Bioinorganic Chemistry
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Lecture-18
Life with Oxygen: Heme Oxygen activity

Hi everybody. Welcome back to the short course of Bioinorganic Chemistry. I have been discussing on the Life with Oxygen in my last 8 lectures. I have discussed in my previous lectures, on how the great oxidizing power of dioxygen is utilized in respiration to produce huge amount of energy. During such respiration process, O_2 is fully reduced to water which would require four protons and four electrons.

However, incomplete reduction of dioxygen produce reactive oxygen species such as superoxide, peroxides and OH radical which are indeed extremely poisonous for our body. Our mother nature has designed superoxide dismutase, catalase and peroxidase which not only destroy those reactive oxygen species but also converts them to something extremely useful for us.

I have then discussed, about the reaction of dioxygen with organic substrates catalyzed by oxygenase enzyme, in which oxygen atoms from dioxygen are incorporated into the final oxidized products that are very useful for our daily life. I also have discussed about various dioxygen carrying proteins in biology. And highlighted how the beautiful design principle adopted by our mother nature, control reversible binding of dioxygen in these proteins. Today I will talk about heme oxygenase which is indeed responsible for the decomposition of the red blood cells, in our own body.

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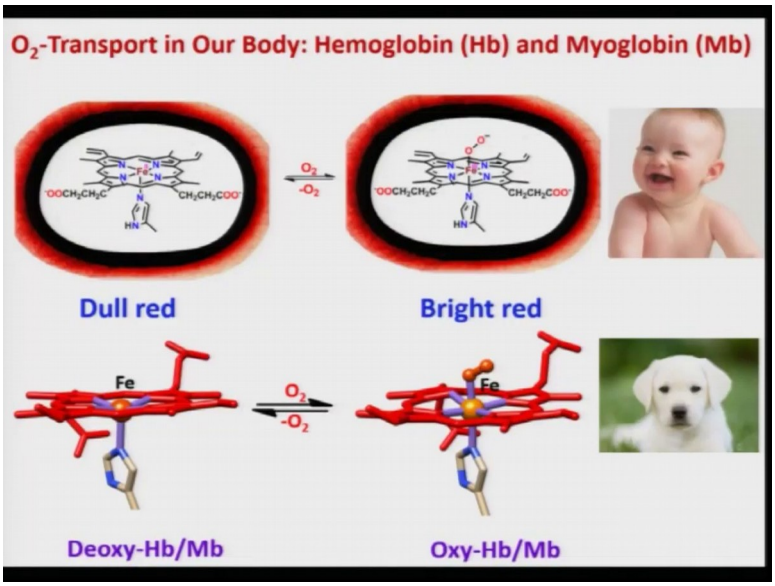

We have discussed earlier, that hemoglobin and myoglobin are responsible for dioxygen transport and storage respectively in our body. In the deoxy form iron center is five coordinate and in high spin state. Once dioxygen binds to iron center oxidation state of iron changes from +2 to +3, while dioxygen becomes superoxide O_2^-; this also results in a sharp color change from dull red to bright red. X-ray structures of both deoxy and oxy form are shown over here.

These two processes are completely reversible like when dioxygen binds to iron center it forms Fe(III)-O_2^-. And when it leaves the dioxygen, it goes back to its initial state deoxy hemoglobin or myoglobin.

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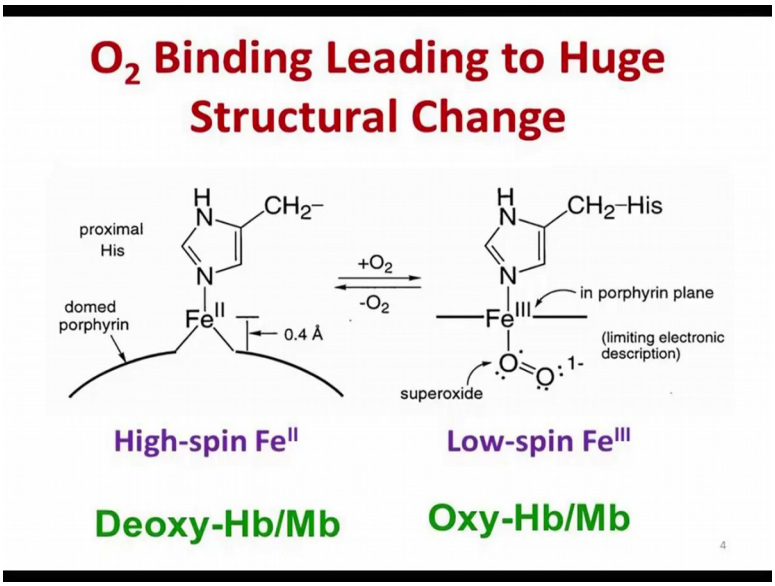

So, this is what is happening like Fe(II) converted to Fe(III)-O_2^- and comes back to Fe(II). And there are of course a conformational change, as we have already discussed that high spin Fe(II) converted to low spin Fe(III) upon dioxygen coordination and then goes back. So, during this process this is what is happening all the time.

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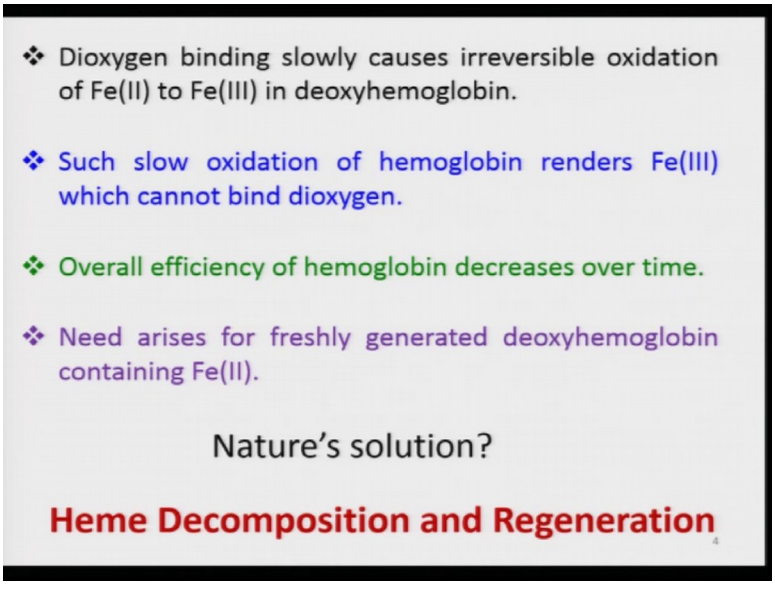

Now this dioxygen binding slowly causes irreversible oxidation of Fe(II) to Fe(III) in deoxy hemoglobin. Once they are doing too many cycles, slowly that iron center getting oxidized. This slow oxidation renders Fe(III) which no longer can bind dioxygen; once it

forms Fe(III) it cannot binds a neutral molecule like dioxygen. Its have to be something like anionic ligand like cyanide, azide, but it cannot bind dioxygen reversibly anymore.

So, overall efficiency of hemoglobin decreases over the time. So, there is a need for freshly generated hemoglobin containing Fe(II). And what's nature solution for it! You will be surprised to see that the solution is in decomposition and regeneration of the heme.

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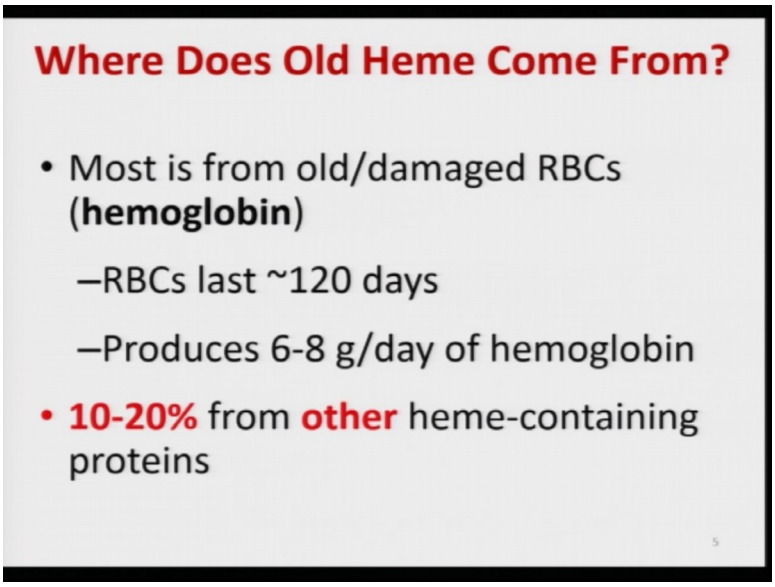

Now, question is where does old heme come from? Mostly it is from red blood cell hemoglobin. As all of us know that the red blood cell has a lifespan of only 120 days, so after that it had to be decomposed. And, basically every day it produces around 6 to 8 gram of hemoglobin, and another 10 to 20 percent of these heme center comes from other heme containing proteins.

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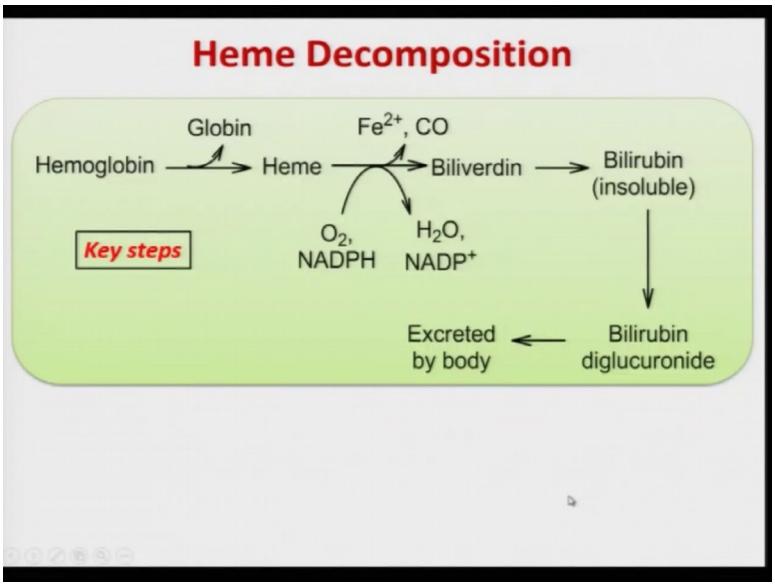

So, these heme centers actually undergo a decomposition, and nature has designed an enzyme called heme oxygenase in order to do this. So, what is happening as you can see that key steps are shown over here and this converts to heme centers upon removal of globin chains. This heme center actually converts to biliverdin by using oxygen as a oxidant and also NADPH which is a reducing agent. And during this process water is being formed and another very interesting gas carbon monoxide is being formed.

Please note that, carbon monoxide we have seen earlier we all know that it is a poisonous gas but that carbon monoxide also being produced in our body. And this carbon monoxide although it is a very small concentration this is very important and it has been said that this probably responsible for signal transfer in our body.

Now, this biliverdin converts to bilirubin which is yellow in color which is, however, insoluble in nature. It had to solubilize first before it can excrete from our body and for that it conjugate with glucuronic acid and formed a water soluble molecule bilirubin diglucuronide and thereby it excrete from the body through urine. So, this is what is happening all the time within our body. And heme oxygenase is basically doing the key role in this heme decomposition process.

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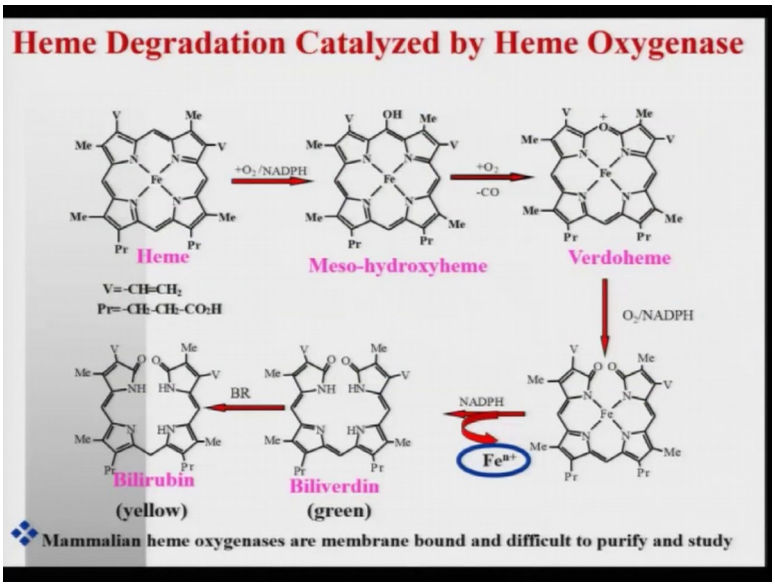

Now, this is how heme undergo decomposition, this heme in presence of oxygen and NADPH, we call it as a coupled oxidation; because oxygen is oxidant and NADPH is reductant. So, when both used together it's called coupled oxidation. So, this heme first convert to meso-hydroxyheme. You see that there is one hydroxy group, which is added at the meso carbon position and this molecule is known as meso-hydroxyheme. Now this meso-hydroxy heme is highly reactive towards dioxygen, it immediately reacts with dioxygen and convert to verdoheme as you can see upon liberation of carbon monoxides.

And this verdoheme again undergo a ring cleavage exercise, in presence of oxygen and NADPH, converts to iron-biliverdin complex. And as you can see that ring is being cleaved now. The terminal carbons are converted to keto over here, And then this iron-biliverdin complex under grow demetallation and this converts to biliverdin which is green in color and then biliverdin reductase converts to bilirubin.

However, during this process there are two things to be noted. The first step is that formation of meso-hydroxyheme which is highly reactive towards oxygen, and responsible for its decomposition to biliverdin and bilirubin. And this bilirubin after conjugation with glucuronic acid excretes through the process. Now another interesting aspects of this reaction is that this iron is getting recycled and reused in heme formations. Please note that there are only 2- 3 percent of the iron we take every day, comes from the

diet, and rest 97-98 percent comes through this recycle process. Still many of us are iron deficient, mostly this woman are iron deficient.

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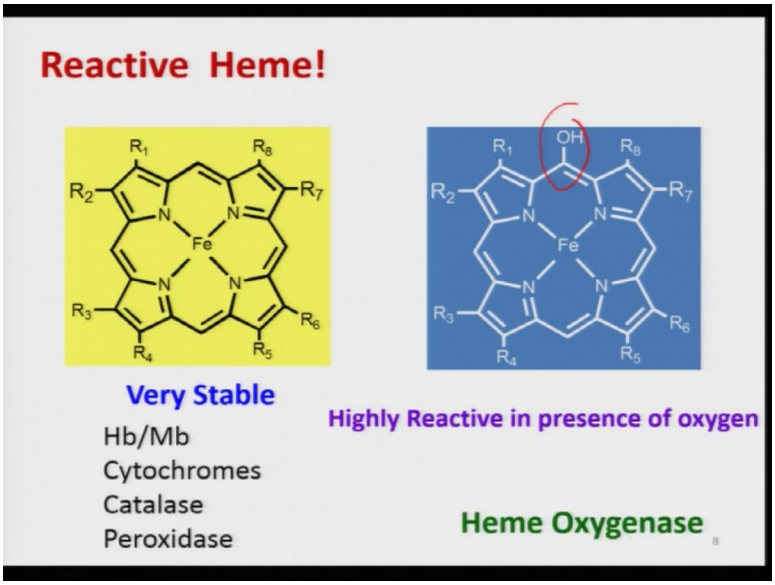

So, interestingly as I have said that the heme centers which are very stable, and this has been used extensively by nature, in a large variety of enzymes and proteins. For example, catalase, peroxidase, cytochrome P450, hemoglobin, myoglobin, cytochromes large varieties of enzymes proteins. However, when it forms this meso-hydroxylation keeping everything intact, it immediately reacts with dioxygen. And the porphyrin ring undergo a cleavage immediately to form bilirubin, this is being done by hemeoxygenase.

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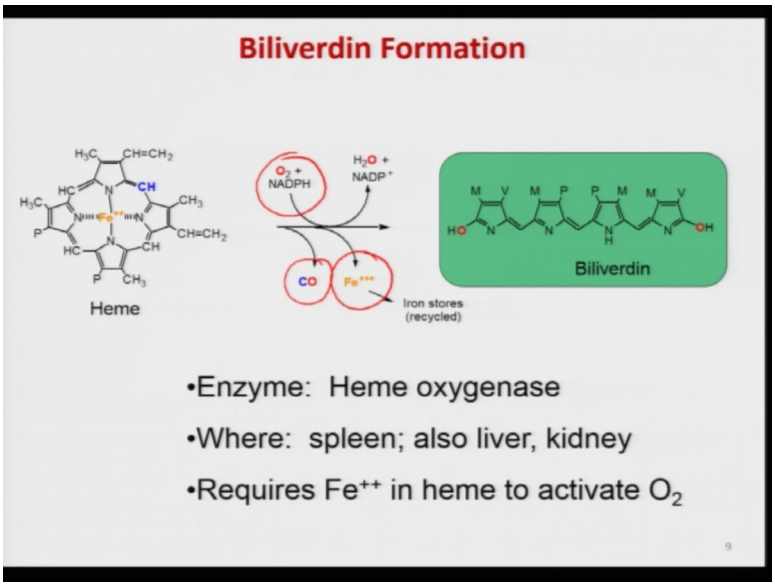

As I have just discussed that heme converted to biliverdin, which is a not a macrocycle; it is an open chain structure, but highly conjugated. And this is forming out of dioxygen and NADPH, which eventually converts to NADP, and produce water liberates carbon monoxides. And of course, as I have just said that iron is getting recycled during this process.

So, this is very important and this recycle around 98 percent of this iron which we require regularly in our day to day activity. And rest 1- 2 percent comes from the diet we take every day. The enzyme which are responsible for this transformation is hemeoxygenase. And we find this in spleen and also in liver, kidney and it requires iron too in heme center to activate dioxygen.

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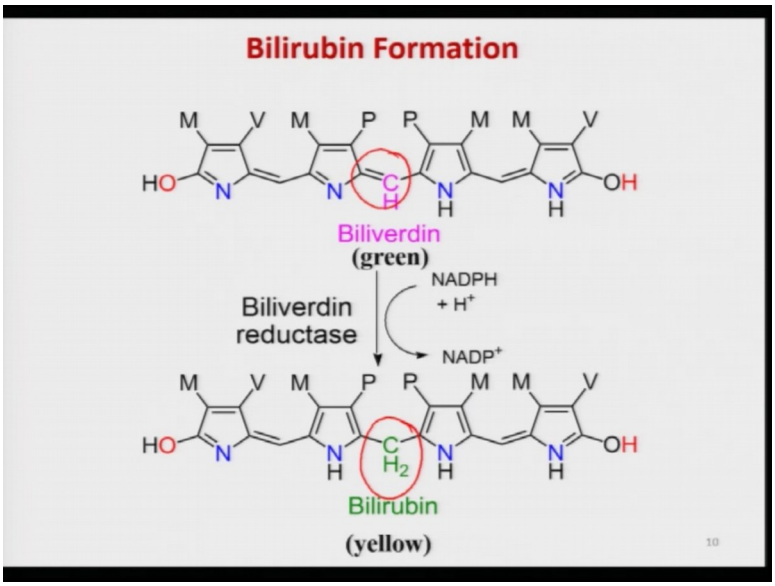

This biliverdin a conjugated open chain structure; it converts to bilirubin, and a biliverdin reductase is responsible for this transformation. So, this double bond is further reduced and -CH converted to -CH_2, and there is a immediate color change. Biliverdin is green and bilirubin becomes yellow.

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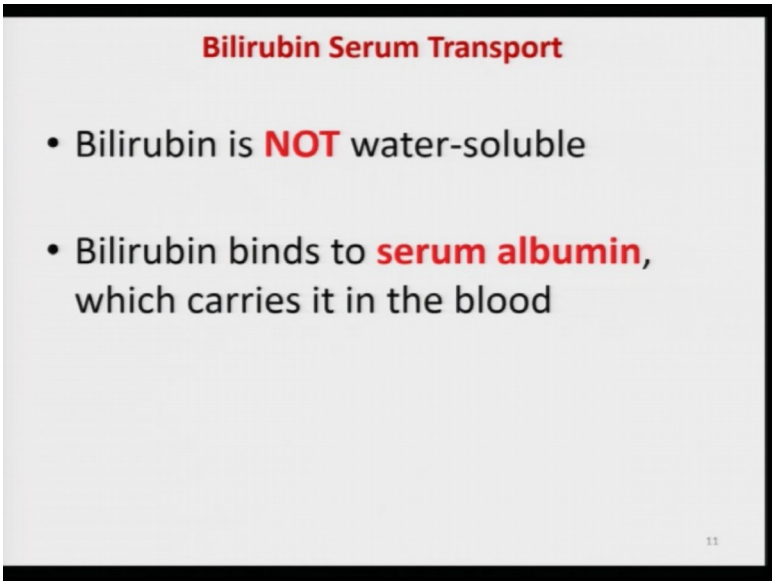

Now this bilirubin is not water soluble, this is a big problem. And this bilirubin binds to serum albumin which carries it in the blood.

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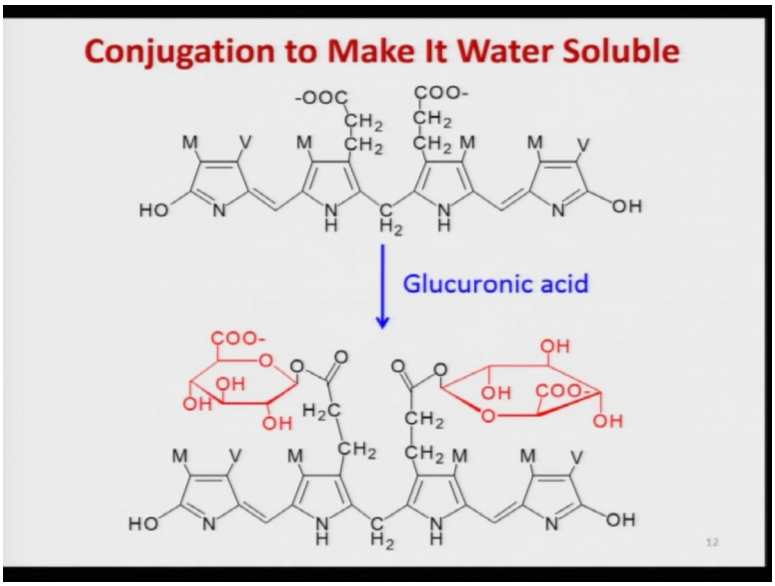

Now, it has to make water soluble, otherwise how it excretes from our body. Bilirubin after conjugation, glucuronic acid converts to a conjugates and it becomes now water soluble and it can excrete through our body.

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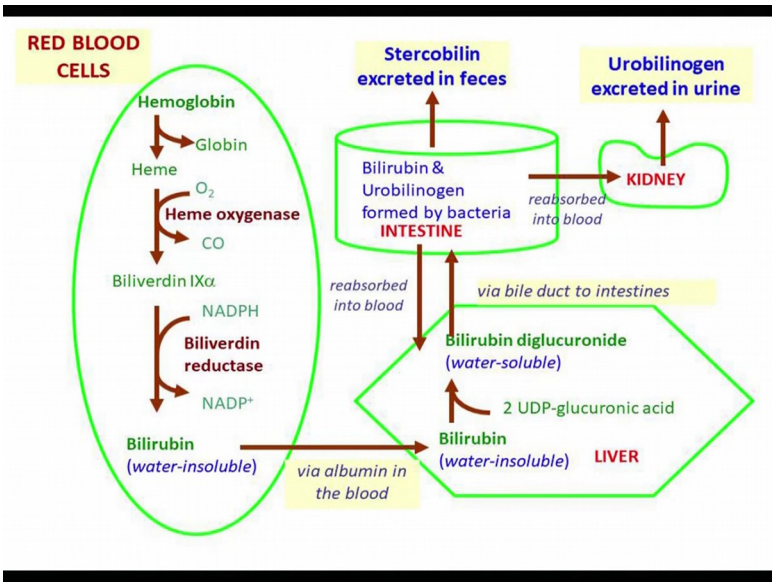

So, if you look at carefully the red blood cell, which is basically the hemoglobin; after removal of the protein chain globin, this heme unit undergo a cleavage by hemeoxygenase. It with the help of oxygen and NADPH which eventually liberates

carbon monoxides which supposed to be highly poisonous. But the small amount of carbon monoxide is highly beneficial for our body it is responsible for various activity.

So, during this process the heme undergo a ring cleavage process, converts to biliverdin. And this biliverdin converts to bilirubin, which is yellow in color and biliverdin reductase is responsible for this transformation. However, as I have just said that bilirubin is indeed water insoluble. It goes to liver and still water insoluble and then after conjugation with new glucuronic acid, this molecule bilirubin becomes water soluble.

And then it goes to intestine, and bilirubin and urobilinogen is formed which actually reabsorbed into the blood. And also it excrete from our body through urine and also it deposits on the face. So, you can see the spots on the face and this is basically stercobilin and the molecule which excretes in urine is known as urobilinogen.

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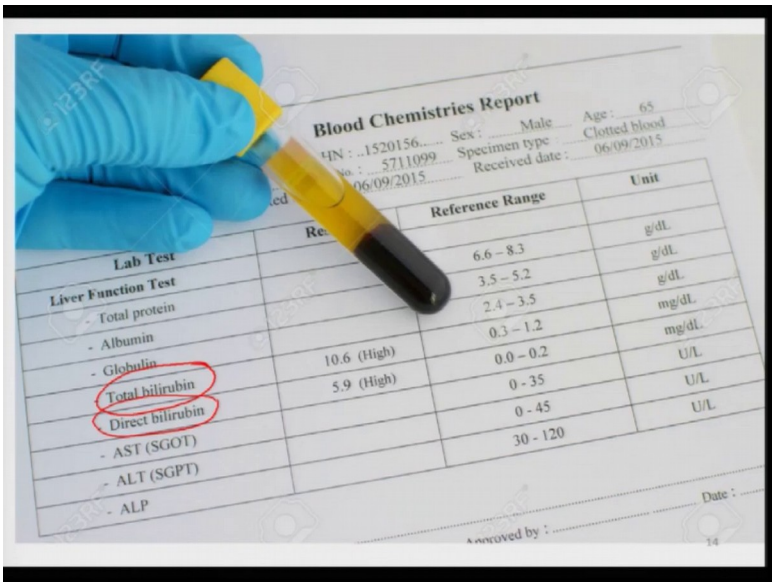

Now, whether you have high level of bilirubin how you know that? Now if you go to a doctor, then the doctor will ask you to test the blood to do the two things, one is how much you have the total bilirubin and direct bilirubin. So, from the values you will get to see that whether you have bilirubin excess in your body.

So, actually this blood is getting decomposed to bilirubin and this bilirubin excretes to the body. This is a spontaneous process all the time it has been happening. But

sometimes if the liver is not very strong what is happening? There can be more bilirubin in your body and that creates lots of problem in our body.

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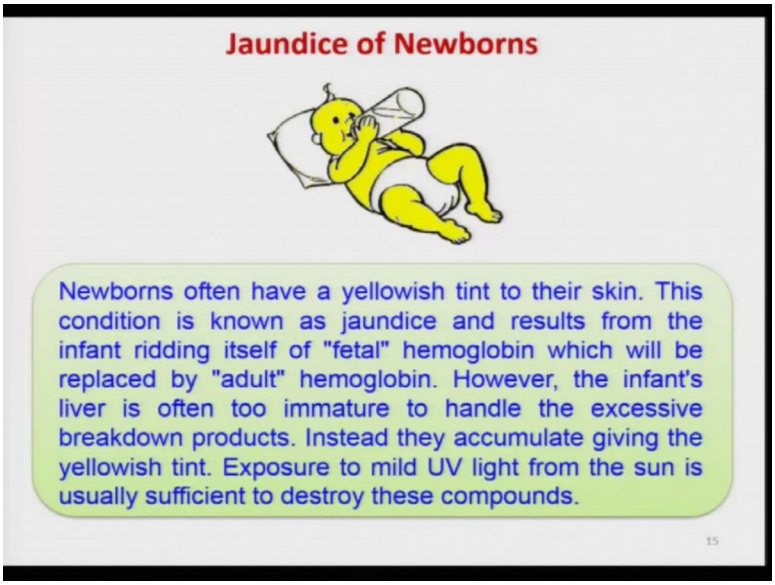

Particularly this is very common for a newborn baby. Newborn baby mostly get a yellowish tint to their skin and this is called newborn jaundice. And why this is happening? When the newborn baby take birth, the fatal hemoglobin need to be converted to a adult hemoglobin. So, fatal hemoglobin will convert to adult hemoglobin and so all the hemoglobin during short period of time will be converting to adult hemoglobin.

And if the liver is not very strong, what would happen that they cannot handle so many bilirubin. And there will be some deposition on the skin and they develop a disease called jaundice. So, it is very common for the newborn baby and ofcourse, upon exposure to mild UV light from the sun it is easily sufficient to destroy this compound. That is the reason in the village you see that mother they expose their baby to the sunlight.

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Now, you see that if you have excess bilirubin in your body, it creates a disease called jaundice. You can see that a person having jaundice in a normal person, and you see that his skin color turns yellow. Particularly these eyeballs are converted to yellow and the baby also turns yellow so, this is very very common.

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And if you go to a doctor like for the newborn baby jaundice, its very easy to cure. If you go to a hospital, so, what they do? They exposed the kid with blue light. So, it's called

blue light treatment. So, you see that the nurse is very happy to see that these kids are getting exposed to blue light and thereby bilirubin is getting destroyed.

And they are also earning lots of money the nursing home hospitals and doctors also earns lots of money out of that, but it is very simple. Of course, there can be some complications, you have to go to the doctor. In the village mostly the mother they expose their kid to sunlight and that UV light is sufficient to destroy this excess bilirubin which is being deposited on the body skin.

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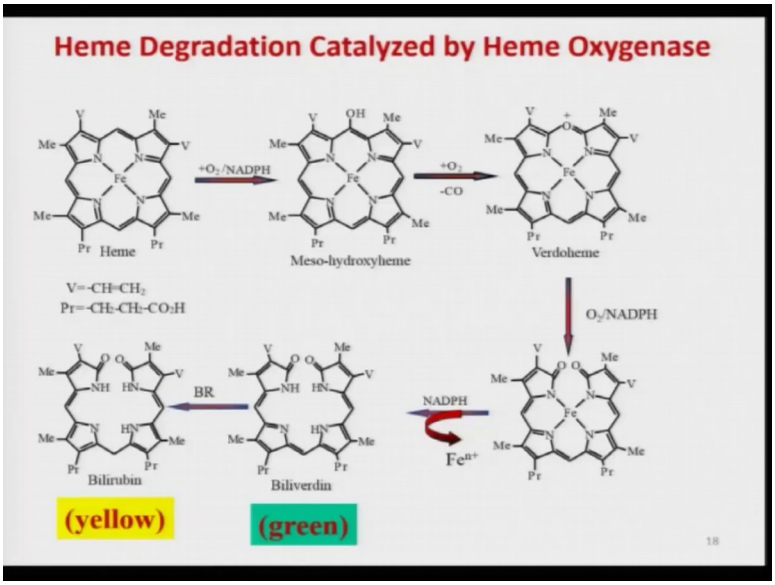

Now going back to this heme degradation process, which is catalyzed by heme oxygenases, I have just discussed. So, heme centre undergo decomposition first formation of meso-hydroxyheme. The heme is dark red in color and then the verdoheme, then iron-biliverdin complex. Then, after demetallation it converts to biliverdin which is green in colour. And this biliverdin converts to bilirubin which is yellow in color.

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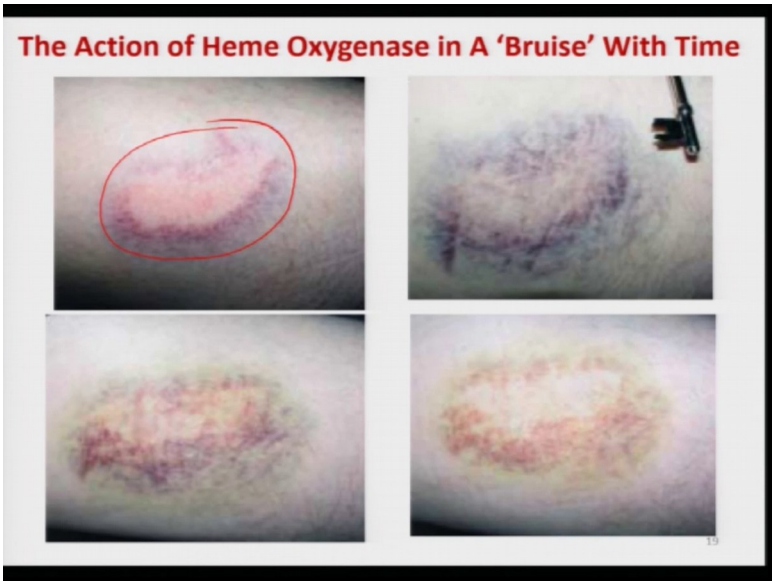

So, action of heme oxygenase, it can be clearly visible if one see the bruise with time. Say if you get a fresh bruise, what would happen? It will be red in color. It is happening because of the red blood cell. So, heme oxygenase comes into picture. This red blood cell getting converted to verdoheme, then biliverdin, which is green in color. And then slowly slowly, it converts to bilirubin which is yellowish in color.

After several days bruise completely gets back original skin color with time. So, the action of heme oxygenase can be clearly seen if you follow a bruise changing the color with time. And this bilirubin actually is strongly antioxidant and thereby it is getting cured automatically. If you have small bruise, you generally need not to visit doctor since it automatically gets cure due to the formation of bilirubin which is indeed a natural antioxidant.

You do not need to use any ointment or medicine normally, indeed this is what is happening in village where doctors are not easily available and indeed no medical facilities are there. However, if you go to the doctor, the doctor will prescribe some ointment which is having some antioxidant that is indeed doing the same job as bilirubin does. However, bilirubin is a natural antioxidant produced in our body for free which helps to cure the wound faster.

In conclusion, I have discussed today about the heme degradation process catalyzed by heme oxygenase. While oxygen binding it completely reversible in our body, Fe(II)

centers in deoxy form of hemoglobin and myoglobin also converts to Fe(III) slowly with time by oxygen. Thus, the overall efficiency of the protein decreases over time.

Nature, therefore designed heme oxygenase to recycle the red blood cell which have lifespan of only 120 days. Bilirubin is formed in the heme degradation process which then excreted from our body while iron getting recycled. This has been a very spontaneous process and happening all the times in our body. However, if there is an imbalance, we will then have several diseases such as jaundice, in which yellow bilirubin is deposited on the skin and the body color turns yellow.

In my next two lectures I will highlight the importance of inorganic elements in medicines. Metal ions play important role in biological processes; you will then see how inorganic chemistry contributes towards such growth.

Thank you.