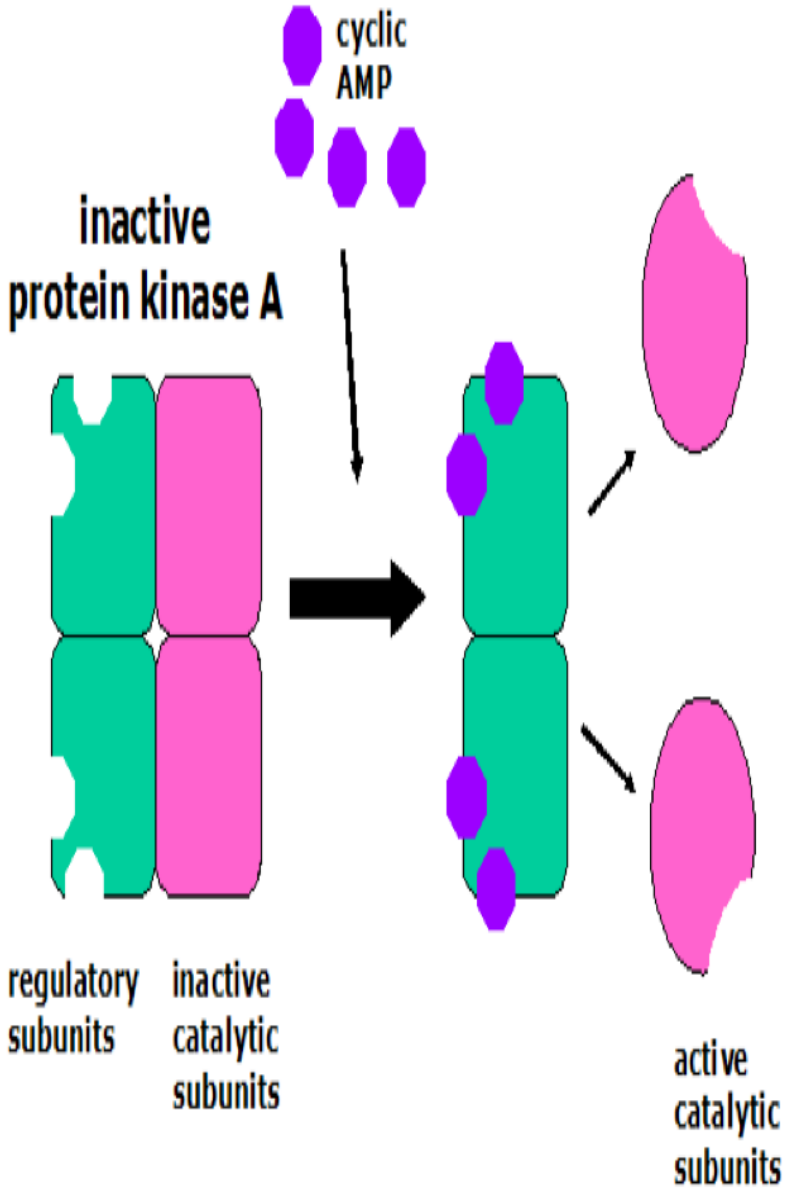
- ✓ Some Enz. initially produced in **inactive form** called **zymogen or proenzyme** as it contains a polypeptide segment that blocks the active site.
- ✓ **Removal of this polypeptide** segment→ activation of zymogen
- ✓ **Examples for zymogens** include: **proteolytic digestive** enzyme: that digest protein like:
  1. **Pepsinogen,**
  2. **Trypsinogen,**
  3. **Chymotrypsinogen,**
- ✓ This inactive form → protect the tissues of origin from **auto digestion** (ie. from digesting itself).



Zymogen Activation by Proteolytic Cleavage

4- Protein-protein interaction

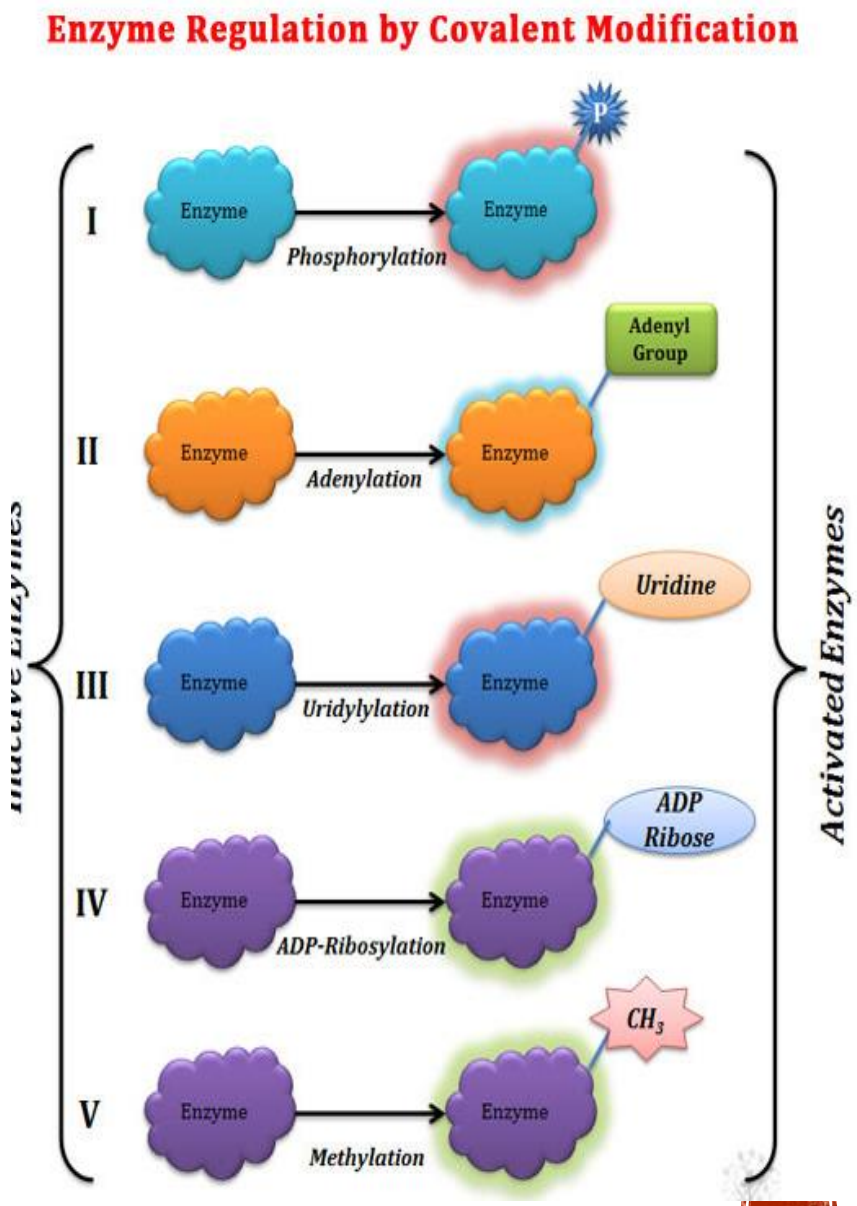
- ✓ Some enzymes are, formed of **inactive form**, consists of catalytic and regulatory subunits.
- ✓ **Activation** of the enzyme occurs by **separation** **of the catalytic subunits from the regulatory subunits.**
- ✓ Eg **Protein Kinas A (PKA)** enzyme :
  - Formed of **4 subunits**, **2 regulatory (2R) and 2 catalytic (2C) subunits.**
  - The **whole** enzyme **(2R2C) is inactive**
  - **cAMP activates** the enzyme by **binding to the 2 regulatory (2R) subunits** → releasing the 2 catalytic **(2C) (active)** subunits.



5- Covalent modification

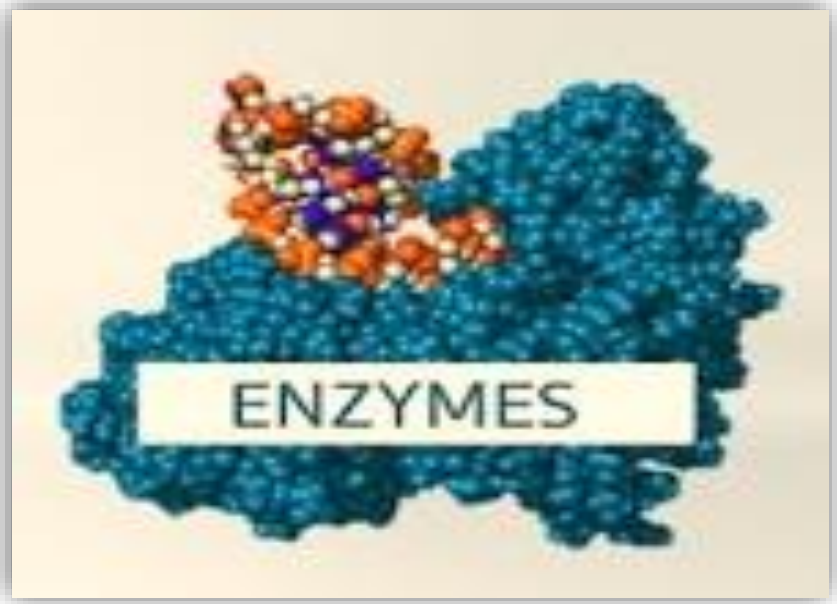
- ✓ It means modification of enzyme activity through formation of **covalent bonds** e.g., Phosphorylation, Acetylation , Methylation

- ✓ **Phosphorylation/ dephosphorylation**
  - ➢ the **most covalent** modification used to regulate enzyme activity
  - ➢ It involve **transfer of phosphate** (of **ATP**) to & from OH group of: **Serine ,Threonine or Tyrosine** AA of the enzyme.
  - ➢ **Two enzymes involved**
    - **For phosphorylation**: **Protein Kinases** → add P
    - **For dephosphorylation: Phosphatases** → remove P
  - ➢ **Some enzymes** activated by phosphorylation other activated by dephosphorylation



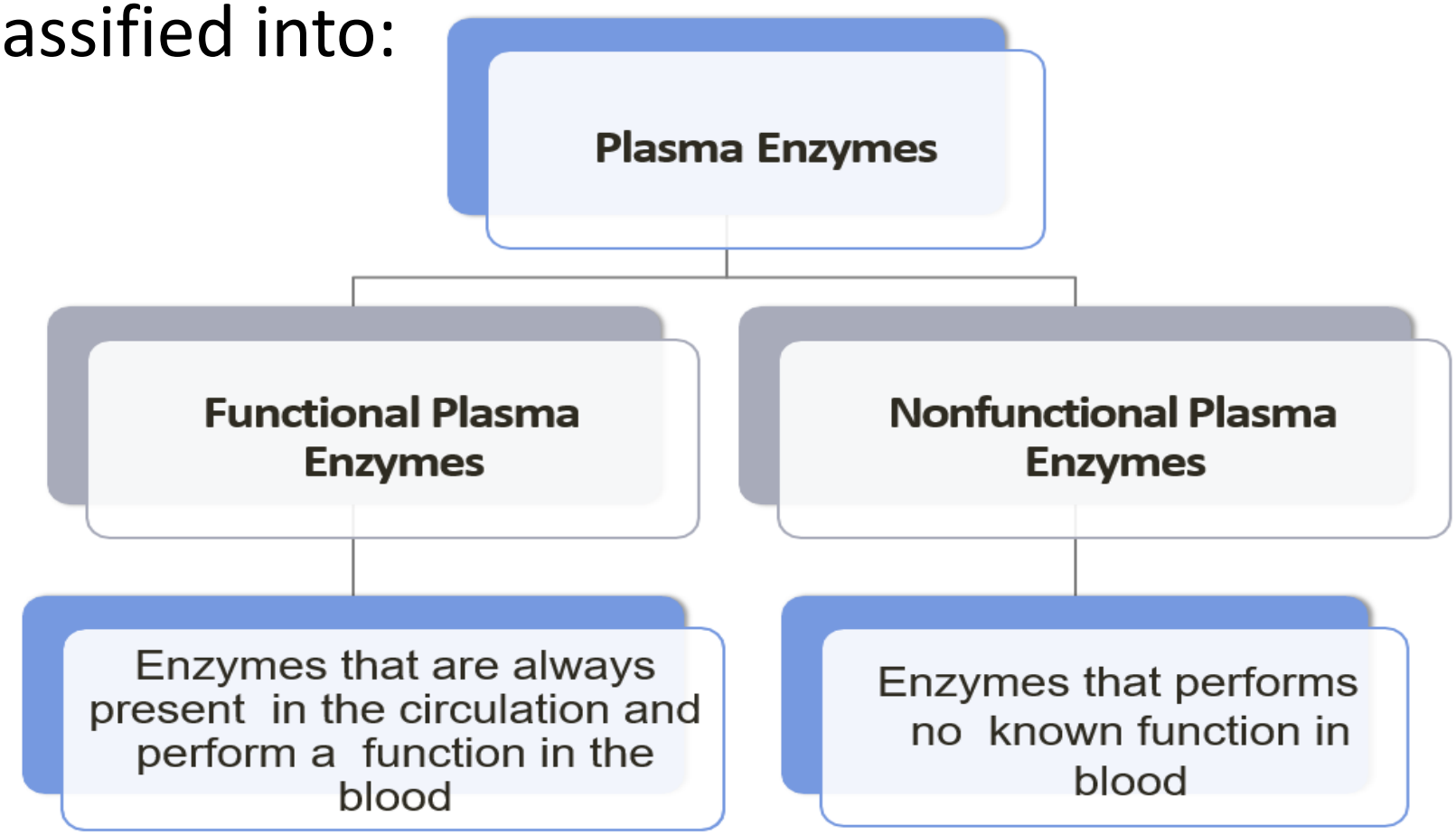
2. Clinical enzymology

A: Plasma enzymes



Plasma enzymes

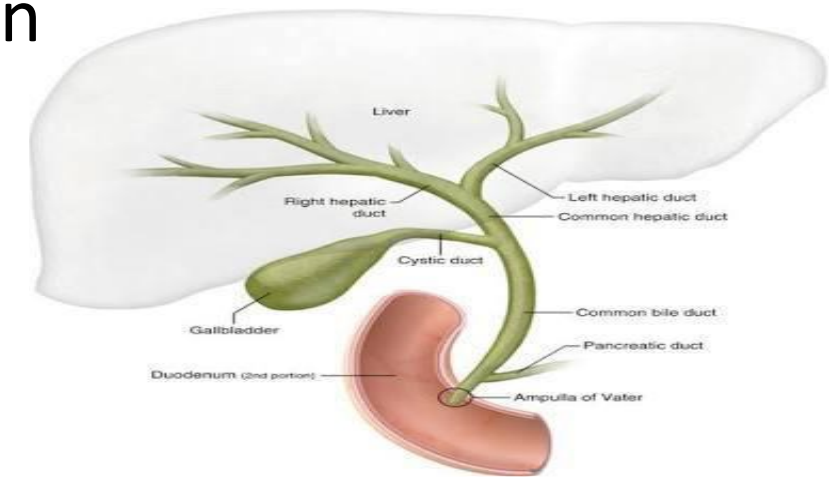
- Plasma contains many enzymes which are classified into:



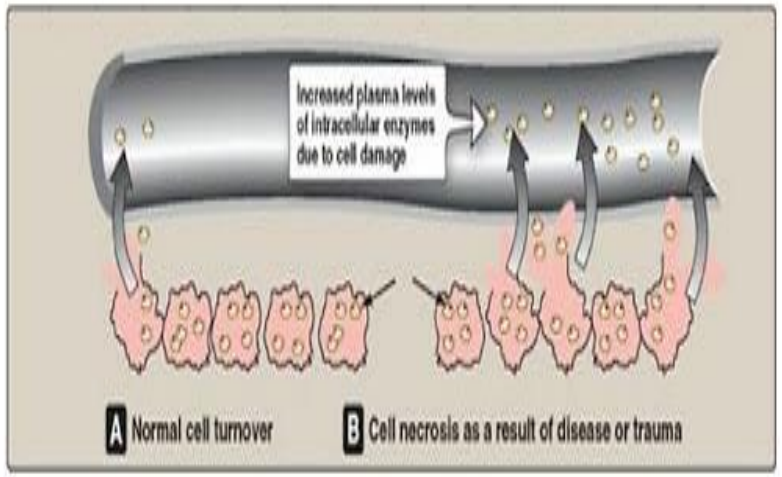
	Functional plasma enzymes	Non-functional plasma enzymes
• **Concentration in plasma**	Present in plasma in higher concentrations in comparison to tissues	Normally, present in plasma in very low concentrations in comparison to tissues
• **Function**	Have known functions	No known functions
• **The substrates**	Their substrates are always present in the blood	Their substrates are absent from the blood
• **Site of synthesis**	Liver	Different organs e.g. liver, heart, brain and skeletal muscles
• **Effect of diseases**	Decrease in liver diseases	Different enzymes increase in different organ diseases
• **Examples**	Lipoprotein lipase pseudo-choline esterase	Amylase & lipase CK & LDH ALT & AST alkaline phosphatase & acid phosphatase

Sources of non-functional plasma enzymes

- **Obstruction of normal pathway.** E.g. obstruction of bile ducts increases alkaline phosphatase.



- **Increase permeability of cell membrane** as in tissue hypoxia.
- **Cell damage with the release of its enzyme contents** into the blood E.g. Myocardial infarctio and viral hepatitis.



Medical importance of non-functional plasma enzymes

Measurement of non-functional plasma enzymes for:

1.Diagnosis of diseases: detection of the diseased organ.

2.Prognosis and follow up of the disease: before and after treatment.

Examples of medically important non-functional plasma enzymes

1. Amylase and lipase enzymes increase in pancreatic diseases.

2. Creatine kinase (CK) enzyme increases in heart, brain and skeletal muscle diseases.

3. Lactate dehydrogenase (LDH) enzyme increases in heart, liver and blood diseases.

Examples of medically important non-functional plasma enzymes

4. Alanine transaminase (ALT) (sGPT) enzymes increases in liver diseases.

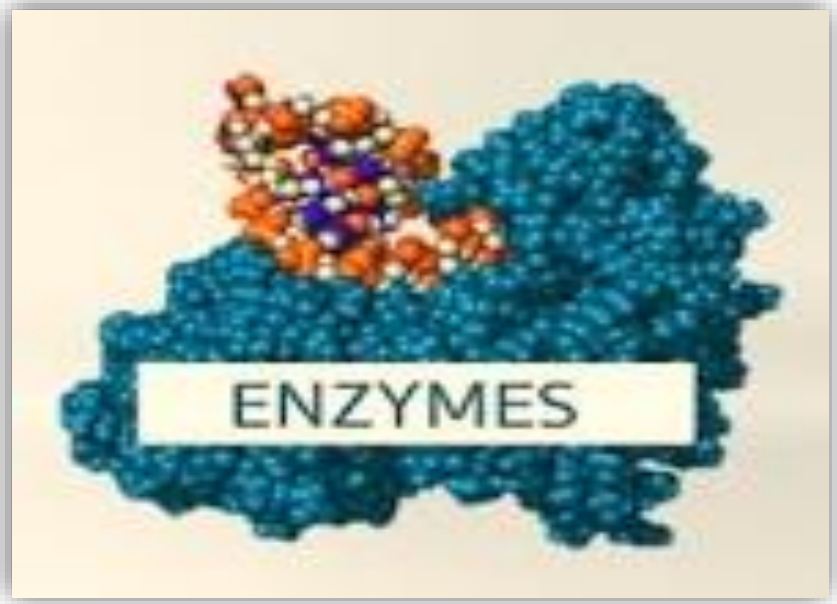
5. Aspartate transaminase (AST) (sGOT) increases in liver, muscles and heart diseases

6. Acid phosphatase enzyme increases in cancer prostate.

7. Alkaline phosphatase enzyme increases in obstructive liver diseases, bone diseases and hyperparathyroidism.

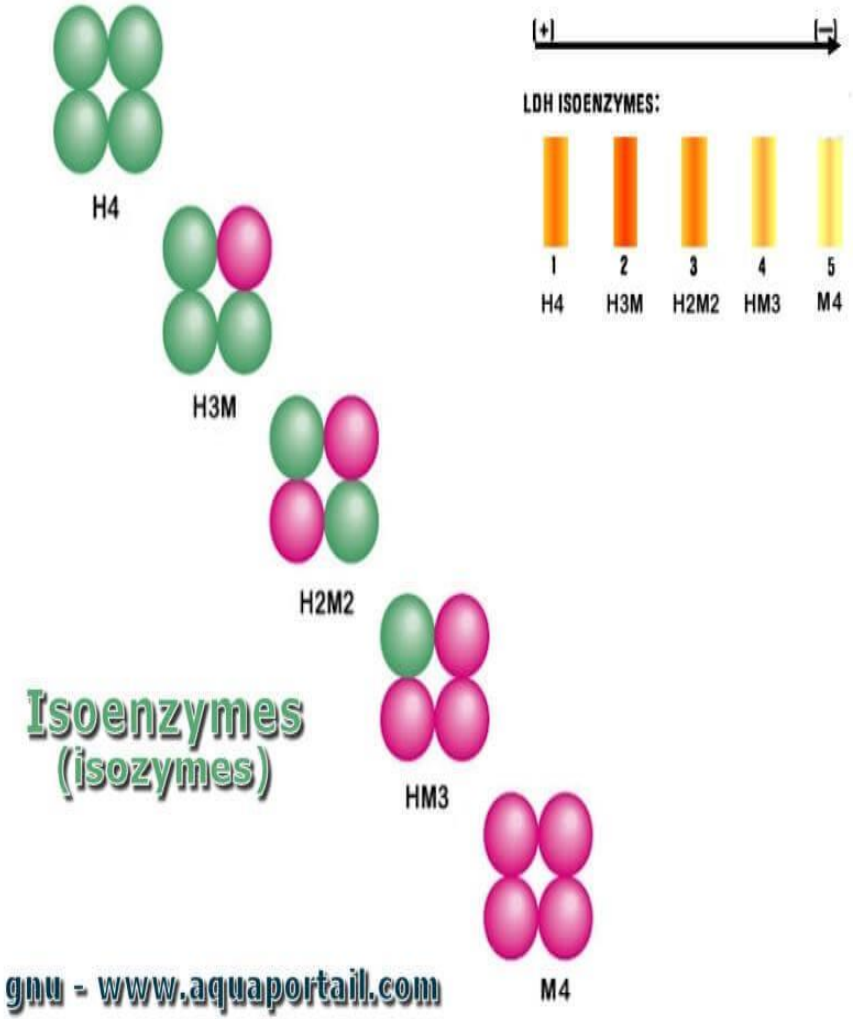
2. Clinical enzymology

B: Isoenzymes



Isoenzymes

- **Iso** means the **same** and **isoenzyme** means the **same enzyme.**
- **Isoenzymes (isozymes)** are **multiple forms** of the enzyme that have the **same catalytic activity.**
- Although they have the same catalytic activity, they are **physically distinct** and **differ in liability to inhibitors**.



❑ Example of isoenzymes

❑ Many enzymes are present in isoenzyme form:

1.Creatine kinase

2.Lactate dehydrogenase

3.Acid phosphatase

4.Alkaline phosphatase

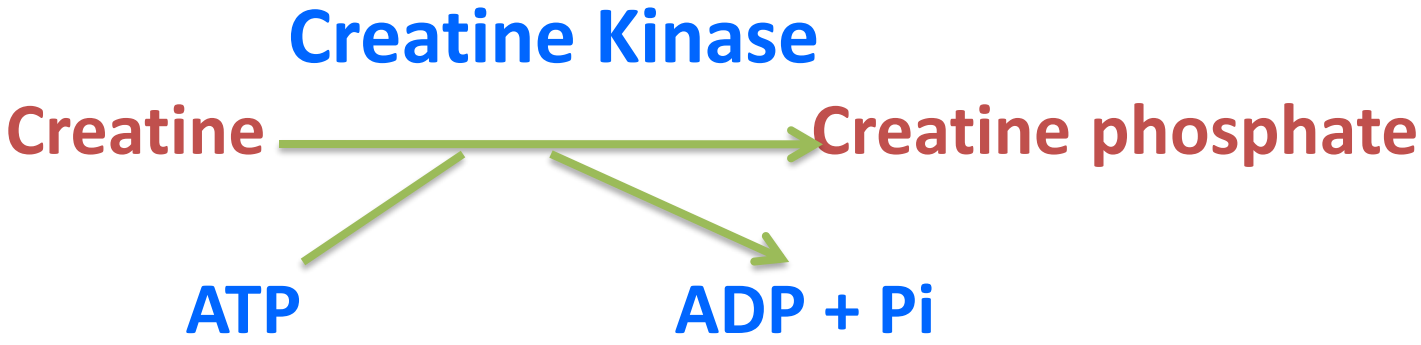
❑Medical importance of isoenzymes

❑ Isoenzymes are not only important for **diagnosis** but also **indicate** the **diseased organ.**

❑Example of isoenzymes

Creatine kinase (CK)

❑ It is an enzyme that catalyzes phosphorylation of creatine.



❑Its level in plasma increases in

1.Brain tumors.

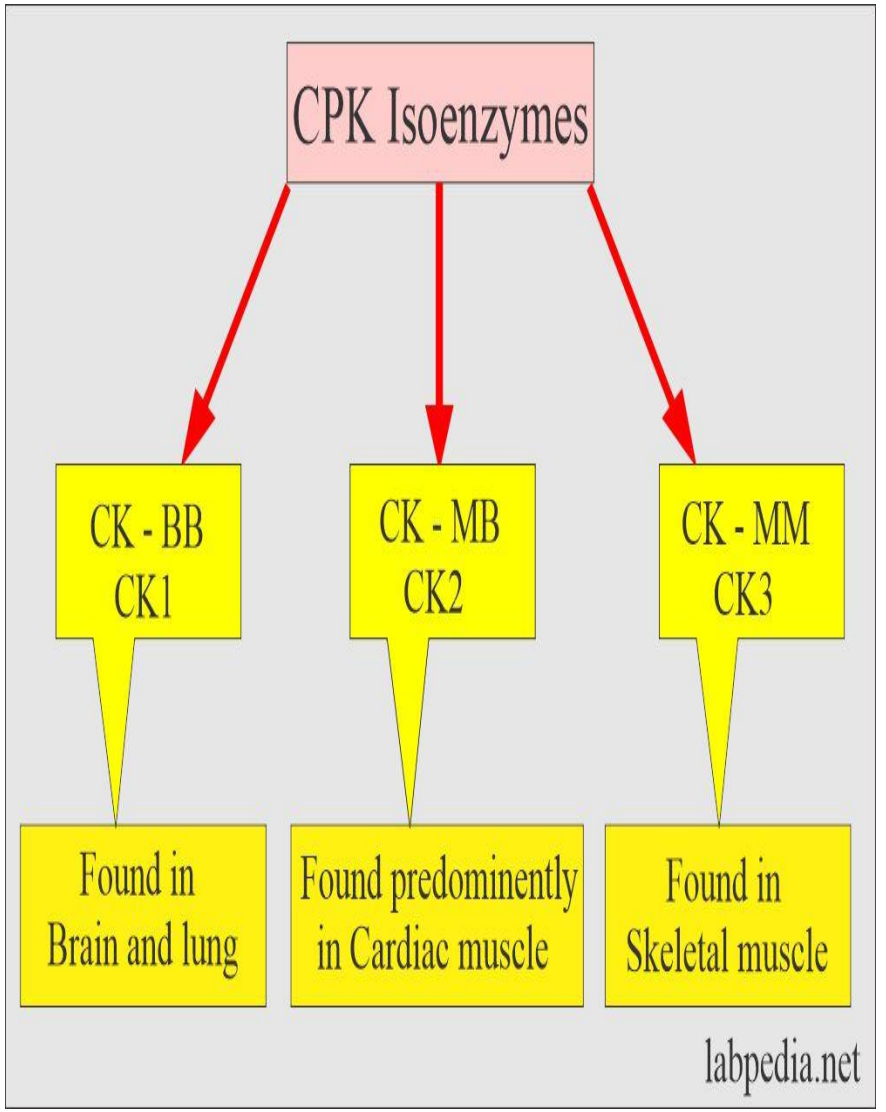
2.Myocardial infarction (heart disease).

3.Skeletal muscle diseases.

❑CK has 3 isoenzymes:

- **CK BB** which increases in **brain tumors.**
- **CK MB** which increases in **heart diseases.**
- **CK MM** which increases in **skeletal muscle** diseases.

❑**CK** isoenzymes are clinically important to **differentiate** between **brain, heart and skeletal muscle** diseases.




A GOAL
WITHOUT
A PLAN
IS JUST A
WISH

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