Biological Inorganic Chemistry
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Lecture 60
Chemotherapy, radiotherapy and contrast agents

Hello, students. So, a very good morning to everybody.

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So, we have reached to the end of this session. So, in module 20 and lecture number 60, where today we will be talking about chemotherapy, how different chemical compounds we can use for therapeutic purposes, then radiation, radiotherapy and contrast agents.

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So, we will try to cover very quickly within this half an hour class that what is called about the nuclear medicine. So, basic understanding about your medical diagnosis sometime we based on that we prepare the diagnostics kits also. The post operative stress, whether we can be remove that particular stress by using simple metal ion and the metal ion based molecules. Then imaging agents, then radiotherapy and radio diagnostics also and radio pharmaceuticals, so basic definitions and their applications and their uses.

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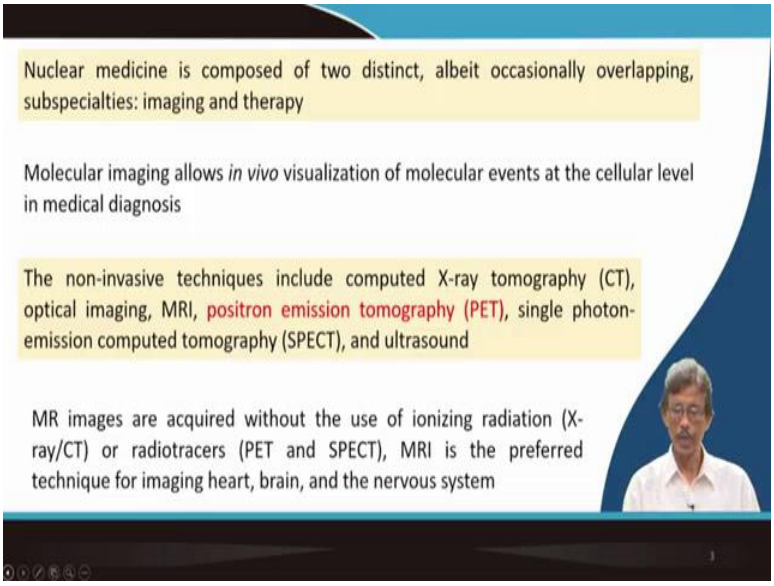

So, what is called, therefore, your nuclear medicine is basically composed of two distinct but overlapping sub-disciplines, one is imaging and another is therapy. So, the nuclear chemistry if we can use for the medicine purpose or the medical purpose, one part of the molecules can be used for the typical imaging where the damage has been caused in your body, and another part we can considered as the therapeutic agents or the therapy, because we call that is also a radiation therapy, because if we need say gamma radiation to kill the abnormal growth or the cancer growth, we call it as the typical radiotherapy for that particular purpose.

So, what we can use there for that, since we are using molecules, the molecular imaging which can go for the complete understanding or seeing the thing, the molecular events what is happening at the cellular level within the cells basically, and is therefore, is the typical rule or rule of the day is your typical medical diagnosis. See, if we have a non-invasive technique, we are not trying to damage anything, which include the CT, the computed x-ray tomography, so is a very useful technique nowadays we all know or we can go for optical imaging.

So, any optical thing, that means optical spectroscopy we know, we know electronic spectroscopy, we get the spectrum. Now, if we can go for a three dimensional or two dimensional imaging like your x-ray plate that can also be considered as a typical optical imaging. And if we go for the magnetic resonance imaging, we call it as MRI, then PET, the positron emission tomography, then photon emission computed tomography, the latest version of your CT is known as a SPECT, a single photon emission computed tomography and sometime we can also use ultrasound for both imaging purpose as well as for your therapeutic purposes.

So, magnetic resonance images basically what we are looking for how we get that. You have a x-ray or CT in case of your ionizing radiation or radiotracers in case of your PET or a SPECT, but in case of MRI is preferred technique for imaging your nervous system, your brain or your heart, because it is based on our NMR technique. NMR is, we call as the nuclear magnetic resonance, but here is the corresponding magnetic resonance imaging. So, we try to use the same technique, but we want to have the imaging process.

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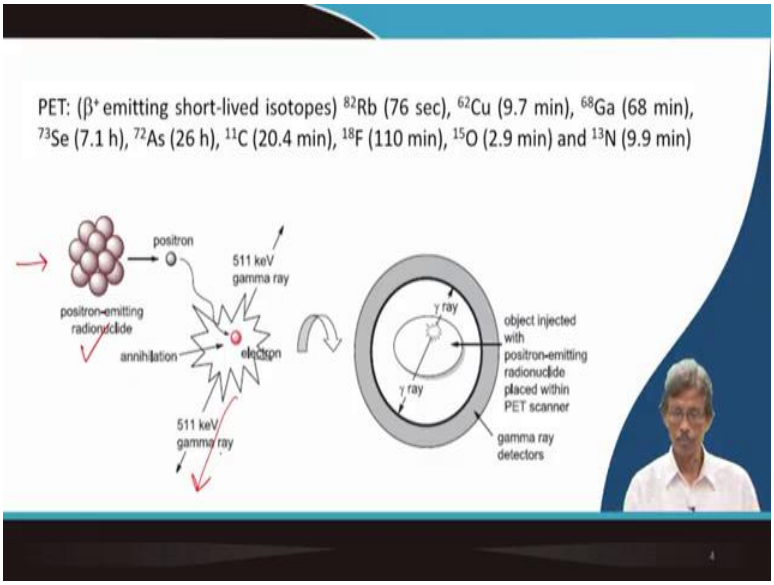

So, in case of your PET, positron emission tomography, so we definitely need to have the corresponding emission of the positron which is beta plus, beta minus is your electron, when beta plus is your positron. So, we need some isotopes. So, short lived isotopes which are capable of emitting beta radiation, beta plus radiation, we can take that.

So, one is that of your rubidium 82. When we number it as is the unstable start lived laboratory prepared isotopes which can give rise to the corresponding positron emission. So, it is very short lived, is very difficult to make this and use this also compared to that your copper 62 which has a lifetime, half lifetime of 9.7 minute, which is pretty well. So, you make it and within 9.7 you have to scan it or you have to use it.

Then gallium 68, which is very important and is easy to remember also, is a half life of 68 minute. So, the isotope number is 68 and the time of your decay, half of this decay is your 68 minutes. So, gradually we are increasing basically for your selenium 73, arsenic 72, carbon 11, fluorine 18, oxygen 15. Fluorine 18 is 110 minute. You see these ranges are very useful. Once you produce the radioisotope you have to take that particular isotope to that particular patient which will be scanned or which will be treated with this particular positron emission.

So, 110 minutes scale or the span is very useful. We can use that particular span for some kind of diagnostics. So, why fluorine is important, why gallium is important that we will also talk, but the fluorine we know that the carbon hydrogen bonds are always there even in your glucose

molecule or many other cases we have the CH backbone even the proteins also. So, if we are able to substitute that hydrogen by simply the fluorine many of these things we get it by substitution of the hydrogen atom attached to the carbon, nitrogen, oxygen many cases we get that by fluorine, but the best way of understanding is that of your carbon hydrogen bonds so we will get it, similarly, by substituting nitrogen, but the half life is pretty short.

So, what do we do with these basically, we have a corresponding nucleotide what do you make it and that nucleotide basically we prepare it. How you make it this radio nucleotide, so artificial radioactivity, basically, so artificial transmutation. You have the stable isotope, you bombard it with something either a neutron or a proton and you get the corresponding radio nucleotide which is not so stable again having some amount of half life like your copper 62. So, the best thing what you should understand is that how you can get the copper 62, which isotope will be taking for the typical nuclear reaction which can give you the corresponding radio nucleotide which will be emitting positron.

So, when positron is emitting it gets electron and you go for the annihilation technique. So, is beta plus and beta minus is typical annihilation liberating two gamma rays and these two are in perpendicular directions is 180 degree apart. So, one will go this side and another will go the other side. So, this particular movement basically in this particular site is about 511 kilo electron volt of energy. So, how you get that if you have a spherical thing or a circular thing, you have the object which is being injected and that will emit the gamma radiation.

So, within the PET scanner, so you have the scanner, you know the detector basically, scanner is nothing but the detector which can detect the radiation which is coming out from that particular corresponding annihilation of the reaction when it is capturing the electron by that of your positron. So, if we are able to get that particular thing that light, your light which is hitting your object and giving you the corresponding photograph, similarly, this is also giving you the corresponding image out of that particular positron.

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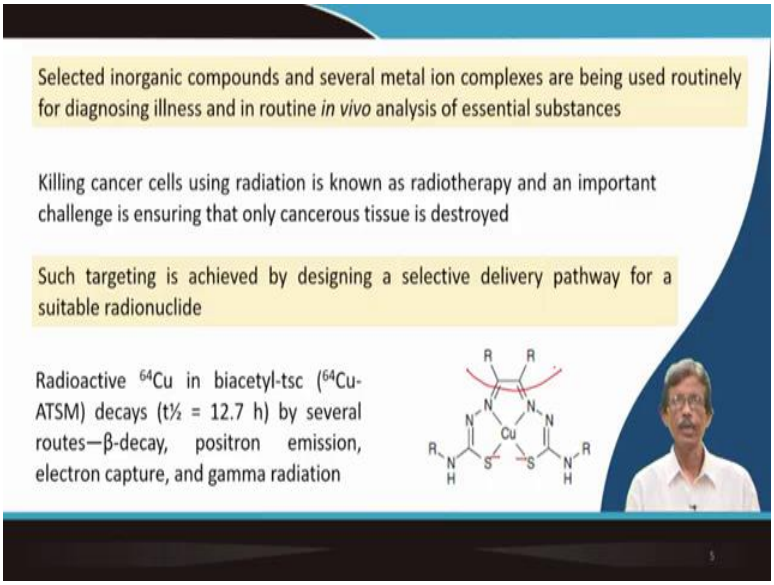

So, many inorganic compounds and several metal ion complexes, so these are the two categories of molecules we are talking here, can be used for diagnosing the illness and is routine for in-vivo, that means within the system, in-vivo analysis of essential substances. So, many such substances we basically can understand how we can kill the cancer cells basically if we have to have some amount of radiation, say gamma radiation, whether gamma radiation can be useful to kill the cancer cell that is known as your radiotherapy. And is an important challenge in ensuring that only cancerous tissues is destroyed, that means selective targeting.

You have to give the radiation to those cancerous tissues and the cancerous cells only. You should not make any harm to the normal tissues or the healthy tissues. So, that is definitely a real challenge to the medical practitioners, to the scientist who are dealing with all these things. So, how to go for the selective targeting that can be achieved if you have a typical selective delivery path using a suitable radio nucleotide. So, you take the radio nucleotide, allow the radio nucleotide to reach there and allow it to go for annihilation reaction such that it can emit the gamma radiation and that gamma radiation can be utilized for some useful purposes.

So, you see if you have the compound which is a copper complex metal ion is a copper metal ion complex and we are not telling whether it is a copper 2 compound or a copper 1 compound because we know that in sulfur environment or thiolate environment you can go for the corresponding sulfur coordination and these two sulfur groups are your S minus. So, this is also

S minus, this is also a S minus, because the thing is telling is not a thiole, is single bond SH, single bond SH. So, is a typical very simple like and backbone. How you get this ligand and get this compound, because not only 62 copper, but you can use the radioactive 64 copper also.

And that 64 copper is also go by several routes like beta decay can go for positron emission, electron capture and gamma radiation. So, these are very useful compounds of copper. So, once we know that the copper, the simple copper 2 plus, the copper 63 what do we know in our laboratory using the laboratory available copper salt as your copper acetate or copper sulfate we can make it. But if you use the radioisotope which can be prepared by some other technique by nuclear bombardment we get that radioisotope and that radioisotope can be utilized for the compound making use of your biacetyl thiosemicarbazide.

So, this particular part, if you have R is equal to CH3, CH3, CH3 groups, two of these groups and C double bond O is known as your biacetyl. And biacetyl when it is condensed with thiosemicarbazide, tsc is your thiosemicarbazide, you get the tetradentate ligand, tetradentate N2S2 ligand and that can bind nicely the copper center. This is because you have to use something which is protecting the copper. It is not only protecting his ad activity, but it will also protect the copper as in this particular bound form. So, the stability of this complex will be more compared to the use of simple metal ion salt as your any other copper salt.

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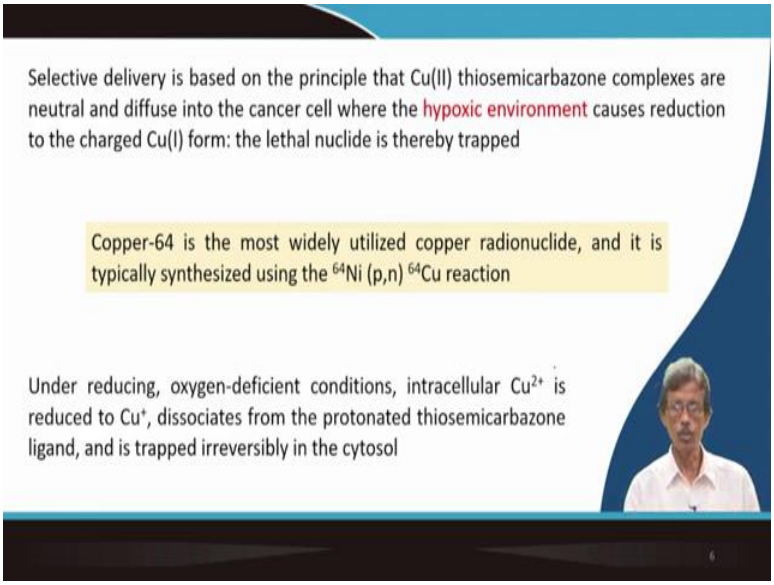

So, how we can go for its corresponding selective delivery? So, the selective delivery will be based on the principle that you have prepared a copper 2 compound which is a thiosemicarbazide complex and which is neutral also because you have two charges on the corresponding thiolate and diffuse into the cancer cell where it is hypoxic in environment. We have already discussed earlier that what is that hypoxic environment. The cancer cells and all these are hypoxic in hypoxic environment because the metabolism is faster, metabolism, the amount of metabolism is also high so you have a corresponding reduced environment, that means less oxygen will be available within the cell.

So, your corresponding reduction potential that means you are trying to go from copper 2 to copper 1 if your reduction potential is matching for that particular oxygen deficit environment what is there within the cell what can happen that though the system is getting administered with the copper 2 compound, but you will reach to a copper 1 compound. And the way it is there that you are trapping the nucleotide as a copper 1 salt, but that copper is still your copper 64. So, is most widely utilized radio nucleotide and is typically synthesize from 64 nickel. Nickel, the stable isotope of nickel is 64. You go for a bombardment proton, neutron type bombardment and you will be getting the corresponding product is your 64 copper.

Then when you have less amount of oxygen within the cell, it will be reduced to copper 2 plus and dissociate from the protonated thiosemicarbazone ligand. If you are able to now protonate that means you have S minus groups, already I told you that you have two S minus groups, when it is bound to copper 2 the stability of the copper 2 compound is different compared to the copper 1, but when it is reaching within the cell your environment is such that is not oxidizing environment but rather it is a reducing environment.

So, the cupric compound or cupric metal ion complex will be reduced to the cuprous metal ion complex. And that particular case if you have the charge more on the ligand backbone, your overall charge on the complex will be 1 minus. So, the corresponding protonation can take place now. So, the thiolate pilot of sulfur if it is protonated, because many number of protons are there which is also dependent on the local pH value of the medium, so if you are able to protonate only one of the sulfur so that sulfur will be SH and it will not be bound to the copper center so it will be a dangling part of the thing.

So, basically when you have the protonated thiosemicarbazone can be there but copper is not happy with four coordination number, it can go to three coordination number or even two coordination number so it will be happy, but it is still bound to the ligand system and therefore it is trapped within the cytosol that means within the corresponding environment the solution within the cell.

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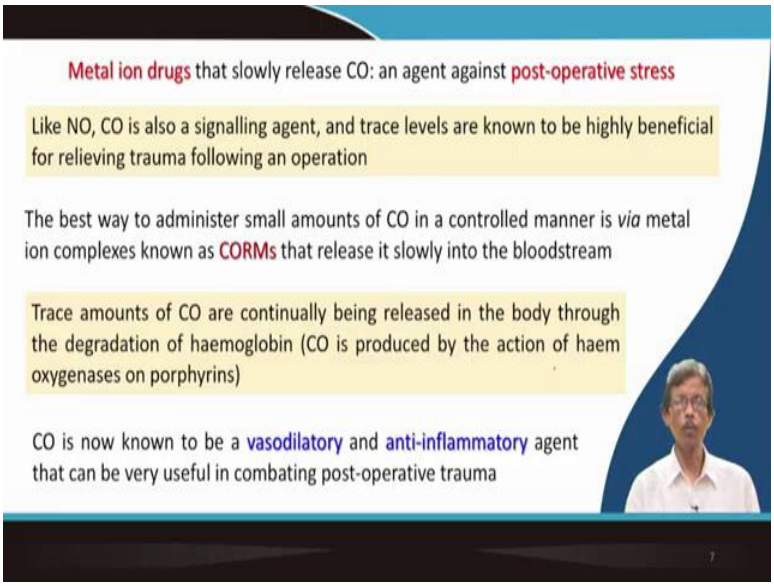

So, similar fashion, in a similar way if we want to go for the release of the carbon monoxide is a very typical example. We know all why we are making some metal and complexes or metal complexes rather. Nickel tetracarbonyl NiCO whole 4 we know. Nickel is in the zero oxidation state and the nickel powder can directly react with the carbon monoxide gas giving you tetracarbonyl nickel zero compound. But this can be used as a very good medicinal compound. It can use for the corresponding post operative stress, if a patient is suffering from a post operative stress, because many thing is happening when some major operation is taking place on a patient so it can be, he or she can be injected with this particular reagent or the metal ion complex or the metal complex which can slowly release the carbon monoxide molecule.

We all know the nitric oxide which is a very good signaling agent. Similarly, similarity is there between carbon monoxide gas and the nitric oxide gas also. So, the trace levels are known to be highly beneficial for relieving trauma following an operation. So, post operative stress

sometimes we call it as a post operative trauma can be removed or can be alleviated if some compound is given which is known as CORM, which is carbon monoxide releasing molecules.

So, what happens therefore that if you administer a small amount of carbon monoxide which will be released slowly from those molecules in a controlled fashion through the use of metal ion complexes within the bloodstream that will be beneficial and that will basically remove the corresponding stress or trauma. When we go for the slow release thing that means the molecule is sitting within the bloodstream of the patient, but it is not so stable within the bloodstream, but it is slowly degrading and it will continuously releasing the carbon monoxide to the system.

The way we know that carbon monoxide is released from our blood molecule also from our hemoglobin and myoglobin molecule because when the purified ending is being cleaved it is producing carbon monoxide. So, it is known as a very useful molecule, is a vasodilatory molecule and anti-inflammatory agent that can be useful in combating many post operative trauma or stress.

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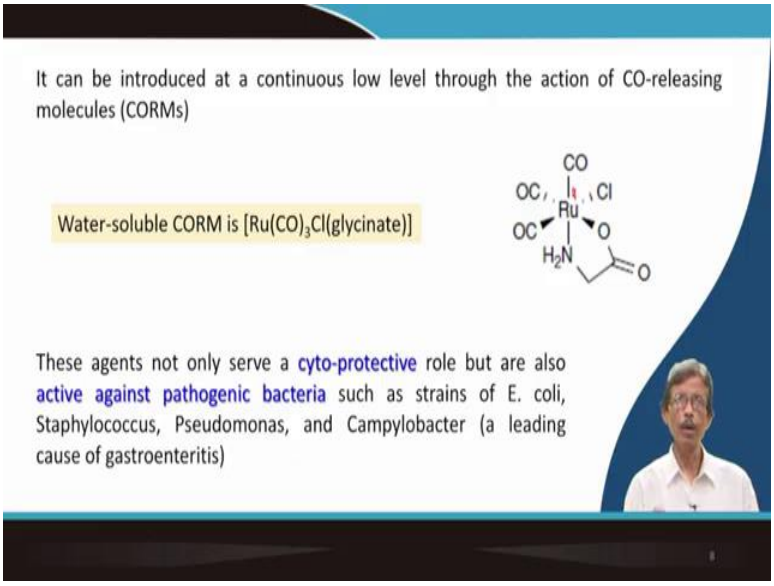

So, it is introduced via a continuous low level release where the molecules CORMs are there. So, one such example of your CORM molecule is the ruthenium center bound to a glycinate anion. A simple amine acid is your glycine, NH2CH2COO minus. When it is bound to a ruthenium center having one chloride group attached to that so it is a ruthenium 2 compound because the carbon

monoxide molecules are neutral, only the glycinate has that charge and the chloride has that charge, so is the bivalent ruthenium compound you can make it and which is also water soluble.

And the interesting thing is that this CORM molecule is also water soluble, is hexacoordinated and bivalent in nature. So, they basically sometimes serve as basically it can protect your cell, it can protect your cytosol, so is a cytoprotective role it can play against many pathogenic bacteria such as strains of E. coli, Staphylococcus, Pseudomonas and Campylobacter. Why Campylobacter, because it is well known that we are suffering all of us are suffering basically if we are having traveled from gastroenteritis.

So, if the thing like this molecule is basically interest from the academic point of view, but if something which is compatible to our body, which is not damaging our other healthy body cells or the corresponding tissues, we can administer some of these CORM molecule which will be a medicinal molecule which can slowly release the carbon monoxide to us.

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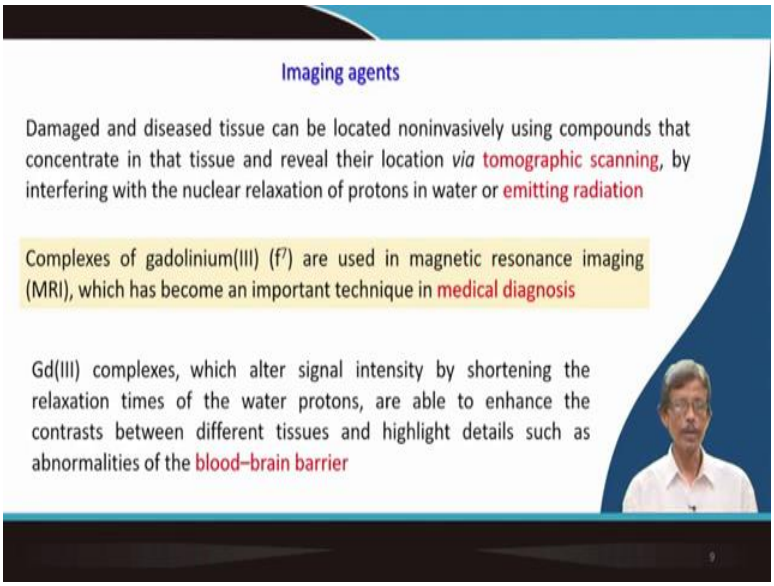

Then what are your imaging agents? So, imaging agents, if you want to get the picture of the damaged or the diseased tissues, we can go for that and some molecules should be injected. So, you have the tomographic scanning which can interfere with the nuclear relaxation of protons in water or emitting radiation. So, tomographic scanning you have, then you have the medical resonance imaging, so that is the nuclear relaxation we can study for MRI images and through

some emitting radiation like your x-ray. So, gamma ray can also be used for that particular purpose.

So, one very important and very beautiful metal ion is your lanthanide ion, which is gadolinium III. And gadolinium III is the f7, which is f7, what f7 is 4f. We know that 3D metal ions are there iron, copper, nickel all are 3D. So, above that you have the 4f so it will be a 4f metal ion site. So, MRI is very good resonance imaging thing. And for your medical diagnosis we can use this particular complex. So, why gadolinium complex, because it can alter the signal intensity by shortening the relaxation, the relaxation, nuclear relaxation process is there, how quickly it can come down to the ground state, for the different water protons, because all these cytosols, all these cells you have the water molecule.

So, if we are able to monitor those relaxation in this particular environment you will be able to image the corresponding area through this particular relaxation process. So, it can also give the details of your blood brain barrier and the different tissues by three, is MRI imaging.

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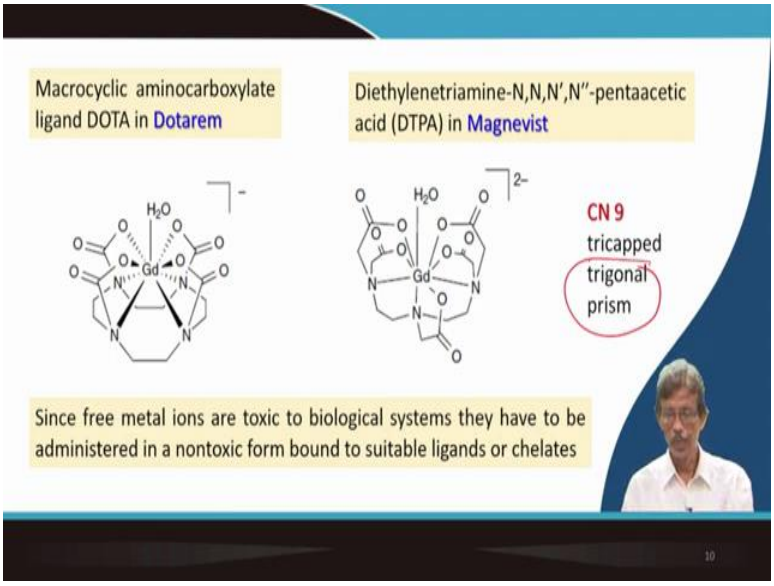

So, you take the ligand, very useful ligand, already we have seen your glycine is a very simple ligand and which can bound to the corresponding metal ion salt like ruthenium II, similarly, other amino carboxylates are also useful which are biocompatible and which has been shown promise for your administration to your body. So, one is your DOTA and the trade name is your Dotarem. So, the dotarem is a gadolinium compound and is substituted amino carboxylate

groups. So, if you have a four nitrogen bearing macrocycle and out of these nitrogens these are all NH groups like your porphyrin so you can have the corresponding substitutions like your glycine.

Similarly, also if you have the backbone as the diethylenetriamine so that diethylenetriamine, if you have the diethylenetriamine, what is that diethylenetriamine, diethylenetriamine is you have three amine functions and which are breezed by corresponding two ethylene backbone so NH2 CH2CH2NH CH2CH2NH2 and those NH functions are further or NH2 functions are further substituted by your carboxylic acid or the acetate functionalities. So, try to remember here that you have a ligand, you should know the ligand and when it is binding your trivalent gadolinium site, gadolinium is a form 4f metal ion, 4f7 metal ion which is a big one and that particular one can give rise to a very useful structure what is the coordination number for all these things.

So, here if you look at it that you will find that four nitrogens are there and four oxygen plus one water molecule, so four plus four plus one, so nine. So, is the coordination number of nine in all these cases. So, what is the geometry? What is the typical geometry? We know when coordination number is six it is octahedral and we all know what is octahedral. So, you have a square plan which is a cap pyramid and you have a bottom pyramidal part. Then if you go to a coordination number seven, what is the geometry. So, the simplest answer is that you put one extra coordination from one of the face of the eight faces of octahedral, you get six plus one that means the coordination number of seven.

How you get a coordination number of nine. So, you must have some good imagination for that. You think for a while. If you look at it that if you have a trigonal prism, you know the prism from your physics classes, you know from your school level, what is prism, so you have one trigonal face and another trigonal face and when it is these are connected so one face and second face and the trigonal face you have the three so three plus two five faces you can have. But if you go for the capping of these square faces, the rectangular faces, if they are all caped like your octahedron you will get six plus three that means nine coordination sides.

So, you have to administer the metal ion complexes. We are not going for the free metal ion. Why the corresponding gadolinium nitrate, gadolinium acetate or even gadolinium oxide or hydroxide is not functioning as a very useful imaging agent. They are not functioning as

magnificent, they are not functioning as dotarem why, because the free metal ions are always toxic like iron that is why always I have a joke. I always say that you are animate. Doctor is not prescribing you iron nail or iron powder. We are taking something as a corresponding iron complex, iron metal ion complex.

So, always you have to go for the removing or little bit alleviation of the toxicity of the free metal ion. The free metal ions are always toxic. Try to remember that. So, that is why the metal ion salts cannot be given as your medicine or any therapeutic agent or your imaging agent. Similarly, your gadolinium cannot be administered in your body in the free form. That is why it will be bound to some ligand and suitable ligands and the chelates you can have which should be non-toxic in your nature.

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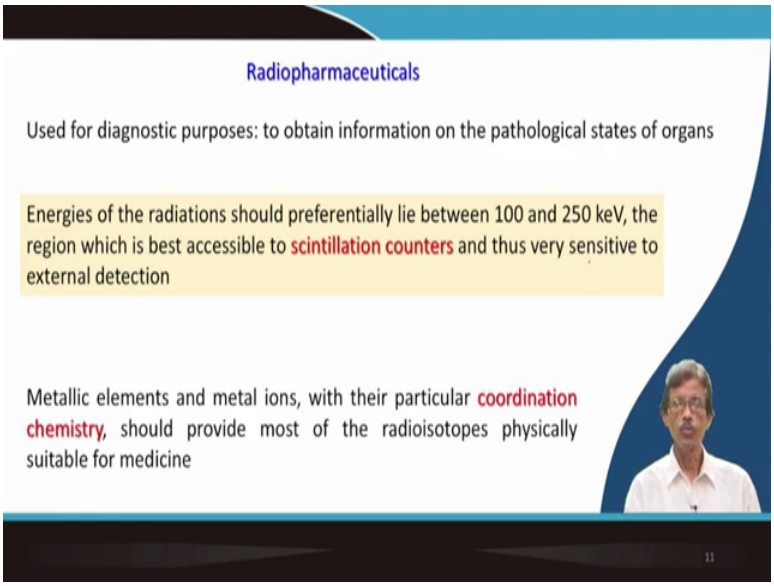

So, next we go for, we know how imaging agents are useful, how the corresponding molecules are important, how the carbon monoxide releasing molecule, how the gadolinium is there, because the gadolinium will give you the corresponding radioactivity, like gallium. So, if we go for something where we use these for diagnostic. Information about the corresponding diseased condition or the pathological state of the, your organ, your most vital organ say kidney, your liver, your lung, your brain, many places you can just track.

What do you go for? We go for the energies of the radiations should preferentially lie between 100 to 250 kilo electron volt only, because earlier we have seen that gamma radiation that

gamma radiation it is highly energetic. So, when the gamma radiation is highly energetic we cannot go for that, because we have to use for the scintillation counters the detectors, so energy should be less within 250 kilo electron volt and we go for that. So, not only all these things, so the metallic elements and the metal ions and their particular coordination compounds should provide most of these radioisotopes which are physically suitable for medicine.

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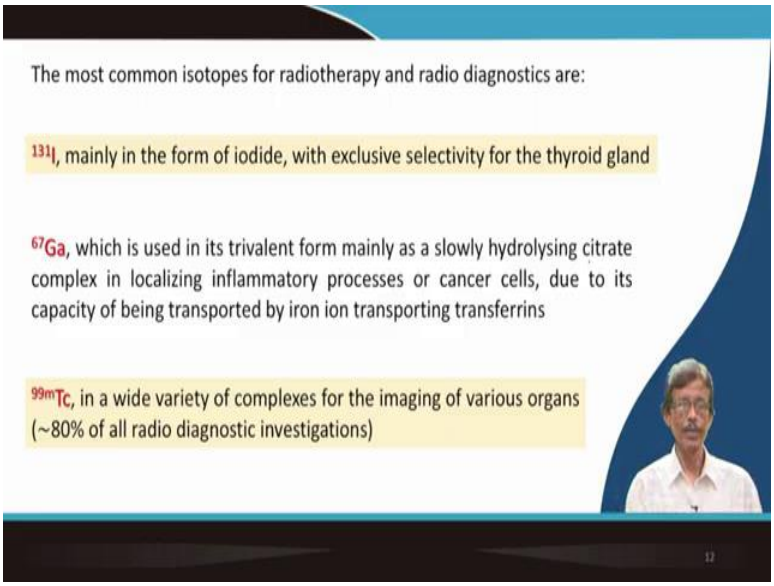

So, we go for these radio diagnostics. What are the isotopes? We all know. Iodine we required that is why we take iodized salt. So, 131 iodine we can use it for your monitoring thyroid gland. So, go for only the radioactivity. Your gallium, not stable gallium is radioactive gallium is 67 which is taken along with cited, cited is your ligand for many cancer cells can be detected and capacity of being transported by iron ion transporting transferrins. We all know that transferrins are useful to bind iron in the trivalent set, gallium is also below aluminium you have gallium so is a trivalent stable state.

So, gallium can also be bound by those transferrins sand be carried by that particular transport mechanism, because by mistake it will trap gallium. But the gallium will be carried by the transferrins to the site where you had the corresponding cancer cell. Then metastable 99m metastable technetium can also be useful.

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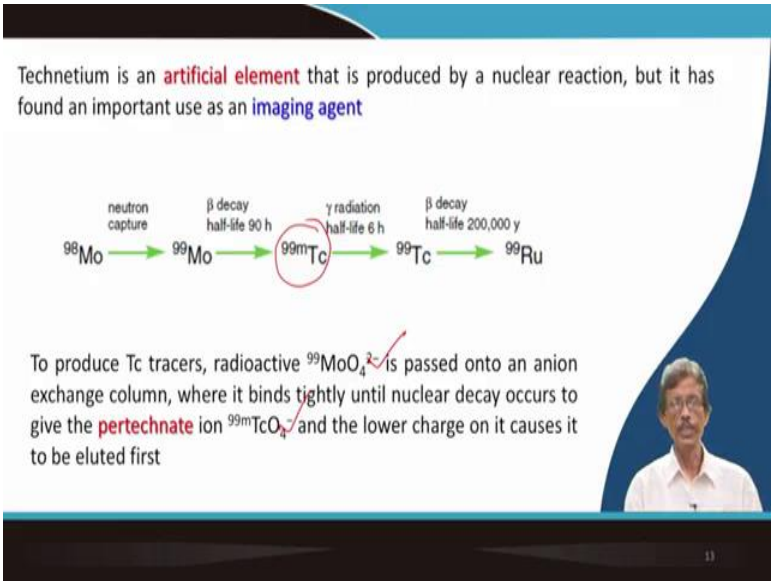

So, that technetium is an artificial element. We do not get its natural form. But how you can produce it, because it is a very useful imaging agent? So, you start with molybdenum 98 and molybdenum 98 you convert it to that of your technetium 99m technetium which is the unstable one, metastable, which will give you the corresponding gamma radiation of half life about six hour so that is why it is useful.

So, how you produce like molybdate, you take that molybdate like permanganate, then the nuclear decay occurs on the pertechnate. So, you have the pertechnate, pertechnate you get and the lower charge on it causes to be eluted first. So, you have the corresponding movement, because you have the charge on the molybdate is 2 minus and here you have the charge as the 1 minus. So, you can separate it out. Once you form it, you have to separate it from the starting material. So, starting molybdate how can we freed out of that your 99m pertechnate.

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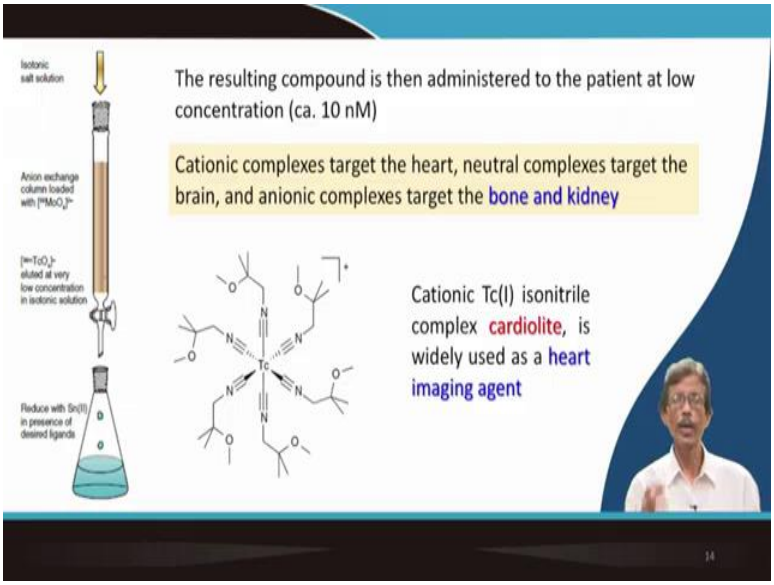

So, very simple technique we will use, because we will be administering the patients with only 10 nanomolar concentration. So, you take that isotonic salt solution. In-situ we can also generate it. You have the anion exchange resin or column fitted with that of your molybdate and then you produce the corresponding technate, pertechnate 99m.

And when you go that you just produced it for this corresponding this particular column if it is happening that particular nuclear reaction, you get it 99m technetium as pertechnate is producing. But if you put it on a conical flask we having some tin 2 chloride that means stannous chloride, it will be present with the ligand. So, ligand is there, you have the reducing agent. So, in-situ we will be producing that particular imaging agent or the technetium salt.

In a similar fashion many other compounds cationic complexes can be used and anionic complexes can be used as well as neutral complexes we can use for heart, bone and kidney imaging. So, one typical example of that imaging is your this particular compound, which is your isonitrile compound. Carbon is bound to the technician center and is catatonic also. That is why the technetium is in plus 1 oxidation state. And the trade name which is available in the market, which is the red in color, so cardiolite is a trade name for that particular molecule is available in the market as heart imaging agent. Why it is for heart, why not is for brain or bone that you should try to understand.

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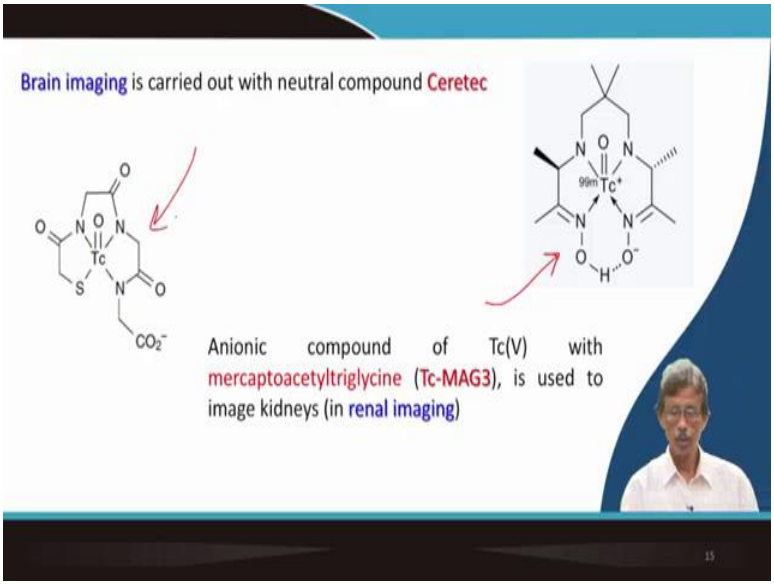

So, brain imaging agent is carried out by the neutral compound which is celetec. If you have the corresponding, the neutral compound, so the neutral compound celetec if you can have, so you get that compound as the technetium V. So, this neutral compound celetec if you get that is an anionic compound this technetium V on the right hand side so this is your technetium V compound which is mercaptoacetyltriglycine and this is your corresponding neutral compound. So, these all basically gives us all these informations nicely in our hand.

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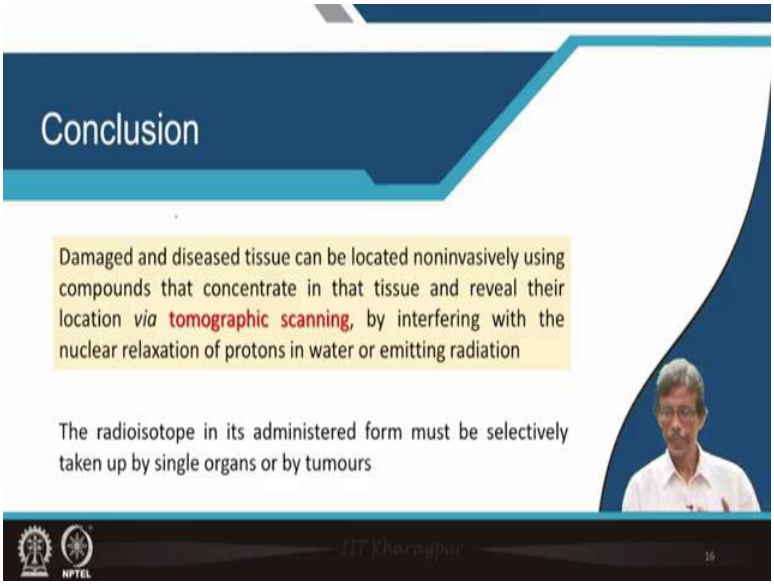

So, what we have seen therefore that what we have seen is that you have the damaged or diseased tissues in hand which is located non-invasively using many diagnostic tools like tomographic scanning or MRI or the corresponding other thing, but the most important one is your nuclear relaxation process for the different protons, because the water protons are useful, therefore, for your corresponding imaging process and when it emit radiation like gamma radiation, you can also detect that.

How we produce the radioisotopes and these radioisotopes we can administer in the form must be selectively taken up by the single organs or the tumors, so that particular form. Why it is specialized for your organ and the tumor that we have discussed, because you have a cationic complex or a neutral complex or the anionic complex. So, three types of complexes are important to go for your brain scanning, for your bone scanning or your kidney scanning.

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So, we can see this as the medical diagnosis for the metal ions, the MIs, in diagnosis and also the book of Crichton. So, thank you very much for your kind attention.