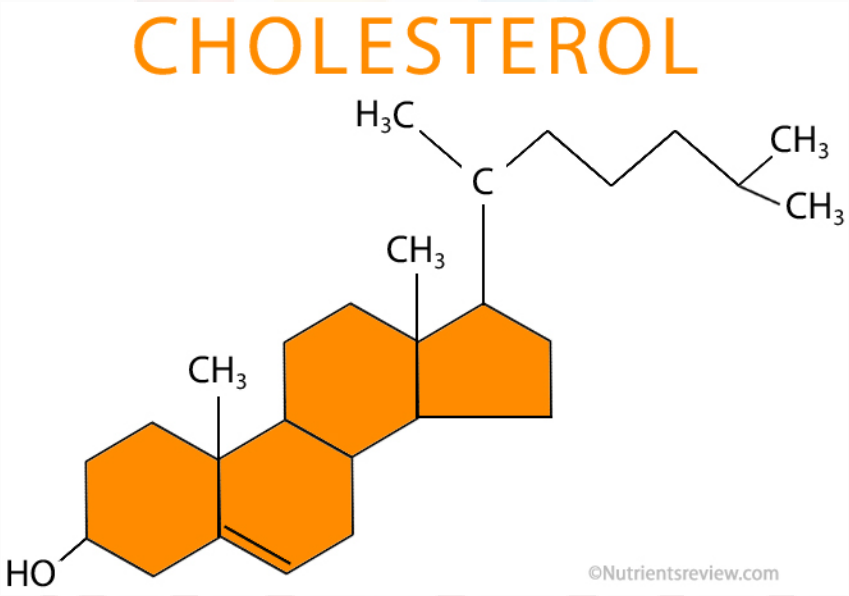
Cholesterol Biosynthesis

Introduction:

- Cholesterol is a lipid with a unique structure consisting of four linked hydrocarbon rings forming the bulky steroid structure.
- There is a hydrocarbon tail linked to one end of the steroid and a hydroxyl group linked to the other end.



- **Functions of cholesterol-**

- Cholesterol is an essential component of the cell membrane
- It is needed to maintain proper membrane permeability and fluidity.
- It is also needed for the synthesis of Steroid Hormones, Vitamin D and Bile Acids.

Cholesterol biosynthesis

- **All 27 carbon atoms of cholesterol are derived from acetyl CoA in a three-stage synthetic process.**

1. Stage one is the synthesis of isopentenyl pyrophosphate, an activated isoprene unit that is the key building block of cholesterol.

2. Stage two is the condensation of six molecules of isopentenyl pyrophosphate to form squalene.

3. In stage three, squalene cyclizes and the tetracyclic product is subsequently converted into cholesterol.

Stage 1:The formation of isopentenyl pyrophosphate from acetyl CoA.

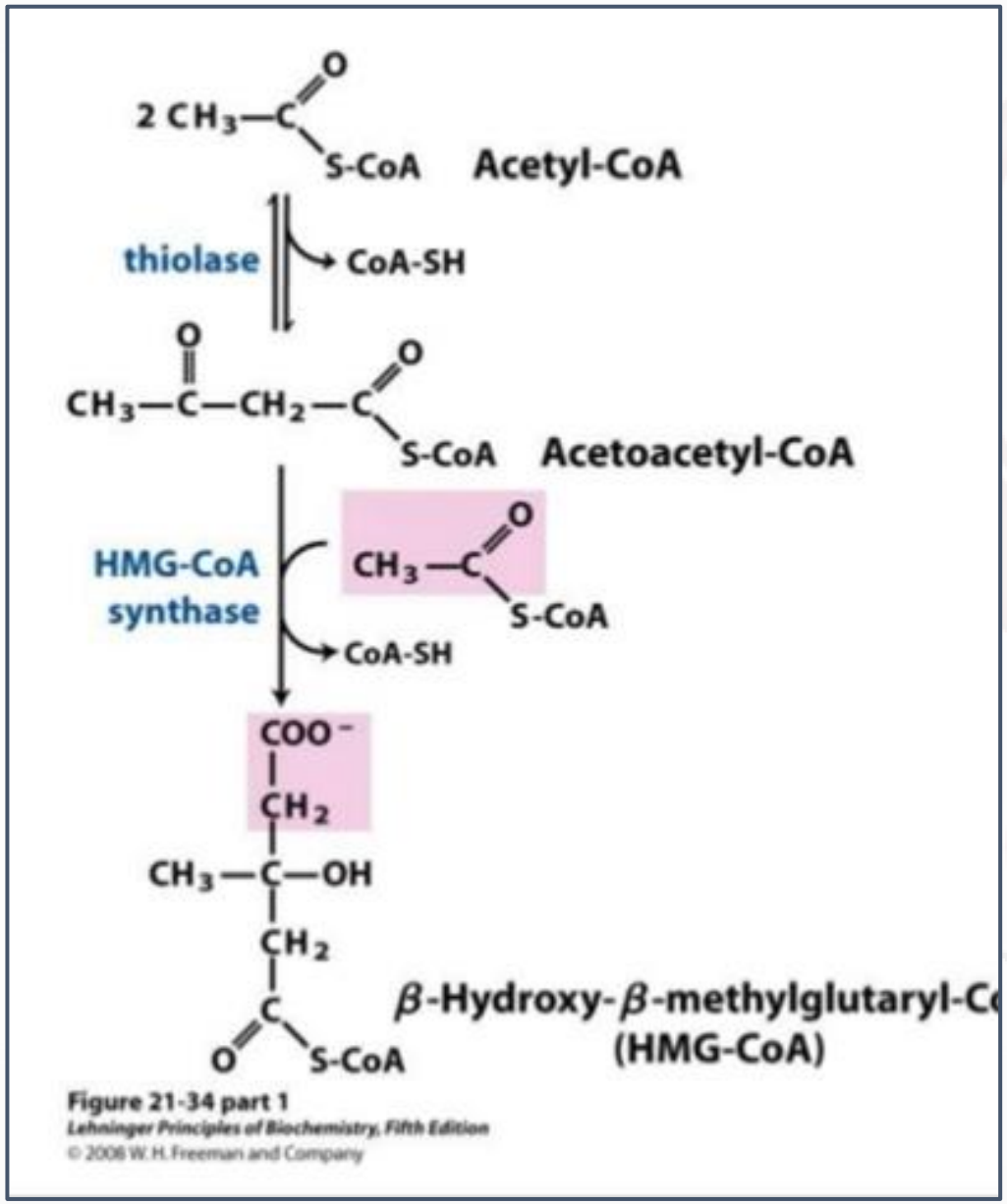
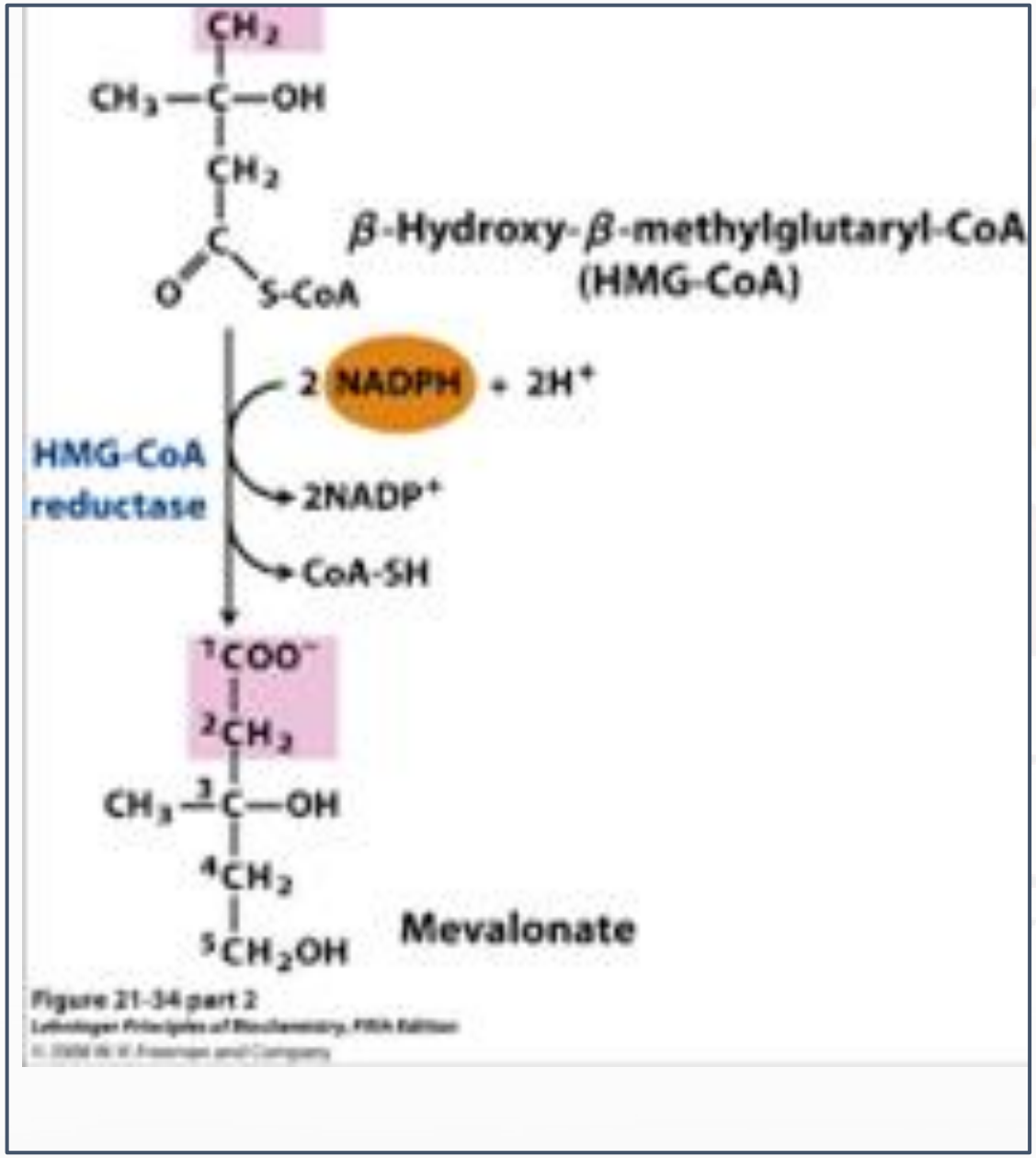


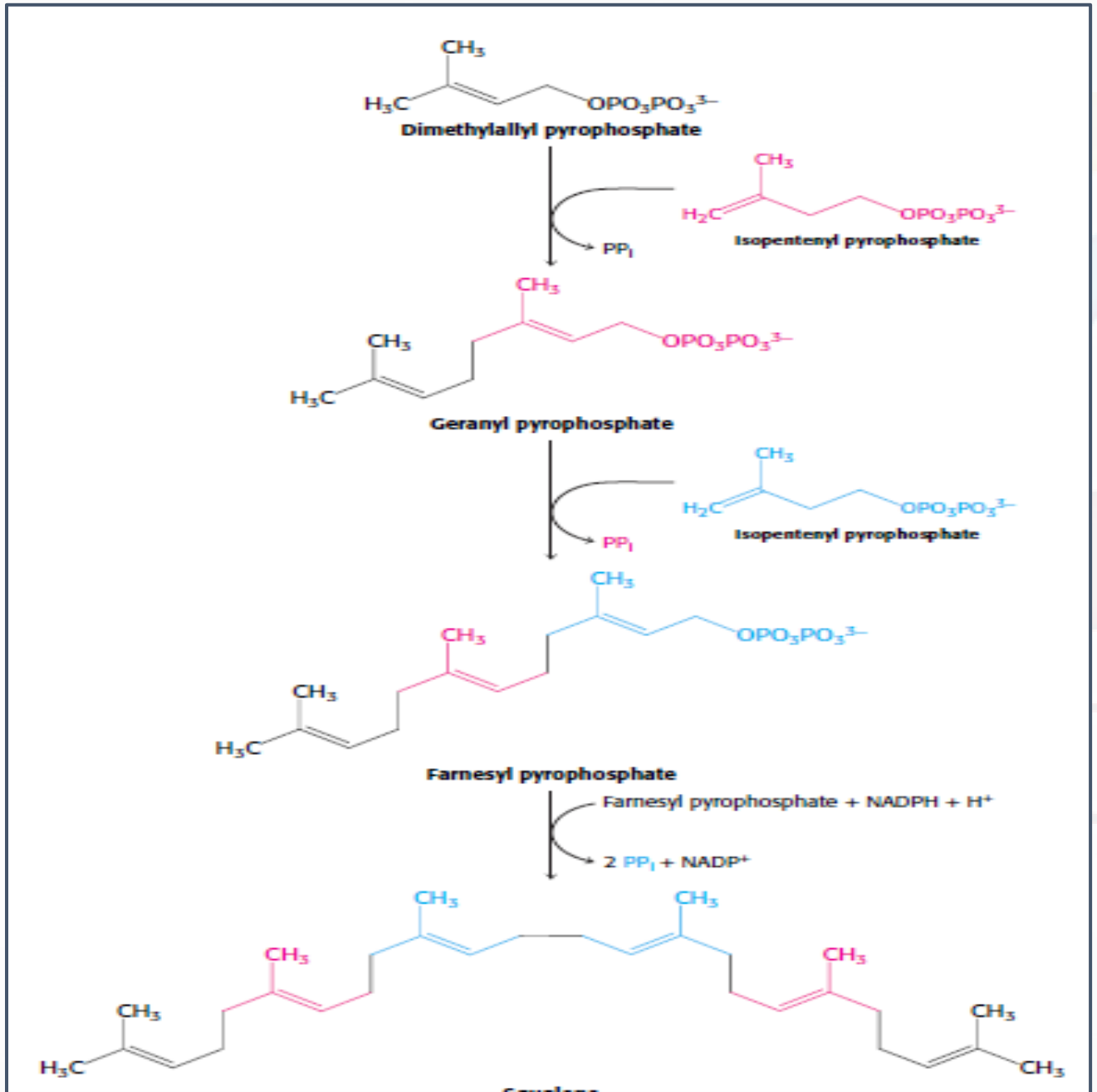
Figure 21-34 part 1
Lehninger Principles of Biochemistry, Fifth Edition

- This set of reactions starts with the formation of 3-hydroxy-3-methylglutaryl CoA (HMG CoA) from acetyl CoA and acetoacetyl CoA.
- This intermediate is reduced to mevalonate for the synthesis of cholesterol.



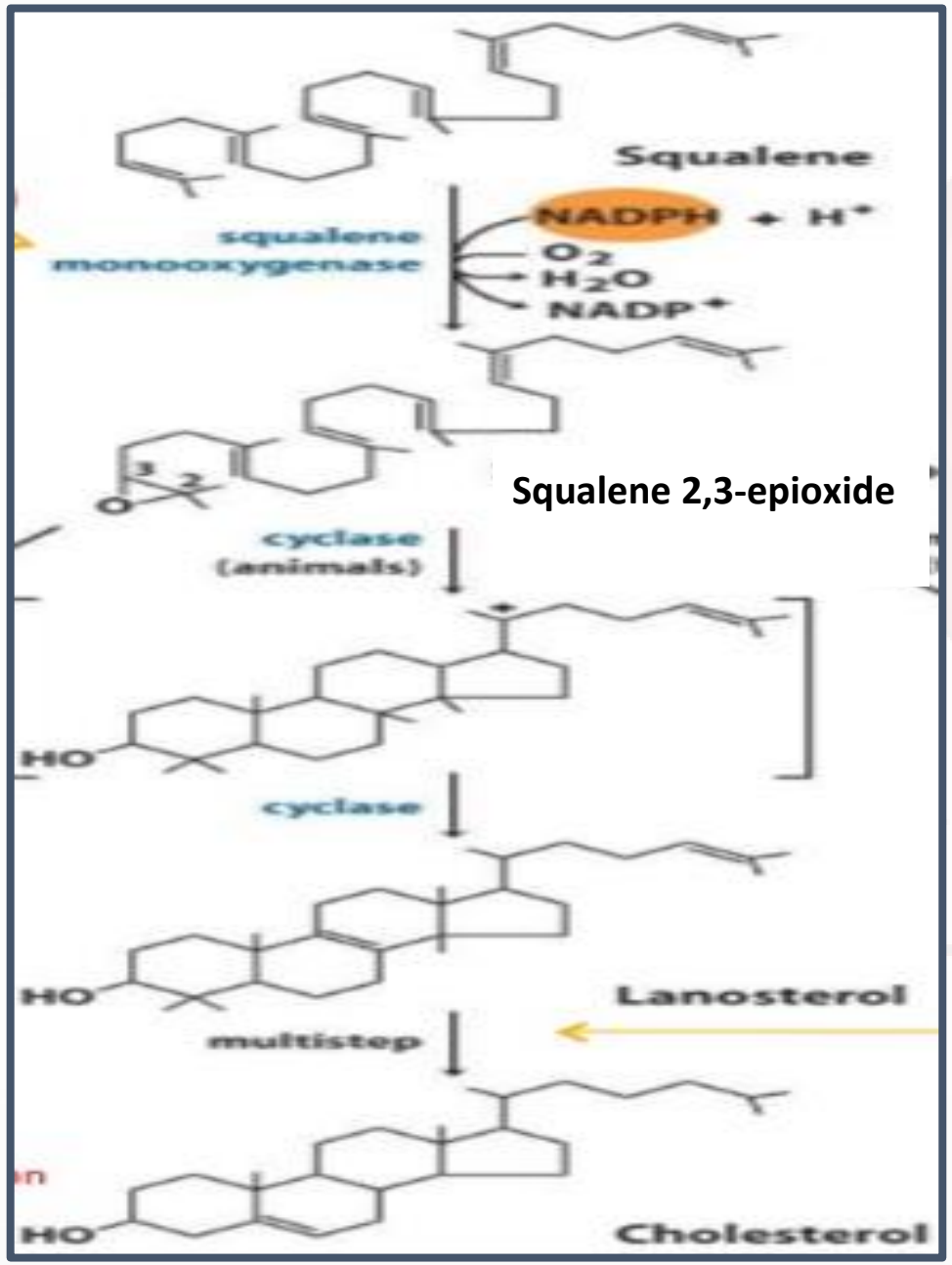
- Mevalonate is converted into 3-isopentenyl pyrophosphate in three consecutive reactions requiring ATP.
- In the last step, the release of CO2 yields isopentenyl pyrophosphate, an activated isoprene unit that is a key building block for many important biomolecules throughout the kingdoms of life.
- **Statins** are a widely prescribed class of drugs to lower cholesterol. Their mode of **action** is primarily via inhibition of HMG-CoA reductase, the rate-limiting enzyme in the cholesterol biosynthesis pathway.

Stage 2: The condensation of six molecules of isopentenyl pyrophosphate to form squalene.



- Two isomeric C 5 units (one of each type) condense to form a C10 compound: isopentenyl pyrophosphate.
- Isopentenyl pyrophosphate and dimethylallyl pyrophosphate condenses to yield geranyl pyrophosphate.
- Geranyl pyrophosphate condenses with isopentenyl pyrophosphate resulting C 15 compound is called farnesyl pyrophosphate.
- The same enzyme, **geranyl transferase**, catalyzes each of these condensations.
- The last step in the synthesis of squalene is a reductive tail-to-tail condensation of two molecules of farnesyl pyrophosphate catalyzed by enzyme **squalene synthase.**

Stage 3: Squalene cyclizes and the tetracyclic product is subsequently converted into cholesterol.



- Squalene is first activated by conversion into squalene epoxide (2,3-oxidosqualene) in a reaction that uses O 2 and NADPH.
- Squalene epoxide is then cyclized to lanosterol by oxidosqualene cyclase .
- Lanosterol is converted into cholesterol in a multistep process by the removal of three methyl groups, the reduction of one double bond by NADPH, and the migration of the other double bond

References:

Lehninger, Albert L., Cox, Michael M.Nelson, David L.**Lehninger** Principles Of Biochemistry. New York : W.H. Freeman, 2008.

Biochemistry. MLA. Berg, Jeremy M, John L Tymoczko, and **Lubert Stryer**. **Biochemistry**. 6th ed. New York, N.Y.: W. H. Freeman, 2006.