Antihyperlipidemic Drugs

The fat speaks….

- “With water, I say, 'touch me not':
  To the tongue, I am tasteful;
  Within limits, I am dutiful;
  In excess, I am dangerous!"

What is Hyperlipidemia?

- Hyperlipidemia a broad term, also called hyperlipo-proteinemia, is a common disorder in developed countries and is the major cause of coronary heart disease.

- It results from abnormalities in lipid metabolism or plasma lipid transport or a disorder in the synthesis and degradation of plasma lipoproteins.

Causes of hyperlipidemia

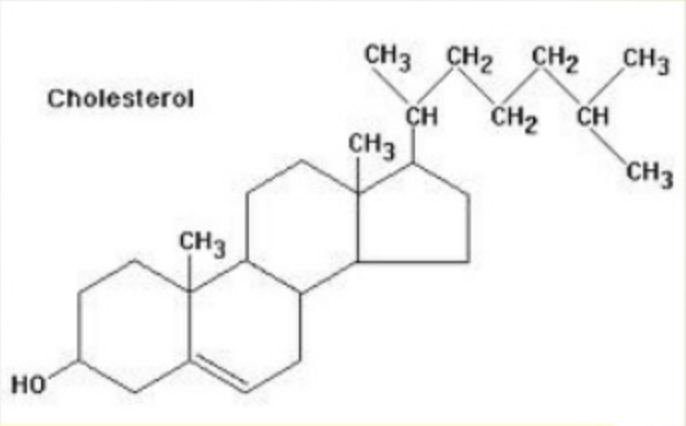
- Mostly hyperlipidemia is caused by lifestyle habits or treatable medical conditions.
- Obesity, not exercising, and smoking, diabetes, obstructive jaundice, and an under active thyroid gland inherit hyperlipidemia.

The biochemistry of Plasma lipids

What are lipids?

Lipids are the heterogenous mixtures of fatty acids and alcohol that are present in the body. The major lipids in the bloodstream are ***cholesterol*** and it's ***esters***, ***triglycerides*** and ***phospholipids.***

Cholesterol

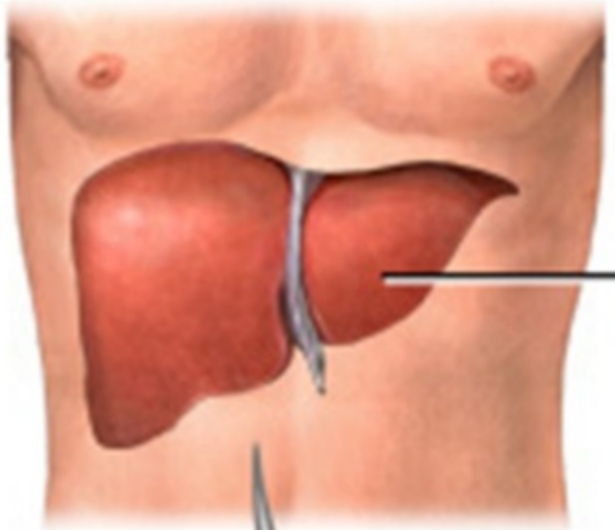


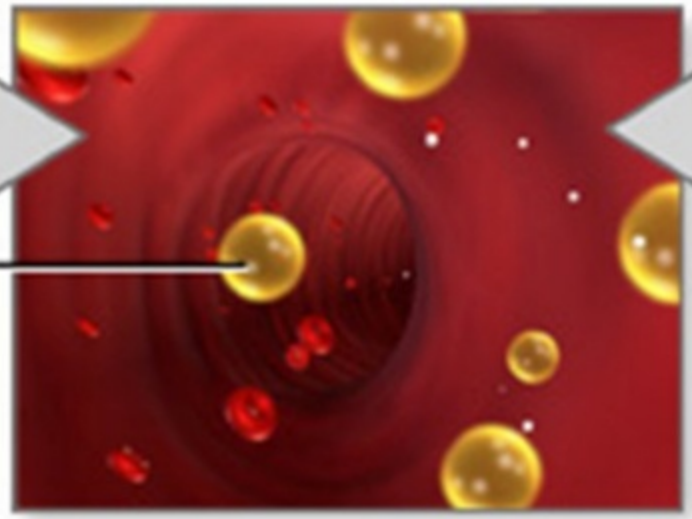
Is C27 steroid that serves as an important component of all cell membranes and important precursor molecule for the biosynthesis of bile acids, steroid hormones, and several fat-soluble vitamins

What are the normal functions of *cholesterol* in the body?

- ✓ It is necessary for new cells to form and for older cells to repair themselves after injury.
- ✓ Cholesterol is also used by the adrenal glands to form hormones such as cortisol, by the testicles to form testosterone, and by the ovaries to form estrogen and progesterone.

Cholesterol is produced by the liver and
we consume it from meat and dairy products



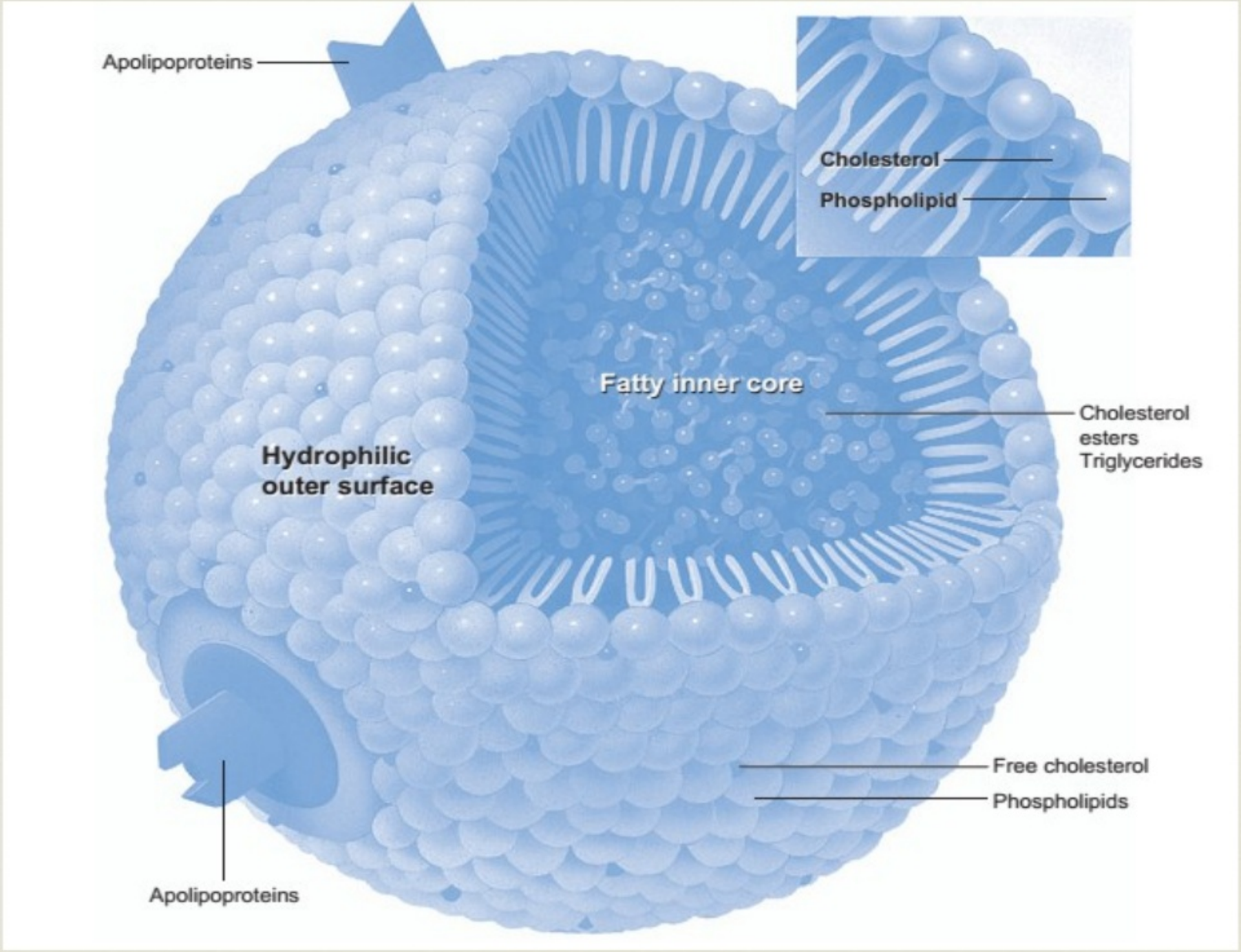


What are the normal functions of *triglycerides and Phospholipids* in the body?

- ***Triglycerides*** supply energy for the body. Triglycerides either meet immediate energy needs in muscles or stored as fat for future energy requirements.
- ***Phospholipids*** are compounds that are used to make cell membranes, generate second messengers, and store fatty acids for the use in generation of prostaglandins

What are lipoproteins?

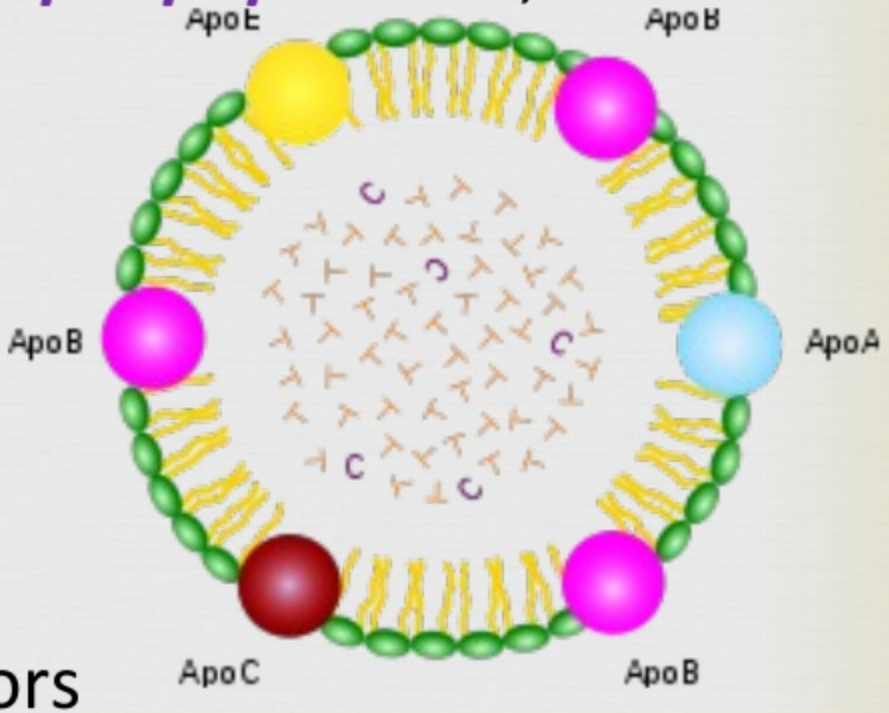
- ✓Since blood and other body fluids are watery, so fats need a special transport system to travel around the body.
- ✓They are carried from one place to another mixing with protein particles, called lipoproteins.
- ✓There are four (or five) types of lipoproteins, each having very distinct job.


Apolipoproteins
Cholesterol
Phospholipid
Fatty inner core
Cholesterol esters
Triglycerides
Hydrophilic outer surface
Free cholesterol
Phospholipids
Apolipoproteins

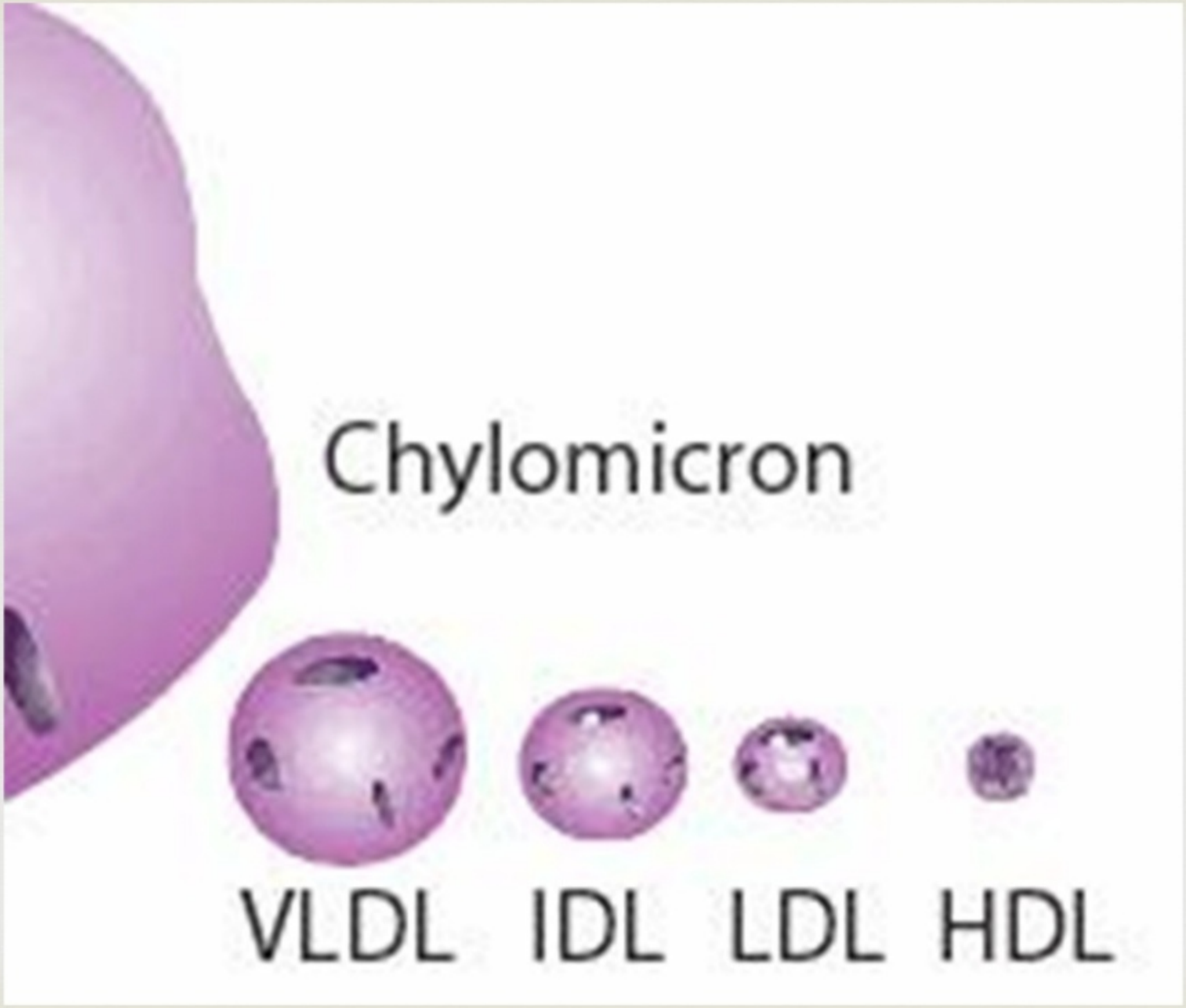
What are lipoproteins?

A **lipoprotein** contains both proteins and lipids, bound to another proteins which is called ***apolipoproteins***, which allow fats to move through the water inside and outside cells.

** provide structural support and stability, binds to receptors

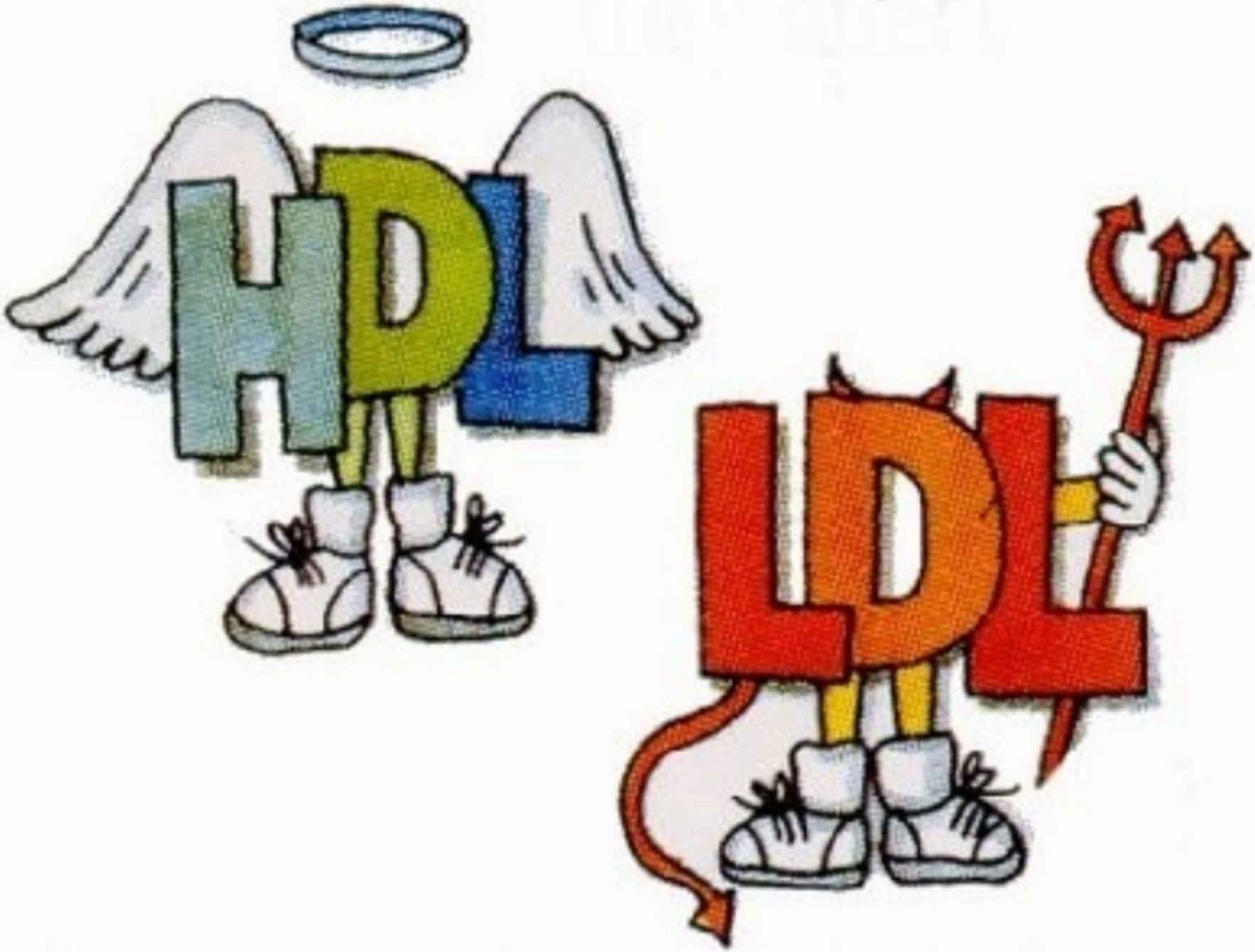


Lipoprotein structure (chylomicron)

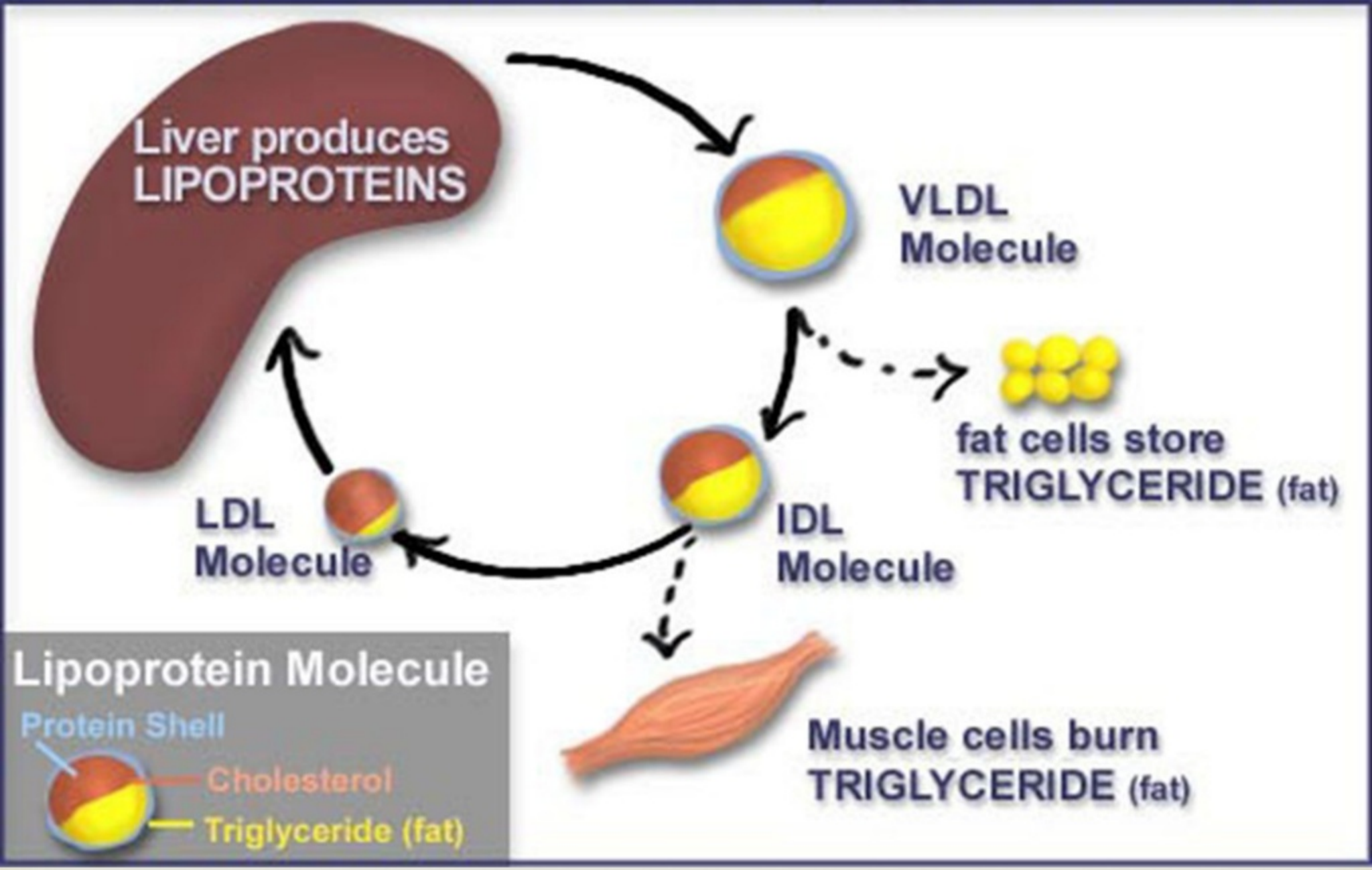

Chylomicron
VLDL
IDL
LDL
HDL

Classification of lipoproteins

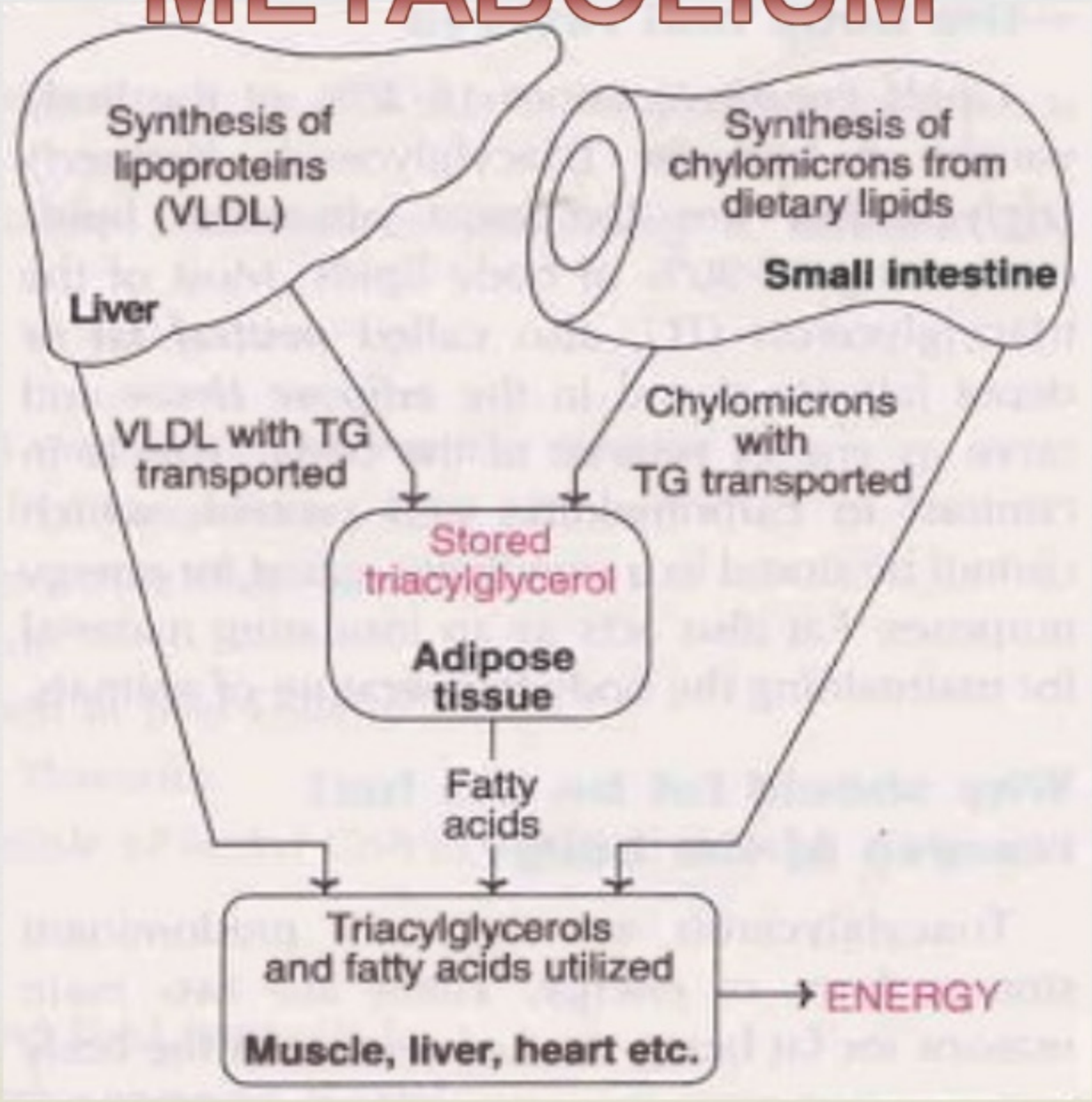
Classification	Composition	Primary function
Chylomicrons	Triglyceride TGs 99%, 1% protein	Transport dietary TGs to adipose tissue & muscle
VLDL	newly synthesized TGs Lipid 90%, 10% protein	Transport endogenous TGs to adipose tissue & muscle
IDL	intermediate between VLDL and LDL	They are not usually detectable in the blood.
LDL	Lipid 80%, 20% protein	Transport endogenous cholesterol from liver to tissues
HDL	Lipid 60%, 40% protein	Collect cholesterol from the body's tissues, and take it back to the liver


HDL
LDL

Life Cycle of Cholesterol-Carrying LIPOPROTEINS



OVERVIEW OF FAT METABOLISM



What is the classification of Hyperlipidemia

Hyperlipidemias are classified according to the **Fredrickson classification** which is based on the pattern of lipoproteins on electrophoresis or ultracentrifugation. It was later adopted by the World Health Organization (WHO). It does not directly account for HDL, and it does not distinguish among the different genes that may be partially responsible for some of these conditions.

GROUPS OF HYPERLIPIDEMIA:

- Primary or familial hyperlipoproteinaemia
- Secondary hyperlipoproteinaemia

The current classification of hyperlipidemias is based on the pattern of lipid abnormality in the blood.

Primary familial hyperlipoproteinaemia

- Subclassified into six phenotypes

  I , II_a , II_b, III, IV, and V based on lipoproteins and lipids

were elevated.

- current literature, however, favour the more descriptive

classifications and subclassification

see table 30.2 in foy's book

Hyperlipoproteinemia	Synonyms	Increased lipoprotein	Treatment
Type I (rare)	"Buerger-Gruetz syndrome", "Primary hyperlipoproteinaemia", or "Familial hyperchylomicronemia"	Chylomicrons by reduced LPL	Diet control
Type IIa	"Polygenic hypercholesterolaemia" or "Familial hypercholesterolemia	LDL+TG	Bile acid sequestrants, statins, niacin
Type IIb	"Combined hyperlipidemia"	LDL and VLDL	Statins, niacin, fibrate
Type III (rare)	"Familial dysbetalipoproteinemia"	IDL	Fibrates, statins
Type IV	"Familial hyperlipidemia"	VLDL	Fibrate, niacin], statins
Type V (rare)	"Endogenous hypertriglyceridemia	VLDL and Chylomicrons	Niacin, fibrate

Secondary hyperlipidemias

- may be due to:
  a. **hypothyroidism**
  b. **nephrotic syndrome**
  c. **diabetes mellitus (NIDDM)**
  d. **chronic renal failure**

Classification of Antihyperlipidemic Drugs

Several different classes of drugs are used to treat hyperlipidemia. These classes differ not only in their *mechanism of action* but also in *the type of lipid reduction and the magnitude* of the reduction.

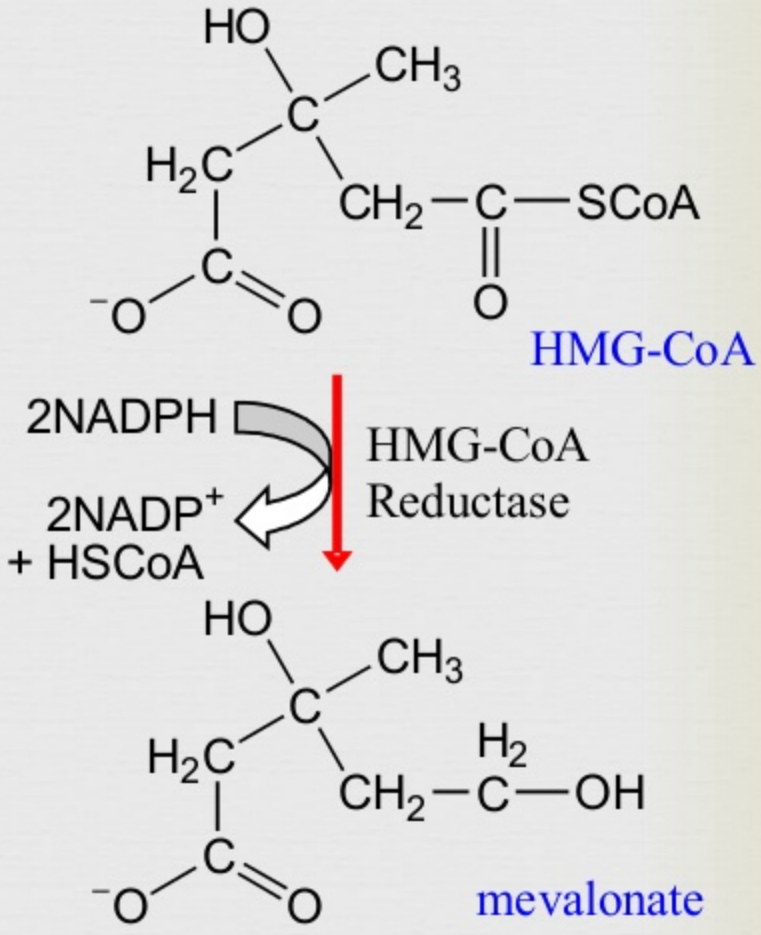
CLASSIFICATION

S.No.	Class	Example
1)	HMG CoA Reductase inhibitors	Lovastatin, Simvastatin, Metastatin, Pravastatin, Fluvastatin, Atorvastatin, Pitavastatin, Rosuvastatin
2)	Fibric acid derivatives	Clofibrate, Fenofibrate, Gemfibrozil, Ciprofibrate, benzaffibrate, Fluvestatin.
3)	Bile acid sequestrants	Cholestyramine, Colestipol
4)	LDL oxidation inhibitor	Probucol
5)	Pyridine derivatives	Nicotinic acid, Nicotinamide
6)	Cholesterol absorption inhibitors	Ezetimibe
7)	Miscellaneous agents	β-Sitosterol, Dextrothyroxine

HMG-CoA Reductase Inhibitor ((Statin))

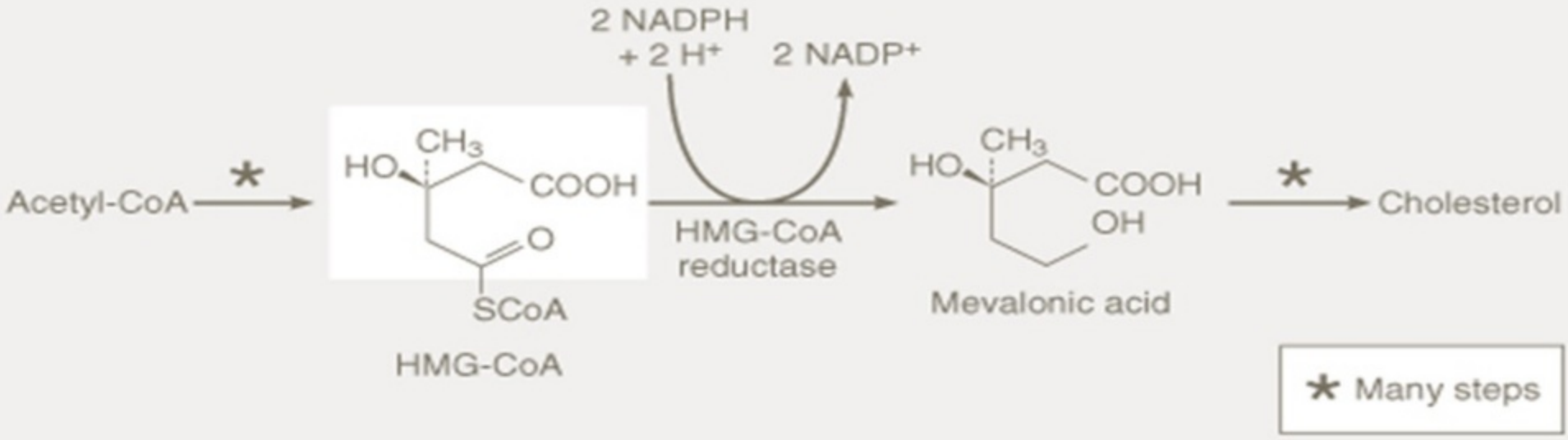
Target: HMG-CoA Reductase (HMGR)

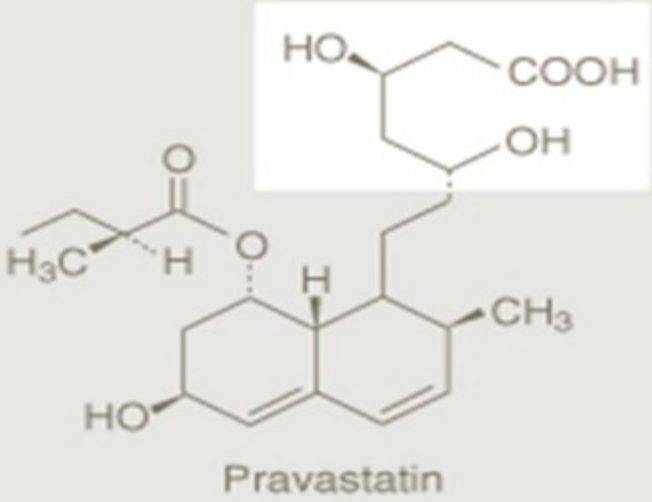
- The enzyme that catalyzes the conversion of HMG-CoA to mevanolate.
- This reaction is the rate-determining step in the synthetic pathway of cholesterol.



3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA)

HMG-CoA reductase inhibitors



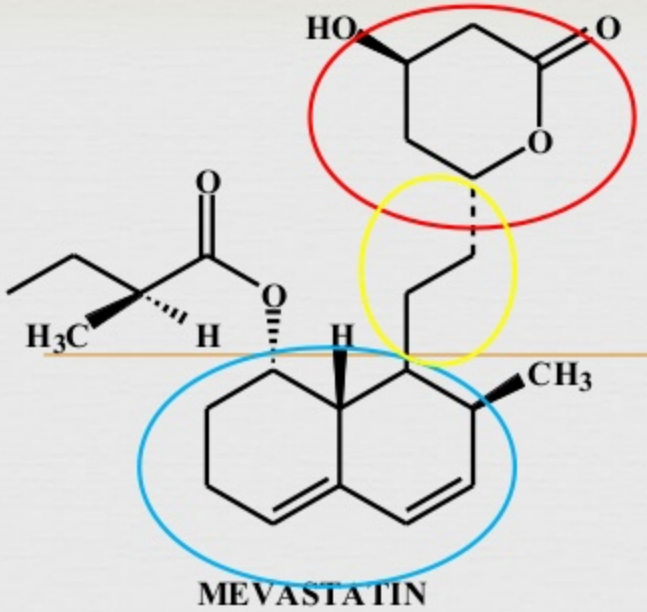


Statins

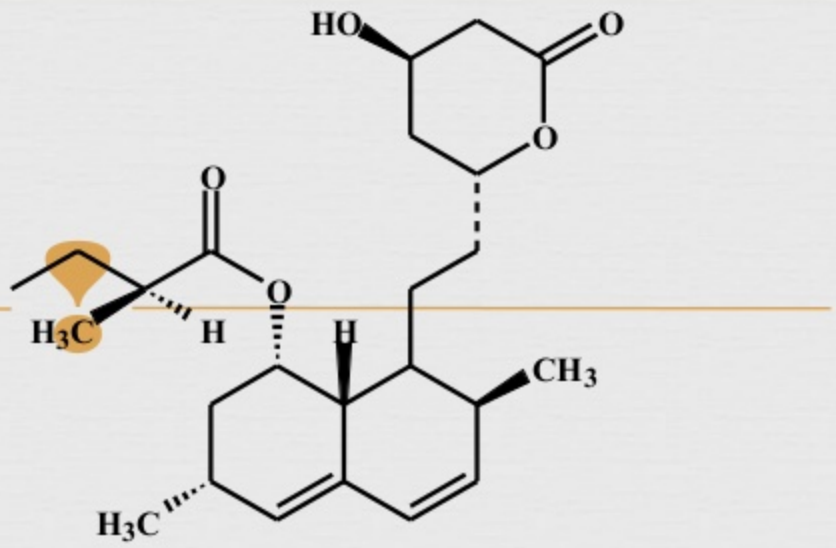
- Lovastatin was isolated from *Aspergillus terreus*.

Today, there are two classes of statins:
Natural Statins: Lovastatin(mevacor), Pravastatin (pravachol), Simvastatin (Zocor).
Synthetic Statins: Atorvastatin (Lipitor), Fluvastatin (Lescol).

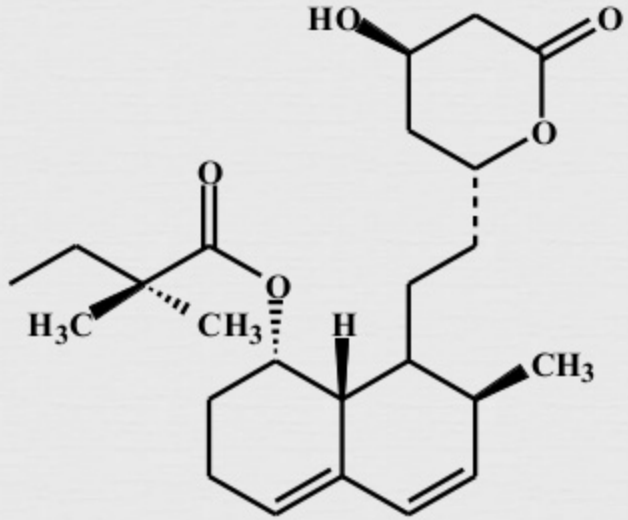
Statins are competitive inhibitors of HMG-CoA reductase. They are bulky and "stuck" in the active site.
This prevents the enzyme from binding with its substrate, HMG-CoA.



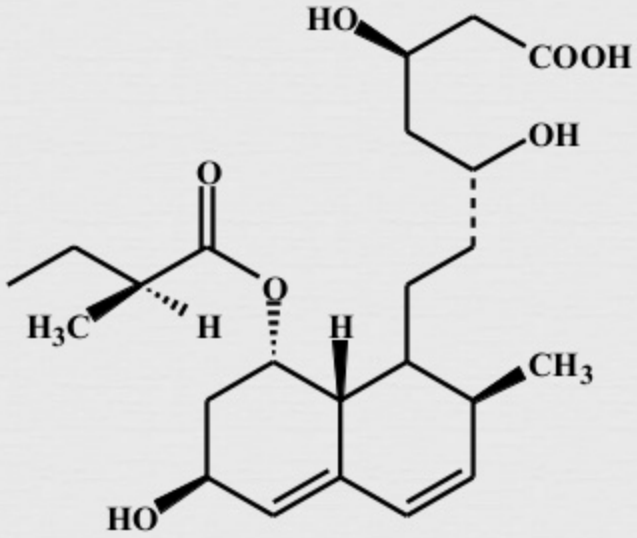
MEVASTATIN



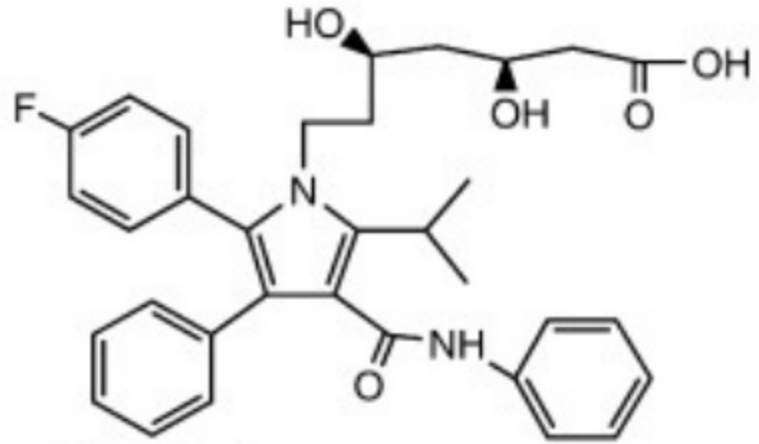
LOVASTATIN (MEVACOR)



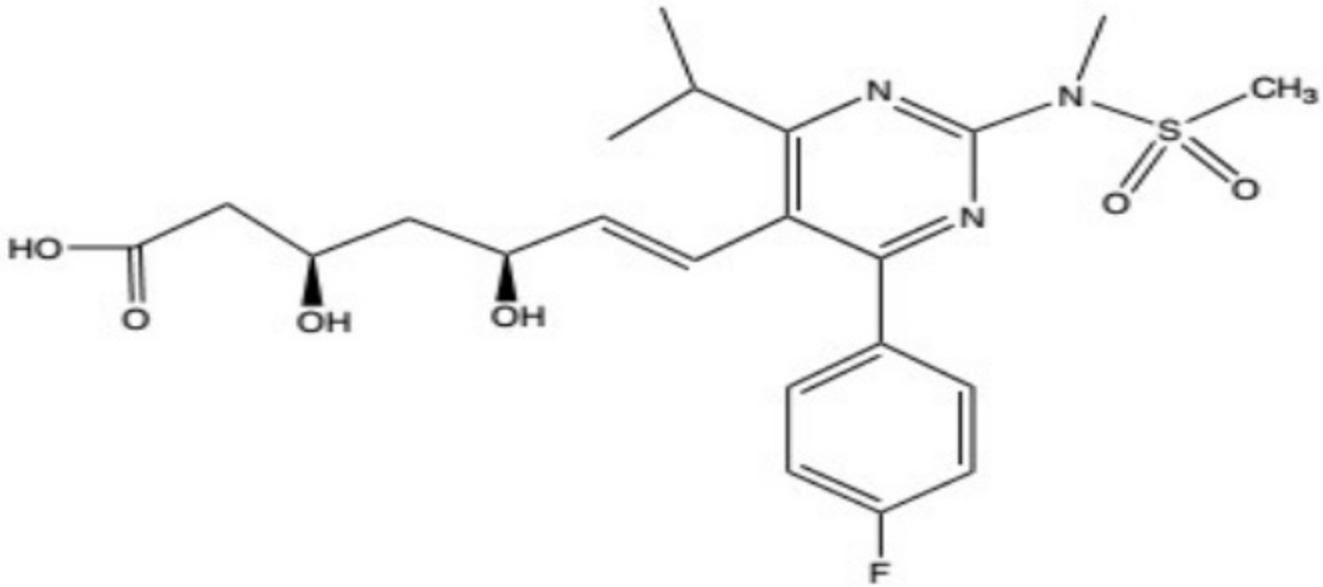
SIMVASTATIN (ZOCOR)



PRAVASTATIN (PRAVACHOL)



Atorvastatin
(Lipitor)



Rosuvastatin

DRUG	ADR	USES
Lovastatin	Increased creatinine phosphokinase, Flatulence, Nausea	Antihyperlipoproteinemi c agent
Simvastatin	Headache, nausea, flatulence, heartburn, abdominal pain	Antihyperlipdemic agent
Pravastatin	GI disturbances, headache, insomnia, chest pain, rash	Antihyperlipoproteinemi c agent
Atorvastatin	Headache, flatulence, diarrhea	Primmary hyperlipidemia and secondary hyper cholesterolemia
Rosuvastatin	Headache, dizziness, constipation, nausea, vomiting	High LDL, total cholesterol, TGs

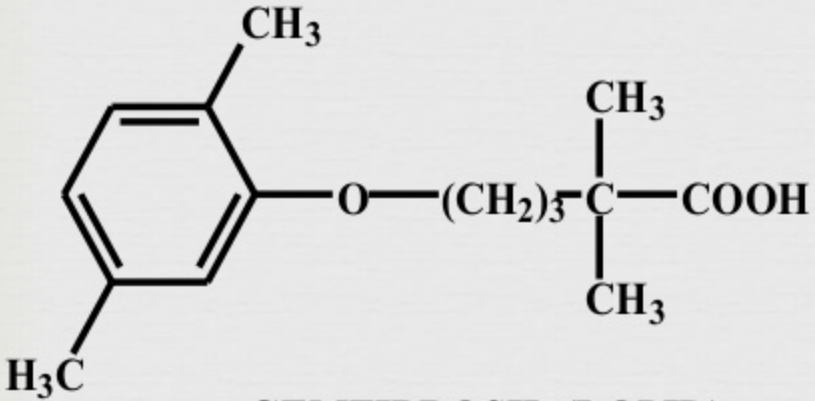
SAR of HMG-CoA reductase inhibitors

The structure should contain

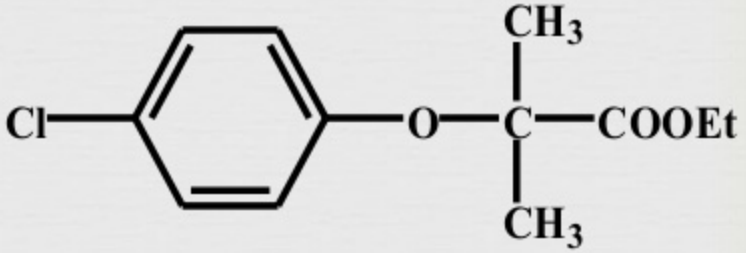
a. lactone ring (*sensitive to stereochemistry of it, ability of ring to hydrolyzed, length of bridge*)
b. Bicyclic rings (*could be replaced with other lipophlic rings, size and shape of it are important for activity*)
c. Ethylene bridge between them

Fibrates

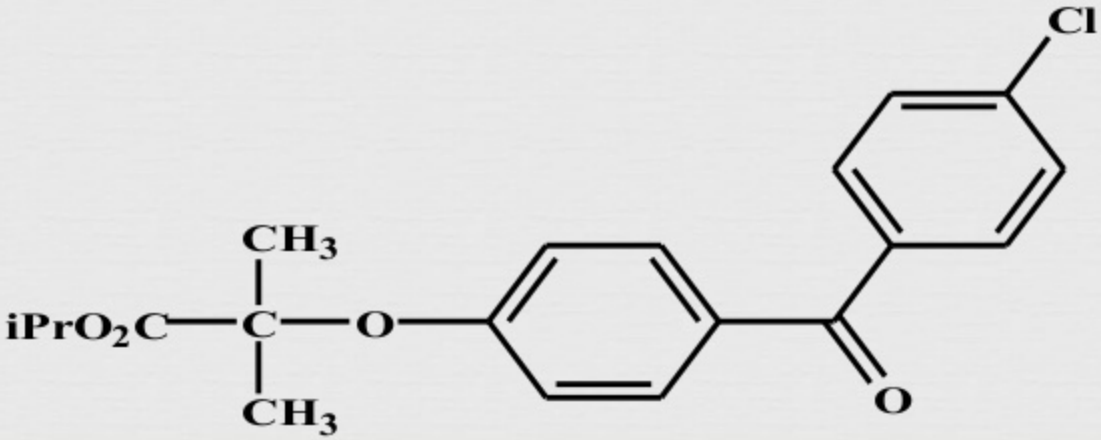
FIBRIC ACID DERIVATIVES



GEMFIBROSIL (LOPID)



CLOFIBRATE (ATROMID-S)



FENOFIBRATE (TRICOR)

Overview

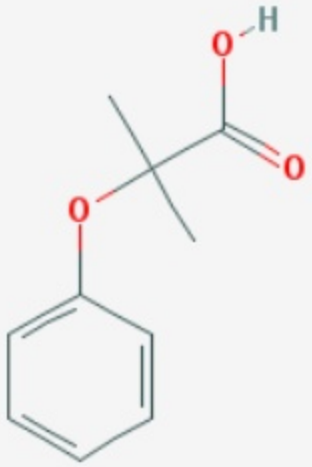
- Fibrates are antihyperlipidemic agents, widely used in the treatment of different forms of hyperlipidemia and hypercholesterolemia
- Fibrates are 2-phenoxy-2-methyl propanoic acid derivatives.
- these drugs stimulate β-oxidation of fatty acids in mitochondria
- This group of drugs is therefore known for decreasing plasma levels of fatty acid and triacylglycerol

Mechanism of Action = works in a variety ways

- Decrease plasma TGs levels more than C levels
- Fibrates lower blood triglyceride levels by ***reducing*** the liver's production of ***VLDL*** (the triglyceride-carrying particle that circulates in the blood) by activation of lipoprotein lipase and speeding up the removal of TGs from the blood. It is supported by PPAR-α.
- Fibrates also are modestly effective in ***increasing blood HDL cholesterol***; however, fibrates are not much effective in ***lowering LDL cholesterol***.

SAR of Fibric acid

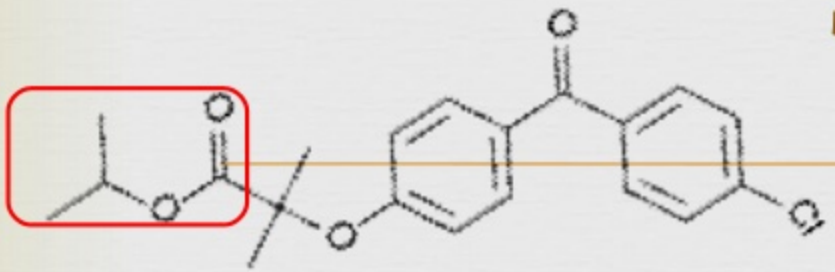
[aromatic ring]-O-[spacer group]-$C(CH_3)_2$-CO-OH



Fibric acid

- They are classified as analogues of isobutyric acid derivatives (essential for activity)

SAR



Fenofibrate

gemfibrozil

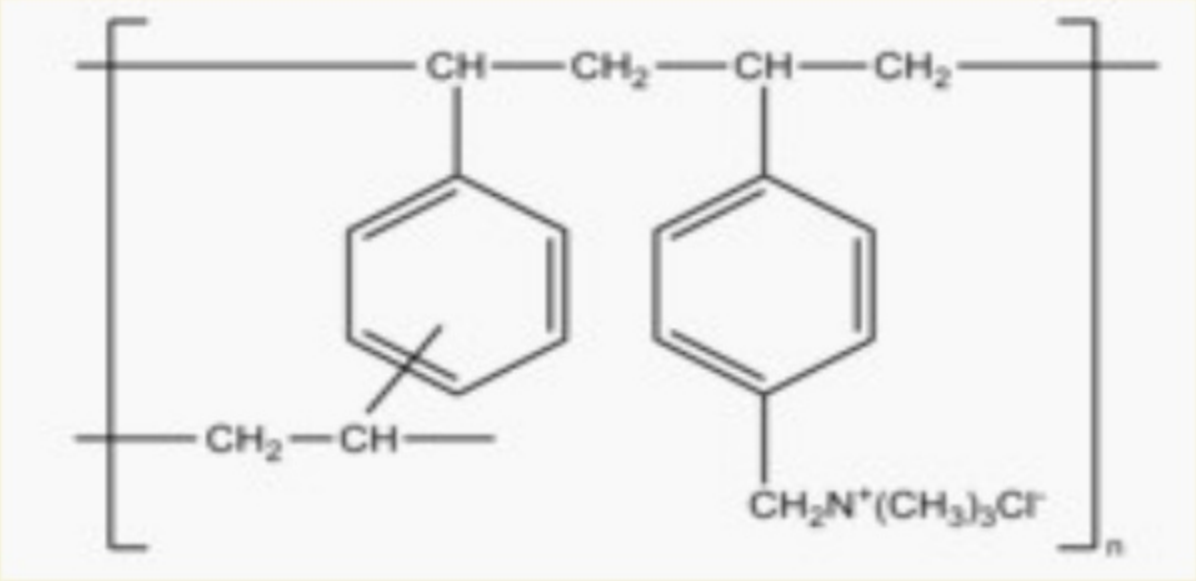
- Fenofibrate contain ester (prodrug)
- Para-subtitution with Cl or Cl containing isopropyl ring increase half-lives.
- n-propyl spacer result in active drugs (gemfibrozil)

DRUG	ADR	USES
Clofibrate	Cholecystitis, gall stone, eosinophilia, pneumonia	Type III Hyperlipoproteinemias
Gemfibrozil	Myositis syndrome, Cholelithiasis, GI disturbances, rash and headache.	Hyperlipidemia
Fenofibrate	Headache, dizziness, asthaenia, fatigue, arrhythmia	More potent hypercholesterolemic and triglycerides lowering agent

Bile Acid Sequestrants

Bile Acid Sequestrants

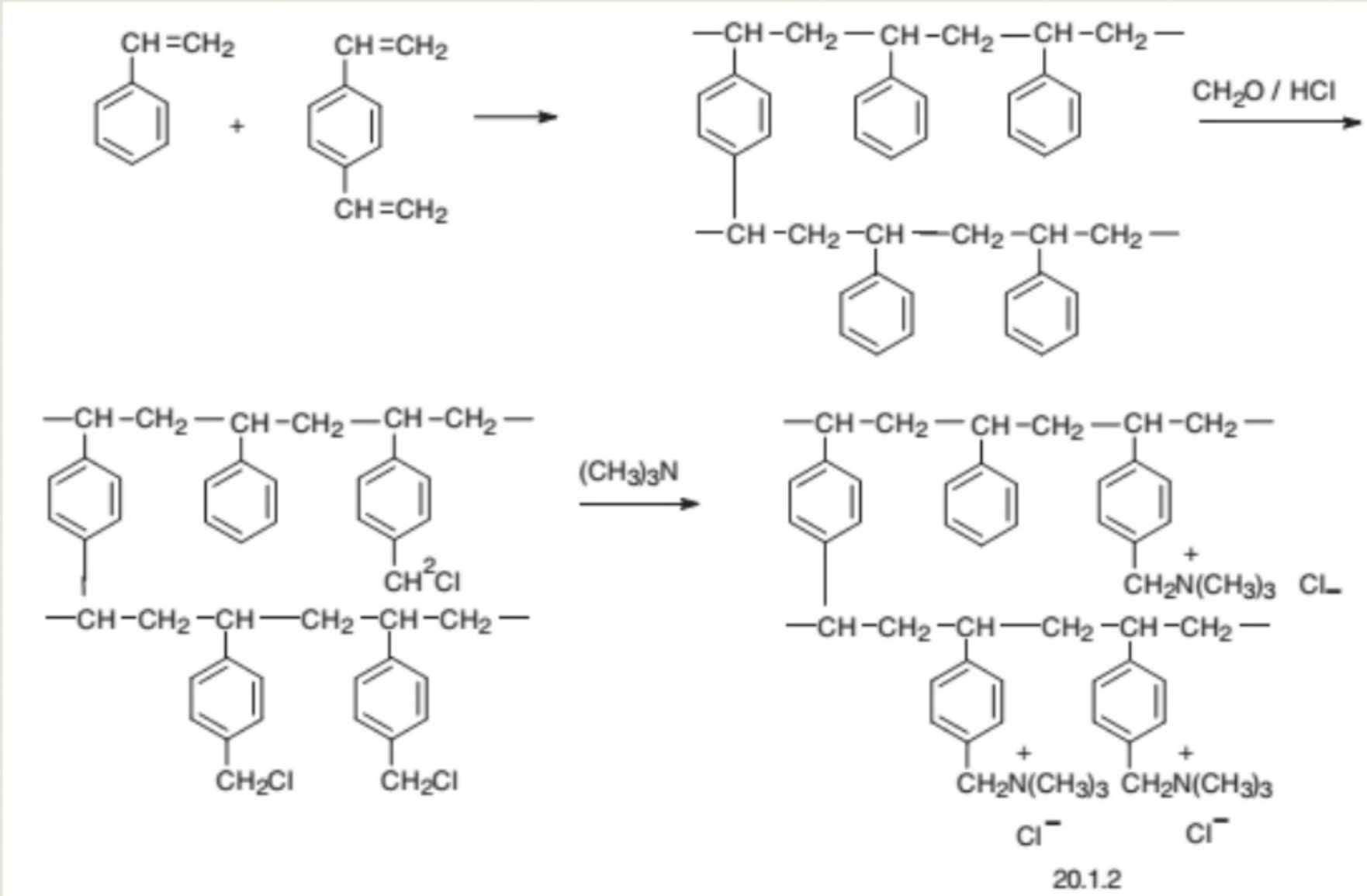
- cholestyramine (Questran)
- colestipol hydrochloride (Colestid)
- colesevelam (tablet form)
- **Also called bile acid–binding resins and ion-exchange resins**



Cholestyramine (Questran)

- is a non-absorbed bile acid sequestrant that is used as a therapy of hyperlipidemia and for the pruritis of chronic liver disease and biliary obstruction.
- is a large, highly positively charged anion exchange resin that binds to negatively charged anions such as bile acids.
- The binding of bile acids to cholestyramine creates an insoluble compound that cannot be reabsorbed and is thus excreted in the feces.

- Moderately effective with excellent safety record
- Large MW polymers containing Cl^-
- Resin binds to bile acids and the acid-resin complex is excreted
  - prevents enterohepatic cycling of bile acids
  - obligates the liver to synthesize replacement bile acids from cholesterol.
- The levels of LDL-C in the serum are reduced as more cholesterol is delivered to the liver
- Little effect on levels of HDL-C and TG.
- Excellent choice for people that cannot tolerate other types of drugs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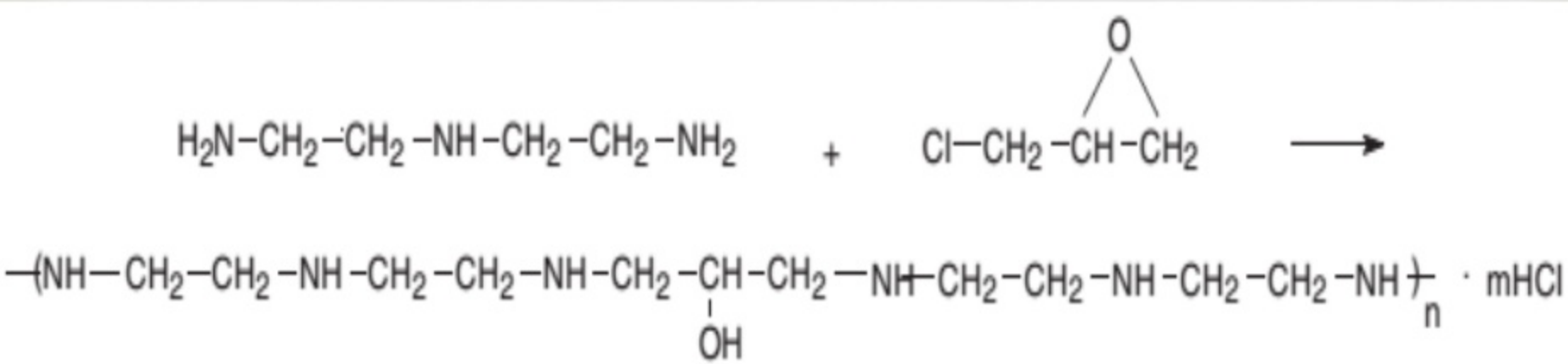
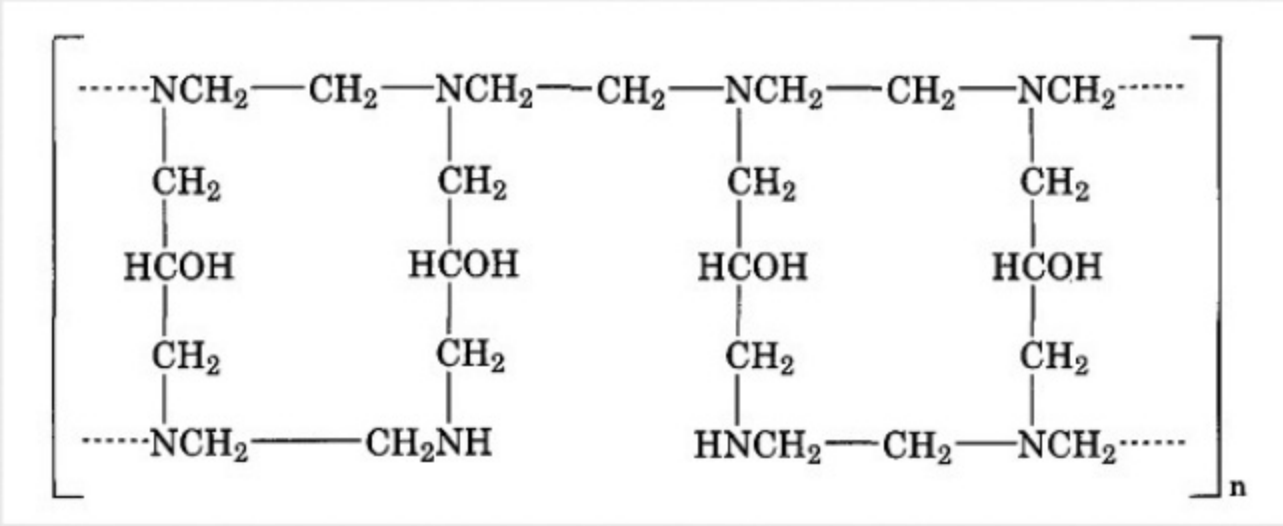
20.1.2

Colestipol





Colesevalam

- A third generation drug of this class……resemble the previous ones but don't contain chloride ions.
- Strictly speaking, it is not an anion exchange resin.
- Selectivity for hydroxylated form of bile acids shows a reduced side effect……reduced constipation.

Adverse effects

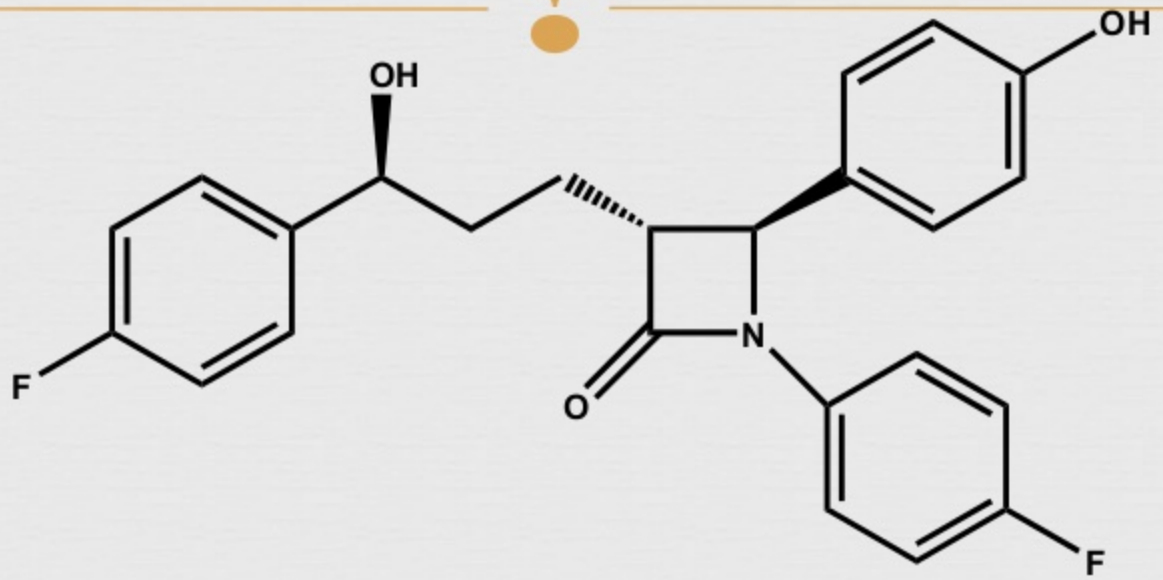
- Constipation
- Heartburn, nausea, bloating
- These adverse effects tend to disappear over time.

Therapeutic Uses

- Type IIa hyperlipoproteinemia.
- Relief of pruritus associated with partial biliary obstruction (cholestyramine).

Ezetimibe
((Cholesterol Absorption Inhibitor))

Ezetimibe (Zetia)



EZETIMIBE

is a drug that lowers plasma cholesterol levels. It acts by decreasing cholesterol absorption in the intestine

Mechanism of action Cholesterol Absorption Inhibitor

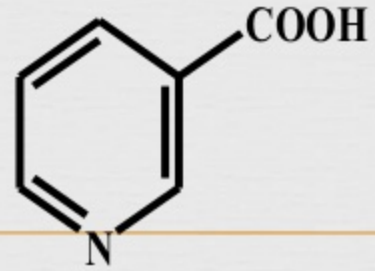
- lowers plasma cholesterol levels by inhibiting the absorption from intestine
- This cause a decrease in the cholesterol delivery to the liver which in turn clears more cholesterol from the blood
- selective in its action ((not interfere with TGs, lipid-soluble vitamins absorption))
- The levels of LDL-C in the serum are reduced as in bile acid sequestrants.

Therapeutic uses

- as monotherapy or in combination with HMGRI for reduction of elevated total cholesterol.

Niacin ((Nicotinic Acid))

NICOTINIC ACID (Niacin)



NICOTINIC ACID (NIACIN)

A water soluble vitamin of the B family;
Once converted to the amide, it is incorporated into NAD

In order to be effective, it has to be dosed at the rate of 1.5 to 3.5 gm daily.
A sustained release dosage form is available

Niacin (Nicotinic Acid)

- **Vitamin B_3**
- Lipid-lowering properties require much higher doses than when used as a vitamin
- Effective, inexpensive, often used in combination with other lipid-lowering drugs

Niacin (Nicotinic Acid)

Mechanism of action

- Increases activity of lipase, which breaks down lipids
- Reduces the metabolism of cholesterol and triglycerides

Indications

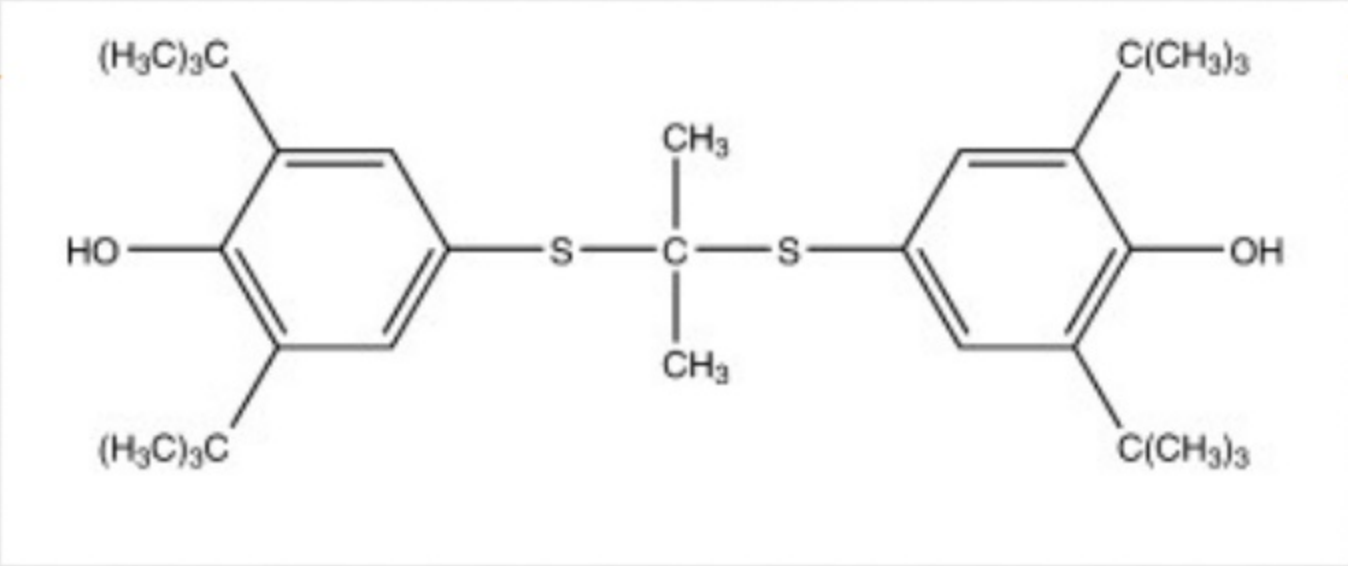
- Effective in lowering triglyceride, total serum cholesterol, and LDL levels
- Increases HDL levels
- Effective in the treatment of types IIa, IIb, III, IV, and V hyperlipidemias

Niacin (Nicotinic Acid)

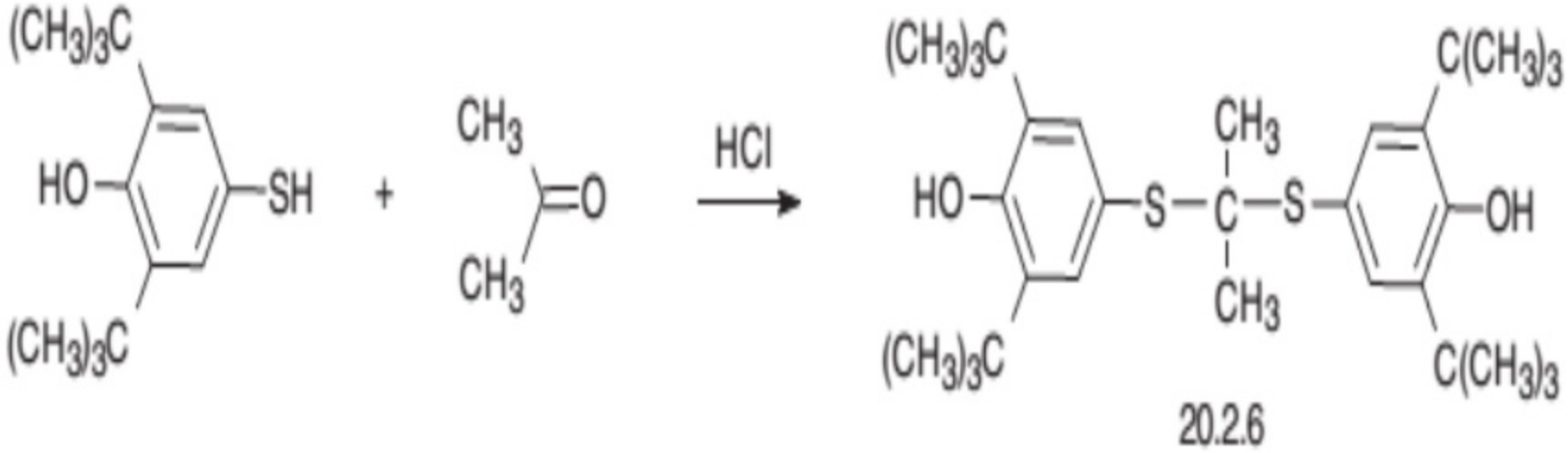
Adverse effects

- Flushing (due to histamine release)
- Pruritus
- GI distress
- Liver dysfunction and jaundice. Serious liver damage is the most important risk.

LDL oxidation inhibitor probucol



- Molecule has two tertiary butylphenol groups linked by a dithiopropylidene bridge, giving it a high lipophilic character with strong antioxidant properties.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OH
C(CH3)3
CH3
CH3
(CH3)3C
C(CH3)3

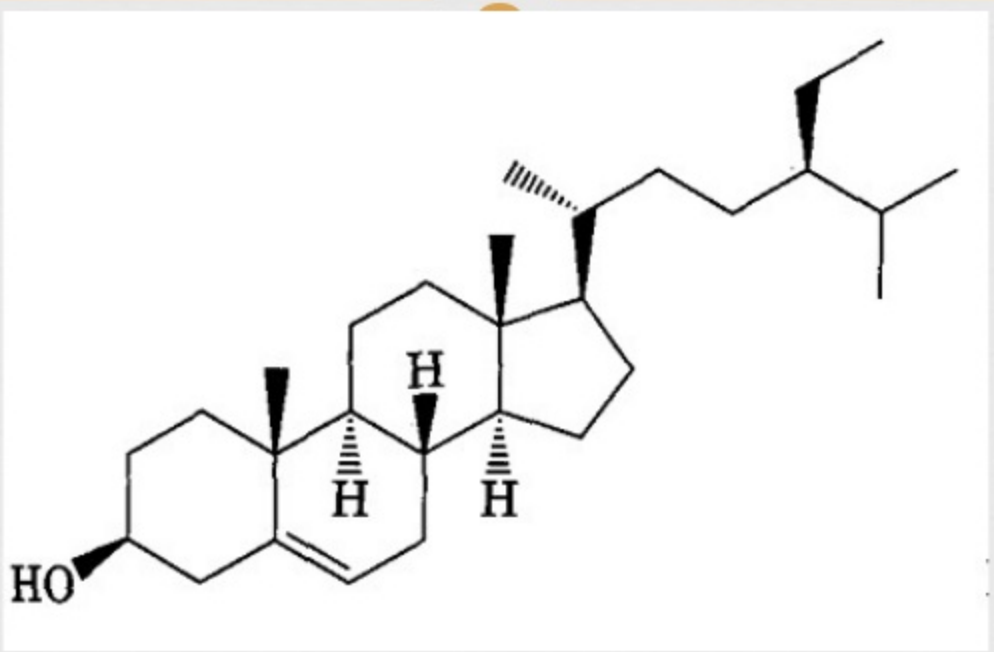
20.2.6

- In humans, it causes reduction of both liver and serum cholesterol levels, but it does not alter plasma triglycerides.
- It reduces LDL
- It reduces to a lesser extent HDL levels by a unique mechanism that is still not clearly delineated.
- The reduction of HDL may be caused by the ability of probucol to inhibit the synthesis of apoprotein A-1, a major protein component of HDL.
- It is effective at reducing levels of LDL and is used in hyperlipoproteinemias characterized by elevated LDL levels.

ADR: GI disorders and prolongation of GI intervals.

Use: It is used as antihyperlipoproteinemic agent.

Miscellaneous agent β-Sitosterol



- Sitosterol is a plant sterol, whose structure is identical with that of cholesterol, except for the substituted ethyl group on C-24 of its side chain.

- Although the mechanism of its hypolipidemic effect is not clearly understood, it is suspected that the drug inhibits the absorption of dietary cholesterol from the gastrointestinal tract.

- Sitosterols are absorbed poorly from the mucosal lining and appear to compete with cholesterol for absorption sites in the intestine.

ADR: Diarrhoea, constipation, GI disturbances

Use: Anti cholesteremic agent and treatment of prostatic oedema.