# Pentose phosphate pathway PPP

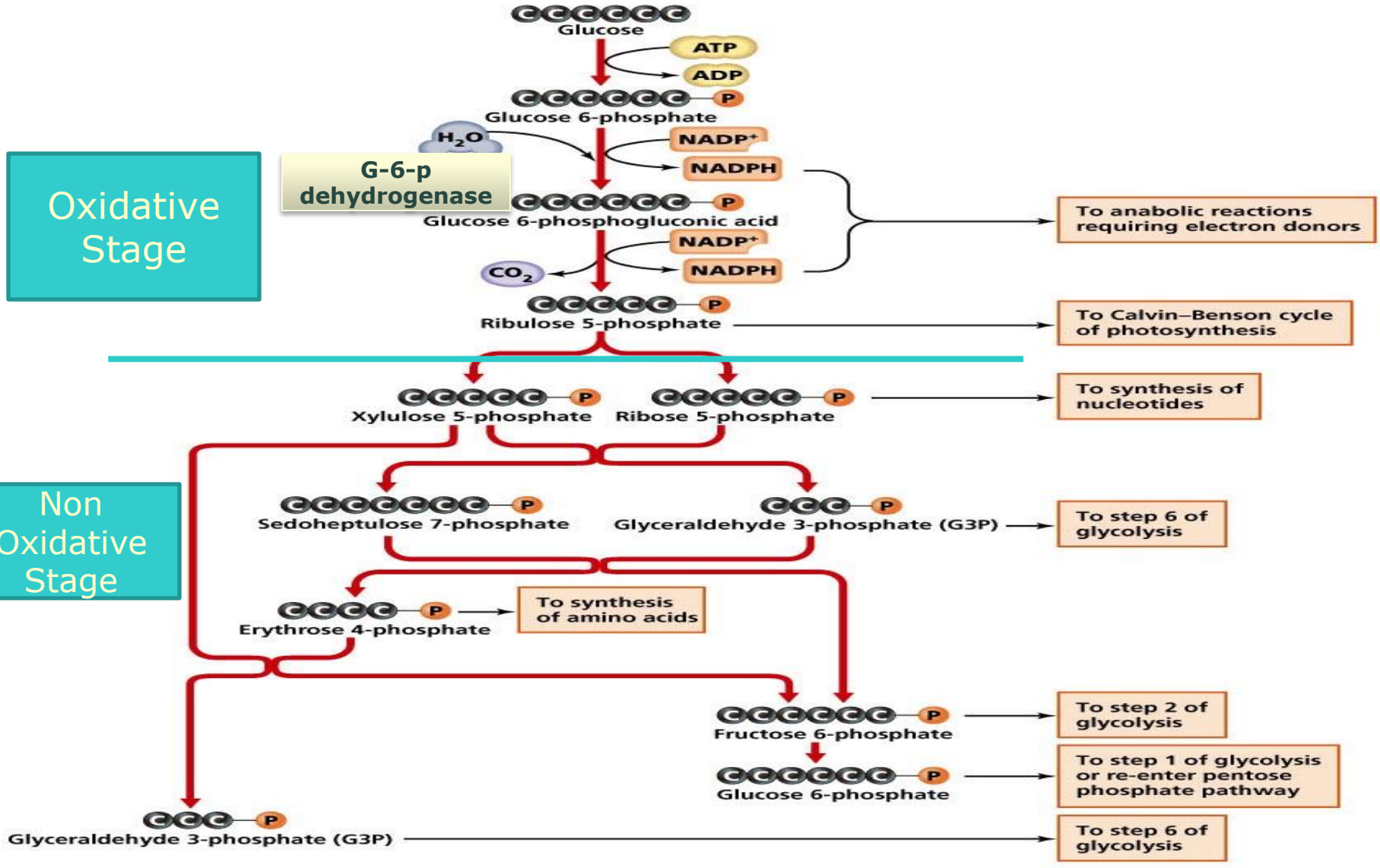
## (Phosphogluconate pathway or the hexose monophosphate shunt)

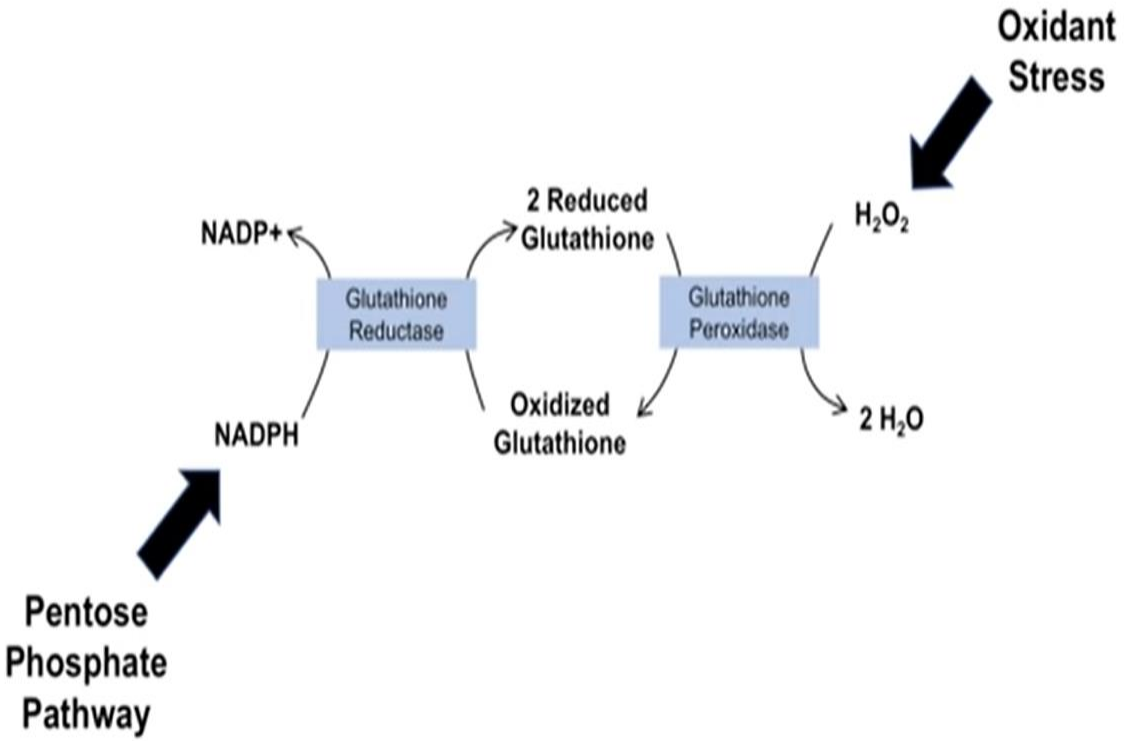
Is a process that generates[1] pentoses (5-carbon sugars) used in the synthesis of nucleotides and nucleic acids and [2]NADPH used in other biosynthesis reactions within cells. (e.g. fatty acid synthesis) also [3]Production of erythrose-4-phosphate (E4P), used in the synthesis of aromatic A.A. It takes place in the cytosol and is found to be most active in the liver, mammary gland, adrenal cortex and Erythrocytes (generate a large amount of NADPH via PPP to prevent oxidative stress of glutathione).

There are two Stages in this pathway. The first is the oxidative phase, in which NADPH is generated, and the second is the non-oxidative synthesis of 5-carbon sugars.

Regulation by Glucose-6-phosphate dehydrogenase is the rate-controlling enzyme of this pathway. It is stimulated by $NADP^+$ to produce more NADPH.

# PPP




Oxidant
Stress
NADP+
2 Reduced
Glutathione
$H_2O_2$
Glutathione
Reductase
Glutathione
Peroxidase
NADPH
Oxidized
Glutathione
2 $H_2O$
Pentose
Phosphate
Pathway

# Health Disorders if PPP malfunction

## Glucose-6-Phosphate Dehydrogenase G6PD

- *Deficiency* of glucose-6-phosphate dehydrogenase can occur
  - 7.5% of world population deficient
  - 35% prevalence in certain areas of Africa
    - May be protective against malaria
  - X-linked Recessive Inheritance
- May cause:
  - *Hemolytic Anemia*
    - After Ingestion of Anti-Malarial Medications
  - *Neonatal hyperbilirubinemia (jaundice)*

**. after eating fava beans (Vicia fava) or being exposed to the pollen of the fava plant. (Favism)**

# Biosynthesis of Fatty Acids

Is the creation of fatty acids from acetyl-CoA and malonyl-CoA precursors through action of enzymes called fatty acid synthases.

It is an important part of the lipogenesis process, which (together with glycolysis) stands behind creating fats from blood sugar in living organisms.

* Acetyl CoA is the source of carbon atom.

* NADPH provides the reducing equivalents.

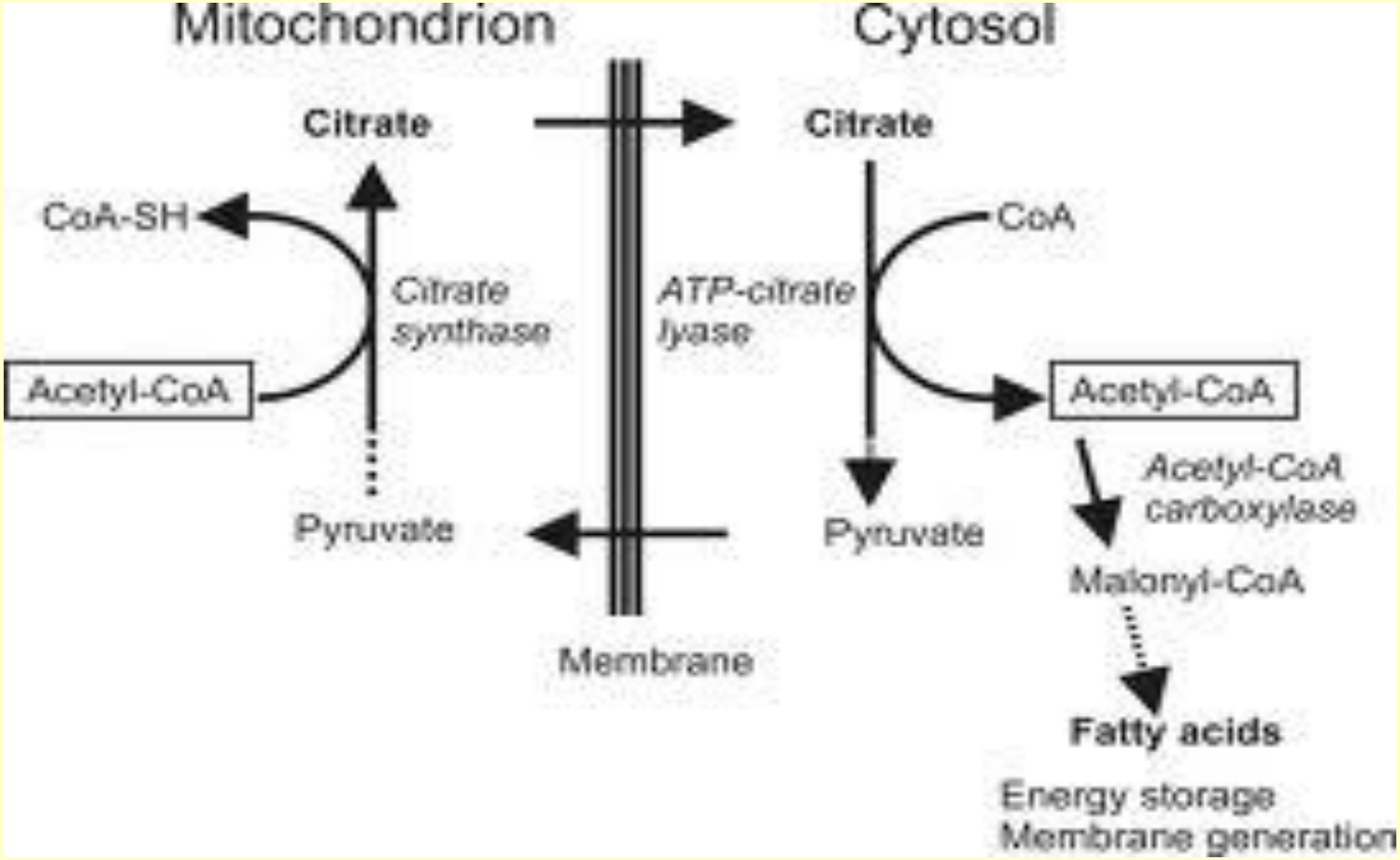
* ATP supplies energy for fatty acid formation.

- Regulation of FA metabolism:

The FA synthesis are coordinately regulated by Three hormons:

- Glucagon and epinephrine inhibit FA synthesis, whereas insulin is anti-lipolytic and stimulates FA biosynthesis.

# Biosynthesis of Fatty Acids



# Biosynthesis of Fatty Acids

Fatty acid synthesis involves 3 stages:

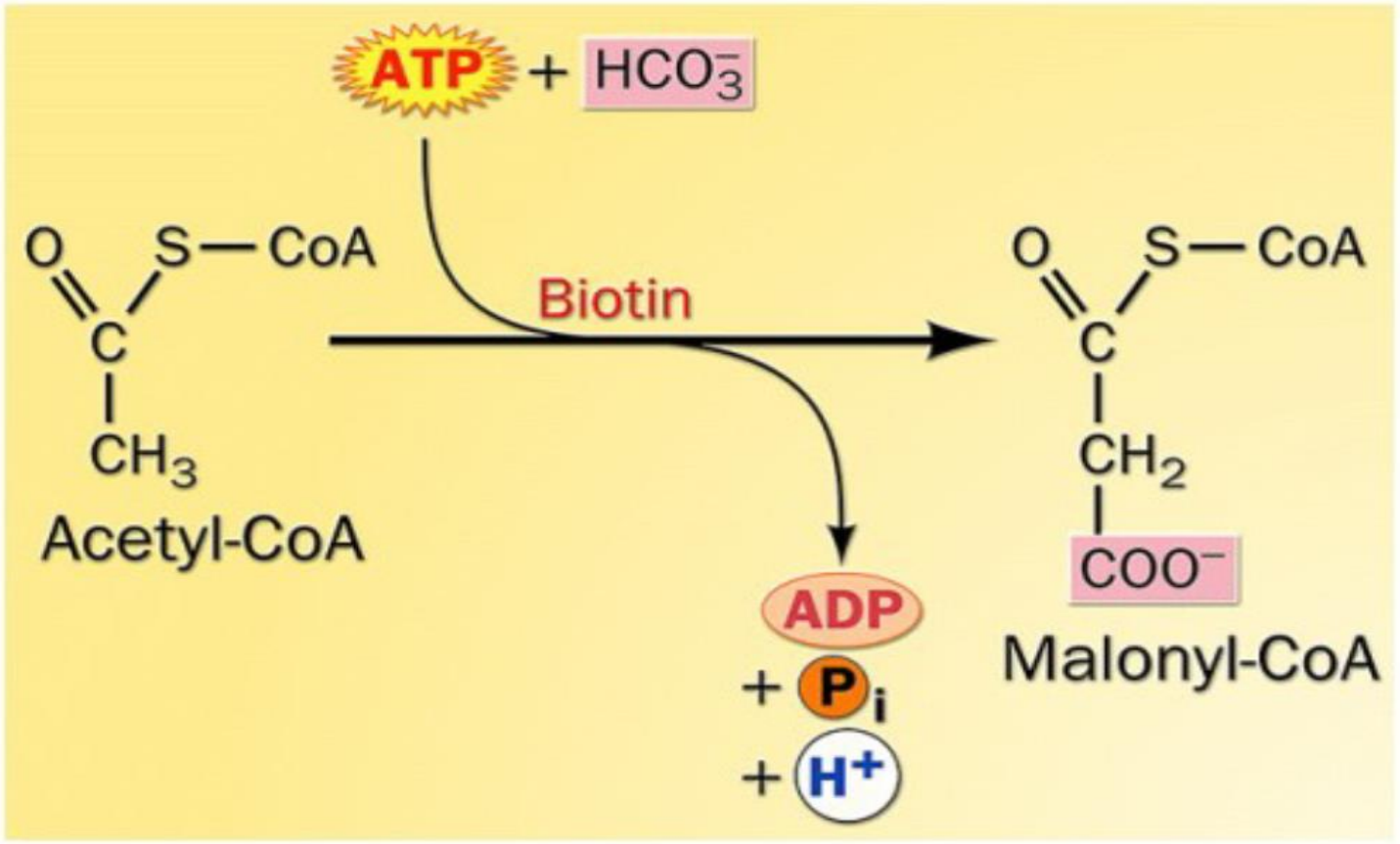
1. production of acetyl CoA & NADPH.
2. formation of malonyl CoA.
3. Reactions of Fatty Acid Synthase (FAS)

- Acetyl CoA is produced in mitochondria by oxidation of pyruvate , F.A., degradation of A.A. & ketone bodies.
- mitochondria is not permissible to acetyl CoA.
- Alternative or bypass is arranged to transfer acetyl CoA to cytosol (called the Citrate Shuttle).

# Biosynthesis of Fatty Acids

- Acetyl CoA condenses with oxaloacetate in mitochondria to convert to malate & with malic enzyme converted to pyruvate.
- Then the pyrovate convert to form citrate which is transported to cytosol to liberate acetyl CoA & Oxaloacetate again.
- In the cytosol Malonyl CoA is synthesized from acetyl CoA by the action of acetyl CoA carboxylase (irreversible reaction).
- Acyl Carrier Protein(ACP): CoA is used as an activator for β-oxidation.
- The acetyl group gets transferred from CoA to ACP by acetyl CoA-ACP transacylase.

# Biosynthesis of Fatty Acids




Activation of acetate : Acetyl-CoA to malonyl CoA

# Biosynthesis of Fatty Acids

- Next, the malonyl group gets transferred from CoA to ACP by malonyl CoA ACP transacylase.
- This results in both arms of Fatty Acid Synthase (FAS) occupied forming acylmalonyl- ACP.
- The COO group of malonyl ACP is removed as $CO_2$ , this results in 3-keto acyl ACP which is converted to a $CH_2$ by a series of reactions reverse to FA β-oxidation.
- The result of the first cycle of fatty acid biosynthesis is a four carbon chain associated to the ACP arm.
- A new malonyl CoA is introduced on the ACP arm.
- For each cycle the acyl group transferred to the α-carbon of malonyl CoA is 2-carbons longer than the previous cycle.
- At the end of 7 cycles a 16 carbon chain is attached to the ACP arm (palmitoyl ACP).

# Biosynthesis of Fatty Acids

## Modification of Palimitic acid

- Palmitic acid is converted to palmityl CoA for modification.
- FA longer than palmitic acid are synthesized by an elongation enzyme system.
- Additional carbons are added in 2-carbon units using malonyl CoA as the donor.
- Unsaturated fatty acids are synthesized by the action of specific enzymes called as fatty acid CoA desaturases which are specific for specific positions of the double bond.

## Essential Fatty Acids:

- Mammals lack the enzymes to introduce double bonds at carbon atoms beyond C9.
- Hence, all fatty acids containing a double bond at positions beyond C9 have to be supplied in the diet. These are called Essential fatty acids (EFA) include: Linoleate (18:2 Δ 9,12) , Linolenate (18:3 Δ 9,12,15) and arachidonic acid (20:4 Δ 5,8,11,14) are derived from these two EFA.

# cholesterol synthesis transport and excretion

- **BIOMEDICAL IMPORTANCE**

Cholesterol is present in tissues and in plasma either as free ch. or as a storage form, combined with a long-chain F.A as cholesteryl-ester

In plasma, both forms are transported in lipoproteins.

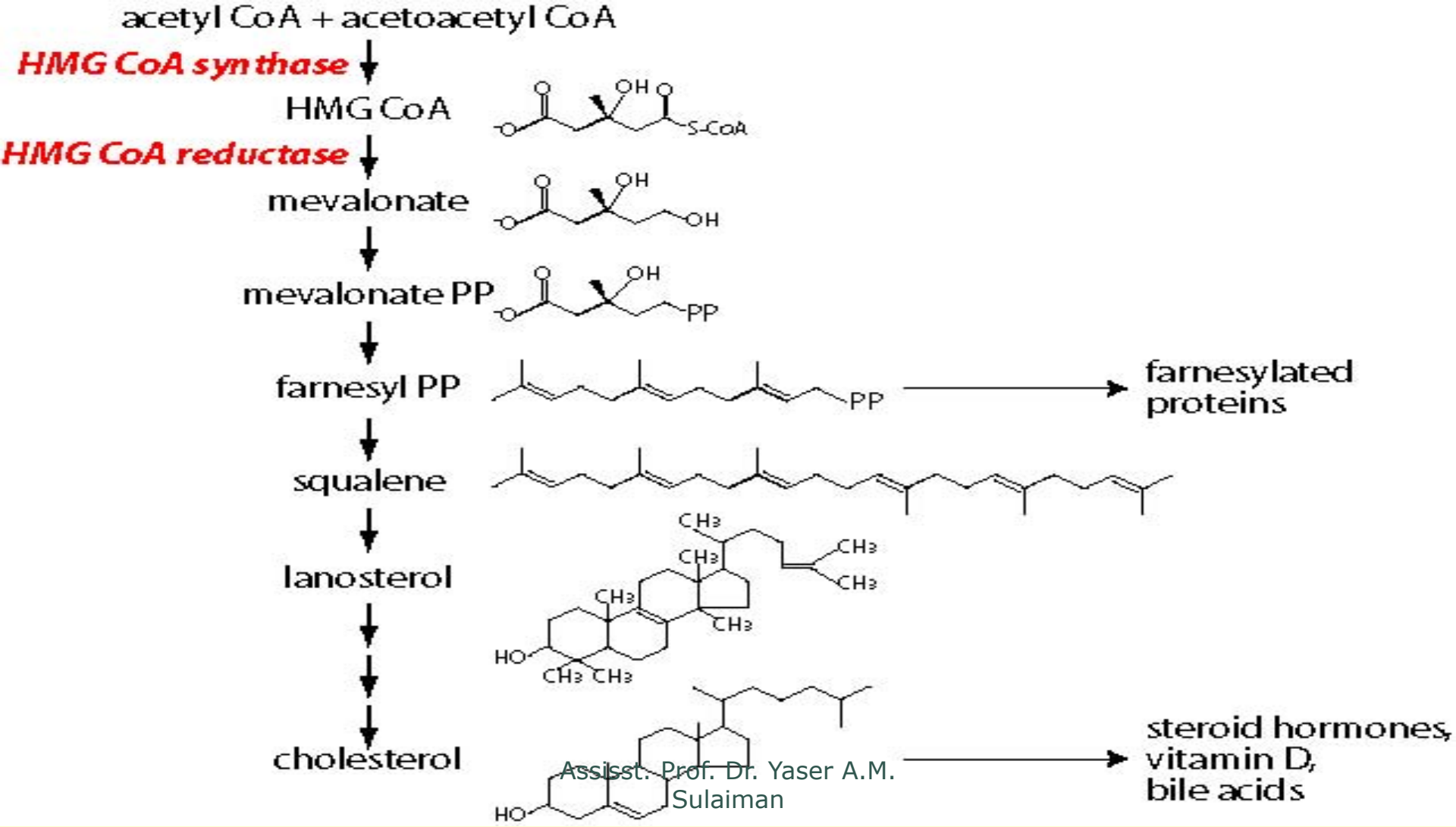
Cholesterol is an (1)essential structural component of membranes and of the outer layer of plasma lipoproteins. (2)It is the precursor of all other steroids in the body such as corticosteroids, sex h., bile acids, and vitamin D. A little more than half the cholesterol of the body arises by synthesis, and the remainder is provided by the diet.

Plasma LDL is the vehicle of uptake of ch. and cholesteryl ester into many tissues. Free ch. is removed from tissues by HDL, transported to the liver, where it is eliminated from the body either unchanged or after conversion to bile acids in the process known as **reverse cholesterol transport.**

# cholesterol synthesis transport and excretion

- All tissues containing nucleated cells are capable of cholesterol synthesis, which occurs in the endoplasmic reticulum and the cytosol.
- The biosynthesis of cholesterol may be divided into five steps:
- (1) Synthesis of mevalonate occurs from Acetyl-CoA (the precursor & the Source of All 27 Carbon Atoms in Cholesterol).
- (2) Isoprenoid units are formed from mevalonate by loss of CO2.
- (3) Six isoprenoid units condense to form squalene.
- (4) Squalene cyclizes to give rise to the parent steroid, lanosterol.
- (5) Cholesterol is formed from lanosterol.

# cholesterol synthesis



# CHOLESTEROL SYNTHESIS CONTROL & EXCRETION

- Regulation of cholesterol synthesis is exerted at the beginning of the pathway, at the HMG-CoA reductase (or 3-hydroxy-3-methyl-glutaryl-CoA reductase or HMGCR) step. The reduced synthesis of cholesterol in starving is accompanied by a decrease in the activity of the enzyme. However, it is only hepatic synthesis that is inhibited by dietary cholesterol. HMG-CoA reductase in liver is inhibited by mevalonate, the immediate product of the pathway, and by cholesterol, the main product which inhibit the HMG-CoA reductase. In addition Insulin or thyroid hormone increases HMG-CoA reductase activity, whereas glucagon or glucocorticoids decrease it.
- **CHOLESTEROL EXCRETION**

About 1 g of cholesterol is eliminated from the body per day. Approximately half is excreted in the feces after conversion to bile acids. The remainder is excreted as cholesterol. Coprostanol is the principal sterol in the feces; it is formed from cholesterol by the bacteria in the lower intestine.