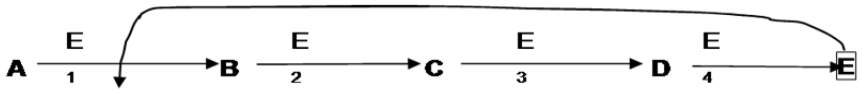
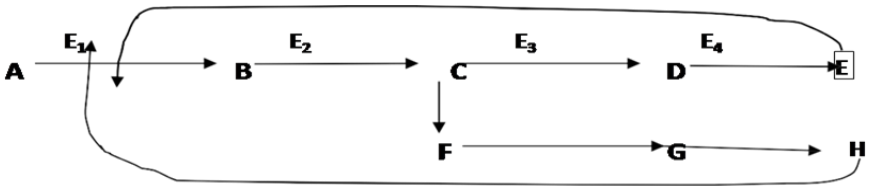
B. Feed Back Inhibition:

• An end product of biosynthetic pathways may directly inhibit an enzyme early in the pathway.



Simple feedback inhibition loop



Multiple feedback inhibition loop

Where A is the substrate, E is the end product, B, C, D are intermediate metabolites, E_1, E_2, E_3 and E_4 are enzymes in biosynthetic pathway.

- Feedback regulation does not affect the enzyme activity but decreased the enzyme quantity and it is slow process.
- Feedback inhibition does not affect enzyme quantity but decreases the enzyme activity and it is fast process.

C- Proenzymes (Zymogens)

- Zymogens are inactive precursors of enzymes, some enzymes secreted in this form, for example pepsinogen,trypsinogen, chymotrypsinogen, prothrombin,clotting factors and Insulin an important metabolic regulator.
- Zymogens or proenzymes acquire full activity only upon specific proteolytic cleavage of one or several of their peptide bond and it's activation is irreversible process .
- Zymogen is inactive because it contains an additionalpolypeptide chain that masks (blocks) the active site of theenzyme.

Biological importance of zymogens

1. Some enzymes are secreted in zymogen form to protect the tissues of origin from auto digestion.

2. Zymogens is to insure rapid mobilization of enzyme activity at the time of needs in response to physiological demands

Activation of zymogens can occur by one of the following methods:

•**Activation by HCl**

Pepsinogen —HCl→ Pepsin

•**Activation by other enzymes:**

Trypsinogen —Enterokinase→ Trypsin

Prothrombin —Thrombokinase + Ca++→ Thrombin

•**Auto activation** i.e. the enzyme activates itself.

Pepsinogen —Pepsin→ Pepsin

Table. Examples of Pancreatic and Gastric Zymogens

Origin	Zymogen	Active Protease
Pancreas	Trypsinogen	Trypsin
Pancreas	Chymotrypsinogen	Chymotrypsin
Pancreas	Procarboxypeptidase	Carboxypeptidase
Pancreas	Proelastase	Elastase
Stomach	Pepsinogen	Pepsin

D- Covalent modification

It means modification of enzyme activity through formation ofcovalent bonds with some specific group:

- Phosphorylation (addition of phosphate group at the hydroxyl group ofserine, threonine or tyrosine) - Phosphorylation is the most common kind of covalent

modification in the enzymes. After covalent modification enzyme get either active or inactive depends on modification. **Phosphatases**: Removal of phosphate group from the hydroxyl group of serine, threonine or tyrosine.

- Methylation (addition of methyl group).
- Hydroxylation (addition of hydroxyl group).
- Adenylation (addition of adenylic acid) etc.

Examples of enzymes inactivated by phosphorylation:

Glycogen Synthetase, which catalyzes biosynthesis of glycogen.

Acetyl CoA carboxylase, an enzyme in fatty acid biosynthesis.

HMG CoA reductase, an enzyme in cholesterol biosynthesis.

Examples of enzymes activated by phosphorylation:

Glycogen phosphorylase that breaks down glycogen into glucose.

Citrate lyase, which breaks down citrate.

Lipase that hydrolyzes triglyceride into glycerol and 3 fatty acids.

E- Protein-protein interaction

- An Enzymes that are formed that have many protein subunits, the enzyme may be present in an inactive form through interaction between its protein subunits.
- The whole enzyme, formed of regulatory and catalytic subunits, is inactive.
- Activation of the enzyme occurs by separation of the catalytic subunits from the regulatory subunits, for example Protein kinase A enzyme is an example for regulation of enzyme activity through protein interaction.
- The PKA having 2R2C domain and it is an inactive form. cAMP (cyclic adenosine monophosphate) activates the enzyme by binding to the 2 regulatory (2R) subunits releasing the 2 catalytic (2C) subunits and hence activating the enzyme.