Introduction to Organometallic Chemistry
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Lecture - 39
Medicinal applications of Organometallic complexes

So, organometallic chemistry is extensively used in the industry in catalysis. However, one often wonders whether it has any implications for everyday life.

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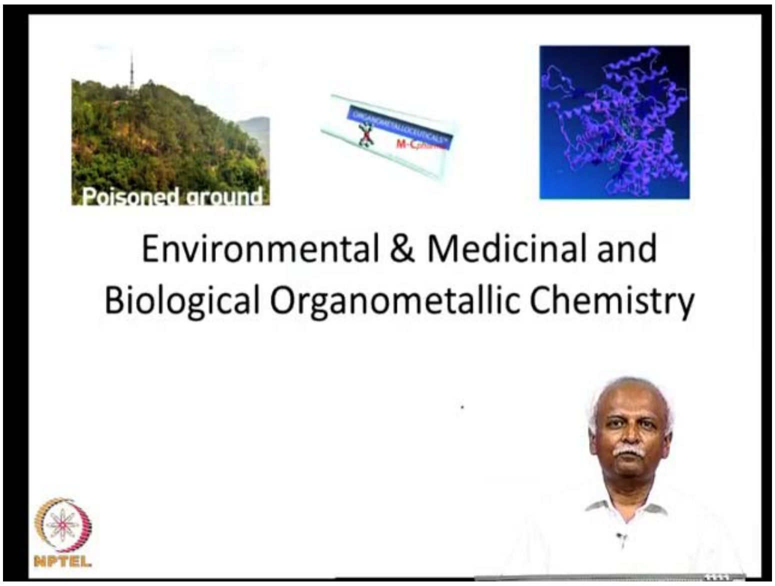

Environmental & Medicinal and Biological Organometallic Chemistry

And today in this lecture, we will consider some aspects which touch our day to day life. And there are three aspects that I want to talk about. One of them is the environmental concerns of organometallic chemistry, and the second one is a biological aspects of organometallic chemistry, and lastly medicinal aspects of organometallic chemistry. In this world today, we often encounter the question is it safe, is it environmentally safe to have these compounds in the laboratory, and if they are released into the environment what would happen to them. So, it is important for us to look briefly at some concerns that we might have.

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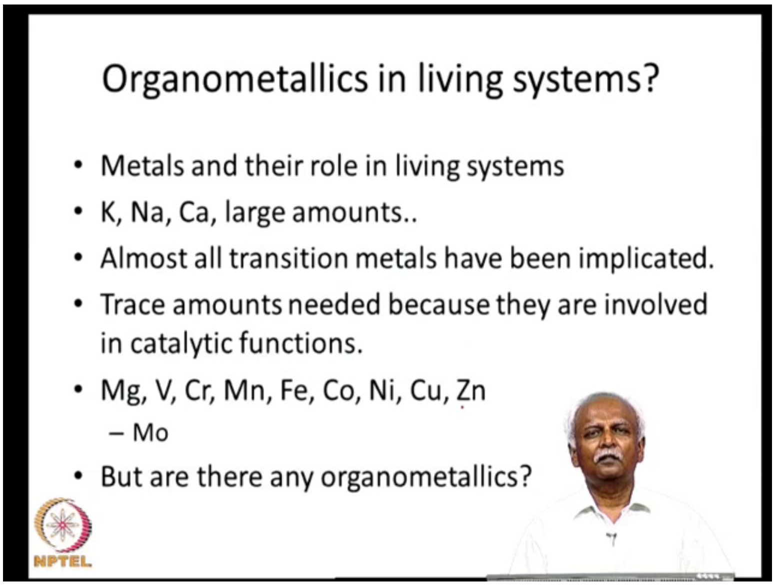

Organometallics in living systems?

- Metals and their role in living systems
- K, Na, Ca, large amounts..
- Almost all transition metals have been implicated.
- Trace amounts needed because they are involved in catalytic functions.
- Mg, V, Cr, Mn, Fe, Co, Ni, Cu, Zn
  - Mo
- But are there any organometallics?

First we will look at biological systems. Are organometallics involved in living systems? It was only recently that people realized that metals have an important role to play in living systems in cells and in biology. It is obvious that people are already aware of the fact that sodium potassium and calcium are there in large quantities in many living systems, but as detection techniques improved. It was obvious the transition metals are often essential for the living systems as well even though they are not found in large amounts. And that is because they are involved in catalytic functions they are not involved in structural roles in many cases they are involved in catalysis.

So, it is important that they are there in the body and in the right amount. If you look at some of the elements that are needed apart from the elements the metals that are needed in large amounts you encounter mostly the three d elements. Vanadium, chromium manganese and up to zinc and probably iron and zinc being there in the largest quantities.

Surprisingly, molybdenum which is there in the fourth row is also involved in living systems although to a lesser extent. So, these are transition metals the metals which are involved in living systems, but what about organometallics that was a question that we asked in the beginning of this projection. And the answer to this question is actually yes there are some organometallics systems that are found in biological systems.

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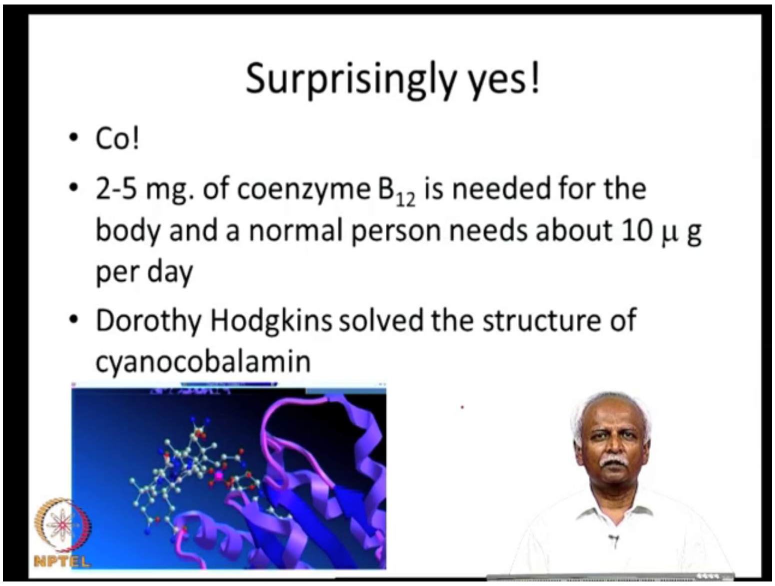

Surprisingly yes!

- Co!
- 2-5 mg. of coenzyme B_{12} is needed for the body and a normal person needs about 10 μ g per day
- Dorothy Hodgkins solved the structure of cyanocobalamin

And surprisingly the element that is found which exhibits some organometallic chemistry is cobalt. And that is cobalt with surprise note and not cobalt one. About 2.52 to 5 milligrams of cobalt is there in the body and a normal person needs at least 10 micrograms of cobalt per day. It was only recently relatively recently the Dorothy Hodgkins solved the structure of cyanocobalamin. The picture of the protein along with this coenzyme in the cyano form is shown for you as a projection here.

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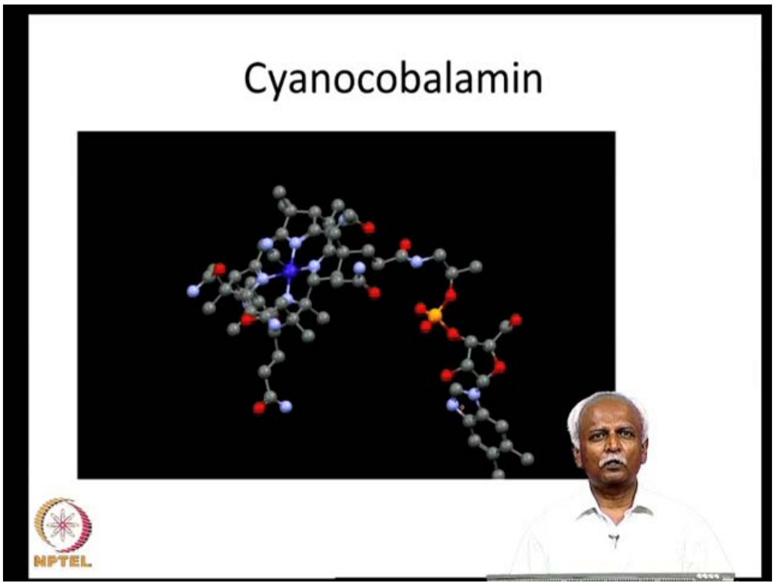

Cyanocobalamin

Let us take a closer look at it here is the structure of the cyanocobalamin. The co factor that is essential for some enzymes to function and you will notice that cobalt, which is pictured as a blue metal in the center of this corrin ring is attached to a cyano group. Now, the organometallic chemistry that involves cobalt and the cobalamin here is not necessarily that of the cyano group, but it has often other groups attached to the cobalt as well and we will look at this in a moment.

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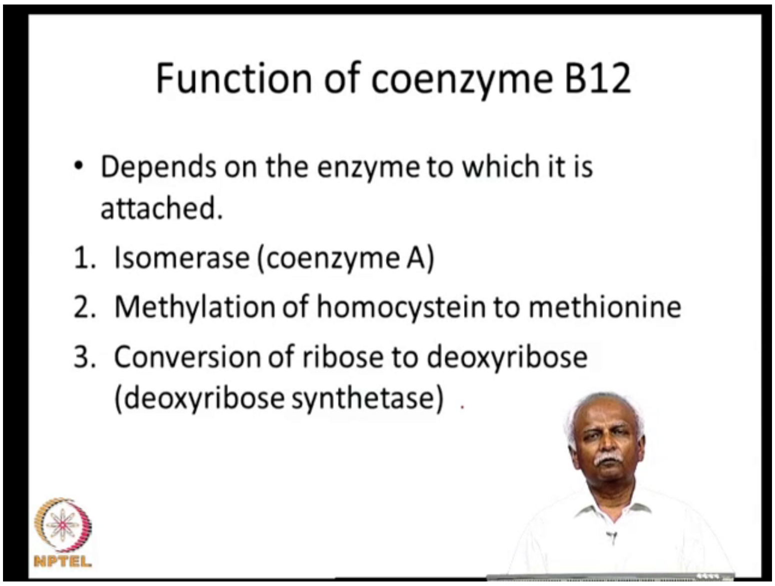

Function of coenzyme B12

- Depends on the enzyme to which it is attached.

1. Isomerase (coenzyme A)
2. Methylation of homocystein to methionine
3. Conversion of ribose to deoxyribose (deoxyribose synthetase)

The function of the coenzyme depends on the enzyme to which it is attached. So, it is surprisingly this coenzyme is found attached to different enzymes, and their functions are also different. So, in spite of the fact that the structure of this coenzyme is identical in all these enzyme environment. The enzyme forms different functions and the cobalt has different groups attached to it according to the need of the enzyme. The three major functions, which I have listed for you here one of them is a isomerism and that is where it is attached to coenzyme a it is attached to an enzyme which carries out isomerization.

Where a group is transferred to one group attached to a carbon is a transferred to an adjacent carbon. So, there is another system which we shall see shortly, where it does a methylation function. And there the cobalt has got a methyl group attached to it. Lastly it also has a de-oxygenation function. It converts ribose to de-oxyribose as you can see this is an extremely important function because this is involved in de-oxyribose synthesis. And you need RNA as much as you need DNA in the living system. So, the coenzyme

B12 is an extremely important a coenzyme and cobalt is absolutely essential for the body although it is present in such small quantities.

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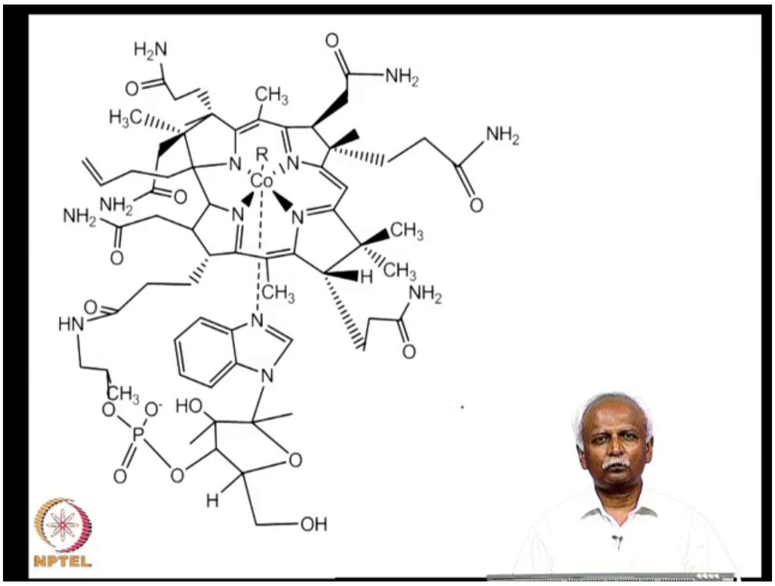

Now, here is a closer look the line diagram of the coenzyme. And you can see that the corrin ring has essentially four nitrogen. One of them is from a saturated ring and so it is an anionic ligand which is coordinated to the cobalt. And the four nitrogen are in a square planar environment approximately square planar environment and cobalt itself is in the plus three oxidation state. And the lower half of the cobalt shown in dotted line is a bond to a histamine nitrogen. That is responsible for having an approximately octahedral environment because on the top you have this R group.

Which I shall mark for you right here this R group which is the variant in various coenzymes in various forms of the cobalamin, you find different r groups which are present in this enzyme, but rest of the groups that are present are the same. And so the function of the cobalamin really depends on what is present in this epical site of the cobalt three plus ion.

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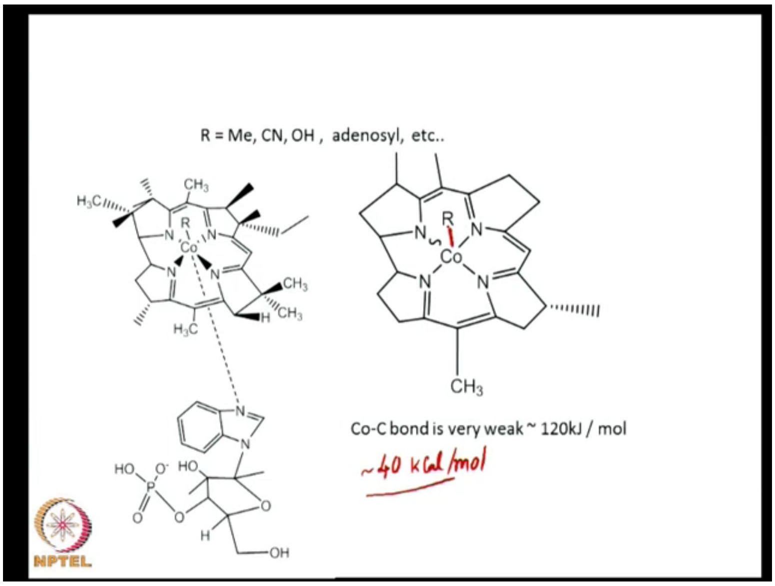

R = Me, CN, OH , adenosyl, etc..

Co-C bond is very weak ~ 120kJ / mol

~40 kCal/mol

Sometimes you have a methyl group and so, it forms as methylation function. Cyanocobalamin is often like a resting state for enzyme you either have a hydroxyl group or an adenosyl group sometimes at the cobalt. So, depending on the function that is required the cobalt changes the epical coordination at this octahedral cobalt three complex that you have here. Now, the corrin ring is quite is quite planar and so you have for this cobalt three plus ion a nice octahedral framework.

And in this octahedral framework the R group, which is attached in the epical position turns out to be a labile position not because it is a cobalt three plus system cobalt three plus systems are generally inert, but the R group. Especially if it is a cobalt carbon bond turns out to be relatively weak. The bond strength has been calculated to be approximately 120 kilo joules per mol and that is works out to be about 40 or little less than 40 kilo calories per mol. For those of you are used to kilo calories this is the value that you have for this bond which I shall now color for you in red. So, that bond is readily broken and is responsible for the unique chemistry of the cobalamin.

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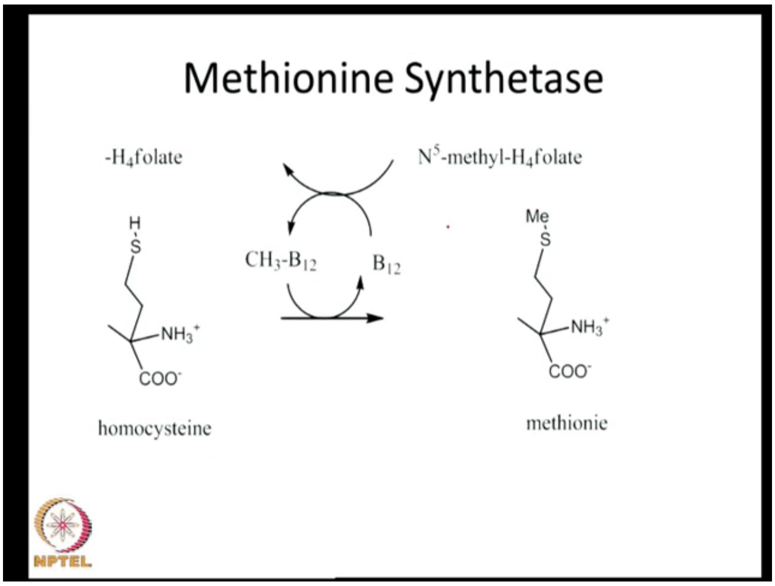

Methionine Synthetase

So, what does it do, here let us just illustrate it for the methionine synthetase where it transfers the methyl group in the body. There are several groups which are often transferred from one molecule to the other and the Folate molecule has got a methyl group at the N 5 position. And this N 5 position the methyl group on the N 5 position is readily transferred to B 12 where it does not have the methyl group. And then it becomes the methyl cobalamin which I am underlining. So, the B 12 without the methyl group is now methylated and it is ready to do this methylation function. And the folate itself is converted from the N 5 methyl folate to the bare folate without the demethylated form.

Now, the homocysteine is converted by the cobalamin the methyl cobalamin to the methionine. So, as this is again an essential function you can see the important role played by the cobalt it is essential for transferring the methyl group from the Folate to the homocysteine. And this cannot be done without the help of this particular enzyme. So, methionine synthetase utilizes the cobalt methyl bond which is fairly weak to transfer the methyl group to the SH group.

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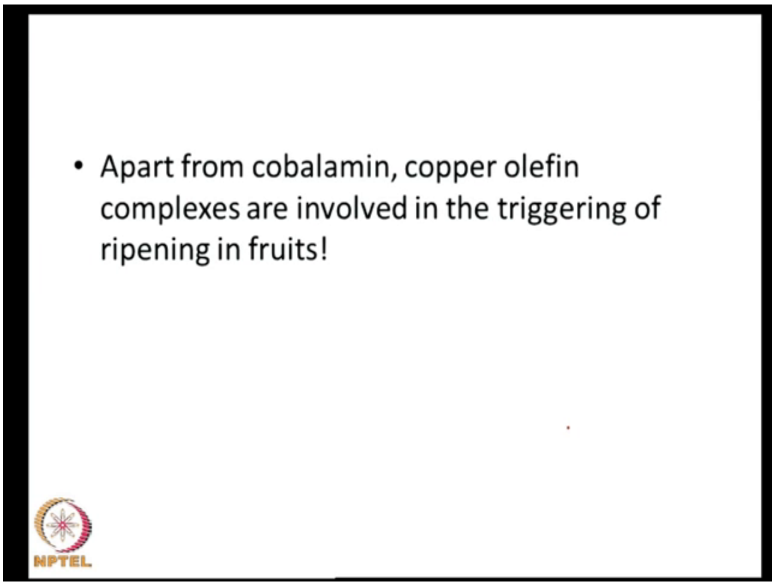

- Apart from cobalamin, copper olefin complexes are involved in the triggering of ripening in fruits!

So, apart from cobalamin there are other systems where organometallic chemistry plays a role. One of the important roles in biology is to trigger the ripening of fruits. Ethylene is often used simple ethylene is used as a ripening agent. And it has been conjectured that the ethylene coordinates to a copper one site on in the fruit. And that is responsible for triggering the ripening. So, an ethylene copper one complex is responsible for this important function in biology so in the fruits.

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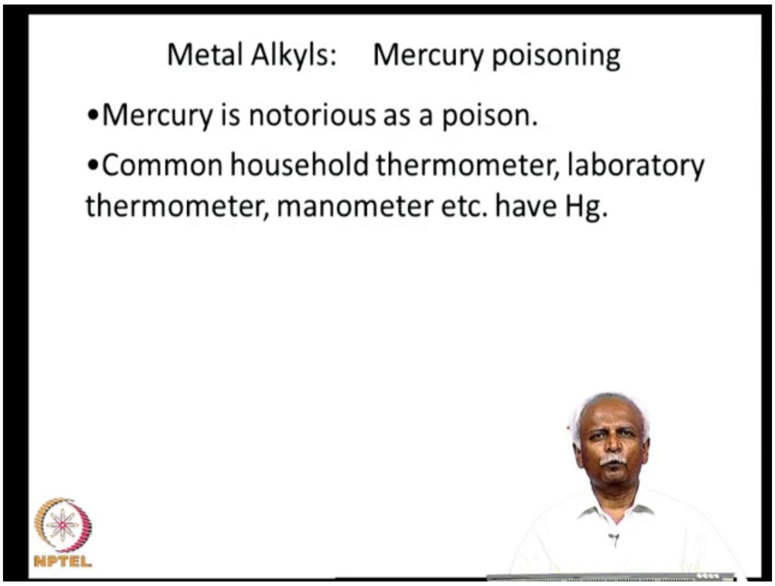

Metal Alkyls: Mercury poisoning

- Mercury is notorious as a poison.
- Common household thermometer, laboratory thermometer, manometer etc. have Hg.

So, these are systems which we have considered where the organometallic compounds are playing an important role. Now, we turn our attention to the environment metal alkyls especially in the context of mercury alkyls turns out to be very deadly poison mercury methyl bond for example, is a deadly poison. And this is the reason why mercury itself is notorious although it is not so obvious because in the household environment. We often use mercury in the laboratory we use a thermometer and in the hospitals mercury manometers are common. Turns out that mercury performs a function because of it is density its conductivity etcetera. A very important function that cannot be replaced by any other liquid common liquid.

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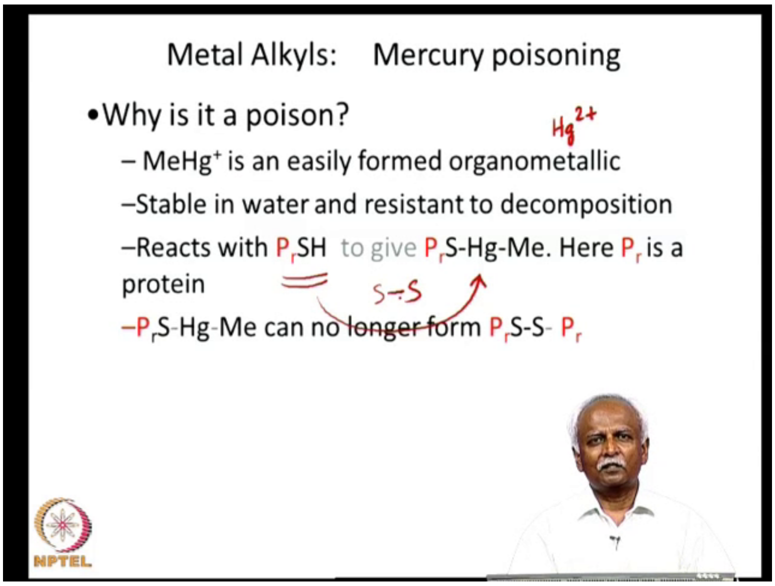

Metal Alkyls: Mercury poisoning

- Why is it a poison?
  - $MeHg^+$ is an easily formed organometallic
  - Stable in water and resistant to decomposition
  - Reacts with P_rSH to give P_rS-Hg-Me. Here P_r is a protein
  - P_rS-Hg-Me can no longer form P_rS-S- P_r

Hg^{2+}

S-S

And so we have to use we have to use mercury and we can why is it a poison in term how can we counter this situation. And now we turn to the fact that methyl Hg plus which is a mercury two ion. So, mercury is present in Hg two plus state. And when it is methylated methyl group is suppose to be an anionic ligand. So, Me Hg plus is the easily formed organometallic group, which turns out to be poisonous. The surprising thing is, it is stable in water unlike many alkyl metal compounds this methyl mercury plus is stable in water.

And it is very difficult to decompose this particular compound. More importantly it exerts its poisoning effect by reacting with proteins, which have got SH groups because mercury itself is thiophilic you can readily understand this reaction. Where the protein

SH group is converted to S-Hg-Me group. And now the protein with an SH is no longer available to form an SS bond. So, we have a difficulty here the protein which originally would have formed an SS bond and it forms this SS bond forms very often a structural role. Is now not there in the protein and as a result the confirmation that the protein adopts would be different and so it turns out to be a bad system.

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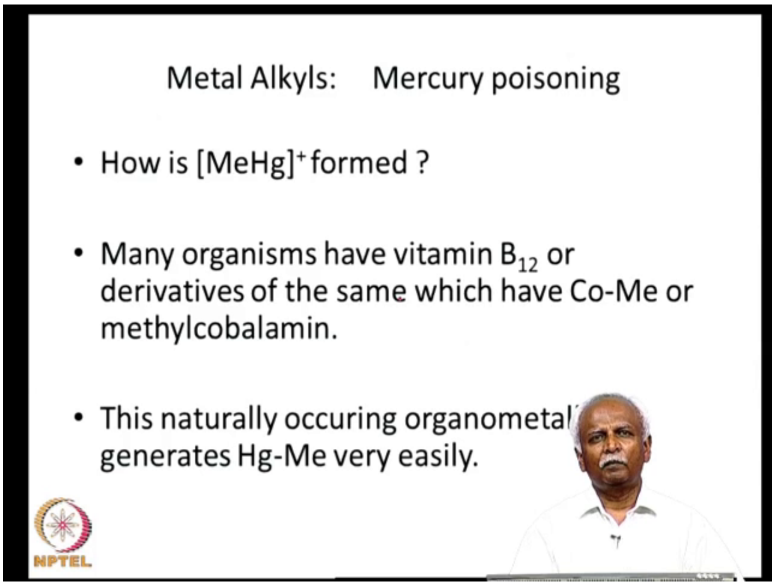

Metal Alkyls: Mercury poisoning

- How is $[MeHg]^+$ formed ?
- Many organisms have vitamin B_{12} or derivatives of the same which have Co-Me or methylcobalamin.
- This naturally occuring organometal generates Hg-Me very easily.

So, mercury turns out to be a poison because it converts the protein from its active form to an inactive form and it results in a detrimental effect. Now, we can ask this question how is this mercury Hg plus formed. So, what is the source of methyl the methyl group and how is it formed it in the first place. Now, many organisms as we just talked about the biological aspect of cobalamin it is quite obvious for you, where the methyl group would have come from because you have that N5 methyl group on the Folate.

And that is readily transferred to the cobalamin, you have a ready source of a methyl group on the cobalt atom of cobalamin. And this methyl cobalamin reacts with mercury and generates methyl Hg plus. And because the methyl group on the cobalt is extremely weak, and the methyl group on the mercury is extremely strong, you have a situation a reaction which goes only in one direction.

And that is to form the Hg-Me compound which is extremely stable and it is very difficult to destroy because of its aqueous stability. And it is extremely toxic to the protein system. So, this is the reason why one has to worry about mercury in the environment because once it is oxidized to Hg two plus Hg two plus in a biological medium is immediately converted into the methyl mercury plus cat ion.

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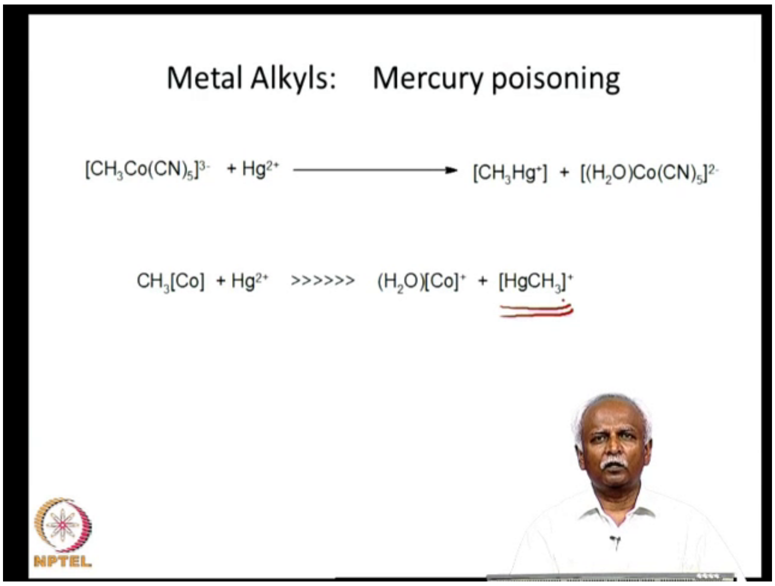

Metal Alkyls: Mercury poisoning

$$[CH_3Co(CN)_5]^{3-} + Hg^{2+} \longrightarrow [CH_3Hg^+] + [(H_2O)Co(CN)_5]^{2-}$$

$$CH_3[Co] + Hg^{2+} >>>>>> (H_2O)[Co]^+ + \underline{\underline{[HgCH_3]^+}}$$

So, now let us look at the in vitro systems. It has been demonstrated that simple cyan cobalt cyanocobaltate complex, the methyl cyanocobaltate complex is capable of converting Hg two plus to the Me-Hg plus system. So, this is not just a conductor which you have, we have some in vitro evidence that it is possible to convert the methyl cobalt system in a three plus state the methyl group is transferred to the mercury and it forms this very stable cat ion so given this information. We now have to worry about how exactly is this mercury going to get into the biological system.

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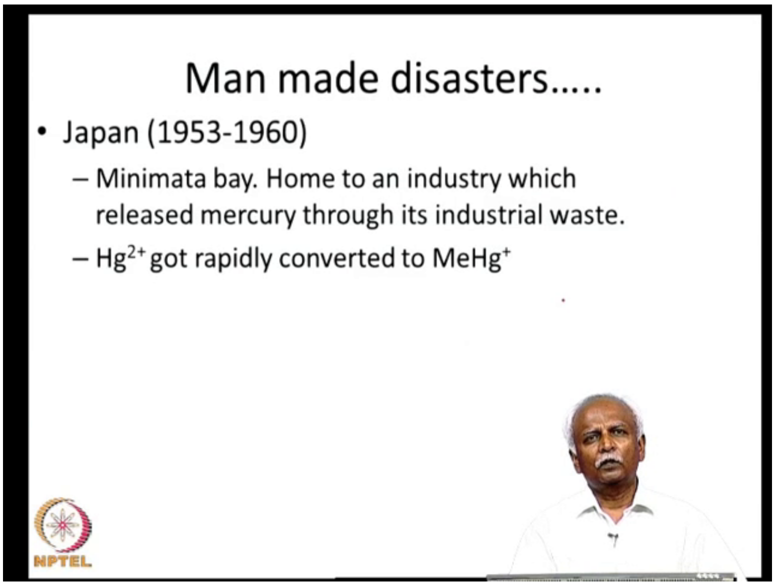

Man made disasters.....

- Japan (1953-1960)
  - Minimata bay. Home to an industry which released mercury through its industrial waste.
  - Hg^{2+} got rapidly converted to $MeHg^+$

Now, there are three or four major disastrous that have happened in the world. And it is instructive to look at how these things happened and how we can watch out for these disasters. The first thing that I want to talk about is the disaster that happened in minimata bay this is a bay in Japan where there was an industry which was releasing mercury through its industrial waste. The amount of mercury that was released into the sea was fairly small amount a small amount of mercury was released into Minimata bay, but this was the first incident and probably more mercury was released than what would be allowed in today’s scenario. This Hg two plus got rapidly converted by organisms in the sea to Me-Hg plus.

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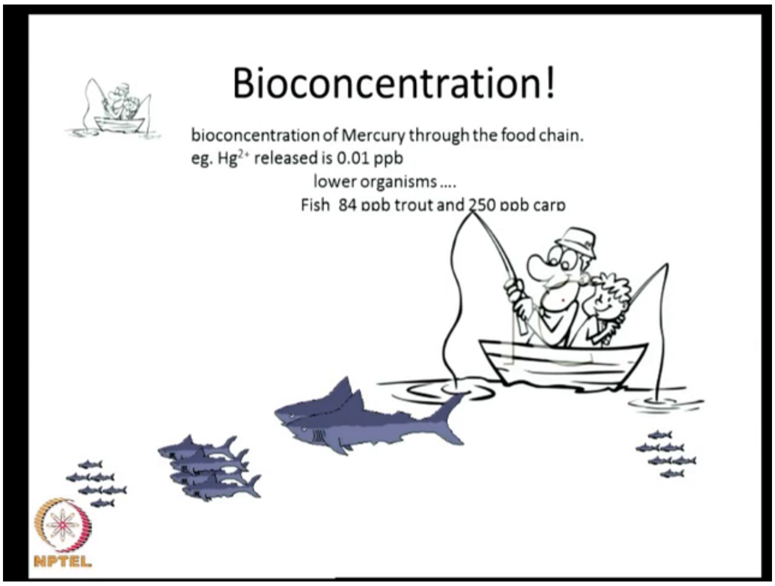

Bioconcentration!

bioconcentration of Mercury through the food chain.
eg. Hg^{2+} released is 0.01 ppb
lower organisms....
Fish 84 ppb trout and 250 ppb carp

And the phenomenon of bio-concentration was responsible for converting the small amounts of methyl Hg plus that was available in the sea water to a very large concentration in the larger fish. The Bio concentration is merely because the small fish tend to ingest this methyl mercury plus. And because the bigger fish are eating the smaller fish slowly the concentration of Me-Hg plus present in the bigger fish keep increasing. In fact it has been demonstrated the small fish might have as little as eighty four ppb parts per billion of the Me-Hg plus.

Whereas, the large fish have as much as 250 parts per billion of mercury. So, what happens is the fact that people are eating the large fish and because they are eating the large fish you tend to ingest lot more mercury than what you would have if you are eating small fish. So, this phenomenon of bio-concentration turns out to be a very important principle and it has played a major role in mercury poisoning.

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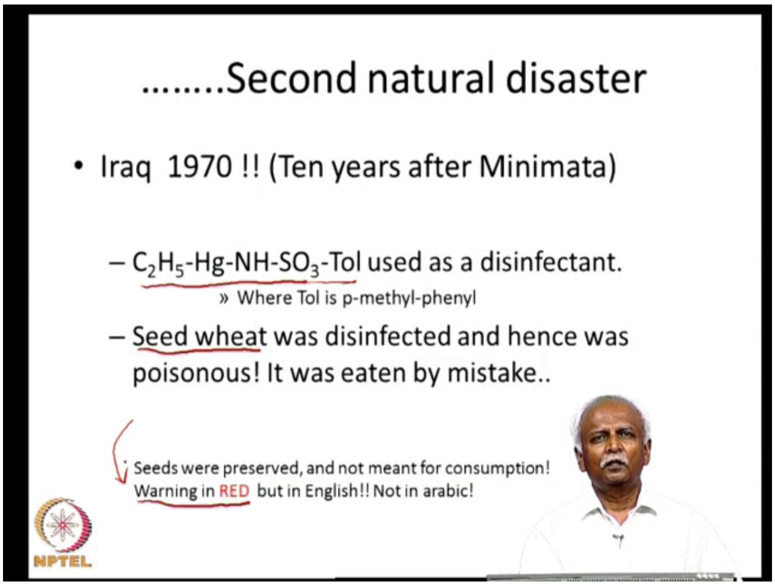

……..Second natural disaster

- Iraq 1970 !! (Ten years after Minimata)
  - C_2H_5-Hg-NH-SO_3-Tol used as a disinfectant.
    - » Where Tol is p-methyl-phenyl
  - Seed wheat was disinfected and hence was poisonous! It was eaten by mistake..

Seeds were preserved, and not meant for consumption! Warning in RED but in English!! Not in arabic!

Large number of people died in Minimata bay, but surprisingly in 1970, ten years after this tragedy which happened in Minimata bay there was another tragedy, which was nothing to do with release of toxic waste from chemicals in a factory. This compound which is a ethyl mercury compound is used as a disinfectant, turns out to be an extremely good disinfectant. And because this disinfectant can be used for protecting seeds that are stored it was normally kept in warehouses, where the seeds that are preserved for the next years sowing is protected from other insects. And so on by using bacteria and so on using this disinfectant.

And in general nobody eats this seed wheat. So, this is specially referred to a seed wheat. The seed wheat is marked as being disinfected with this particular mercury compound and the warning sign was in fact written in red. It is very unfortunate that the warning was actually in English and not in Arabic the local language that was used in Iraq. As a result people in Iraq who had by some wrong means got hold of this seed wheat. They should not have obtained the seed wheat, but they obtained the seed wheat and consumed it probably due to a situation, where there was a drought and there was a hardship for wheat and so, this seed wheat was taken and consumed.

Now, this resulted in a major disaster many people were affected by mercury because of this particular incident. So, here again you can see that one has to be extremely careful while using mercury. Although it plays a very important role it can be a disaster situation due to some wrong information or other.

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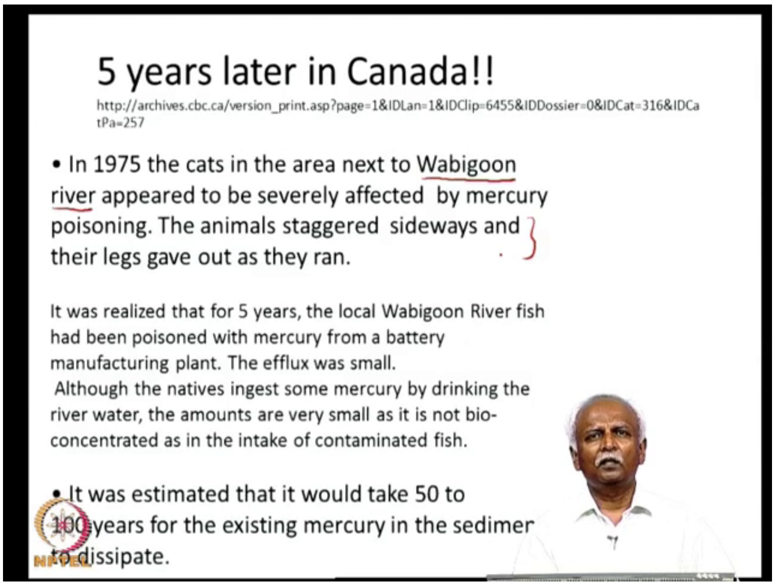

5 years later in Canada!!

http://archives.cbc.ca/version_print.asp?page=1&IDLan=1&IDClip=6455&IDDossier=0&IDCat=316&IDCatPa=257

- In 1975 the cats in the area next to Wabigoon river appeared to be severely affected by mercury poisoning. The animals staggered sideways and their legs gave out as they ran.

It was realized that for 5 years, the local Wabigoon River fish had been poisoned with mercury from a battery manufacturing plant. The efflux was small.
Although the natives ingest some mercury by drinking the river water, the amounts are very small as it is not bio-concentrated as in the intake of contaminated fish.

- It was estimated that it would take 50 to 100 years for the existing mercury in the sedimer to dissipate.

Now, it turns out that it was in 1970. In 1975, five years after this disaster in Iraq. An incident happened which was again reminiscent of what happened in Japan. Here in Japan it was released into the sea mercury was released into the sea here a factory was releasing mercury into a river. And that river was by a Indian settlement, these are west Indian settlements or red Indian settlement. And the people were feeling the cats caught in this Wabigoon river to the and it turned out that because of this Bio concentration, the fishes were having a high concentration of mercury and so the cats were affected.

And one realized that they have the typical mercury systems, where they lost stability, they had some nervous disorders, and people realized that there must have been some mercury leakage. And after some investigation, it was found out that this factory which was responsible for the release of mercury was in fact in by the side of the river, where the river was being contaminated by the sediments that were there which would take nearly hundred years to dissipate.

So, this a this is a river that has been permanently literally permanently contaminated because of this efflux from this factory, which was probably a small amount. And it was not affecting the native Indians who are also consuming this river water, but because of this fish bio-concentration the cats were affected. Unfortunately, some warning sign has been raised and it is unlikely to cause further damage, but it would take a long time for the place to be cleared of mercury.

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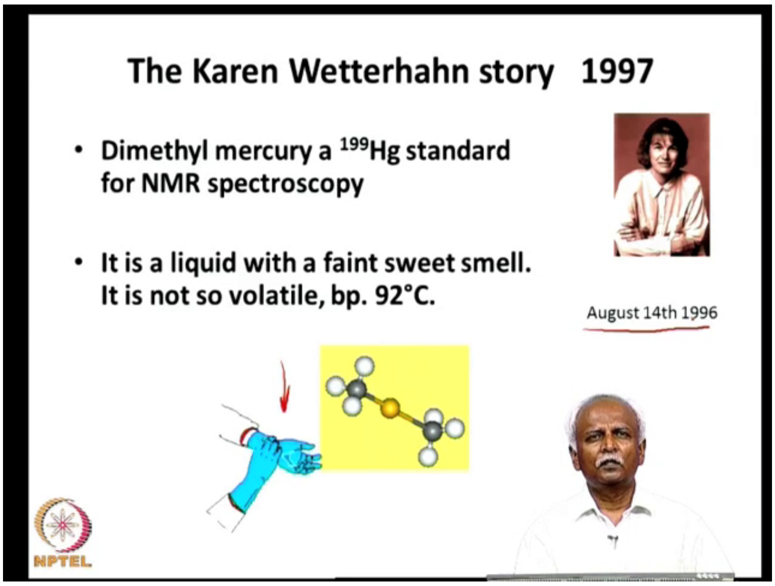

The Karen Wetterhahn story 1997

- Dimethyl mercury a ^{199}Hg standard for NMR spectroscopy
- It is a liquid with a faint sweet smell. It is not so volatile, bp. 92°C.

August 14th 1996

Now, that was in the year that was in 1975 and those are the three major disasters that I wanted to say. And now I wanted to just give you this information that has happened fairly recently and it is the warning sign for those are working in the laboratories. Here in a laboratory in the us in Boston a scientist Karen Wetterhahn was a professor who was working in this Evilly school. And unusual for a professor she was working in the laboratory. And she was actually making a measurement a making an NMR measurement and dimethyl mercury is a standard for organo mercury compounds.

Once again she was well aware of the dangers of dimethyl mercury she was using gloves, but there was a small pin hole in the glove and although she was using it in the hood she was extremely careful about handling it. On august 14th 1996 a small amount a extremely small amount of this liquid fell on her bare hands through the pin hole that was there in the gloves, she quickly removed the gloves.

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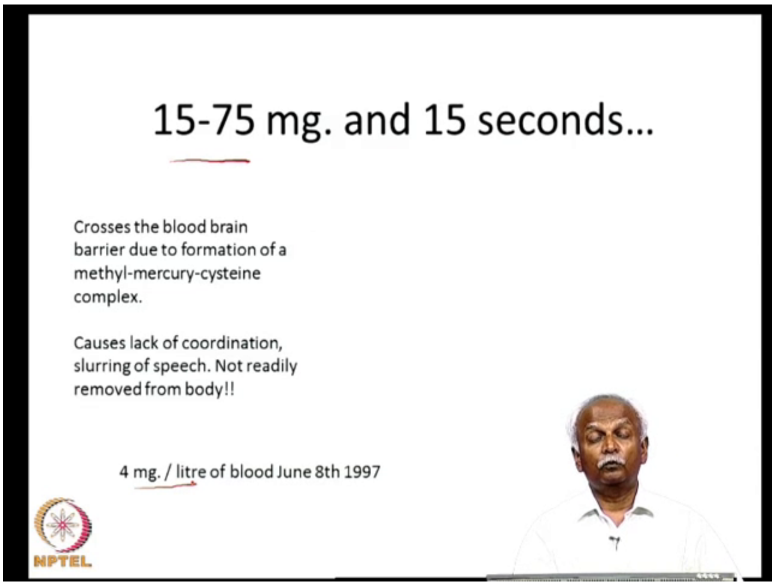

15-75 mg. and 15 seconds…

Crosses the blood brain barrier due to formation of a methyl-mercury-cysteine complex.

Causes lack of coordination, slurring of speech. Not readily removed from body!!

4 mg. / litre of blood June 8th 1997

But about 15 seconds of exposure of this methyl mercury compound on her hands was enough for the mercury to cross from the skin into the blood. And it was sufficient to cross the blood brain barrier. So, this is the incident which clearly told that dimethyl mercury is also an extremely poisonous compound. And it quickly forms a methyl mercury cysteine complex the same complex, which would be formed by the SH groups in proteins and it results in wide spread poisoning. Pretty soon she lost coordination the slurring of speech and within a space of 6 to 8 months she encountered severe debilitating effects because of that mercury poisoning.

In fact on June 8th when her mercury levels were monitored it was found that she had 4 milligrams per liter of blood. And that means more than 15 milligrams about 6 liters a maximum of 6 liters a blood is present in the body. And so it must have been more than 15 milligrams although it was estimated that the drop that went into her hand would have been anywhere between 15 to 75 milligrams. It was found that 4 milligrams per liter of blood was found in of 4 milligrams of mercury was found in her blood.

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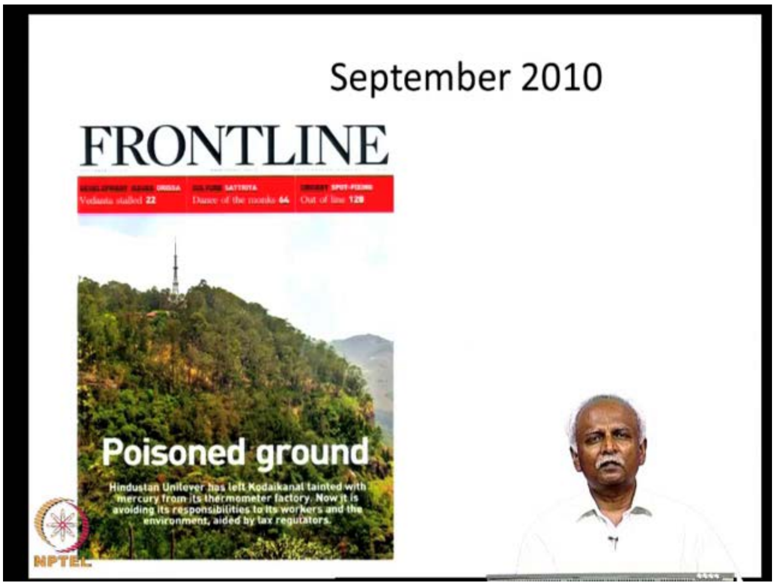

September 2010

FRONTLINE

Vedanta stalled 22 | Dance of the monks 64 | Out of line 128

Poisoned ground

Hindustan Unilever has left Kodaikanal tainted with mercury from its thermometer factory. Now it is avoiding its responsibilities to its workers and the environment, aided by tax regulators.

But she died quite right after that she passed away quickly after 1997. And I think it was in august that she passed away. So, that was a very sad incident where a chemist who knew the difficulties of handling mercury compounds succumbed to an accident. Closer home in September 2010 there was this article in frontline, which mentioned that in Kodaikanal a place in South India.

The ground has been poisoned with mercury, which has come out from a factory which was using mercury for making thermometers. So, this is reminiscent of the Wabigoon river incident because what is going to happen is we do not know how long it would take for the mercury that has fallen into the ground to dissipate and reach some revelate. So it because Kodaikanal is in a hill station this is a matter of concern.

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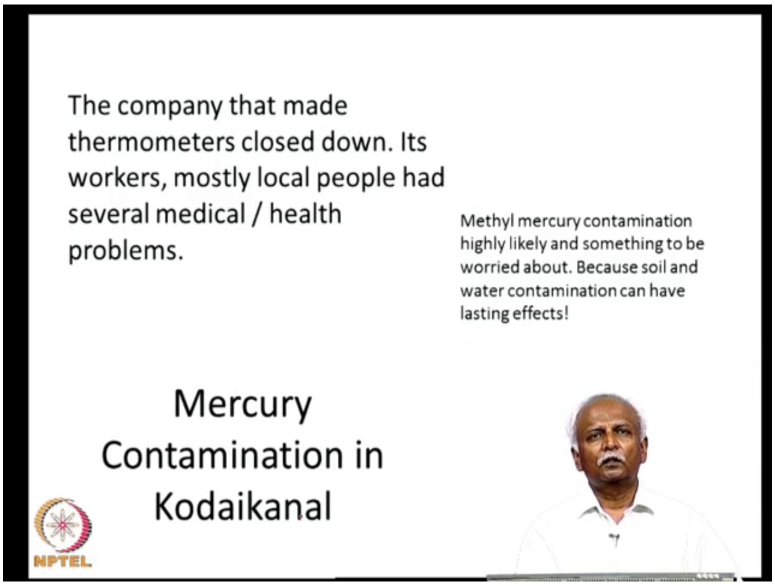

The company that made thermometers closed down. Its workers, mostly local people had several medical / health problems.

Methyl mercury contamination highly likely and something to be worried about. Because soil and water contamination can have lasting effects!

Mercury Contamination in Kodaikanal

The company itself was closed down and in fact it was noticed that some local people who are workers in the factory had severe medical and health problems, but a cursory examination suggested that this was not due to mercury. But hopefully this methyl mercury contamination will not affect us in the future, but it has to be worried about because of what I just mentioned that it takes a very long time for this methyl mercury bond to be broken. And as a result in its possible that it can have a serious consequence later on.

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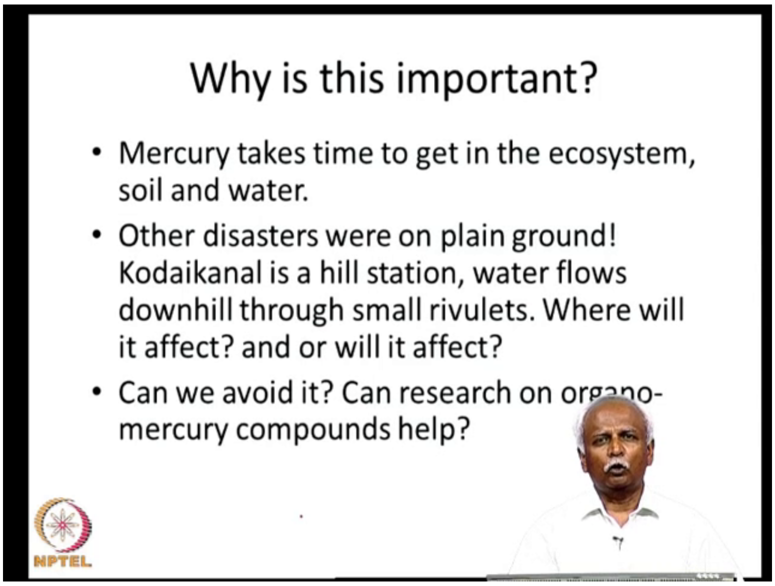

Why is this important?

- Mercury takes time to get in the ecosystem, soil and water.
- Other disasters were on plain ground! Kodaikanal is a hill station, water flows downhill through small rivulets. Where will it affect? and or will it affect?
- Can we avoid it? Can research on organo-mercury compounds help?

Once, it gets into the ecosystem especially the soil and water it can rapidly affect people and living systems. And so it is important for us to look at organomercury compounds and see how one can disinfect or how one can remove the ill effects of this methyl mercury bond. This is still an unsolved problem, but it both serves as a warning and as a challenge to the organometallic chemist.

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Methylmercury Levels Spiked After Tennessee Coal Ash Spill

- By Mark Schrope
- Latest News Web Date: January 3, 2013 http://cen.acs.org/articles/91/web/2013/01/Methylmercury-Levels-Spiked-Tennessee-Coal.html
  Environmental Disaster: Bacteria in nearby rivers transformed mercury from the nto more harmful form

The stories that have come on the basis of a methyl mercury have not stopped yet. This year in January 3rd 2013, there was another incident in Tennessee USA where it was found that there is a mercury poisoning.

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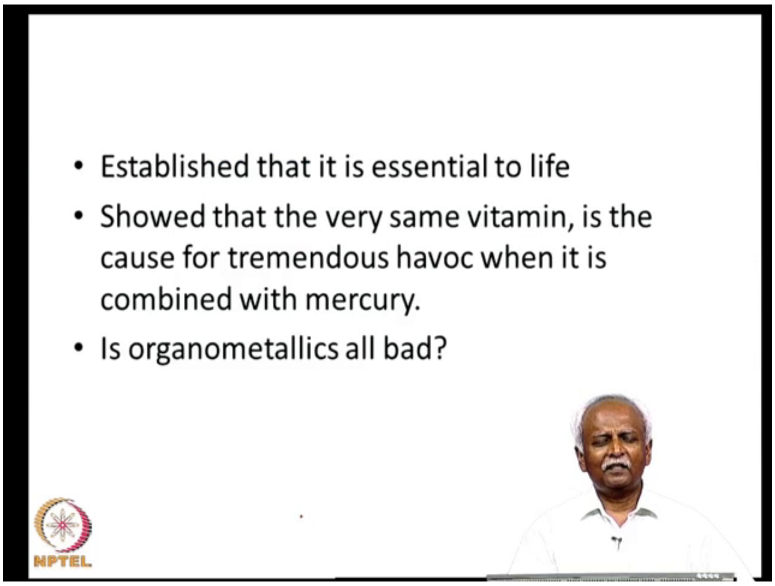

- Established that it is essential to life
- Showed that the very same vitamin, is the cause for tremendous havoc when it is combined with mercury.
- Is organometallics all bad?

So, let me end this another disastrous set of incidents which shows that methyl mercury and organometallic mercury compound is extremely toxic and is a cause for concern. It has been established that it is the organometallics is essential to life especially, when it comes to the cobalt methyl bond. And the very same methyl cobalt bond is responsible for converting mercury which is not toxic otherwise to a lethal methyl mercury plus compound. So, is organometallics all bad, I have given you two incidents one two situations one where it is essential for life and other incidence, where it is quite a disastrous situation.

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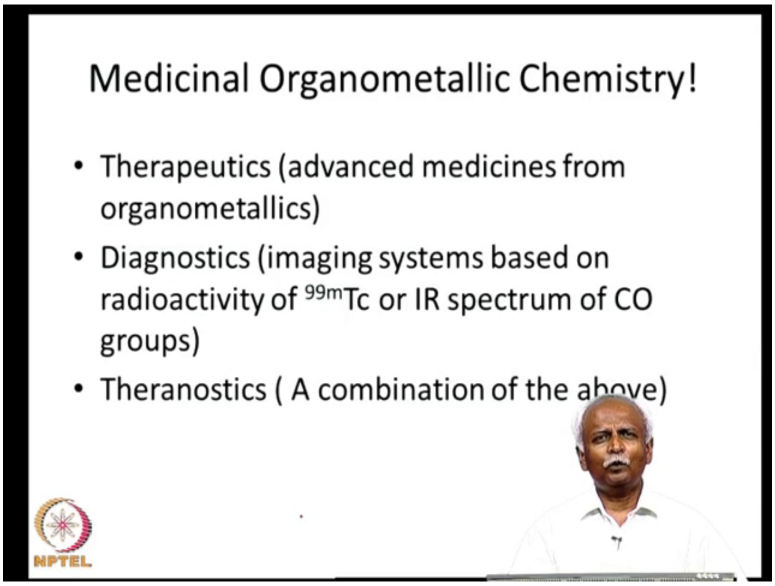

Medicinal Organometallic Chemistry!

- Therapeutics (advanced medicines from organometallics)
- Diagnostics (imaging systems based on radioactivity of ^{99m}Tc or IR spectrum of CO groups)
- Theranostics (A combination of the above)

Now, I want to end this discussion with something good and that deals with medicinal organometallic chemistry organometallic compounds. As we have seen in the introduction provide us with an unique opportunity of combining the good effects of organic chemistry and the good effects of transition metals and main group metals. And not only do they combine the good effects they give us new properties as a result of combining these two unique elements together. So, these have been utilized very effectively for making therapeutics advanced medicines from organometallics have been made and they have been able to tackle diseases as other organic compounds have not been able to.

Secondly, they have also been used for diagnostics imaging systems are important in today's world, where it is now possible to figure out what is going on inside the body without cutting open the body. And so it is possible to use 99 m technetium. 99 m is a meta stable isotope of technetium the man made metal. And 99 m technetium when combined with an organic ligand turns out to be an extremely useful system for imaging the heart it is called the compound is called cardiolite. And we will come to its function it has also been organometallic compounds have also been used in combination with metal carbonyls for a variety of functions including people are exploring, the use of using the strong co stretch for diagnostics.

Lastly by combining therapy and diagnosis it is possible to generate compounds, which can be used for theranostics. This is a term which just says that both for therapy and for diagnostics you use the same compound. The advantage is that one would be able to one can figure out where the compound is present in the body and treat it and follow the treatment as the disease progresses and as the curing progresses. This is an extremely important and valuable tool and this has been possible with some organometallic compounds.

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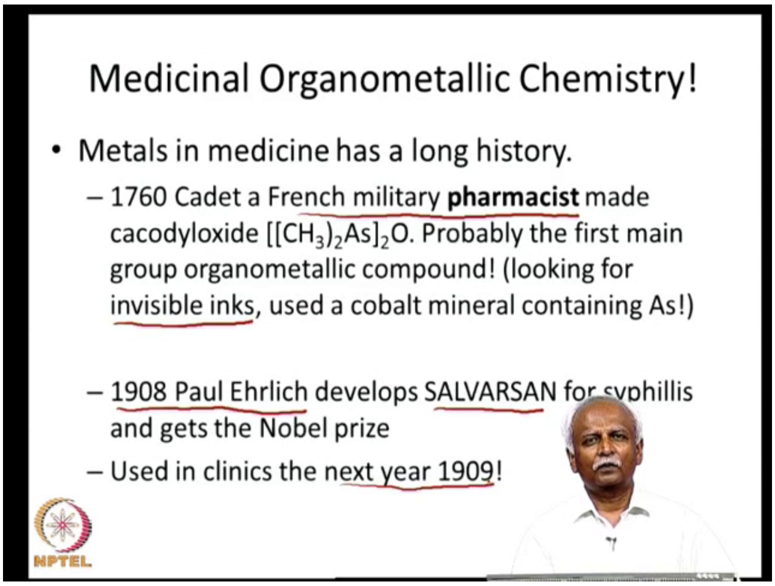

Medicinal Organometallic Chemistry!

- Metals in medicine has a long history.
  - 1760 Cadet a French military **pharmacist** made cacodyloxide $[(CH_3)_2As]_2O$. Probably the first main group organometallic compound! (looking for invisible inks, used a cobalt mineral containing As!)
  - 1908 Paul Ehrlich develops SALVARSAN for syphilis and gets the Nobel prize
  - Used in clinics the next year 1909!

Medicinal organometallic chemistry actually has a long history. In 1760 a French military pharmacist they were called pharmacist, but they were actually chemist. This was a chemist who was trying to make not medical compounds, but he was working in a pharmacy and he was trying to make a cobalt based invisible ink. Many of you would be familiar with the invisible ink that you can make with cobalt and he was looking for a way to make invisible ink with a cobalt containing mineral.

And this was for military purposes, but during the course of this he made probably the first main group organometallic compound, which was a methyl arsenic compound, but that was nearly not necessarily for medical purposes. It was in 1908 that Paul Ehrlich developed the first real arsenic compound which was called Salvarsan. Salvarsan was used for treating syphilis and he quickly got the Nobel Prize for this fantastic discovery. What is more amazing is that in 1908 he made the compound and practically within a year he was able to use it on human subjects.

This is now an impossibility because of the controls that we have on using chemicals on human subjects. In those days it was possible to quickly test it. One scientist for example, used it on his own daughter because there was no other medicine available and it was possible in those days to speed up this process of bench clinic. So, to speak of converting the medicine that is discovered in the lab to the clinical trials.

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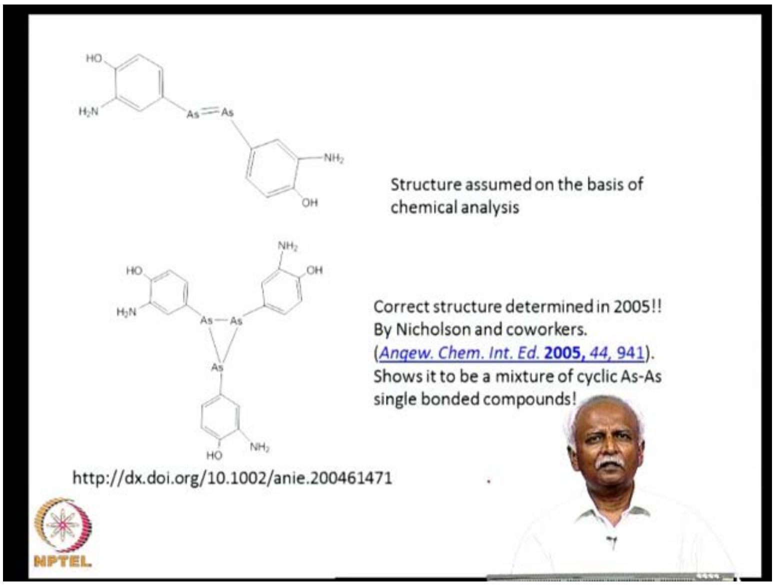

Structure assumed on the basis of chemical analysis

Correct structure determined in 2005!!
By Nicholson and coworkers.
(*Angew. Chem. Int. Ed.* **2005**, *44*, 941).
Shows it to be a mixture of cyclic As-As single bonded compounds!

http://dx.doi.org/10.1002/anie.200461471

Interestingly, Salvarsan was re-investigated recently the original structure or the structure that was assumed for Salvarsan was this arsenic dimer, where there was an arsenic double bond. This double bond was proposed on the basis of the molecular and the chemical analysis elemental formula that was written to satisfy the trivalent nature of arsenic, but recently there was a re-investigation of the compounds that was that were present in Salvarsan. And it turns out to be not a single compound, but a mixture of compounds polynuclear systems and the simplest of them is a trimetric structure. There is no mistake in the nature of the compound that is that has been the nature of the compound or the structure that has been assigned to Salvarsan.

It is just that double bonded arsenic compound would be less stable and its natural that the dimer converts itself to the trimetric structure that I have shown for you here, which would have only single bonds and this is a common occurrence in many main group chemistry. So, the cyclic form is the stable form and what was what is present in Salvarsan is the cyclic form that I have shown for you and that was discovered only as recently as 2005.

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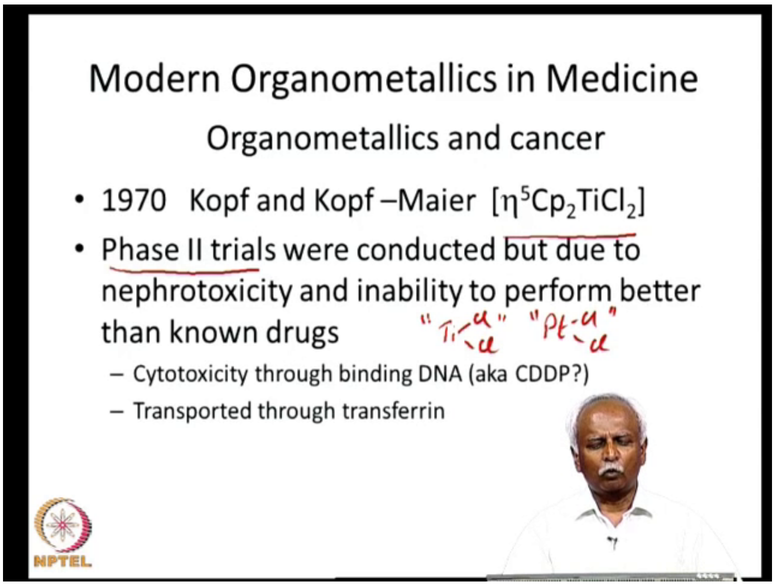

Modern Organometallics in Medicine

Organometallics and cancer

- 1970 Kopf and Kopf –Maier [$\eta^5Cp_2TiCl_2$]
- Phase II trials were conducted but due to nephrotoxicity and inability to perform better than known drugs
  - Cytotoxicity through binding DNA (aka CDDP?)
  - Transported through transferrin

So, apart from Salvarsan when cisplatin was discovered. Cisplatin was the dichloro diamin group attached to platinum two plus and this compound excited an extraordinary interest in the inorganic chemist because it was now possible to treat cancer in a way that was not possible earlier. So, 1970 Kopf and Kopf-Maier two people decided to investigate Cp2 Ticl 2 a compound which we have encountered earlier for cancer therapy and they found that this was an extremely good anticancer agent. In fact it was so good that it entered phase two trials. And unfortunately the drug had to be abandoned because of the fact that it was not better than the known drugs.

And this was partly because the way in which it was eliminated and partly because of the way in which the biological systems made or transformed Cp2 Ticl 2 to molecules that lost the Cp group and became oligomers. And these oligomers were in fact nephrotoxic in other words they could not be excreted through the kidney and so there was toxicity to the kidney. And they had to abandon the use of this drug.

And also it was shown that although the original idea was to use the Ticl two bonds. Just like one would use the platinum cl-cl bonds. The similarity between cisplatin which had this group and the Cp2 Ticl 2 which has this group was thought of as the reason for this activity. It was taught that they would bind DNA and make DNA inactive, but that did not turn out to be true because of its decomposition in the body.

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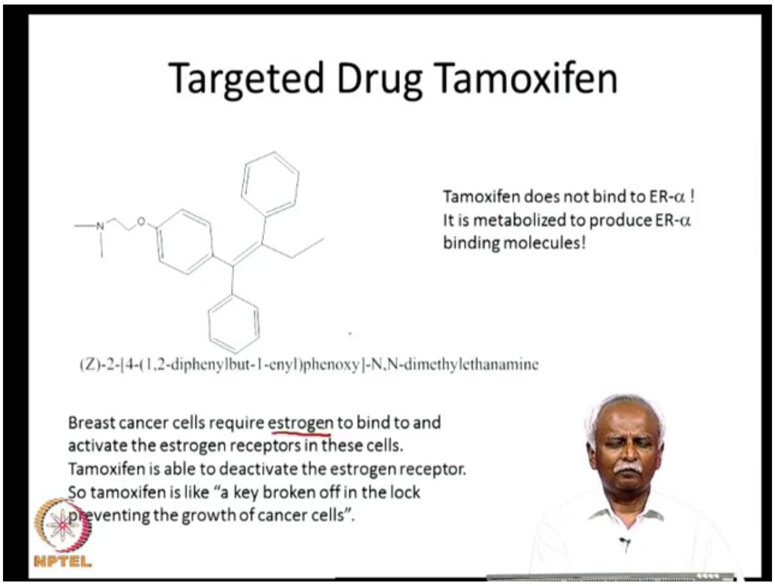

Targeted Drug Tamoxifen

Tamoxifen does not bind to ER-α ! It is metabolized to produce ER-α binding molecules!

(Z)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-N,N-dimethylethanamine

Breast cancer cells require estrogen to bind to and activate the estrogen receptors in these cells. Tamoxifen is able to deactivate the estrogen receptor. So tamoxifen is like "a key broken off in the lock preventing the growth of cancer cells".

And it was shown that it was actually transported through transferring. Now, it turn to a tamoxifen. Tamoxifen is a targeted therapy for breast cancer because breast cancer cells require estrogen. A estrogen binding compound was shown to be a good way to target breast cancer. So, tamoxifen is like a key broken in the lock preventing the growth of cancer cells. So, it does not interestingly it does not bind to er alpha the estrogen receptor, but the metabolates of tamoxifen, which is the molecule shown here are the ones which bind ER alpha.

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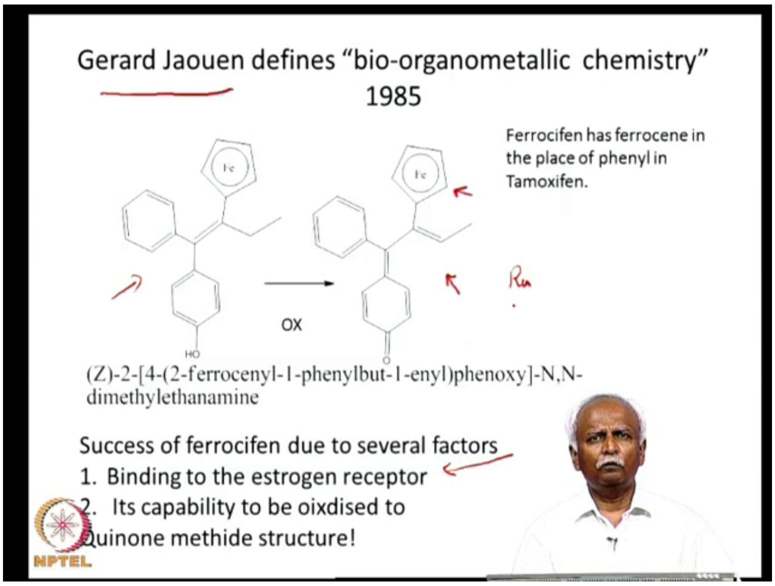

Gerard Jaouen defines "bio-organometallic chemistry" 1985

Ferrocifen has ferrocene in the place of phenyl in Tamoxifen.

Ru

(Z)-2-[4-(2-ferrocenyl-1-phenylbut-1-enyl)phenoxy]-N,N-dimethylethanamine

Success of ferrocifen due to several factors

1. Binding to the estrogen receptor
2. Its capability to be oixdised to Quinone methide structure!

Gerard Jaouen defined the term bio-organometallic chemistry and he was the one who made this ferrocifen which is an analog of tamoxifen. Which has got a phenyl group in this position instead of a phenyl group we now have a ferrocenyl unit. Interestingly, this particular molecule is successful not only because of the binding to the estrogen receptor, but it is also because it is converted to the oxidized form which is a quinone methide. The quinone methide structure is well known for its anticancer activity and it is because of this a transformation which is possible only with the iron analog if you replace ferrocifen with the corresponding analog of ruthenium the molecule loses its activity.

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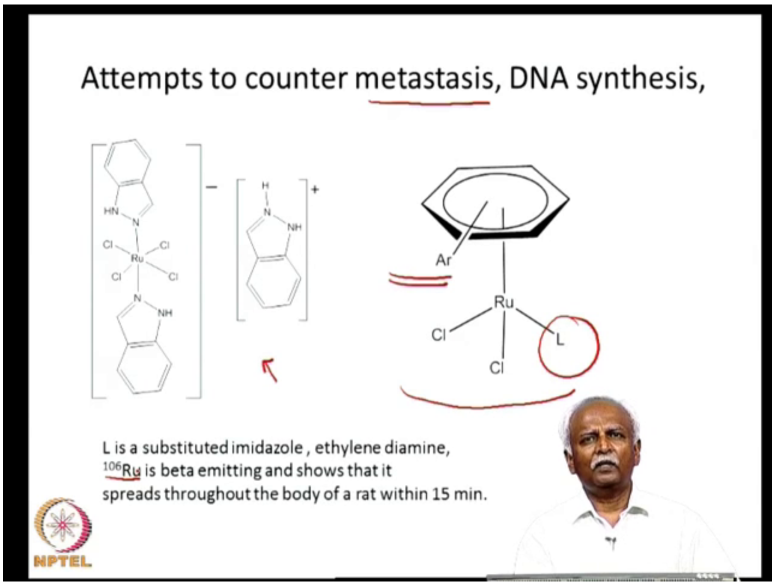

Attempts to counter metastasis, DNA synthesis,

L is a substituted imidazole, ethylene diamine, ^{106}Ru is beta emitting and shows that it spreads throughout the body of a rat within 15 min.

And it was shown that not only is it active against estrogen receptive cells, but it can also work against other cells. Now, turns out that we can use these molecules organometallic molecules in a variety of ways. Cisplatin only targets DNA and it works against cancer by attaching itself to DNA and preventing the cell replication surprising. There is more to cancer than just cell replication. One of them is the disastrous fact that cells might do undergo metastasis.

Metastasis is the process by which the cancer which is present in one part of the body rapidly gets transported to another part and it has been shown that this ruthenium complex which is shown here it can stop metastasis. And several analogs of this molecule including organometallic molecules have been shown to counter metastasis and not only can one stop replication by binding to the DNA.

DNA synthesis has been stopped by a large number of molecules, which have this general structure these are piano stool structures and people are shown that by changing the AR group that is present here. And the L group that is present on the ruthenium it is possible to modify the activity of this general molecule, which is an excellent anticancer agent. Recently it has been shown using labeled ruthenium isotropically labeled ruthenium, which is a beta emitter that this framework is capable of rapidly moving from one part of the body to another.

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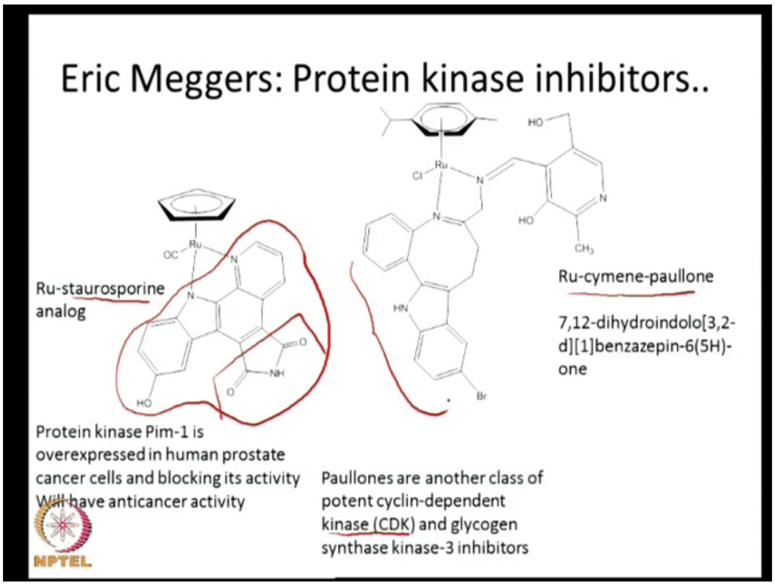

Eric Meggers: Protein kinase inhibitors..

Ru-staurosporine analog

Ru-cymene-paullone

7,12-dihydroindolo[3,2-d][1]benzazepin-6(5H)-one

Protein kinase Pim-1 is overexpressed in human prostate cancer cells and blocking its activity Will have anticancer activity

Paullones are another class of potent cyclin-dependent kinase (CDK) and glycogen synthase kinase-3 inhibitors

Another way to handle cancer is to use kinase inhibitors. Eric Meggers is one person who has pionate. This particular methodology and he has also used this ruthenium half sandwich complexes and here I have shown for you two different protein two different kinases. One is a cyclin dependent kinase, which helps in the cycle in the cell cycle in progressing the cell cycle and another is a protein kinase, which is responsible for protein synthesis. And it is this protein kinase which is present in large amounts in the cancer cells and staurosporine, which is a molecule which I will the framework of which I will mark for you here is has been used this particular recognition element is present in staurosporine.

And this has been used to make an organometallic molecule, now by hooking it on to the ruthenium cp ring you have generated a new type of a complex and it is an effective kinase inhibitor. And here is another system which is a paullone again a benzadizepin moiety which is this moiety which is shown for you here this benzadizepin is extremely effective in inhibiting some cyclin dependent kinases. These have been this ruthenium complex has have also been shown to be anticancer active.

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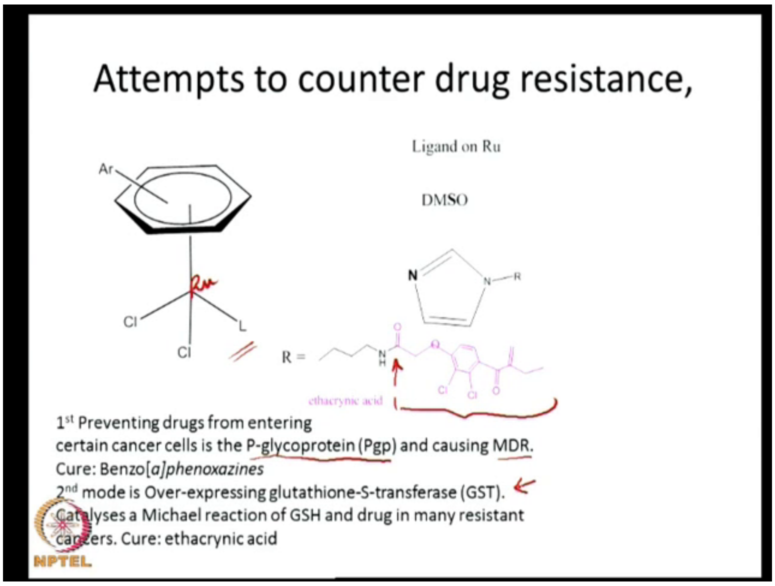

Attempts to counter drug resistance,

1^{st} Preventing drugs from entering certain cancer cells is the P-glycoprotein (Pgp) and causing MDR.
Cure: Benzo[*a*]*phenoxazines*
2^{nd} mode is Over-expressing glutathione-S-transferase (GST).
Catalyses a Michael reaction of GSH and drug in many resistant cancers. Cure: ethacrynic acid

Now, cancer is a problem not only because it spreads rapidly it metastasis it is also a problem because it develops drug resistance. There are many drugs including cisplatin which rapidly encounter drug resistance and there are two ways one is to prevent the drug from getting into the cell another is to efflux the drug, or push it out from the cell by some proteins. So, the prevention of the drug from going inside is done by glycoprotein's. And that is what the major causes for the drug resistance and benzodiazepine hooked onto the half sandwich system turns out to be an excellent way by which you can prevent that.

And here is this glutathione S transferase which is responsible for deactivating many drugs. Now, this deactivation can be stopped by the use of ethacrynic acid, which is the unit which is shown here this ethacrynic acid, which will have a cooh group at this position has been linked onto this half sandwich complex. And it has been a dual purpose drug the ruthenium now functions as anticancer agent and it is this ethacrynic acid, which stops the glutathione S transferase from bringing about drug resistance.

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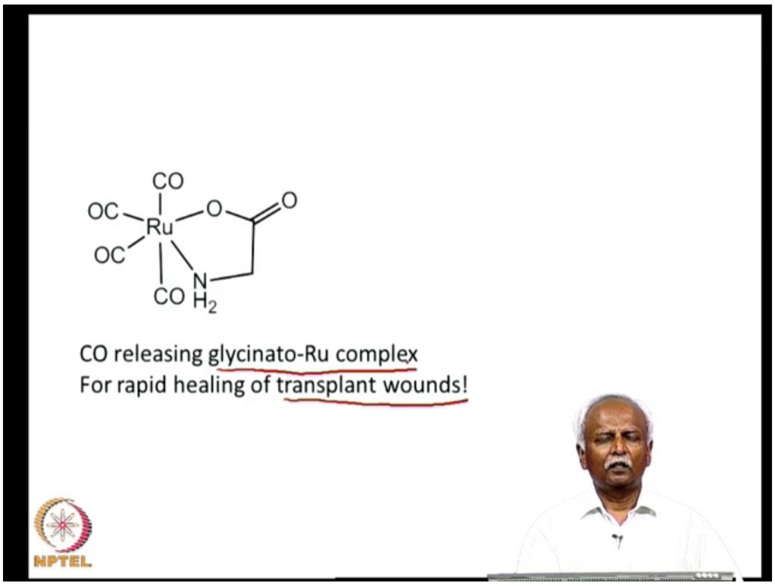

CO releasing glycinato-Ru complex
For rapid healing of transplant wounds!

One more example for the metal containing organometallics. Carbon monoxide is a signaling molecule in the body although it is a poison in large amounts it is used for rapid healing of wounds. Especially, when there is a transplant wound it is important to have small amounts of carbon monoxide in the vicinity to rapidly heal the wound. And it has been shown that this glycinato ruthenium complex can be used for using for using it along with some other compounds to heal transplant wounds.

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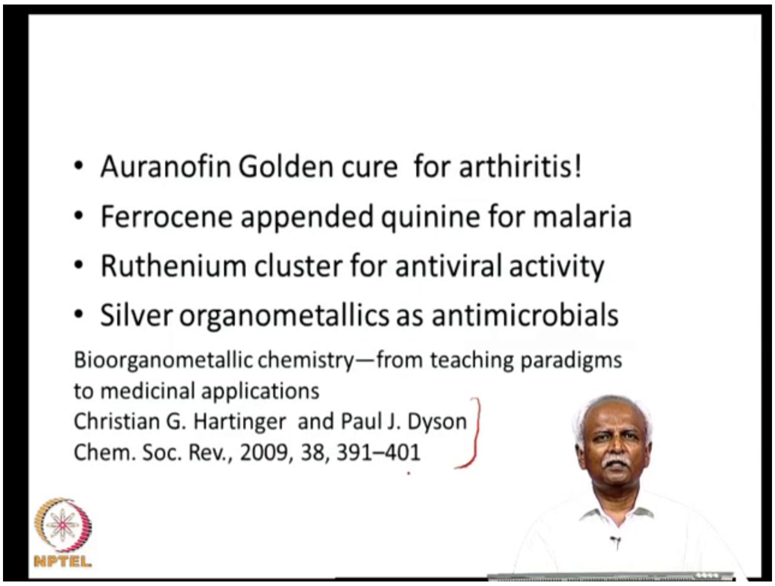

- Auranofin Golden cure for arthiritis!
- Ferrocene appended quinine for malaria
- Ruthenium cluster for antiviral activity
- Silver organometallics as antimicrobials

Bioorganometallic chemistry—from teaching paradigms
to medicinal applications
Christian G. Hartinger and Paul J. Dyson
Chem. Soc. Rev., 2009, 38, 391–401

This list does not end here, we have auranofin which can be used for arthritis. We can use ferrocene appended for malaria, ruthenium clusters for antiviral activity, silver organometallics for antimicrobials and so on. For a recent article which lists some of these molecules and describes this you can refer to this particular reference, which I have listed for you here. And tells you how wonderfully organometallics is changing the phase of therapy in the medicinal world.

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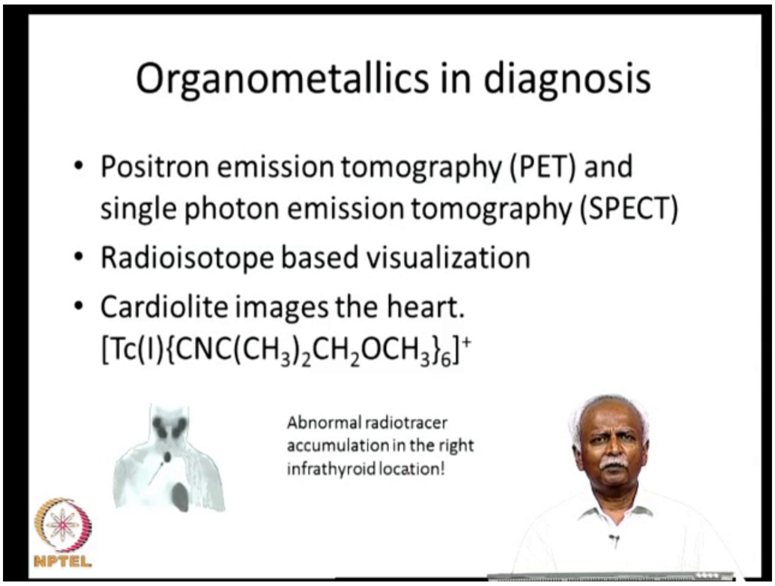

Organometallics in diagnosis

- Positron emission tomography (PET) and single photon emission tomography (SPECT)
- Radioisotope based visualization
- Cardiolite images the heart. $[Tc(I)\{CNC(CH_3)_2CH_2OCH_3\}_6]^+$

Abnormal radiotracer accumulation in the right infrathyroid location!

Organometallics is also used for diagnosis. I told you about technetium it is used for radio tracing using technetium 99. In this picture here a patient who has an abnormal accumulation in the thyroid infrathyroid location can be identified very readily using this technetium compound, which is an isocyanide complex of technetium. One is a complete organometallic compound that is used.

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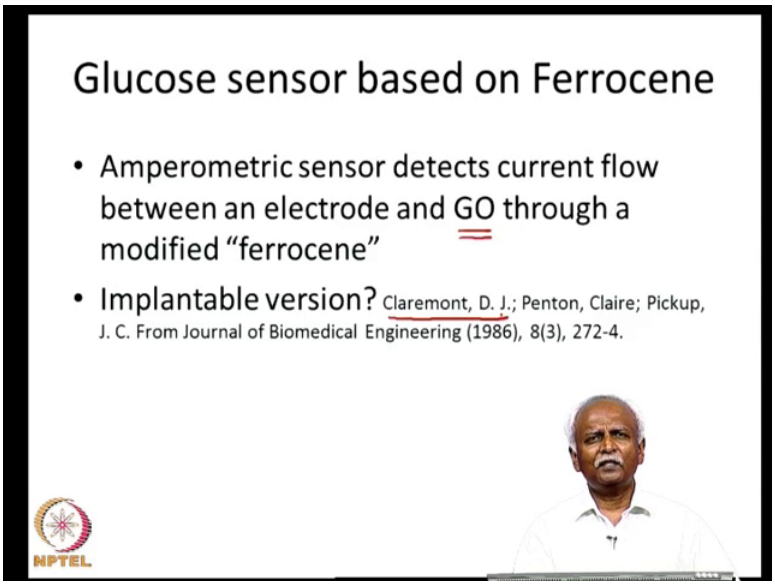

Glucose sensor based on Ferrocene

- Amperometric sensor detects current flow between an electrode and GO through a modified "ferrocene"
- Implantable version? Claremont, D. J.; Penton, Claire; Pickup, J. C. From Journal of Biomedical Engineering (1986), 8(3), 272-4.

Glucose sensors for ferrocene have also been made. In this particular case ferrocene is merely an electron transfer agent. Ferrocene is an excellent molecule because it reversibly transfers an electron. And a ferrocene glucose sensor often utilizes the current which flows from the electrode to a system which is oxidizing the glucose using a glucose oxidize enzyme. So, the glucose oxygen are present and the amount of glucose is measured very sensitive in a very sensitive fashion using amperometric detector and the person who has been spare reading this effect is claremont. And he has in fact suggested that one would be able to make an implantable version of a implantable version of this glucose sensor in the body.

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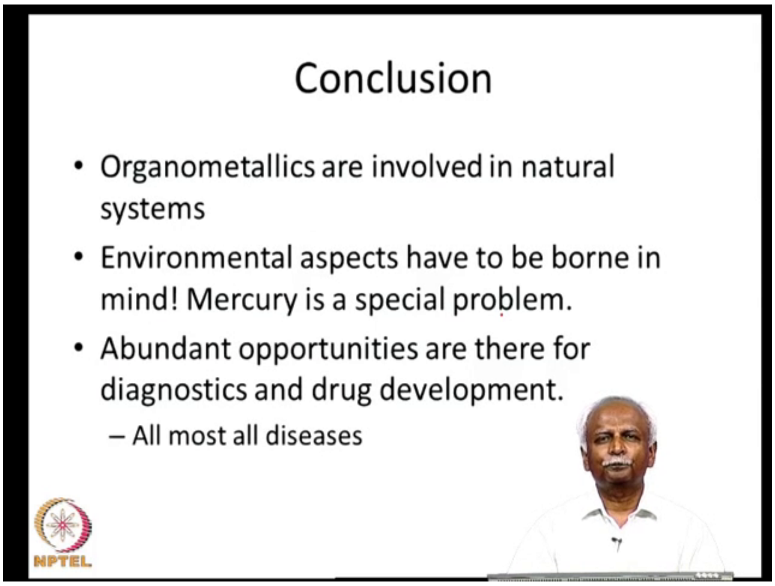

Conclusion

- Organometallics are involved in natural systems
- Environmental aspects have to be borne in mind! Mercury is a special problem.
- Abundant opportunities are there for diagnostics and drug development.
  - All most all diseases

So, you can see that organometallic compounds are present ubiquitously in natural systems. Although the ubiquitous cobalamin is the only major organometallic which is present in the body. It has a very important effect on the body and is important for the living system, but converts mercury into a very special problem by converting it into methyl mercury plus.

And lastly we have seen that there are abundant opportunities for making new drugs both for diagnosis and for therapy. And almost all diseases could be benefited by making new organometallic compounds, which will effectively treat the disease or detect the disease. And to this end organometallics, organometallic chemists are pressing all their efforts.