Bioinorganic Chemistry
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Lecture - 19
Metals in Medicine: Introduction to Medicinal Inorganic Chemistry

Hi everybody, welcome back to this short course of Bioinorganic Chemistry. Today I will be talking about Metals in Medicine. Bioinorganic chemistry is a rapidly developing field and there is enormous potential for applications in medicine not only for the essential elements, but also for non-essential and even radioactive elements.

Medicinal inorganic chemistry offers real possibilities to pharmaceutical industries which have traditionally been dominated by organic chemistry alone. But the discovery of truly novel drugs with new mechanisms of action. Metal ions play important roles in biological processes, we have seen in my previous lectures and the field of knowledge concerned with the applications of inorganic chemistry to therapy or diagnosis of disease each medicinal inorganic chemistry.

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Among the natural sciences medicinal inorganic chemistry is still considered a rather young discipline by many, but this is contrary to the historically proven use of metals in pharmaceuticals which trace back to the ancient civilizations of Mesopotamia, Egypt, India and China.

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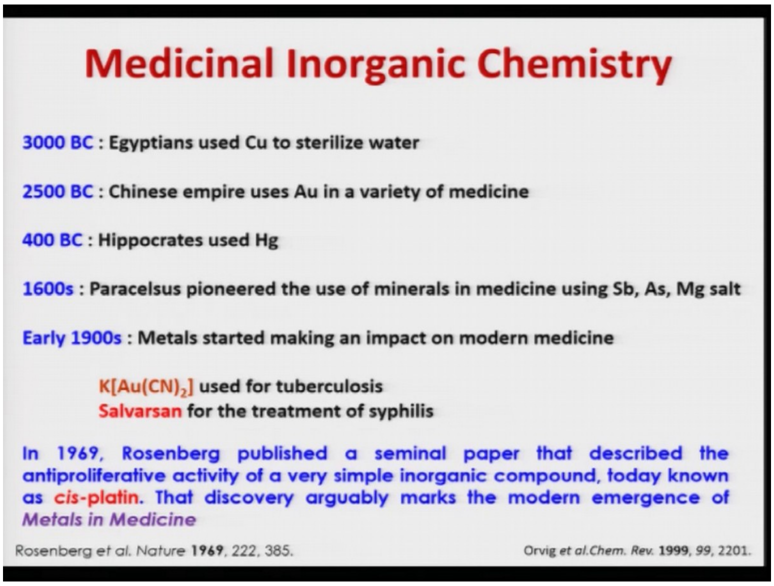

Indeed medicinal inorganic chemistry has been practiced; however, for almost 5000 years as far back as 3000 BC the Egyptian used copper to sterilize water. Gold was used in a variety of medicines in Arabia and China 3005 years ago more as a result of precious nature of gold than of its known medicinal activities.

Various iron remedies are used in Egypt about 1500 BC around the same time that zinc was discovered to promote the healing of wounds. It is only in the last 100 years; however, the medicinal activity of inorganic compounds has slowly been developed in a rational manner. Starting in the early 1900 with gold for tuberculosis, various antimony compound and also various gold salts in a number of different conditions.

If you look back in 1969, Rosenberg published a seminal paper that described the terrific activity of a very simple inorganic compound, today known as *cis*-platin. That discovery arguably marks the modern emergence of Metals in Medicine.

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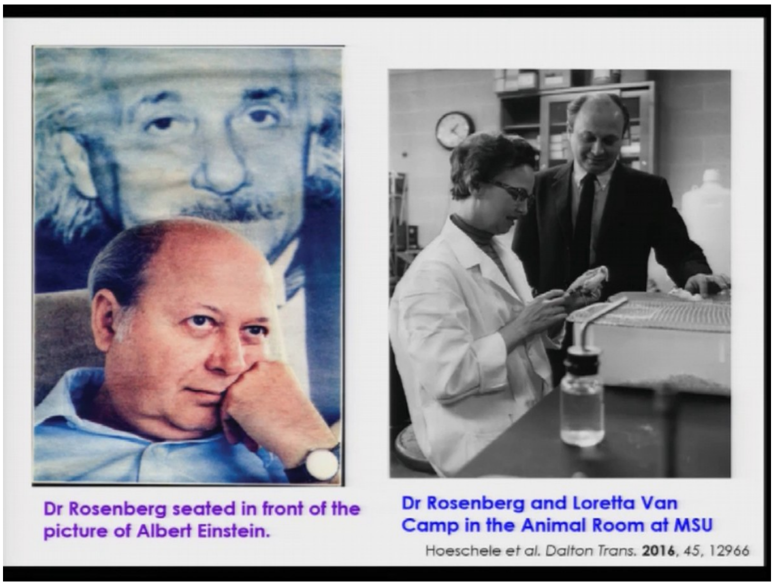

Now, this is picture of Dr. Rosenberg, seated in front of the picture of Albert Einstein. Rosenberg's and Loretta Van Camp picture is shown here in the animal room at Michigan State University.

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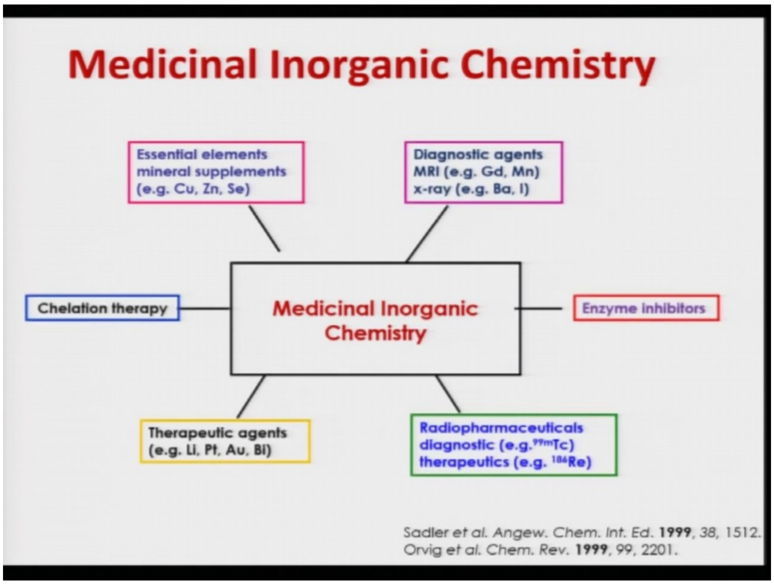

Now, medicinal inorganic chemistry as I have just said a new branch of chemistry and it has many diverse field. It deals with essential element mineral supplements it also talks about chelation therapy, therapeutic agents, radiopharmaceuticals, enzyme inhibitors, diagnostic agents many many aspects are discussed in the medicinal inorganic chemistry.

So, you can see that it is a highly interdisciplinary in nature, I will now take a joy ride to highlight the importance of inorganic elements in medicines in this short course of bioinorganic chemistry.

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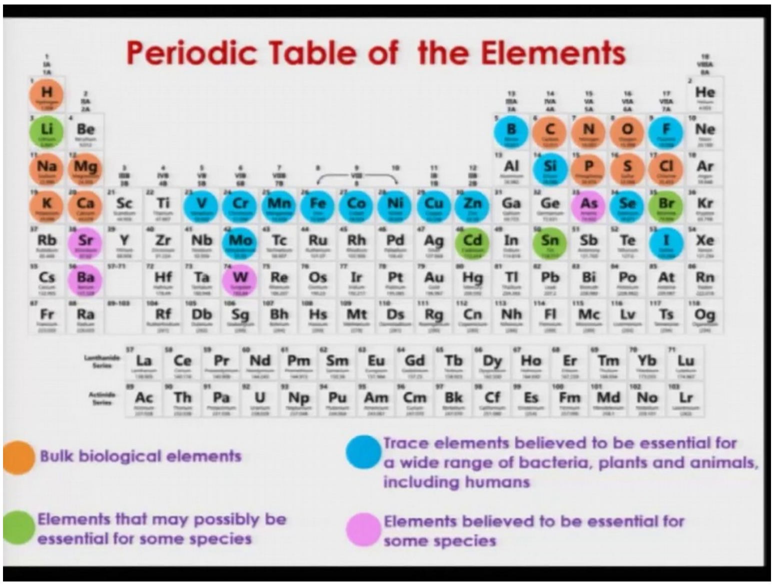

This is what is the periodic table of elements, as you can see that bulk biological elements are highlighted in brown and this blue one vanadium, chromium, manganese, iron these are all trace elements believed to be essential for a wide range of bacteria, plants and animals including humans. The green one is the elements that may possibly be essential for some species and pink also these are elements believed to be essential for some species. These elements are indeed utilized by nature for various activities.

If you look at this entire periodic table the other elements are not even utilized in biology because of various reasons which I have discussed in my earlier lectures in details.

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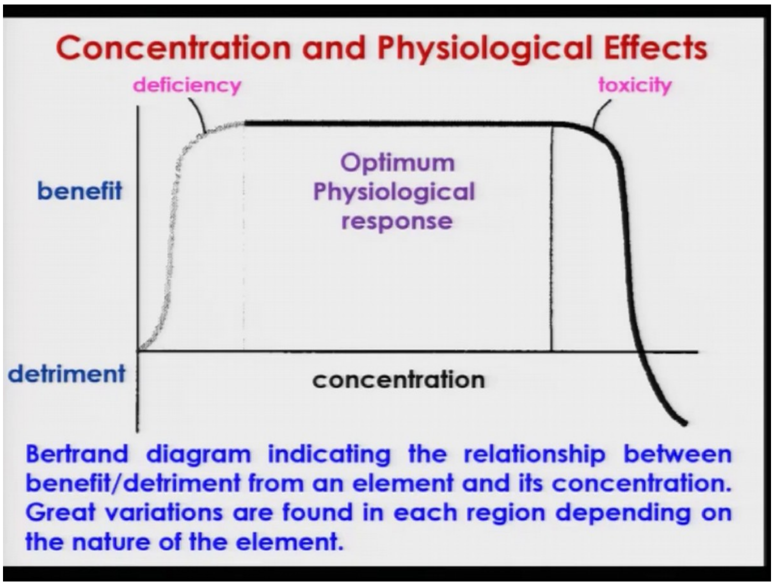

This is what is Bertrand diagram indicating the relationship between the benefit from an element and its concentration as I have also discussed earlier. There have to have an optimum physiological response for every elements present in the biological system even if it is an essential.

And if one has less concentration or more concentration both are actually detrimental for our life, if it is less concentration diseases will come out of those deficiencies of this element and if it is more concentration it will leads to toxicity. And this is nicely represent that we need to have optimum concentration for our good health.

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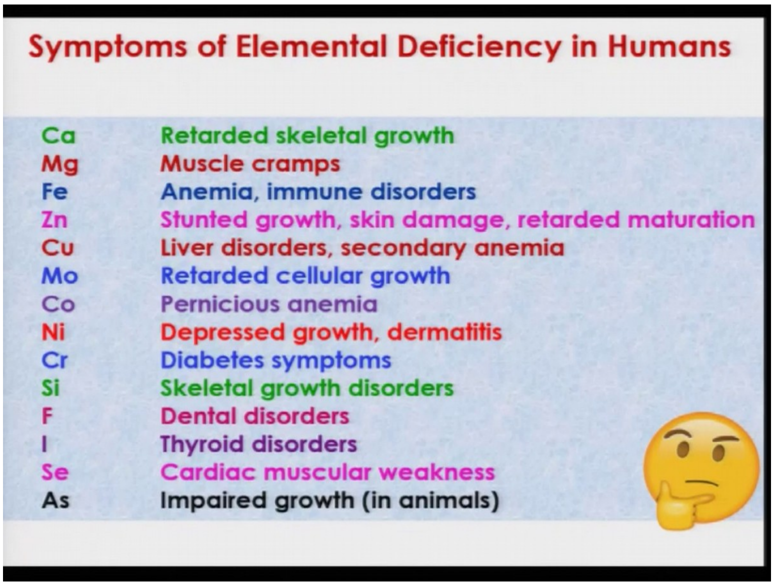

I am showing a table where the symtoms of elemental deficiencies in human like calcium retarded skeletal growth, magnesium, iron, anemia, zinc skin damage, copper liver disorder, molybdenum retarded cellular growth, cobalt pernicious anemia like all these are listed over here. And as you can see that if you have deficiency in these elements then it causes various problems in our day-to-day life.

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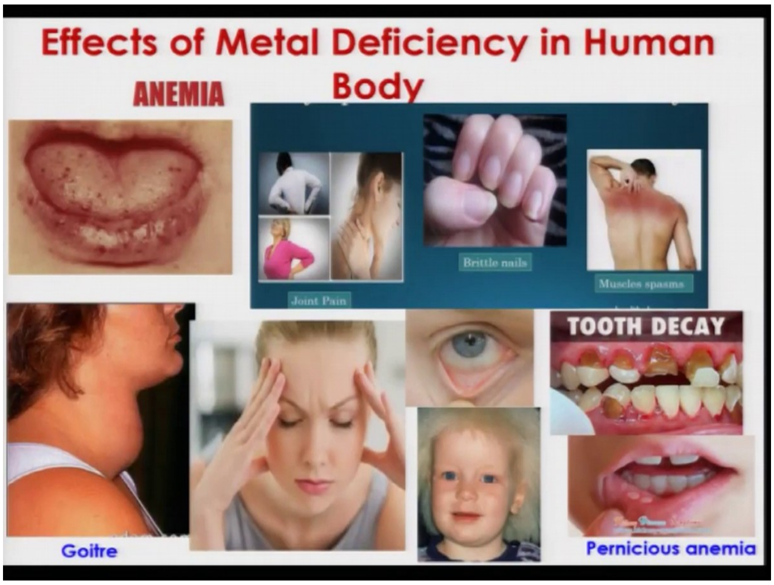

Now, some of these effects of metal deficiency in human is shown here.

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And I am not going to discuss all in details, if you have deficiency of certain metals you need to take medicines to supplement that deficiency and some of these medicines are shown over here.

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Toxic Effects of Some Non-Biological Metals

Metal (Class)	Effect of Excess	Comments
Aluminum (hard, Al^{3+})	Implicated in Alzheimers disease	May interact with phosphates, may cross-link proteins.
Cadmium (soft, Cd^{2+})	Renal toxicity	Blocks sulfhydryl groups in enzymes and competes with zinc. Stimulates metallothionein synthesis and interferes with Cu(II) and Zn(II) metabolism.
Mercury (soft, Hg_2^{2+}, Hg^{2+})	Damage to central nervous system, neuropsychiatric disorders	CH_3Hg^+ compounds are lipid-soluble.
Lead (soft, Pb^{2+})	Injuries to peripheral nervous system, disturbs heme synthesis and affects kidneys	Pb^{2+} may replace Ca^{2+} with loss of functional and structural integrity. Reacts with sulfhydryl groups, replaces Zn^{2+} in δ-aminolevulinic acid dehydratase.
Thallium (soft, Tl^+)	Poisonous to nervous systems, enters cells via K^+ channels	Although similar to K^+, Tl^+ binds more tightly to N and S ligands.

Now, I will be showing now the toxic effects of some non-biological metals you can see that aluminum, cadmium, mercury, lead and thallium these are not important for our life and thus non-biological metal ions. These causes lots of problem in our day-to-day life and they are poisonous, and once they are poisonous then how you can remove from the biological system.

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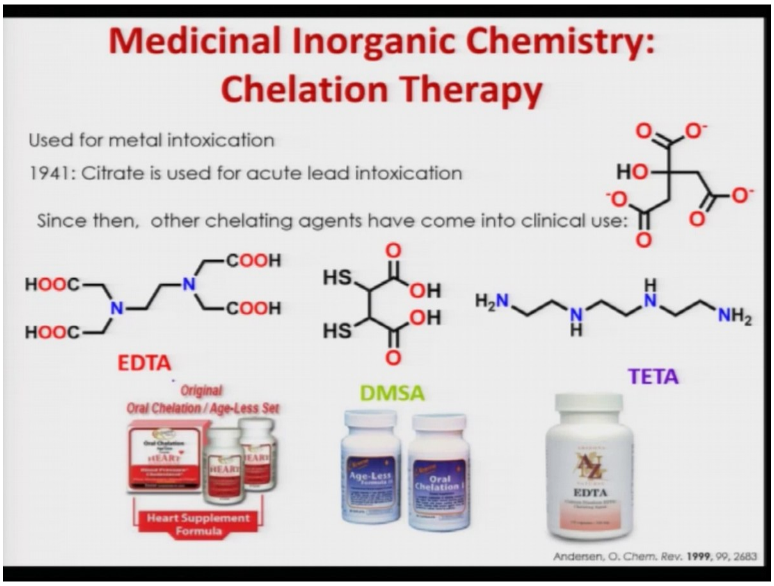

Indeed the chelation therapy which can remove those metal which are toxic in our body. As one can see in 1941 citrate is being used to treat acute lead intoxication. Since then, other chelating agents has been designed and some of them are shown here these are very popular EDTA, DMSA and one can buy it in the market.

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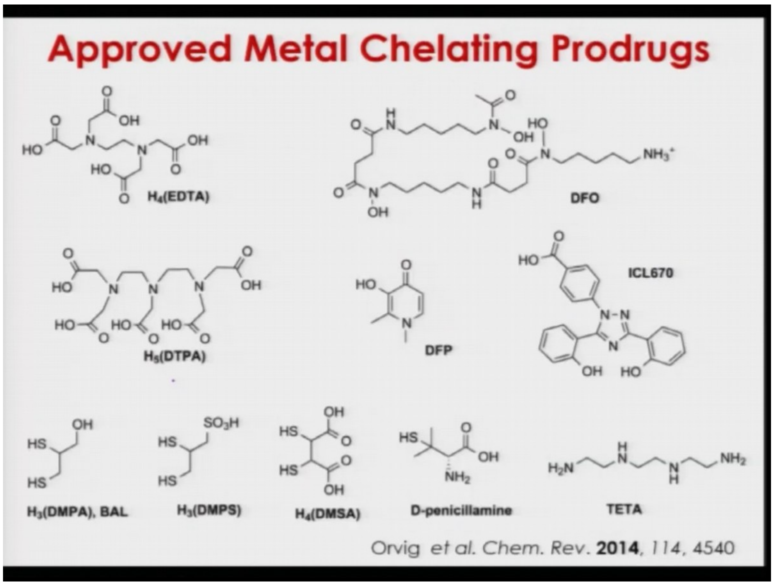

And these are some of approved metal chelating prodrugs and they selectively bind those poisonous metals and make a strong complex and then it is removed from our body. So, this is a very powerful therapeutic technique people have been using for a quite long time now.

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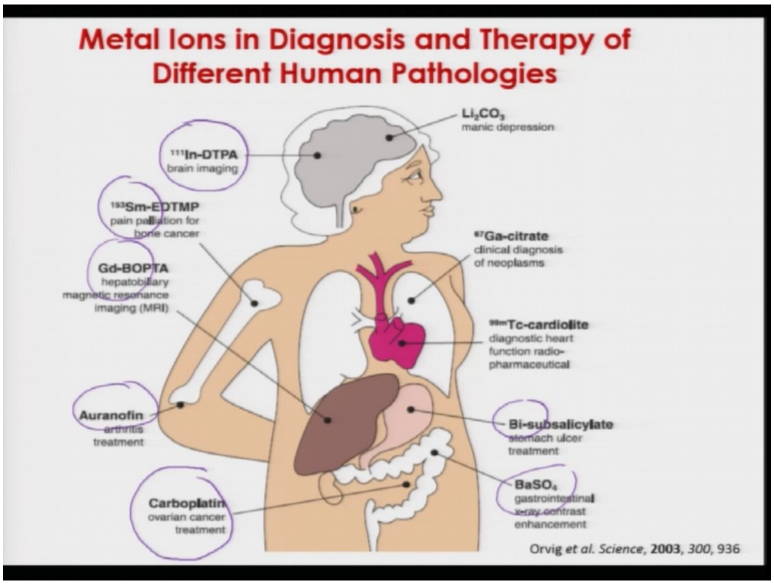

The metal ions in diagnosis and therapy of different human pathologies are shown here. So, as one can see that this indium metal is utilized for brain imaging ^{153}Sm is also used for bone cancer, the gadolinium being used for magnetic resonance imaging, auranofin this is a gold complex which is utilized for arthritis treatment.

Carboplatin which I am going to discuss in my next lecture in details is a platinum complex has been extensively used for cancer treatment, barium sulfate X-ray contrast agent, bismuth being used to treat ulcer, a meta stable isotope of technetium is utilized as a diagnostic heart function radiopharmaceutical. So, you can see this there are many metals ion they are utilized diagnosis and therapy of different human pathologies.

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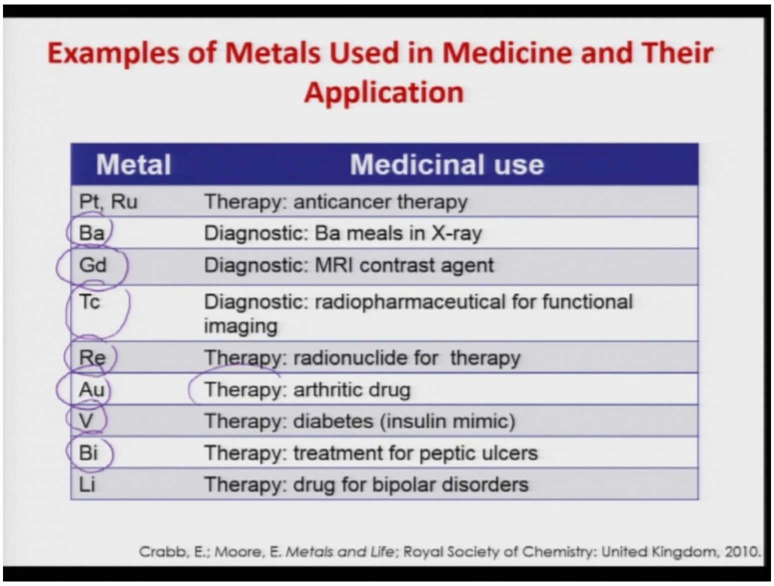

I will show you here the examples of metals that are used in medicines and their various applications. As one can see that platinum and ruthenium they are used in therapy as a anti-cancer drug, barium being used as a diagnostic in X-ray, gadolinium is being used as a MRI contrast agent.

Technetium is used for radiopharmaceutical for functional imaging, rhenium radionuclide for therapy, gold also therapy arthritic drugs, vanadium used in therapy in diabetics, bismuth used in therapy for treatment for peptic ulcers, lithium used in therapy drugs for bipolar disorder. So, these are some of these metal ions that are popularly used in medicines.

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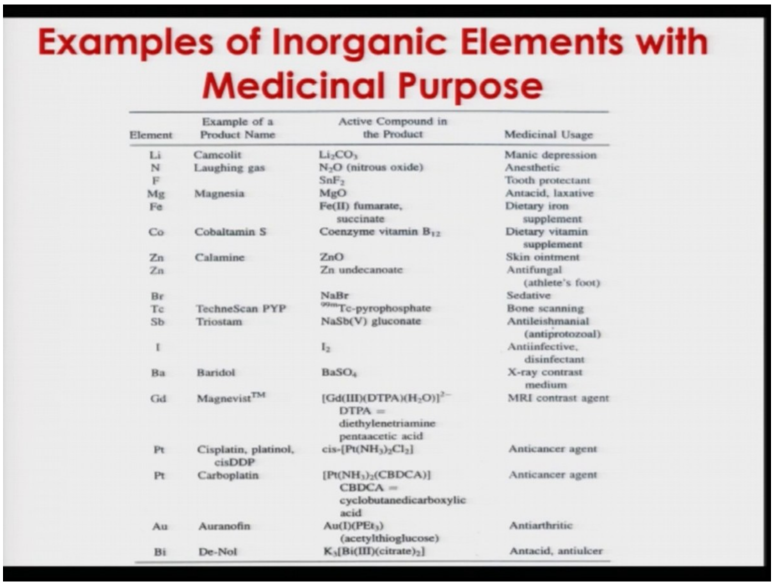

Examples of Inorganic Elements with Medicinal Purpose

Element	Example of a Product Name	Active Compound in the Product	Medicinal Usage
Li	Camcolit	Li_2CO_3	Manic depression
N	Laughing gas	N_2O (nitrous oxide)	Anesthetic
F		SnF_2	Tooth protectant
Mg	Magnesia	MgO	Antacid, laxative
Fe		Fe(II) fumarate, succinate	Dietary iron supplement
Co	Cobaltamin S	Coenzyme vitamin B_{12}	Dietary vitamin supplement
Zn	Calamine	ZnO	Skin ointment
Zn		Zn undecanoate	Antifungal (athlete's foot)
Br		NaBr	Sedative
Tc	TechneScan PYP	^{99m}Tc-pyrophosphate	Bone scanning
Sb	Triostam	NaSb(V) gluconate	Antileishmanial (antiprotozoal)
I		I_2	Antiinfective, disinfectant
Ba	Baridol	$BaSO_4$	X-ray contrast medium
Gd	Magnevist™	$[Gd(III)(DTPA)(H_2O)]^{2-}$ DTPA = diethylenetriamine pentaacetic acid	MRI contrast agent
Pt	Cisplatin, platinol, cisDDP	cis-$[Pt(NH_3)_2Cl_2]$	Anticancer agent
Pt	Carboplatin	$[Pt(NH_3)_2(CBDCA)]$ CBDCA = cyclobutanedicarboxylic acid	Anticancer agent
Au	Auranofin	$Au(I)(PEt_3)$ (acetylthioglucose)	Antiarthritic
Bi	De-Nol	$K_3[Bi(III)(citrate)_2]$	Antacid, antiulcer

And here I have shown examples of inorganic elements with medicinal purpose. A large number of elements which are being used in a day-to-day basis in our life and we use many of these products. The list is very long and I am not going to discuss all them in details, but you can see that inorganic elements are being regularly utilized for this kind of medicinal purpose.

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Some of this clinically approved metallodrugs are shown over here.

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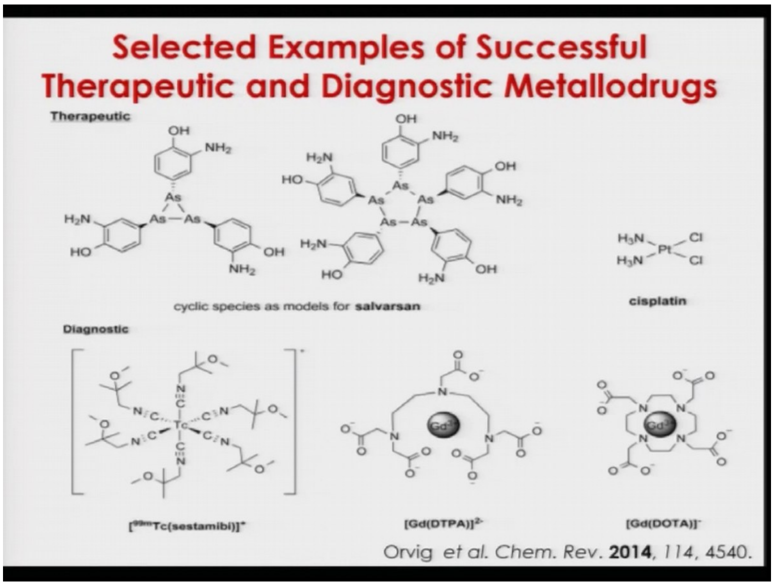

Here I am showing some examples of successful therapeutic and diagnostic metallodrugs like you can see that in salvarsan is basically the arsenic metal is utilized this is cyclic species as models for salvarsan. *Cis*-platin will be talking in details about this drug molecule, diagnostic where this technetium is popularly utilized, gadolinium complexes are shown here which are popularly utilized as a MRI contrast agents.

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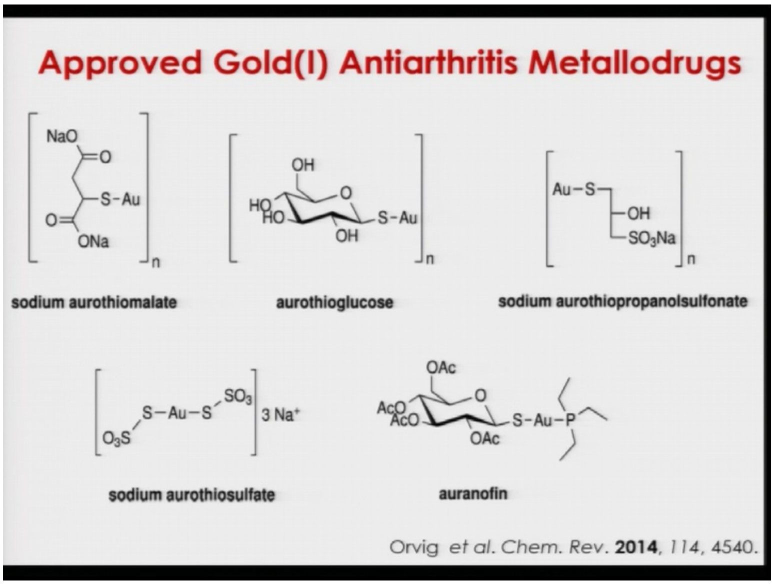

Here I am showing the approved gold I arthritis metallodrugs, you can see that auranofin is shown over here there are others, gold I complexes which are also utilized to treat arthritis in our day-to-day basis, these are also approved drug.

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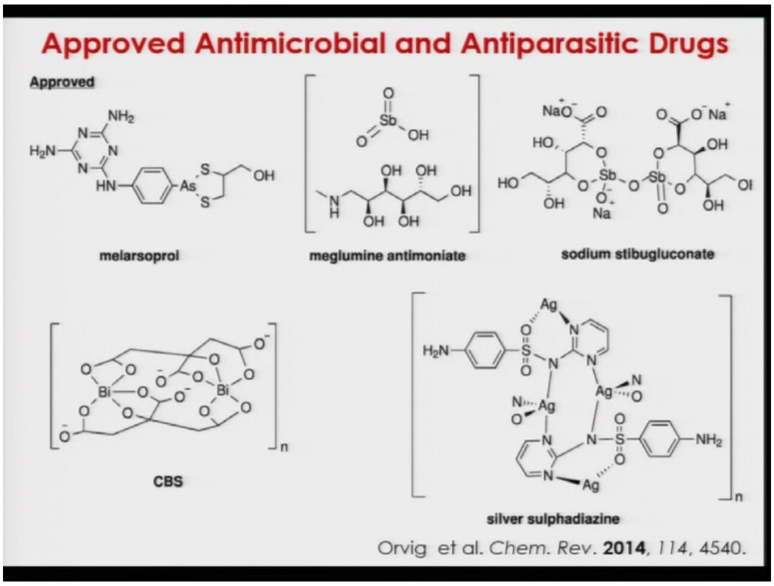

Now, here I am showing they approved antimicrobial and anti-parasitic drugs, you can see that in these drugs this arsenic metals are being utilized also here also sodium and antimony is used here bismuth is being utilized, here it is silver is being utilized, you see that so many drugs are there where several metal ions are utilized and these are very important for their activity.

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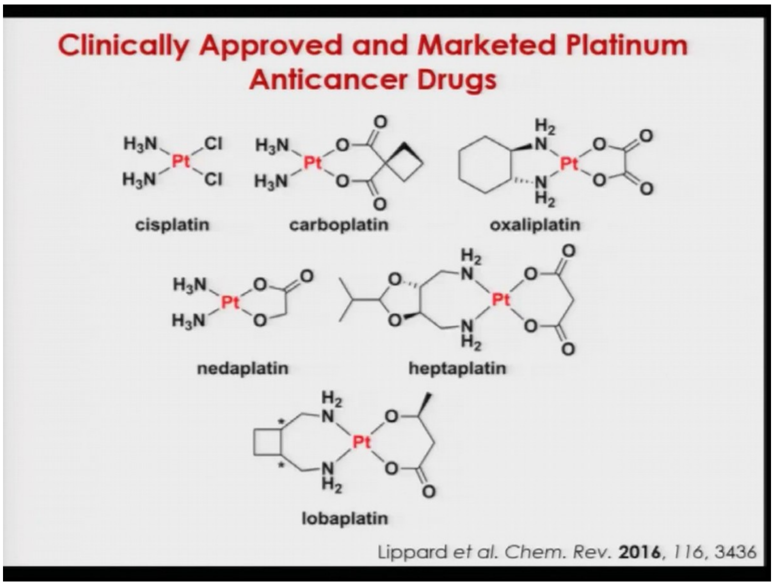

I am showing here the clinically approved and marketed platinum anti-cancer drugs like *cis*-platin, carboplatin the structure is shown here, oxaliplatin, nedaplatin, heptaplatin, lobaplatin is also shown here. You see this is the structure and these are all clinically approved and you can buy this anti-cancer drugs in the medical shops.

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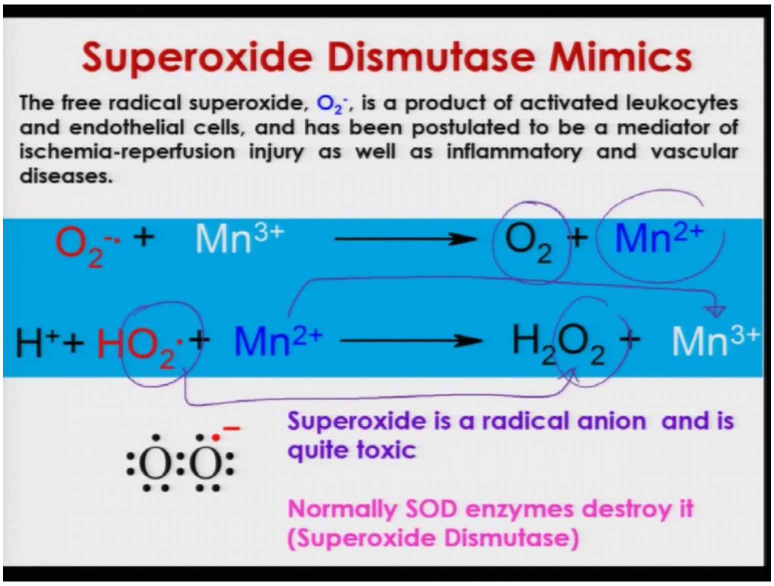

In my previous lectures I discussed the superoxide is extremely poisonous in our body and responsible for various diseases and some of them are inflammatory and vascular diseases. There are several drugs which can destroy the superoxides and which are one of this popularly used superoxide dismutase mimics is shown here this manganese complex. And indeed this manganese, there is a redox active metal ion which oxidized and reduced superoxide to convert dioxygen and peroxides. This Mn(III) which oxidize superoxide to oxygen get reduced to Mn(II) and this Mn(II) reduce the superoxide to peroxides and Mn(II) will be oxidized to Mn(III) .

So, you can see that this manganese is a redox active metal ion and how it destroyed the superoxides which is a radical and highly toxic in nature. Of course, in our body superoxide dismutase enzyme is there to destroy the superoxide which are being formed, but we also need some medicines which can also destroy the superoxides and converts to oxygen less harmful product like oxygen and peroxides.

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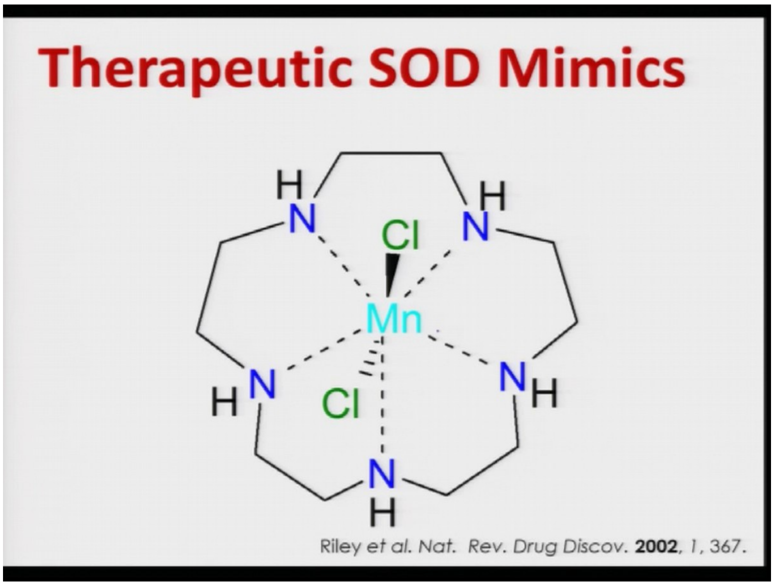

So, one of this therapeutic SOD mimics is shown here you see that this is manganese complex and which actually destroy the superoxides and converting to less harmful products like oxygen and peroxides.

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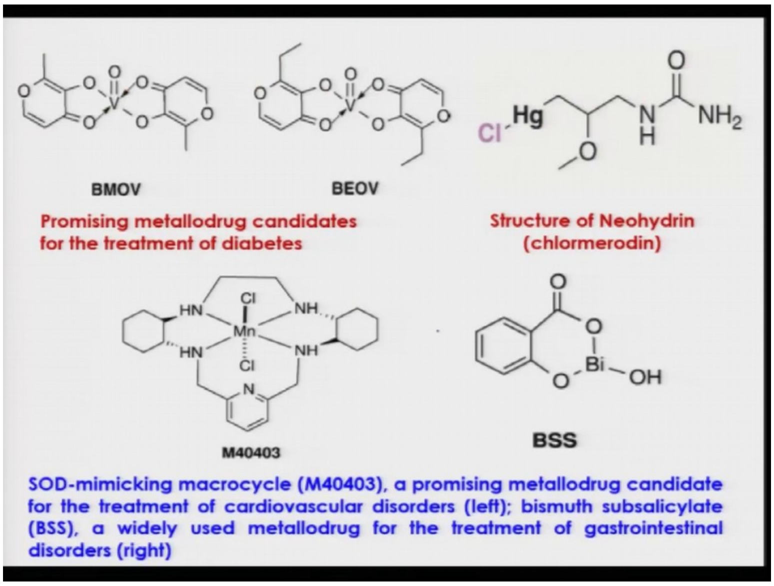

I am showing here some promising metallodrugs are used for the treatment of diabetics; any oxovanadium species these are very promising metallodrug candidate for the treatment of diabetics. Similarly this is the mercury complex you see that the structure of neohydrin is shown here which contains mercury. And I have just discussed that SOD mimicking macrocycle is a manganese complex which destroyed the superoxides into oxygen and peroxides. And the bismuth complex is shown over here which is widely used metallodrug for the treatment of gastro intestinal disorder.

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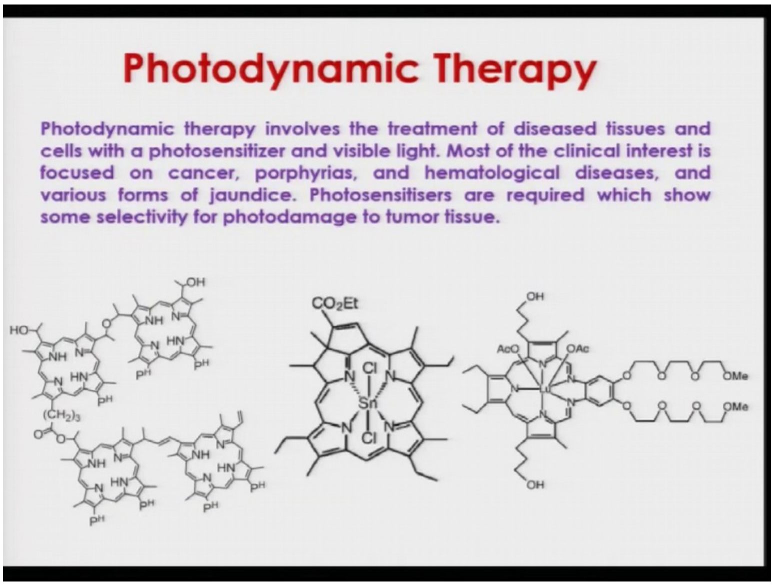

Photodynamic therapy is another treatment for the diseased tissues and cell with a photosensitizer and visible light. Most of the clinical interest is focused on cancer, porphyrias and hematological diseases and various forms of jaundice. Some of these photosensitizer are shown over here you see this is photofrin is a approved drug and there is also tin complex there is also another metal complex which you can see that they are utilized in photodynamic therapy.

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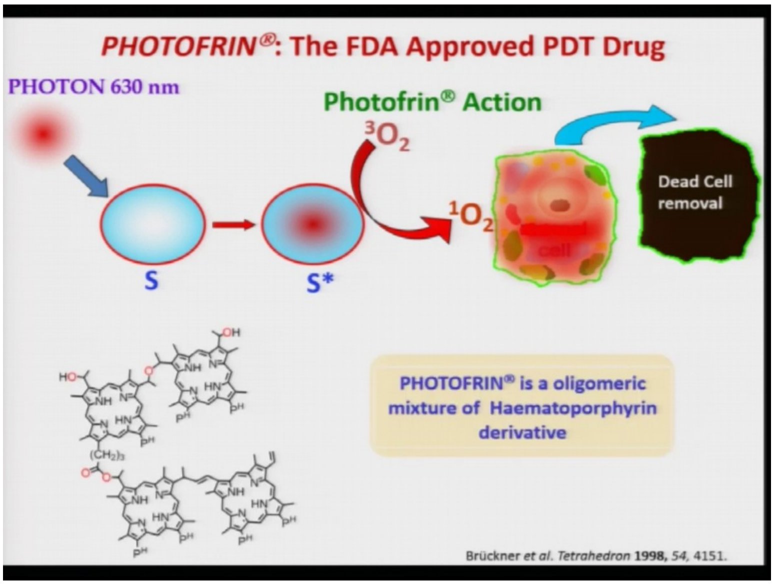

I will now show, how this photofrin which is an FDA approved PDT drug is responsible for photodynamic therapy. Now, the photon which actually excite this photosensitizer and convert it into the excited state. The excited state of photo print actually convert this triplet oxygen to singlet oxygen and as you all know that singlet oxygen is highly reactive immediately destroy the cancer cell into the dead cell.

So, if you have a cancer cell and if you can generate singlet oxygen in that region cancer cell would be converted to the dead cell utilizing that singlet oxygen and photofrin which has been used as a photosensitizer here in this photodynamic therapy.

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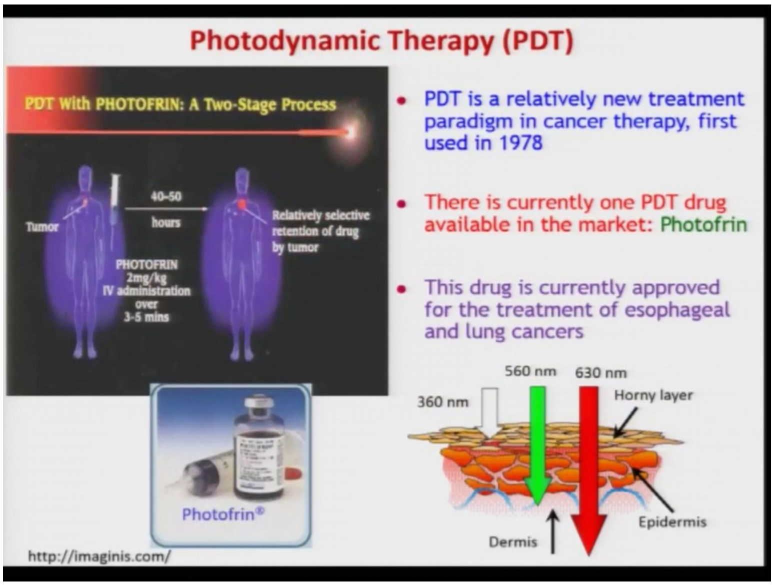

I will now talk about little bit on photodynamic therapy. The PDT is relatively new treatment in cancer therapy first used in 1978, there is currently one PDT drug available in the market photofrin and this drug is currently approved for the treatment of some cancers. And as you can see that what is happening one need to inject this drug and this drug actually accumulates selectively by the tumor cells and this tumor cell once you shine light say mostly that the red light; why red, because red light indeed penetrates the tissue more compared to the other lights.

And then what would happen this photosensitizer will be excited and eventually this photosensitizer converts this triplet oxygen to extremely reactive singlet oxygen and thereby destroy the cancer cell. So, this is one of the very popular treatment being used by cancer patients.

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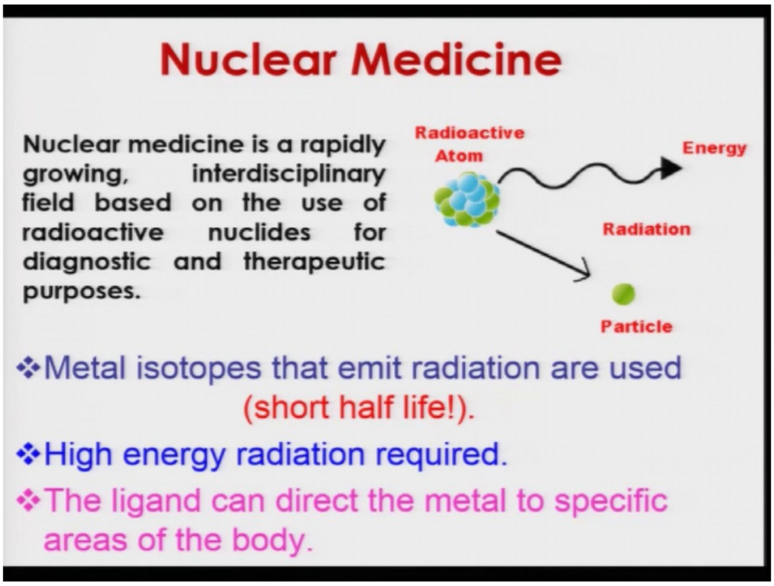

I will now talk about the nuclear medicines. Nuclear medicine is a rapidly growing interdisciplinary field based on the use of radioactive nuclides for its diagnostic and therapeutic purpose. So, this is the radio atom which emits energy and one like to utilize this radiation for something very useful. The radioactive atoms that emit radiations are used and the half life should be short enough to be utilized properly, high energy radiation is required, the ligand can direct the metal to specific area of the body.

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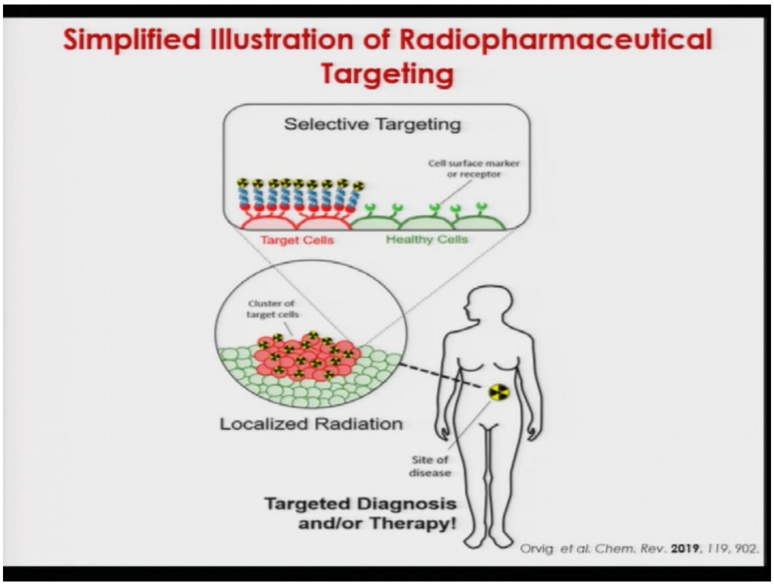

So, here is the simplified illustration of radiopharmaceutical targeting, you see that this is what is the site of disease and the radiopharmaceutical should target selectively those cells which are actually affected and the other cell should not be disturbed.

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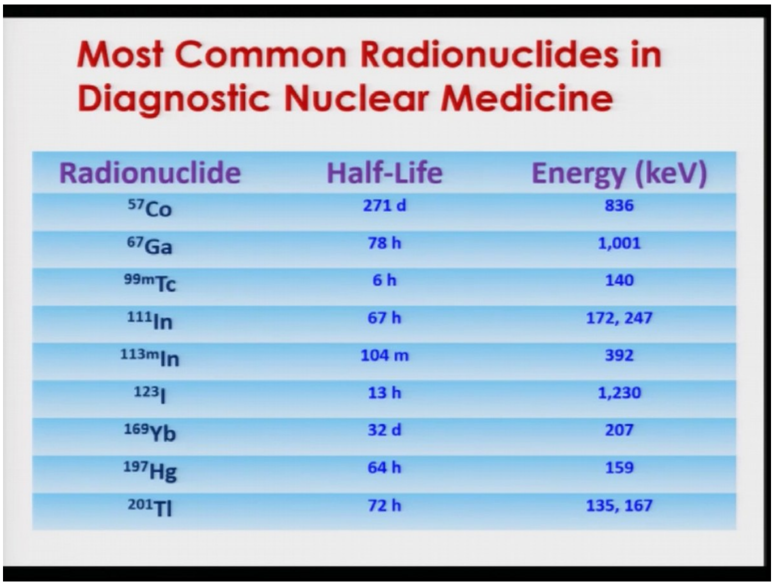

Radionuclide	Half-Life	Energy (keV)
^{57}Co	271 d	836
^{67}Ga	78 h	1,001
^{99m}Tc	6 h	140
^{111}In	67 h	172, 247
^{113m}In	104 m	392
^{123}I	13 h	1,230
^{169}Yb	32 d	207
^{197}Hg	64 h	159
^{201}Tl	72 h	135, 167

Now, most common radionuclides in diagnostic nuclear medicines are shown over here. So, radionuclides which are having short half-life and high energy is widely used. The popular radionuclides which are generally used in nuclear medicines are shown here and they are producing high energy which have been utilized in the nuclear medicines.

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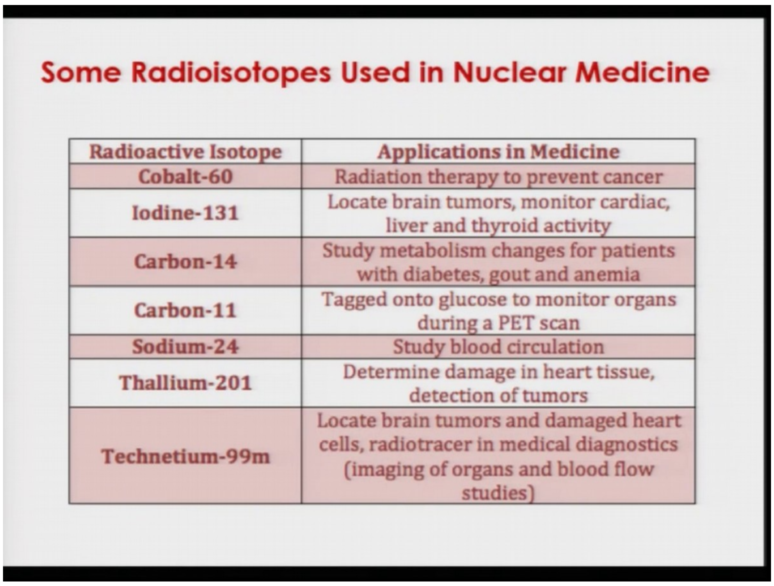

Radioactive Isotope	Applications in Medicine
Cobalt-60	Radiation therapy to prevent cancer
Iodine-131	Locate brain tumors, monitor cardiac, liver and thyroid activity
Carbon-14	Study metabolism changes for patients with diabetes, gout and anemia
Carbon-11	Tagged onto glucose to monitor organs during a PET scan
Sodium-24	Study blood circulation
Thallium-201	Determine damage in heart tissue, detection of tumors
Technetium-99m	Locate brain tumors and damaged heart cells, radiotracer in medical diagnostics (imaging of organs and blood flow studies)

So, some of these radio isotopes that are also used in nuclear medicine is shown here, these are ^{60}Co the applications in medicine is radiation therapy to prevent cancer; ^{131}I locate brain tumors, monitor cardiac, liver and thyroid; ^{14}C study metabolism changes for patient with diabetics, gout and anemia; ^{11}C used for tagged onto glucose to monitor organs during a PET scan; ^{24}Na study blood circulation; ^{201}Th determined damage in heart tissues, detection of tumors; ^{99m}Tc species this locate brain tumors and damaged heart cell, radio tracer in medical diagnostics.

So, you see these metal ions and their radioactive isotopes are utilized in nuclear medicine for various therapeutic and diagnostic purpose.

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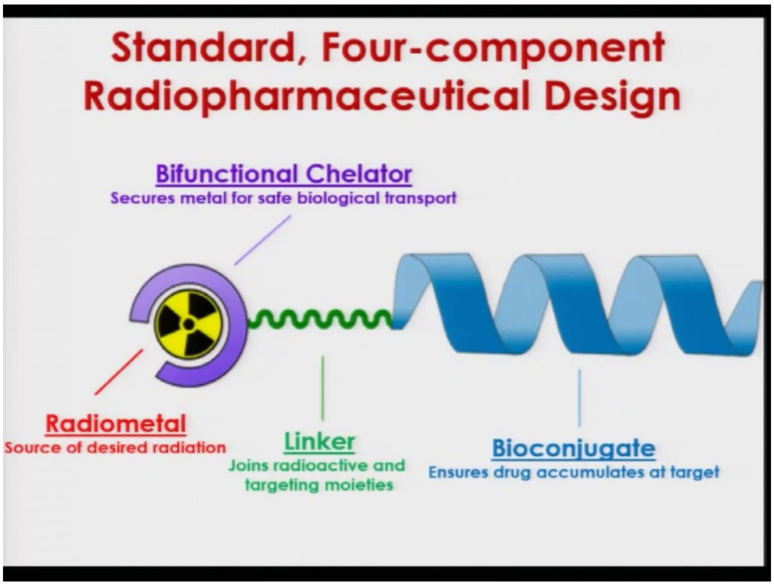

Now, this is a schematic representation for standard four component radiopharmaceutical design, say radioactive metal is shown here it is source of all desire radiation. Now, this metal ion will be complexed by some chelators say, bifunctional chelator. The bifunctional chelators actually chelates this radioactive metal ion and secures the metal for safe biological transport. Here, this is a linker which joins radioactive and targeting moieties, bio-conjugates are shown over here which ensure drug accumulates at the target only.

So, you see there are four component in this design and if one needs to design a proper drug then one has to look for all this four component for its proper radiopharmaceutical use you need to choose the right radioactive metal, you need to choose a chelator which can chelate this metal ion and save for our life also. Less toxic you need to have the proper linker which indeed can join this radioactive metal and targeting moieties. And bio-conjugates which actually ensures that drug only accumulates at the target then and then only it will be a very successful design and one need to look these all these four aspects very carefully.

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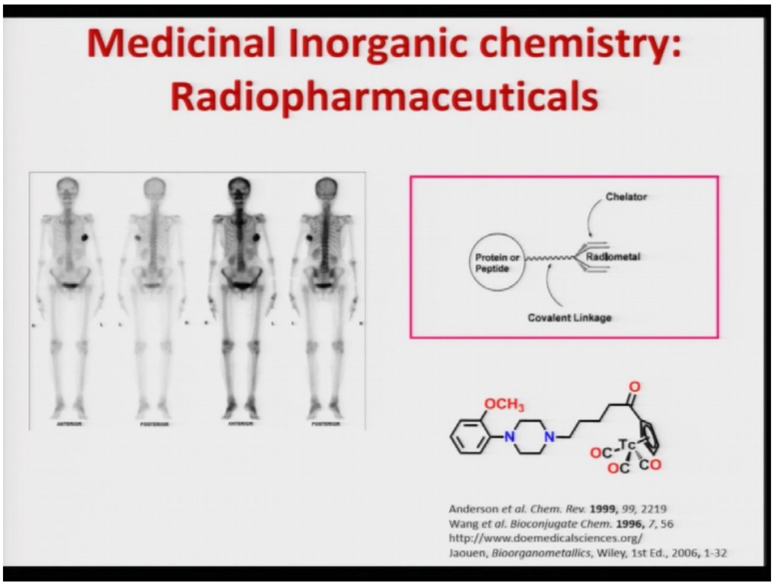

So, one such example is shown over here. So, this is a technetium complex you see that this is the radioactive metal technetium is being used which is being chelated with the some ligand and then this is the molecule which are popularly used and you can find this molecule in the market, it has been used in this imaging of the body.

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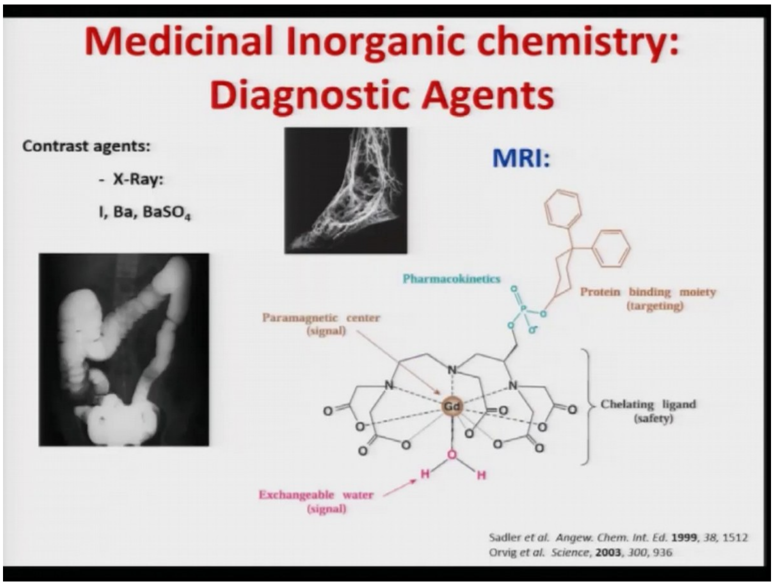

The metal complex also used as a diagnostic agents; for example, like for X-ray the contrast agents are iodine, barium indeed barium sulfate is being utilized for MRI contrast agent, this is a gadolinium complex. So, the design is such that there have to have a chelating ligand which can safely bind the metal.

Here it is a gadolinium it can be also manganese. Only thing is that this have to be paramagnetic and the water is ligated and this binding should be weak. So, that it can be exchangeable with the nearby water molecule and this is what is the protein binding moiety which is responsible for the targeting and this is what is a typical MRI contrast agent which are used as a diagnostic agents.

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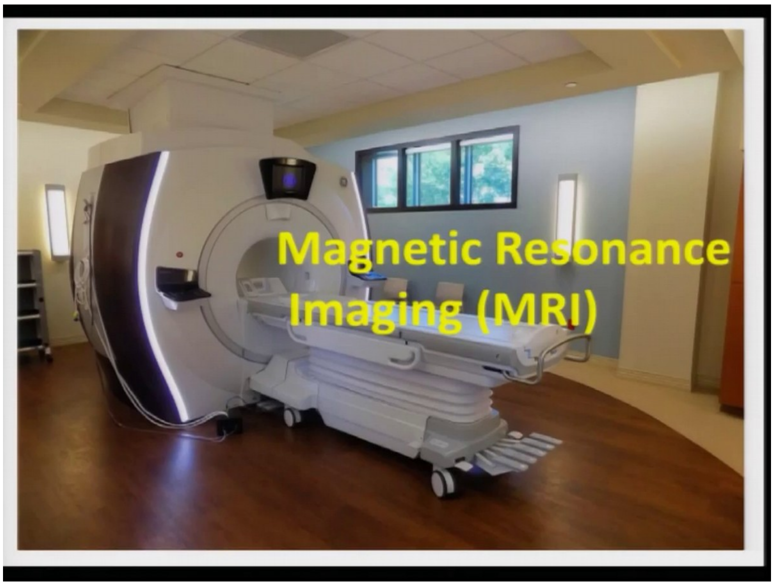

I will be now talking little bit about this Magnetic Resonance Imaging. So, here is a typical magnetic resonance imaging instrument so on.

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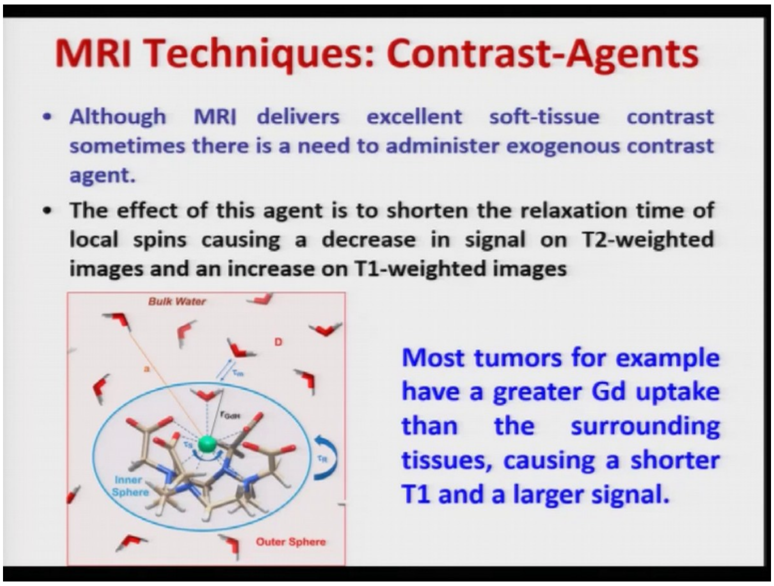

And for magnetic resonance technique sometimes we need contrast agent although magnetic resonance delivers excellent soft tissue contrast, sometimes there is a need to administer exogenous contrast agent. The effect of this agent is to shorten the relaxation time of the local spin causing a decrease in signal on T2-weighted images and then increase on T1-weighted images. T1 and T2 are the relaxation time, one is spin-spin relaxation and another one is spin-lattice relaxation.

And a typical contrast agent is shown over here as you can see water molecule is ligated, metal have to be paramagnetic there should be unpaired electrons on the metal and this water can be exchangeable neighboring bulk water. Now, most tumorous cells for example, have a greater gadolinium uptake than the surrounding tissues, causing a shorter T1 and a larger signal. So, one can easily trace the tumorous cell.

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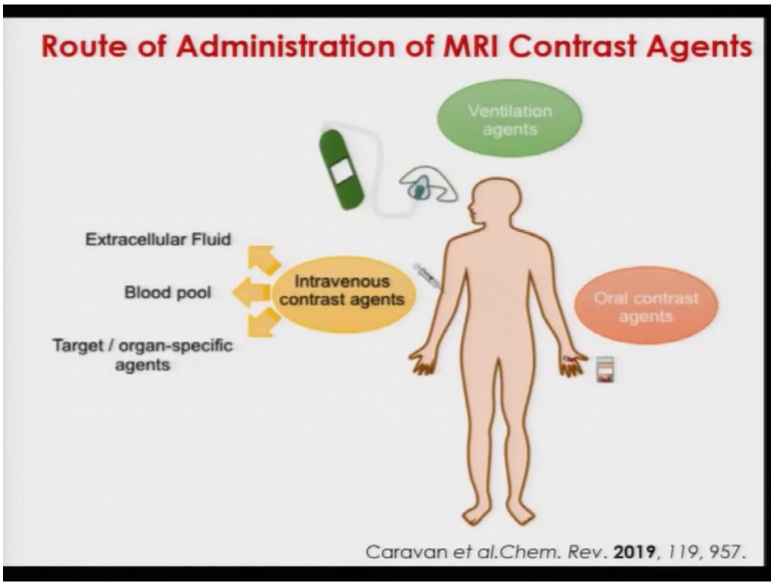

So, this is what is the route of administration of MRI contrast agent in a pictorial way it has been shown. So, intravenous contrast agent will be injected you can have also the oral contrast agent, it will go to the blood, it will be circulated throughout the body; however, the contrast agent will accumulate more on the tumorous cell because they are fast growing cells. So, it will accumulate more and then it can be detected very easily from the rest of the part.

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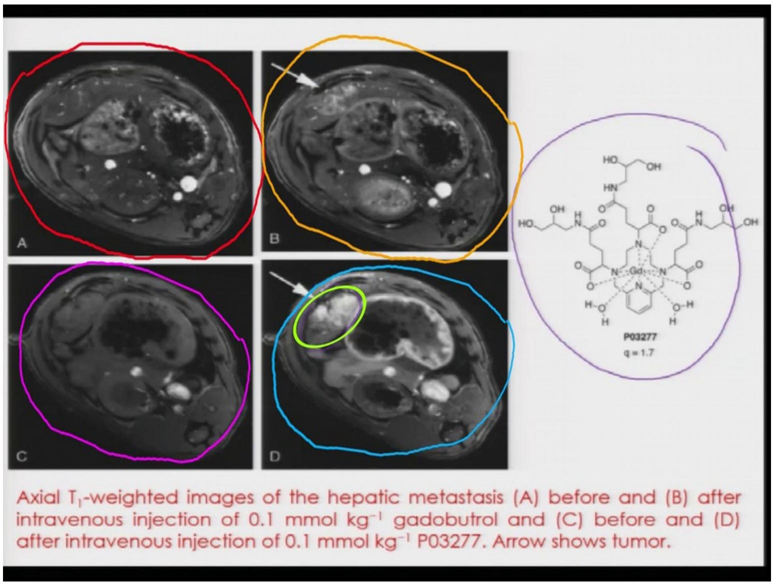

Here is an axial T1 weighted image of the hepatic metastasis before and after intravenous injection of 0.1 mmol kg^{-1}. Gadobutrol and C and D are after intravenous injection of 0.1 mmol kg^{-1} of this gadolinium contrast agent. You can see this tumor clearly visible over here while you one use this gadolinium contrast agent.

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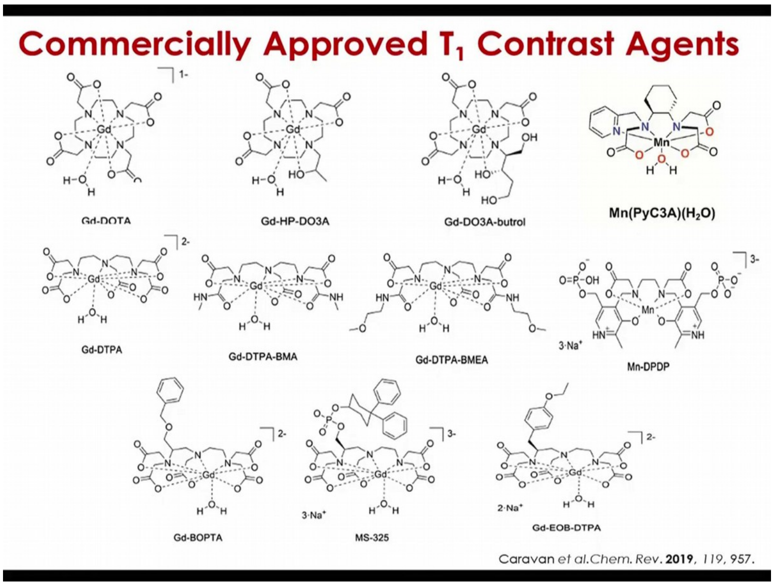

Now, commercially approved T1 contrast agents are shown over here as one can see most of them are gadolinium containing complex and manganese complexes are also utilized as a contrast agent and these are all approved drug which as these days utilized.

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Now, where we are now lots of new drugs and new possibilities for the metals in medicines; however, there is much research to be done. Now go back to the laboratory and make new drugs and so, that they can be successful as a medicines in future. In summary, I have tried here to give just a brief overview of various practical applications of metal ions in diagnostic and therapeutic applications. It is now clear that inorganic chemistry will have an important role to play in medicine in the future.

Future challenges in the field are to develop more efficient predictive methods for metal based compounds of therapeutic interest. Varying ligand choice is one obvious way of altering the endogenous distribution of metal ions; however, no specific guidelines are available to predict the effects. We can expect medicinal inorganic chemistry to rise to such challenges. In my next lecture, I will discuss more details about the platinum based anti-cancer drugs and their mechanistic actions.

Thank you.