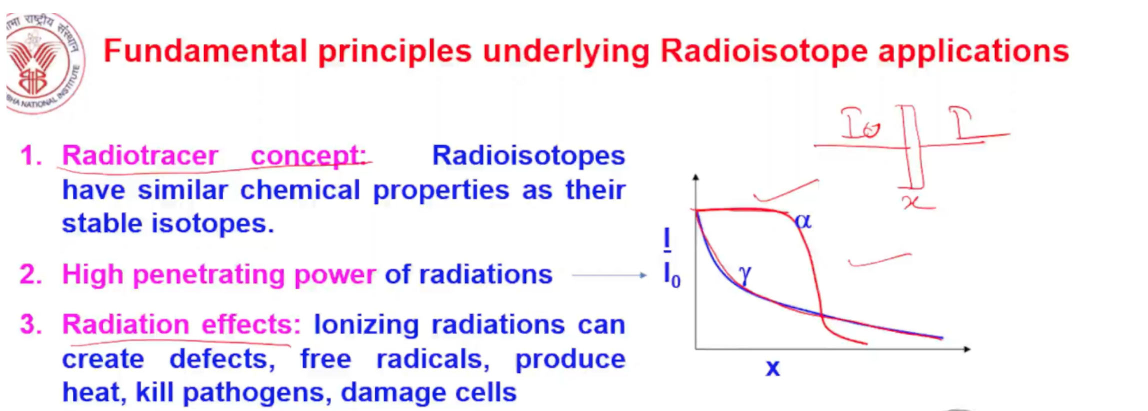
Applications of radioisotopes: Healthcare

B.S.Tomar

Homi Bhabha National Institute

Lecture-20, Module-1

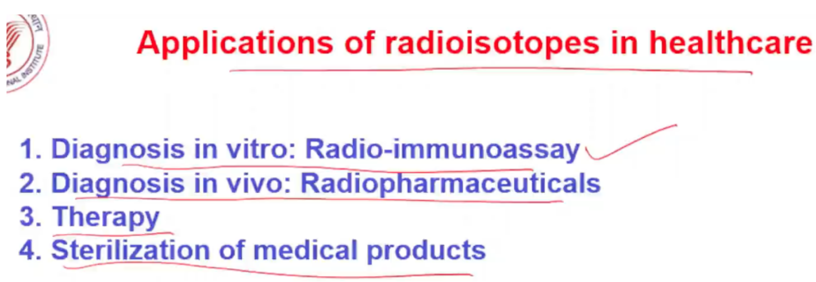
Hello everyone. So far we have been discussing the fundamentals of nuclear chemistry and then some of the analytical techniques based on nuclear phenomena and also the radiochemical techniques. Today's lecture I will describe some of the applications of radioisotopes in societal applications in the service of mankind, like healthcare, industry and so on. So before going to the actual applications, let me explain what are the fundamental principles underlying these radioisotope applications. So there are mainly three concepts or three properties of these radiations that enable them to be useful in many, many fields. So I will just explain them.



The first one is the radio tracer concept. I had also explained it earlier in one of the lectures on the tracer-based analytical techniques. And the underlying principle is that the radioisotopes have the same chemical properties as their stable isotopes. So this property of radioisotopes helps them to trace the path of their stable isotopes. You take any industry or even a chemical reaction where you want to understand the mechanism of the chemical reaction, then you can label one of the atoms with the radioactive atoms and see how this particular reagent is moving in the chemical system. Like sulfur, you know, sulfur containing chemicals, their reactions can be studied by sulfur-35 labeled compounds. In fact, many of the reaction mechanisms have been understood using radio tracers, radioisotope labeled compounds. So we will discuss that application in many, many areas.

Second property of these radiations is that these radioisotopes emit radiations that are highly penetrating. And because of that high penetration power, you will find many, many applications of radioisotopes in industry like radiography or even in the non-destructive testing investigations. You will see there are many of them. So this is the main concept. They can penetrate through thick absorbers like what I have shown here is that alpha particles will travel this way. Like if we have a transmission experiment, then I/ I_0 will follow for alpha particles. They will travel of same distance and after that there will be sudden fall. That is a typical transmission graph for alpha particles. Whereas the gamma radiation will follow exponential decay. So like the Beer-Lambert law. So you can make use of this intensity decrease with thickness of absorber in many, many applications.

And the third is the effects of radiation. Now, ionizing radiation can create defects. They can generate free radicals. They can produce heat. They can even kill pathogens and they can damage the cells. And these properties of these radiations find them very useful in medicine. For example, in cancer treatment, therapy of cancer and also modifying materials by polymerization or you can create defects in materials like diamonds. You can create the different colors in diamonds and add to their value. They produce heat. You can use them as a source of heat like the ^{238}Pu is used in satellites as a source of heat. You can power like pacemakers. Then they can kill pathogens so that this is utilized in food technology, you can prevent the sprouting of the vegetables, delayed ripening of fruits and many, many applications. They can even induce mutations in seeds and you can produce improved varieties of crops by using radiation induced mutations. So, the list is endless and I will cover some of the examples of these three concepts in my talk.



Okay, so first let me, in this particular talk discuss the applications of radioisotopes in healthcare. And these applications could be based on radio tracer concept or they could be based on the radiation effects on the human body. So, all sort of applications can come. So, in radioisotope applications in healthcare, one of them is in-vitro. That means in the test tube in the laboratory, you can do analytical determinations of the different biological components of our human blood or many other bio fluids you can determine.

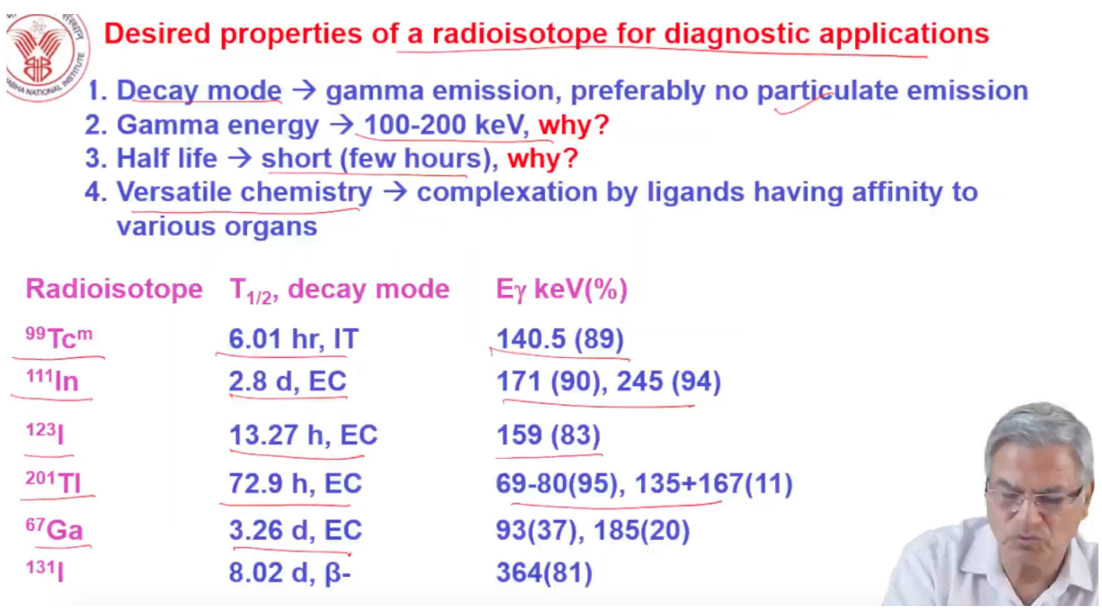
For example, we discussed in the radio analytical techniques, the radioimmunoassay where you can determine the concentration of T3, T4, TSH or even other like prostate specific antigens you can determine by using labeled antigens and interacting them with antibodies and then finding out the concentration of these molecules at very, very low levels like nanomolar concentrations. But they are done in the laboratory. In-vivo, in the body, if you introduce the radioisotopes, then you can do investigations of diseases and the chemicals that are introduced in the body in-vivo, they are called radiopharmaceuticals. They are like medicines, they are pharmaceutical compounds, but they are labeled with the radioisotopes. So, we will discuss them in this lecture.

And also the radioisotopes by virtue of their radiation effects, by virtue of killing the tumor cells, we can use them in therapy. And lastly, the sterilization of medical products. These medical products, the implements, the tools, the scissors, the tweezers and different implements used in operations. So, they have a chance of getting infected again during handling. So, in this particular case, what happens, you can pack them, you can pack them in cardboard boxes, take them to the plant for irradiation and after irradiation, they will be opened only when they are being used for the operation. So, you can sterilize the medical products, surgical tools by using radiation. I will not discuss this much in this particular talk, but I will talk about other, first two, diagnosis and the therapy.

Okay, so now let us discuss what are radiopharmaceuticals. So, radiopharmaceuticals are pharmaceutical compounds, but they are labeled with the radioisotopes. So, a special radiochemical formulation, the formulation is a radiochemical, it's a compound of adequate purity. So, it should have a desired radiochemical purity, radionuclidic purity, that is what we mean by adequate purity and pharmaceutical safety. So, there are pharmacopoeia for different quality control measures to be taken with regard to its pH, sterility, pyrogenicity and so on. So, it should be suitable for oral or intravenous administration to humans for performing a diagnostic test or for treatment. So, any compound to be injected intravenously or orally in the human body has to pass the tests of this kind of quality control measures. So, the pharmaceutical safety is important, so that we will discuss in my talk.

So, this is a general definition of radiopharmaceutical. Now, radiopharmaceutical can be used in diagnosis of diseases, wherein we image, we take the image of an organ, it could be static or we can see the dynamic flow of the body fluid of the blood, then we can get the dynamic image of an organ, how the metabolism is taking place in the human organ. So, that you can do using diagnostic applications, where you inject the radioisotope labeled compound and then in the body, wherever this radioisotope is going, that particular organ we can take the image in static or in a dynamic or you can have sequential images. So, this is another application. And then we have the therapeutic applications, where you can use radionuclides externally, it's called teletherapy, from outside you can expose the cancerous tissues and kill them or we can introduce the radioisotope in the body, either by a sealed source in a cavity or by using a radioisotope labeled compound.

So, these radioisotopes which are introduced in the human body in the form of a compound, radiopharmaceuticals, they have to have particulate emission like alpha or beta minus, so that they can do the damage to the cancerous tissues. So, radio pharmaceuticals, if you inject into the human body, then they are required to have particulate emission beta, alpha, so that they can kill the tissues in their vicinity. So, that is the kind of requirement we have for radio pharmaceuticals in therapy.



Okay, so let us see for diagnosis, diagnostic applications, what are the kinds of radioisotopes we can choose for diagnosis. So, one of them is the decay mode. The decay mode, see what we are doing, we are going to take the image of the organ in which the radioisotope is distributed, so it should preferably emit only gamma ray. So, it should not be emitting a particulate because that particulate will unnecessarily damage the tissue. So, there are not many radioisotopes which will be not emitting particulate because the gamma is emitted only after beta or alpha decay. But there are like internal transitions.

So, isomeric state is there like technetium-99m, it will decay by only internal transition with 140 keV gamma ray and having half-life of 6 hours. That is an ideal for diagnostic radio pharmaceutical. First is that it should not emit preferably any particulate emission. The second is that the energy of the gamma ray should be in the range of 100 to 200 keV. Why? Because if it is below the 100 keV energy, then it will be stopped in the body itself, it will not come out of the body. And if it is more than 200 keV, then the efficiency of detection will be low. So, 100 to 200 keV is the optimum range of gamma energy for a good image. That is the reason why the gamma energy should be in 100 to 200 keV. More than 200 keV, efficiency will go down, less than 100 keV, the gamma ray will not come out of the body, it will be attenuated by the human body. Half-life should be short, preferably few hours. Again, the reason why it is so because you do not want the radioisotope to be in the body after the image has been taken.

So, it should come out of the body or it should die down in the body itself. So, that few hours half-life is optimum for the diagnostic investigation. And lastly, it should have a versatile chemistry. That means it should be able to complex different ligands and those ligands having affinity to different organs. So, a particular metal ion in different oxidation state will be ideal because different ligands may bind metal ions in different oxidation state.

Some of the examples of these radioisotopes that are used in diagnosis are Technetium-99m. Ideally, in fact, it is called the workhorse of nuclear medicine, about 80% of the nuclear medicine investigations worldwide for diagnosis are done using Technetium-99m. So, gamma ray energy is ideal, half life is ideal. Indium-111, ideal gamma ray energy, but half life is little long. ^{123}I, half life and gamma ray wise ideal.

That is why there is a huge demand for ^{123}I, though it requires a Xenon target, enriched Xenon-124. Tl-201, you can see half life and gamma in these are quite good. Gallium-67, 3.26 days and good gamma energy. And iodine-131, though the half life is long, you will find in many applications, it is very, very useful. It can be used in both diagnosis and therapy. It has the gamma ray energy, it has the particulate emission option.

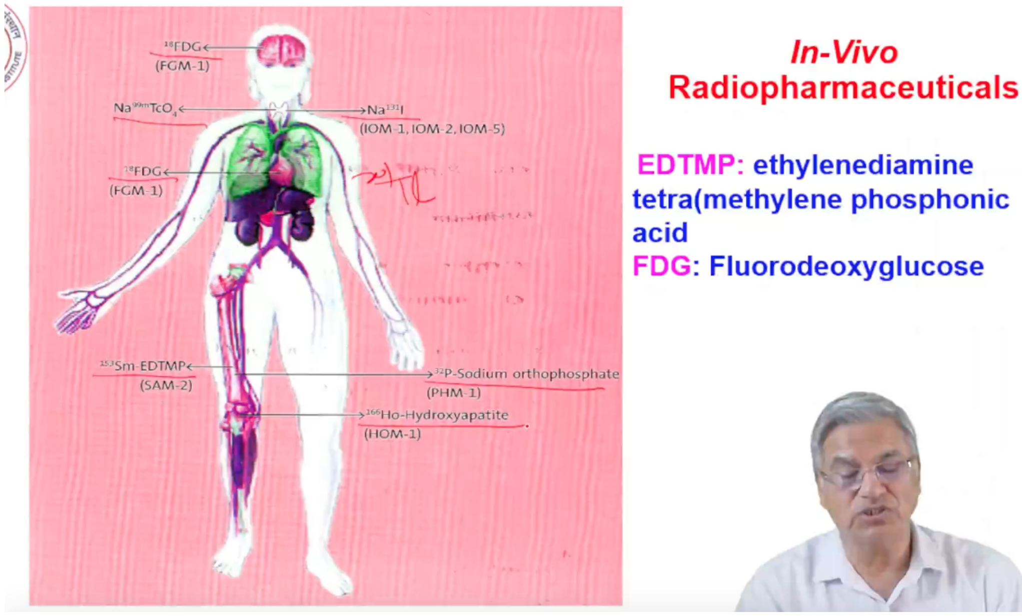
Radiopharmaceutical quality control

	Physico-chemical control	Radiochemical control	Biological control
1.	Physical inspection	Radioactive concentration	Sterility (for injectables)
2.	pH	Radionuclidic purity	A pyrogenicity (for injectables)
3.	Chemical purity	Radiochemical purity	Organ distribution
4.	Particle size (where applicable)		

Now, once you label a compound and prepare the radiopharmaceutical, there are certain pharmaceutical quality control measures you must establish. And this belong to the physico chemical control, radio chemical control and biological control. In physico-chemical properties, you should inspect the solution that it should be clear, this would not be any turbidity. pH should be the proper zone, which will be compatible with the body. The chemical purity of the compound, there should not be any other impurities. And sometimes you use in the particulate form, you know, some microspheres are used for some treatment. So the particle size should be in the proper range. The radio chemical control with regards to radioactivity concentration, what is the concentration of radio isotope, it is millicurie or microcurie or nanocurie. So depending upon the requirement specified by the doctor, the doctor and nuclear medicine personnel should specify that concentration.

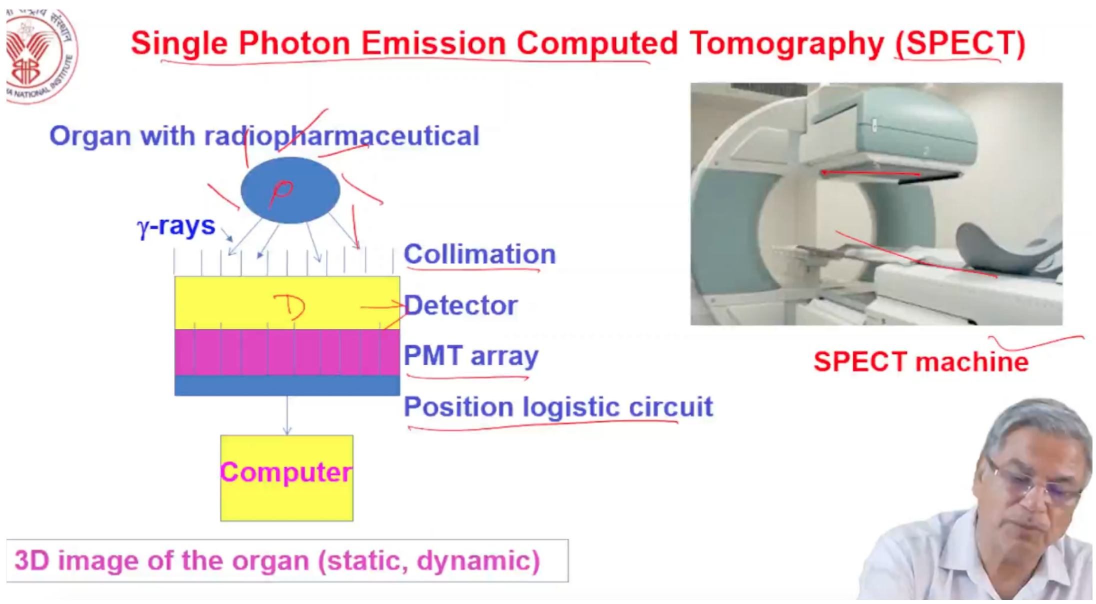
Radio nuclidic purity, there should be no unwanted radio isotopes. And the radio chemical purity, the chemical form of that molecule should be whatever is the desired one. For example, if you have chlorine in ^{18}F-FDG, then FDG there should not be any other derivative of FDG. So that kind of purity has to be established.

So there are measures to determine the radio chemical purity by that thin layer chromatography or paper chromatography, the radio nuclidic purity by gamma spectrometry, radioactive concentration by counting the sample. Then you have the biological control, sterility for injectables, it should be sterile. It should be the apyrogynic, means it should not produce heat in the body. So this is an important requirement of the pharmaceutical and it should be distributing in the organ of your interest. So these are the properties that a radio-pharmaceutical should have.



Okay, so I have just given you a figure that whatever different organs in the body which are likely to get affected by a disease, then there are radio-pharmaceuticals, both in terms of the radioisotopes as well as the molecule for which there have been developments to produce those kinds of pharmaceuticals, which will be selectively going to the particular organ. For example, if you want to see the glucose metabolism in the brain, then you have F-18 labeled FDG. If you want to see the thyroid uptake, thyroid functioning, whether there is any malfunctioning of thyroid, you can use sodium iodide labeled with ^{131}I or even you can do technetium-99m because technetium also can go to thyroid. Then for heart you have FDG and there is thallium-201 also will go to heart, so you can use for stress test. Then for bones you have ethylenediamine tetra(methylene phosphonic acid), ^{153}Sm labeled, EDTMP or you can have P-32 labeled orthophosphate. Again for the bones you have holmium-166 hydroxyapatite.

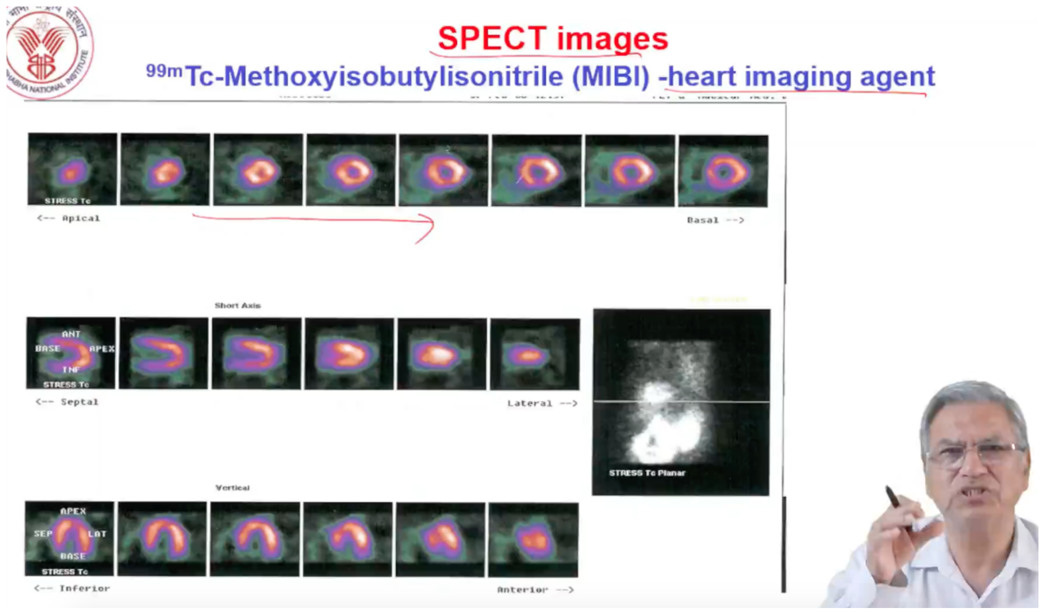
There are some of the few you will find that for example for the prostate, there are prostate specific antigens. So if you label that antigen with a particular compound like lutetium, it will selectively go to prostate and you can do the image as well as you can do the treatment of the prostate. So for every organ, almost every organ in the human body you will find there is a particular pharmaceutical and there is a proper labeling isotope. So you can do imaging of different organs of the body.



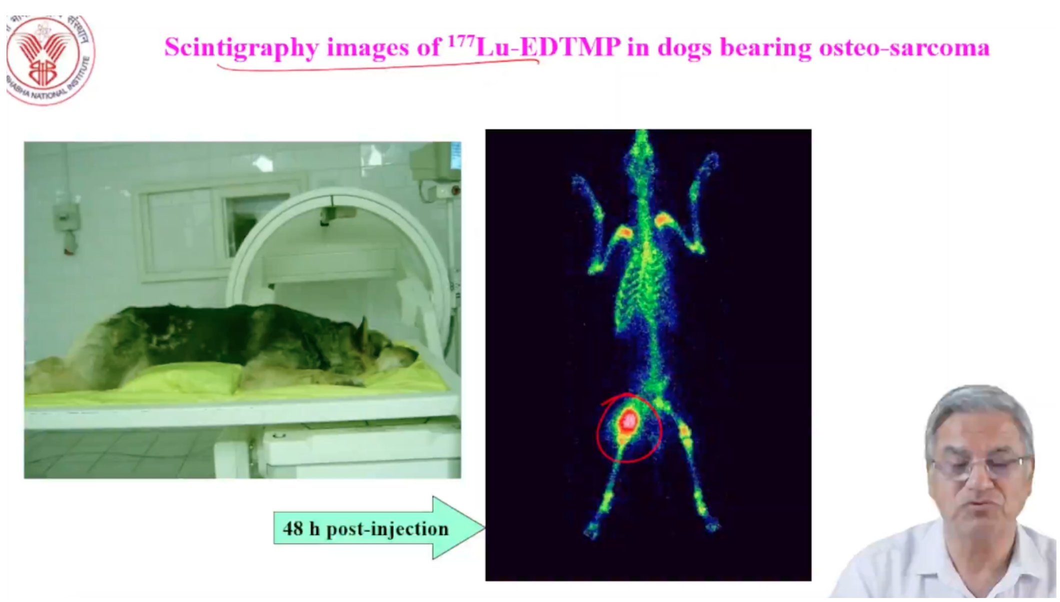
Now what are the experimental techniques for this? You have this technique for imaging called scintigraphy and it is also called the single photon emission computed tomography, (SPECT). So the principle of SPECT is that suppose you have the organ which is containing the radioisotope here and this organ is now in the human body, it is emitting gamma radiations isotropically. So from outside this is the machine for SPECT. So this is the camera, the patient is made to lie on this and the camera will detect the gamma rays coming out from the organ. Now the radioisotopes are emitting gamma rays in all directions but you have detector only one side and you want to take the spatial image, so as a function of space how the organ is distributed, that means how the activity is distributed in the organ.

So you have a detector where the gamma ray is made to pass through collimators. So it will go at a particular angle so that tells you in which bin this gamma ray has come. This is segmented kind of system. So this collimation helps you finding out the place from which the gamma ray has come. Then the gamma rays are detected by the detector, mostly scintillators NaI(Tl), or BGO type of scintillators and there are PMT photomultiplier tubes to convert the signal, the photons converted into electrons at a PMT and then there is a position sensitive circuit to identify from which place in the organ the particular gamma ray has come.

Like for example this collimation will give you this particular position. So we can see in organ and we can construct the image by the help of a computer. So that is the principle behind the SPECT. So it essentially gives you the 3D image of the organ in static or in dynamic form. Like this is just to give an example, SPECT images like for this Technetium-99m labeled MIBI, it is called MIBI, methoxy isobutyl isonitrile and it is a heart imaging agent.



When you inject intravenously this Technetium-99m MIBI and after 15 minutes you take the image of the heart of the person from outside. Externally noninvasively you are monitoring the gamma rays that are coming out of the human body and you can see as a function of time when the heart is pumping the blood you can see the different images, different cross sections of the heart and if a particular portion has got infructuous that means if the blood is not reaching there, the muscles are dead, the doctor can identify which portion of the heart has become infructuous means it is dead. So that kind of an investigation can be done using the pharmaceuticals labeled with proper radioisotopes.



Similarly you have this scintigraphy image of Lutetium-177 labeled EDTMP in dogs which are found to be having osteo-sarcoma. You can see this is how you keep the patient in the SPECT machine and you can see the inflammation, so the sarcoma that the particular tumor in the animal can be seen by the bright intensity of the radiation.

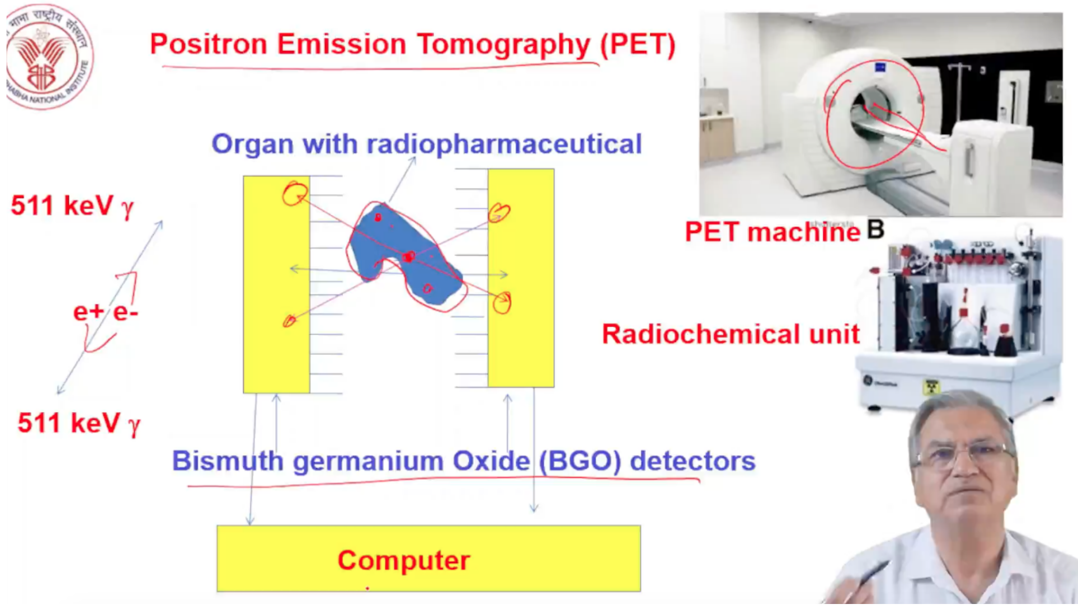
The radioisotope is going and depositing energy there. So you can see that with Lutetium-177 not only can do the diagnosis by means of gamma ray, you can also do the treatment because the therapeutic application requires emission of high energy beta particles which Lutetium-177 emits. Now that was the SPECT imaging, so you use a single photon emitting radioisotope and you take the camera and it will take the image of the organ. But the resolutions in the SPECT are not very high and therefore the positron emission tomography (PET) has become now more popular because of the resolution in terms of the space. The spatial resolution is excellent in PET and for PET you require a positron emitter. The positron emitters are carbon-11, nitrogen-13, oxygen-15, fluorine-18 and also gallium-68.

Positron Emission Tomography

Radionuclide	$T_{1/2}$ (min)	$E_{\beta+}$(MeV)	Production route
^{11}C	20.39	0.96	$^{14}N(p,\alpha)$
^{13}N	9.965	1.19	$^{16}O(p,\alpha)$
^{15}O	2.037	1.72	$^{15}(d,n)$
^{18}F	109.77	0.635	$^{18}O(p,n)$
^{68}Ga	68	1	$^{67}Ga(\alpha,p2n)$ $^{68}Ge \rightarrow ^{68}Ga$ (generator)

You can see their half-lives are minutes and the way they are produced. So F-18 is in fact these days most commonly used because it is having a half-life of about two hours. So from the cyclotron they can be transported to the hospitals whereas the other isotopes carbon-11, nitrogen-13, oxygen-15 their half-lives are even less than 20 minutes and so they require the cyclotron to be present in the hospital. So immediately you transport the pharmaceutical to the hospital within few minutes and then you can do the PET analysis. But fluorine-18 you can take from cyclotron to other hospitals in the city and another thing is gallium-68 is another very interesting pair, it's a generator.

You have germanium-68 decaying to gallium-68 and you can take the generator to the hospital and we milk the gallium-68 which is then injected into the human body for PET investigations. So this is the principle behind the positron emission tomography.

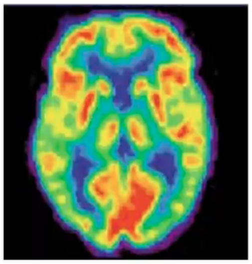


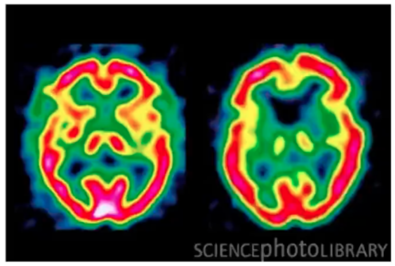
You have a ring of detectors which is not single detector you have a ring and it is like MRI. So the patient is made to lie here, the detectors encircle the patient. So suppose you have an organ here which is odd shape organ and then from different parts of this organ the gamma rays, the positrons are anyway annihilated so gamma rays are emitted and the 511keV gamma ray they are emitted at 180 degrees so you know the positron annihilation and so from a particular point you will see that the two detectors will receive an event at 180 degrees.

Similarly this event, two events are coming from this place so because of the coincidence phenomena you can identify from which place in the organ the 511keV gamma ray has come. So this is the schematic you have this is actually an angular one this is a circle it's a cylinder type of thing and then this is the BGO detector and it's like a circular array and then this data are fed to the computer to do the investigation to simulate the distribution of activity in the organ. So the PET cyclotron is a very compact machine and once you produce the positron emitter you have to have the very fast chemistry there is a radiochemical unit which will separate the radiochemical and then you can label them and then transport to the hospital.

SPECT vs PET

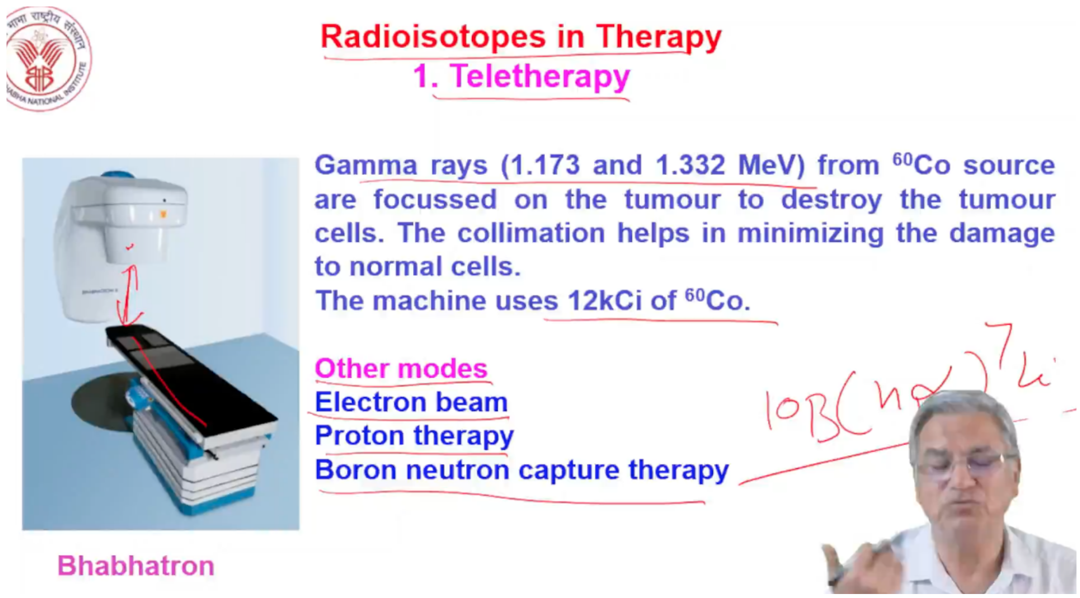
Images of brain obtained using SPECT (Left) and PET (Right)





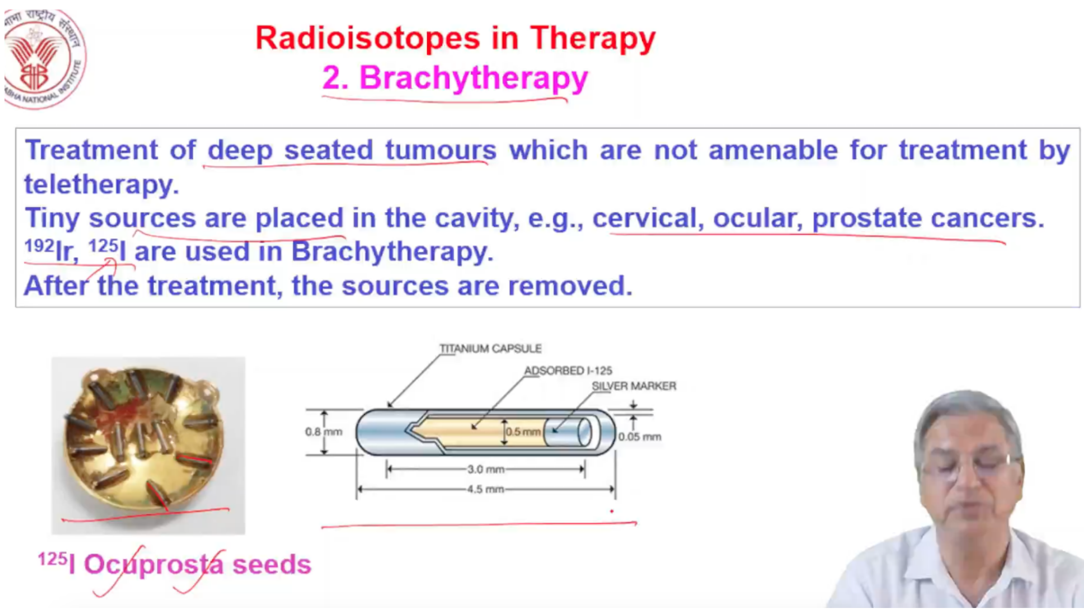
So this is the general principle of the PET machine and the images that you get from the SPECT versus PET you can see this is the image of a brain using SPECT and PET so you can see the marked improvement in the image of the brain using PET compared to SPECT image. That is why now the PET is becoming very popular among the nuclear medicine practitioners.

Now let me come to the another application of radio isotopes that is, therapy of cancer and here there are three techniques one of them is teletherapy as the name itself implies the radio isotope is from outside the body and you focus the beam of the gamma ray onto the organ that is to be irradiated. People use Co-60 source which is emitting high energy gamma rays 1.17 and 1.33 MeV and the gamma rays are focused on the tumor so you have to put it in the proper shield and then allow only a beam of gamma ray to come though the gamma rays are emitted in all directions but you are collimating the gamma ray to come to a particular tumor so there is a huge activity required because you cannot focus the gamma ray only you can collimate. So about 12000 Curies of Co-60 is used in one machine for teletherapy.



So this is where the patient lies and this is the source. It is in the shield and Co-60 is emitting gamma ray to irradiate the particular organ. So though Co-60 is most commonly used there are now advancements going on you can produce gamma ray from electron beam by means of Bremsstrahlung. You can use protons for therapy and you can use boron neutron capture therapy that means suppose you want to produce protons you can have a neutron source for treatment of cancer so you use boron and the neutron will induce the reaction in the boron and give you alpha and lithium-7, via $^{10}B(n,\alpha)^{7}Li$. So this alpha and lithium-7 are now heavy charged particles and they will damage the cancerous tissue. So you have to take boron labeled compound nearby that organ and bombard with neutrons selectively because boron has very high cross section for neutrons you can damage the cancerous cells by using this technique.

So there are many techniques which are being used for cancer treatment one of them is teletherapy other one is brachytherapy. Not all cancers can be treated by teletherapy because from outside you cannot take the gamma ray to particular organ particularly the deep suited tumors like cervical cancers, prostate cancers, ocular cancers, eye cancers, etc.. So these are deep suited so you may unnecessarily damage the other organs so those tumors which are not amenable by teletherapy they are treated by brachytherapy.



In brachytherapy you use tiny sources which can be placed in a cavity and particularly people use ^{192}Ir and ^{125}I. ^{125}I has a half life of 60 days and gamma ray energy is 35 keV or so and ^{192}Ir has about 100 to 200 keV gamma rays.

So you put the sources for a particular period of time and after that these are sealed sources so they are not going to the bloodstream you can just take them out after proper exposure. These are the typical you know this needle shaped pins they are sealed sources they are called acu-prosta seeds because they can be used for ocular cancer and prostate cancer. So they are made in the laboratories and this is the typical drawing of the seed you can see the length of this is 4.5 mm and the diameter is of the order of 0.8 mm. So very thin tiny needles and wires can be placed behind the eye and can be placed in the other places of the human body. So wherever you want to do the treatment like prostate cancer so you want to irradiate the prostate with this gamma rays you can do that.

And then lastly, we have the radionuclide therapy. Radionuclide therapy is like radio-pharmaceuticals used for diagnosis that you can tag the pharmaceutical with a radioisotope which is emitting the particulate emission and then do therapy. So the radiopharmaceutical will take the radioisotope to particular organ and the radioisotope will emit the particulate radiation alpha or beta and that will kill the cancerous cells.

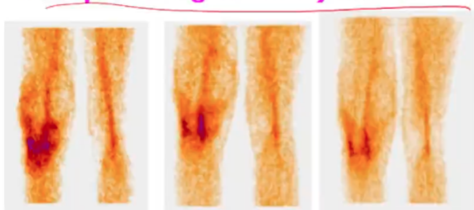
So ^{131}I is used for thyroid disorders, Yttrium-90 for treatment of arthritis and phosphorus-32 for skin cancer. Yttrium-90 and phosphorus-32 are pure beta emitters. The high energy beta is destroys the tumor cells and so for example iodine-131 you can use the beta for thyroid disorders. So even for therapeutic agents you know if you have some joint diseases like arthritis then there are radioisotopes like Yttrium-90, Erbium-169, Rhenium-186 they can be used for treatment of diseases.

3. Radionuclide therapy

1. ^{131}I based treatment of thyroid disorders
2. ^{90}Y for treatment of arthritis
3. ^{32}P for skin cancer

High energy β- destroys the tumour cells

Therapeutic agents for joint diseases: ^{90}Y, ^{169}Er, ^{186}Re



^{90}Y-hydroxyapatite for treatment of arthritis

After treatment | After 3 months | After 6 months

One of the examples you can see here immediately after the treatment of arthritis you know so there is some fluid deposition and that you can take the image of that knee with these radioisotopes after three months of treatment and after six months of treatment you can see that the patient is recovering that particular inflammation is going off. So this image is taken with Yttrium-90 hydroxyapatite for treatment of arthritis. So we can use these radioisotopes which are emitting particulate radiation for treatment of many types of diseases.

And lastly there are theragnostic means therapy and diagnosis. So they have dual purpose of not only doing therapy but also diagnosis. So this is a new concept coming up last few years now.

Theragnostic Radiopharmaceuticals

Radioisotopes having dual properties (particulate and γ emission)

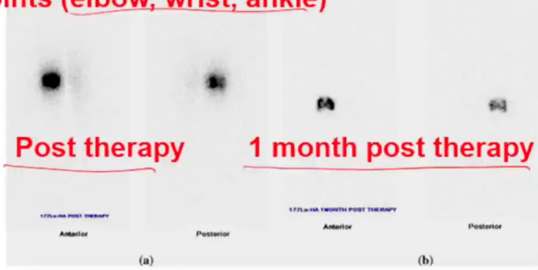
The efficacy of therapeutic radiopharmaceutical can be monitored

Examples:

^{131}I (β^-, γ-364 keV, 8 days)

^{177}Lu (β^-, γ-208 keV(10%), 112 keV (6%), 6.7 days)

^{177}Lu-HA for treatment of arthritis of medium-sized joints (elbow, wrist, ankle)



The radioisotopes having dual properties so they emit particulate radiation like beta, alpha and also they emit gamma radiation and therefore they can be used for both diagnosis and therapy. So for example when a patient is undergoing iodine therapy you can monitor the therapy what is happening to the patient as a function of time using gamma ray emission. So iodine-131 is one of the isotopes it has got a beta minus and a gamma ray. And ^{177}Lu is another isotope which has got very good chemistry ideal gamma ray energy 100 to 200, half-life and particulate radiation. So this is the image of lutetium-177 hydroxyapatite which is used for treatment of arthritis in medium-sized joints like elbow, wrist and ankle.

And you can see immediately after therapy and then after one month of the therapy how the inflammation is vanishing as a function of time. So this is how one can carry out investigations of therapeutic applications of radioisotopes. You can do teletherapy, you can do brachytherapy and if the tumor in the glands sometimes even the brachytherapy will not help. So you can go for radionuclide therapy and the theranostic ones help you not only in therapy but also in diagnosis as a function of time while the therapeutic treatment is going.

So that's all I have to say in this particular one. In the next lecture I will talk about the other applications of the radioisotopes in industry and so on. Thank you very much. Thank you.