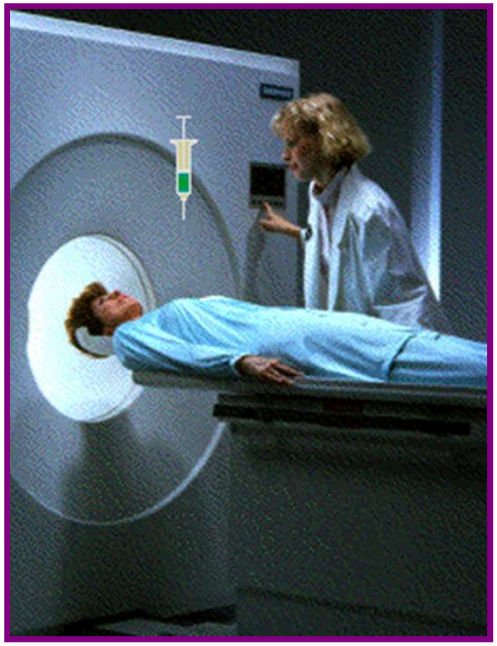
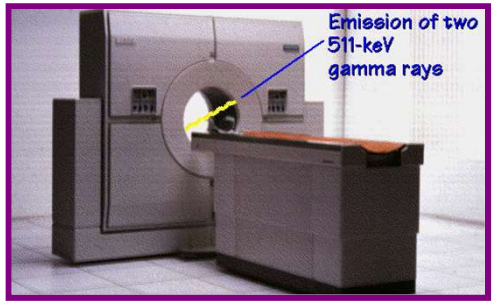
University of Tripoli
Department of Nuclear Engineering
NE 639

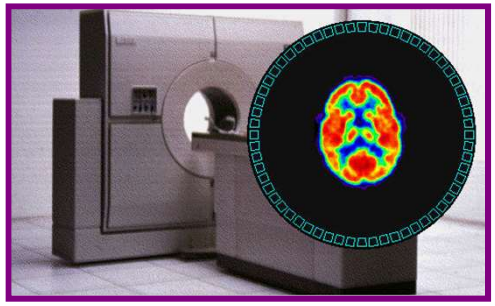
THE PHYSICS OF RADIONUCLIDE IMAGING

Lecture 2

Radiopharmaceuticals for radioisotope imaging







- The nucleus

Nuclear Notation

Mass number

$A = Z + N$

Chemical symbol

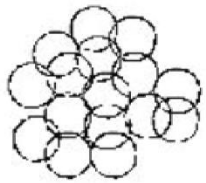
$$^{A}_{Z}X$$

Atomic Number (Proton number)

N = neutron number

The nucleus is comprised of a similar number of protons and neutrons.

- **Neutrons**
  neutral charge
  1.008665 AMU
- **Protons**
  + charge
  1.007276 AMU



$$^{16}_{8}O$$

Oxygen 16

16 nucleons
8 protons
8 neutrons

Size of the nucleus

Radius of the atom and the nucleus for copper 63.

Cu Atom Size

In lecture 02, the radius of the outer shell electrons (M shell) for copper was deduced from the unscreened Bohr relationship;

$$r_m = \alpha_H \left(n^2/Z\right)$$

$$r_{Cu} = .52917\left(3^2/29\right)$$

$$r_{Cu} = .16, Angstroms$$

α_H is the 'Bohr radius'

Cu Nucleus Size

Scattering experiments suggest that nuclei are roughly spherical and have essentially the same density:

$$\rho_n = 2.3 \times 10^{14}\ g/cm^3$$

$$r_A = r_o A^{1/3}$$

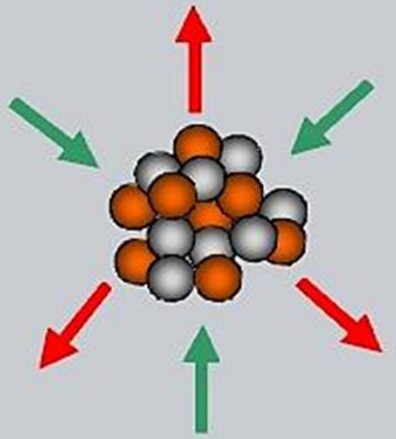
$$r_0 = 1.2\times 10^{-15}, m$$

$$r_{63} = 4.8\times 10^{-5}, Angstroms$$

1 fermi = 10^{-15} m = 1 femtometer (fm) = 10^{-5} Angstroms

Forces in the nucleus

Nuclear Forces and Stability



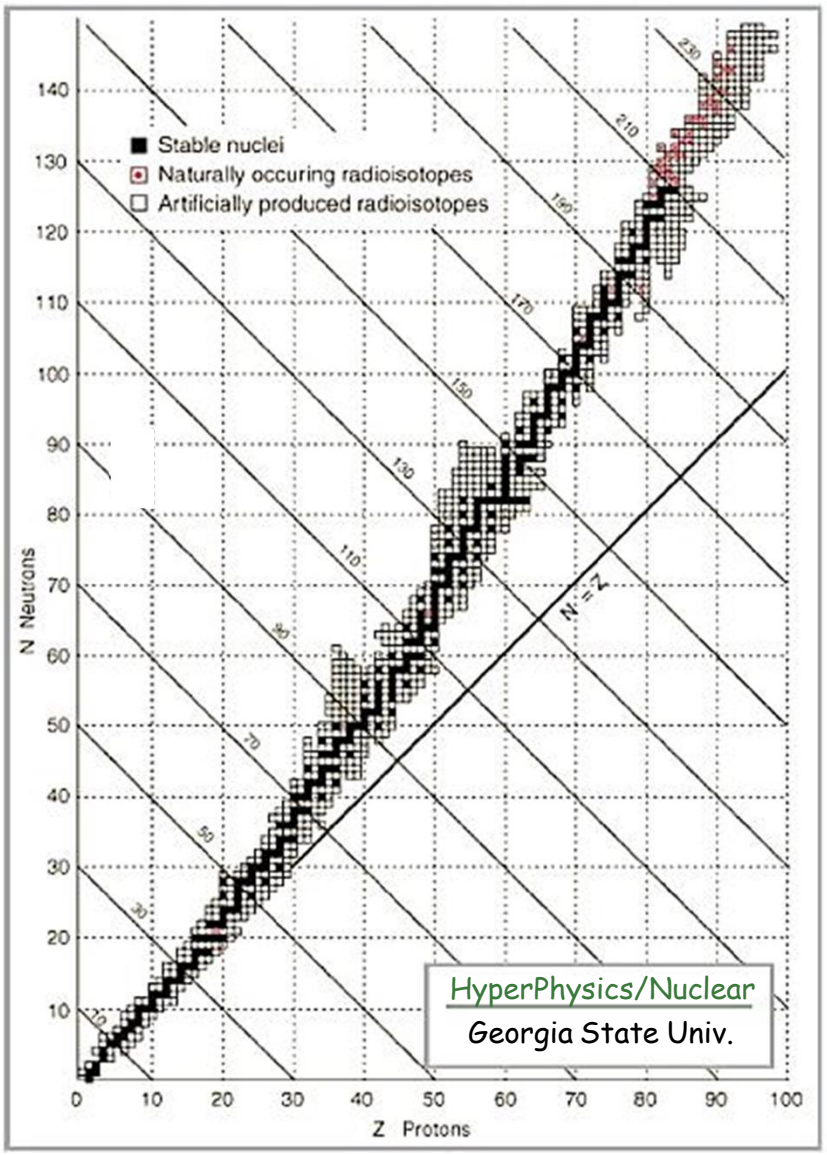
- Nucleons are held in the nucleus by a 'strong force' with a 'short range' of about 1 fermi.
  Yukawa (1935) proposed that the short range strong force came about from the exchange of a massive particle which he called a meson. The strong interaction is now thought to be mediated by gluons, acting upon quarks and anti-quarks.
- Strong repulsive forces result from the charged protons in the nucleus. +
- Quantum mechanical descriptions of the nucleus explain why the most stable configurations tend to result when neutrons and protons are paired.

^4He

Nuclei with even numbers of protons and neutrons are particularly stable.

n/p ratio

- Stable light nuclei lie close to the N=Z line, but the stable isotopes of heavier nuclei require an excess of neutrons to be stable.
- The neutrons contribute to the attractive strong interaction and moderate the strong electrostatic repulsion of the protons.



isotope, isobar, isotone

Stable Nuclides

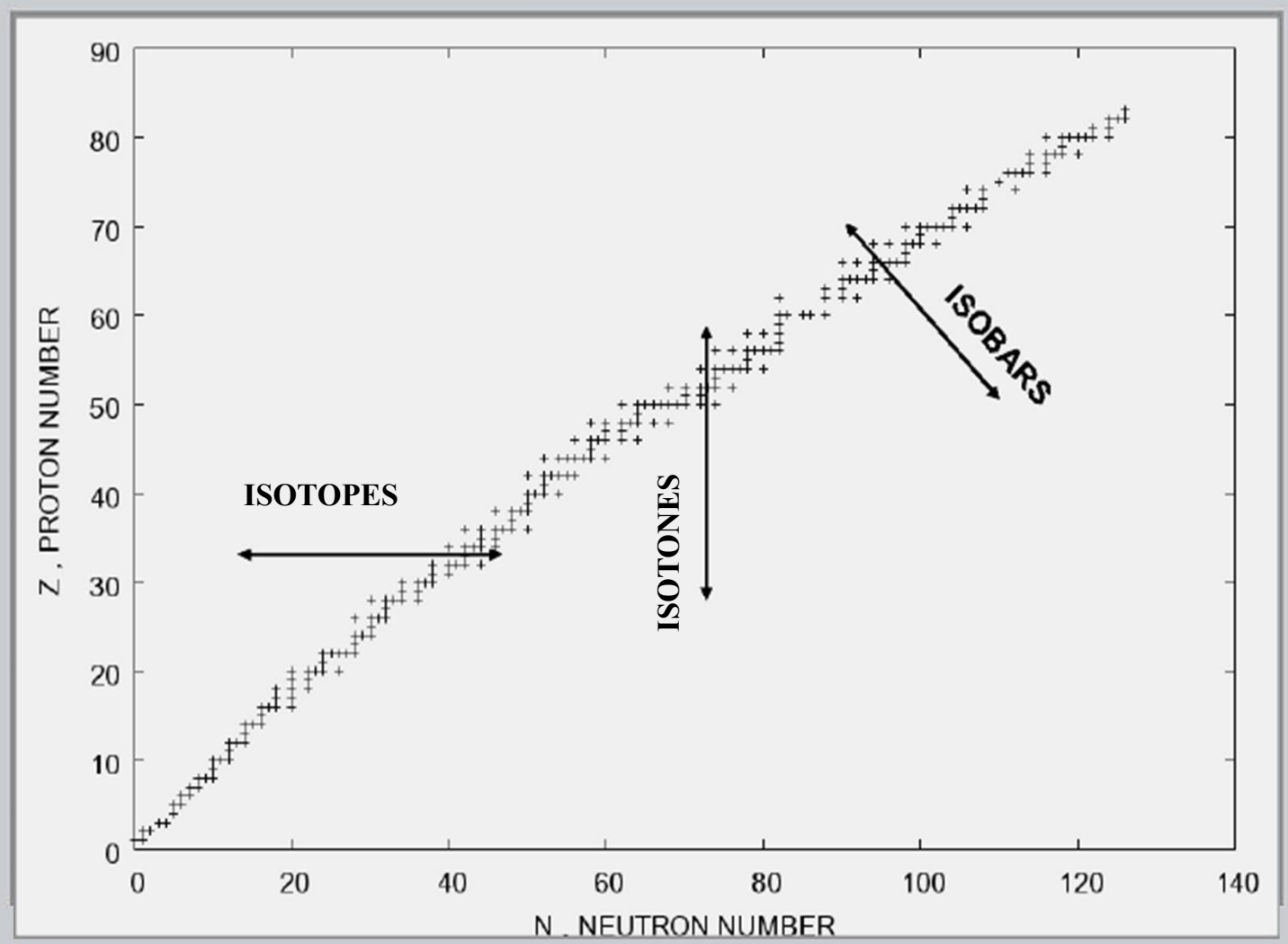
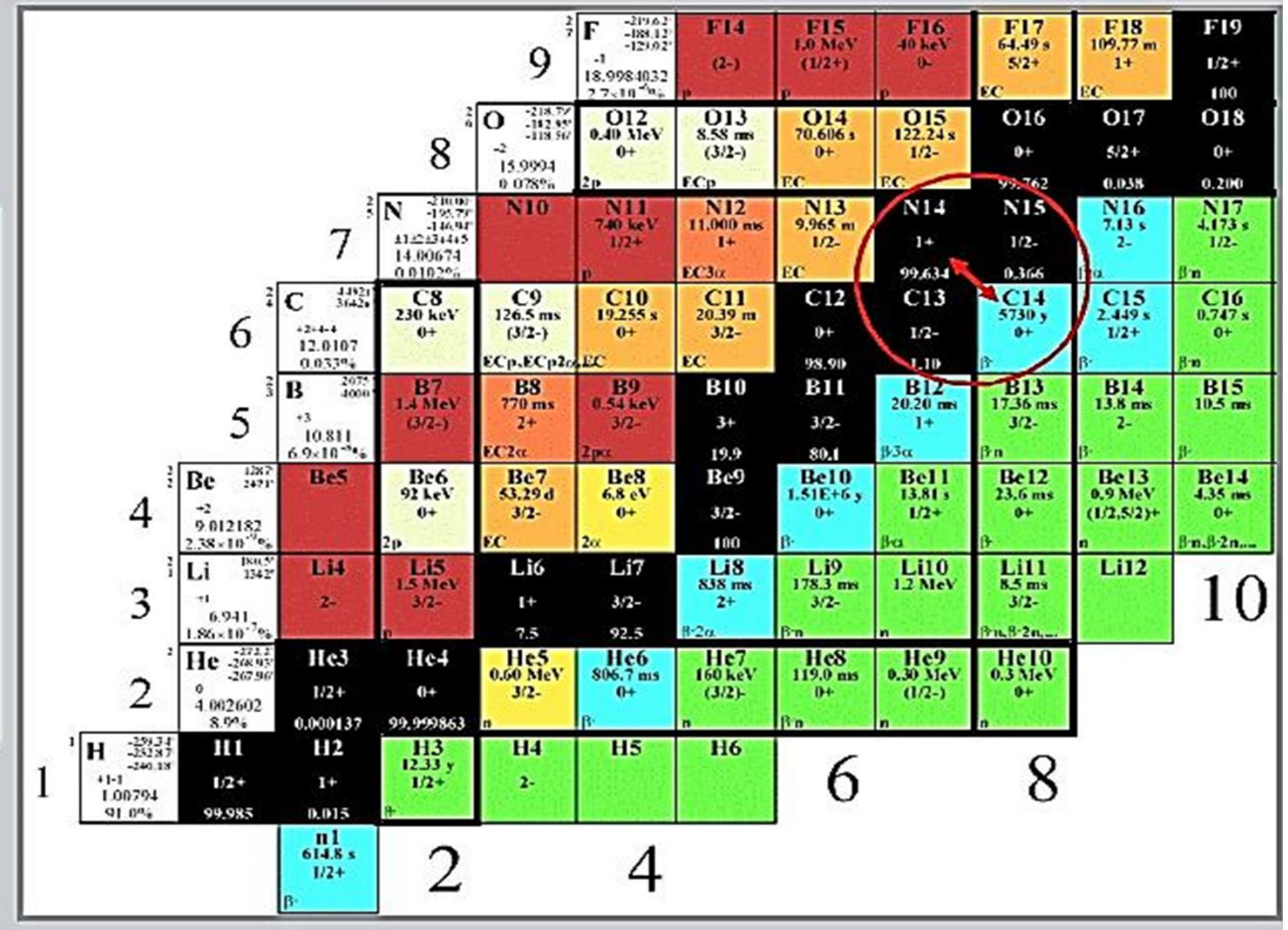


Table of Isotopes

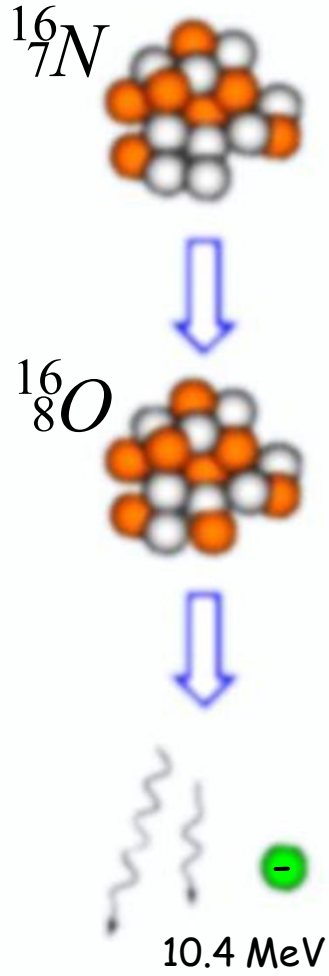
Chart of the Nuclides (1998)
LBNL Isotopes Project
http://ie.lbl.gov/toi/index.asp



Radiocarbon Dating - http://en.wikipedia.org/wiki/Radiocarbon_dating

Nuclear Decay

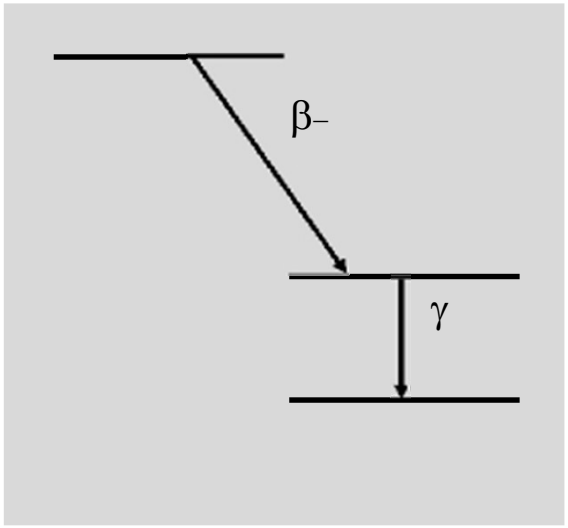
- An unstable nuclei may spontaneously change its neutron to proton ratio and become more stable.
- The resulting 'daughter' nuclide has slightly less mass than the 'parent' nuclide.
- The energy equivalent to the mass difference is released as energetic photons (gamma rays) or light particles (electrons, positrons) in which case the nucleons in the daughter are the same as the parent.
- Some heavy nuclides may eject a particle with 2 protons and 2 neutrons, an alpha particle, with a net reduction of nucleons in the daughter nucleus.



Beta Decay

ν - The neutrino is an elementary particle with minimal mass and no charge.

Decal Level Scheme

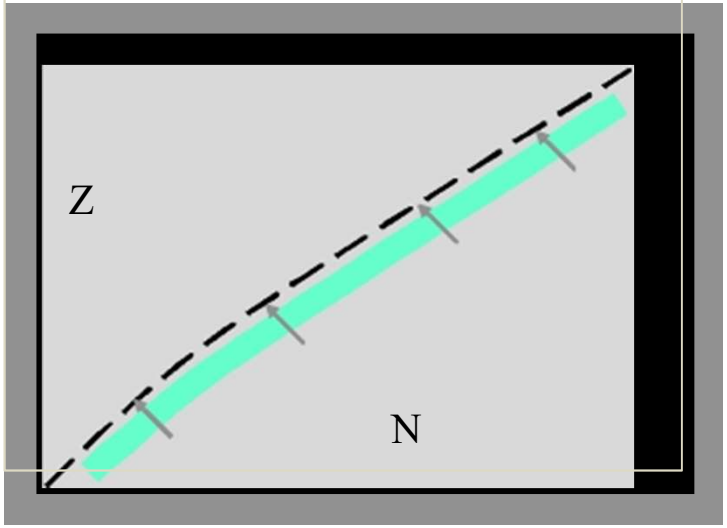


After decay, the daughter isotope is often in a excited state that relaxes with gamma ray emission

Reconfiguration of the nucleus

β-(beta) emission

$n \Rightarrow p+ + e- + \nu + energy$



Effect:

Neutron ➔ Proton

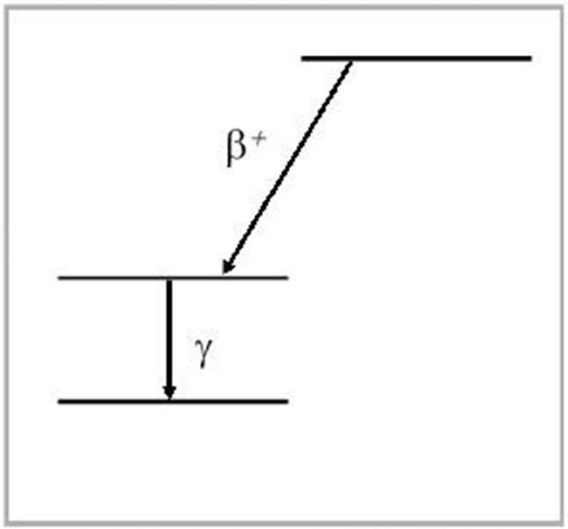
III.E.2 – Positron Decay

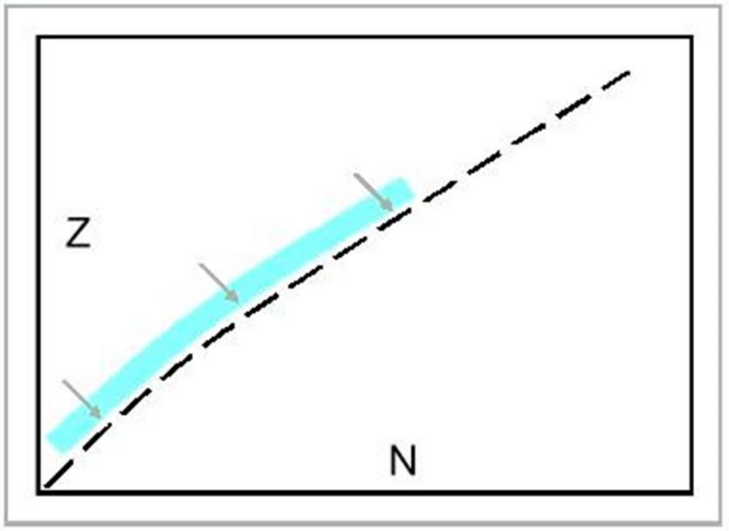
Reconfiguration of the nucleus

β^+ (positron) emission

$$p^+ \Rightarrow n + e^+ + \nu + energy$$

Decal Level Scheme





Positron decay is more probable for low Z nuclides as a method to reduce the proton number and increase neutrons.

Effect:

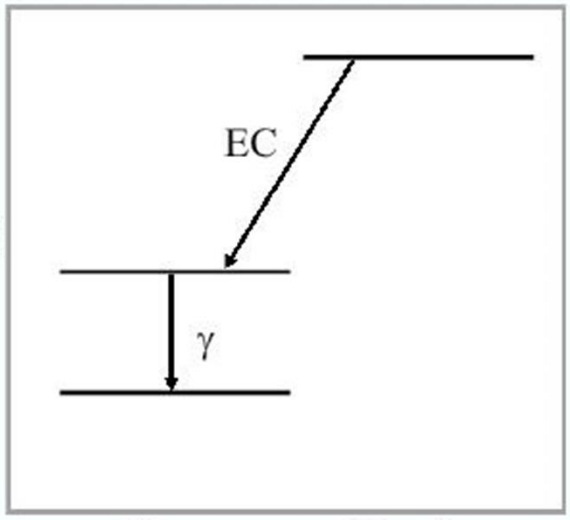
Proton ➔ Neutron

Electron Capture

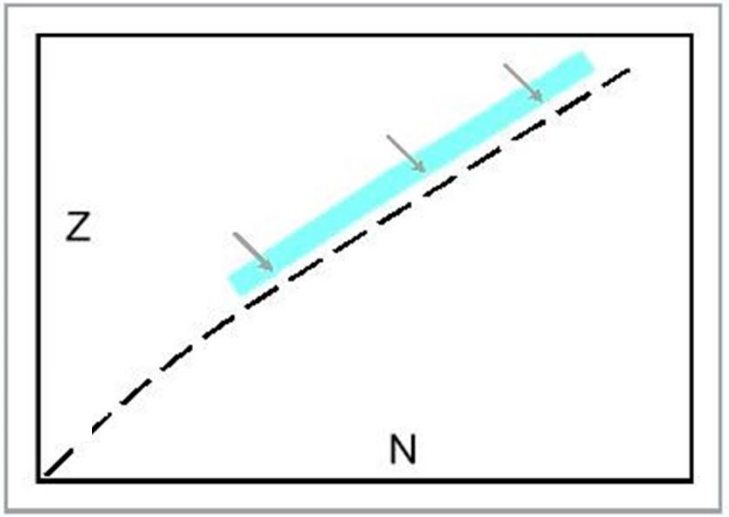
Reconfiguration of the nucleus
Electron Capture

$$p^+ + e^- \Rightarrow n + \nu + energy$$

Decal Level Scheme



Electron capture is more probable for high Z nuclides as a method to reduce the proton number and increase neutrons.



Effect:

Proton ➔ Neutron

Isotope decay rate

- For a sample with N nuclei of a radioactive nuclide, the rate of decay in disintegrations per second is given by a differential equation for amount of activity, A, based on a decay constant, λ (l/sec).

$$A = \lambda N = -dN / dt$$

- This simple differential equation is easily solved for N and therefore for A.

$$A = \lambda N_0 e^{-\lambda t} = A_0 e^{-\lambda t}$$

- The time for a radioactive sample of A_o activity to decay to an activity equal to 1/2 of A_o is known as the half-life, $T_{1/2}$

$$T_{1/2} = \frac{\ln(2)}{\lambda} = \frac{.693}{\lambda}$$

The SI unit for activity (**A**) is the Becquerel (Bq) which is equivalent to 1.0 disintegrations per second. The traditional unit of activity in the Curie (Ci) where 1.0 Curie is equal to 3.7×10^{10} disintegrations/second or 37 GBq. For radionuclides used in nuclear imaging, activities are often in the range from 1 to 20 mCi (40 to 800 MBq).

Gamma ray emission fraction

- It is important to recognize the difference between the gamma ray emission rate of a radioactive sample and the decay rate in Bq.
- For example, Fluorine-18 decays with a 110 minute halflife to stable Oxygen-18. The decay may occur by either electron capture (EC) or positron (β^+) decay. The β^+ decay occurs for .967 of the decays with the remaining fraction occurring for EC.
- Since each β^+ decay produces 2 511 keV gamma rays, radioactive decay produces an average of 1.93 gamma rays per disintegration ,

$$N = f_g A = 1.93 A$$

Total gamma emission

- It is often necessary to determine the total number of gamma rays emitted over a period of time.
- This is obtained by integrating the exponential decay relation over the time period, T.

$$N = \int_0^T N(t)dt = \int_0^T f_\gamma A(t)dt$$

$$= f_\gamma A_0 \int_0^T e^{-\lambda t} dt$$

$$= f_\gamma \frac{A_0}{\lambda}\left(1 - e^{-\lambda T}\right)$$

Isotope Production)

Isotope Production

1) Production Methods
2) Radioisotope generators
3) Reactor production of 99Mo

Production Methods

Radionuclides are produced by transforming the neutron-proton composition of a nuclide. Four methods are:

Neutron capture

Neutrons, typically from a nuclear reactor, are absorbed by a target material to create a

- radioactive product.

Nuclear fission

The byproducts of nuclear fission from spent reactor fuel elements are separated to obtain

- radioisotopes.

Charged particles bombardment

Energetic charged particles, typically protons or

- deuterons, strike a target material.

Nuclear decay

A radioactive parent nuclide is used to generate a radioactive daughter product.

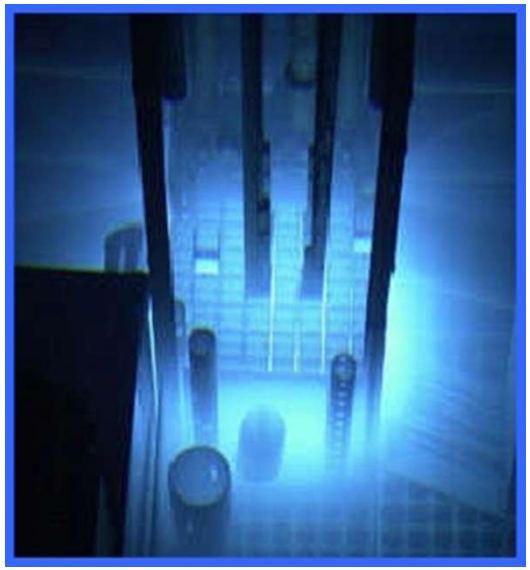
Neutron Capture

Reactor Produced – Neutron Capture

$$n + {}^{98}Mo \Rightarrow {}^{99}Mo + \gamma$$

Isotope production by neutron capture produces radioactive material that is relatively free of other radioactive contaminants

NOTE: This method is not currently used for 99Mo production. It requires high flux reactors because of the low cross section of 98Mo.



Ford Nuclear Reactor
Phoenix Memorial Lab
University of Michigan

Nuclear fission

Reactor Produced – Fission Byproducts

$$ {}^{1}_{0}n + {}^{235}_{92}U \Rightarrow {}^{99}_{42}Mo + {}^{133}_{50}Sn + 4\ {}^{1}_{0}n $$

Isotope production by separation of fission byproducts produces radioactive material that is prone to contamination with unwanted radioactive isotopes

Isotopes, Reactor produced

Reactor produced radioisotopes:

neutron rich, beta decay

- Molybdenum-99 (66 h):
  Used as the 'parent' in a generator to produce technetium-99m.
- Xenon-133 (5 d):
  Used for pulmonary (lung) ventilation studies.
- Iodine-131 (8 d):
  Widely used in treating thyroid cancer and in imaging the thyroid, renal (kidney) blood flow and urinary tract obstruction.

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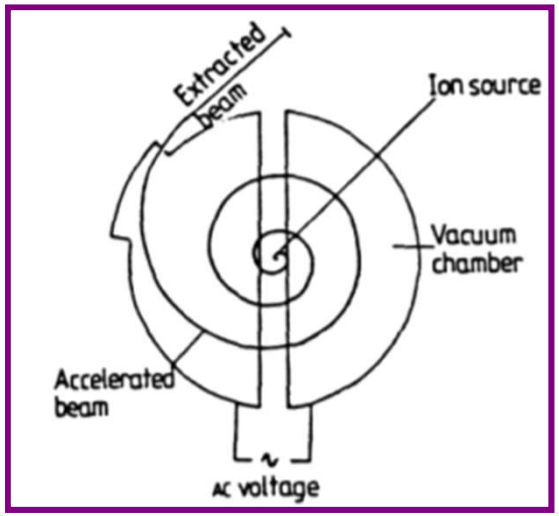
CHARGED PARTICLE INDUCED REACTIONS are based on the use of accelerators. Charged particles like protons, deuterons or alphas are accelerated to energies between 1 to 100 MeV and bombard a target material.

The most used accelerator type is the cyclotron, where the charged particles are accelerated by oscillating accelerating potentials perpendicular to a deflecting magnetic field.



Cyclotron Production

Charged Particle Bombardment

$$^{1}_{1}p + {}^{18}_{8}O \Rightarrow {}^{18}_{9}F + {}^{1}_{0}n$$

Energetic charged particles from an accelerator strike a target to produce a radioisotope from reaction that add the charged particle to the nucleus and remove neutrons.

(p, α)	(p,n)	(p , 2n)
(d, α)	(d,n)	(d , 2n)
	...	...

Examples of typical reactions in the target are listed in the table

Isotope	Principal gamma-ray energy (keV)	Half-life	Reaction
^{11}C	511 (β^+)	20.4 min	$^{14}N(p,\alpha)^{11}C$
^{13}N	511 (β^+)	9.96 min	$^{13}C(p,n)^{13}N$
^{15}O	511 (β^+)	2.07 min	$^{15}N(p,n)^{15}O$
^{18}F	511 (β^+)	109.7 min	$^{18}O(p,n)^{18}F$
^{67}Ga	93 184 300	78.3 h	$^{68}Zn(p,2n)^{67}Ga$
^{111}In	171 245	67.9 h	$^{112}Cd(p,2n)^{111}In$
^{123}I	159	13 h	$^{124}Te(p,2n)^{123}I$ $^{127}I(p,5n)^{123}Xe \rightarrow {}^{123}I$
^{201}Tl	68–80.3	73 h	$^{203}Tl(p,3n)^{201}Pb \rightarrow {}^{201}Tl$

The advantage of production via charge particle interaction is the large difference in Z between the target material and the radionuclide. That allows good physical and chemical separation procedures.

Cyclotron produced radioisotopes: proton rich, positron/EC decay

- ^{11}C (20 min), ^{13}N (10 min), ^{15}O (2 min)
  Short lived positron emitter synthesizedwith organic compounds for specialized PET imaging.

- Fluorine-18 (110 min):
  Positron emitter commonly synthesizedwith Fluoro-2-Deoxyglucose, FDG, for PET imaging procedures.

- Thallium-201 (73 h):
  Used for diagnosis of coronary artery disease, heart conditions such as heart muscle death, and for location of low-grade lymphomas.

Nuclear Decay

Radioisotope daughter product

$$^{99}_{42}Mo \xrightarrow[66\ hr]{\beta^-} {}^{99}_{43}Tc^{m} \xrightarrow[6\ hr]{Isomeric} {}^{99}_{43}Tc + \lambda$$

Some isotopes can be conveniently obtained by collected the daughter product resulting from the decay of a radioactive parent.Technetium resulting from 99Mo . decay, exists in a metastable state that decays to the ground state with a half life of 6 hours.

Radioactive series decay.

- A radioactive series involves the decay of a parent isotope, A, to a daughter isotope, B, with decay constant λ_A. and isotope B decays to C with decay constant λ_B;

$$A \xrightarrow{\lambda_A} B \xrightarrow{\lambda_B} C$$

- The number of atoms of A is described by;

$$A = A_o e^{-\lambda_A t}$$

- The atoms of B depends on the production from the decay of A and the loss by the decay of B. It's behavior over time is governed by a differential equation;

$$\frac{dB}{dt} = A\lambda_A - B\lambda_B = \left(A_o e^{-\lambda_A t}\right)\lambda_A - B\lambda_B$$

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Radioactive series decay.

- Following the derivation in Evans (pg 477), the solution of this differential equation for B will be of the form ;

$$B(t) = A_o\left(h_A e^{-\lambda_A t} + h_B e^{-\lambda_B t}\right)$$

- If this expression and it's derivative, dB/dt, is substituted into the prior differential equation and terms collected, we get;

$$e^{-\lambda_A t}\left(h_A\lambda_A - \lambda_A + h_A\lambda_B\right) = 0$$

- And therefore;

$$h_A = \frac{\lambda_A}{\lambda_B - \lambda_A}$$

- The coefficient h_B depends on the value of B at time t. For $B = 0$ at $t = 0$, $h_B = -h_A$ and thus;

$$B(t) = A_o \frac{\lambda_A}{\lambda_B - \lambda_A}\left(e^{-\lambda_A t} - e^{-\lambda_B t}\right)$$

99-Mo to 99m-Tc decay.

- For technetium generators, 99-Mo as A decays to 99m-Tc as B with a probability of 0.876 and a half-life of 66 hours. Otherwise it decays directly to stable 99-Tc.
- The metastable 99m-Tc relaxes to the 99-Tc ground state with a 6 hour halflife by emitting a 140 keV gamma ray (see Sorenson, App C).
- After several days, the second exponential in the preceding equation becomes zero and the 99m-Tc activity reaches equilibrium

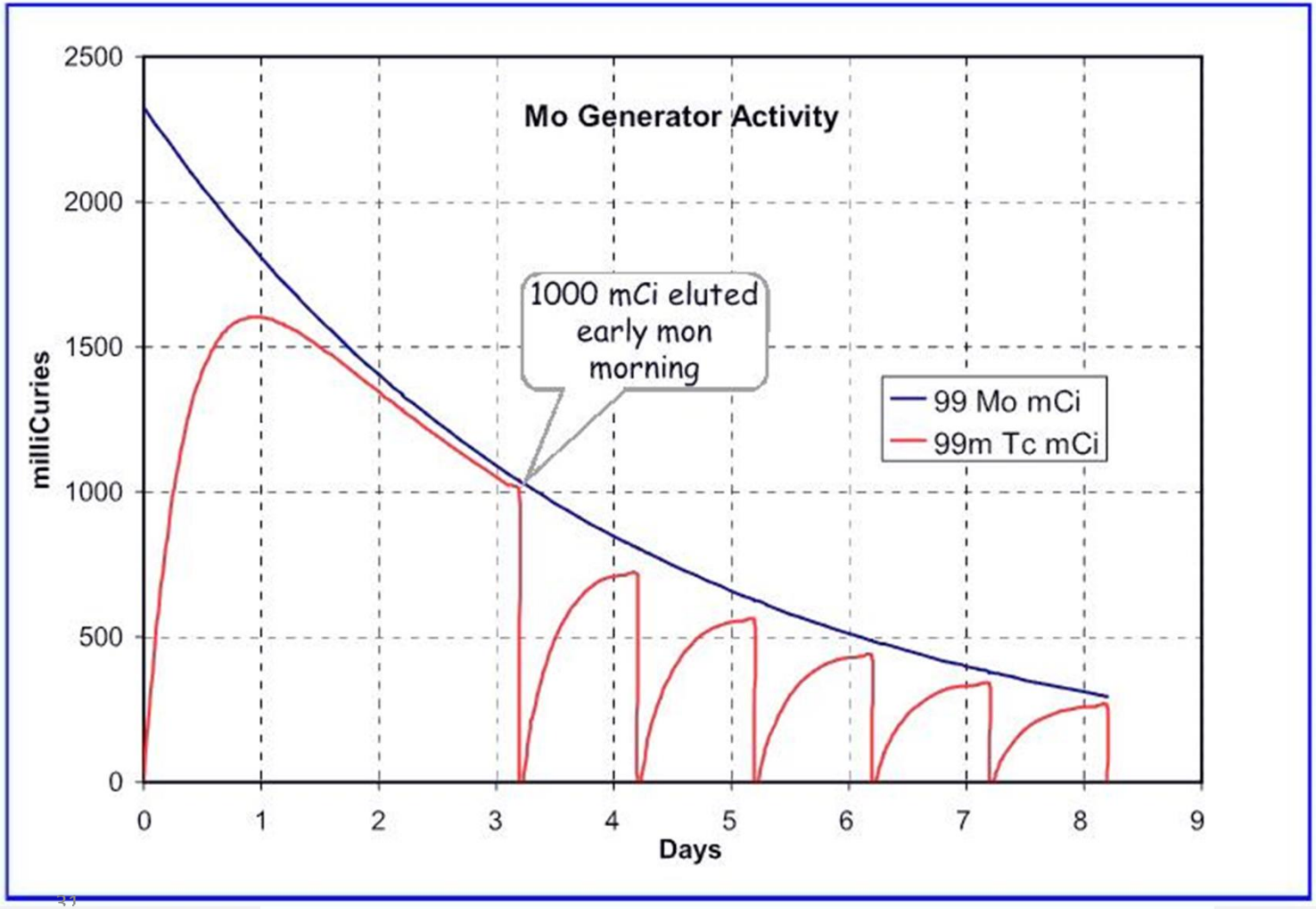
$$(\lambda_B B) = 0.876 \frac{\lambda_B}{\lambda_B - \lambda_A} \left(\lambda_A A_o e^{-\lambda_A t} \right)$$

The 99m-Tc activity in disintegrations per second, $B^{Tc}(t)$, is thus equal to $(0.876 * 1.1 = 0.96)$ times the 99-Mo activity, $A^{Mo}(t)$.

- If all of the 99m-Tc is eluted from the generator at time Te , the 99m-Tc activity will return to equilibrium ($t > T_e$) as described by;

$$B^{Tc}(t) = 0.96 A^{Mo}(T_e) \left(e^{-\lambda_{Mo}(t-T_e)} - e^{-\lambda_{Tc}(t-T_e)} \right)$$

- 99-Mo to 99m-Tc decay.



In a generator such as the Mo-99/Tc-99m radionuclide generator in which the half-life of the mother nuclide is much longer than that of the daughter nuclide, 50% of equilibrium activity is reached within one daughter half-life, 75% within two daughter half-lives. Hence, removing the daughter nuclide from the generator ("milking" the generator) is reasonably done every 6 hours or, at most, twice daily in a Mo-99/Tc-99m generator.

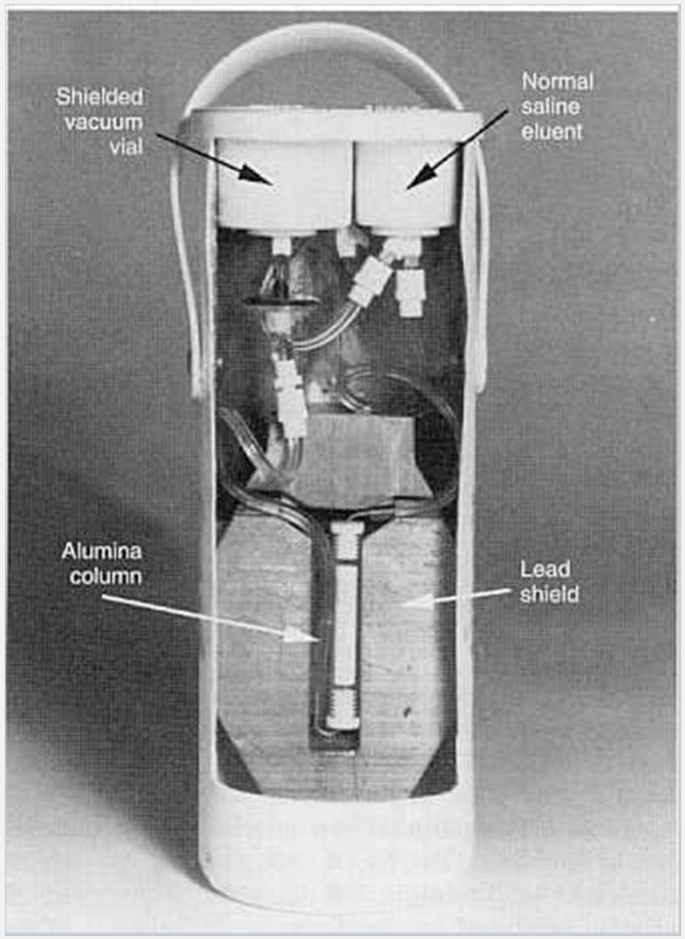
Most commercial Mo-99/Tc-99m generators use column chromatography, in which Mo-99 is adsorbed onto alumina. Pulling normal saline through the column of immobilized Mo-99 elutes the soluble Tc-99m, resulting in a saline solution containing the Tc-99m which is then added in an appropriate concentration to the kits to be used. The useful life of a Mo-99/Tc-99m generator is about 3 half lives or approximately one week. Hence, any clinical nuclear medicine units purchase at least one such generator per week or order several in a staggered fashion.

Radionuclide Generator system used to generate a radionuclide for routine clinical practice. The most widely used generator system is the molybdenum-99/technetium-99m generator on which much of current routine nuclear imaging relies.

In this generator, the mother nuclide Mo-99 decays into the daughter nuclide Tc-99m with a half life of 2.7 days, which itself has a half life of 6 hours (technetium (Tc)
Other generator systems have been built, among them a Sr-82/Rb82 generator for PET imaging, with Rb82 having a half-life of 2 minutes and behaving like thallium Tl and a Rb-81/Kr81m generator which yields a short-lived (13 s) krypton (Kr) gas for ventilation studies. These generator systems are so expensive that their clinical use is only feasible in centers with a very large patient throughput.

99m-Tc generators.

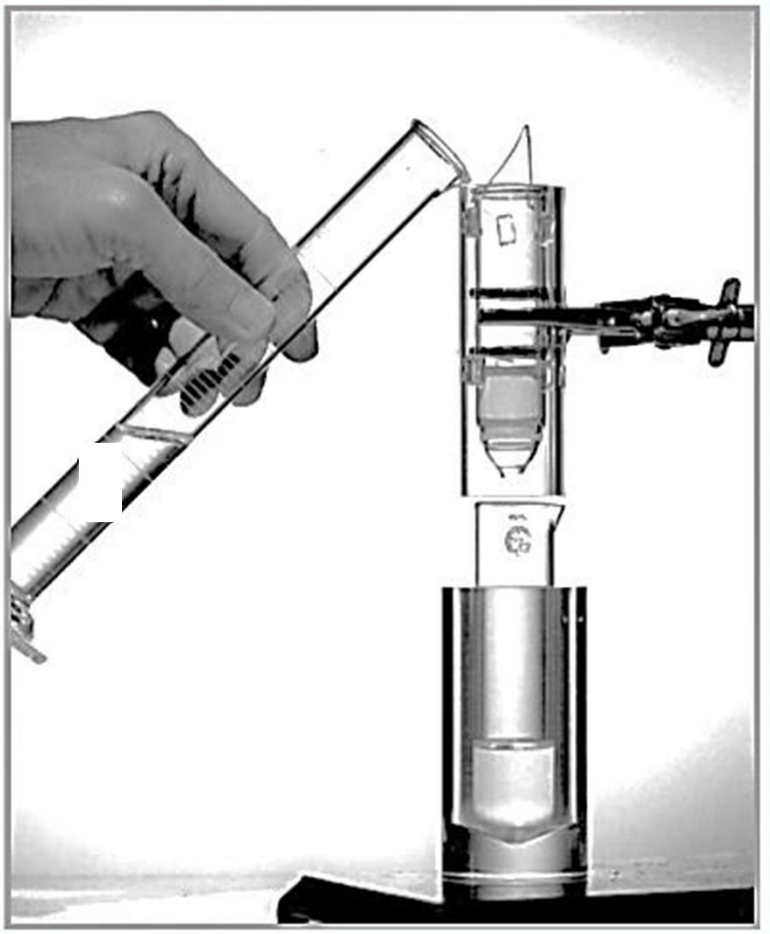
- In a generator device, the column is a small tube contained within a lead shield.
- Sterile saline in a medical vial is placed on a needle connected to the input line.
- A vacuum vial is then placed on a needle connected to the output line to draw the saline through the column.



99m-Tc generator, from Sorenson

Radioisotope generators.

- A simple 99m-Tc generator can be made by permanently adsorbing 99-Mo material on a porous aluminum oxide (alumina) column as molydate.
- The 99m-Tc daughter product, which is chemically present as pertechnetate, is separted of by washing with a sodium chloride solution.

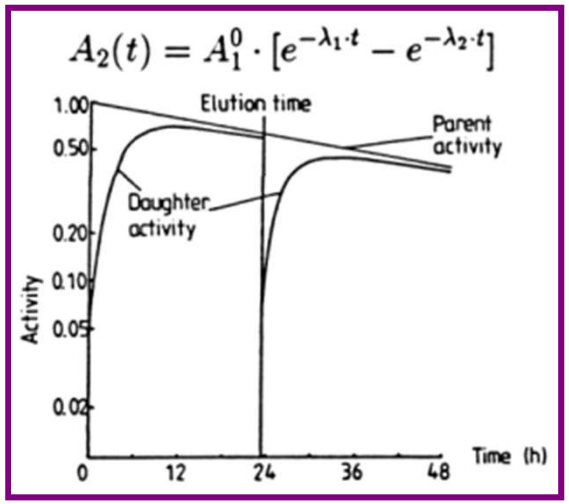


An original 99m-Tc generator, BNL, 1958

RADIONUCLIDE GENERATORS allow to separate chemically short-lived radioactive daughter nuclei with good characteristics for medical imaging from long-lived radioactive parent nuclei. Typical techniques used are chromatographic absorption, distillation or phase separation.

This method is in particular applied for the separation of the rather short-lived $^{99}Tc^{m}$ ($T_{1/2}$=6 h) from the long lived ^{99}Mo ($T_{1/2}$=2.7 d).

Applying the radioactive decay law the growth of activity of the daughter nuclei A_2 with respect of the initial activity of the mother nucleus A_1^0 can be expressed in terms of their respective decay constants λ_2 and λ_2 with $\lambda_2 \gg \lambda_1$:



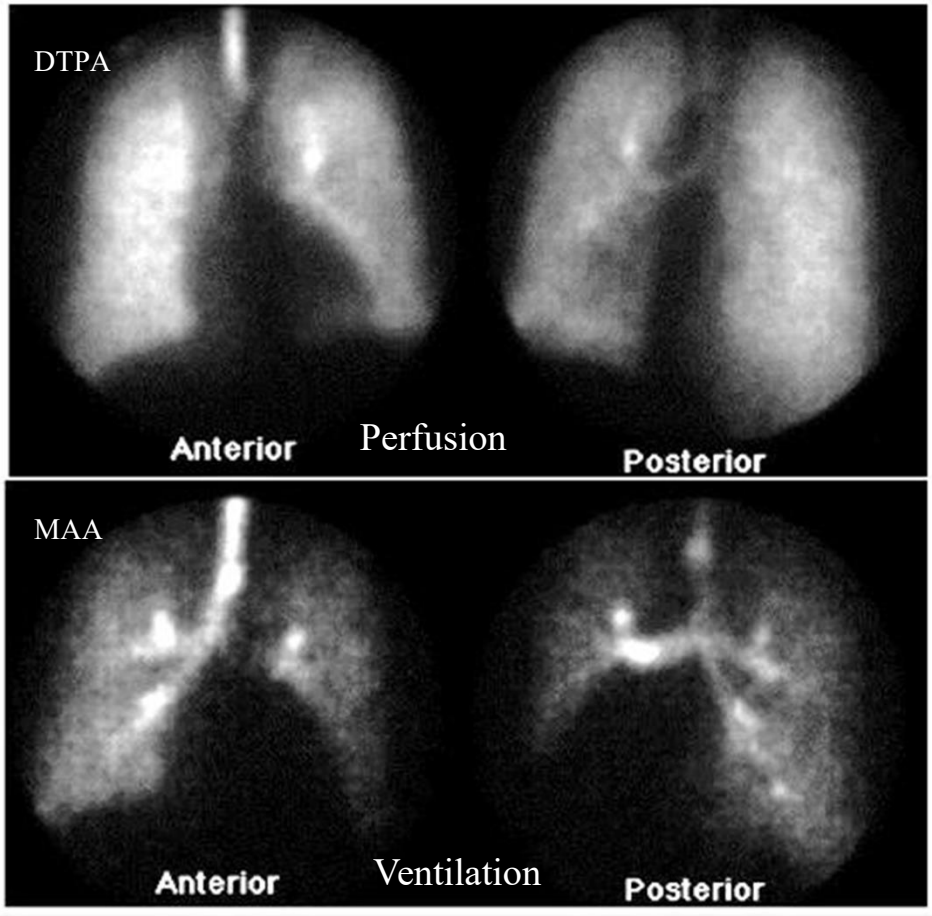
Milking cow analogy

The table lists typical generator produced radionuclide.

Parent P	Parent half-life	Mode of decay P→D	Daughter D	Mode of decay of D	Daughter half-life	Gamma-ray energy from daughter (keV)
^{99}Mo	2.7 d	β^-	^{99}Tc^m	IT	6 h	140
^{82}Sr	25 d	EC	^{82}Rb	EC β^+	1.3 min	777 511
^{68}Ge	280 d	EC	^{68}Ga	EC β^+	68 min	511
^{52}Fe	8.2 h	EC β^+	^{52}Mn^m	EC β^+ IT	21 min	511
^{81}Rb	4.7 h	EC	^{81}Kr^m	IT	13 s	190
^{62}Zn	9.1 h	EC β^+	^{62}Cu	EC β^+	9.8 min	511
^{178}W	21.5 d	EC	^{178}Ta	EC	9.5 min	93

Tc-99m Lung Scans

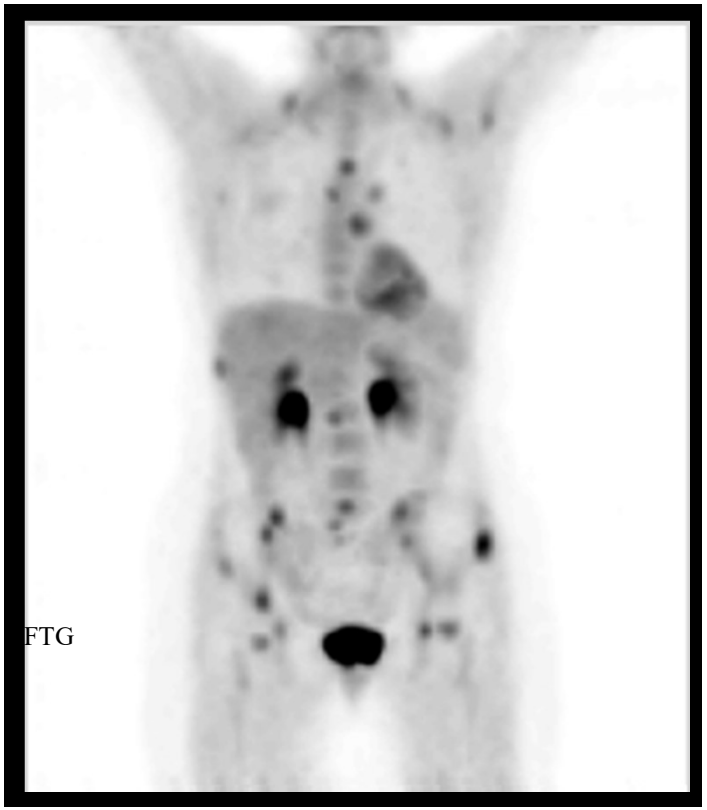
- Tc-99m Macro Aggregated Albumen (MAA)
- Tc-99m Pentetate (DTPA) aerosal



- Images from a portable ventilation perfusion examination indicate absent ventilation to the left lower lung. Perfusion to the left lower lobe is minimally decreased.
- Bronchoscopy was performed and a large mucous plug in the bronchus to the left lower lobe was removed. The patient rapidly improved.

From MIR Teaching File - gamma.wustl.edu/home.html

18FTG



47 yo Female with a history of breast Cancer. PET FDG images demonstrate multiple metastasesthat were not detectedon CT or bone scans.

F-18 fluorodeoxyglucose (FDG)

- The distribution of 18F-FDG is a good reflection of the distribution of glucose uptake and phosphorylation by cells in the body.
- It is retained by tissues with high metabololic activity, such as most types of malignant tumors.
- The production of ^{18}F-FDG is usually done by proton bombardment of ^{18}O-enriched water, causing a (p,n) reaction in the ^{18}O to produce ^{18}F. The ^{18}F is then collected and immediately attached to deoxyglucose in a "hot cell"
- The labeled FDG compound (T1/2 = 110 min) is rapidly shipped to points of use by the fastest possible mode.

Others

Other commonly used radiopharmaceuticals

• Tc-99m Sulfur Colloid	Liver Scan
• Tc-99m Sestamibi	Cardiac Perfusion
• Tc-99m Exametazime	Brain Perfusion
• Tc-99m Succimer (DMSA)	Kidney Scan and Function
• Tc-99m Red Blood Cell	Blood Pool Imaging
• Xe-133 gas	Lung ventilation imaging
• Ga-67 citrate	inflammatory lesions
• Th-201 chloride	Heart muscle imaging

NOTE: these pharmaceutical are used for nuclear medicine imaging including SPECT. We will consider PET agents later.

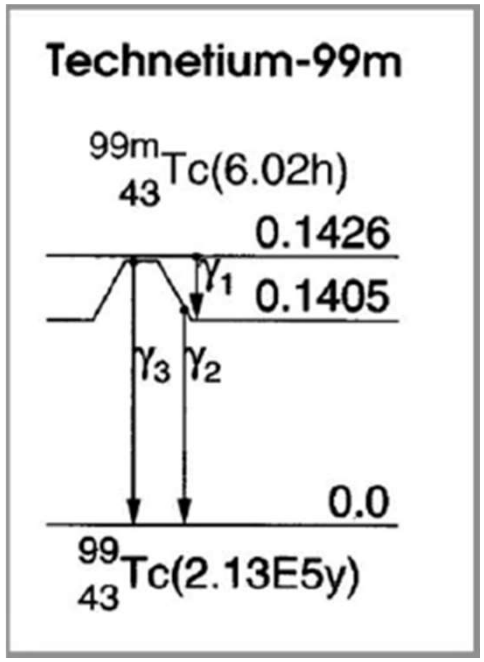
Ideal Radiopharmaceutical Properties.

1. Single gamma ray emitted.
2. No charged particle emission.
3. Half-life:
   - Long enough to permit imaging.
   - Short enough to reduce dose.
4. Gamma energy:
   - High enough to escape the body.
   - Low enough to permit efficient detection
5. Molecular chemistry that enables useful pharmaceutical compounds

Ideal Radiopharmaceutical Properties.

Tc-99m comes close to the characteristics desired of an ideal isotope:

- The decay scheme is dominated by a single gamma ray.
- As an isomeric transition, no charged particles are emitted from the nucleus, although low energy conversion electron are produced with low probability.
- The half life of 6 hours is convenient for daily procedures.
- The 140 keV energy escapes relatively well and is effectively detected by 3/8" thick detector crystals.
- Tc chemistry is not nearly as good as for C, N, and O. However, overtime numerous effective compounds have been developed.



Details of the Tc 99m decay characteristicscan be found in Sorenson Appendix C where the yield of 140.5 keV gamma rays per disintegration is listed as 0.89 with 0.11 as internal conversion.