Organic Chemistry in Biology and Drug Development
Prof. Amit Basak
Department of Chemistry
Indian Institute of Technology, Kharagpur

Lecture – 61
Cholesterol Biosynthesis

Welcome back. We were discussing the Biosynthesis of Cholesterol. We discussed how the C 5 units are formed. The C5 units are basically two tautomeric forms- one is γ, γ-dimethyl allyl pyrophosphate and another is isopentenyl pyrophosphate.

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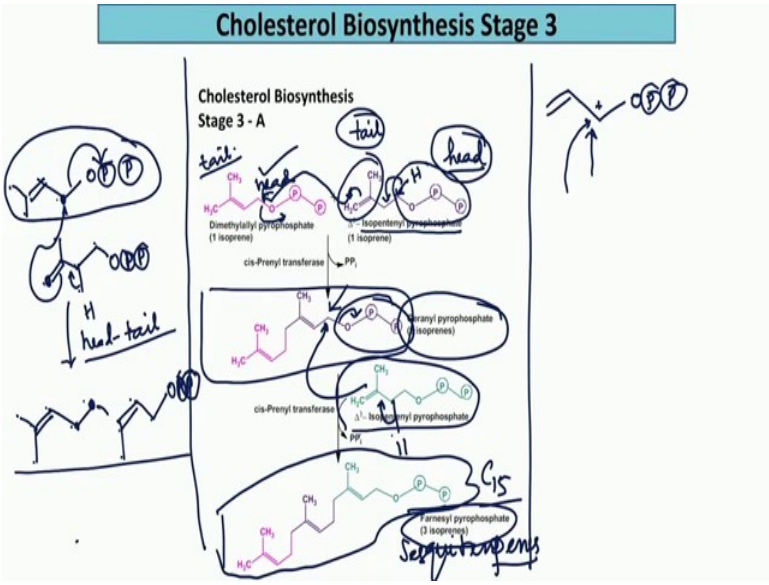

We have also identified the tail group and the head group. The head group of this diallyl pyrophosphate is facing to the tail portion of the isopentenyl pyrophosphate.

Now, this will be a very good leaving group because it is an allyl system. Allyl systems are very good leaving groups because S_N1 reaction will be very good because the cation is positively charged. Even it goes well for S_N2 reaction because these p orbital stabilize the developing orbitals with the nucleophile and the carbon. So, that is very reactive carbon. Hydrogen from here will activate this carbon. Mechanism is same as tautomerism where the hydrogen is lost. It activates this carbon towards having a

negative charge. It is a potential nucleophile. That now attacks the head carbon and kicks out the pyrophosphate. There is a head-tail combination.

We will get C-10 unit and it is called geranyl pyrophosphate. These are isoprene units. These things came from degradation of rubber. Here isoprene units are combining. So, it is said that it is a condensation of 2 isoprenes.

Geranyl pyrophosphate has a very good leaving group because this is again allyl to the double bond. So, another isopentenyl pyrophosphate by a similar mechanism can displace this and a compound of C15 unit is obtained. So, this is called farnesyl pyrophosphate; this is a sesquiterpene.

Geranyl pyrophosphate can have different isomers where the double bond changes position. They are called citral and you know citronellol are the constituents of the home disinfectant phenyl. The very good perfumes like geraniol, citral, and citronellol are actually differing from the position of the double bond.

Basically 3 isoprene units are doing S_N2 substitution to form C-15 unit. Now, the task is to join this C-15 unit into another C 15 unit.

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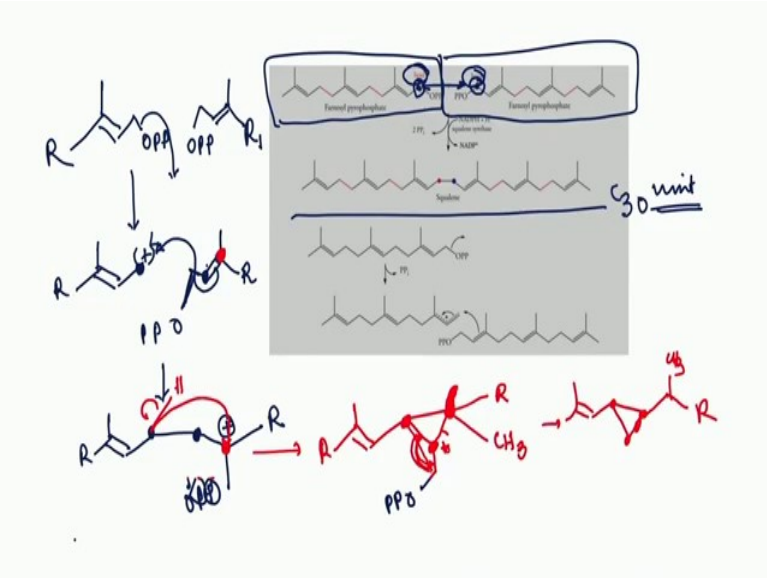

Then two farnesyl pyrophosphates combine with each other. This is also the head-tail combination.

Here two heads combine with each other. It was proved by labeling experiment. Because they use labeled carbon here and they found that the labels are actually this carbon-carbon bond.

The product is C-30 unit and it is called squalene.

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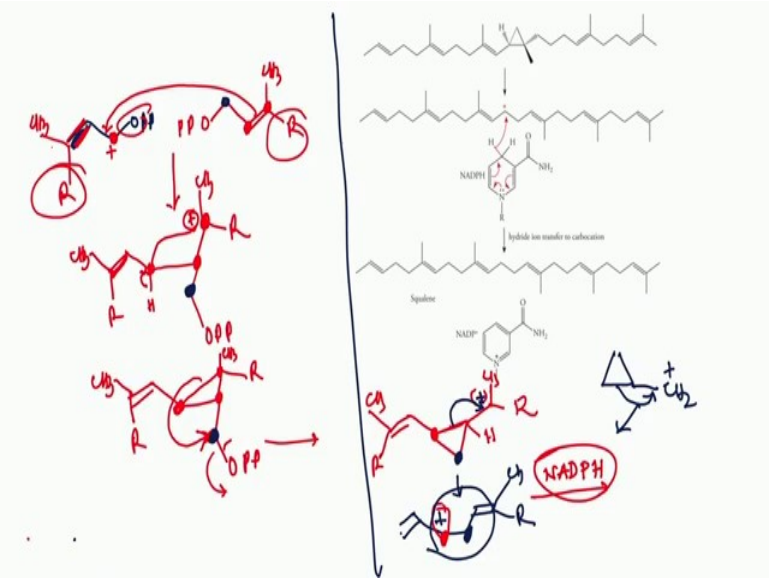

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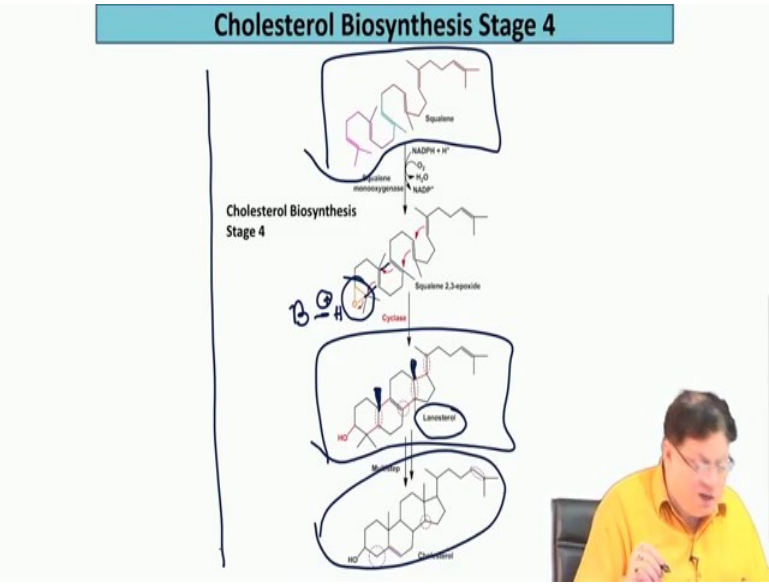

Now I will show the mechanism. Squalene is nothing but a long chain. It can fold into this fashion and the squalene forms an epoxide here. This is called squalene epoxide 2, 3 epoxide.

We will talk about the cascade or domino reactions. At first, an enzymatic acid *i.e.* B-H^+ protonates this epoxide. Epoxides are susceptible to acid catalyzed ring opening. So, it will open definitely from this side because that cation is stabilized.

So, now, this is going to attack here. First you form the ring. Then this is going to attack here and you form the second ring because when these double bond moves it forms a cation here. Then that double bond attacks here. It is a cascade reaction that forms a plus here. These attacks here and forms a plus here. Now these attacks here that forms the 5-membered ring. So, this is the first sterol which is called lanosterol.

This methyl is beta and this methyl is also beta. This stereochemistry is maintained. It is an extraordinary reaction. Lanosterol forms squalene epoxide and this is ultimately converted into cholesterol. How this squalene is formed?

Remember the structure of farnesyl pyrophosphate. We will write double bond and then OPP. Put R here and then it is a reaction between the head group. So, another OPP and then you have a double bond here and a methyl. This double bond also has a methyl here. It is like an S_N1 mechanism. The C-5 units were added by S_N2 mechanism. If it goes by S_N1 type basically you form the cation and this is also possible because this is a stabilized allyl cation. These double bond now will migrate like this.

Let us now discuss the head to head combination of farnesyl pyrophosphate to squalene. In one of the arm, the pyrophosphate leads generating a cation which is stabilized by the allylic double bond. Then there is this double bond which moves generating a carbon carbocation at this tertiary center and that forms a carbon-carbon bond. After seeing this positive charge hydrogen will lose from here and that anion quenches the carbocation and forms a cyclopropane ring.

Now, there is a rearrangement of the cyclopropane by kicking out this pyrophosphate. Now that carbon-carbon bond formation has taken place but in the process you have again created a positive charge.

A cyclopropylmethyl cation is generated and from this cyclopropylmethyl cation, homoallylic cation is formed by Demjanov rearrangement. So, basically you have a double bond, you have a methyl, you have a side chain, you have a positive charge. Now,

a NADH or NADPH dependent enzyme which is acting as a reducing agent delivers a hydride here. Thus homoallylic cation is reduced.

Just have a quick summary. At first, there is head-head combination. So, one pyrophosphate at generates a cation. The double bond attacks the cation. Then hydrogen is lost forming a cyclopropane. Then there is a rearrangement of the cyclopropane generating a cyclopropylmethyl cation. So, that will definitely open up to form a homoallylic cation and that homoallylic cation will be reduced by NADPH. Two squalenes are combined by this fashion.

The cascade reaction gives you the first steroid lanosterol and ultimately cholesterol is formed.

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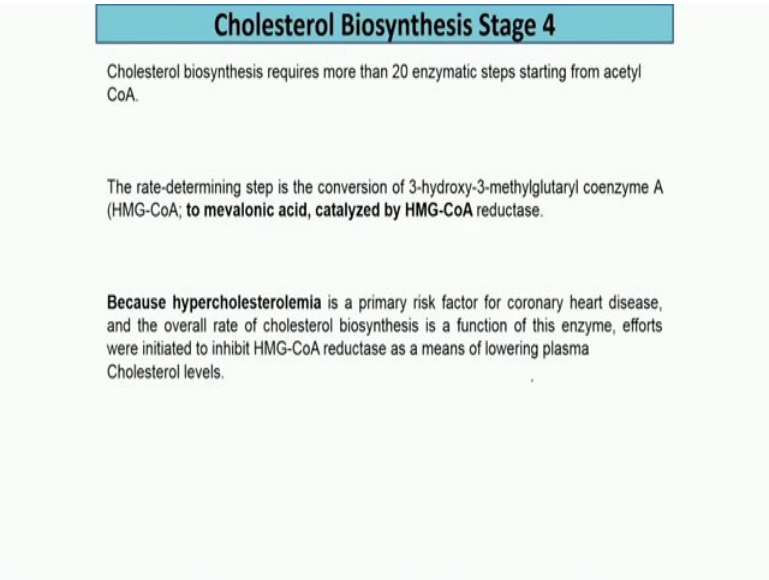

So many steps are involved in the biosynthesis of cholesterol. Now how can we stop or modulate the biosynthesis of cholesterol? Scientists have found that the rate limiting step of this biosynthesis is the formation of mevalonate from HMG-CoA.

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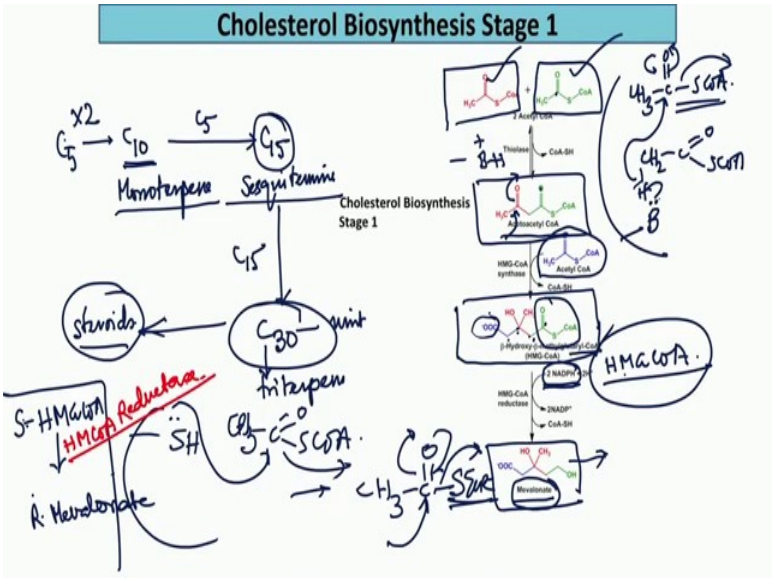

In the rate limiting step, S-HMG-CoA is reduced to R-HMG-CoA by the enzyme called HMG-CoA reductase. So, what you need a reversible inhibitor of HMG-CoA reductase. Fortunately, nature has provided us these compounds to rescue of mankind.

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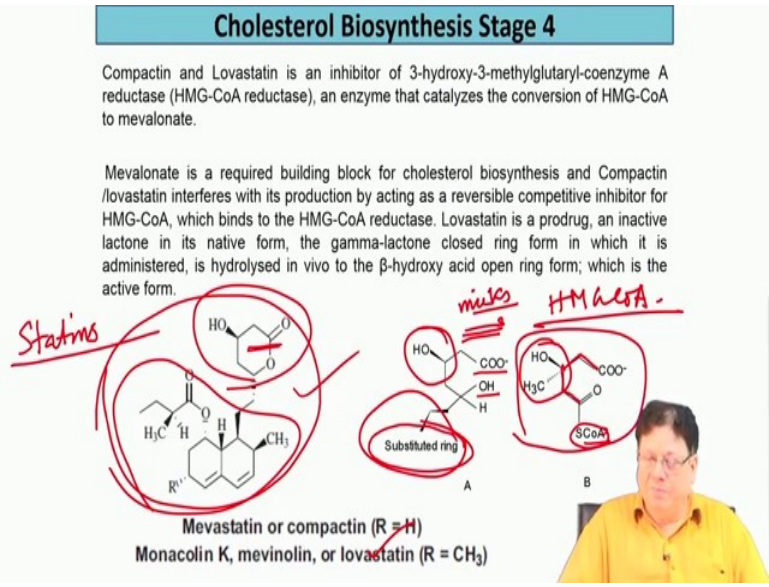

These compounds are collectively called statins and you will be surprised to know that these statins are the largest selling drugs in the world. They work remarkably well. If you have the hypertension you can always control the cholesterol by taking the statin. Several statins are now available. But, remember these are natural products and there are some

semi-synthetic statins. Semi-synthetic means you change the natural product at some places by synthetic methods.

If you look at the statin, the statin has this type of bicyclic decalin type system and hydroxy delta lactone. The question is why it will act as a reversible inhibitor? If you open this lactone by hydrolysis it will have CO_2 minus OH and on this side you have this substituted ring pattern. If you take HMG-CoA the substrate is going into mevalonate. This is HMG-CoA and CoA is a very large molecule.

This CoA part is being mimicked by the substitute at ring but the other component is so similar. You have this tetrahedral and you have this CH_2CO minus. So, basically that mimics the HMG-CoA as simple as that. All this statins work by that principle and they are extremely good. They are reversible in nature and now there are different compounds like lovastatin, rosuvastatin available. See, once first generation compounds come then the second generation third generation comes. Remember these are the largest selling drug in the world today because it is a lifestyle disease.

This is all about the cholesterol biosynthesis and hypercholesterolemia means high cholesterol content. So, that ends up. There are many drugs which I have not been covered. I know that but this is the bridged course. We have tried to cover many topics which are extremely important in daily life. We tried to give you a glimpse of the development of drugs.

There is organic chemistry in the entire course like any antibacterial compounds, their mechanism of action, beta lactamase reaction, beta lactamase inhibitors, neuro transmitters, angiotensin converting enzyme inhibitor - it comes down to writing the molecules to see what is the nature of the active site and the interaction is studied. But, it is basically the flow of electronic and steric factor in organic chemistry that goes into the biology.

We will take few extra classes to revisit the courses and will discuss some problems.