Production of radioisotopes by charged particle irradiation

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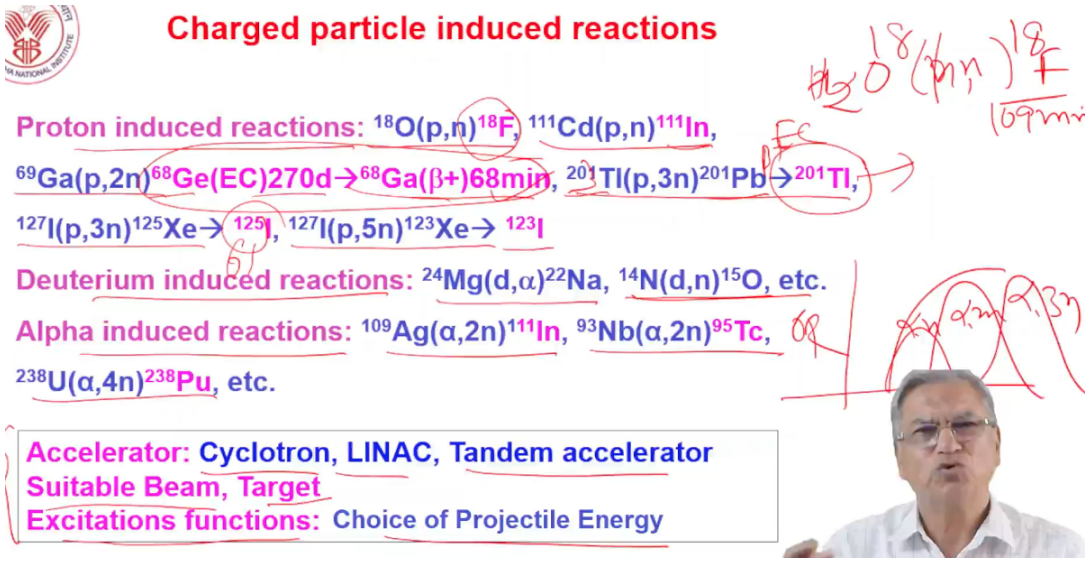
Lecture-15, Module-2

Hello everyone. In the previous lecture, I discussed about the production of radioisotopes while irradiating the targets with neutrons. And also we discussed how you can produce the carrier-free radioisotopes by different means.



In this particular part, I will discuss the radioisotope production using charged particles and also some of the other aspects of radioisotope production like what are the ways, how the radioisotopes are handled after irradiation. And particularly in Indian context, what are the mechanisms and processes by which the radioisotopes are produced and supplied to the users. So in the charged particle irradiation, you can use a cyclotron or a linear accelerator or a tandem accelerator.

Tandem is two-stage accelerator. And then depending upon the irradiation time, the facility that is available to you, you can get the radioisotopes. You need the suitable beam and the target. So the knowledge of nuclear reaction will be very much useful in choosing what beam, what target.

If you have a cyclotron and it is giving proton beam, then you already have the projectile fixed. So now you can fix the target, accordingly go for radioisotope production. Before you go for the radioisotope production, you need to know the excitation function. That means the cross section σ_R versus energy of the projectile. This is the total cross section and you will have the excitation functions of different products like (α, n), (α, 2n), (α, 3n)

and so on. So depending upon the excitation function for a particular radioisotope, you have to choose the energy of the projectile and also make sure that it is available from the machine that you are going to use. So these aspects we have already discussed in the previous lectures on nuclear reaction. Now we come to see what are the isotopes that can be produced using proton, deuteron and alpha particles.

The heavy ions as projectiles can be used for radioisotope production, but you will find that the heavy ions are having multiple charges. So the currents are low and you may produce many other isotopes which may not be useful. So mostly for commercial applications or applications in industry or healthcare, whatever radioisotopes are produced, they are either produced using protons or alpha particles, deuterium, using cyclotrons because cyclotrons very high beam intensities. Beam intensity means current in microamperes. So one microampere of proton will have 6.24×10^{12} particles per second. Accordingly, one microampere of alpha particles, suppose alpha particle one microampere current will have, it is a 2^+ charge state, $6.24 \times 10^{12}/2 = 3.12 \times 10^{12}$ particles /s That is how typical currents, some of the accelerators produce milliamp currents like for medical cyclotrons, you want very high activity of a short-lived isotope, you go for milliamp current, 1 milliamp, 10^{15} alpha particles or protons per second.

That is the kind of intensities we use. So proton induced reactions are used to produce ^{18}F, you can produce ^{111}Cd, ^{111}In and ^{18}F is used in PET, the positron emission tomography. So this ^{18}F is having only 109 minutes half life, so about 2 hours and so you irradiate H_2O^{18} (p, n) ^{18}F and you have to do very quick chemistry because the half-life is only 109 minutes. And you tag a glucose molecule, fluoro deoxyglucose with F^{18} and then you can transport it to hospital for PET operations. This ^{111}In also is used in the diagnosis of diseases, ^{111}In emits gamma lines in 100 to 200 keV range.

So it is also used in the nuclear medicine. Again another isotope, $^{69}Ga(p, 2n)^{68}Ge$ (EC) $270d \rightarrow {}^{68}Ga$ (β+)68 min. The ^{68}Ge has a half-life of 270 days which decays to ^{68}Ga which is a β+ emitter and hence it is a PET radioisotope. Any β+ emitter being short lived are ideal for PET diagnosis, positron emission tomography. So you can have a generator system, germanium gallium generator system.

So because you have to supply this ^{68}Ga to the hospitals, so in the hospital you can have a ^{68}Ge column for milking ^{68}Ga every few hours. Similarly, ^{201}Tl is used in stress test, single photon emission computer tomography. Irradiate ^{201}Tl, this is actually $^{201}Tl(p, 3n)^{201}Pb \rightarrow {}^{201}Tl$ which is emitting the β+ or electron capture to give rise to ^{201}Tl. And this has half-life of few days, you can use it in scintigraphy camera.

^{125}I, 60 days is another isotope of iodine used in, it emits a low energy gamma ray and it is used in radio-immuno assay of iodine in thyroid hormones. ^{127}I (p, 3n)$^{125}Xe \rightarrow {}^{125}I$. You can also produce by ^{127}I (p, 5n)$^{123}Xe \rightarrow {}^{123}I$. So some of the isotopes of ^{123}I, ^{125}I apart from

^{131}I, ^{131}I is a beta emitter and these are decaying by electron capture and hence emit x-rays and low energy gamma ray. So depending upon the type of application you can choose which isotope of iodine is suitable.

Deuterium beams are used to produce ^{22}Na and ^{15}O. ^{22}Na is a positron emitter, though it is not used in PET because it has got a half-life of about a year or two. So but it is a source for calibration. It emits 511 keV gamma rays. If you want to calibrate your system and you can study chemistry of positronium. So ^{22}Na is a positron source and many chemistries of positronium atoms are done with ^{22}Na. In fact, there are positron beams. You can take a source of ^{22}Na which is emitting positron and you can accelerate these positrons to use for many applications. ^{15}O is a beta emitter and you can use this for the PET analysis, short-lived isotope produced by $^{14}N(d, n)^{15}O$ reaction. For alpha induced reaction, again, ^{111}In, ^{95}Tc, ^{238}Pu.

Plutonium-238 is a heat source for the space applications. In satellites, you need power. Typically, one gram of plutonium-238 gives about two watts. So typically, that is the kind of wattage you can get from plutonium-238 at a heat source. So these are the isotopes that are produced in cyclotrons. There will be many, I am just giving you the examples.

Cyclotron produced radioisotopes

Nuclide	$T_{1/2}$	Decay mode	Reaction
^{22}Na	2.6 y	β+(91%), EC	$^{24}Mg(d,\alpha)^{22}Na$
^{57}Co	271.94 d	EC	$^{58}Ni(p,2n)^{57}Co$
^{68}Ga	68 min	β+	$^{69}Ga(p,2n)^{68}Ge(270d) \rightarrow {}^{68}Ga$
^{111}In	2.8 d	EC	$^{112}Cd(p,2n)^{111}In$
^{123}I	13.27 h	EC	$^{124}Te(p,2n)^{123}I$ $^{124}Xe(p,3n)^{123}Cs \rightarrow {}^{123}Xe \rightarrow {}^{123}I$
^{201}Tl	72.912 h	EC	$^{203}Tl(p,3n)^{201}Pb \rightarrow {}^{201}Tl$
^{11}C	20.39 min	β+	$^{14}N(p,\alpha)^{11}C$
^{13}N	9.965 min	β+	$^{16}O(p,\alpha)^{13}N$
^{15}O	122.24 s	β+	$^{14}N(d,n)^{15}O$
^{18}F	109.77 min	β+	$^{18}O(p,n)^{18}F$
^{103}Pd	16.991 d	EC	$^{103}Rh(p,n)^{103}Pd$

There are more isotopes, in fact, we will come along with them and discuss further. So many radioisotopes which are not produced in reactors and many isotopes which have different types of applications where you require carrier free, it may not be possible by reactor, so you go for accelerators. So this is a list of cyclotron produced radioisotopes. $^{24}Mg(d, \alpha)^{22}Na$, $^{58}Ni(p, 2n)^{57}Co$. You can directly produce ^{68}Ga or you can go for $^{69}Ga(p, 2n)^{68}Ga$ reaction. $^{112}Cd(p, 2n)^{11}1In$, $^{124}Te(p, 2n)^{123}I$, tellurium or xenon as a target material, $^{124}Xe(p,3n)^{123}Cs \rightarrow {}^{123}Xe \rightarrow {}^{123}I$, $^{203}Tl(p, 3n)^{201}Pb \rightarrow {}^{201}Tl$. $^{14}N(p, \alpha)^{11}C$, $^{14}N(d, n)^{15}O$ these are

all positron emitters, short-lived ones, you can see, 20 minutes, 9 minutes, 122 seconds and 109 minutes. They are all positron emitters. Some of these isotopes are actually, the cyclotrons coupled with the PET facility are directly produced, half-lives are very short. So these are the reactions used for producing these positron emitters and they are widely used in PET radio-pharmacy. ^{103}Pd, 16 days, again ^{103}Rh(p, n)^{101}Pd reaction.

So you will find, there are hundreds of radioisotopes having different applications. So what we can do, you can just suppose you want to trace the path of an element, take the nuclear chart, look for the isotope having suitable half-life decay characteristics and then see in what way you can produce that particular radioisotope. So having the knowledge of nuclear reactions, you should be in a position to find out a reaction which will give you the desired isotope, proper yield, particular activity and you know whatever activity you need and particular chemical form also to be able to do the chemistry and deliver it to the users.

So let us compare the radioisotope production in a reactor and the cyclotron with different attributes. You can see here in the case of a reactor; reactor is a big sea of neutrons. So you can irradiate large amount of target material like cobalt metal, you can irradiate 20 grams, 100 grams. But in a cyclotron where the beam is travelling, first of all the beam dimensions are very small, few millimeters, so you cannot irradiate large quantity. Even if you irradiate a larger foil, it will not bombard that material. Only a very small section of the target will be irradiated.

So small amount of target will be irradiated in the cyclotron. So cyclotron I am saying is representative of the accelerator, but most of the time you will find the most of production by charged particles is mostly done in cyclotrons.

Reactor vs Cyclotron

	Reactor	Cyclotron
Amount of target	Large amount of target can be irradiated	Small amount of target can be irradiated
Specific activity	Generally low	High
No. of targets at a time	Many	One
Irradiation time	Can be kept long	Usually less
Type of decay	β^-	β^+/EC
Cost of production	low	high

So I am just comparing reactor and cyclotron, but this is also valid for any charged particle accelerator. Accordingly, the specific activity is generally low in reactor neutron irradiation, particularly by (n,γ) reaction, you get the isotope of the same element. There have been cases like multiple neutron capture or more like this one beta decay, (n, γ) product beta minus decay, then you can get carrier free. But in general, if you irradiate the target material by (n, γ), you will get low specific activity.

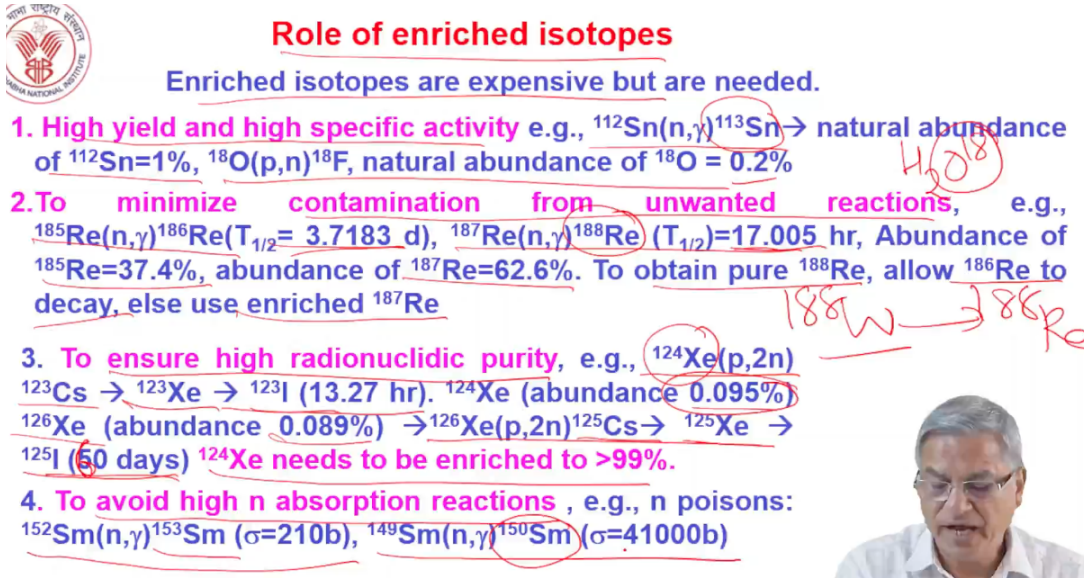
In cyclotron, you are using a charged particle, so you are changing the atomic number of it. So you can radiate the isotope compared to target. Therefore, you have very high specific activity of the useful isotopes. Number of targets at a time in a reactor, you can irradiate large number of radioisotopes in the target materials.

So at a time, many targets are being irradiated and you can just remove which one you want to remove depending on the time of irradiation and their half life. So you can irradiate many targets in the reactor. So throughput is very high, but in a cyclotron, at a time only one target. Suppose you have multiple beam lines; but at a time, the beam will go in a particular beam line. So there is no point putting irradiation in other beam lines at that point of time. At a time only one target irradiation.

Irradiation time can be kept long in a reactor, like cobalt-60, you irradiate for years. Half life is 5.27 years, so that you can irradiate for one year. In the case of accelerators, you cannot hold the accelerator for one target production exclusively. So usually the irradiation time will be one or two hours. And the beam time is very costly. Cyclotron operations are very costly. Type of decay of radio-isotopes producing reactors, mostly beta minus, but in the case of cyclotron producing radio-isotopes, beta plus. So they are neutron deficient. That is the only difference.

And the cost of production accordingly in the reactor is low, but in the accelerator it is very high. So you have to weigh, you have to optimize the cost also. But when you are delivering to, industry for some applications or in hospitals, so whatever is the cost that will go into the annual cost of the operation. All these factors are important to choose what is that method of production of radioisotope.

So you may get a low specific activity in the reactor, but it is cheaper. You want to go for high specific activity in cyclotron, you have to pay for it. That is how you have to assess the situation and plan. Now many times, you know, many elements have multiple isotopes and you want to produce a particular isotope, again gamma or charged particle, but there will be side reactions. Other isotopes also will interfere. They will produce other activity which will not be required. And so at that point of time, you need to have enriched isotopes. So if an element has got multiple isotopes and you want to irradiate a particular isotope, you need to get rid of the others, which are not useful. So enriched isotopes are required and isotope enrichment is a very expensive process. So that adds the cost to the whole production of the radioisotopes. They are expensive, but at many times they are inevitable. You cannot afford to not have the enriched targets.



So I will just give you some examples, what are the situations in which you need the enriched targets. So there are situations where you want the radioisotope with high yield and high specific activity. For example there are situations wherein the target should give only tye desired radioisotope. That time you cannot have the other isotopes. You see, just to give an example, $^{112}Sn(n, \gamma)^{113}Sn$. So you want ^{113}Sn which is used in medicine. Now the abundance of ^{112}Sn is only 1%. You can see here, other isotopes of tin will also capture neutrons or the volume, you see 99% of the tin is other isotopes. So if you produce ^{113}Sn, bulk of the tin is still the natural tin.

And so the activity produced of ^{113}Sn will be very small because ^{112}Sn is only 1%. So what you do, you try to enrich ^{112}Sn in the sample so that the specific activity will go up yield also will go up. Similarly, ^{18}F that you want to produce for PET operations, ^{18}O is very small percentage, 0.2%. Bulk of the oxygen is ^{16}O. So if you irradiate natural water, you will get very small activity of ^{18}F because ^{18}O has very small abundance. So what you do, you enrich water in ^{18}O. So you have H_2O^{18} and you can irradiate, you can enrich ^{18}O up to more than 95%. See this is a low mass number. So it is easy to enrich the low mass elements. These are the situation when you necessarily need to enrich the target in the desired isotope.

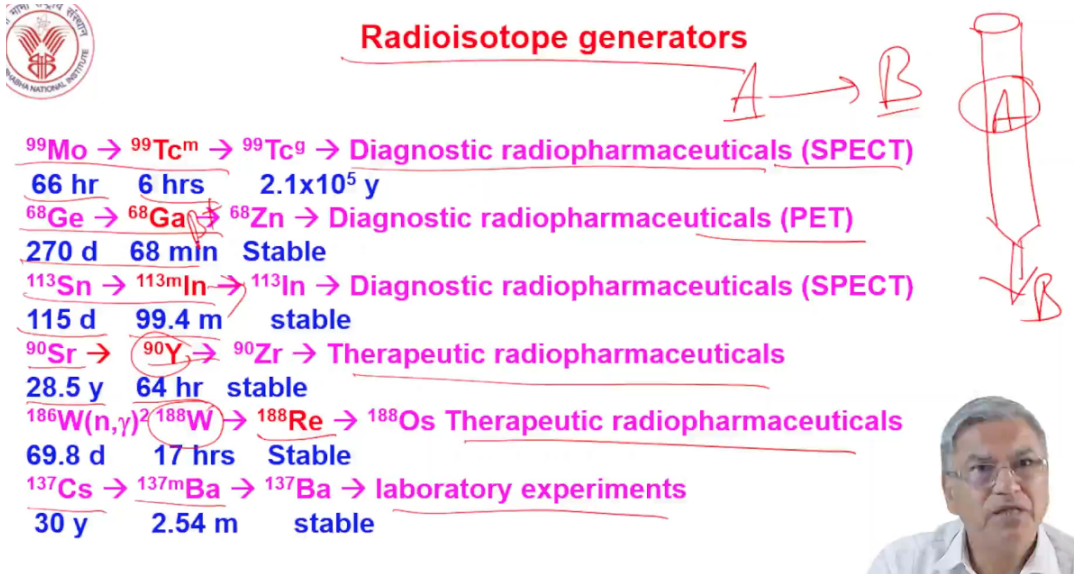
Second requirement is to minimize contamination from unwanted reactions. You are looking for a particular isotope, but there are other target isotopes which may give you unwanted activity which is not desired. For example, $^{187}Re(n, \gamma)^{188}Re$. We want ^{188}Re for our application, but there is another reaction $^{185}Re(n, \gamma)^{186}Re$ which is not required. So you have one isotope, three days, other isotope, 17 hours. Abundance of ^{185}Re is 37%. ^{187}Re is 62%. So these are the two reactions concurrently happening. Your isotope of interest is actually ^{188}Re, which is used in therapeutic techniques. So you have to, to obtain pure ^{188}Re, you have to allow ^{186}Re to decay. But how you can allow it to decay?

^{188}Re is shorter than ^{186}Re. So it is not possible to allow ^{186}Re to decay. Therefore, what you do? You use enriched ^{187}Re. That is what I was telling you that ^{188}W, if you have, you can produce by two neutron capture, that will give you ^{188}Re. And so these problems are not there. So by (n, γ) route, if you produce ^{188}Re, it will be contaminated with ^{186}Re, which is longer than ^{188}Re. So in those situations you require necessarily enriched isotope.

Similarly, again here also, this is similar to that radionuclide purity means that the sample should be pure with respect to particular radioisotope. And there can be parallel reactions. For example, you want to get ^{123}I, irradiate ^{124}Xe(p, 2n)^{123}Cs→^{123}Xe→^{123}I. But the abundance of ^{124}Xe is only 0.095%. So if you irradiate natural Xe, it has got very low abundance and so you get very small activity. ^{126}Xe also has got about same abundance as ^{124}Xe and that also gives you by similar reaction ^{124}Xe (p, 2n) ^{125}Cs. And so this is actually 60 days. So ^{125}I is longer than ^{123}I. And so it will always contaminate your spectrum. So if you have ^{123}I produced by ^{124}Xe(p, 2n) reaction, you will invariably have ^{125}I which is longer lived. Therefore, there will be always contamination. Therefore, you need to enrich ^{124}Xe up to more than 99%. The gaseous isotopes are easy to enrich. Different methods are there available for isotope enrichment. And so the enrichment of isotopes is a very common technology these days and many vendors are available to supply enriched targets.

There are situations where the target element may contain isotopes which have very high neutron absorption process. So you want to produce one isotope of that element but the other isotopes may have very high neutron absorption process. So they will suppress the neutron flux in that position. So they act as neutron poisons. Means the isotopes which have very high cross section for neutron capture, they act as neutron poison. They will actually absorb the neutrons and reduce the flux. For example, you want ^{153}Sm for many medical applications. You irradiate ^{152}Sm(n, γ) and you get ^{153}Sm. Half life is about 46 hours. But if you see here, you have ^{149}Sm(n, γ)^{150}Sm. Though ^{150}Sm is stable, it will not give you any activity. But the very high cross section 41,000 barn of ^{149}Sm(n, γ), this high cross section will reduce the neutron flux. Most of the neutrons will be captured by ^{149}Sm. And so it's like a neutron poison. So it will affect the neutron economy in that position and your yield of ^{153}Sm will be less.

So these are the reasons where you need to have enriched isotopes. There are other ways also where you can have radioisotopes. I have separated this class of radioisotopes because they are very handy in many applications.



Now I give you some of the generators. Radioisotopes generators means you have a parent daughter relationship. You have a long lived parent and short lived daughter. And so you can put in a column or say, A is here and you can milk B. So it's called cow, you milk the cow. So you can hold the parent isotope in the column and you can go on milking. I discussed in the ^{99}Mo case, you can milk ^{99m}Tc from ^{99}Mo generator. These are called radioisotope generators. And they are very popular these days because you can send the people who are manufacturing these generators, they can sell the generators to the hospitals and hospitals have their own hospital radio pharmacy. They can go on milking the isotope of interest.

So ^{99}Mo is the parent of ^{99m}Tc. ^{99m}Tc is the workhorse of nuclear medicine, particularly for the diagnostic applications. So SPECT, single photon emission computed tomography. You are doing the imaging of an organ. You inject a compound labelled with ^{99m}Tc. And when it is going in the bloodstream, particular organ, where the blood is flowing, you can take the image like for example, heart imaging.

If there is a heart attack, then what part of the heart is infructuous can be seen. So 66 hours and 6 hours is ideal transient equilibrium. You can go on milking ^{99m}Tc. Another pair is Germanium-68 and Gallium 68, it's a beta plus emitters. So for PET radio-pharmaceuticals, you can use this generator, 270 days and 68 minutes, ^{113}Sn and ^{113}In. ^{113}In is the radioisotope useful for diagnostic radiopharmaceuticals. And so you can milk it from ^{113}Sn having half life 115 days and this is 99 minutes. This internal transition, it a pure gamma emitter like ^{99m}Tc. So they are ideal for imaging. ^{90}Sr, 28 years, ^{90}Y, 64 hours. And so this is again another pair where ^{90}Y is used in therapeutic pharmaceuticals.

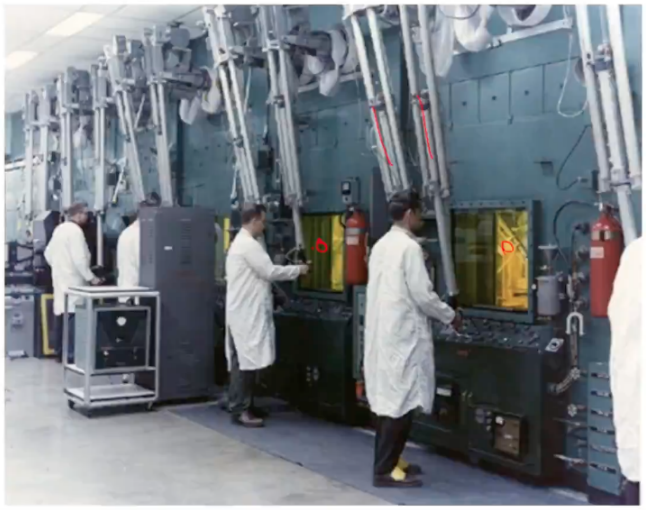
^{188}W, the parent to the ^{188}Re, which is used in therapeutic pharmaceuticals. And ^{137}Cs, ^{137}Ba used in the laboratory experiments for the gamma ray half-life determination. And many applications you will find. ^{137}Cs is also used in blood radiators. So these are other ways of producing radioisotopes.

Dhruva reactor hall

Now I will just briefly discuss some of the activities in India. In India, we have the, in Trombay campus, we have the CIRUS reactor. That's not functioning now, but we have the Dhruva reactor, which is producing radioisotopes. And there is a sequence of events: irradiate in the reactor, take it to the chemical laboratory and then process them, send to other agency for distribution in the country.

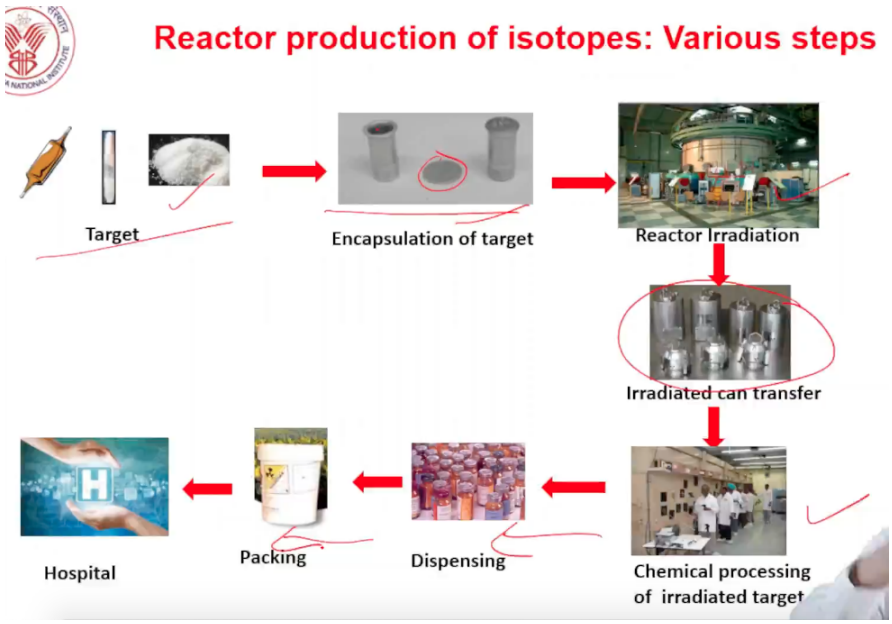
So inside the Dhruva, we have the reactor hall. Inside the reactor hall, these are the facilities for experiments, neutron scattering and other things. But inside the reactor, you will have the conditions where you can load the sample, irradiate them for a specific period of time, and then take out for processing.

Radioisotope processing hot cells at Trombay



After the irradiation in the reactor, you bring them to the hot cells. Hot cells, you can see the yellow color in the windows. These are lead glasses because the inside the hot cells, the radioisotopes of very large activity, the curies, hundreds of curies are being handled. And the person who are handling them should not get the radiation dose. So the viewing window is not pure glass, it is made of lead glass. So lead will attenuate the gamma ray, so the personnel are not getting much gamma dose. So that is why you add lead, and some color will develop in the window, and also the radiation, because of the radioisotope sources, they also have the tendency to generate colors in the glass.

So the viewing window, and these are the master slave manipulators. You can manipulate them and do the chemistry inside the hot cell. You may have to open the can, do different chemistry, transfer from one port to other port. So all these operations are done in the sealed hot cells.



This is a complete sequence of the radioisotope production. You have the targets, you can have powder, you can put them in the tube, and then seal in the aluminum cans. You fill the powder into this one, and then you can do welding, irradiate in the reactor. This has to go for quality check so that it does not leak. And then after this, you bring in the shieled casks from the reactor, stainless steel or lead pots. They have to be transported to the processing laboratory where the people do operations in the hot cell to separate the particular radioisotope of interest.

They are then dispensed. You can bring it in the vials, properly capping them so that there is no leakage. There has to be a quality check. Many times the sterility also have to be checked if it is for direct injection to the human being. Then these are packed into the lead pots, and then we have the package. You have to give the proper package so that people can identify what's the dose, what is the activity and all that. And then these, they are supplied to the hospitals by the agency.

Medical cyclotron facility at VECC Kolkata

Isotope ($T_{1/2}$ hrs)	Nuclear Reaction	Application
^{67}Ga 78.3	^{68}Zn(p, 2n) ^{67}Ga	Soft tissue tumor imaging
^{201}Tl 73.5	^{203}Tl(p,3n) ^{201}Pb, (9.4h) ^{201}Pb (EC/β+) ^{201}Tl	Myocardial perfusion imaging
^{123}I 13.3	^{124}Xe(p,pn) ^{123}Xe →^{123}I	Thyroid uptake/ imaging
^{18}F 1.8	^{18}O(p, n)^{18}F	Glucose metabolism
^{68}Ga 1.1	^{68}Zn(p,n)^{68}Ga	Neuroendocrine tumors

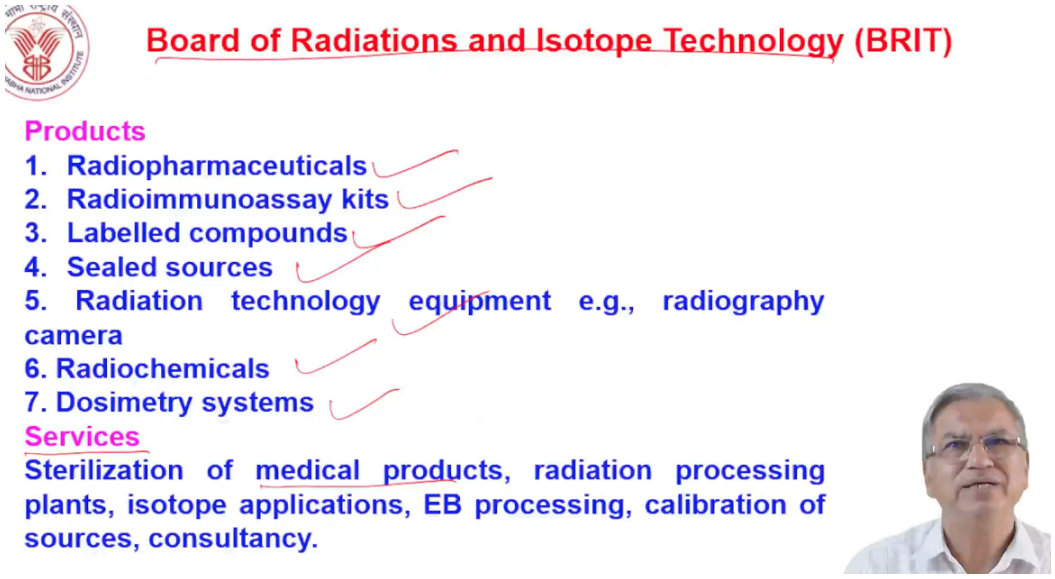
For the charge particle irradiation in our country, we have a medical cyclotron facility at Kolkata. It has been commissioned some time back. And this will give you proton beams of 30 MeV. And then you can produce radioisotopes which are positron emitters or electron capture emitting radioisotopes like ^{67}Ga, ^{201}Tl, ^{123}I, ^{18}F, ^{68}Ga by different types of reactions, (p, 2n), (p, 3n), (p, n), etc., reactions.

So I just discuss how they are produced in this discussion. And so like ^{67}Ga soft tissue tumor imaging, the ^{201}Tl for myocardial perfusion imaging, ^{123}I for thyroid imaging, ^{18}F for glucose metabolism and ^{68}Ga for PET analysis of neuroendocrine tumors. So these are the kind of activities that are being produced at Medical Cyclotron Kolkata. And in the country, there are several PET cyclotrons now available. Private hospitals have medical cyclotrons for PET isotopes.

Medical cyclotrons for PET

PET radiopharmaceuticals: Labelling the radioisotope with a molecule, e.g. ^{18}F labelled FDG. → Automated radiochemical processing unit

And particularly ^{18}F is produced in these cyclotrons. You have the 16 MeV proton beam bombarding H_2O^{18} that gives you ^{18}F. And then there is an automated radiochemical processing unit. And now within a few seconds or few minutes you will get the compound labeled with the ^{18}F. Then it can be directly sent to hospitals for PET imaging.



These are the kind of facilities that are available. So in our country, the board of radiation and isotope technology, it's called BRIT, is the agency to supply different radioisotopes for different kits. And they provide the services for industry, in medicine, medical industry, normal industry and many others. Whoever wants a device, you will find pharmaceuticals, radioimmunoassay kits, if you want labeled compounds, sealed sources or even technology, radiographic camera, radio-chemicals, dosimetry systems, all are supplied by BRIT. You can go to the website of the BRIT and see what products they are supplying. And for the larger products, medical products, sterilization, processing, vulcanization of rubber and many other applications, you can use electron beam processing for insulation or cables, consultancy, calibration of radioisotopes. All the facilities services are provided by BRIT in the country. So you can go to the website and see what are the things they do.

So I'll stop here and thank you very much for your attention. I hope you are getting a feel of what the radioisotopes can do and how you can produce them in our facilities. Thank you very much.