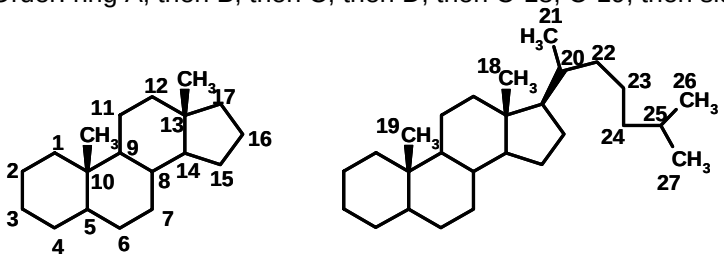
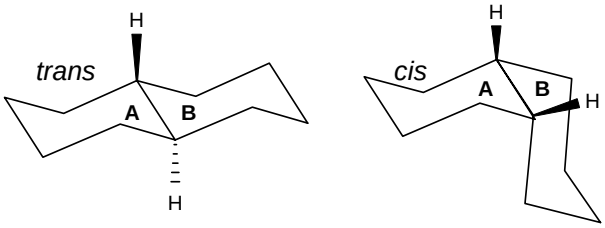
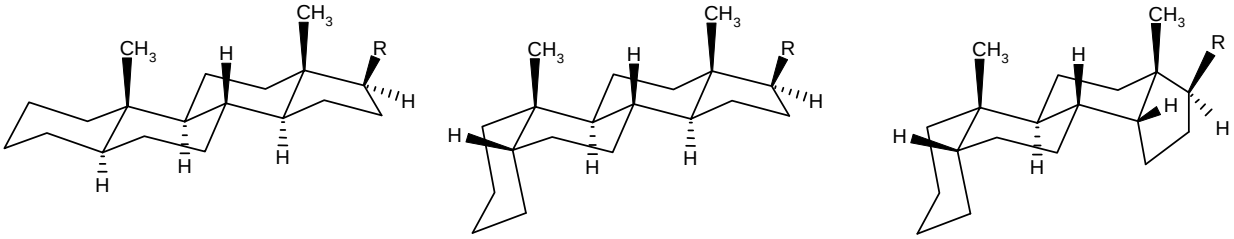
√ **Structure and Numbering** cyclopentanoperhydrophenanthrene skeleton
Order: ring A, then B, then C, then D, then C-18, C-19, then side chain




√ **Configurational Isomers**

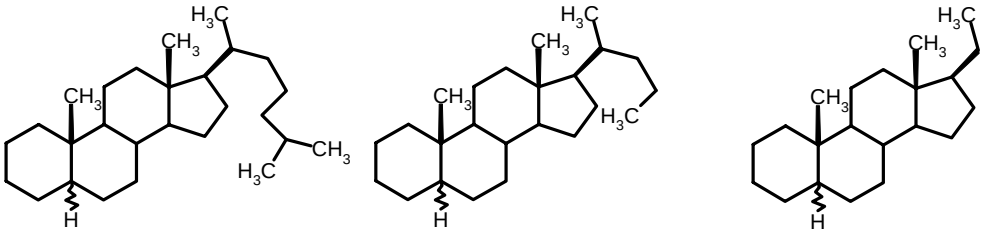



√ **3D Structure of Steroids**

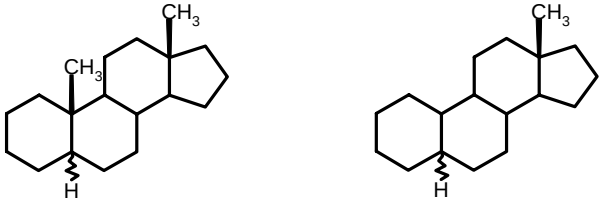



*trans-trans-trans* *cis-trans-trans* *cis-trans-cis*

√ **Classes and Nomenclature**




*Cholestanes (27 Cs)* *Cholanes (24 Cs)* *Pregnanes (21 Cs)*



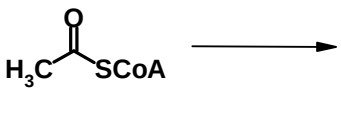

*Androstanes (19 Cs)* *Estranes (18 Cs)*

√ **α- and β-orientation**

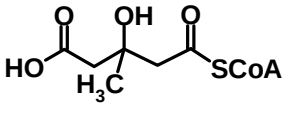
Substituents oriented towards the angular methyls (groups at C-10 and C-13 positions) are named β-substituents. These are groups that are drawn with bold bonds (——).

Substituents oriented away from the angular methyls (groups at C-10 and C-13 positions) are named α-substituents. These are groups that are drawn with cross-hatched bonds (**-----**).

√ **Cholesterol Biosynthesis**

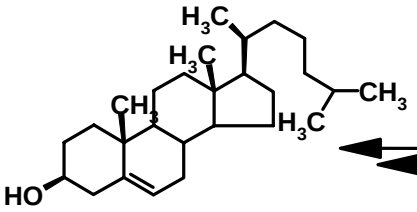


*acetyl Coenzyme A*

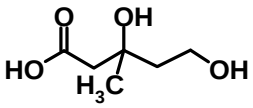


*(S)-3-hydroxy-3-methyl-glutaryl-CoA*

HMG CoA reductase

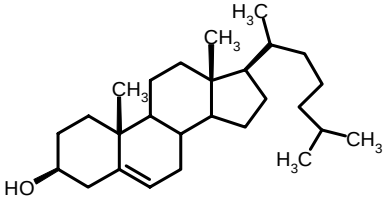


*cholesterol*

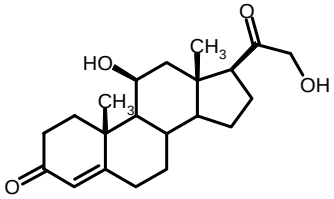


*(R)-mevalonic acid*

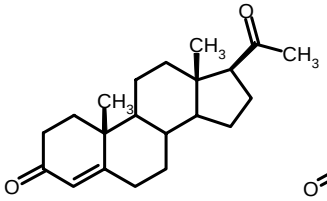
√ **Important Steroids** (Remember structure and practice drawing)



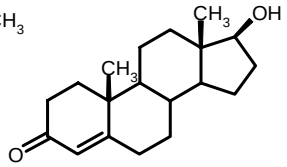
*Cholesterol*



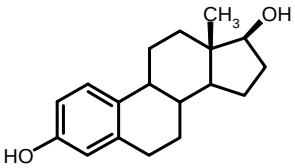
*Hydrocortisol*



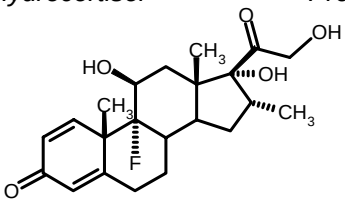
*Progesterone*



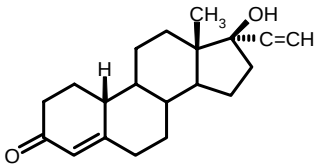
*Testosterone*



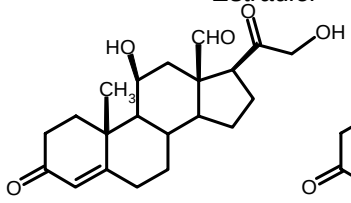
*Estradiol*



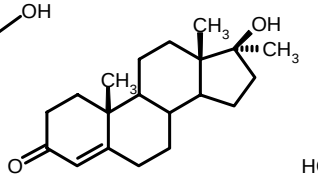
*Dexamethasone*



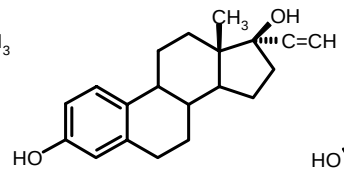
*17α-Ethinyl-testosterone*



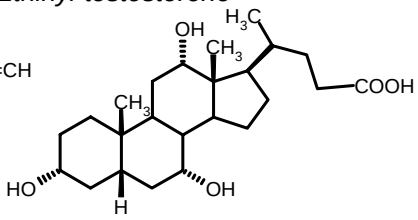
*Aldosterone*



*17α-methyltestosterone*



*17α-Ethinyl-estradiol*

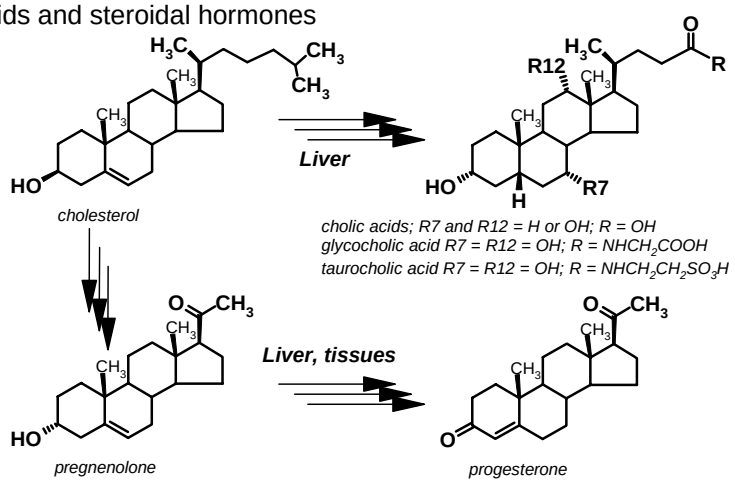


*Cholic Acid*

**Points to Ponder**

- What is the general structure of steroids?
- How are carbons numbered?
- How are rings oriented with respect to each other?
- How are steroids named?
- How many configurational isomers are possible for steroidal skeleton? What is α- and β-orientation?
- What is the 3-dimensional structure of steroids?
- How is cholesterol biosynthesized? What is the key step in the biosynthesis?
- What are the different classes of steroids? Which steroid falls under what class?

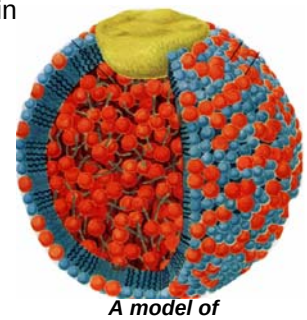
√ **Metabolism of Cholesterol** conversion to bile acids and steroidal hormones




√ **Arteriosclerosis** excessive deposition of endogenous products of blood in arteries; results in atherosclerosis

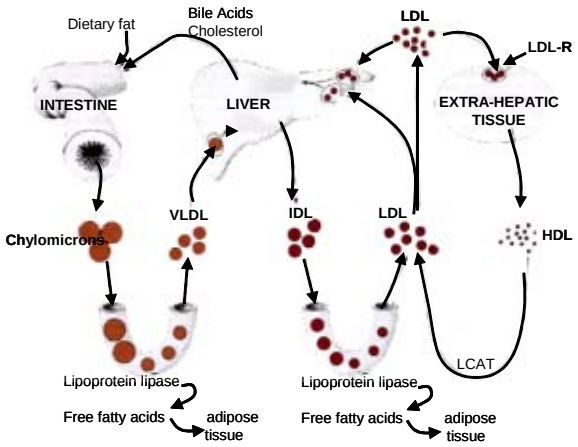
√ **Role of Cholesterol** increases the risk for coronary heart disease

√ **Lipoprotein Particles** facilitate enhanced cholesterol transport in blood; these are non-covalent, aggregates of lipids and proteins; lipids include triglycerides, cholesterol, cholesteryl esters, and phosphoserines; proteins include apo-lipoprotein A, B, C, E, etc.; types of lipoprotein particles include: chylomicrons, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL).

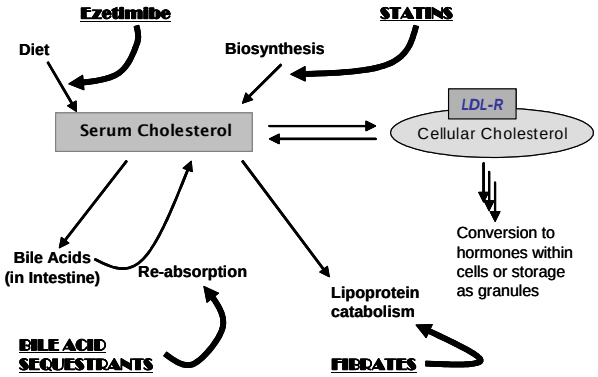


***A model of lipoprotein particle***

√ **Mechanism of Lipid Transport** Dietary fat with cholesterol (C) and triglycerides (TG) are absorbed in the intestine and released in the blood stream as chylomicrons. Lipoprotein lipase acts on these particles to release some free fatty acids that deposit in adipose tissues. The remnants of chylomicrons are picked up by liver. After further clean up liver releases VLDL in the blood. LPL works on these particles releasing more free fatty acids and changing them to IDL and LDL. There are LDL receptors on the cell membranes of the extra-hepatic cells which allow LDL entry into cells. This is how C reaches cell interior, where it is esterified and stored. Excess cholesterol suppresses the biosynthesis of LDL-receptors so that cholesterol intake decreases. Repackaged LDL particles called HDL are then released into the blood stream. These particles are sensed by the liver through the HDL-receptors. Thus the liver gets constant information as to how much LDL and HDL are present in the blood.



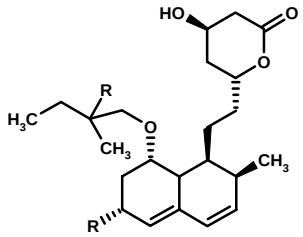

√ **Strategy for Controlling Hyperlipidemia** Current anti-hyperlipidemic agents target several mechanisms to control high cholesterol in serum. Ingestion of cholesterol from diet is reduced by cholesterol absorption inhibitors. The biosynthesis of cholesterol is reduced by statins. Bile acid sequestrants reduce bile absorption thereby enhancing cholesterol metabolism, while fibrates increase lipoprotein catabolism thereby transforming more LDL into HDL. Other miscellaneous drugs also exist in market that function through mechanisms which are not clear.



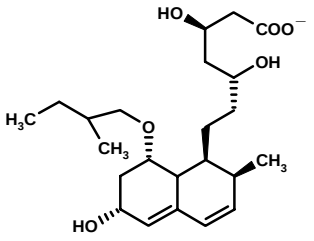
√ **Hyperlipidemia** the state wherein excess lipids (cholesterol and triglycerides) are present in blood. Several types of hyperlipidemias are classified. These include the type I, IIa, IIb, III, IV and V, each with its unique lipid profile and treatment protocol. National Institute of Heart, Lung and Blood suggests that LDL levels of less than 100 are optimal, 100 – 129 are above optimal, 130 – 159 are borderline high, 160 – 189 are high and > 190 are very high. Likewise, total cholesterol level of < 200 is desirable, 200 – 239 is borderline high, and > 240 is high. An HDL cholesterol level of >60 is considered very good, while levels of < 40 need improvement.

√ **Anti-hyperlipidemic Drugs in the Market** Statins, fibrates, bile acid sequestrants, ezetimibe, nicotinic acid, and probucol

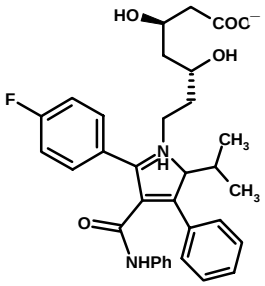
√ **Statins** 1) are reversible, competitive inhibitors of HMG-CoA reductase with a KI ~ 1 nM; 2) have the same absolute configuration at the 3-OH as the substrate; 3) have an alcohol group at the 5 position instead of the CoA-ester in substrate; 4) have a large lipophilic substituent replacing the CoA feature to enhance affinity



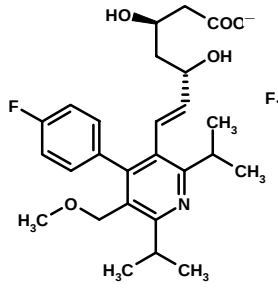
Mevastatin $R_1 = R_2 = H$
Lovastatin $R_1 = H$; $R_2 = CH_3$
Simvastain $R_1 = R_2 = CH_3$



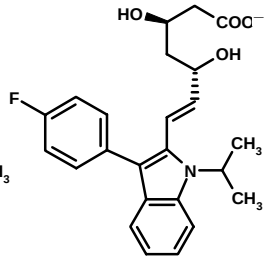
Pravastatin



Atorvastatin

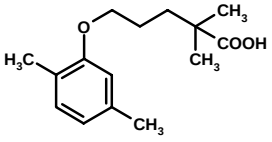


Cerivastatin

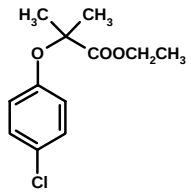


Fluvastatin

√ **Fibrates** 1) in use since 1981; 2) second most powerful anti-lipidemic agents; 3) primarily decrease triglycerides; 4) affect lipoprotein catabolism by increasing the action of LPL.

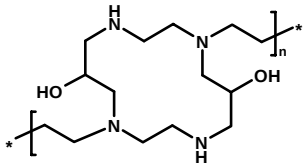


Gemfibrozil

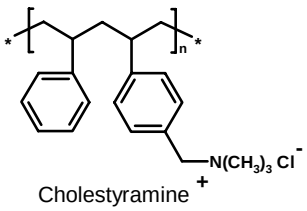


Clofibrate

√ **Bile Acid Sequestrants** 1) anion exchange resins; 2) water insoluble and inert to digestive enzymes; 3) not absorbed through intestine; 4) positively charged nitrogen containing; 5) sequester bile acids; 6) enhance conversion of cholesterol to bile in the liver; 7) lower serum LDL levels)

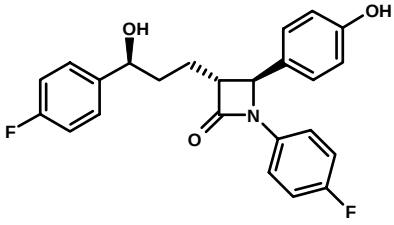


Colestipol



Cholestyramine

√ **Ezetimibe** 1) approved in Oct. 2002; 2) prevents absorption of cholesterol from the intestine; 3) reduces LDL, TC and TG, and increases HDL



Ezetimibe

**Points to Ponder**

- What is the importance of lipoprotein particles? What are they made of? How do they differ? What is the overall mechanism of lipid transport? What pathways are available to control serum cholesterol? Why are statins competitive inhibitors of HMG-CoA reductase? What is the mechanism of colestipol and cholestyramine action? How does ezetimibe function? What will happen if instead of a quaternary amine in cholestyramine, we introduce an aromatic amine, e.g. Ar-$NHCH_3$?