Cholesterol Metabolism

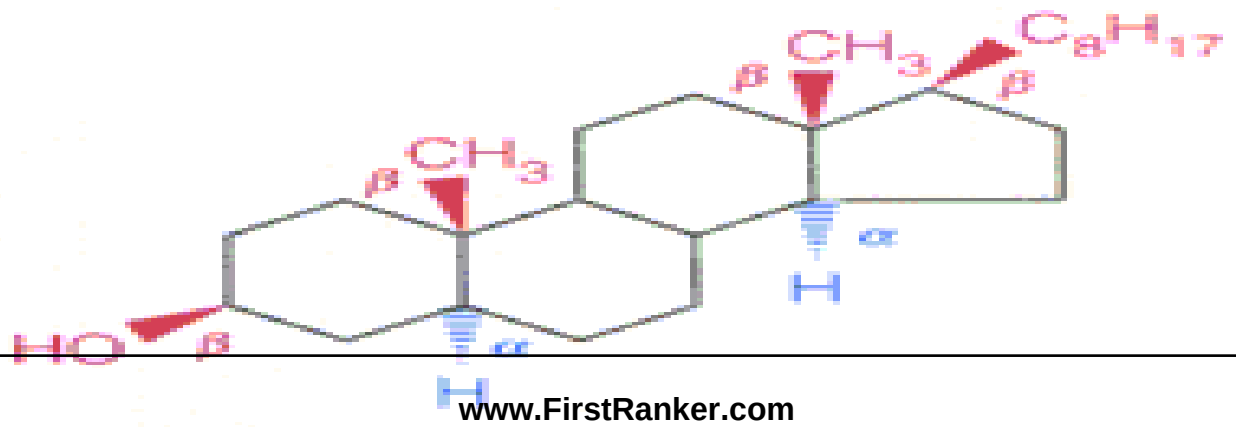
How Is Cholesterol Generated,Operated,Destructed In Human Body?

Chemical Structure Of Cholesterol

Recapitulation

(a) Perhydrocyclopentanophenanthrene

(b) Cholesterol



(c) Two-dimensional representation of cholestanol

Structural Aspects Of Cholesterol

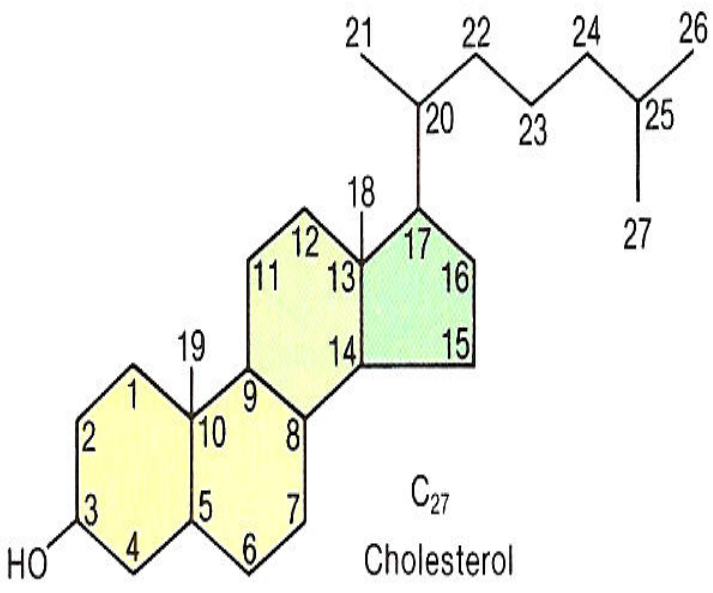
- **Cholesterol** is a **C27 compound**.

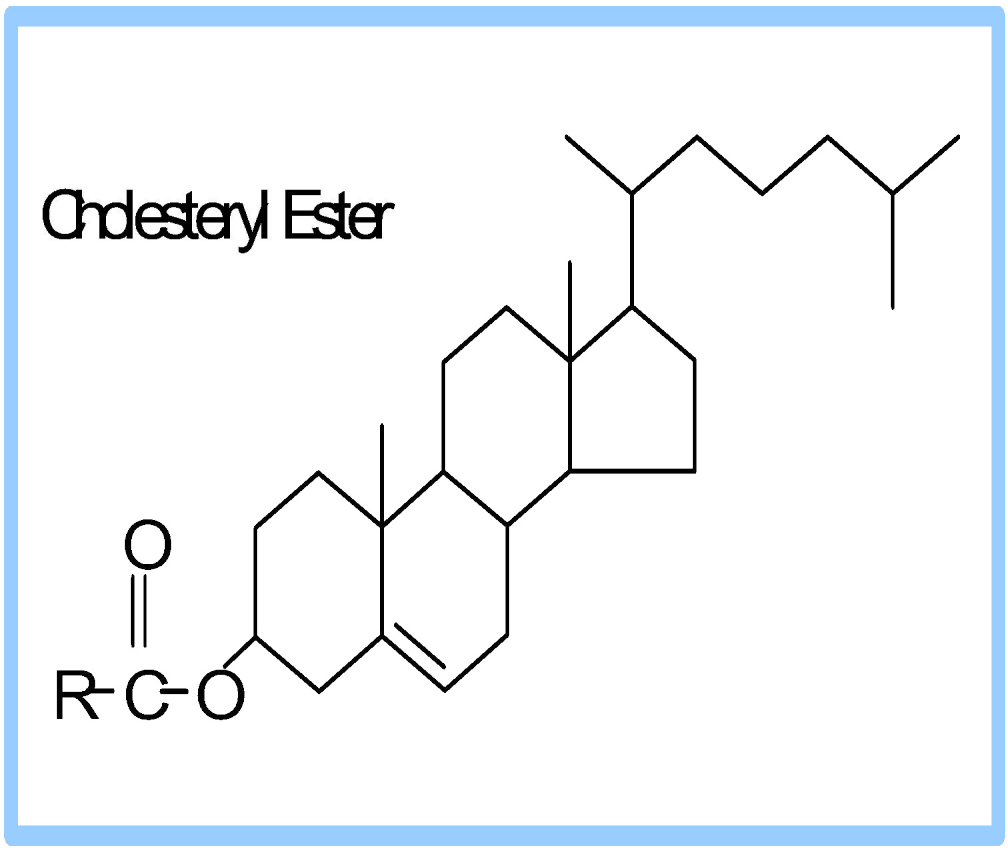
- Cholesterol has a parent nucleus **Cyclo Pentano Perhydro Phenantherene Ring**.

Two Forms Of Body Cholesterol

Cholesterol Forms

Free Cholesterol And Esterified Cholesterol



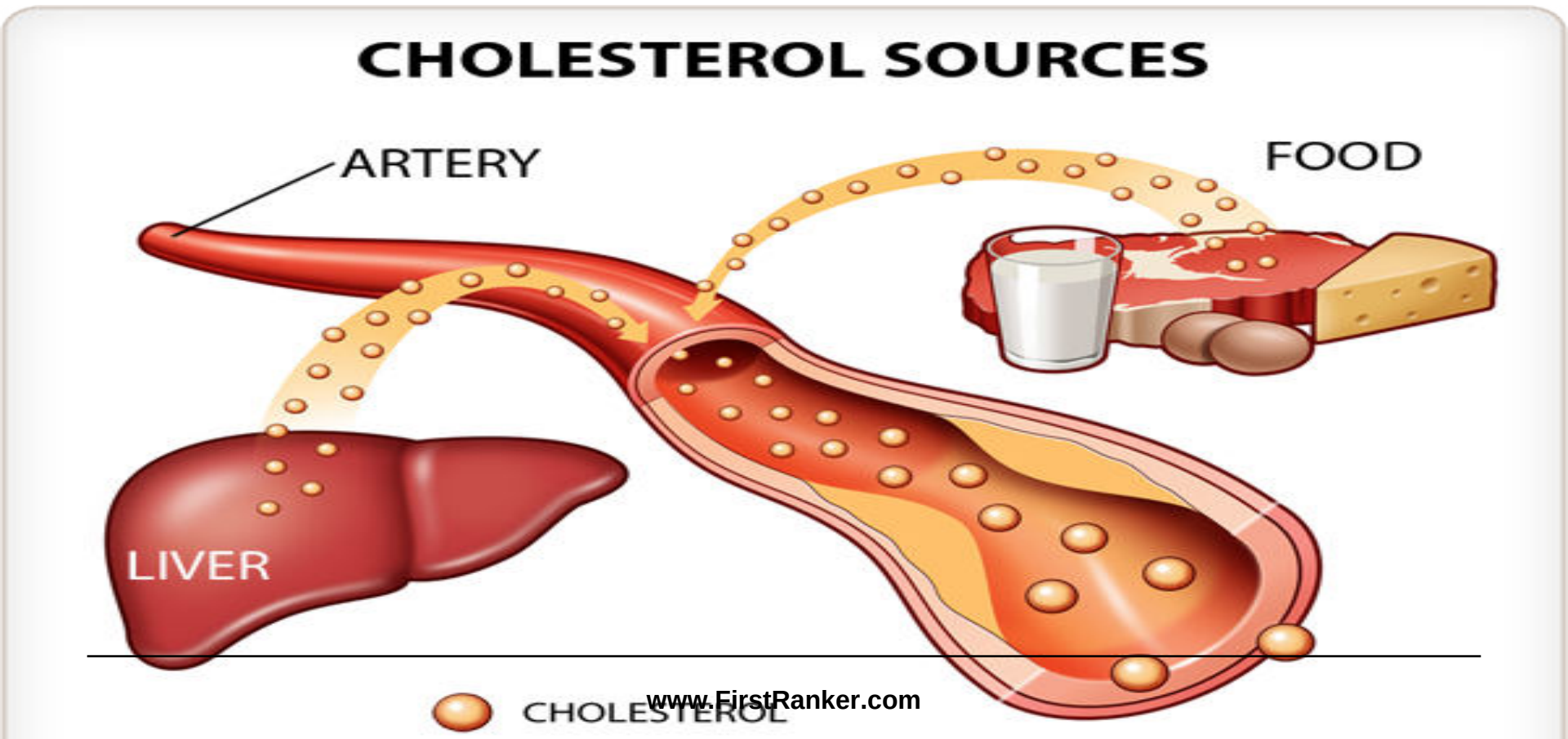


- **Free Cholesterol** is a **derived Lipid (30%)**

- **Cholesterol Ester** is a simple Lipid and a body **Wax. (70%)**

- **Cholesteryl Ester** is a **storage and excretory form** of Cholesterol which is found in most tissues.

Sources Of Body Cholesterol



Endogenous And Exogenous Sources Of Body Cholesterol

- **About 1 g/day originates by biosynthesis**
- **About 0.3 g/day extracted from food**

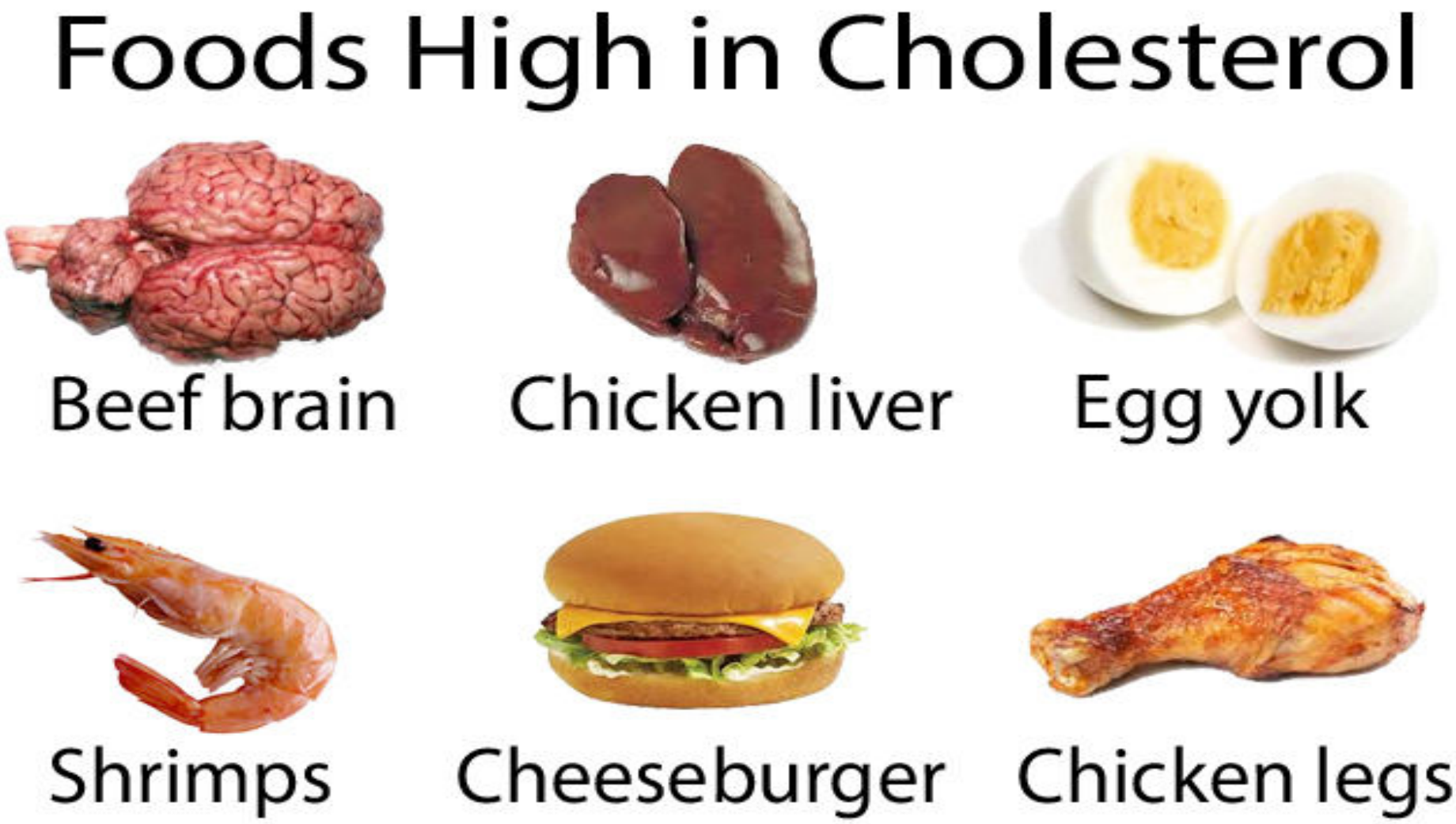
✓80% Endogenously produced by Liver (0.8 gram/day)

✓20% Exogenously comes from digestive tract (0.3 gm/day)

- Assume **400 mg** is an **intake** of dietary Cholesterol per day
- It **absorb about 50% Cholesterol**
- **200 mg** is **absorbed** from GIT
- **800 mg** of Cholesterol is from **de novo synthesis**

Exogenous Sources Of Cholesterol

(Animal Sterol)



Cholesterol Biosynthesis

Is To Provide

Endogenous Source Of Body Cholesterol

Amount Of Cholesterol Biosynthesis

- **Endogenously about 1 gm/day** of Cholesterol is biosynthesized.

- **Ingestion of excess of Carbohydrates elevates Cholesterol biosynthesis.**

Conditions Favoring For Cholesterol Biosynthesis

- Biosynthesis of Cholesterol takes place:
  - **In well fed condition**
  - When excess of **free cellular Glucose**
  - On stimulation of **Insulin**

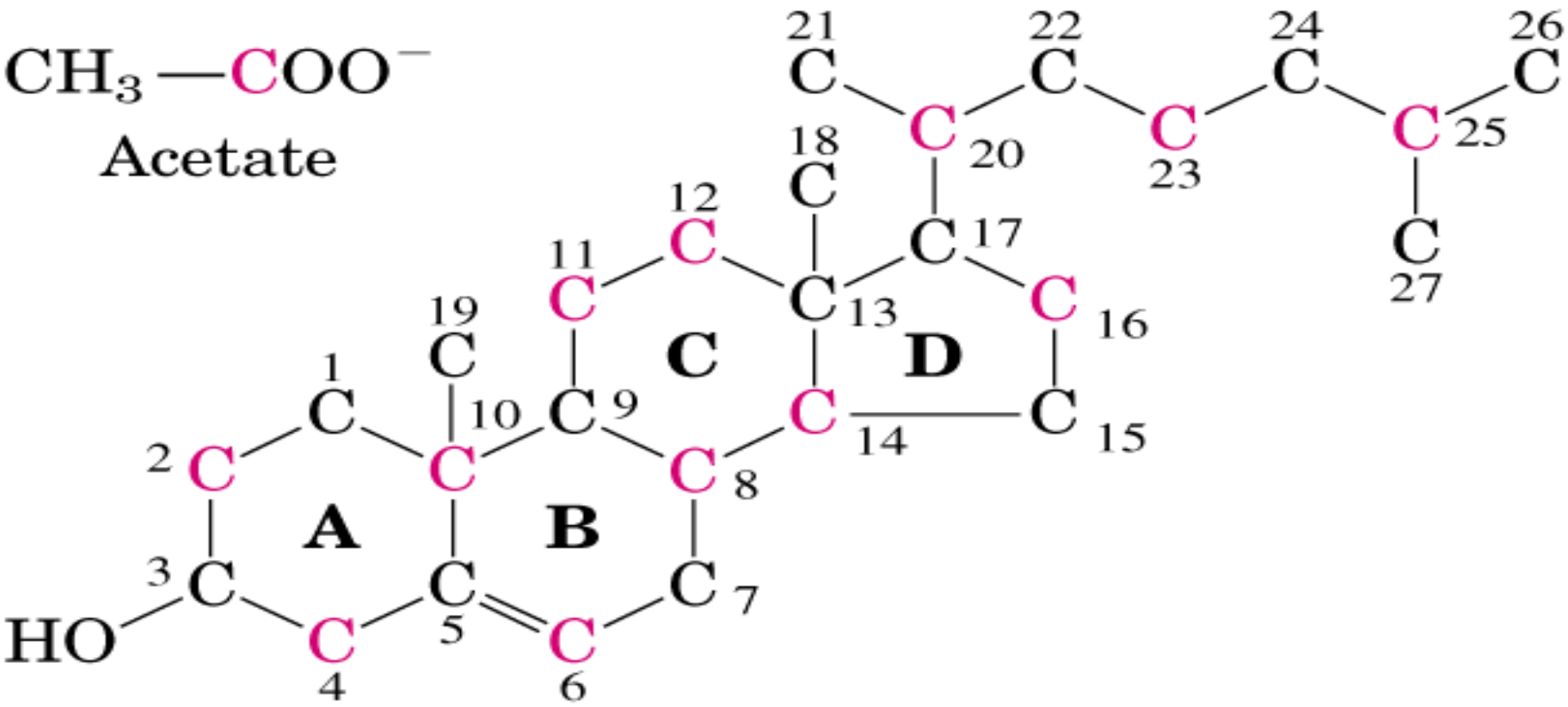
Glucose Regulates Cholesterol Biosynthesis

- **Increased** free and excess of cellular **Glucose**

- **Increases rate** of **endogenous Cholesterol biosynthesis**

- **Amount of Cholesterol biosynthesis depends upon**
- **Availability of Acetyl-CoA obtained from Glucose metabolism in a well fed state.**

Cholesterol Synthesis
Simplicity to Complexity



Cholesterol

- All **27 carbon units** of Cholesterol Structure are biosynthesized using

- **2 carbon moiety Acetyl-CoA** units ,**obtained from Glucose metabolism**.

Site Of Cholesterol Biosynthesis

Organs and Cellular Site For Cholesterol Biosynthesis

Organs Involved For Cholesterol Biosynthesis

- **Liver (80%)**
- Intestine (10%)
- Skin (5%)
- Adrenal Cortex
- Ovaries , Testes , Placenta
- Arterial walls (some extent)

- Cholesterol Synthesizing Enzymes are **partly located in:**

  –Cytoplasm

  –Endoplasmic Reticulum

Requirements For Cholesterol Biosynthesis

Requirements For Reductive Biosynthesis Of Cholesterol

- **Metabolic Precursor- Acetyl CoA** (Obtained from excess Glucose metabolism)
- **Enzymes ,Coenzymes and Cofactors**
- **16 NADPH +H^+** (Through HMP Shunt)
- **36 ATPs**

Translocation Of Acetyl CoA From Mitochondrial Matrix To Cytosol

- Cholesterol is biosynthesized from **Cytosolic Acetyl CoA**
- Which is transported from Mitochondria via the **Citrate transport system.**

Stages Of Cholesterol Biosynthesis

- **Biosynthesis of Cholesterol** is a very **complex process**
- **To understand divided in 5 Stages**
- Requires **more than 25 steps.**

- **Stage 1.**
- **Acetyl-CoA forms HMG-CoA and Mevalonate.**

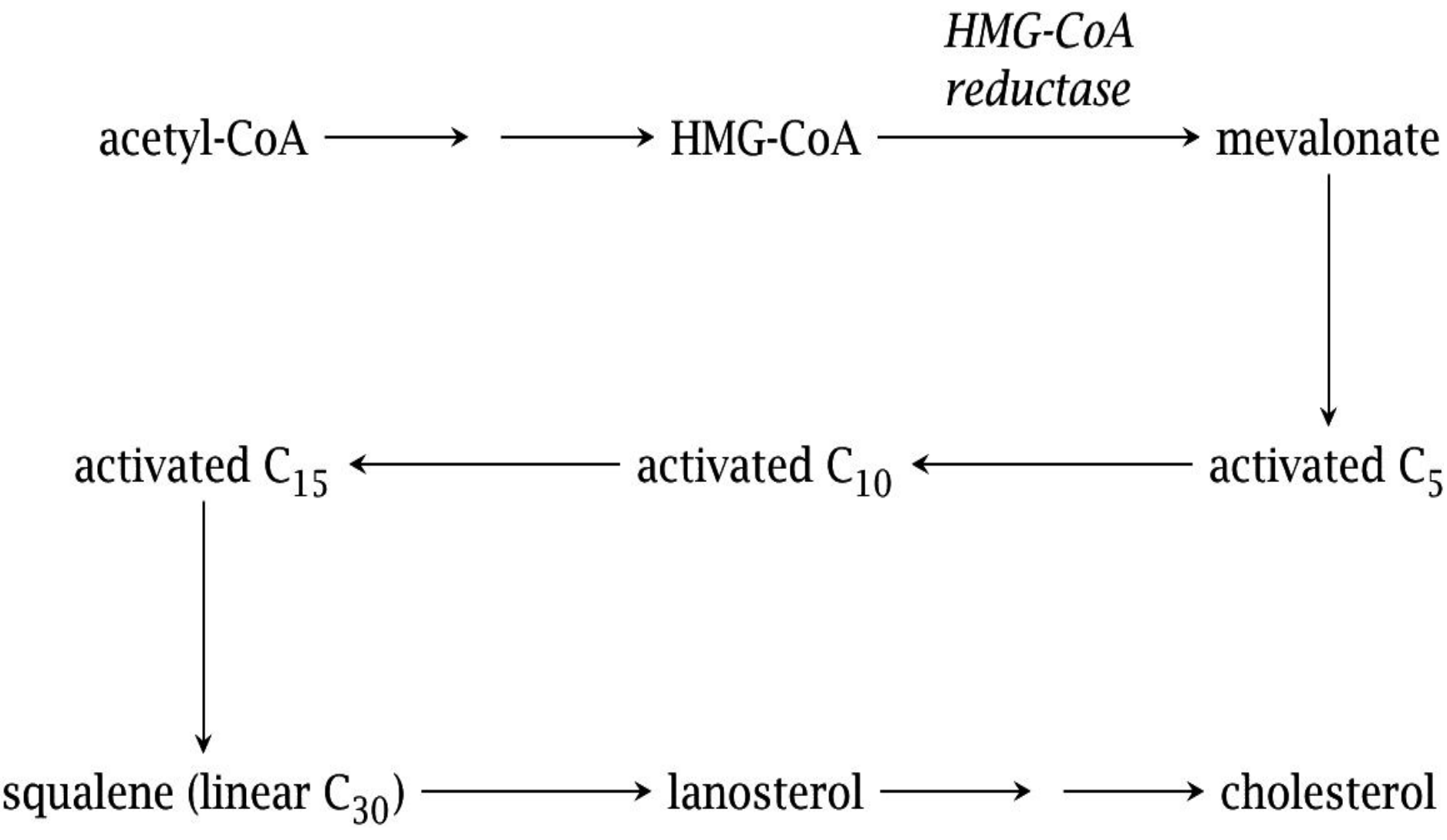
- **Stage 2.**
- **Mevalonate forms Active Isoprenoid units(C5)**

- **Stage 3.**
- **6 Isoprenoid units form Squalene (C30)**

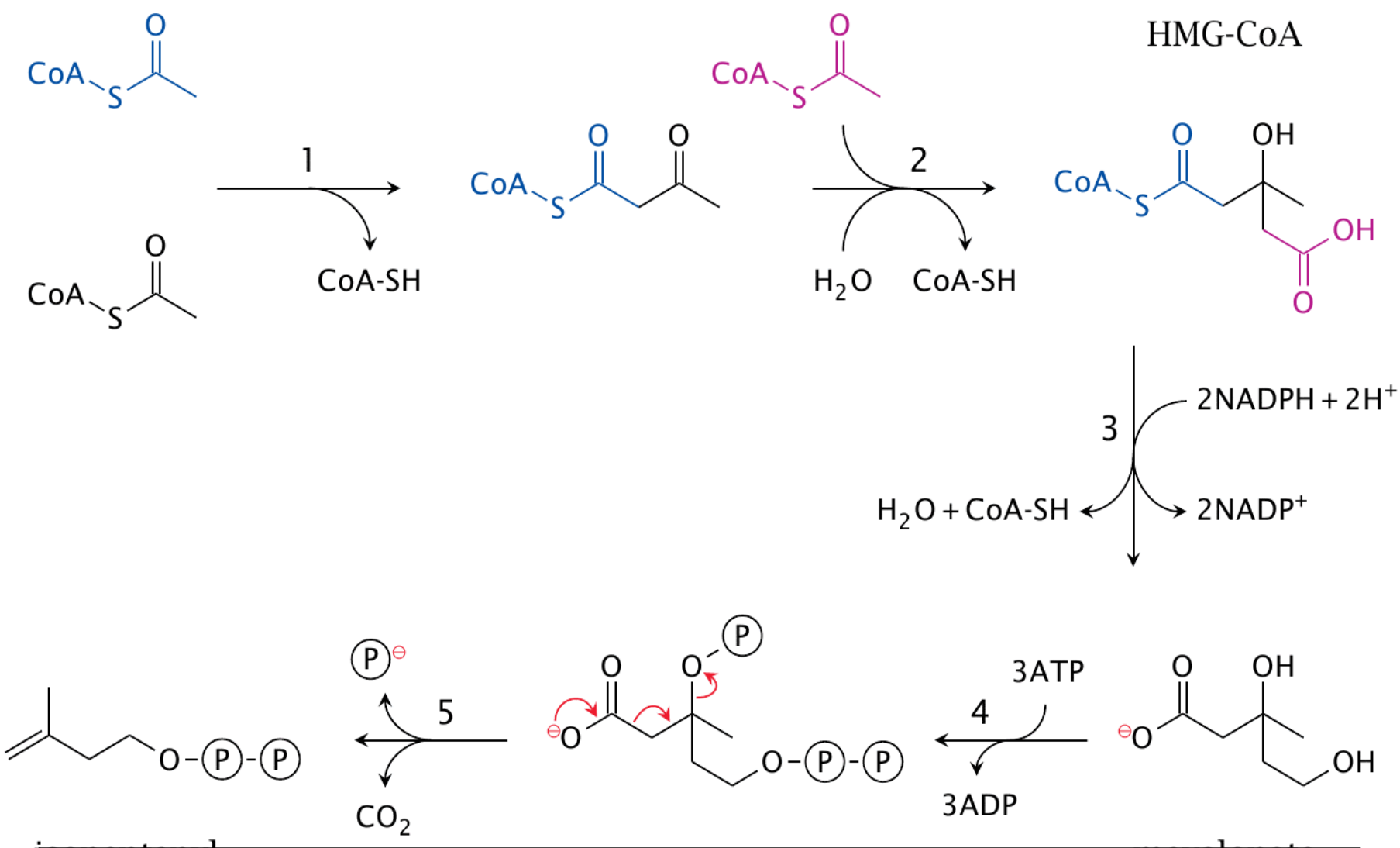
- **Stage 4.**
- **Squalene is converted to Lanosterol**

- **Stage 5.**
- **Lanosterol is converted to Cholesterol(C27)**

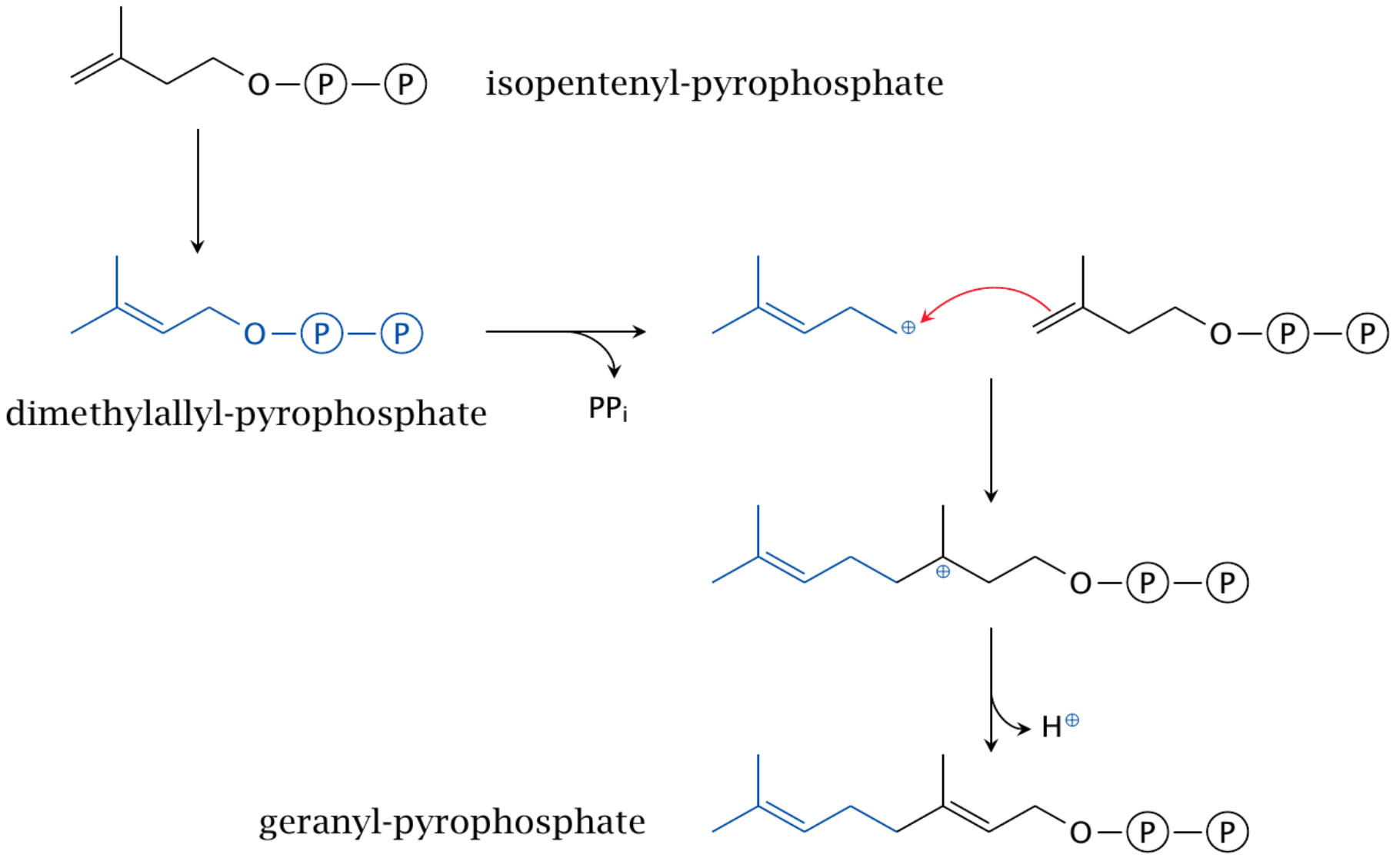
Overview/Outline of Cholesterol Synthesis



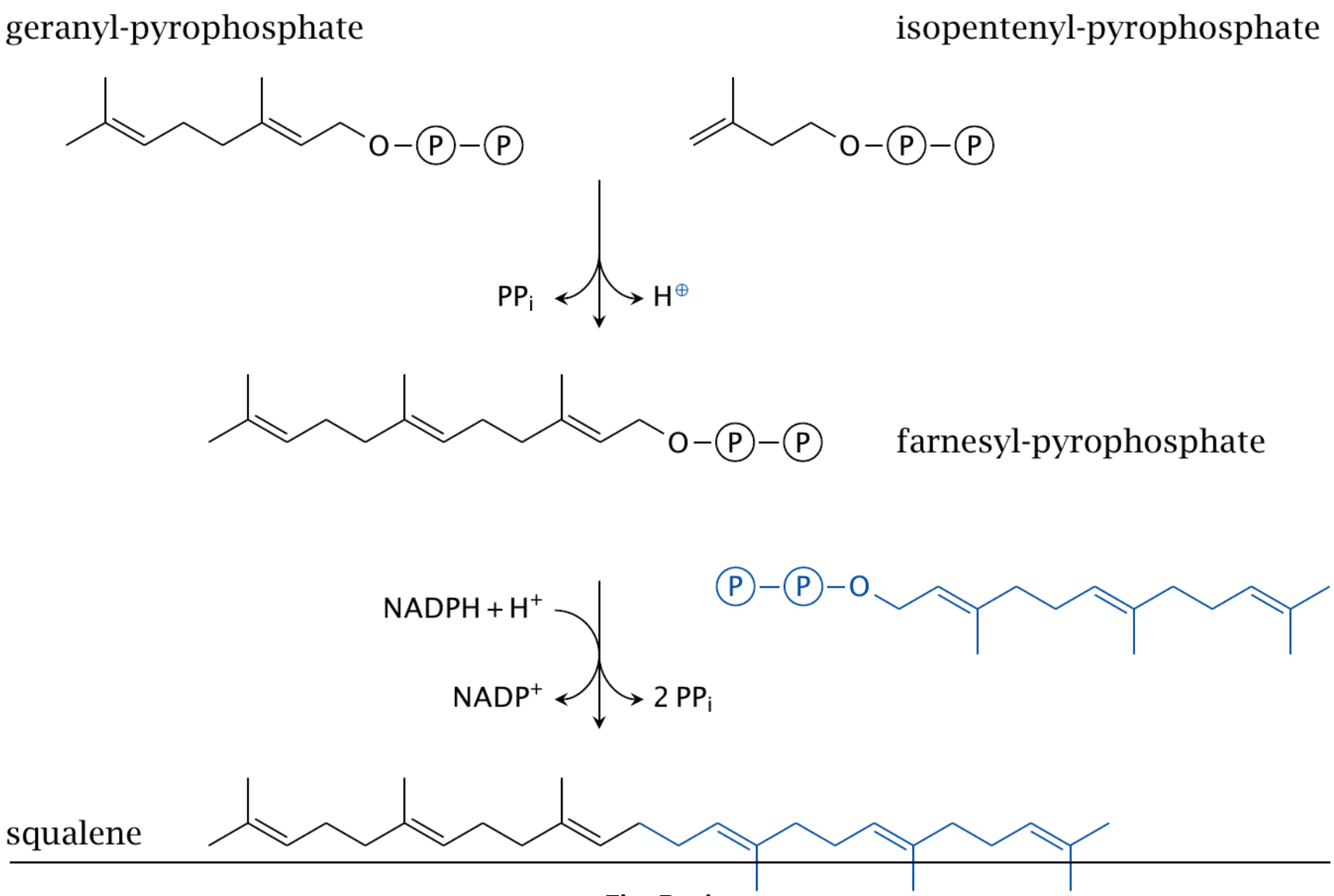
Initial Activation Steps in Cholesterol Synthesis



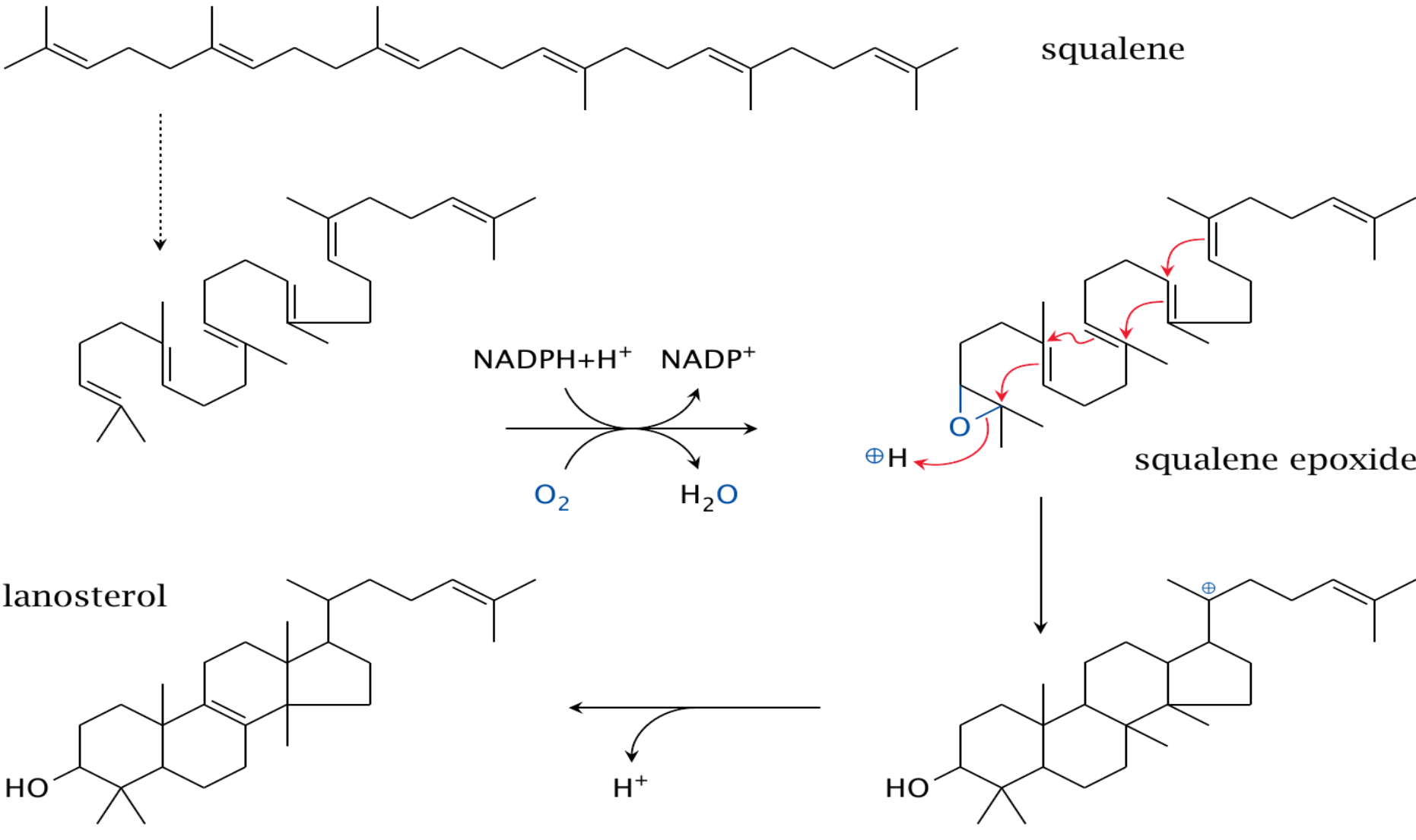
Formation of a C_{10} intermediate GPP



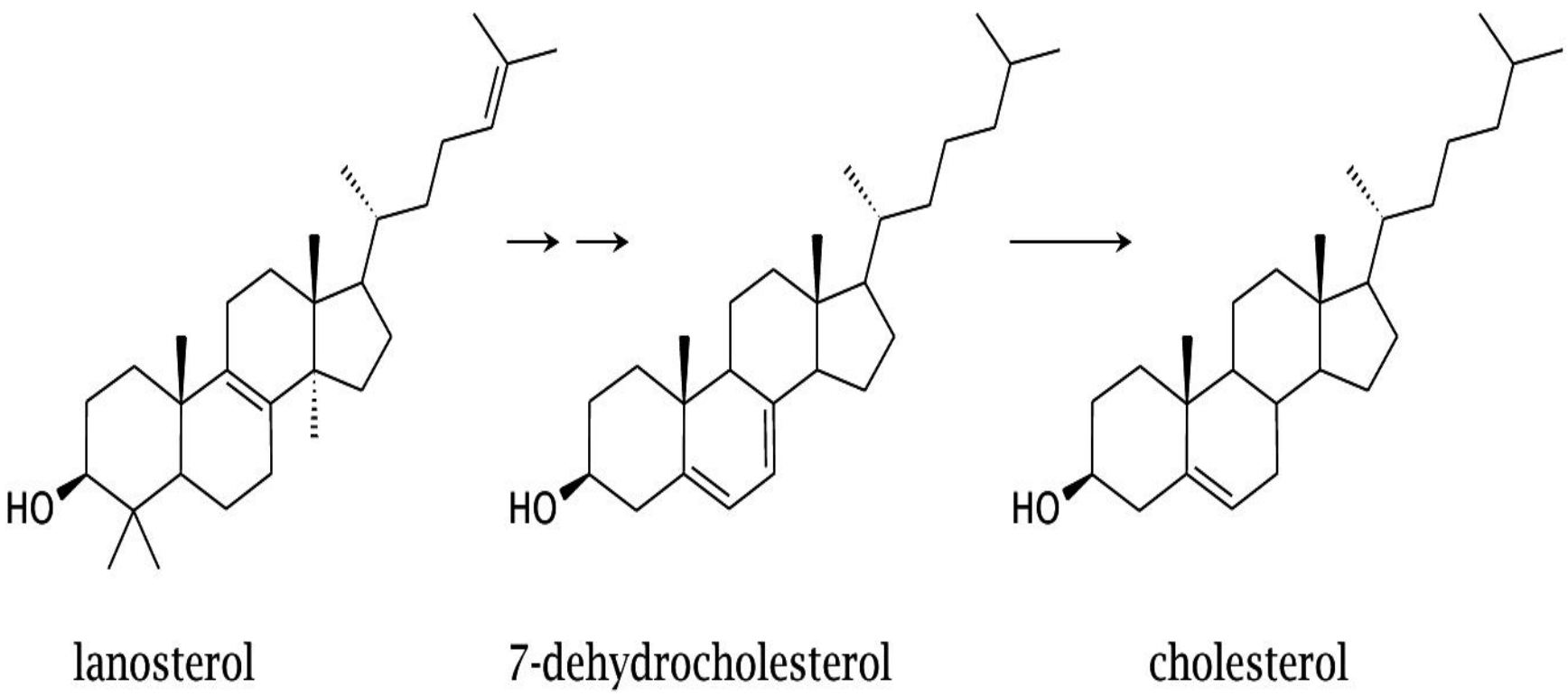
Formation of C_{15} and C_{30} intermediates



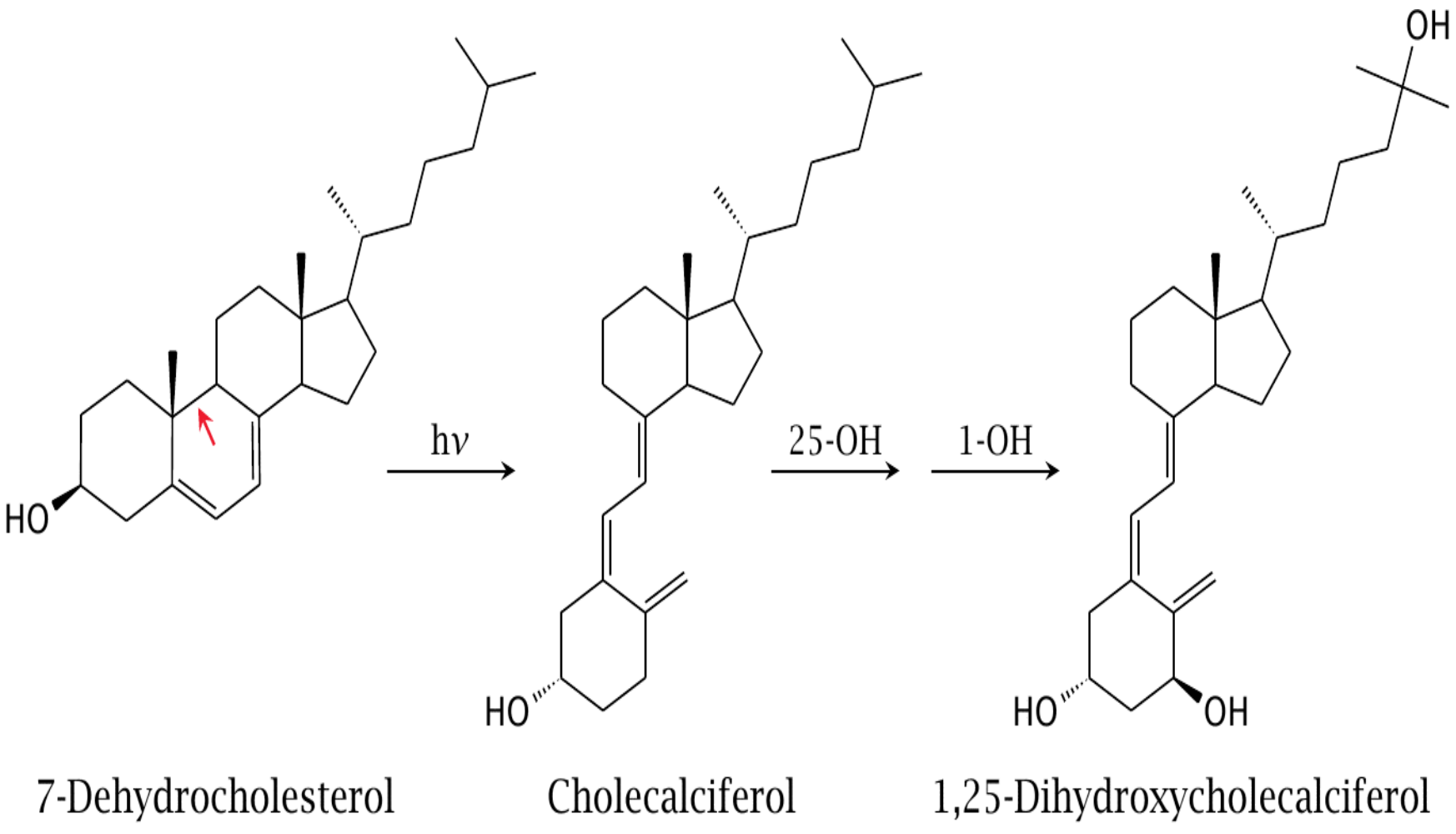
Squalene cyclization yields the first sterol intermediate

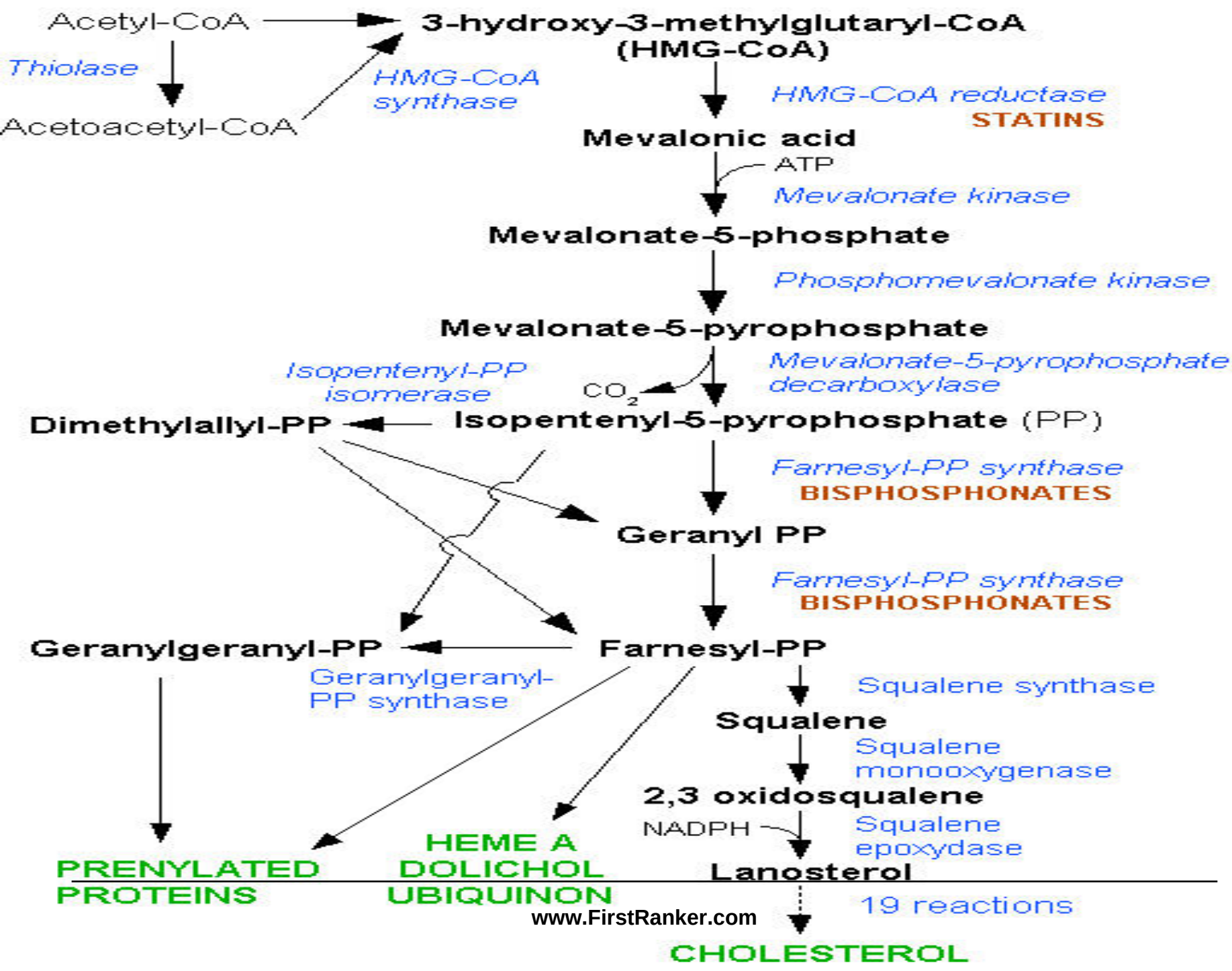


Demethylation, desaturation and saturation steps convert Lanosterol to Cholesterol



UV-dependent synthesis of Cholecalciferol

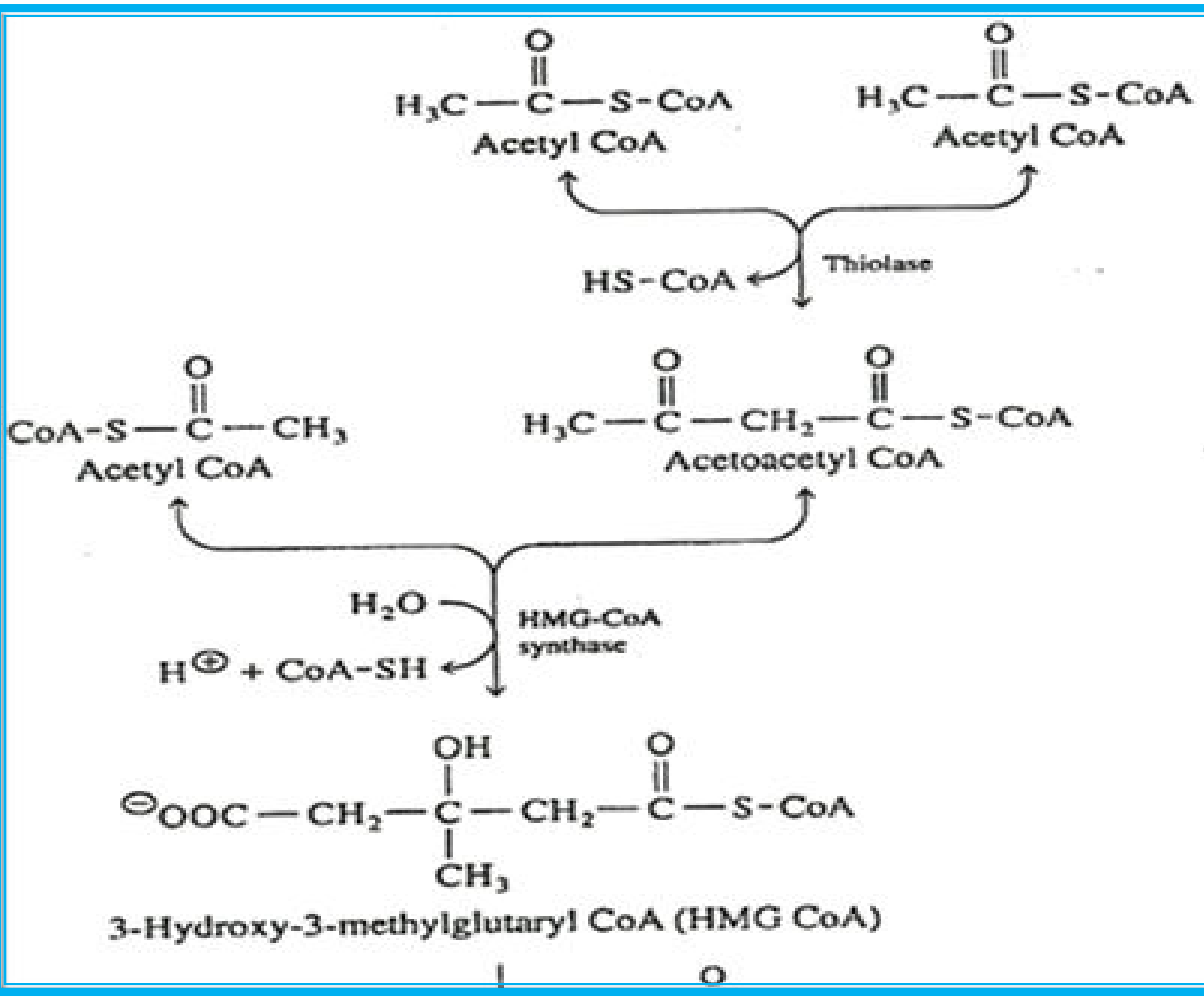




Stage I

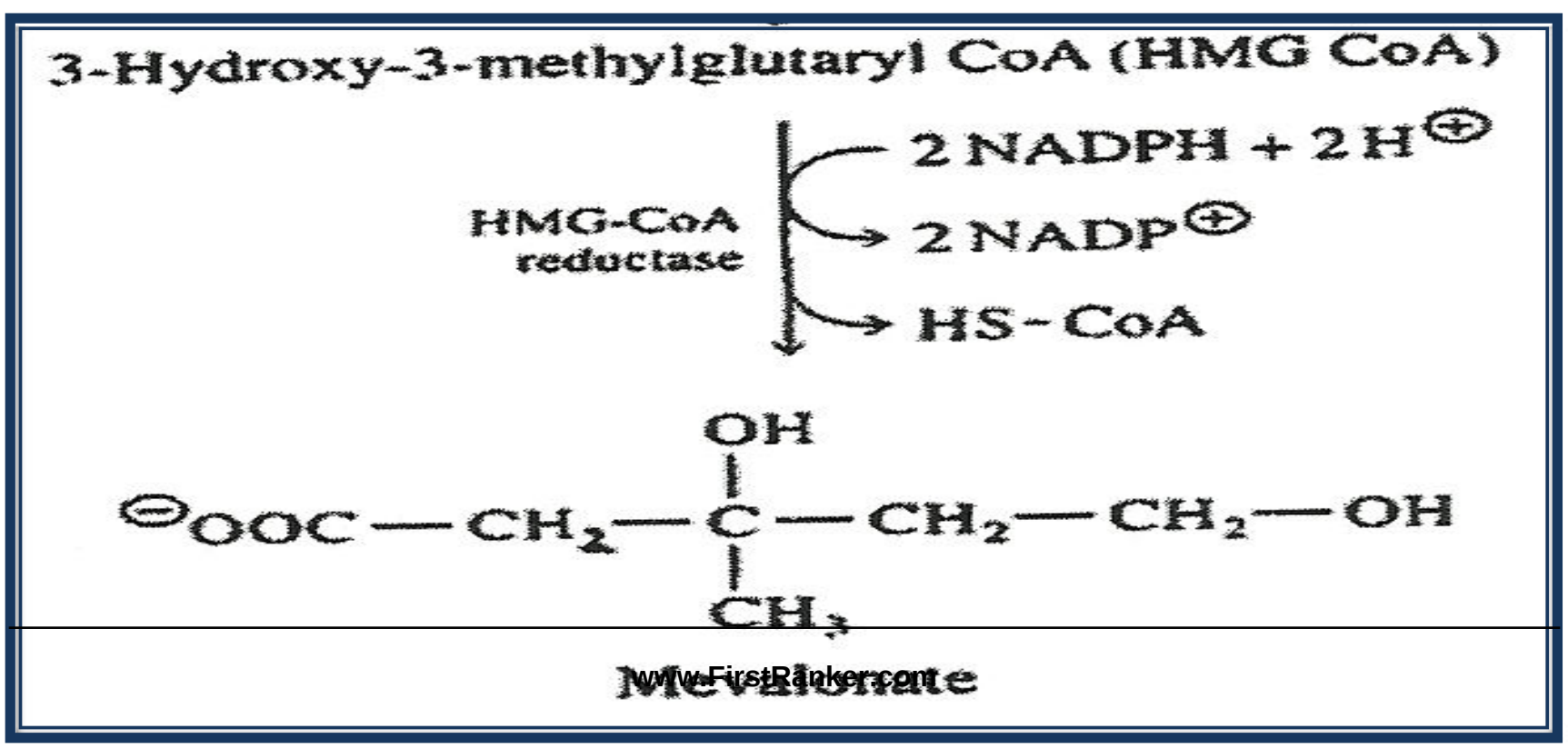
Synthesis Of HMG CoA and Mevalonate

It starts by the condensation of **three** molecules of **Acetyl CoA(C2)** with the formation of **HMG CoA (C6)** **by HMG CoA Synthase** **(As like In Ketogenesis)**



HMG CoA is Reduced to Mevalonic acid (C6) by reaction requiring **NADPH+H+** and enzyme **HMG CoA Reductase.**

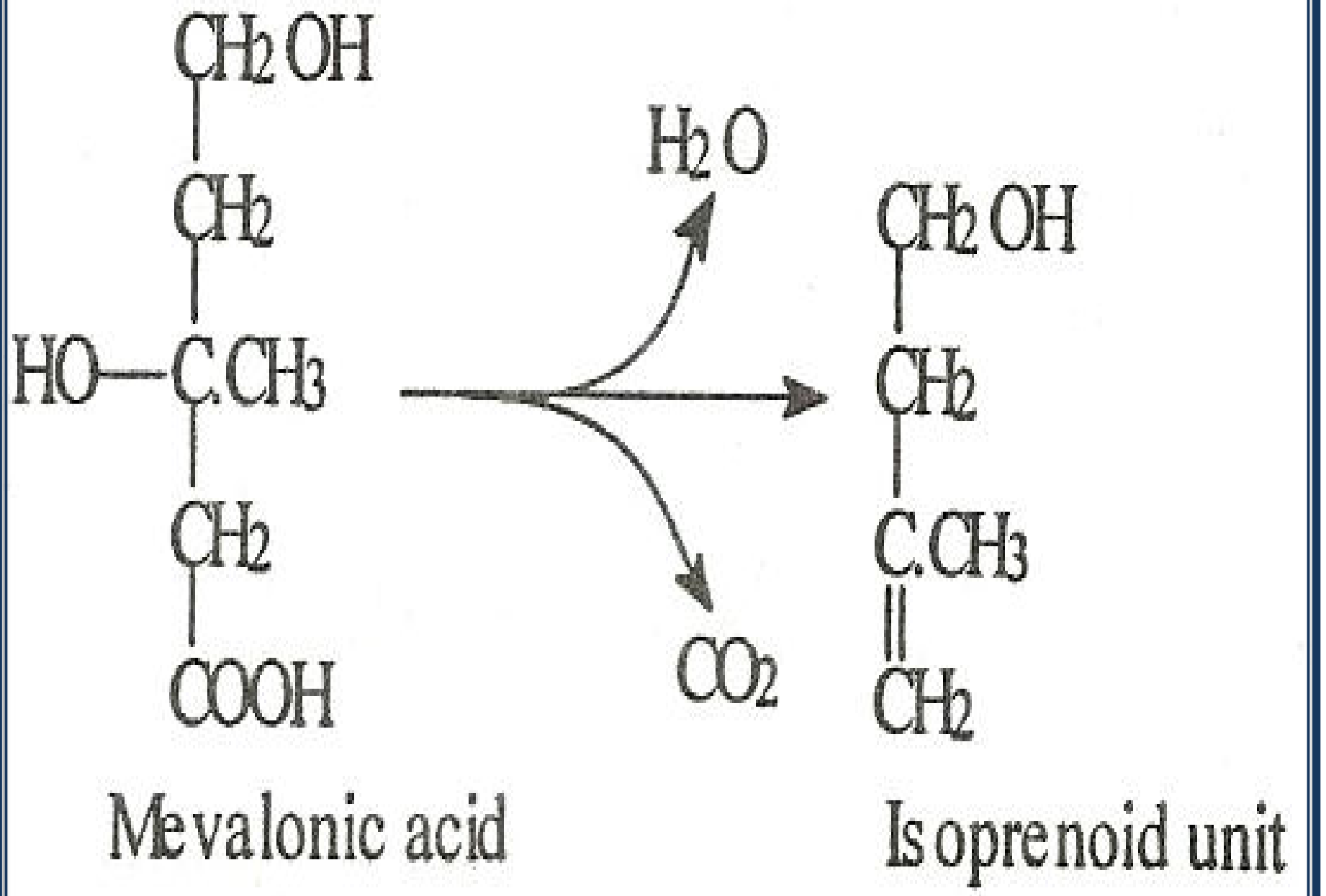
Two molecules of NADPH are consumed in the reaction.



Stage 2
Formation Of Isoprenoid Unit Isopentenyl Pyrophosphate (IPP)

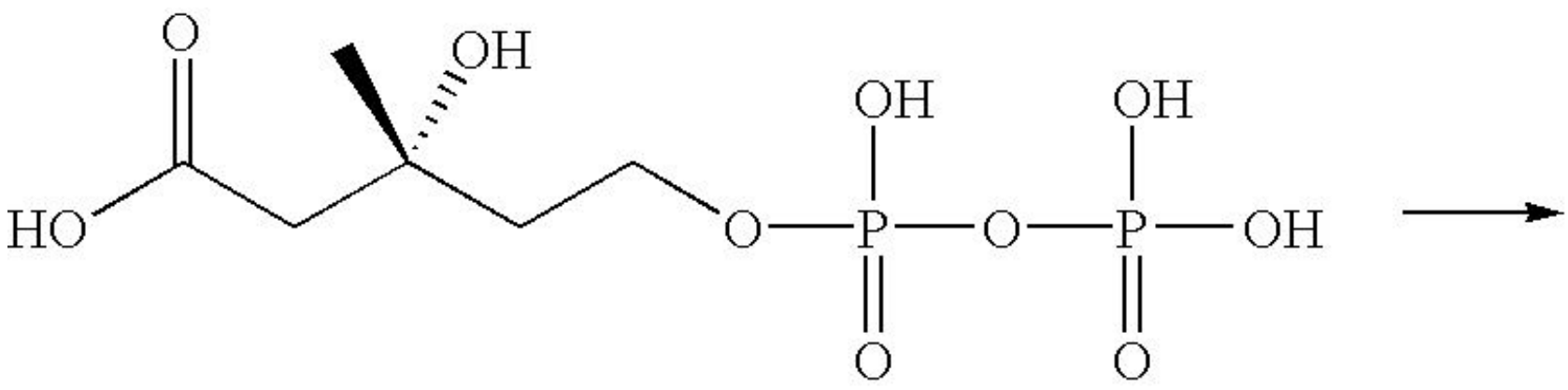
- **Mevalonate** in three subsequent steps is
  - **Phosphorylated with ATPs**
  - **Dehydrated and**
  - **Decarboxylated**

- To form Isoprenoid unit(C5)- **Isopentenyl pyrophosphate(IPP).**

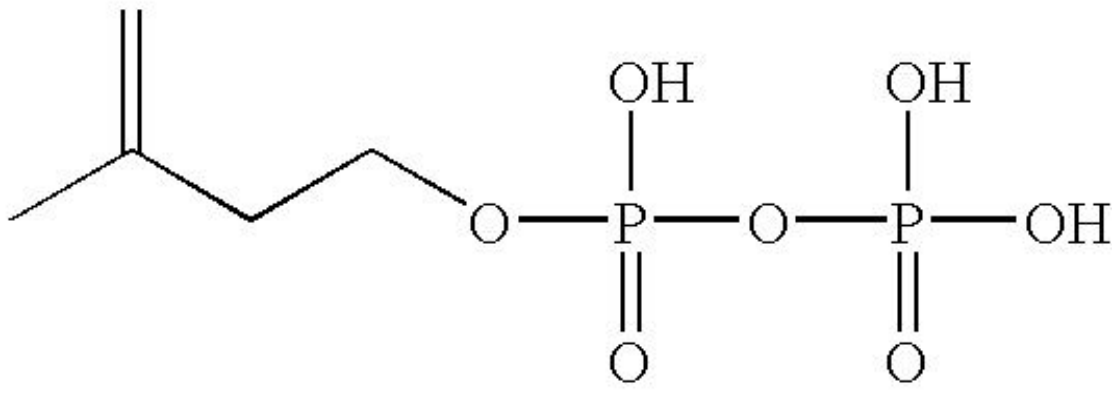


Mevalonic acid

Isoprenoid unit



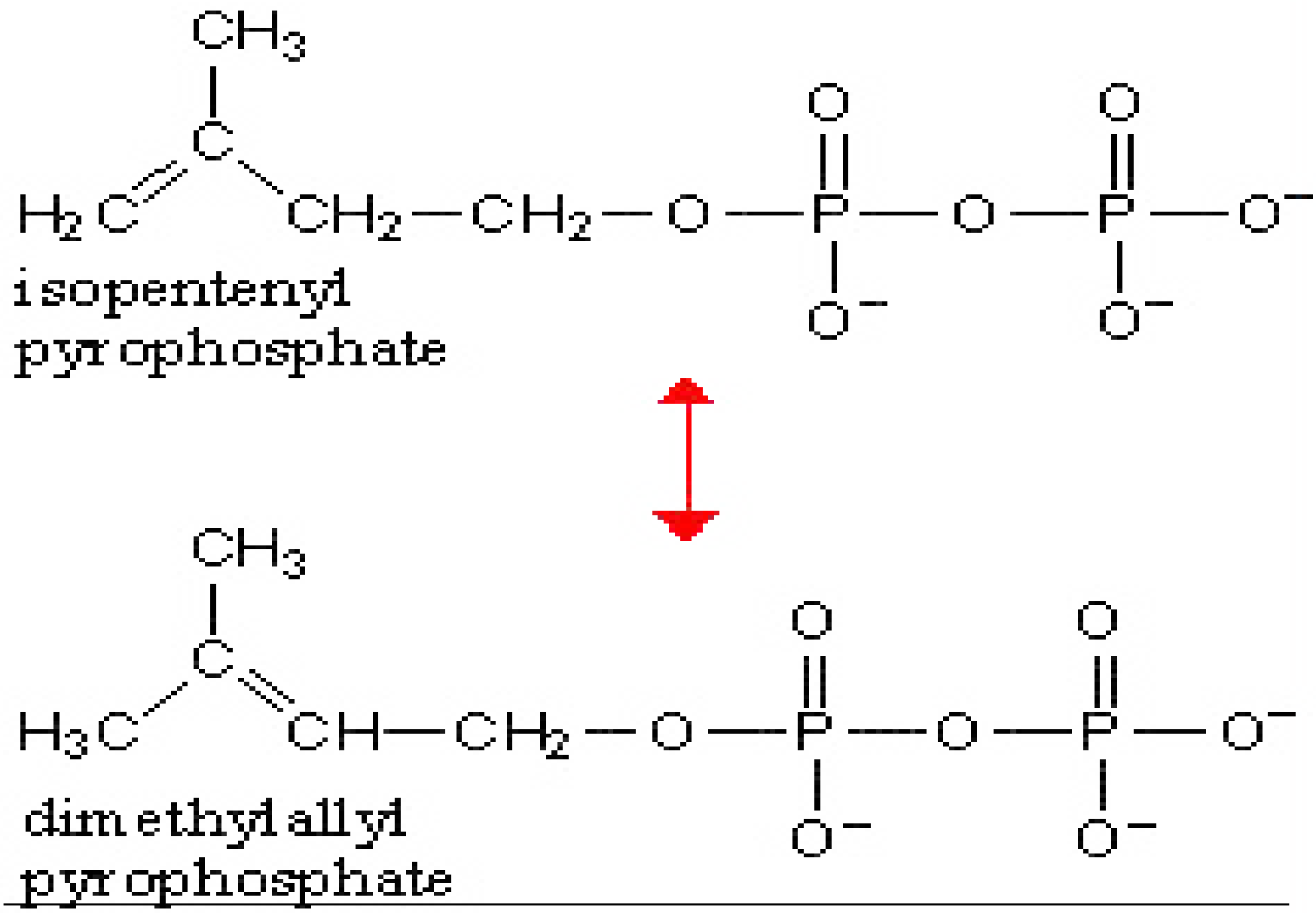
Mevalonate 5-diphosphate

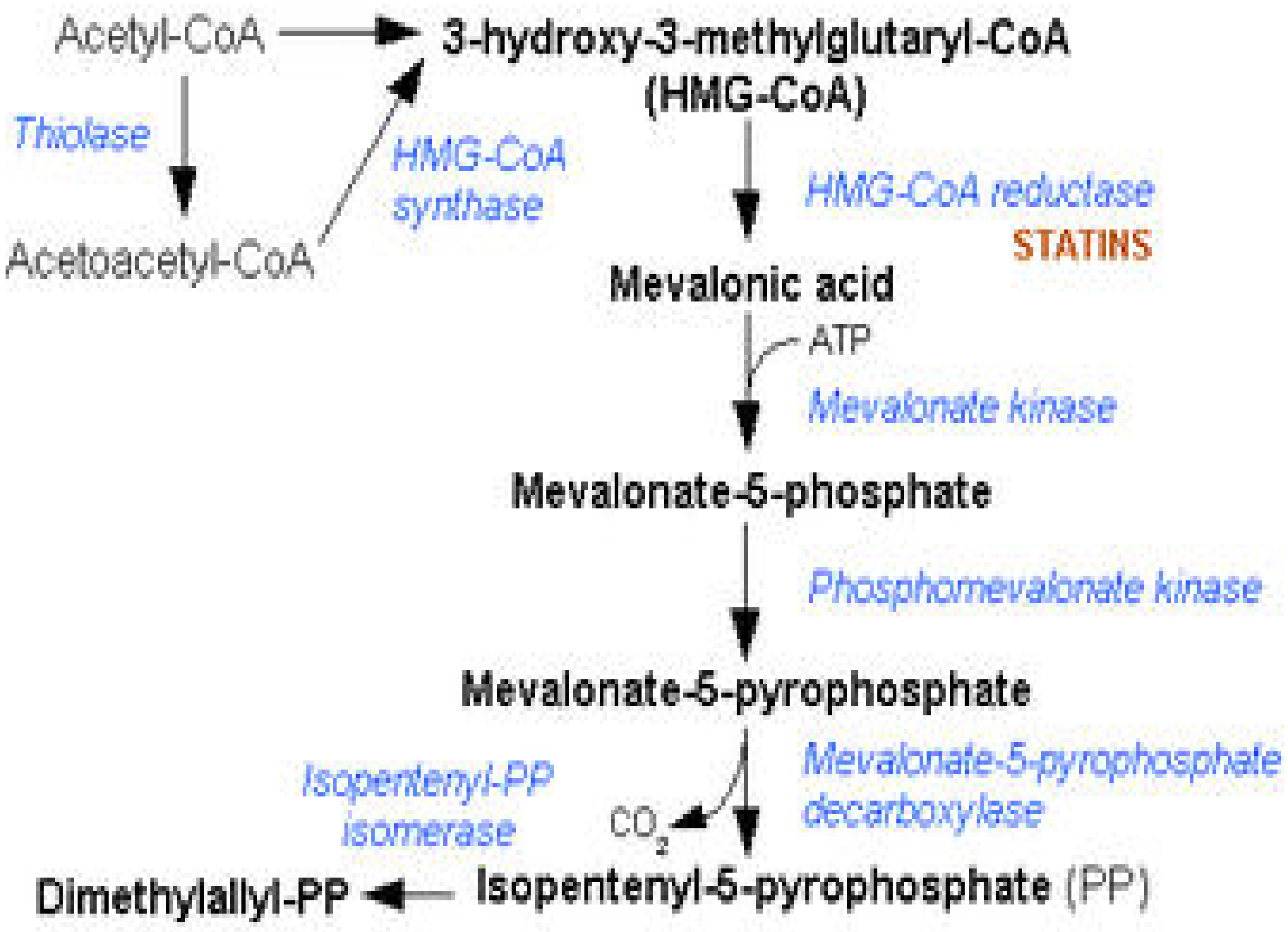


Isopentenyl pyrophosphate

Isomerization Of IPP To DPP

- Isopentenyl Pyrophosphate (IPP-C5) is **isomerized to** **Dimethylallyl Pyrophosphate** (DPP-C5) with the **Isomerase** activity





Stage 3
Synthesis Of Squalene (C30)

Formation Of Geranyl Pyrophosphate (GPP-C10)

- **IPP** (C5) and **DPP** (C5) get condensed to form **Geranyl Pyrophosphate** (GPP-C10)

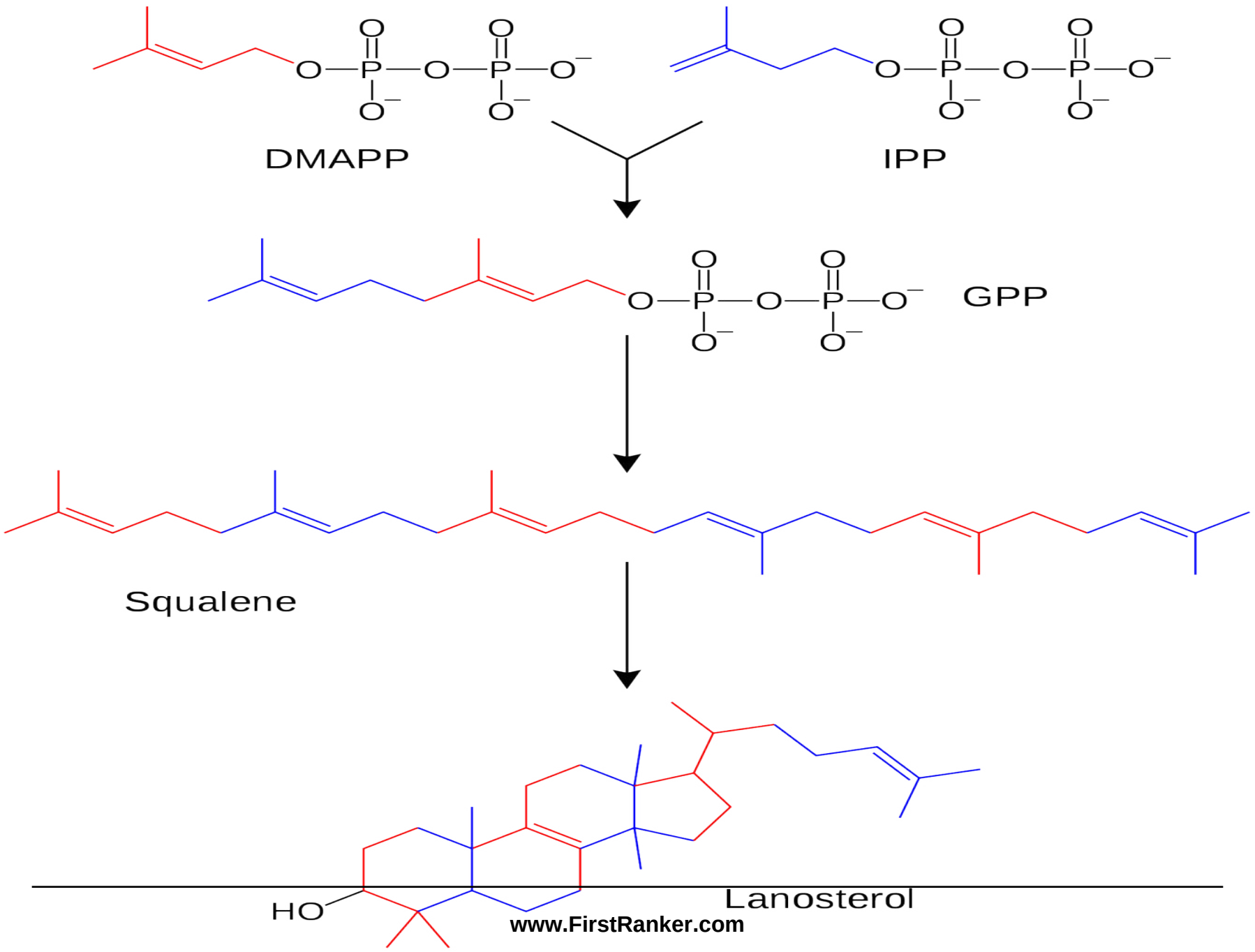
Formation OF Farnesyl Pyrophospate (FPP- C15)

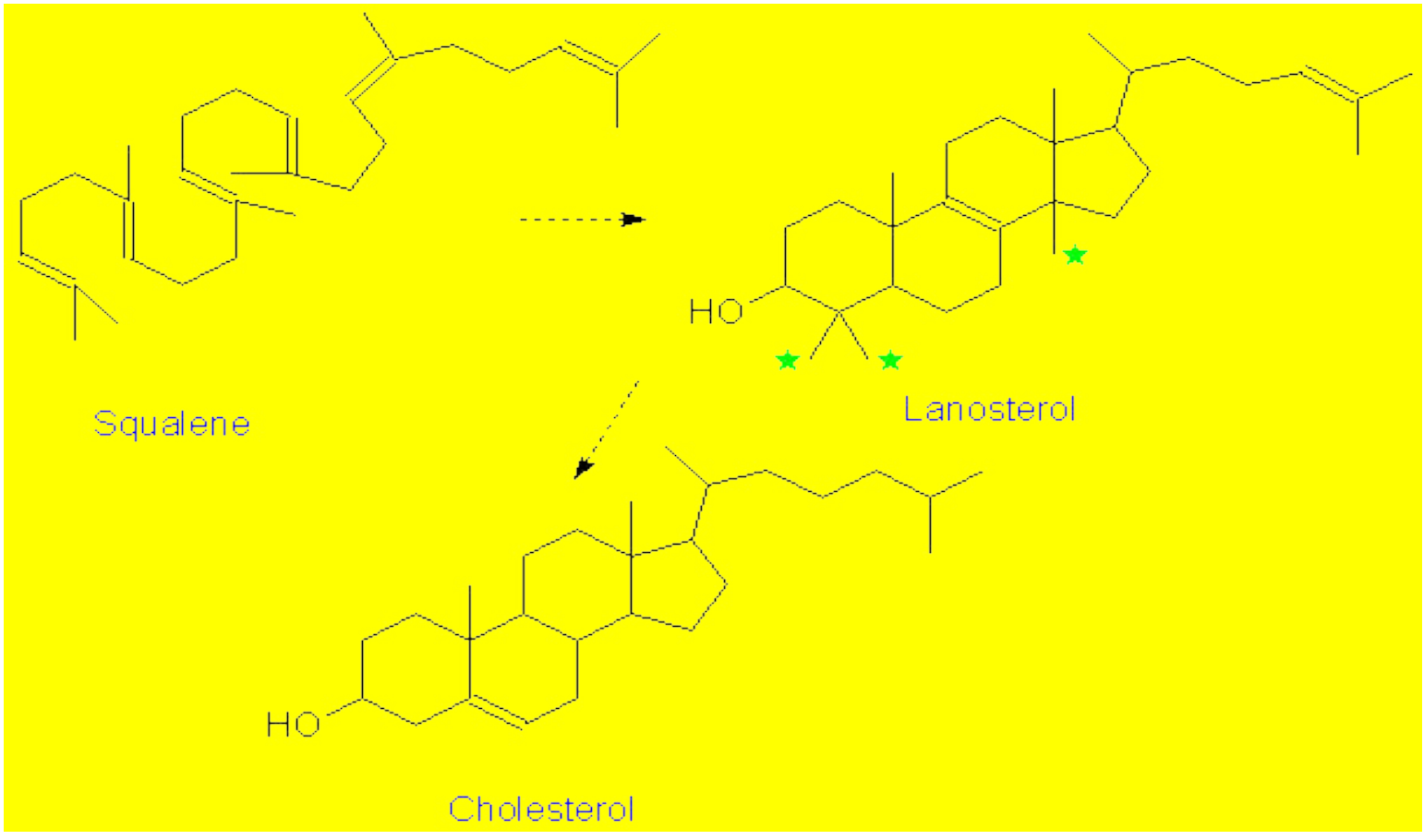
- 1 molecule of **GPP condenses** with 1 molecule of **IPP** to form **Farnesyl Pyrophospahte** (FPP-C15)

Conversion Of FPP(C15) to Squalene (C30)

- Two molecules of FPP get condensed to **generate Squalene.**
- At smooth Endoplasmic Reticulum with the catalytic activity of **Squalene Synthase** Coenzyme **NADPH+H+** and Cofactors **Mg , Mn and Co**

Sage 4
Conversion Of Squalene To Lanosterol

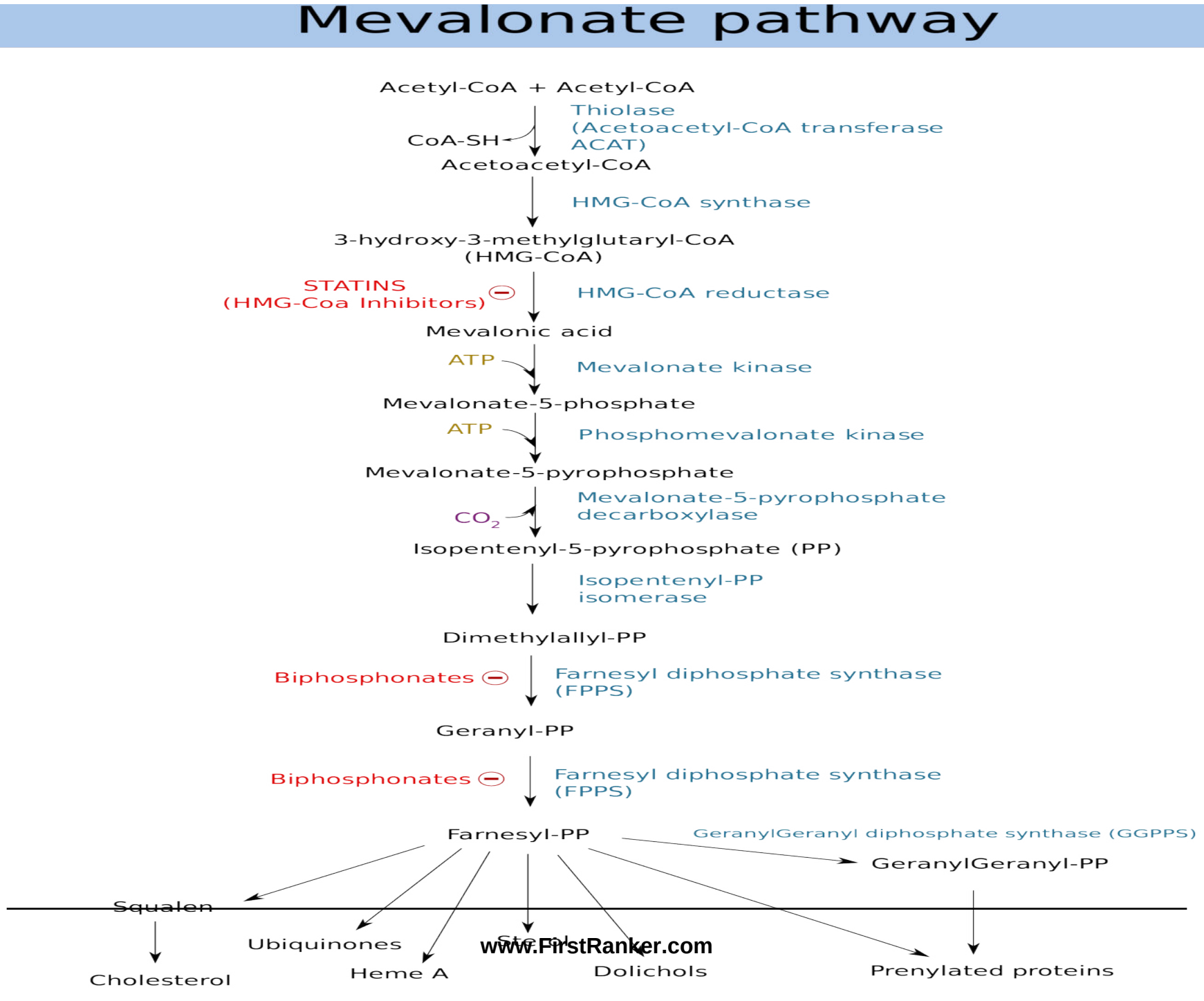




Stage 5
Transformation Of
Lanosterol To Cholesterol

- Lanosterol is converted to Cholesterol with many sequential steps

- With an **intermediates Zymosterol and Desmosterol**



Regulation Of Cholesterol Biosynthesis

HMG-CoA Reductase

- Is **regulatory/ key enzyme** of **Cholesterol Biosynthesis**.

- This enzyme is **stimulated and inhibited as per requirement of bodies need.**

- **Enzyme HMG-CoA reductase has half-life of 3 hrs.**

- **Degradation of HMG-CoA reductase depends on Cholesterol levels.**

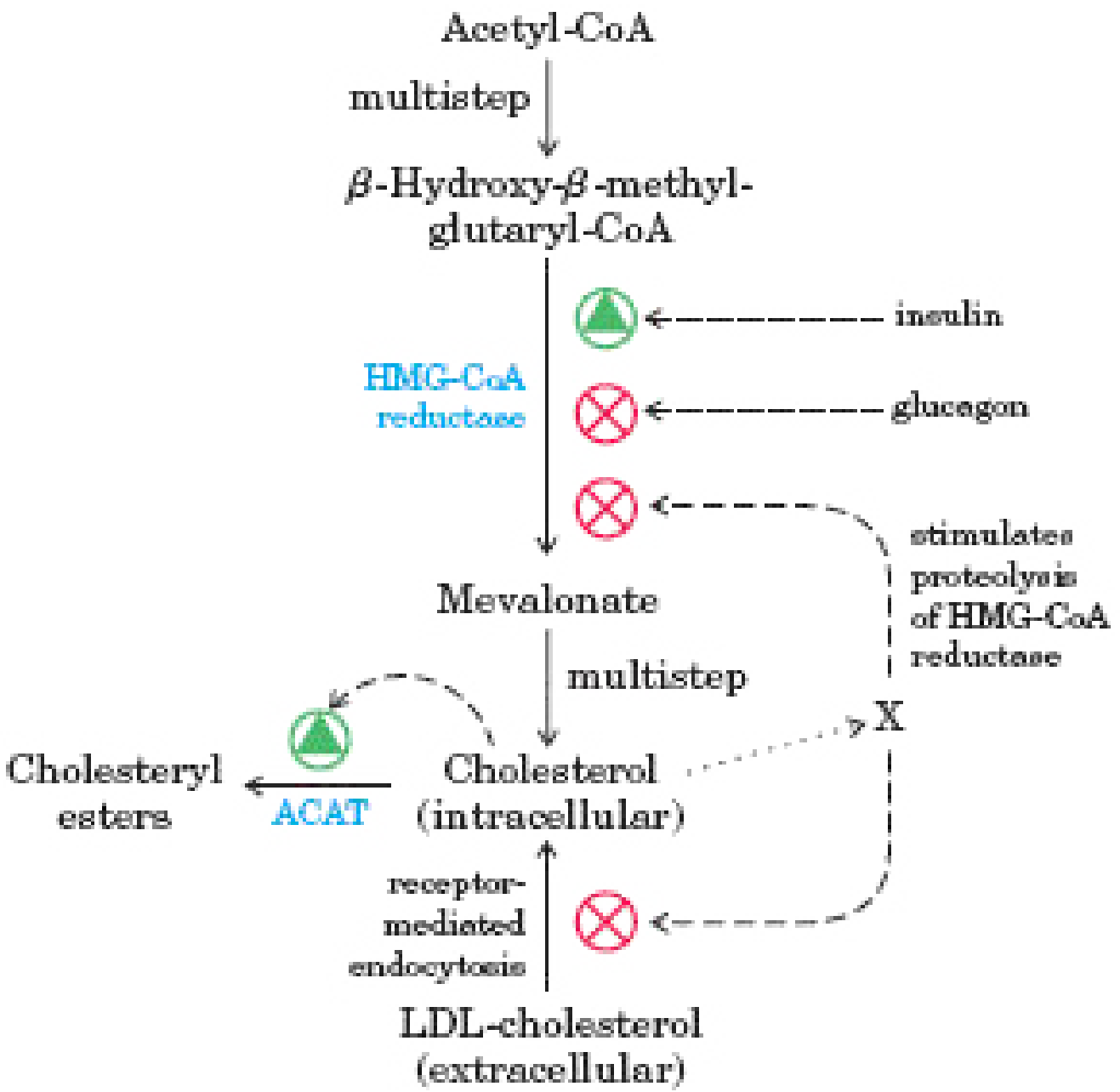
Modes Of Cholesterol Regulation

- Hormonal Influence
- Covalent Modification
- Feedback Inhibition

Hormonal Regulation

- **Insulin In well fed state:**
  - **Stimulates** and increases **HMG CoA Reductase**
  - **Increases** Cholesterol Biosynthesis

- **Glucagon and Glucocorticoids in emergency states:**
  - **Inhibits** HMG CoA Reductase.
  - **Decreases** Cholesterol Biosynthesis.



Covalent Modification Of Regulatory Enzyme HMG CoA Reductase

Phosphorylation And Dephosphorylation Of HMG CoA Reductase

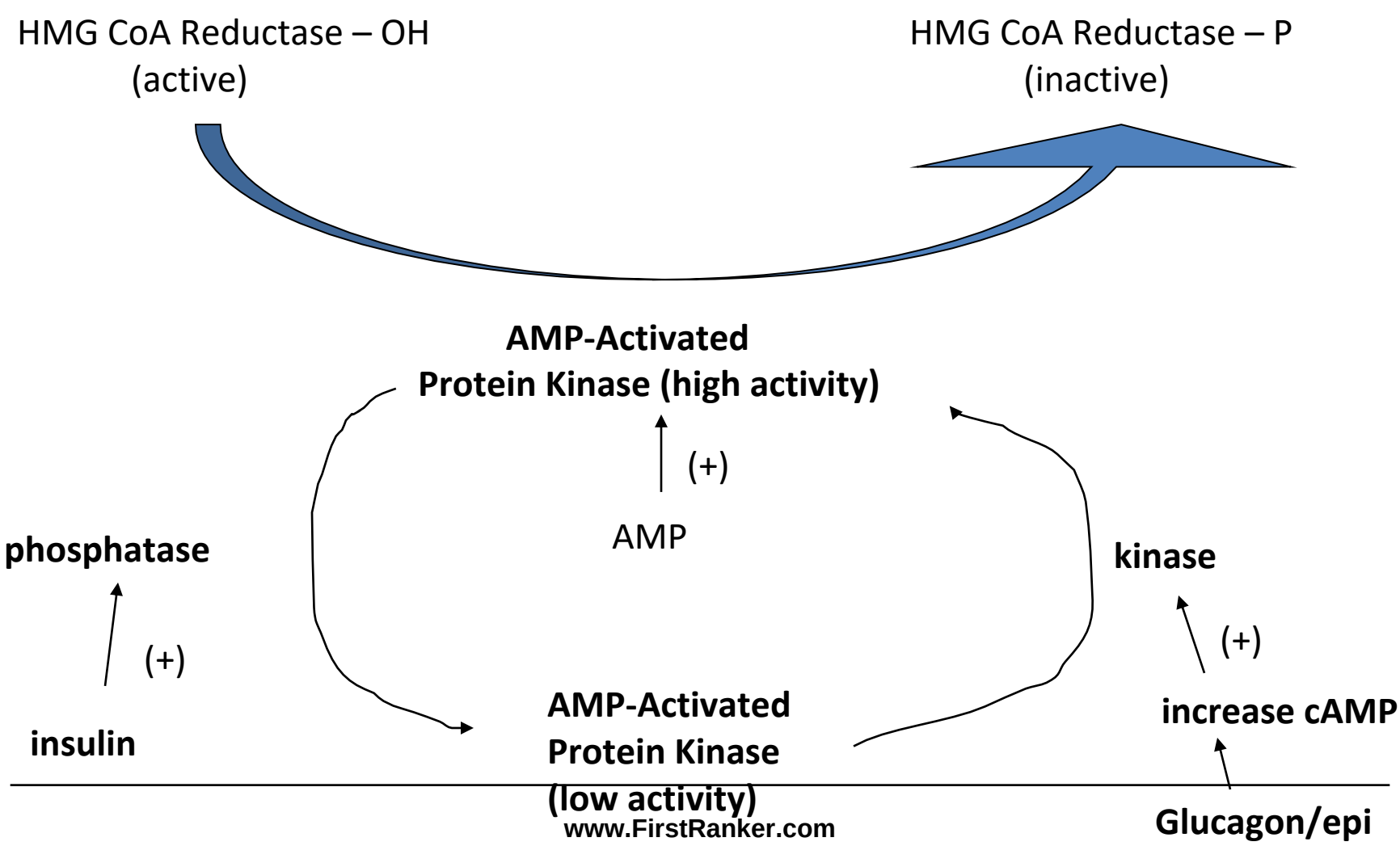
- **Short-term regulation** of Cholesterol biosynthesis is by

- **Phosphorylation & dephosphorylation** of Key enzyme **HMG CoA Reductase**

- **Phosphorylated –HMG CoA Reductase- Inactive Form**

- **Dephosphorylated-HMG CoA Reductase- Active form**

HMG CoA Reductase - Phosphorylation



- **Under influence of Hormone Insulin**
- **HMG CoA Reductase is Dephosphorylated**
- Which **activates HMG-CoA Reductase.**
- This **increases Cholesterol Biosynthesis.**

- Under influence of Hormone **Glucagon**
- **HMG CoA Reductase** is Phosphorylated by **cAMP-dependent Protein Kinases.**
- **Phosphorylation** of the Enzyme **inactivates HMG-CoA Reductase**
- **This inhibits Cholesterol Biosynthesis.**

- Glucagon, Sterols, Glucocorticoids & low ATP levels

- **Inactivate HMG-CoA Reductase**.

- **Insulin, Thyroid hormone, high ATP levels**
- **Activate the key enzyme HMG-CoA Reductase.**

Cholesterol Biosynthesis Regulated By Feed Back Inhibition

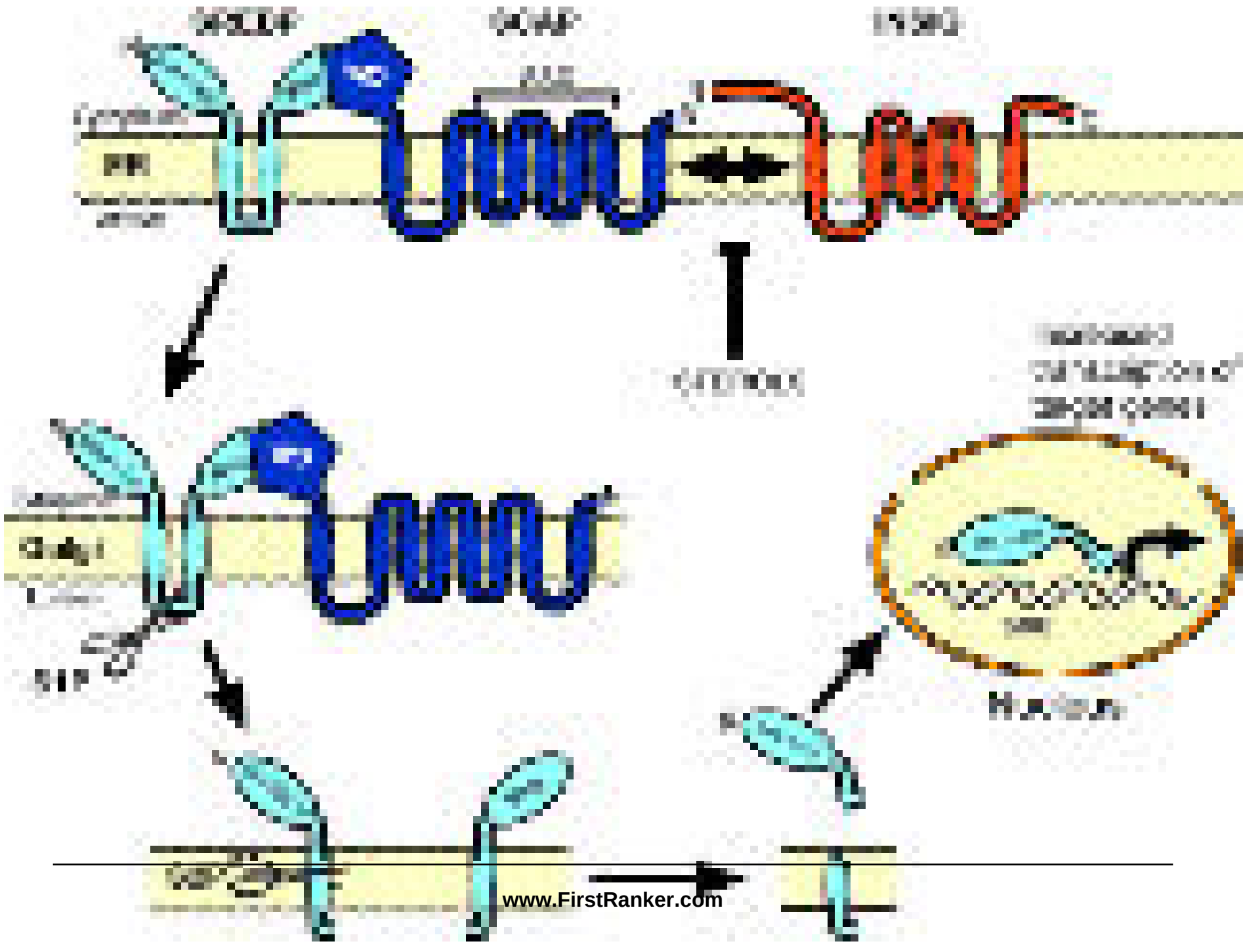
- **Sufficient amounts of body Cholesterol** regulate its biosynthesis
- By **feed back inhibition** of **Enzyme HMG CoA Reductase.**

- **Ingestion of Cholesterol inhibits endogenous cholesterol synthesis** (control exerted at both transcriptional and translational levels).

- **Gene expression (mRNA production) is controlled by Cholesterol levels**

Cholesterol Synthesis
Transcription Control

- Rate of HMG-CoA Reductase mRNA synthesis is controlled
- By **transcription factor** **Sterol Regulatory Element Binding Protein** **(SREBP)**



Competitive Inhibitors Of Cholesterol Biosynthesis

- **Drugs like Statins- Lovastatin ,Simvastatin**
- **Competitive inhibitors** of key Enzyme **HMG CoA Reductase** of Cholesterol biosynthesis.
- **Decreases Endogenous Cholesterol Biosynthesis**

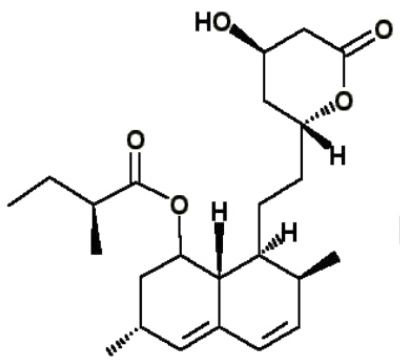
Lovastatin Inhibits Cholesterol Biosynthesis

- **Lovastatin (Mevinolin) blocks HMG-CoA Reductase activity and prevents biosynthesis of Cholesterol.**
- **Lovastatin is an (inactive) Lactone**
- **In body, Lactone is hydrolyzed to Mevanolinic acid, which is a competitive inhibitor of HMG CoA reductase.**

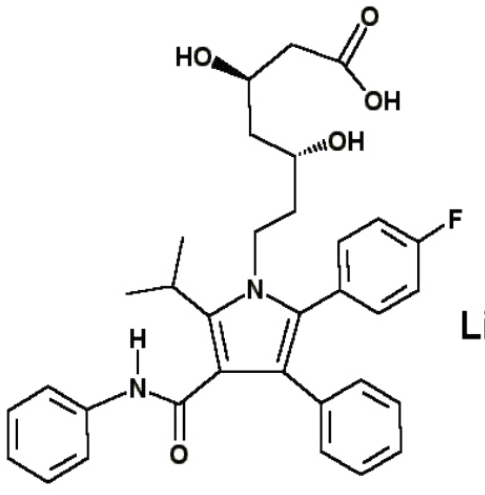
Drugs Lowering Cholesterol

- **Statins** – decrease HMG CoA Reductase activity

Statins



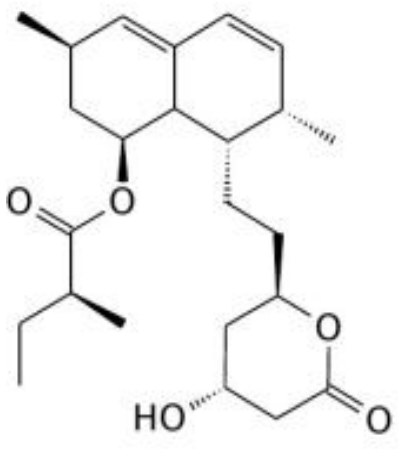
Mevacor (lovastatin)



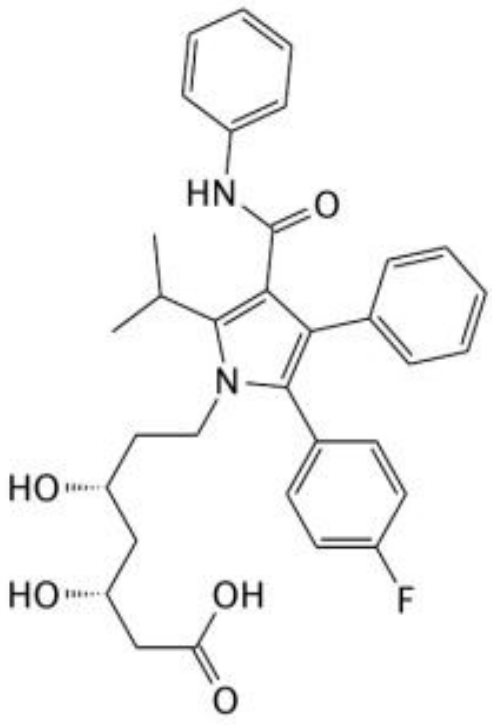
Lipitor

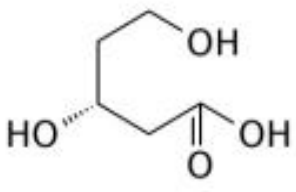
"Statins" Competitively Inhibit HMG-CoA Reductase

Mevastatin

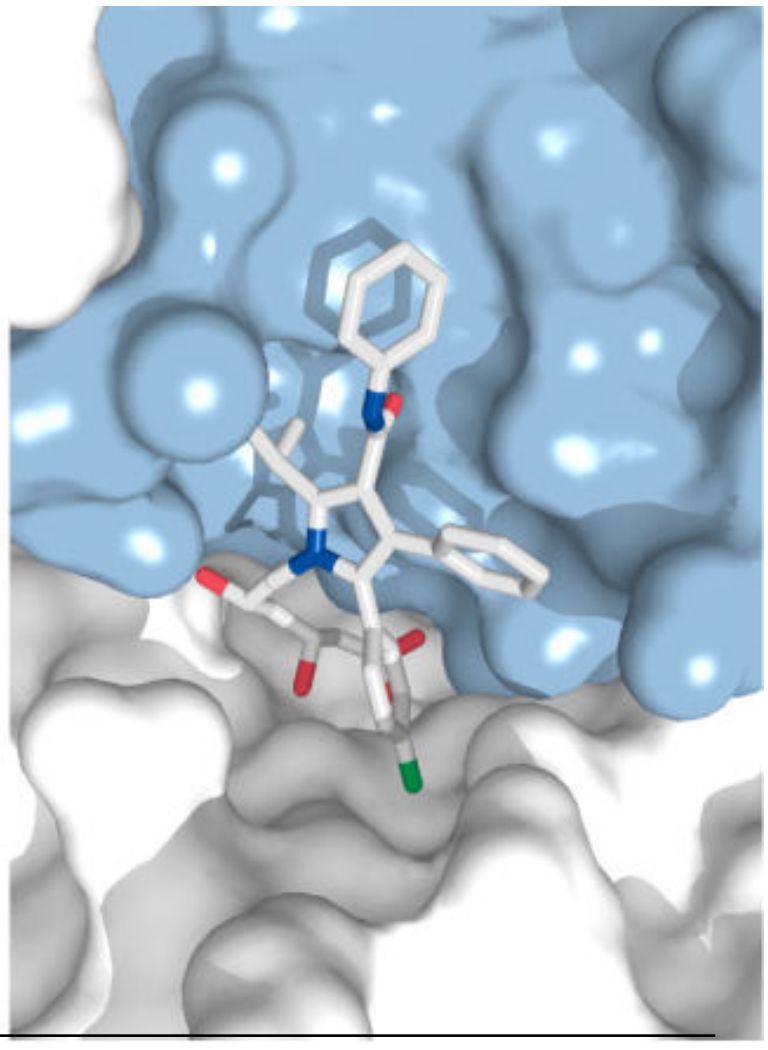


Atorvastatin





Mevalonate



Effects Of "Statins"
(HMG-CoA Reductase Inhibitors)

- **Action**: Competitively inhibits **HMG-CoA Reductase**, key enzyme for *de novo* cholesterol biosynthesis.

- **Effects Of Statins in Human body**:
- Cells express more LDL receptors
- Decreases serum LDL levels
- Increased HDL levels
- Increased HDL/LDL ratio
- Suppresses production of VLDL in Liver

- **Advantages**: Specific; Effective; Well-tolerated.

- **Disadvantages**: Hepatotoxicity; myopathy; most expensive; contradicted in pregnant and nursing women.

- **Bile salts** inhibit **intestinal** HMG CoA Reductase.

Cholesterol Transport

Lipoproteins Involved In Cholesterol Transport In Blood

- Chylomicrons/ULDL
- LDL
- HDL

- **Chylomicrons transport dietary exogenous form of Cholesterol**

- **From intestine to Liver** through lymph and blood

- **LDL** transports **Endogenous Cholesterol**

- From **Liver to Extrahepatic tissues.**

- **HDL transports, Cholesterol for its excretion**

- **From Extrahepatic tissues to Liver.**

Cholesterol Esterification

- In human body Cholesterol is present in two forms:
  - **Free Cholesterol (30%)**
  - **Esterified Cholesterol (70%)**

- **Cholesterol** when has to get **excreted out** of the body

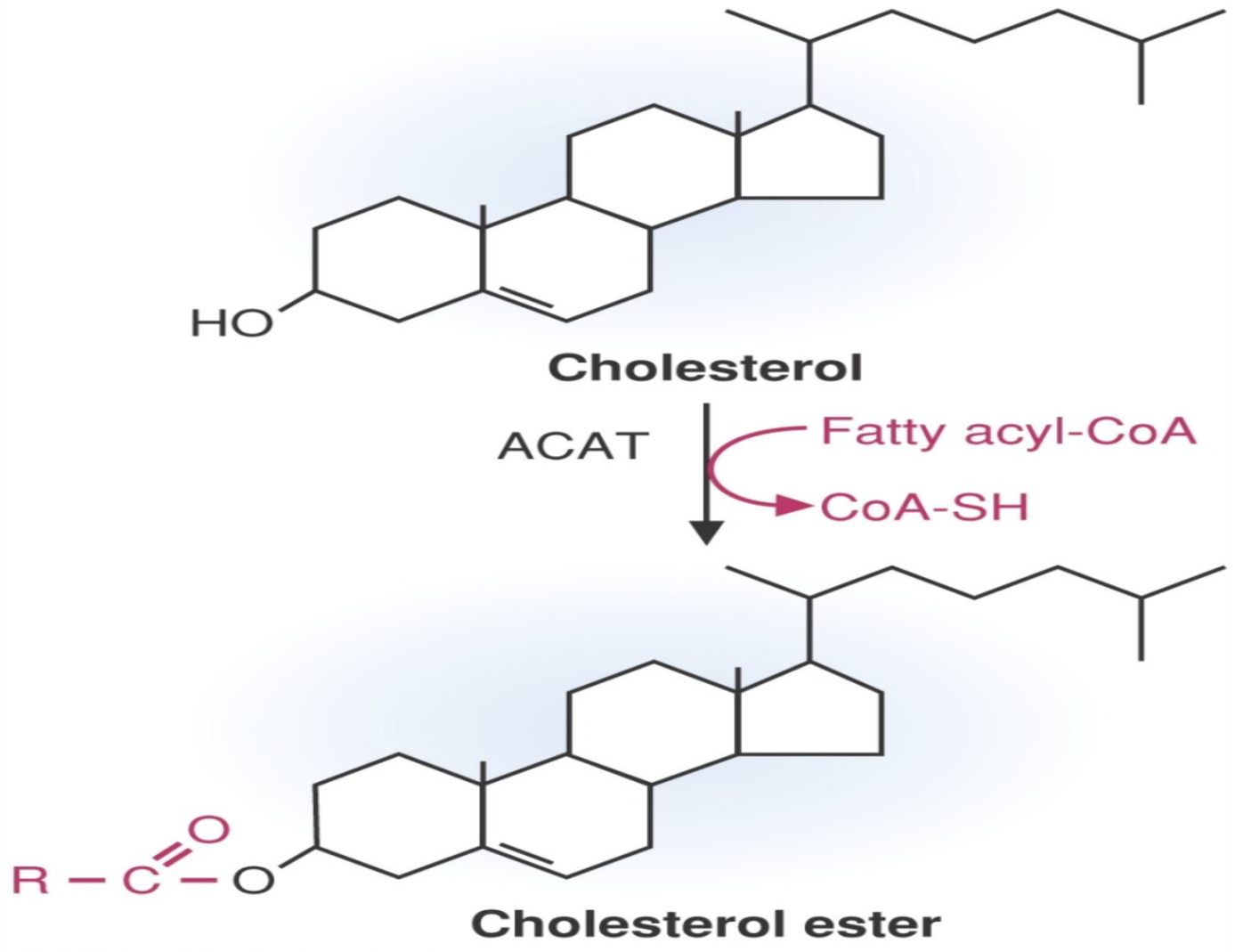
- It gets esterified to **Cholesterol Ester** and transported for its excretion.

Cholesterol Esterification Enzymes

- **Acyl Cholesterol Acyl Transferase activity (ACAT)**

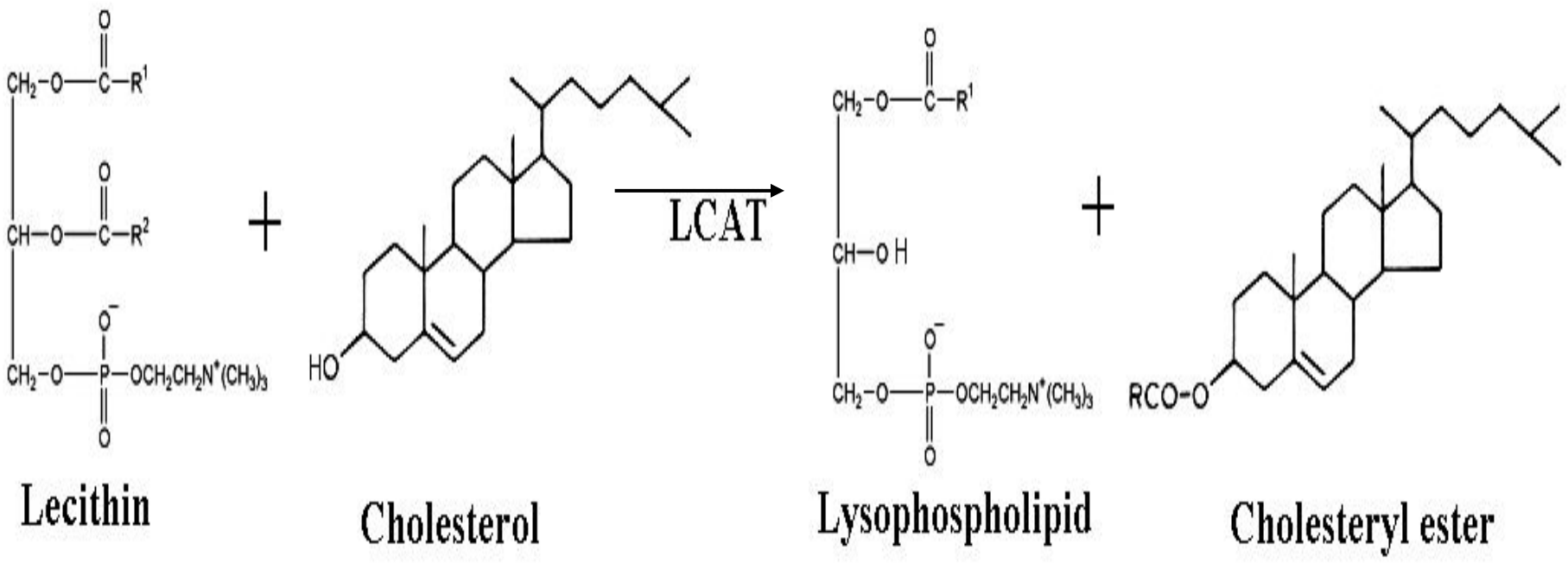
- **Lecithin Cholesterol Acyl Transferase activity (LCAT)**

Cholesterol Esterification



LCAT
(Lecithin: Cholesterol Acyltransferase)

Formation of Cholesterol Esters in Lipoproteins



- Acyl-CoA: Cholesterol Acyl Transferase (ACAT) is an **ER membrane protein**
- **ACAT** transfers fatty acid of CoA to C3 Hydroxyl group of Cholesterol
- Excess Cholesterol is stored as Cholesterol esters in cytosolic lipid droplets

- **LCAT activity** is associated to **Lipoprotein HDL.**
- **HDL is responsible for transporting of Cholesterol Ester from extra hepatocytes to Liver for its excretion.**

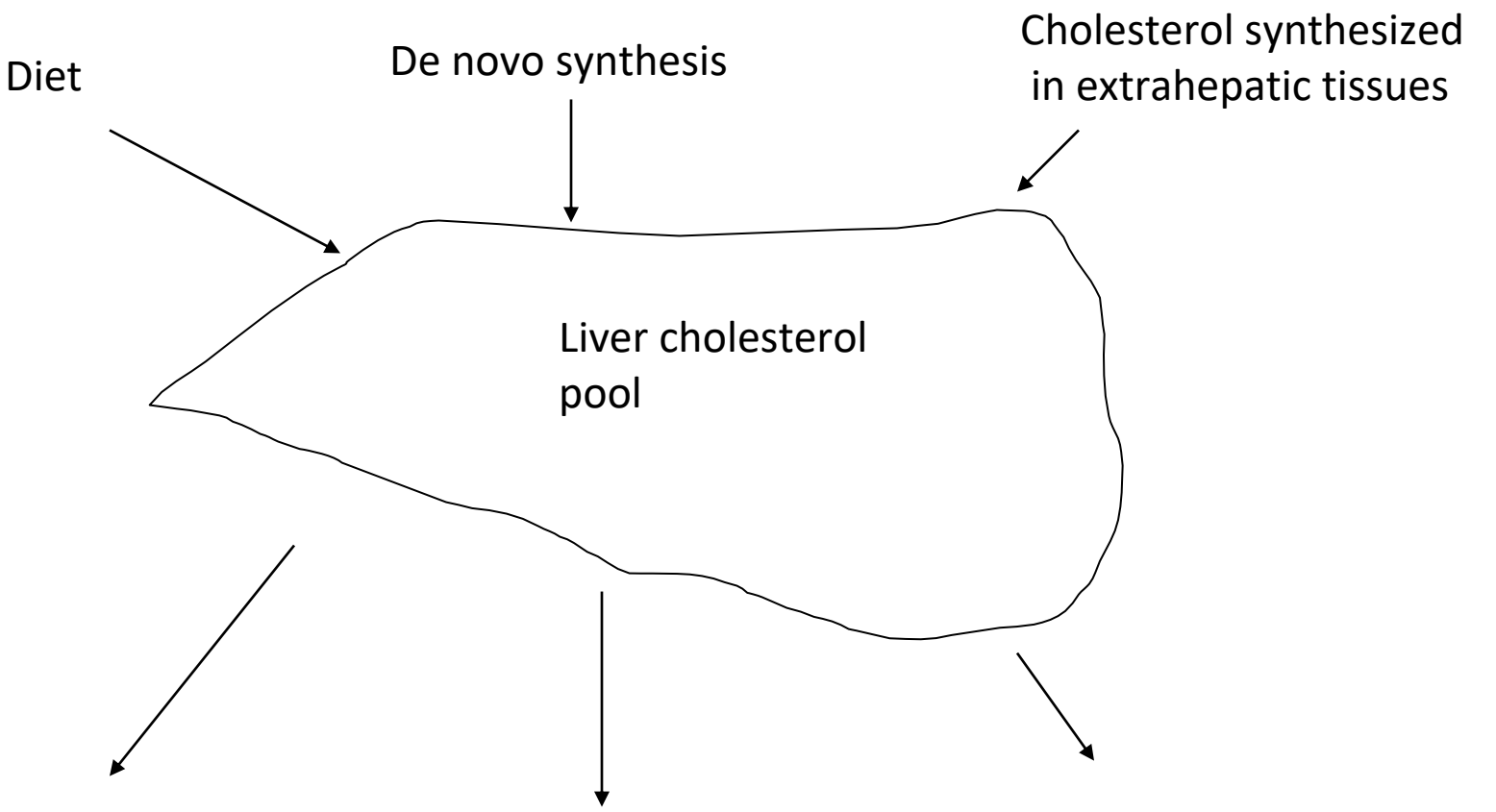
Deficiency And Types Of LCAT By Mutations In LCAT Gene

- **Familial LCAT deficiency- Complete LCAT deficiency**

- **Fish-Eye disease- Partial deficiency.**
- Fish-eye disease progresses, corneal cloudiness worsens
- Can lead to severely impaired vision.

Functions Of Cholesterol

Fates of Cholesterol



Fates Of Body Cholesterol

- Cholesterol in human body is **component of various biomembranes of cells.**
- **Cholesterol helps in nerve impulse conduction**
- Cholesterol is a **precursor for**
- Bile acids
- Vitamin D
- Steroidal Hormones-
  - Aldosterone
  - Estrogen
  - Progesterone
  - Testosterone

Cholesterol

Pregnenolone

Progesterone

Cortisol (glucocorticoid)

Affects protein and carbohydrate metabolism; suppresses immune response, inflammation, and allergic responses.

Corticosterone (mineralocorticoid)

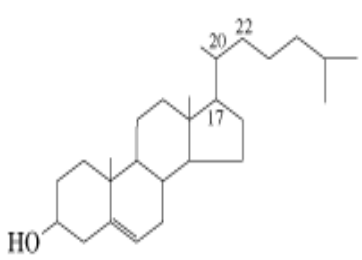
Aldosterone (mineralocorticoid)

Regulate reabsorption of Na^+, Cl^-, HCO_3^- in the kidney.

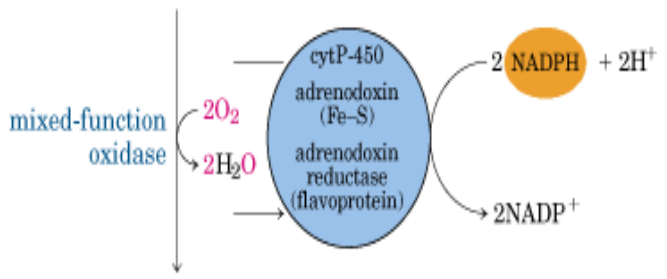
Testosterone

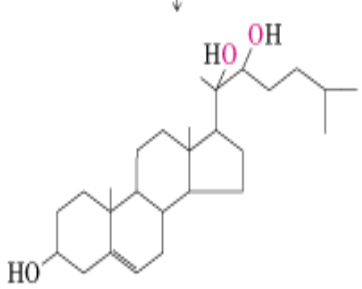
Estradiol

Male and female sex hormones. Influence secondary sexual characteristics; regulate female reproductive cycle.

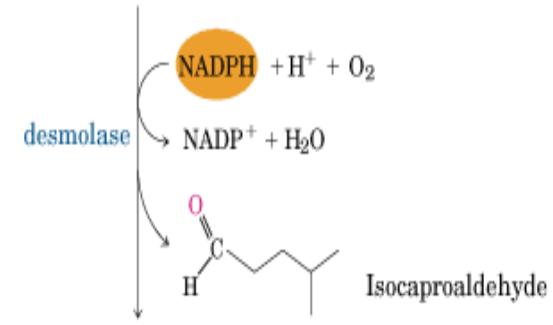


Cholesterol

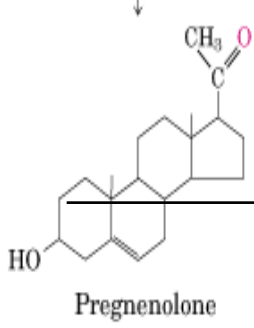




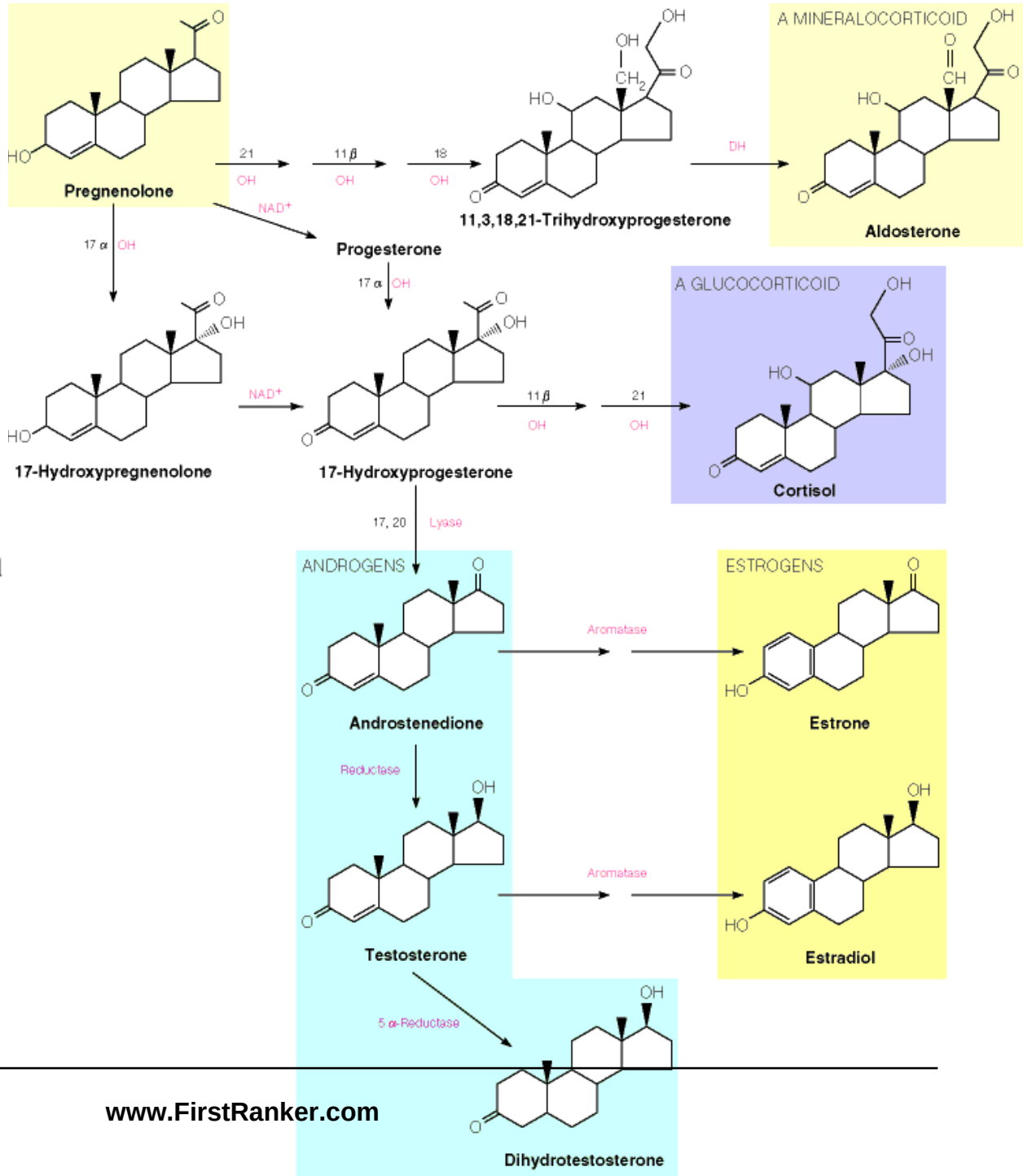
20,22-Dihydroxycholesterol



Isocaproaldehyde



Pregnenolone



- Remember Cholesterol **is not an energy producing Lipid**.

Cholesterol Degradation and Excretion

- About **1 gram** of **Cholesterol** is **catabolized and excreted out** of body **via Bile.**

- Cholesterol is mostly converted to **Bile acids and Bile salts and excreted**.

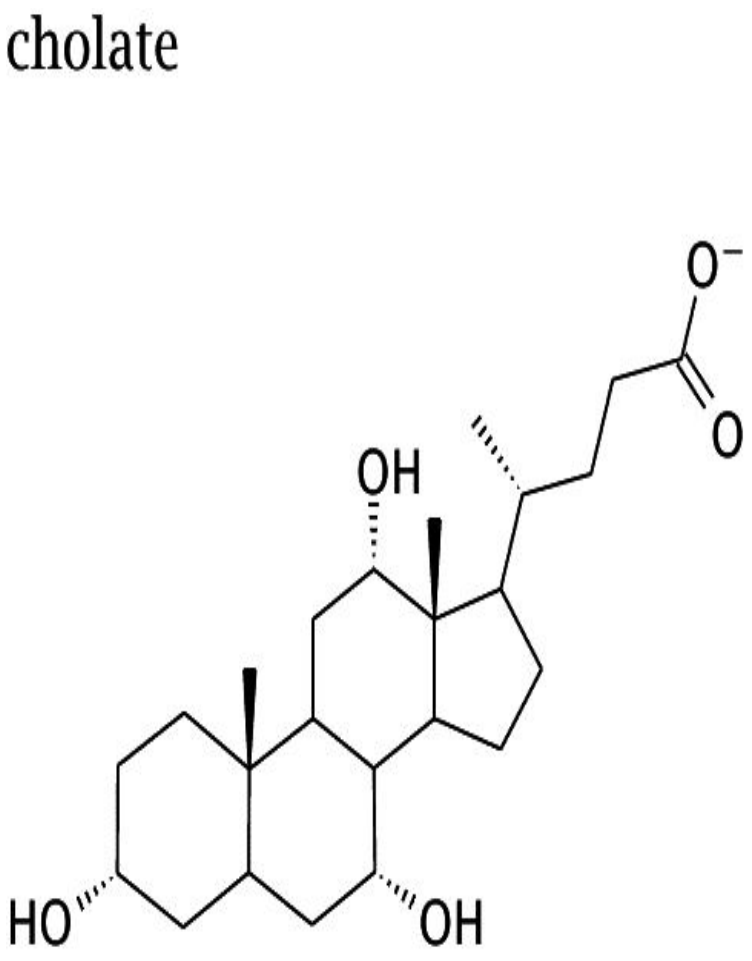
- **Thus Cholesterol** is **excreted** in form of **Bile acids and Bile salts.**

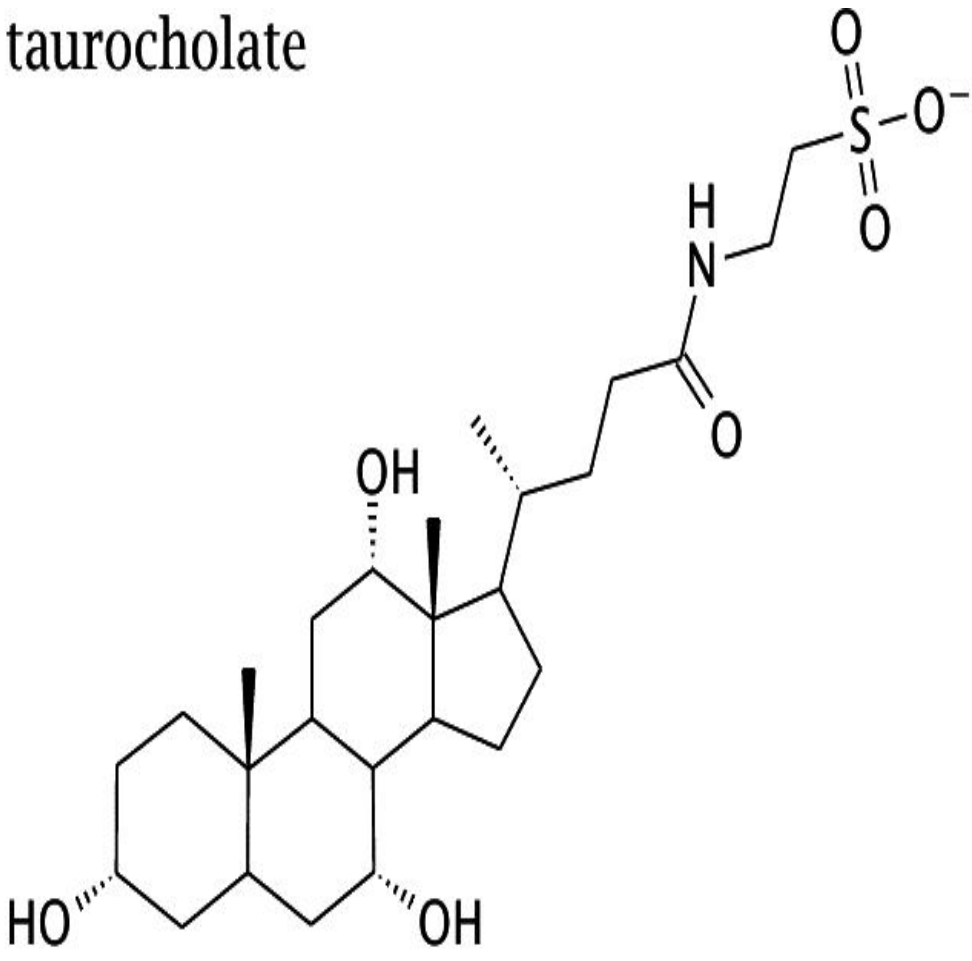
Bile Acids Formed From Cholesterol

- **Primary Bile Acids:**
  - Cholic Acid
  - Cheno Deoxy Cholic Acid

- **Secondary Bile Acids:**
  - Glycocholic Acid
  - Taurocholic Acid
  - De- Oxycholic Acid
  - Lithocholic Acid

Bile acids are Derived from Cholesterol





- **Bile acids , Bile Salts and Cholesterol** are **carried through bile to intestine for its excretion**.

- Thus **half of body Cholesterol is degraded to Bile acids** and **excreted through feces.**

- **Cholesterol** is **modified** by **intestinal bacterial flora to**

- **Cholestenol and Coprostenol which are** then excreted out in feces.

Balance Of Cholesterol Metabolism

- A person is **healthy when** there is a **perfect balance** between
  - **Cholesterol Biosynthesis**
  - **Cholesterol Utilization**
  - **Cholesterol Excretion**

- This **minimizes chances of Cholesterol deposition in blood and tissues.**

- **Bile acids synthesized from Cholesterol** in Liver are **carried through bile**

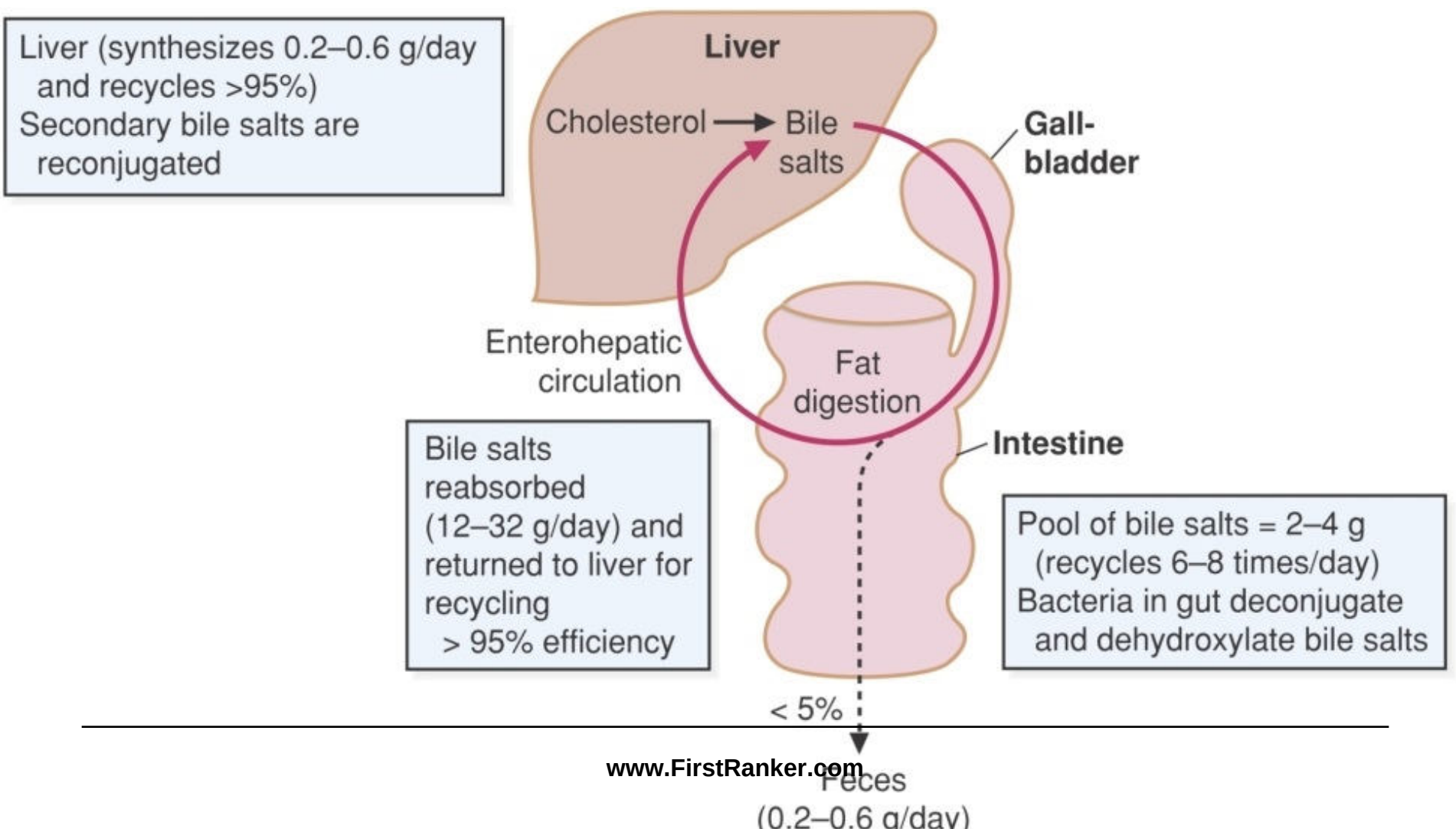
- **Released into intestine** and reabsorbed in Jejunum and Ileum.

Bile Acids are Transformed To Bile Salts

Role Of Bile Salts

- Bile Salts are **effective detergents**
- They are **biosynthesized in the Liver**
- Stored & concentrated in the Gallbladder
- **Bile salts in Intestine facilitates in digestion and absorption of intraluminal lipids**
- Through **formation of emulsions and mixed micelles.**

Efficiency OF Bile Salts Recycling



Blood Cholesterol And Its Clinical Significance

OPTIMAL CHOLESTEROL LEVELS

Adult Normal Reference Ranges Of Lipid Profile

ANALYTE	REFERENCE RANGE
Total cholesterol	140-200 mg/dL
HDL cholesterol	40-75 mg/dL
LDL cholesterol	50-130 mg/dL
Triglyceride	60-150 mg/dL

Remember

- Blood Cholesterol is associated to Lipoproteins in 2 forms:

  - **Free cholesterol (30%)**
  - **Esterified Cholesterol (70%)**

Hypercholesterolemia Causes, Conditions And Consequences

Hypercholesterolemia

- **Abnormal high levels of Cholesterol more than reference range** in blood circulation is termed as Hypercholesterolemia.

Classification of Plasma Cholesterol Concentrations

Total cholesterol (mg/dl)	Classification
< 200	Desirable
200 - 239	Borderline
≥ 240	High

LDL Cholesterol

- Less than 100 mg/dl Optimal
- 100 to 129 mg/dl Near or above optimal GOOD Cholesterol
- 130 to 159 mg/dl Borderline high
- 160 to 189 mg/dl High
- 190 mg/dl and above Very high/ BAD Cholesterol

HDL Cholesterol Scavenging Action

Less than 40 mg/dl
Low level. A major risk factor for CAD

40 to 59 mg/dl
Moderate levels considered significant low risk

60 mg/dl and above
High level. Considered protective against CAD

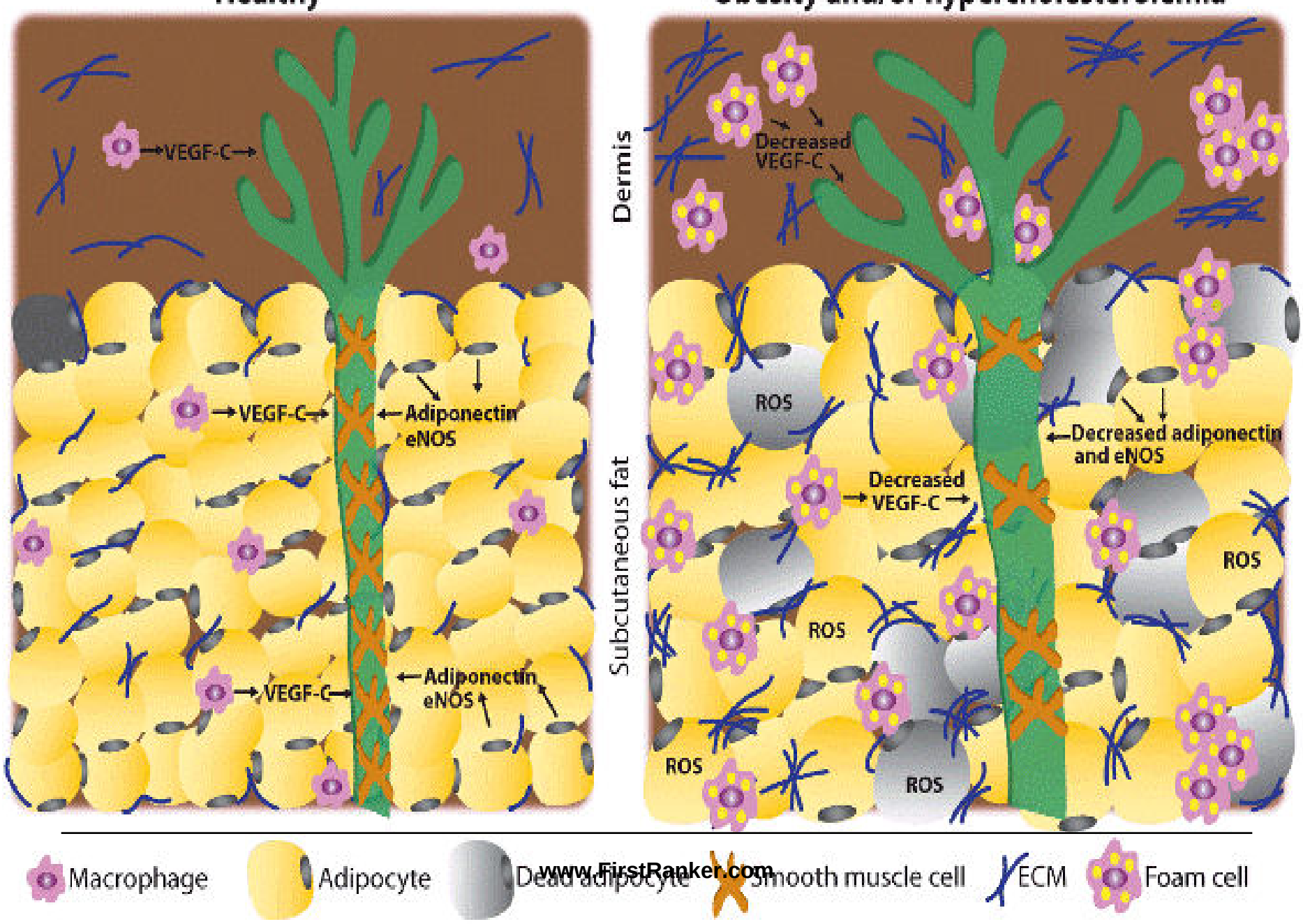
> 100 mg/dl very high is considered as bad

Types And Causes Of Hypercholesterolemia

- **Primary Causes: Genetic (Non modifiable)**
  - **LDL Receptor defects**
  - **CETP inhibition**
  - **Age, Gender**

- **Secondary Causes- Life style derangements**
  - **Wrong eating habits**
  - **Sedentary life style**
  - **Addictions-Smoking , Alcoholism**

Figure 2



Clinical Conditions Of Hypercholesterolemia

- **Obesity- Diabetes mellitus**

(Increased Intake / increased Biosynthesis)

- **Nephrotic Syndrome – Protein loss**

(Defective Lipoprotein metabolism which is not internalized)

- **Obstructive Jaundice**

(Bile duct obstruction no excretion and regurgitation of Bile in Blood)

- **Hypothyroidism**

(Decreased Catabolism and decreased Excretion)

Inherited Hypercholesterolemia

- Inherited Hypercholesterolemia is a **genetic cause**

- Caused due to **defective LDL receptors on tissues.**

- **Increases LDL –Cholesterol in blood**

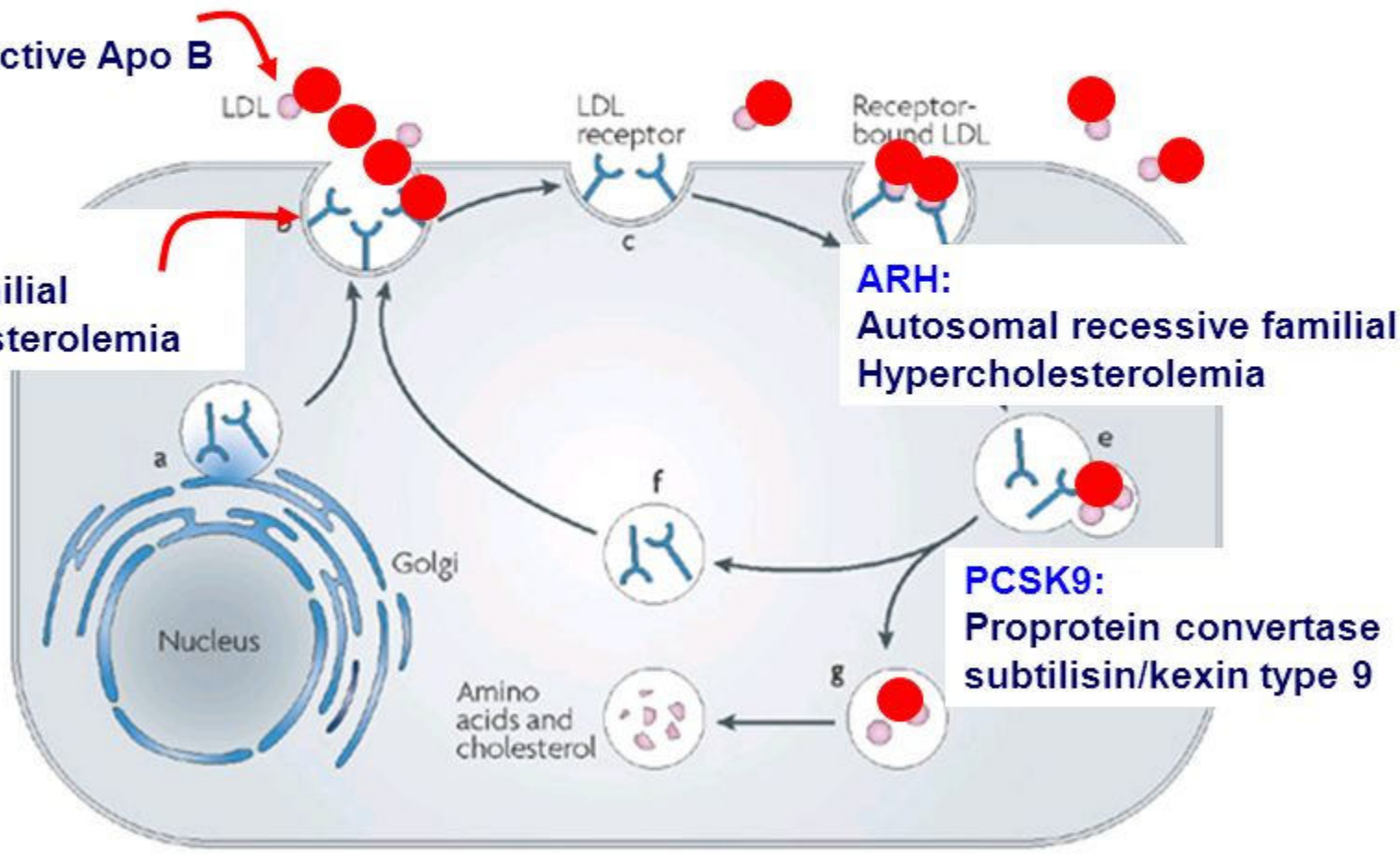
SIMON BROOME DIAGNOSTIC CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA[1]	
Point	**Criteria**
1	Total cholesterol levels > 290mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L) in adults. Total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L)
2	Tendon xanthomas in the patient or tendon xanthomas in a first or second degree relative.
3	DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.
4	Family history of myocardial infarction before age 50 years in a second degree relative or before age 60 years in a first degree relative.
5	Family history of elevated total cholesterol > 290 mg/dL (7.5 mmol/L) in an adult first or second-degree relative. Family history of elevated totacl cholesterol > 260 mg/dL (6.7 mmol/L) in a child, brother, or sister 16 years or younger.
DIAGNOSIS	
Definite familial hypercholesterolemia = 1+2 or 3 Possible familial hypercholesterolemia = 1+4 or 5	

1. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. *American journal of epidemiology*. 2004;160:407-420.

Molecular Causes of Familial Hypercholesterolemia (FH)

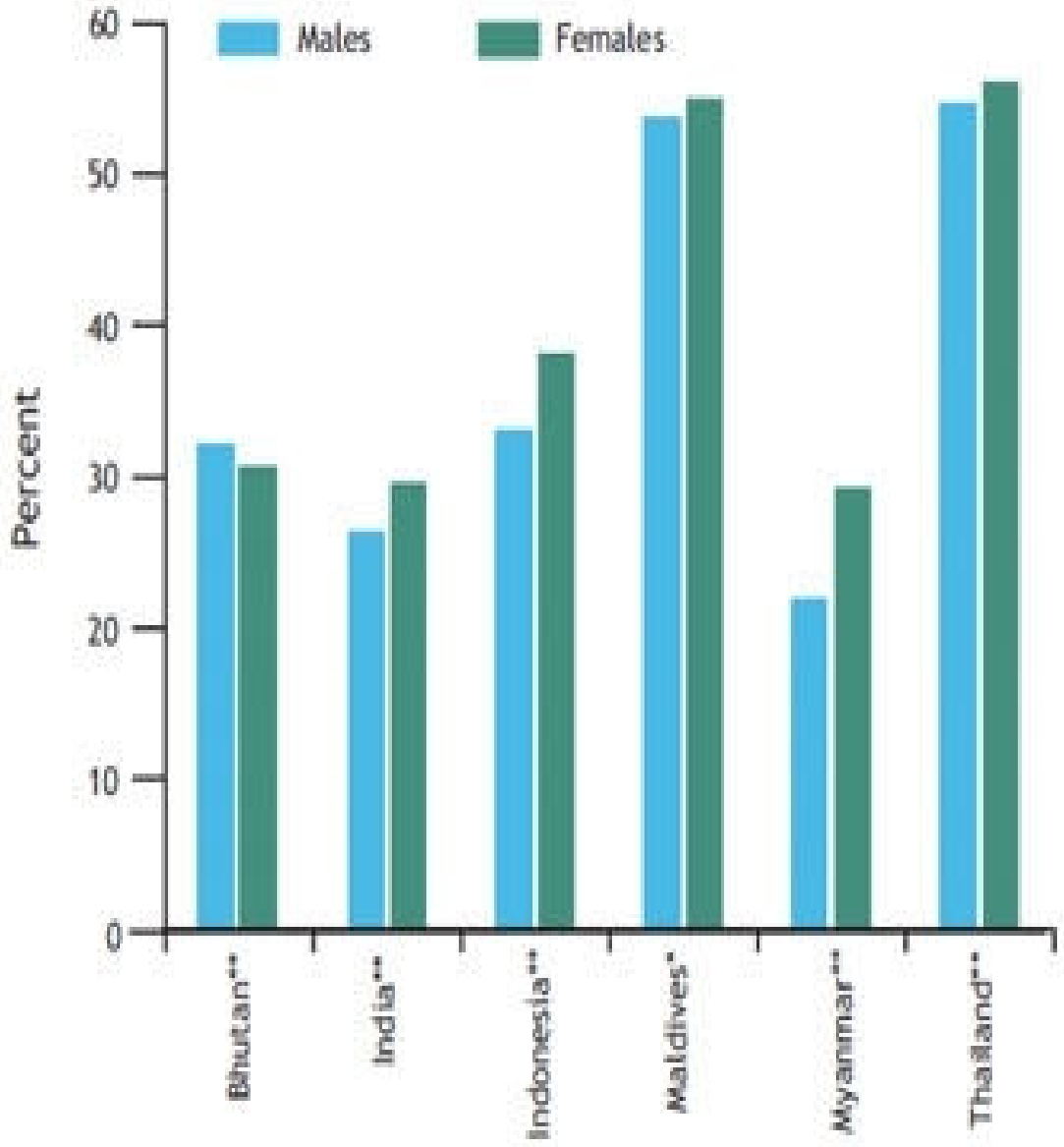
ApoB:
Familial defective Apo B

LDL-R:
Primary familial hypercholesterolemia



Nature Reviews | Drug Discovery

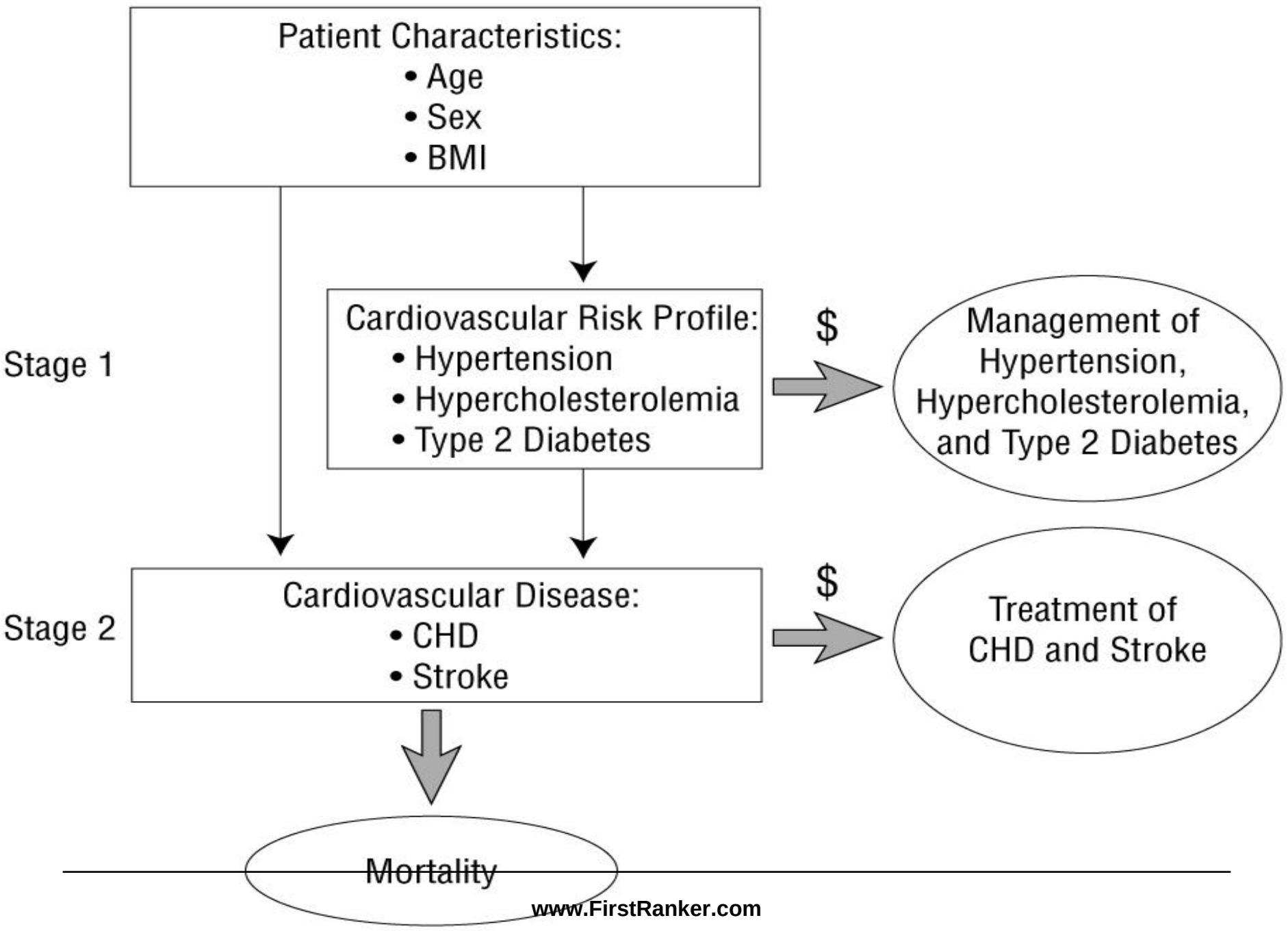
Consequences Of Hypercholesterolemia



One third to one half of adults have raised cholesterol

Source: World Health Organization. Global status report on noncommunicable diseases 2010. Geneva, 2011.
Data adjusted for 2008 for comparability

Consequences of High Cholesterol



High blood pressure - will damag the cells of inner walls of arteries

stimulate

Increase of Blood Cholesterol in the area of cellular damage

start

Atherosclerosis

(hardening of the arteries)

limit

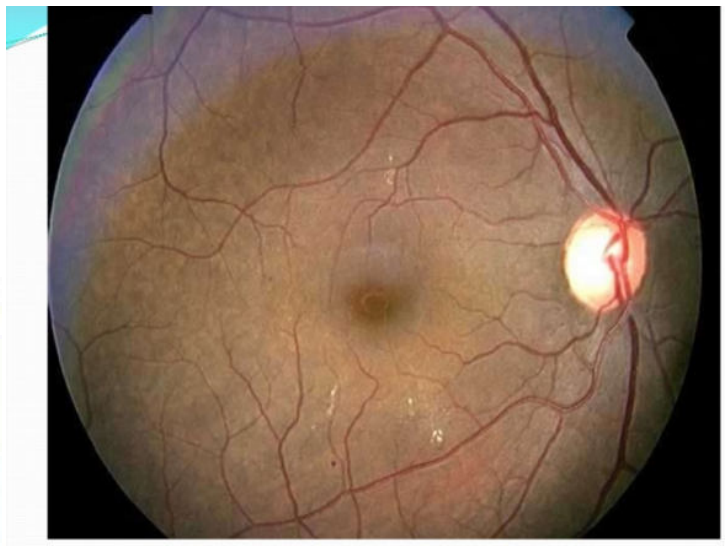
Blood and Oxygen supply to body organs :

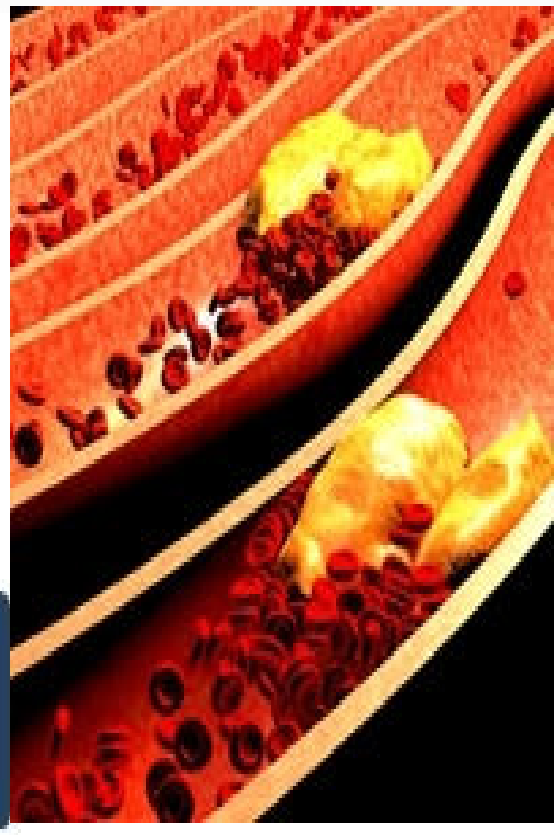
(brain; heart; kidney; extremities)

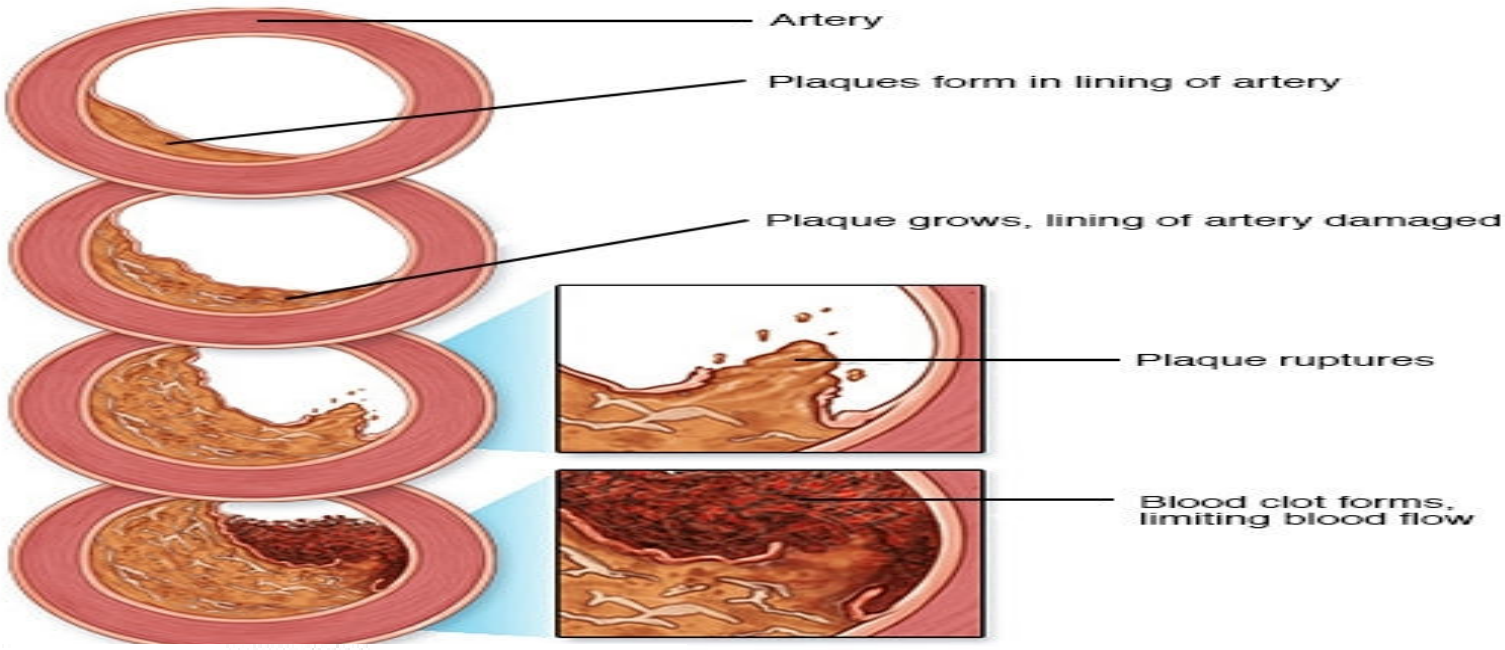
lead

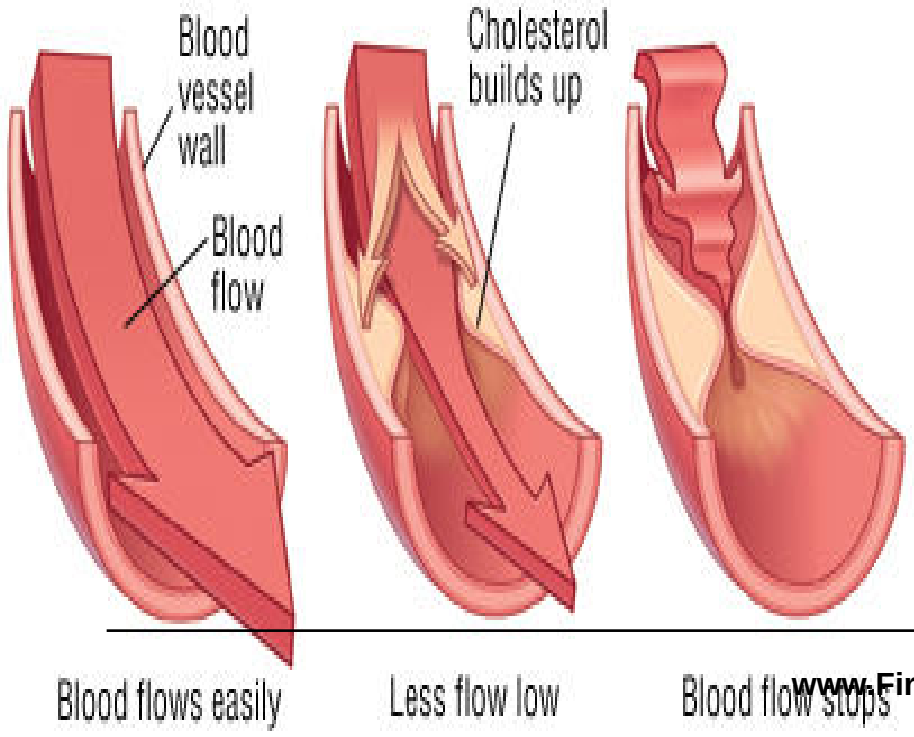
Serious Health Conditions:

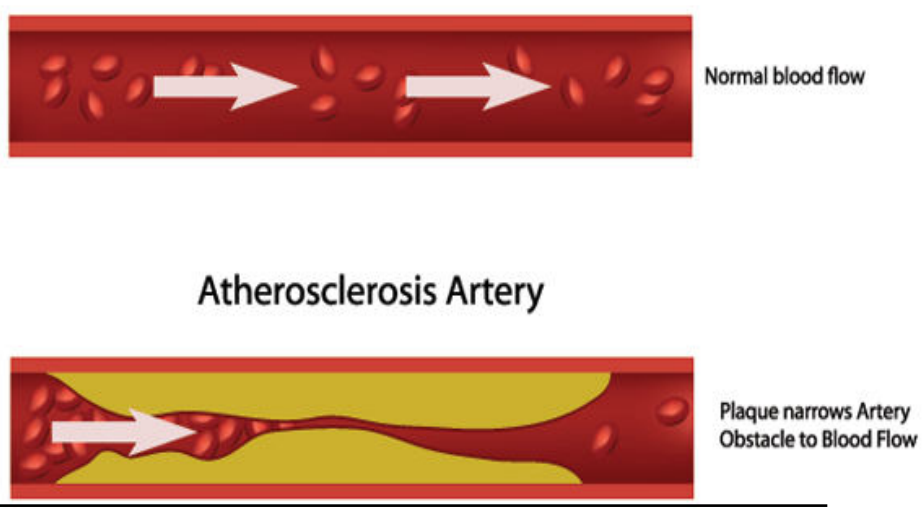
- Angina (chest pain); Heart attacks; Renal failure; Heart failure; Strokes; Blood clots; Aneurysms.











Consequences Of Hypercholesterolemia

- Increased risk of **Atherosclerosis**
- Stimulates **plaque/thrombus formation**
- May **occlude arteries** and
- Leads to **tissue infarction**

- **Infarction** is **irreversible damage to tissues due to absence of Oxygen and Nutrient.**
- **Infarction of Brain is Stroke**
- **Infarction of Heart is MI**

Long term consequences

Possible

- Hypertension
- Cardiovascular disease
- Gestational diabetes mellitus
- Pregnancy-induced hypertension
- Ovarian cancer

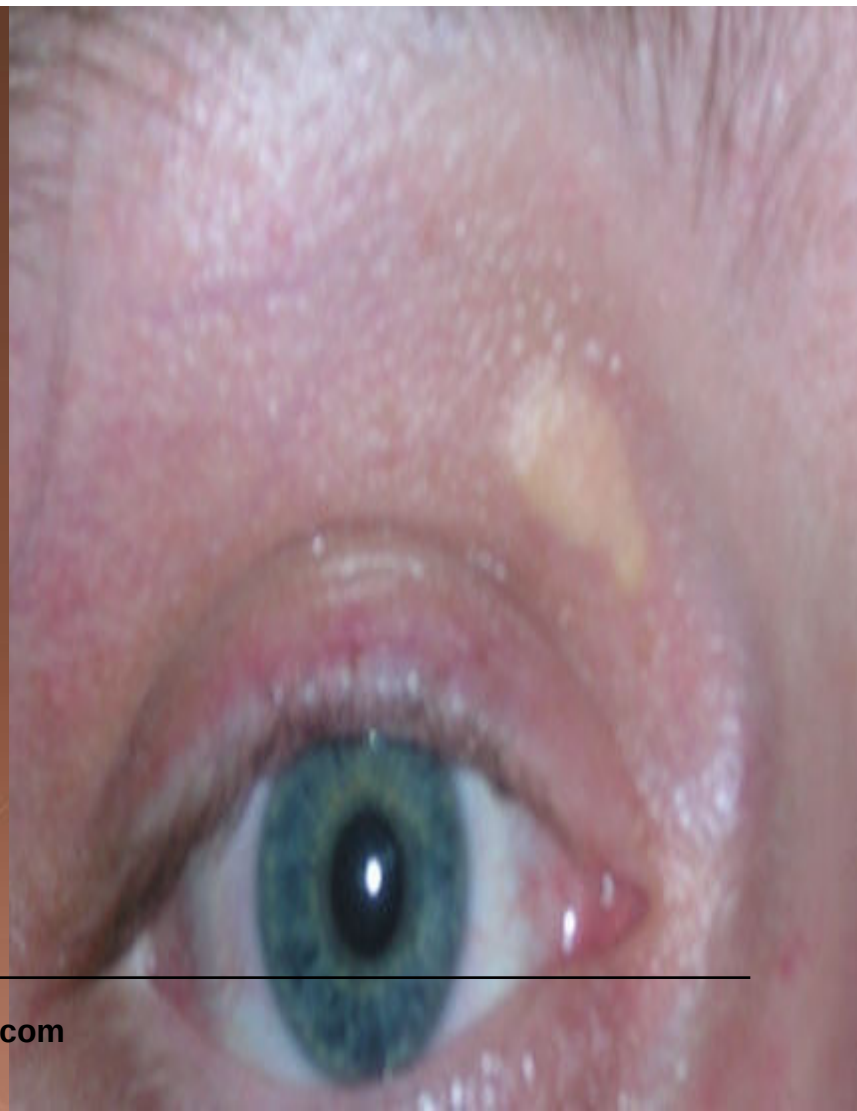
Unlikely

- Breast cancer

Signs And Symptoms Of Hypercholesterolemia

Physical signs

- High cholesterol levels normally do not cause any symptoms.
- Cholesterol may be deposited in various places in the body that are visible from the outside
- Xanthelasma are yellow plaques that occur most commonly near the inner canthus of the eyelid, more often on the upper lid than the lower lid.



Physical Stigmata of Hyperlipemic States

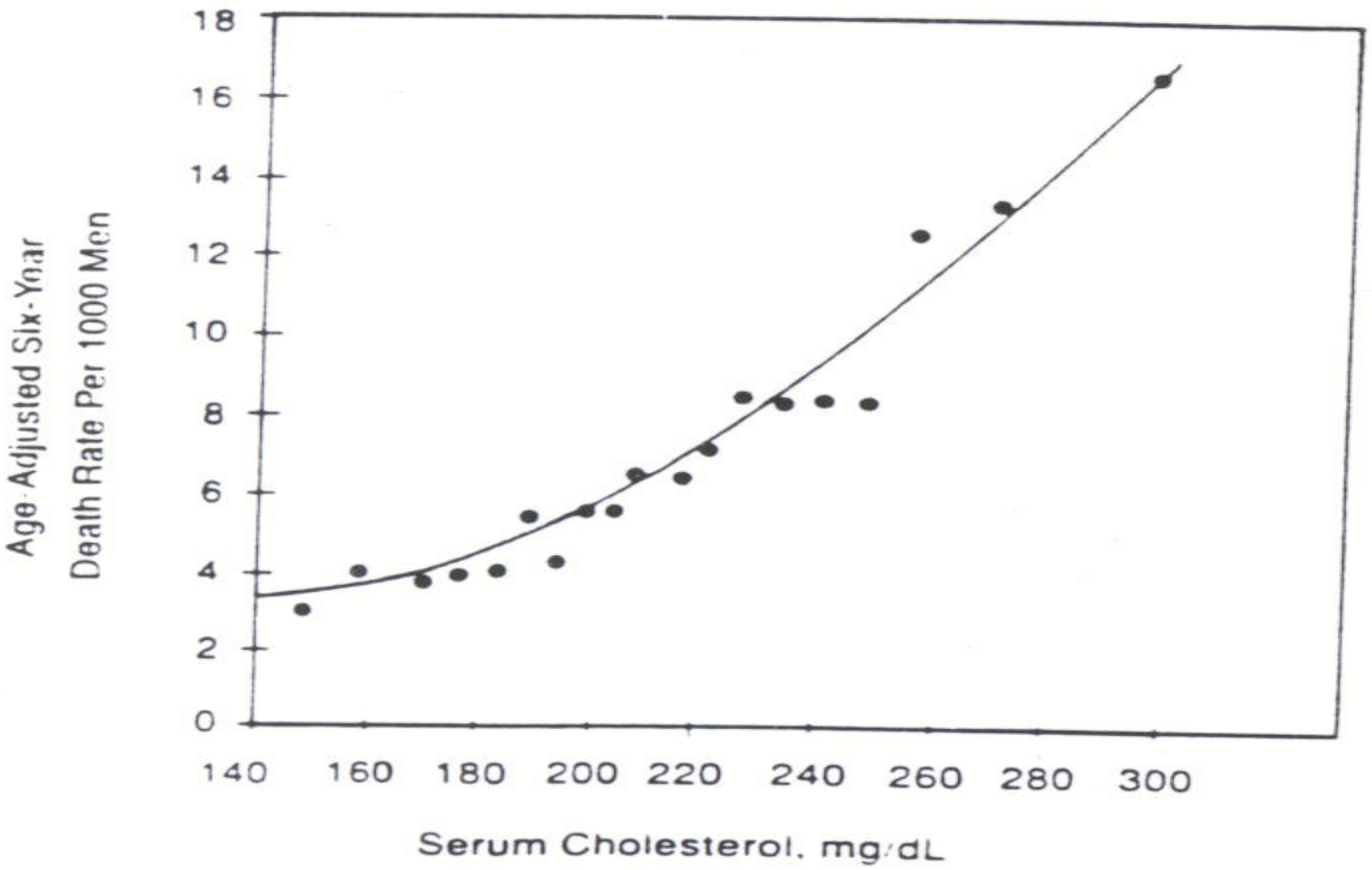
State	Appearance	Lipid Abnormality
Eruptive xanthomas	Small, yellow, domed lesions with erythematous base	Hypertriglyceridemia
Tuberous xanthomas	Larger, domed lesions, often confluent and found on extensor surfaces	Hypercholesterolemia
Xanthelasma	Pale yellowish-white plaques along the eyelids	Hypercholesterolemia
Corneal arcus	White or gray ring surrounding the cornea	Hypercholesterolemia

MORTALITY RELATED DUE TO HIGH CHOLESTEROL

- ✓ 1 cause of death: Cardio-vascular diseases
- ✓ 3 cause of death: Cerebro-vascular diseases
- ✓ 1 + 3 = ~ 40% of all deaths

(Higher risk for Alzheimer & Chronic Liver disease)

Trends Of Increased Cholesterol And Death Rates



HDL cholesterol levels lower than <40 mg/dl)
increase a person's risk of developing coronary artery disease, especially in people who also have high total cholesterol levels.

- **HDL Cholesterol levels greater than 100 mg/dl**

- **Also increase risk in developing coronary artery disease and Stroke.**

CHOLESTEROL PROFILE IMPROVEMENT STRATEGY

- **IMPROVING DIET**
- **LIFE STYLE MODIFICATIONS**
  - **REGULAR EXERCISE**
  - **SMOKING, ALCOHILISM CESSATION**
  - **STRESS REDUCTION**
  - **WEIGHT CONTROL**
  - **BEHAVIOR CHANGE**

- When diet changes fail.
- **Hypolipidemic drugs** will reduce serum Cholesterol and Triacylglycerol.

Therapeutic Principle: Lowering Blood Cholesterols

- **Inhibition** of **Cholesterol biosynthesis**

- **Inhibition** of **Cholesterol uptake from GIT**

- Inhibition of Bile acid reuptake

- LDL apheresis (Taking away)

- Inhibition of **Cholesterol Ester Transfer Protein (CETP)** to some extent increases HDL levels.

- **Cholestyramine Resins:**

  Block reabsorption of bile acids.
- **Sitosterols:**

  acts by blocking the absorption of Cholesterol from the gastrointestinal tract.
- **Mevocore or Lovastatin:**

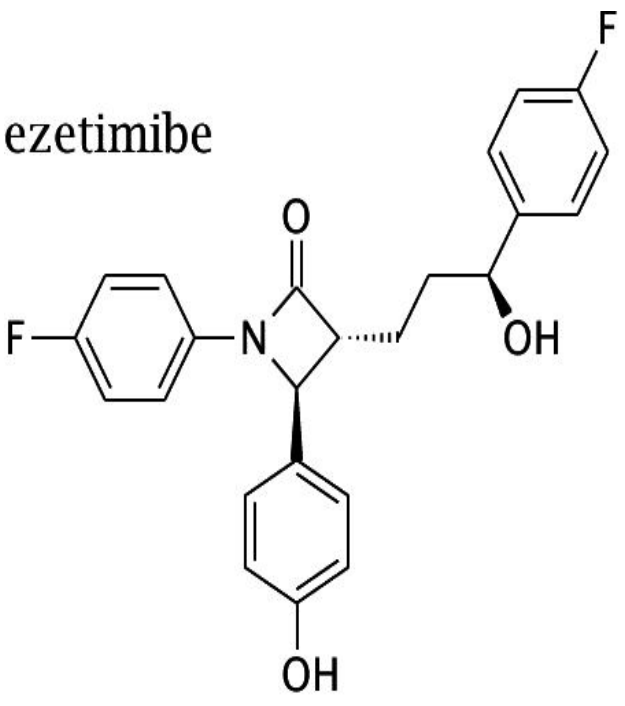
 inhibitors of HMG-CoA Reductase

HYPOLIPIDEMIC DRUGS

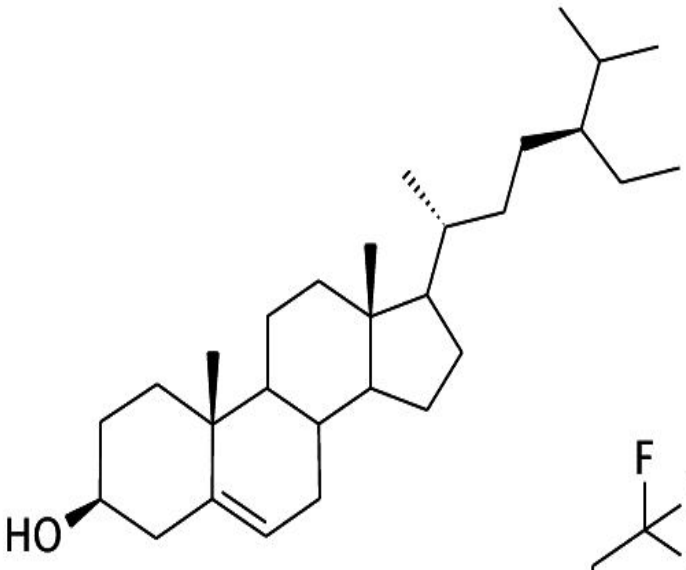
- **Statins** - The statins act as competitive inhibitors of the enzyme HMG-CoA reductase.
- **Fibrates** such as **Clofibrate** and **gemfibrozil** act mainly to lower plasma triacylglycerols by decreasing the secretion of triacylglycerol and cholesterol-containing VLDL by the liver.
- **Ezetimibe**- ezetimibe, reduces blood cholesterol levels by inhibiting the absorption of cholesterol by the intestine
- **Bile Acid Sequestrants (Resins)**-Bile acid sequestrants bind bile acids in the intestine and promote their excretion in the stool. To maintain the bile acid pool size, the liver diverts cholesterol to bile acid synthesis

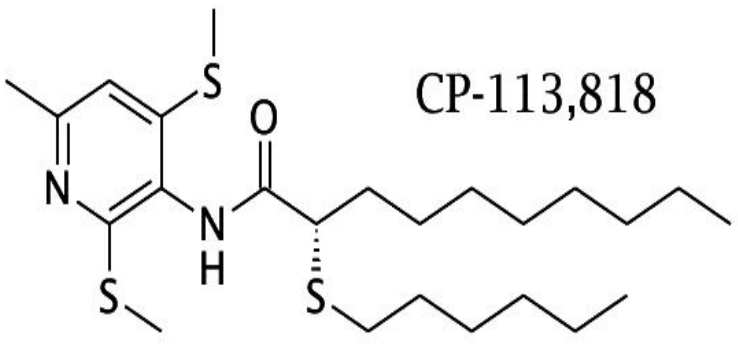
Drugs Inhibitors of Intestinal Cholesterol Uptake

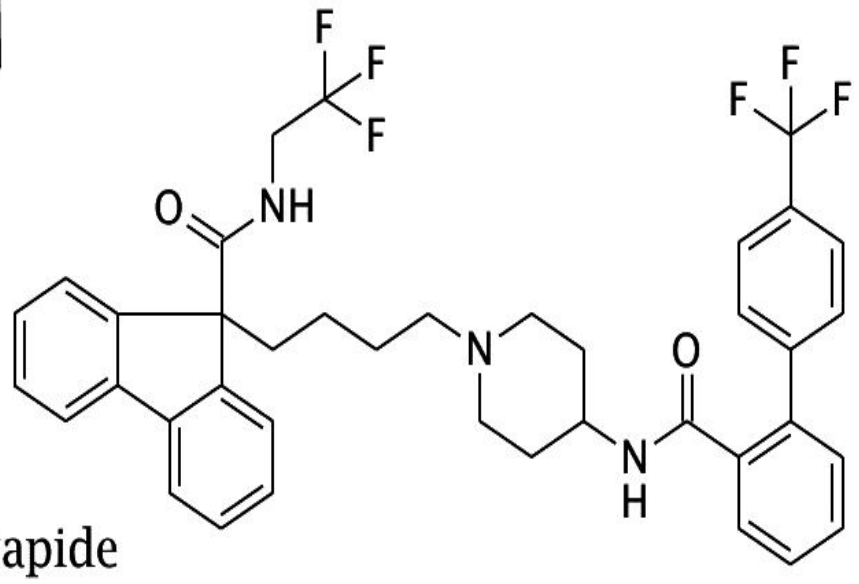
ezetimibe



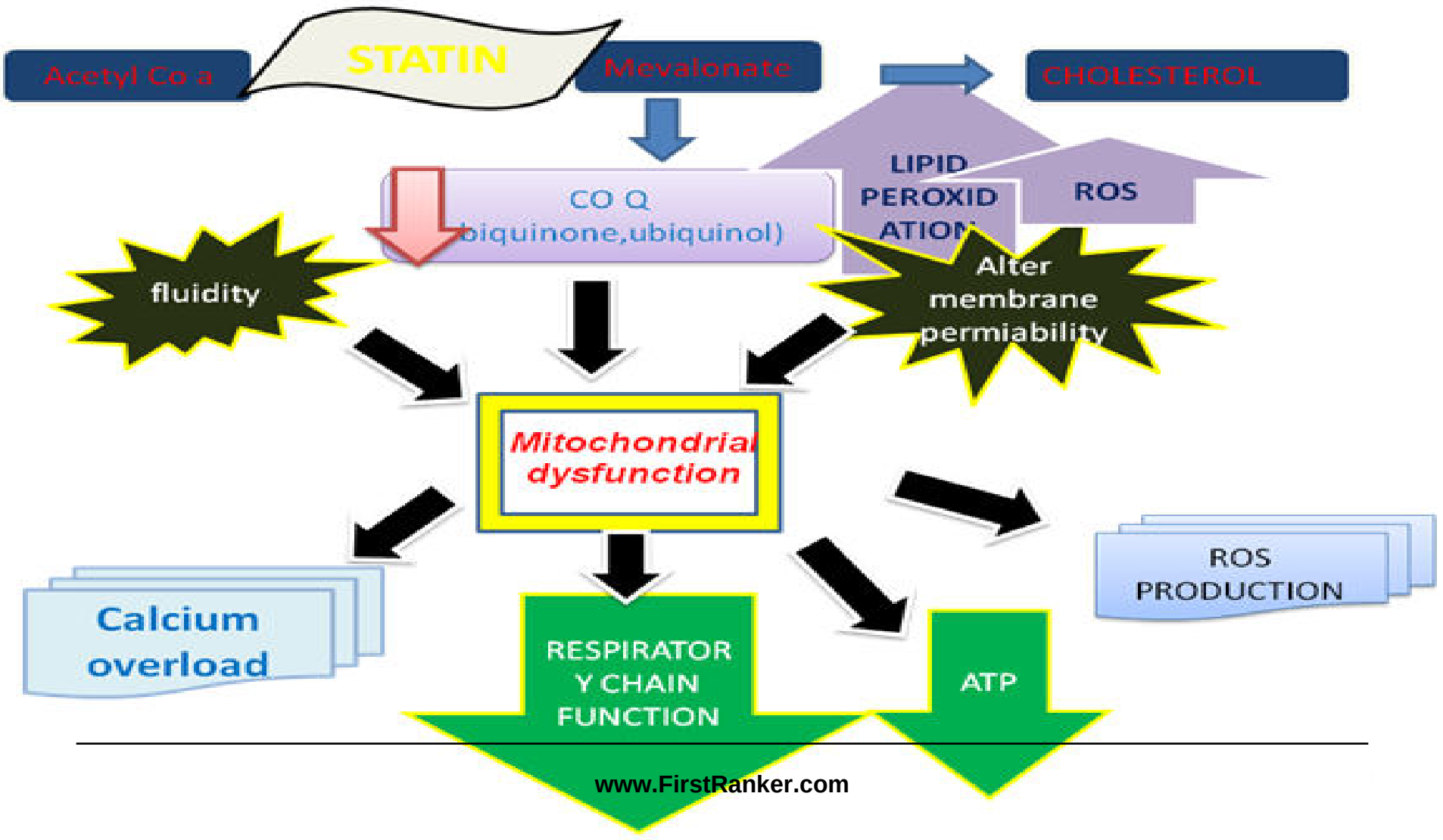
sitosterol







Effect Of Long Duration Of Drug Usage



Hypocholesterolemia
Causes, Conditions And Consequences

Hypocholesterolemia

- Abnormal **low levels of Cholesterol below reference range** in blood circulation is termed as **Hypocholesterolemia.**

Causes Of Hypocholesterolemia

- Poor Ingestion
- Low Biosynthesis
- More Uptake &Utilization
- More Excretion
- Increased Hypolipidemics

Conditions Of Hypocholesterolemia

Physiologically Cholesterol low in Children's

- Malnutrition

(Decreased Dietary Glucose & Cholesterol)

- Malabsorption

(Poor absorption of Cholesterol in biliary insufficiency)

- Hyperthyroidism

(Increased utilization)

- Pernicious Anemia
- Hemolytic Anemia

(Increased utilization for erythropoiesis and for composition of bile for bilirubin excretion through bile)

- Liver Disorders

(Decreased biosynthesis)

Secondary hypocholesterolemia

Less obvious

- Malingancy
- Fever
- Traumatism-Critical Care Medicine 25(8)1437-9,1997
- Inflammatory disease(RA, SLE)
- Depression illness

Consequences Of Hypocholesterolemia

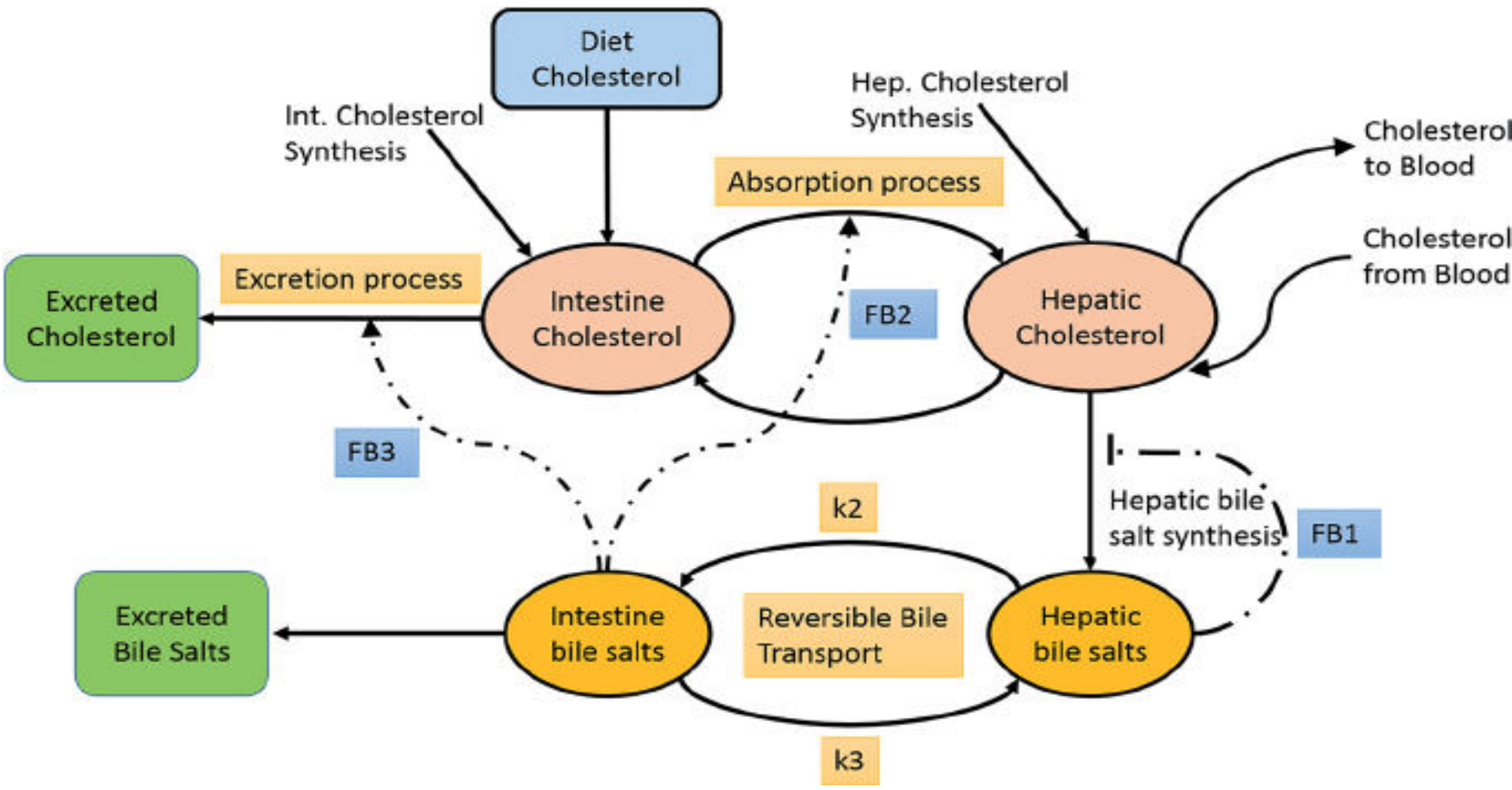
- Affects all functions of Cholesterol
- Improper structural aspects of cell membrane
- Cells,tissues,organs defects
- Steroidogenesis decreased
- Low Vitamin D
- Poor nerve impulse conduction
- Neurological disorders

- Lack of menstrual periods, estrogen deficiency
- Irregular menstrual periods
- Lowered testosterone levels
- Elevated cortisol levels
- Thyroid adaptation

Malignance and Hypocholesterolemia

- Cytokine effects on different enzymes of lipid metabolism.
- High expression of LDL receptors on tumor cell-Molecular Pharmacology52(3)445-55,1997
- Marked hypochoelsterolemia in cases with adrenal adenoma-enhance catabolism of LDL and LDL receptors
- Hypocholesterolemia may be associated with low serum antioxidant reserve,possibly increasing susceptiblity to oxidatative stress-Free Radical Research 25(3):329-45,1996
- May result from the conversion of cholesterol to bile acids suppression(suppressed levels of a circulating marker for bile acid synthesis-Cancer letters 170(2):165-75,2001 Sep 20

Overview Of Cholesterol Metabolism



Role of Transporters ABCG5 (G5) and ABCG8 (G8)

- **ABCG5 (G5) and ABCG8 (G8)** Cholesterol transporter
- Acts in Liver and Intestine
- **Prevent accumulation** of dietary cholesterol.
- Mutations in either G5 or G8 Genes cause sitosterolemia, a recessive disorder
- Characterized by Cholesterol accumulation and premature coronary atherosclerosis