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Medical Cyclotron

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1. Introduction

In this chapter we intend to illustrate the reader about the use of Cyclotrons to produce easy handle radioisotopes, to be used for medical diagnostics or therapies in Nuclear Medicine. Firstofall, we will describe different activation processes to generate artificial radioisotopes, characteristics needed to be safely used in medicine, such as the relationship between fathers and daughters that can compromise patient or environment health. It also will be describe radioisotopes desire behavior inside human body in order to clarify which isotopes can be activated or not in a cyclotron facility to be used in human medical applications. Nuclear Medicine radioisotopes must fulfill four main characteristics in order to be easy handle by operators and be easily and quickly disposed by patients and not to represent environmental radioactive contamination harm, so they have to have:

1. Low activity
2. Low energy
3. Short half life
4. Decay to a stable daughter

In Nuclear Medicine, equipment also has to have a high sensitivity to small amounts of radiation and to different types of radioisotopes. The ideal radioisotopes must be easily eliminated by the patient just after the study has been done in a short period of time which is a function of the physical half life of the isotope and the patient excretion system. The total time elapse for patient elimination of any trace of radioisotope used for study is known as Effective Half Life Time $T_{1/2}^{\text{eff}}$ and is related to the time isotope population is reduced to its half due to the radioactive decay of father to daughter (Physical Half Life) $T_{1/2}^{\text{phy}}$ and the time patient systems needs to eliminated of isotope from it system (Biological Half Life) $T_{1/2}^{bio}$ in this way:

$$\frac{1}{T_{1/2}^{eff}} = \frac{1}{T_{1/2}^{phy}} + \frac{1}{T_{1/2}^{bio}}$$

So it is not easy to find natural occurrence radioisotopes to fulfill this equation in order to make $T_{1/2}^{\text{eff}}$ shorter than biological times of cellular repair. Fortunately in mid 20Th century, there was a huge development of activation processes when man learn how to manipulate atom and its nuclei, so now we have a big amount of radioisotopes for an equally big amount of pacific applications. There are two kinds of manmade machinery capable of modify stable nuclide: Nuclear reactors and particle accelerators. Accelerator can also be

divided into two big groups: Linear accelerators and spiral path accelerators or Cyclotrons. The radioisotopes used in Medicine can be from natural ocurrences like ^{137}Cs (used in the last century in Teletherapy machines and in low dose rate brachytherapy) or ^{192}Ir (used nowadays in high dose rate brachytherapy), or can be produced in Reactors or Cyclotrons. Most common reactor products used in Medicine are:
For diagnostic purposes: ^{51}Cr, ^{125}I, ^{131}I, ^{59}Fe, ^{42}K, ^{177}Lu, ^{99}Mo (fission product), ^{75}Se, ^{24}Na, ^{99m}Tc, ^{133}Xe (fission product), ^{159}Yt.
For therapeutic purposes: ^{213}Bi, ^{60}Co, ^{165}Dy, ^{169}Er, ^{125}I, ^{131}I, ^{192}Ir, ^{212}Pb, ^{177}Lu, ^{103}Pd, ^{32}P, ^{188}Re, ^{186}Re, ^{153}Sm, ^{89}Sr (fission product), ^{90}Y (fission product).
For diagnostic and therapeutic or other purposes: ^{60}Co, ^{166}Ho, ^{125}I, ^{99}Mo (fission product), ^{177}Yt.
Most common radioisotopes produced in Cyclotrons used in Medicine are:
For diagnostic purposes: ^{11}C, ^{13}N, ^{15}O, ^{18}F, (PET studies), ^{64}Cu, ^{67}Ga, ^{68}Ga, ^{111}In, ^{123}I, ^{124}I, ^{81m}Kr, ^{99}Mo (activation product), 82Rb, 201Th.
For therapeutic purposes: ^{67}Cu.
For diagnostic, therapeutic or other purposes: ^{57}Co, ^{82}Sr, ^{68}Ge. All of them have to fulfill the four conditions mentioned above.
Knowing all this restrictions radioisotope has to accomplish, to be safely used in human, now we can talk about the characteristics of a cyclotron to produce such an isotope. Later in this chapter we will describe such an installation regarding shielding, environmental safety, radiopharmacy lab, etc.
In Venezuela, we start to install the first baby cyclotron for medical purposes on 2001, so our last section of this chapter is to illustrate how this installation works and how its programs has been accomplish to the present date.

2. Basic physics of particle activation

"Particle activation" means "artificial radioactivity" or "man made radioisotopes", far away from "natural radioactivity" which is a basic characteristic of our Universe, that has been present all over the universe history, and it contains only four natural decay series characterized by their numbers of nucleons as is shown in Table 1., artificial radioactivity is a very young phenomena born in 20th century.

Series	Parent	Nucleons	Stable end
THORIUM	$^{232}Th_{90}$	4n	$^{208}Pb_{82}$
NEPTUNIUM	$^{237}Np_{93}$	4n+1	$^{209}Bi_{83}$
URANIUM	$^{238}U_{92}$	4n+2	$^{206}Pb_{82}$
ACTINIUM	$^{235}U_{92}$	4n+3	$^{207}Pb_{82}$

Table 1. Natural decay series.

Firstofalll we have to define radioactivity: It is a property of nature in which atoms have such a big amount of energy so they need to discharge it to the surrounding media. The aim of it is to become stable, i.e. have the less amount of energy need to exist, because atom stability is the more cost/efficiency retail in matter. Atom then has design some method to discharge energy and diminish it energy level to become stable. Radioactive atoms can emit some energy packs splitting them in pieces of several dimensions and energy content to reach its stability:

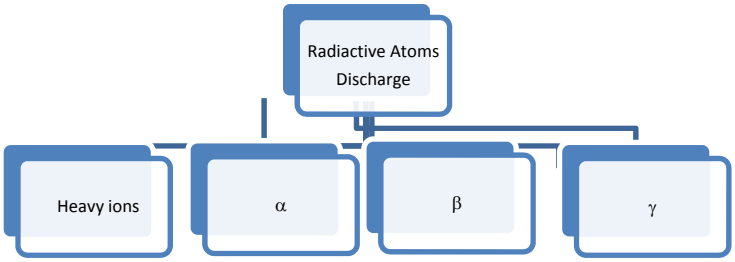


Fig. 1. Decay mode of radioactive atoms to reach stability.The action of atoms to split means mass and energy transfer to media. For example, in a ^{226}Ra atom energy excess push it to split out a ${}_{2}^{4}He$ nucleus (an alpha particle) and 1.4 MeV package of pure energy and another atom of ^{222}Rn, so where there was one atom now there are three different species born out it mass and energy

There are several methods for atoms to transfer energy to the media. Remember Einstein´s principle of $E = mc^2$, which means energy is matter and matter is energy. So in their attempt to become stable emits energy/matter to discharge it excess in several ways as in figure 1.
And scientist began to use this atom fraction to hit different nucleus of known atoms and to observe which was the results of the reverse experiment.
Back in 1929, Ernest Lawrence device a Cyclotron to fulfill his own need to generate high speed ions without needing high voltages he has not access to in Berkeley University. This history began 10 years before when Lord Rutherford used alpha particles coming from Madame Curie´s ^{226}Ra as projectiles to impact a Nitrogen nucleus to transform it into Oxygen.

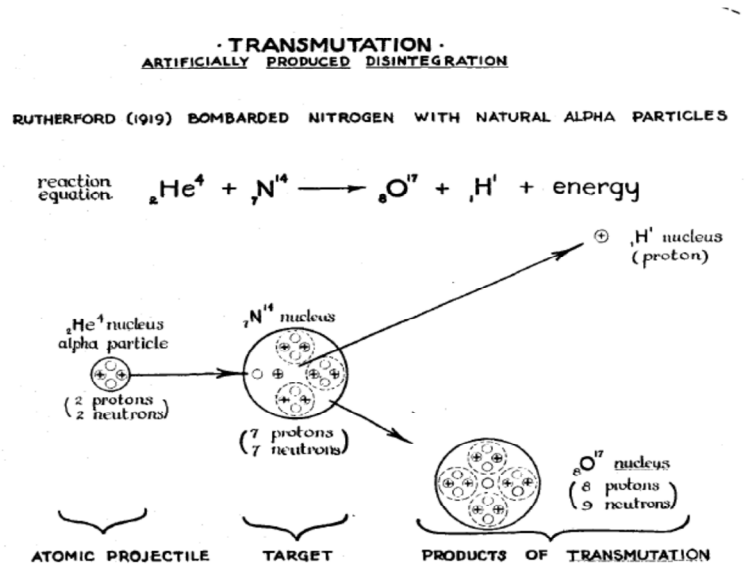
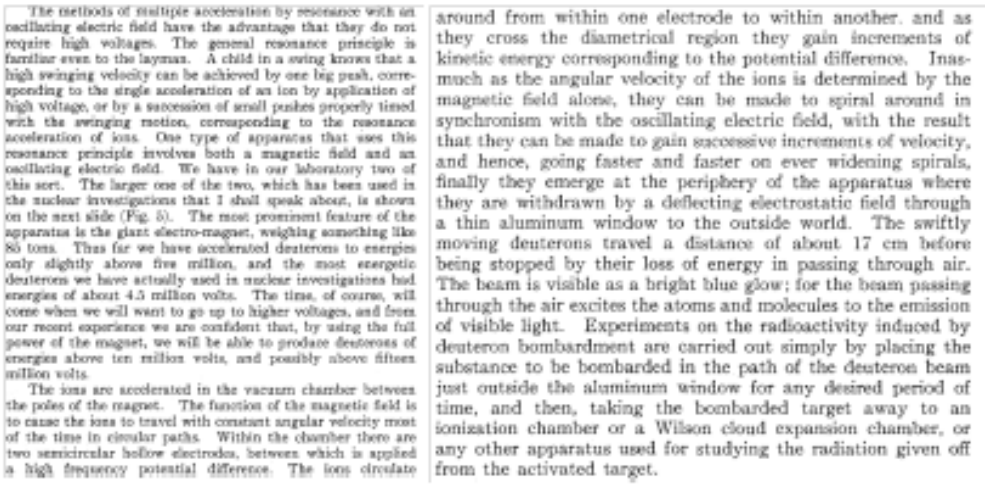


Fig. 2. Lawrence´s illustration about Rutherford Experiment.

In the same line of thoughts, Lawrence needs more projectiles to study this new phenomena. That 15th century dream of turning Lead into Gold was now though to be possible. Radioisotopes not always decay to a stable daughter but they continue trying, emitting different kinds of particles until they reach stability. In the sake for such stability they transform themselves into a partner they "believe" is more stable: The fifteen Century "Transmutation of Matter" occurs not for lead to become gold but something alike. Men made transmutation, which arise to be only the modification of the "positive electricity in the atomic nucleus", as Lawrence said.[1] He described his method of accelerating particles in Cyclotron as "resonance method" or "method of multiple acceleration:



The methods of multiple acceleration by resonance with an oscillating electric field have the advantage that they do not require high voltages. The general resonance principle is familiar even to the layman. A child in a swing knows that a high swinging velocity can be achieved by one big push, corresponding to the single acceleration of an ion by application of high voltage, or by a succession of small pushes properly timed with the swinging motion, corresponding to the resonance acceleration of ions. One type of apparatus that uses this resonance principle involves both a magnetic field and an oscillating electric field. We have in our laboratory two of this sort. The larger one of the two, which has been used in the nuclear investigations that I shall speak about, is shown on the next slide (Fig. 5). The most prominent feature of the apparatus is the giant electro-magnet, weighing something like 85 tons. Thus far we have accelerated deuterons to energies only slightly above five million, and the most energetic deuterons we have actually used in nuclear investigations had energies of about 4.5 million volts. The time, of course, will come when we will want to go up to higher voltages, and from our recent experience we are confident that, by using the full power of the magnet, we will be able to produce deuterons of energies above ten million volts, and possibly above fifteen million volts.

The ions are accelerated in the vacuum chamber between the poles of the magnet. The function of the magnetic field is to cause the ions to travel with constant angular velocity most of the time in circular paths. Within the chamber there are two semicircular hollow electrodes, between which is applied a high frequency potential difference. The ions circulate around from within one electrode to within another, and as they cross the diametrical region they gain increments of kinetic energy corresponding to the potential difference. Inasmuch as the angular velocity of the ions is determined by the magnetic field alone, they can be made to spiral around in synchronism with the oscillating electric field, with the result that they can be made to gain successive increments of velocity, and hence, going faster and faster on ever widening spirals, finally they emerge at the periphery of the apparatus where they are withdrawn by a deflecting electrostatic field through a thin aluminum window to the outside world. The swiftly moving deuterons travel a distance of about 17 cm before being stopped by their loss of energy in passing through air. The beam is visible as a bright blue glow; for the beam passing through the air excites the atoms and molecules to the emission of visible light. Experiments on the radioactivity induced by deuteron bombardment are carried out simply by placing the substance to be bombarded in the path of the deuteron beam just outside the aluminum window for any desired period of time, and then, taking the bombarded target away to an ionization chamber or a Wilson cloud expansion chamber, or any other apparatus used for studying the radiation given off from the activated target.

Fig. 3. Lawrence description of Cyclotron accelerating method.

Few time pass, until man used that newly produce radioactive material to treat and diagnoses different affections. John Lawrence, Ernest brother was the first to use his brother product ^{32}P to treat leukemia starting the medical applications of cyclotron products.

Method of particle activation then, need a Nuclear Reactor or an accelerator (Cyclotron, Syncrothron or Linac) to be produced: Nuclear Reactor is an installation in which big rod of natural occurring radioisotopes are set inside a pile with some stable, neutron absorbent, material. The radioisotopes (Th, U) initiates a chain reaction, the stable rod (such as carbon (graphite)) are used to absorb chain reaction debris, in order to moderate the amount of energy (heat) that is produce by nuclear reactions.

They are considered of two kinds: *Power Nuclear Reactors* which are dedicated to use the energy to produce electricity, for example, boiling water to move turbines with the steam and in this way produce electric power. *Nuclear Research Reactors* are used as a source of neutron of different energies to impact different atoms nuclei to become radioactive. In both cases they need the fission product from the original radioactive atom to undergo the chain reaction. For example, ^{235}U absorb a neutron, it become ^{236}U and this split into ^{92}Kr and ^{141}Ba with several neutron that can impact other ^{235}U and become ^{236}U to repeat the reactions.

[1] E.O.Lawrence:(1939) University of California: "Artificial Radiactivity" speech.

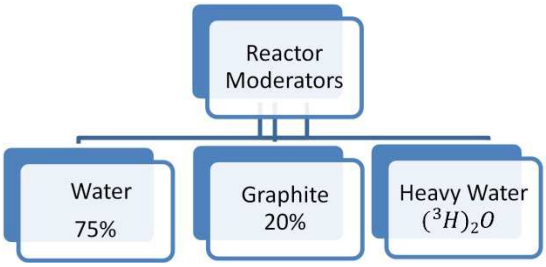


Fig. 4. Materials for particle absorption in a Reactor.

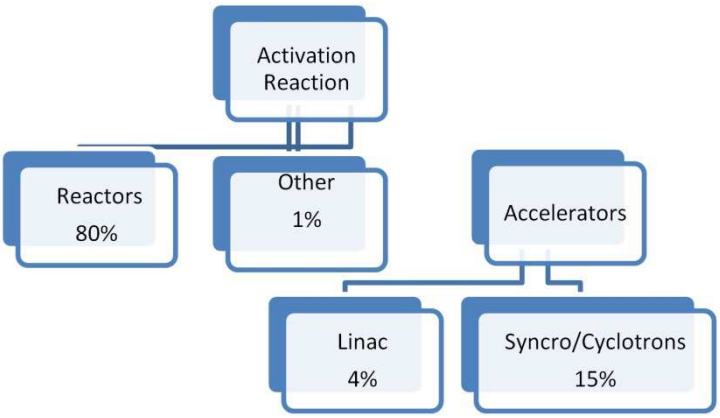


Fig. 5. Percentage of activation products worldwide coming from Reactors or Cyclotrons including medical, industry and research production.

In the other hand, cyclotron are electrical machines that generates particle acceleration thru helping them to undergo a circular or elliptical path in which particles gain energy by external manipulation of electric an magnetic fields.
Cyclotrons comes from a bigger family of electrical machines called Accelerators, because the make particles to gain energy letting them gain kinetic energy by applying electrical and magnetic fields to the particle trajectory so it can absorb energy from the media where it is travelling. Back to high school physics we can understand easily how cyclotrons accelerate particles: you must remember that force in an electrical field is:

$$F = qE \tag{1}$$

And also you remember that when you have and electrical and magnetic fields you can write

$$\vec{F} = q(\vec{v} \times \vec{B}) \tag{2}$$

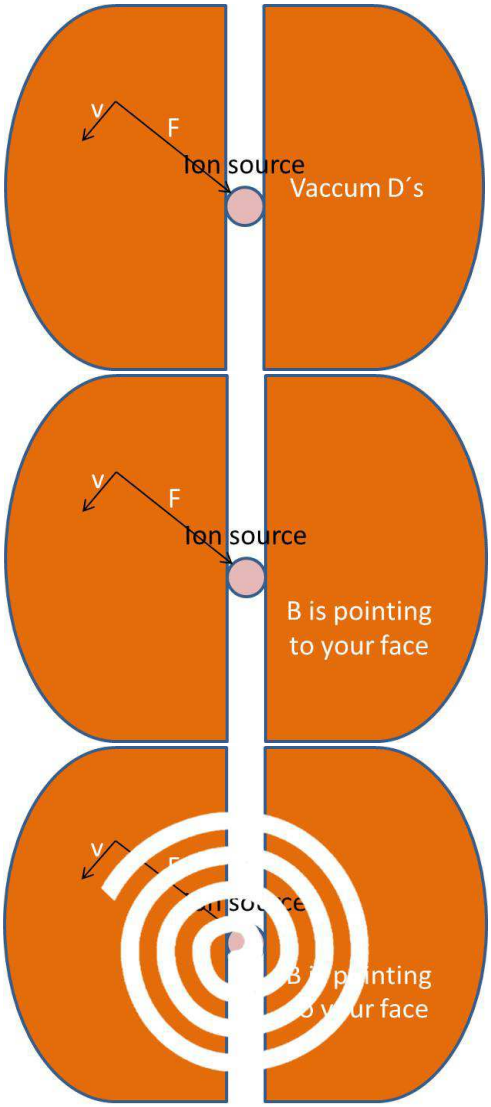


Fig. 6. Cyclotron schematics: a) ion input location, b) $\vec{B} = \vec{v}x\vec{F}$, c) Ion path.

Where q is the charge, v is the velocity and B is the magnetic field
Or in its escalar form

$$F = qvB \tag{3}$$

But you know that when you send a particle in a circular path also the centrifugal force yields:

$$F = \frac{mv^2}{r} \tag{4}$$

Where m is the mass of the particle to be accelerated and r is the radius of the circular path. If you equal 3 with 4 you can obtain the radius you need for a particular energy you want

$$r = \frac{mv}{qB} \tag{5}$$

Velocity has two components, linear that is tangential to the spiral trajectory and angular that is about circular path cover by the particle, so

$$v = \omega r \tag{6}$$

Where ω is the angular velocity and

$$\omega = 2\pi f \tag{7}$$

Where f is the angular frequency of the movement, so using 3 and 4 we can know about cyclotron frequency

$$\frac{mv^2}{r} = qvB \tag{8}$$

Because potential energy has to become kinetic energy so,

$$qV = \frac{mv^2}{2} \tag{9}$$

Where V is the potential between the d´s where the particle gain energy

$$v^2 = \frac{2qV}{m} \tag{10}$$

$$where\ V = Er = vB \tag{11}$$

So $v = \frac{rqB}{m} = \omega r = 2\pi f r$ and finally

$$f = \frac{qB}{2\pi m} \tag{12}$$

And remembering Einstein, particles with this energies travels near speed of light

$$f = \frac{qB}{2\pi\gamma m_0} \tag{13}$$

With

$$\gamma = \frac{1}{\sqrt{1-(v/c)^2}} \tag{14}$$

3. Methods of particle activation

Alpha particle Bombardment: Using natural produced alpha particles light elements can be activated, and as far as Pottasium. Such projectile induce the emission of a proton, the liberation of energy and a transmutation, not all the transmutation products are radioactive Neutron Capture: Firstly observed when matter is bombarded with deuteron, which also involve the emission of a proton, as we will illustrate forward.

4. Reaction of particle activation

1. Nuclear Activation in Reactors:

   (n,γ) Reaction: Radioactive capture: Undergo mostly by thermal neutron

$$^{59}_{29}Co + ^{1}_{0}n \longrightarrow ^{60}_{29}Co + \gamma \qquad \text{(s=36 b)}$$

$$^{98}_{42}Mo + ^{1}_{0}n \longrightarrow ^{99}_{42}Mo + \gamma \qquad \text{(s=0.12 b)}$$

In such a reaction father and daughter are of the same chemical species so they cannot be separated, reason why the target must have a very high enrichment rate.

(n,α) Reaction followed by β- decay

$$^{130}_{52}Te + ^{1}_{0}n \longrightarrow ^{131}_{52}Te \xrightarrow{\beta^-} ^{131}_{53}I + \gamma$$

Tellurium and iodine are easily chemical separated

(n,p) Reaction: Neutron Capture

$$^{32}_{16}S + ^{1}_{0}n \longrightarrow ^{32}_{15}P + ^{1}_{1}H$$

$$^{58}_{28}Ni + ^{1}_{0}n \longrightarrow ^{59}_{28}Co + ^{1}_{1}H$$

This is similar to the first reaction produced in his cyclotron that be named "neutron capture" despite he was using deuterium as projectile, he observed that neutron stayed inside target nuclear and the remaining mass was expel as a proton.

(n,α) Reaction: Light fission

$$^{6}_{3}Li + ^{1}_{0}n \longrightarrow ^{3}_{1}H + ^{4}_{2}He$$

2. Activation Equation:

$$\frac{dN_1}{dt} = \Phi \sigma_{act} N(t)$$

Where:

N_1 = Atoms of the target

Φ = Neutron flux

σ_{act} = Activation cross section

$N(t)$ = Number of atoms activated in a time period elapsed t

So, the number of activated atoms is:

$$N_1 = \Phi \frac{\sigma_{act} N(t)(1 - e^{-\lambda t})}{\lambda}$$

And the activity of the sample is:

$$A = \lambda N_1 = \Phi \sigma_{act} N(t)(1 - e^{-\lambda t})$$

t is the time of irradiation in seconds

A is the activity at the saturation value that is a function of reactor neutron flue at which target has been exposed.

3. Nuclear reaction in cyclotron production

(p,n) Reaction

$$^{18}_{8}O + ^{1}_{1}H \longrightarrow ^{18}_{9}F + ^{1}_{0}n$$

(d,α) Reaction:

$$^{20}_{10}Ne + \longrightarrow ^{18}_{9}F + ^{4}_{2}He$$

(p,α) Reaction

$$^{14}_{17}N + ^{1}_{1}H \longrightarrow ^{11}_{6}C + ^{4}_{2}He$$

$$^{16}_{8}O + ^{1}_{1}H \longrightarrow ^{13}_{7}N + ^{4}_{2}He$$

(d,n) Reaction

$$^{14}_{7}N + ^{2}_{1}H \longrightarrow ^{15}_{8}O + ^{1}_{0}n$$

$(d,2n)$ Reaction

$$^{68}_{30}Zn + ^{2}_{1}H \longrightarrow ^{65}_{31}Ga + 2^{0}_{1}n$$

$$^{124}_{52}Te + ^{1}_{1}H \longrightarrow ^{123}_{53}I + 2^{1}_{0}n$$

$(\alpha,2n)$ Reaction

$$^{65}_{29}Cu + ^{4}_{2}He \longrightarrow ^{67}_{31}Ga + 2\,^{1}_{0}n$$

5. Differences and similarities between reactors and cyclotrons

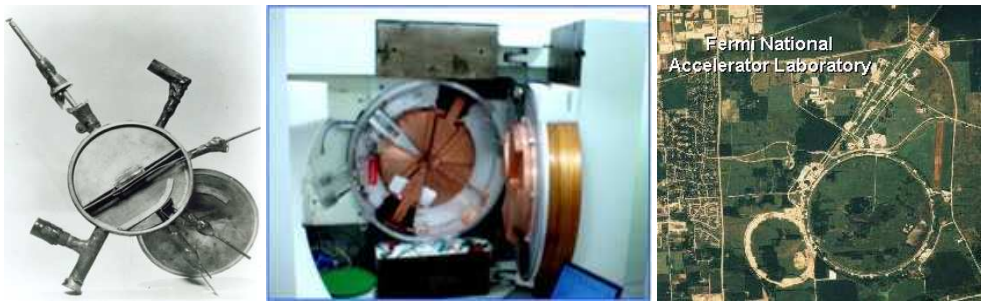
Cyclotron is not the only way of activating matter. Going through history, side by side cyclotron development in America, Europe was devoted to the natural radioactive material discovered by many scientists, from Madame Curie (1898), Pierre, Irene and also Joliot till Enrico Fermi, Otto Hahn, Lise Meitner and Fritz Strassman (1939). Neils Bohr and Jhon A. Wheeler published their explanation of the method for moderating, "modulating", chain reactions in a paper published only 2 days after WWII starts in 1939. The first reactor was then brought into criticality in Fermi´s Lab on December 2nd, 1942 in very controlled experiment including radiation safety and protection considerations. Proving that chain reaction can be controlled, it was matter of time to find uses for the products obtain from a nuclear reactor. The neutron from reactors are projectiles for many (n,p), (n,β), reactions to produce many radioisotopes. So time has come to begin talking about which of all this radioactive products can be used in medicine. The first radioactive material used in humans with medical purposes was 226Ra, (1898) used by Madame and Mousier Curie to treat skin lesion they called "benign". Their daughter Irene used 214Bi to measure blood flow, this two products come directly from the ^{238}U natural decay series. By the artificial radioisotopes side, the first one was that ^{32}P John Lawrence (1929) used to treat leukemia. After of it, a lot of radioisotopes and a lot of uses have been developed for diagnostic and therapy uses, so for this time, we can say that the radioisotopes used in Medicine distributions is as it is shown in Table 2:

	Reactors Produced		**Cyclotrons Produced**
	Fission Products	Neutron activation	
Diagnostic Purposes	^{133}Xe, ^{99}Mo	^{51}Cr, ^{125}I, ^{131}I, ^{89}Sr, ^{153}Sm, ^{59}Fe, ^{177}Lu, ^{42}K, ^{75}Se, ^{24}Na, ^{99m}Tc, ^{159}Yt	^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{57}Co, ^{82}Sr, ^{68}Ge ^{64}Cu,^{67}Ga, ^{68}Ga, ^{111}In, ^{123}I, ^{124}I, ^{81m}Kr, ^{82}Rb, ^{201}Tl
Therapeutic Application	^{89}Sr, ^{90}Y	^{213}Bi, ^{60}Co, ^{165}Dy, ^{169}Er, ^{125}I, ^{131}I, ^{192}Ir, ^{212}Pb, ^{177}Lu, ^{103}Pd, ^{32}P, ^{186}Re, ^{188}Re, ^{153}Sm	^{67}Cu, ^{57}Co, ^{82}Sr, ^{68}Ge

Table 2. Distribution of the radioisotope production for medical applications.

Like the Curie's began using their newly discovered natural radioisotopes to treat cancer lesion in the skin, very short time after the construction of the cyclotron and the production of its radioisotopes, makes the medical applications to be easily spread.
But there is another mechanism for particle activation and it comes from the nuclear reactor where a bunch of natural radioisotopes "bars" are used to produced spontaneous fission products to aim the nucleus of stable atom or its electronic crown.
Nowadays reactors are the core of the nuclear power plants, but in their beginnings they were developed for research proposes to military applications only. Due to the natural "nuclear fuel" reactors were better in cost/efficiency fashion and in the late 30's and early 40's many budgets and efforts were driven to their construction to regulated nuclear chain reaction and its control, until the atomic bomb development to win WWII.

But passing thru that dark hour, all the money spend in its development seems to be not that important.
And cyclotron has to compete (and win) against reactors that were redeeming themselves by producing "atoms for the peace" trying to justify the large budget assign to them during WWII.
And for a long period of time the guilt drop the balance to reactors side until middle 70's when positron emission tomography arised based in a component containing ^{18}F: ^{18}FDG (Fluorodexoxy glucose).
This isotope was only produced in cyclotron and the compound could be synthetized in a straight forward relative easy way.
This made cyclotrons an Hospital equipment because, due to the short half-life of ^{18}F, it was necessary to stablish the supplier so near to the costumer as it can be, and being a hospital a places were pureness and asepsie is well know, and treat with reverential respect, which other place would be better to activated pure ^{18}F and synthetize the ^{18}FDG in a sterile form to be safe to apply in human.
And between 1929 and 1974 lot of things happened to cyclotron to develop its actual characteristic. From Lawrence Cyclotron to Hospital one, until CERN´s a lot of energy has pass through.



a) b) c)

Fig. 7. Different cyclotron size: a) Lawrence´s first one, b) Venezuela First one (courtesy of Dorly Coehlo), c) Fermi National Laboratory at CERN.

And size matters, and Cyclotrons win as best hospital candidates due to Reactors are bigger, harder and difficult to be set in a hospital installation. Can you imagine a nuclear reactor inside a health installation? Radiation Protection Program will consume all the budget available. Size, controlled reactions, electrical control, made cyclotrons easy to install, and baby cyclotrons come selfshielded so hospital don´t need to spend money in a extremely large bunker. Now on, we are going to talk about our first experience with the set up of a baby cyclotron for medical uses inside the first PET installation in Latin America. "Baby" means its acceleration "D" diameters are suitable to be set inside a standard hospital room dimensions, with all its needs to be safetly shielded for production transmision and synthetized for human uses for imaging in Nuclear Medicine PET routine. When we ask why Cyclotrons are better than reactors for radioisotopes production to be used in Medicine, we also have to have in mind that they has:

1. Less radioactive waste
2. Less harmful debris

3. They can be installed inside hospital decentralizing radioisotope production.
4. Almost zero risk of nuclear accidents (Because there is no chain reaction to control)
5. There is no risk of nuclear proliferation

Compare with a reactor.

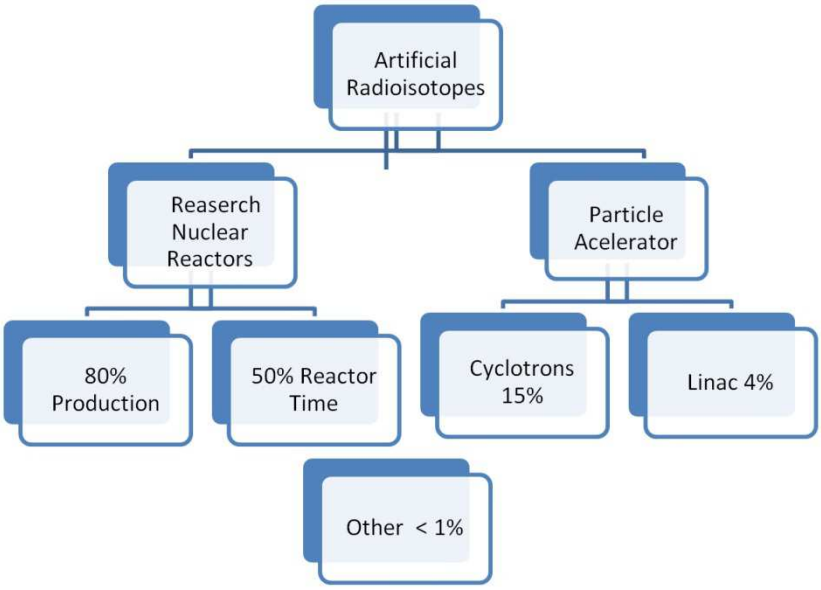


Fig. 8. Artificial radioisotopes.

a) b)

Fig. 9. Difference in size between a) Venezuelan medical cyclotron (courtesy of Indira Lugo) and b)Venezuelan research reactor (in desuse).

Medical Cyclotrons generally often comes with 4 targets to activated: Fluor 18, Oxigen 15, Nitrogen 13 and Carbon 11. In Venezuela we have one with only one target to activated fluor 18 to sintethized ^{18}FDG, for PET studies.

6. Activation products medical uses

Remembering what we want for a radioisotopes to be safely used in medicine, Natural decay series has had a very bad performance. For example, ^{226}Ra was used in Medicine until users realized that its daughter was ^{222}Rn, a gas. Since ^{226}Ra was encapsulated in stainless steel tubes the accumulation of Radon from Radium decay inside the tube, cause the gaseous pressure to increase in a non controlled way, so more than 10 years after its encapsulation, the gas pressure was so high as to break the capsule and escape. So as ^{222}Rn is a radioactive gas and it half life is not short (almost 4 days), contamination was hard to contain, so Radium use was declined.

Fig. 10. Radium Tubes.

Activation products from Cyclotrons are in general of short half life, so the control can be focus in the energy users can handle. In such a way, we can say activation products can be tailored to our needs. But medical uses are little complicated. Nuclear Medicine consist in mix the radioisotope with a pharmaceutical product which is characterized by the organ they are going to address the isotope. What Nuclear Medicine really needs is to send the radioisotope to get inside the organ we want to study, and as the radioisotope is inside a molecule that can be metabolized by this organ, this metabolization function can be easily watch and measure with the appropriate radiation detectors. The name "radiopharmaceuticals" refers to the metabolically stable combination of a biochemical molecule to which radioisotope in bind that act as the vehicle through which, organ of interest can be reach. There are several mechanism for the radioisotope to join the address molecule such as:

1. Ionic compound: In which the radioisotopes determine the metabolic route to be follow as in ^{131}I to thyroid uses, because thyroid likes iodine and do not distinguish between different isotopes of the same element iodine.

2. Isotopic Exchange: In which the radioactive isotope goes to replace the stable isotope of it own species
3. Incorporation: In which radioisotope get inside the molecule but not interacting with the chemical compound, so it did not change its structure neither biochemical nor physical properties
4. Coprecipitation: In which radionuclide is precipitated in the same reaction with the chemical compound. Many are the radioisotopes that can be combined with different molecules to be address to different parts of human body with diagnostic or therapeutic purposes, so we can group them as in the table below:

Imaging:

Isotope	Symbol	Z	T1/2	Decay mode	Photons Energy	β energy	Uses
Fluorine-18	^{18}F	9	109.77m	β+	511 (193%)	0.664 (97%)	PET: Cancer detection and monitoring of treatment progress, in flurodexoxiglucose. (FDG) Tracer in flurothymidine (FLT) and fluromisonidazole (F-MISO), and ^{18}F-choline
Gallium-67	^{67}Ga	31	3.26d	EC	93 (39%)	185 (21%), 300 (17%)	SPECT: Tumor imaging, infections localization
Krypton-81m	^{81m}Kr	36	13.1s	IT	190 (68%)	-	Refrigerant
Rubidium-82	^{82}Rb	37	1.27m	β+	511 (191%)	3.379 (95%)	Tracer in positron emission tomography
Technetium-99m	^{99m}Tc	43	6.01h	IT	140 (89%)	-	Pulmonary ventilation studies.
Indium-111	^{111}In	49	2.80d	EC	171 (90%)	245 (94%)	Brain studies, infection and colon transit studies.
Iodine-123	^{123}I	53	13.3 h	EC	159 (83%)	-	Gamma emitter: diagnosis of thyroid function, without the beta radiation of I-131.
Xenon-133	^{133}Xe	54	5.24d	β-	81 (31%)	0.364 (99%)	Studies of pulmonary function and organic blood flow.
Thallium-201	^{201}Tl	81	3.04d	EC	69-83* (94%)	167 (10%)	Diagnostic aid in the form of thallous chloride TI 201
Carbon-11	^{11}C	6	20.39m	β+	--	0.96 (100%)	PET: Studies of brain physiology: epileptic focus, dementia, etc
Nitrogen-13	^{13}N	9	9.965m	β+	--	1.2 (100%)	PET: Cardiology
Oxygen-15	^{15}O	8	122.24s	β+	--	1.8 (100%)	PET: Cardiology and cancer detection
Cooper-64	^{64}Cu	29	13 h	β+	--	0.65 (61%) 0.58(39%)	genetic studies: copper metabolism: Wilson's and Menke's diseases. PET: tumours, and therapy.
Cooper-67	^{67}Cu	29	2.6 d	β^-	--	0.56 (100%)	Beta emitter therapy
Gallium-68	^{68}Ga	31	68 min	β^+	--	1.90 (100%)	PET: tumor detection, daughter in ^{68}Ge generator
Germanium-68	^{68}Ge	32	271 d	EC	--	0.1 (100%)	^{68}Ga generator parent

Therapy:

Isotope	Symbol	Z	T1/2	Decay mode	Photons energy	β energy
Yttrium-90	90Y	39	2.67d	β-	-	2.280 (100%)
Iodine-131	131I	53	8.02 d	γ, β-	364 (81%)	0.807 (100%)

Table 3. Common Isotopes Used in Nuclear Medicine for diagnostic studies or therapy procedure.

In the table above we can see some radioisotopes that say they are parent or daughter in a generator, but what is a generator?

7. Generators

In Nuclear Medicine environment, sometimes is useful to have a regular provision of radioisotopes for studies to be performed without the restrictions of providers time dependences, for example when studies has to be done anytime of the day in emergency conditions. If physician suspects an infection in a patient admitted in Emergency Room, it will be of utmost usefulness to have Nuclear Medicine images done with appropriate radiopharmaceuticals to solve the question about the most effective treatment to be offer to the patient. Either way, sometimes in Cardiology it is of high importance to know about percentage of isquemic muscle, but patient has not the luxury of time to undergo a catheterism, so it is more effective and quick to have Nuclear Medicine images and cine of the heart. In many cases like this, have a good availability of radiotracers make the differences between a correct and opportune answer or a misdiagnosis.
This is the reason why radioisotopes generators have become so popular beside the fact that in countries like Venezuela where there is no nuclear production, sometime become very hard to warranty a regular supply. A radioisotopes generator is a device in which you can contain a pair father/daughter in which the daughter is the product of interest for studies purposes and father only come to generate the full amount of daughter needed. Due to the short half life we need for the radioisotope to be safe handle in hospital conditions, it would be useful to find a pair father and daughter that warranty the in time provision of radioisotope needed. During the generator useful life father has to decay completely to the useful daughter so it can be easily recharged, disposed or returned to provider. Such pair must that accomplish some conditions like:

1. Father has to have long enough half life (physical) such as to overcome travel time from provider to user. In this way father will be generating enough amount of daughter that can be extract in site for studies and will continue generating daughter to fulfill the needs for its entire useful time.
2. Father must be shipped in pyrogen free condition
3. Daughter has to decay in a sufficient short life be secure for image acquisition and radiation protection of patient
4. Father and daughter have to have different chemical characteristics so the can be easily separate to be sure the daughter is so pure to be safe for human applications and there are no traces of the father in the injection solution.

5. This separation must be passive in terms of no violent chemical reaction must be involved in the process, to warranty the chemical safeness
6. The daughter must be eluted with a human compatible solution to warranty biological safeness
7. The human intervention would be minimum to warranty the minimum exposure to radiation
8. Radiation protection now is not the unique concern but chemical and biological protection is also very critical
9. The granddaughter must be of very long time as to be consider stable

After radiochemist discover some pairs of father/daughter that accomplish this characteristics, some were built in a shielded container to be send to hospital to extract the daughter. It makes radiosotopes clinically useful and commercially available.

Medicine is not the only client for radioisotopes generator, also we will talk about some other uses of them that are increasing its popularity thru years. So let´s have a few words about their relationship. As in any father/daughter relationship there are different kinds, in radioactive "family" we can talk about two kind of equilibrium that this families reach, they are called transient and secular equilibrium. Equilibrium meaning when father and daughter exist in significant proportion to one another. Secular equilibrium is a condition that they can reach when father physical half life is 2 or 3 magnitude orders greater that daughter´s (100 to 1000 times greater). It means when daughter decay many times father seems no to be affected. While transient equilibrium is a condition that is reach when father physical half life is about 10 times daughter´s. It is, when daughter decay few times father can decay to its 50%, i.e a full half life. Note that if physical half life of the daughter is larger that the father equilibrium can never be reach because father will be ever alone.

Secular Equilibrium Generators

$$^{68}Ge \xrightarrow{\varepsilon,275d} {}^{68}Ga \xrightarrow{\beta^+,\varepsilon,\gamma,1.14\,h} {}^{68}Zn$$

$$^{81}Rb \xrightarrow{\beta^+,\varepsilon,4.7h} {}^{81m}Kr \xrightarrow{\gamma,13s} {}^{81}Kr$$

$$^{82}Sr \xrightarrow{\varepsilon,25d} {}^{82}Rb \xrightarrow{\beta^+,\varepsilon,\gamma,75s} {}^{82}Kr$$

$$^{113}Sn \xrightarrow{\varepsilon,118d} {}^{113m}In \xrightarrow{\gamma,1.7\,h} {}^{113}In$$

Transient Equilibrium Generators

$$^{99}Mo \xrightarrow{\beta^-,\gamma,67h} {}^{99m}Tc \xrightarrow{\gamma,6\,h} {}^{99}Tc$$

$$^{188}W \xrightarrow{\varepsilon,275d} {}^{188}Rh \xrightarrow{\beta^-,17\,h} {}^{188}Os$$

Although this last one has a promising future in metastatic disease pain reliever and as a monoclonal antibody marker, the most popular generator in Nuclear Medicine is the Mo/Tc one. It is Techenetium is highly biocompatible in the Nuclear Medicine fashion so it can be used in a large number of studies.

This Mo/Tc generators can be produced in cyclotrons or reactors and as in many radioisotope produced, the advantages of using that from cyclotron in front of that of

reactors is that in cyclotron you can use ^{98}Mo enriched target to be activated by neutron irradiation in a (n,γ) reaction, while ^{99}Mo coming from fission include very expensive production beside the complex regulations due to the highly enriched Uranium targets.

TARGET ORGAN	^{99m}Tc RADIOPHARMACEUTICALS
Brain	DTPA (DiethylTriaminoPentacetic Acid) ($CaNa_3{}^{99m}Tc$)
Brain Perfusion	ECD (EthylCysteinate Dimer)
Kidneys	DTPA (DiethylTriaminoPentacetic Acid) Calcium Gluconate Lactobionate Calcium Glucoheptonate Manitol Dextrose Penicilamine 2,4 dimercaptosuccinic acid
Liver	^{99m}Tc Sulphur Sn Hidroxide Sodium Phytate Sodium Calcium Phytate
Lungs	Inorganic Macroagregate Albumin Macroagregates Microspheres (50μ)
Bone	Poliphosphate Monofluorphosphate Diphosphonate Pirophospate (MDP) Metilendiphosphonate
Dynamic Studies	Albumina Microspheres (0.5-4 μ)
Tumors	Bleomicine Tetracycline Citrate
Spleen	Red Blood Cell Markers
Spleen and Bile	Vitamine B6 glutamic HIDA (Hepatobiliary IminoDiacetic Acid)
Blood Pool	^{99m}Tc Albumina
White Blood Cell or platelets (infection or inflammation)	^{99m}Tc HMPAO (HexaMethylPropileneAmineOxime)

Table 4. Radiuopharmaceuticals used with ^{99m}Tc for diagnostic studies.

8. Baby cyclotron characteristics

Baby cyclotrons are known as a hospital equipment be cause they are build to fulfill the medical proposes, in general, they can afford until 4 targets to activated most of radioisotopes needs to do PET studies

In Venezuelan experience the first installed cyclotron has the following characteristics:

- Generated beam for activation: H +
- Energy required for the activation: 9.6 MeV
- Output Beam minimal current: 50 μ A
- Material to Activate: $H_2{}^{18}O$
- Activation Product: $^{18}F^-$ (fluorine ion).
- Running average activity: 800 mCi
- Activation efficiency: Greater than 60%

Also the device dimensions where 3.6 x 2 x 2 m^3 for the acceleration d´s and inner shielding. And the room has to have at least 7 x 5 m^2 only for the cyclotron and another 6 x 5 m^2 for the synthesis lab. But the very concerning issue is the weight of the entire system, only in inner shielding it has 37 tons and the magnet alone has a weight of 11 tons the full system is over 50 tons

This cyclotron produce protons of 9.6 millions of electron volts (MeV) of energy with a maximum current of 50 μA, the target is made of oxigen to transmute to fluor. In this activation process there are some particles going out the path of the main beam so they have to be stopped by the inner shielding as to warranty 10 μSv/h at 1 m from shleding and 1 m from floor. Also the magnetic regulation permit 1 G at 6 m from the center of the D´s

8.1 Venezuelan medical cyclotron

In our experiences, the utmost importance matter in a Cyclotron is the Quality Assurance Program in which must be include:

1. Electrical Aspects
2. Mechanical and performance aspects and
3. Radiation Safety Aspects

In a broad approximation, we can say that:

8.1.1 Electrical aspects that have to be under control are:

- On/off switches
  - For operation
  - For Emergency
- Failure Interlocks
  - Safety Interlocks
    - Audible alarm
    - Luminous alarm
- Processing unit connection
- Selfdiagnostic

8.1.2 Mechanical and performance aspects to be under control are:

- Radiofrequency
  - Driver

    - Stability
- Mechanical movements of inner and outer doors
- Beam Energy
- Output flux
- Output dose and exposition
- Target effectiveness
- Activation effectiveness

8.1.3 Radiation Safety aspects to be under control are:

- Area classification and signs
- Area monitorization
- Personal dosimetry
- Activation control
- Airborne debris
- Chimney
- Personnel Medical Check up:
    - Previous to begin working in the facility
    - Annual (prevocational) check up
    - Posterior to end laboral relationship with the facility
- Shielding
- Radiation Safety Committee

8.1.4 Daily journey: Also three aspects need to be controlled step by step, accounting to:

- Radioisotope Production
- Handling radioactive material for studies
- Possible emergency

8.1.4.1 In radioisotope production it must be carefully checked:

- Pre-start conditions
- Area and ventilation ducts monitoring during cyclotron is on
- Activation and contamination control after cyclotron is turn off
- Pre and post Hot Cell monitoring
- Radioactive waste disposal entry and release record
- Fractionation residues and contamination
- Radioactive waste disposal
    - Place design
    - Waste classification
    - Decay rate
    - Free release dates

8.1.4.2 Radioactive material handling for diagnostic studies

- Total activity produced in a cyclotron run
- Fractionation doses
- Patient injection site and procedure

- Patient waiting room= Controlled area
- Adverse reaction, contraindication, diabetic patients

8.1.4.3 Possible emergencies

- Coolling system failure
- Door interlocks during cyclotron is on
- In use production line rupture
- Vial rupture
  - Inside hot cell
  - Inside fractionation hood
  - Outside

8.1.4.4 Radioactive material spills

- Inside hot cell
- Inside fractionation hood
- During transportation

This a resume of our general procedure manual, reproduced for physicians to know about all procedures that will be under their responsibility because they are legally, the responsible for the facility and its practices, as is establish in BSS and many other documents regarding medical practice. Here we only intent to introduce a general framework about medical cyclotrons so we will only mention some useful concepts and its application in a new facility.

8.1.5

Regarding to electrical aspects we must emphasize that failure interlock never must be deactivated, before the in charge expert check it out and solve the situation, only after he/she sign the log describing the solution, operation can continue. It is important to remember that ignoring this interlocks and alarms has conducted, many times, to major accidents injuring personnel and patients.

Before turning on cyclotron for a production run, the following operation parameters must be checked:

STEP ONE: MORNING CHECK OUT BEFORE TURNING CYCLOTRON ON: (EXAMPLE)

Water leakage	***NO***		
Normal operative ventilation	***OK***		
Electrical power on, stable and normal	*Control cabinet*		***OK***
	Rf cabinet		***OK***
Vacumm	$7x10^{-7}$ mbar (7×10^{-5} Pa)		
Water conductivity	5 μSiemens		
Water cooling temperature	***20±2 ºC***		
Gas valves	*Production*	Máx 0.5 MPa (73 psi)	
	Operation	3 ±0.1 MPa (435 ± 14 psi)	
	Transport	0.5 ±0.2 MPa (73 ±29 psi)	
Shielding closed	***OK***		
Nobody in	***OK***		

Cyclotron door closed	***OK***
Room door closed	***OK***
Safety system on (green)	***OK***

8.1.6

On mechanical and performance settings it is important to become religious with the daily log for parameters to be safely establish before start working, to be sure of, what we want to obtain is what we really will obtain after cyclotron runs in the desire conditions

STEP TWO: TUNNING ON CYCLOTRON (EXAMPLE)

Turn on all the computers		
Run autocheck		
Define in the console	Current	
	Irradiation time	
	Charge	
	Activity	
	Target water level	

8.1.7

For personnel safety there exist three types of emergency interlocks:

- Radiological emergency: as described
- Ergonomical emergency: as feet trapped under the cyclotron doors
- Nature emergency: earthquake, flood, etc

8.1.8

In radiation safety aspects it is important to notice that radiation protection is not a solely part body but a team work . Everybody in the facility must be involved in Radiation Protection (RP) tasks and in the Radiation Safety (RS) Program and must be accomplish this minimal recommendations:

RADIATION PROTECTION BASIC RECOMMENDATIONS: (EXAMPLE)

1.	Use your badge all the time you are in the facility (body, ring, alarm dosimeters)
2.	Use also the handy personal monitor that has been assign to you anytime you access the supervised and controlled areas
3.	Inside cyclotron room, hot lab and fractionation lab, use cloak, glove and glasses
4.	Do not use decorative rings (jewelry), scarf, bracelet or any other accessory that could transport contamination outward
5.	Never get in cyclotron room during production
6.	Never use mouth pipettes
7.	Never handle radioactive material outside cells or hoods
8.	Use long forceps or tweezers
9.	Never use controlled fridge for food or beverage
10.	Radioactive waste must be dispose by its nature and classification in the selected area for them

11. Monitor your working area before and after each assignation and whenever a contamination is suspected
12. Wash your hands before living controlled area
13. Monitor your hands before living controlled area and return to 12 until background is reached. In any case contact RSO
14. Record every activity (cyclotron, Hot Lab, Synthsys lab, Fractionation Lab) in corresponding log
15. Any unusual event must be report in corresponding log
16. In any radiological event communication chain must be follow
17. In case of inhalation or ingestion follew corresponding emergency procedure as it is written

8.1.8.1

In such a large facility it is mandatory to exist an ad hoc committee known s "Radiation Safety Committee" (RSC) as it is establish in Venezuelan safety standard NVC3299. In our case, this comitte must ever be conformed by:

1. Radiation Safety Officer
2. One delegate from maintenance and engineering department
3. One delegate from directive or administrative board
4. One delegated of security department
5. One delegate from technician staff
6. One delegate from nursing staff
7. One delegated from physician (at least)

Many other specialist, physician, physicist, chemist can be include

8.1.8.2

For radiation area classification, national standard recommendation will be follow as in NVC 2257: Any area must be classified as "Controlled" if in any moment of daily operation the exposition rate is above 0.5 mR/h. In this sense , cyclotron room, synthesis lab, hot lab, injection room pet/ct room are controlled areas by default. Classification of different areas will be consult to RSC and RSO and will be solve only after 24 h continuous measurements, and any other consideration in standard classification may be voted and solved by more that 75% of delegates

This is the figure that will take all the decisions regarding al RS concerns and its decisions must be voted to win with more of the 75% of the committee delegates.

In radioisotope uses (for diagnostic or therapies) any patient application can be supervised by committee and logs must be all time up to date. All the details for all the task mentioned above must be clearly describe in each procedure manual and clearly understand by any of the participant of each task

Notification chain must also be clearly establish and accomplish from personnel who needs to report, thru RSO, until the National Regulatory Authority

8.1.8.3 Cyclotron Cycle

- In cyclotron room protons hits water target transmuting ^{16}O into ^{18}F.
- In Hot Lab ^{18}F ions are measured in activity, pureness, pyrogenicity, volume, etc
- Synthesis Lab FDG is produced by substitution of oxygen ion by the activated fluorine ion inside the molecular chain yielding to labeled ^{18}FDG

8.1.8.4 Parasite Activation

One of the most relevant issues in Cyclotron facility is the activation of the materials inside the cyclotron room during daily operation. As cyclotron room is a close and hardly shielded facility all activation products will ever be contained inside its room and the activation levels will only be monitored and measured during providers maintenances, in this opportunity, frotis are taken of the most suitable materials to be activated and they are measure in spectrometer. On the other hand, gaseous activation is continuously monitored with proper devices set inside the chimney. As first defense line, the facility has a 200 m circuit through which gaseous particles travel during 24 hours before getting into the chimney to be release to the atmosphere. As our cyclotron do not have gaseous target all the airborne particles come from the air inside the room, so they are characterized by their extremely short half lives, around nano or micro seconds. Periodcally, frotis are taken from the chimney to be measure in spectrometer.

For any maintenance that need the "backdoor" of the cyclotron to be removed, exposition rate must be below 0.5 mR/h as it is establish in NVC2259. If it is not, maintenance personnel must wait until this level is reached.

Finally, it must be said that in operation conditions Cyclotron is fully shielded allowing a maximum of 10 mSv at 1 m in the axial direction of the magnet, and such a value is only reached one or twice a day in the production time that is less than 2 hours accounting all the running.

8.2 Synthesis laboratory

In Pet studies a cyclotron is nothing without radiochemical laboratory , because cyclotron only produce the ion, in our case, ^{18}F and it has to be joined to the glucose analogue molecule (fluordexoxiglucose) to be driven to the body. In it fluor is send into molecule via electrophilic fluorination or nucleophilic fluorination reaction in which stable fluor is substitute by the activated ^{18}F.

Fig. 11. Synthesis Lab in Venezuelan Cyclotron facility (courtesy Dorly Coehlo)

8.3 Patient radiation protection

Before finishing let´s have few words about the protection of patients. In patient protection we have to had in mind not only the physical half life because sometimes biological half life is longer and radiation protection must to be concern to the excretion system of patient so Nuclear Medicine define an effective half life to take into account the two contributions to patient doses coming from physical and biological behavior of radioisotope. Biological half live is the time living organism needs to excrete any radioisotope trace of radioactive material. It depends no only of physical time but on effectiveness of excretion system of the body. So effective life is :

$$\frac{1}{T_{1/2}^{eff}} = \frac{1}{T_{1/2}^{phy}} + \frac{1}{T_{1/2}^{bio}}$$

ISOTOPES	HALF LIVES (days)		
	$T_{Physical}$	$T_{Biological}$	$T_{Effective}$
^{3}H	4.5×10^{3}	12	12
^{14}C	2.1×10^{6}	40	40
^{22}Na	850	11	11
^{32}P	14.3	1155	14.1
^{35}S	87.4	90	44.3
^{36}Cl	1.1×10^{8}	29	29
^{45}Ca	165	1.8×10^{4}	164
^{59}Fe	45	600	42
^{60}Co	1.93×10^{3}	10	10
^{65}Zn	244	933	193
^{86}Rb	18.8	45	13
^{90}Sr	1.1×10^{4}	1.8×10^{4}	6.8×10^{4}
^{99m}Tc	0.25	1	0.20
^{123}I	0.54	138	0.54
^{131}I	8	138	7.6
^{137}Cs	1.1×10^{4}	70	70
^{140}Ba	12.8	65	10.7
^{198}Au	2.7	280	2.7
^{210}Po	138	60	42
^{226}Ra	5.8×10^{5}	1.6×10^{4}	1.5×10^{4}
^{235}U	2.6×10^{11}	15	15
^{239}Pu	8.8×10	7.3×10^{4}	7.2×10^{4}

Table 4. Physical and Biological half lives

Radioisotopes like P and Sr like to stay in bone, so as far as they can be used to treat bone lesions the maximize its doses due to the combination of physical and biological exposure. Phosphorous decay faster so Sr is better to treat bone metastasis due to it relatively long physical and biological half life. For diagnostic studies Tc has proven to be the best due to its short physical and biological lives, so it is excrete from the body just after images has be taken.

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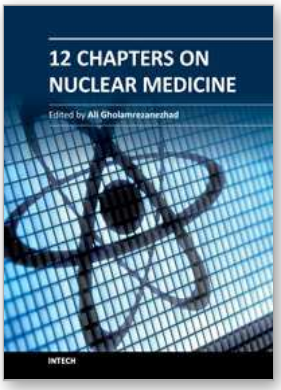

12 Chapters on Nuclear Medicine

Edited by Dr. Ali Gholamrezanezhad

ISBN 978-953-307-802-1
Hard cover, 304 pages
Publisher InTech
Published online 22, December, 2011
Published in print edition December, 2011

The development of nuclear medicine as a medical specialty has resulted in the large-scale application of its effective imaging methods in everyday practice as a primary method of diagnosis. The introduction of positron-emitting tracers (PET) has represented another fundamental leap forward in the ability of nuclear medicine to exert a profound impact on patient management, while the ability to produce radioisotopes of different elements initiated a variety of tracer studies in biology and medicine, facilitating enhanced interactions of nuclear medicine specialists and specialists in other disciplines. At present, nuclear medicine is an essential part of diagnosis of many diseases, particularly in cardiologic, nephrologic and oncologic applications and it is well-established in its therapeutic approaches, notably in the treatment of thyroid cancers. Data from official sources of different countries confirm that more than 10-15 percent of expenditures on clinical imaging studies are spent on nuclear medicine procedures.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Reina A. Jimenez V (2011). Medical Cyclotron, 12 Chapters on Nuclear Medicine, Dr. Ali Gholamrezanezhad (Ed.), ISBN: 978-953-307-802-1, InTech, Available from: http://www.intechopen.com/books/12-chapters-on-nuclear-medicine/medical-cyclotron

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