Production of Radionuclides

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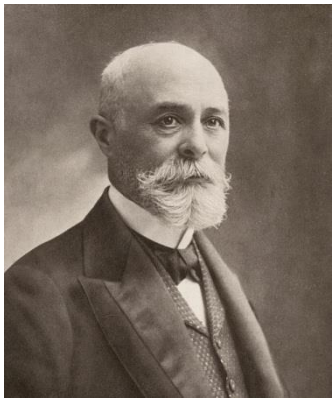
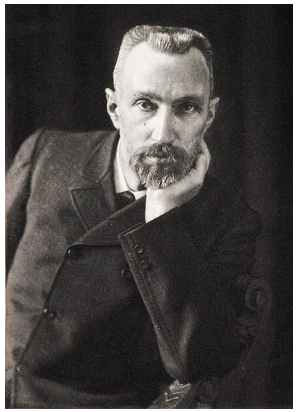
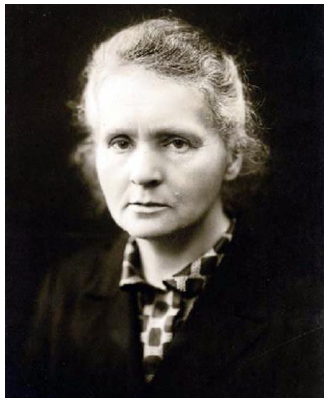
Introduction – History



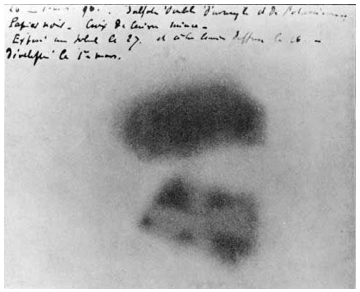
Antoine Henri Becquerel
1852-1908
1903 Nobel Prize in Physics



Pierre Curie
1859-1906
1903 Nobel Prize in Physics



Marie Curie
1867-1934
1903 Nobel Prize in Physics
1911 Nobel Prize in Chemistry



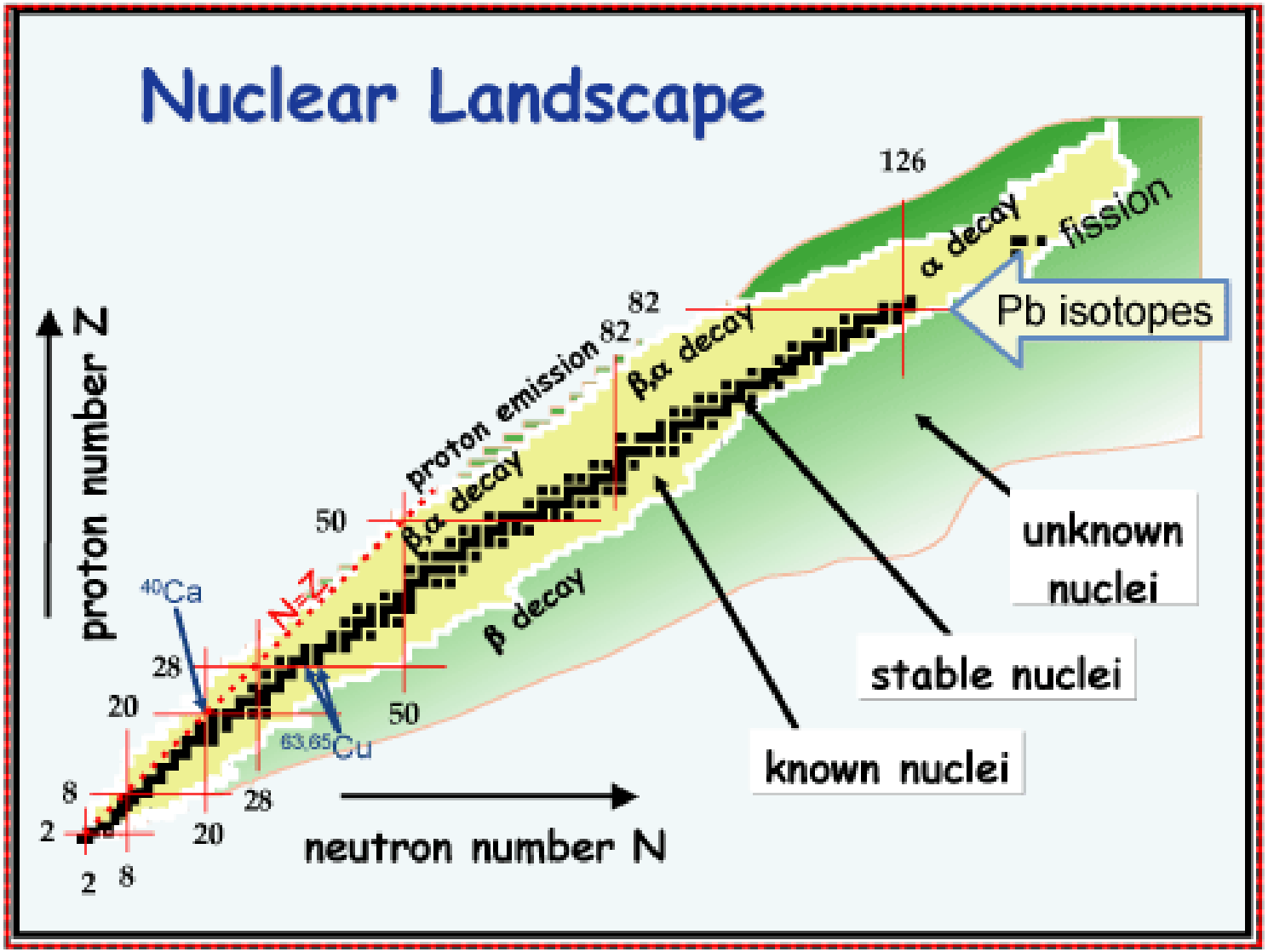
Potassium uranyl sulfate

"in recognition of the extraordinary services they have rendered by their joint researches on the radiation phenomena discovered by Professor Henri Becquerel"

"in recognition of her services to the advancement of chemistry by the discovery of the elements radium and polonium, by the isolation of radium and the study of the nature and compounds of this remarkable element."

- The work of Pierre and Marie Curie, E. Rutherford, and F. Soddy has shown that all elements found in nature with an atomic number greater than 83 (bismuth) are radioactive.

Chart of the Nuclides



Introduction – History

Irène Joloit-Curie
1897-1956
1935 Nobel Prize in Chemistry

Jean Frédéric Joliot-Curie
1900-1958
1935 Nobel Prize in Chemistry

"in recognition of their synthesis of new radioactive elements"

$$^{27}Al + {}^{4}He \rightarrow {}^{30}P + {}^{1}n$$

- At present, more than 2700 radionuclides have been produced artificially in the cyclotron, the reactor, and the linear accelerator.
- The type of radionuclide produced in a cyclotron or a reactor depends on the irradiating particle, its energy, and the target nuclei.

Radionuclides Commonly Used in PET

stable Isotope	natural abundance		$T_{1/2}$	Decay modes (%)	Main γ KeV (%)	β_{max} MeV (β_{ave})	Production
		PET radionuclides					
^{12}C	98.9	^{11}C	20.39 min	β^+ (99.8) EC (0.2)	511 (199.5)	0.960 (0.386)	$^{14}N(p,\alpha)^{11}C$
^{14}N	99.6	^{13}N	9.96 min	β^+ (99.8) EC (0.2)	511 (199.6)	1.198 (0.492)	$^{16}O(p,\alpha)^{13}N$
^{16}O	99.8	^{15}O	122.24 s	β^+ (99.9) EC (0.1)	511 (199.8)	1.732 (0.735)	$^{14}N(d,n)^{15}O$ $^{15}N(p,n)^{15}O$
^{19}F	100	^{18}F	109.8 min	β^+ (97) EC (3)	511 (193.5)	0.633 (0.250)	$^{18}O(p,n)^{18}F$ $^{20}Ne(d,\alpha)^{18}F$
^{127}I	100	^{124}I	4.18 d	β^+ (23) EC (77)	511 (46); 603 (62.9); 723 (10.3)	2.138 (0.820)	$^{124}Te(p,n)^{124}I$ $^{124}Te(d,2n)^{124}I$
^{69}Ga	60	^{68}Ga	67.71 min	β^+ (89) EC (11)	511 (178.3)	1.899 (0.829)	$^{68}Ge/^{68}Ga$ generator
^{71}Ga	40						

Radionuclides Commonly used in SPECT

	$T_{1/2}$	Decay modes (%)	Main γ KeV (%)	β_{max} MeV (β_{ave})	Production
SPECT radionuclides					
^{99m}Tc	6.01 h	IT	140 (89.1)		^{99}Mo/^{99m}Tc generator
^{123}I	13.27 h	EC	159 (83.3)		^{124}Te(p,2n)^{123}I
^{67}Ga	78.27 h	EC	93 (39.2); 185 (21.2); 300 (16.8)		^{68}Zn(p,2n)^{67}Ga
^{111}In	67.31 h	EC	171 (90.7); 245 (94.1)		^{111}Cd(p,n)^{111}In ^{112}Cd(p,2n)^{111}In
^{201}Tl	72.91 h	EC	167 (10.0)		^{203}Tl(p,3n)^{201}Pb: ^{201}Tl
^{133}Xe	5.24 d	β^-	81 (38.0)	0.346 (0.100)	^{235}U fission

Introduction – Q energy

- This energy requirement arises from the difference between the masses of the target nucleus plus the irradiating particle and the masses of the product nuclide plus the emitted particles.

$$Q = (\sum masses_{reactants} - \sum masses_{products}) \text{ x } (931.5 \text{ MeV/dalton})$$

Example. Calculate the energy change, in MeV, for the nuclear reaction below. Is the reaction exoergic or endoergic?

$$^{235}U \rightarrow {}^{231}Th + {}^{4}He$$

Q = [(235.0439) – (231.3063) – (4.0026)] x (931.5 MeV/dalton)

= 6.68 MeV

Introduction – Q energy

- An example of a simple cyclotron produced radionuclide is ^{111}In, which is produced by irradiating ^{111}Cd with 12-MeV protons in a cyclotron. $^{111}Cd\ (p, n)^{111}In$

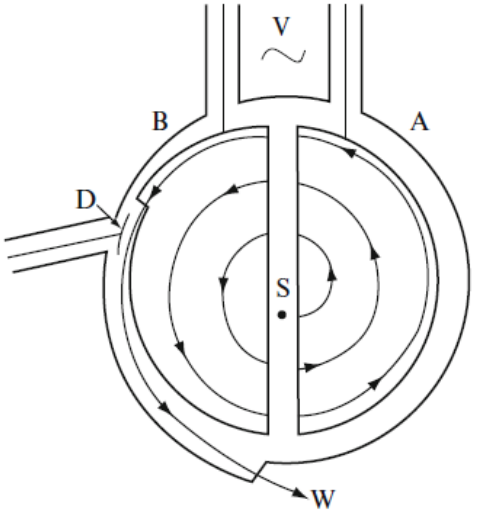
- As another example, relatively high-energy nuclear reactions induced in ^{89}Y by irradiation with 40-MeV protons are listed below.

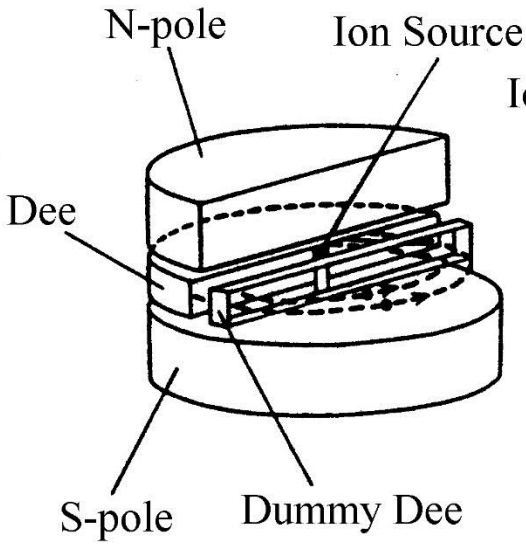
$$
\begin{aligned}
^{89}Y + p(40\ MeV) &\rightarrow {}^{89}Zr + n \\
&\rightarrow {}^{89}Y + p \\
&\rightarrow {}^{88}Zr + 2n \\
&\rightarrow {}^{88}Y + pn \\
&\rightarrow {}^{88}Sr + 2p \\
&\rightarrow {}^{87}Zr + 3n \\
&\rightarrow {}^{87}Y + p2n
\end{aligned}
$$

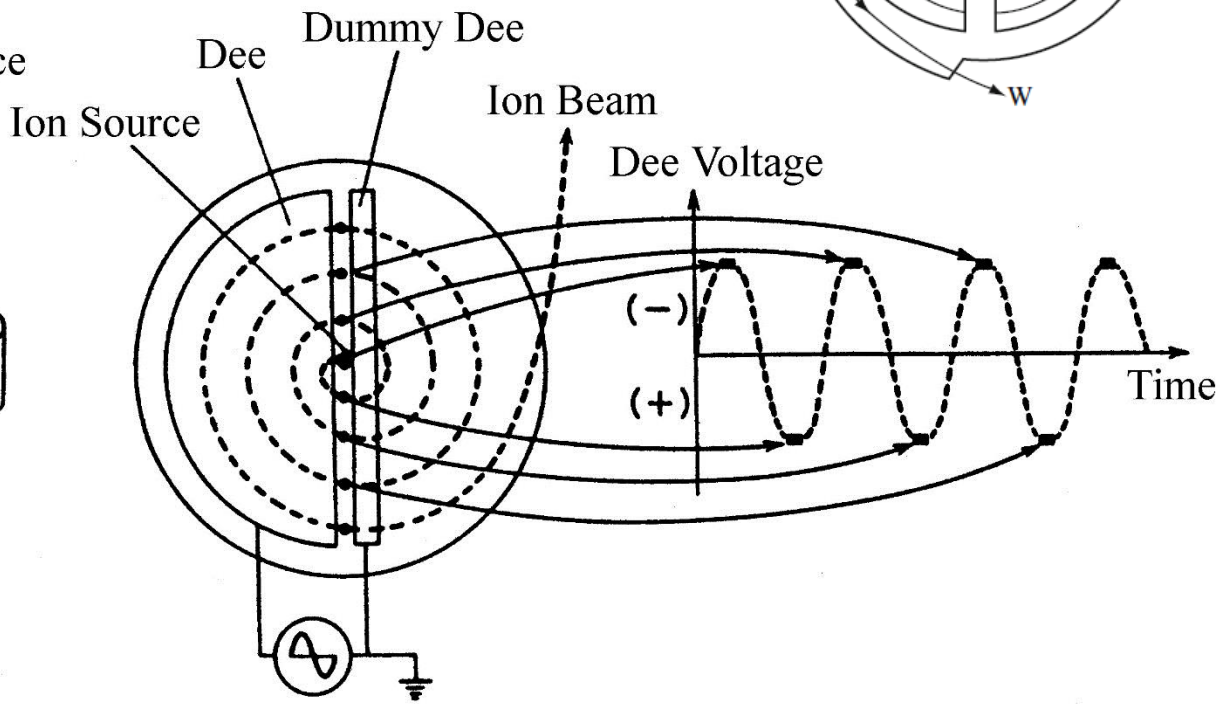
Cyclotron Produced Radionuclides – cyclotron

Ernest O. Lawrence
1901-1958
1939 Nobel Prize in Physics

"for the invention and development of the cyclotron and for results obtained with it, especially with regard to artificial radioactive elements".







Cyclotron Produced Radionuclides – Gallium-67

- Gallium-67 can be produced by several nuclear reactions such as $^{66}Zn(d, n)^{67}Ga$, $^{68}Zn(p, 2n)^{67}Ga$, and $^{64}Zn(\alpha, p)^{67}Ga$.

- After irradiation the target is dissolved in 7N HCl and carrier-free Ga-67 is extracted with di-isopropyl ether (DIPE). The organ phase is then evaporated to dryness in a water bath and the residue is taken up in dilute HCl for supply as gallium chloride. It may be complexed with citric acid to form gallium citrate.

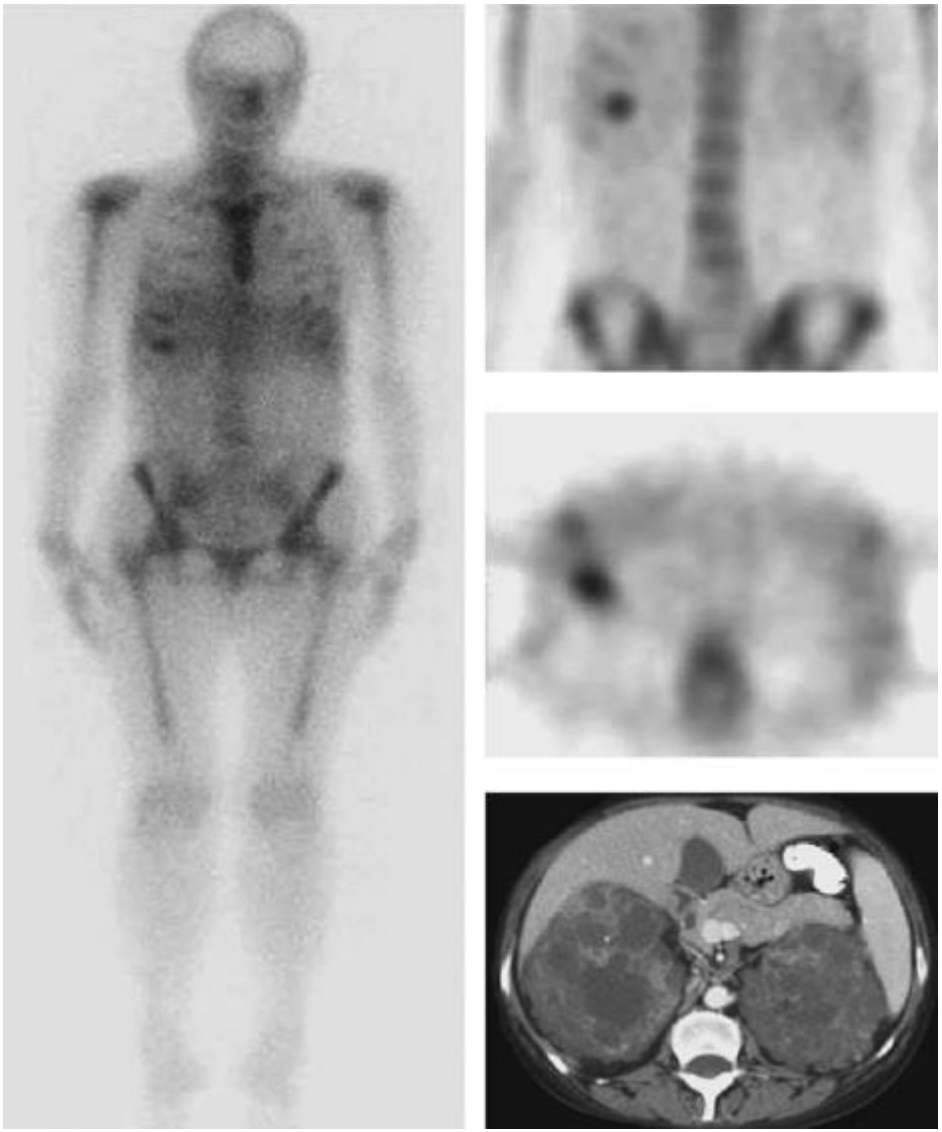
- Enriched target?

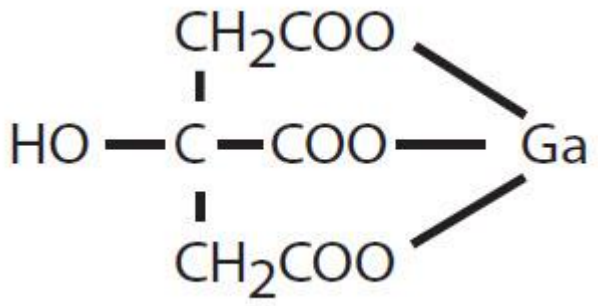
  side rxn: $^{67}Zn(p, 2n)^{66}Ga$ $\quad t_{1/2} = 9h$

  $$^{66}Zn(p, 2n)^{65}Ga \xrightarrow{EC} {}^{65}Zn$$

  15.2 min 244 d

^{67}Ga-citrate



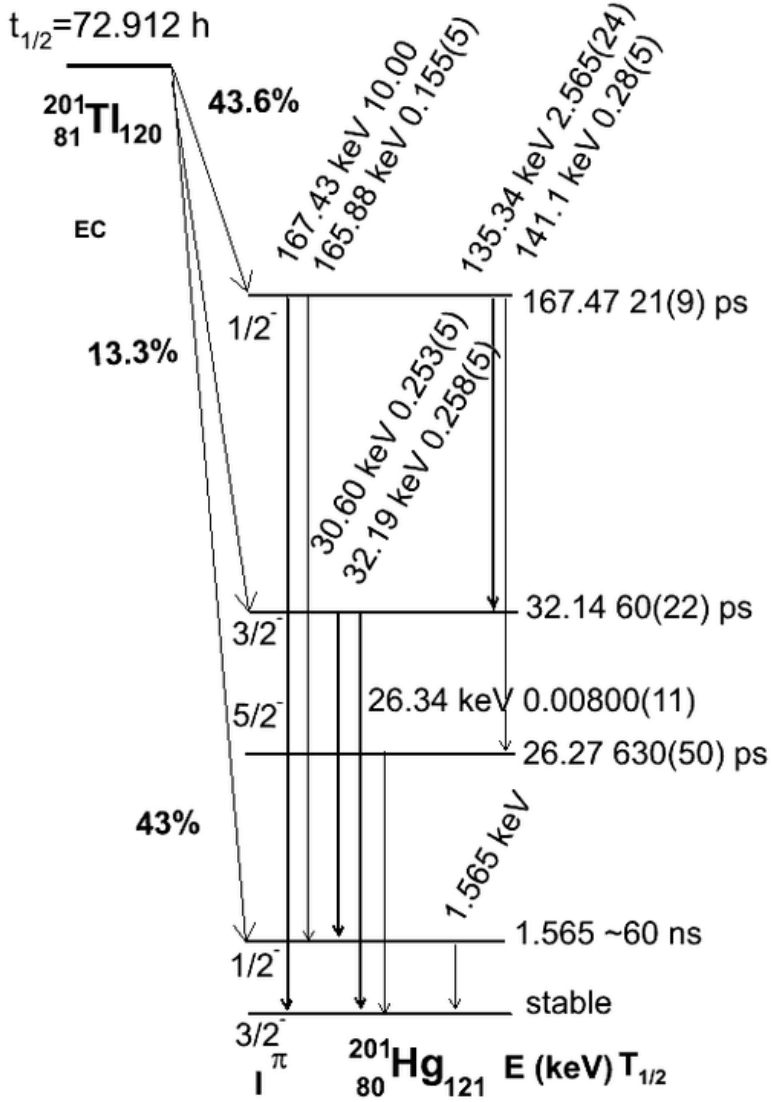


^{67}Ga-citrate scintigraphic imaging showing the infected focus in the right hypochondrium; however, the morphologic changes due to polycystic disease that are visible with CT do not provide an accurate location in the liver or kidney.

Cyclotron Produced Radionuclides – Thallium-201

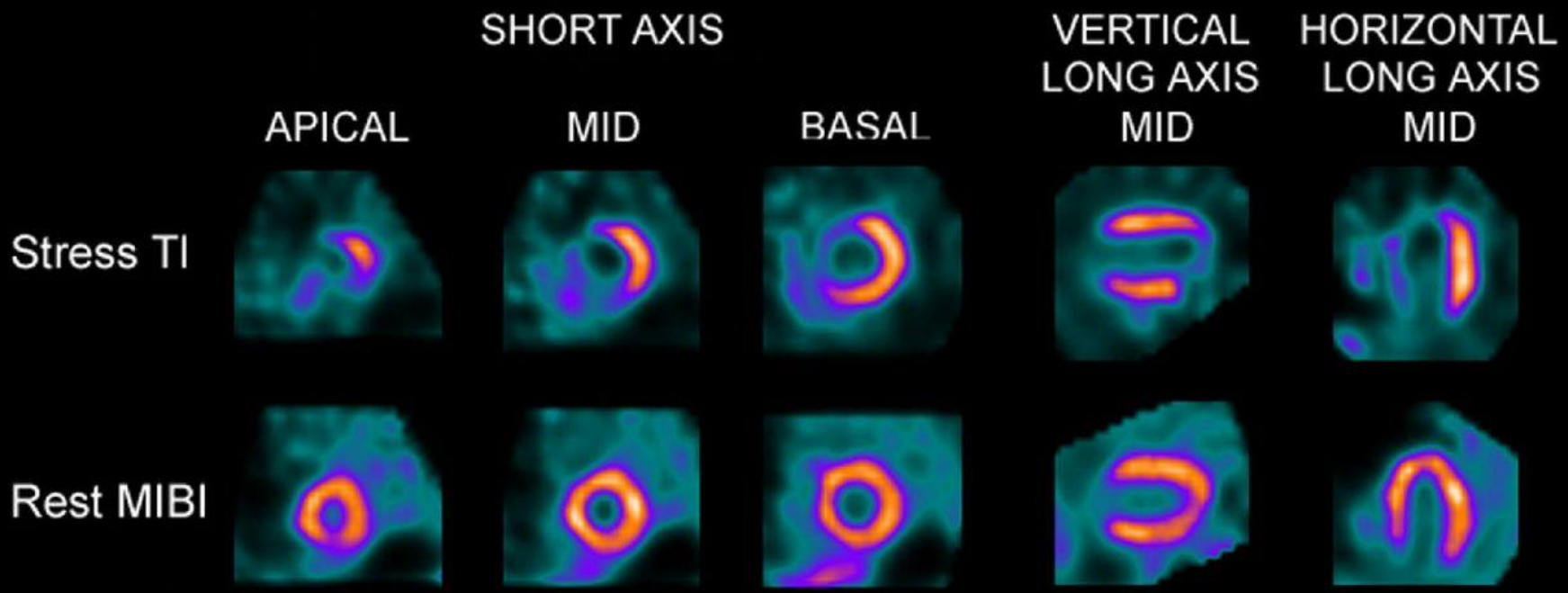
- Tl-201 is primarily produced by the $^{203}Tl(p, 3n)^{201}Pb$ reaction, whereby Pb-201 decays to Tl-201 with a half-life of 9.4 h.
- After irradiation, the natural Tl target is dissolved in concentrated HNO_3 and then evaporated to dryness. The residue is dissolved in 0.025 M EDTA and passed through a Dowex resin column. Most Tl is absorbed on the column, while ^{201}Pb passes through.
- The eluate containing ^{201}Pb is allowed to decay for 30-35 h to produce ^{201}Tl and is then passed through a Dowex 1 x 8 column.
- $^{201}Tl^{3+}$ adheres to the column and ^{201}Pb passed through. $^{201}Tl^{3+}$ is eluated with hydrazine-sulfate solution, reducing Tl^{3+} to Tl^{+}.

Cyclotron Produced Radionuclides – Thallium-201



- It decays by E.C. to its stable mercurt-201 daughter, with a physical half-life of 73 h.
- The photons available for imaging are mercury K-characteristic x-rays ranging from 69 to 83 keV (95% abundant) and gamma rays of 167 keV (10%) and 135 keV (3%).
- Thallium is a metallic element in the IIIA series of the Periodic Table of the Element. In pharmacological doses, thallium is a poison, but is nontoxic in the tracer doses used.

Cyclotron Produced Radionuclides – Thallium-201



Tl-201/rest Tc-99m sestamibi (MIBI) high-speed myocardial perfusion imaging shows extensive defects in anterior, septal, and apical walls as well as transient ischemic dilation on exercise MPI of a 56-year-old man with atypical chest pain. Invasive coronary angiography revealed occlusion of the mid-left anterior descending artery. Note the absence of significant extracardiac activity on the rest Tc-99m MIBI images despite initiation of imaging 2 min after rest injection.

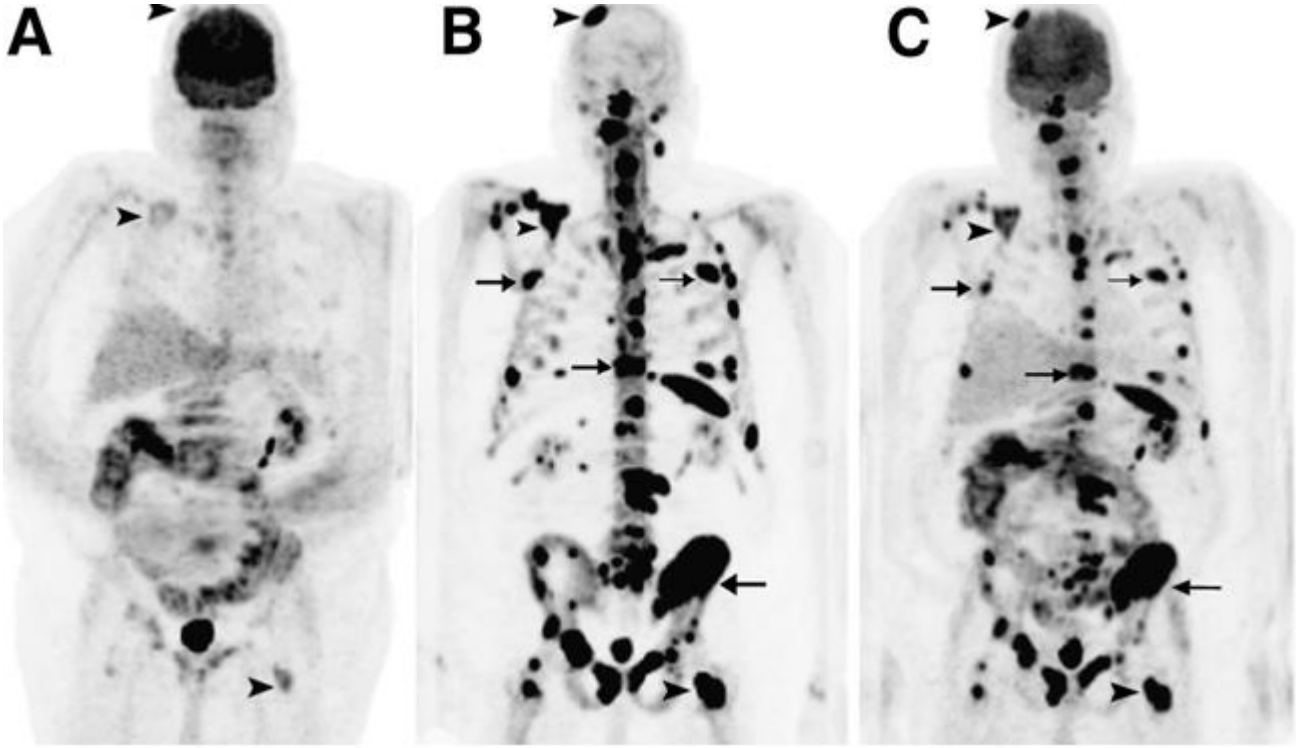
Cyclotron Produced Radionuclides – Fluorine-18

- F-18 has a half-life of 110 min and is commonly produced by the $^{18}O(p, n)^{18}F$ reaction on a pressurized ^{18}O-water target.

- F-18 is recovered as F^- ion from water by passing the mixture through a column of quaternary ammonium resins, and ^{18}O-water can be reused as the target.

- F-18 is used primarily to label glucose to give ^{18}F-FDG for myocardial and cerebral metabolic studies. It is also used to label many potential ligands for a variety of tumors and currently ^{18}F-NaF is used for bone imaging.

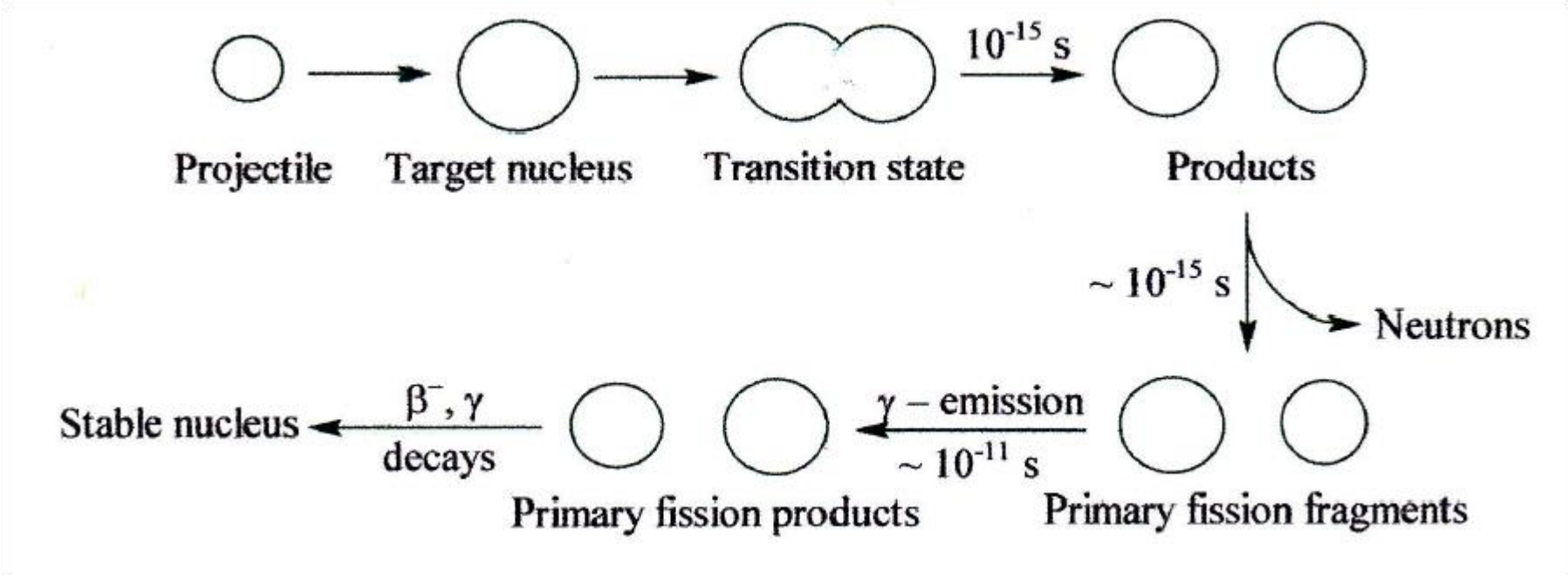
^{18}F-FDG + ^{18}F-NaF PET Imaging



A 68-y-old man with colon cancer. (A) MIP image of ^{18}F-FDG PET shows faint radiotracer uptake in several skeletal lesions (arrowheads). (B) MIP image of ^{18}F PET shows intense radiotracer uptake in multiple bone lesions, including better visualization of lesions seen on ^{18}F-FDG PET (arrowheads) and more extensive skeletal metastases (arrows). (C) MIP image of combined ^{18}F/^{18}F-FDG PET shows skeletal lesions noted on ^{18}F PET (arrowheads).

Neutron-induced Fission

- A neutron is captured by a heavy nuclide to form a compound nucleus. This nucleus then splits into two smaller fragments and emits two or three free neutrons, along with about 200 MeV of energy per nucleus fissioned.



Reactor Produced Radionuclides – Fission

- Fission is defined as the breakup of a heavy nucleus into two fragments of approximately equal mass, accompanied by the emission of two or three neutrons with mean energy of about 1.5 MeV.

thermal neutron (0.025eV)

$$^{235}_{92}\mathrm{U} + ^{1}_{0}\mathrm{n} \rightarrow ^{236}_{92}\mathrm{U} \rightarrow ^{131}_{53}\mathrm{I} + ^{102}_{39}\mathrm{Y} + 3^{1}_{0}\mathrm{n}$$

$$\rightarrow ^{99}_{42}\mathrm{Mo} + ^{135}_{50}\mathrm{Sn} + 2^{1}_{0}\mathrm{n}$$

$$\rightarrow ^{117}_{46}\mathrm{Pd} + ^{117}_{46}\mathrm{Pd} + 2^{1}_{0}\mathrm{n}$$

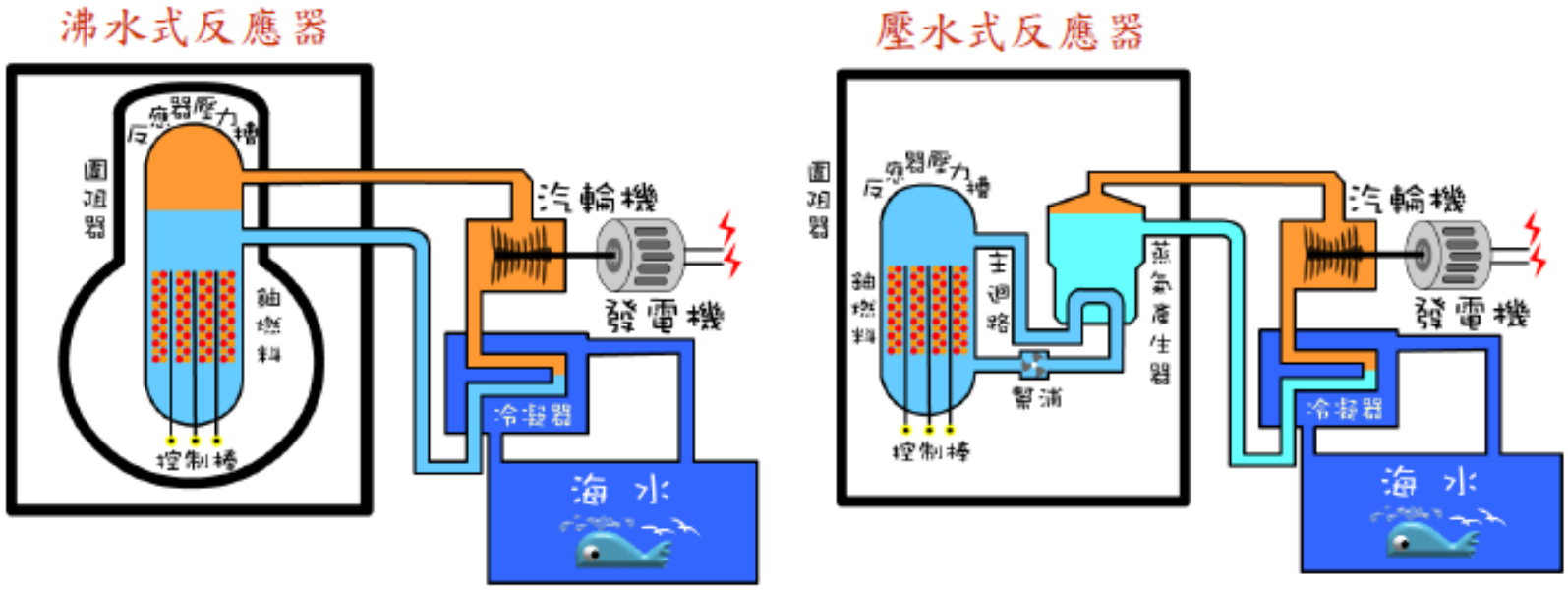
$$\rightarrow ^{133}_{54}\mathrm{Xe} + ^{101}_{38}\mathrm{Sr} + 2^{1}_{0}\mathrm{n}$$

$$\rightarrow ^{137}_{55}\mathrm{Cs} + ^{97}_{37}\mathrm{Rb} + 2^{1}_{0}\mathrm{n}$$

$$\rightarrow ^{155}_{62}\mathrm{Sm} + ^{78}_{30}\mathrm{Zn} + 3^{1}_{0}\mathrm{n}$$

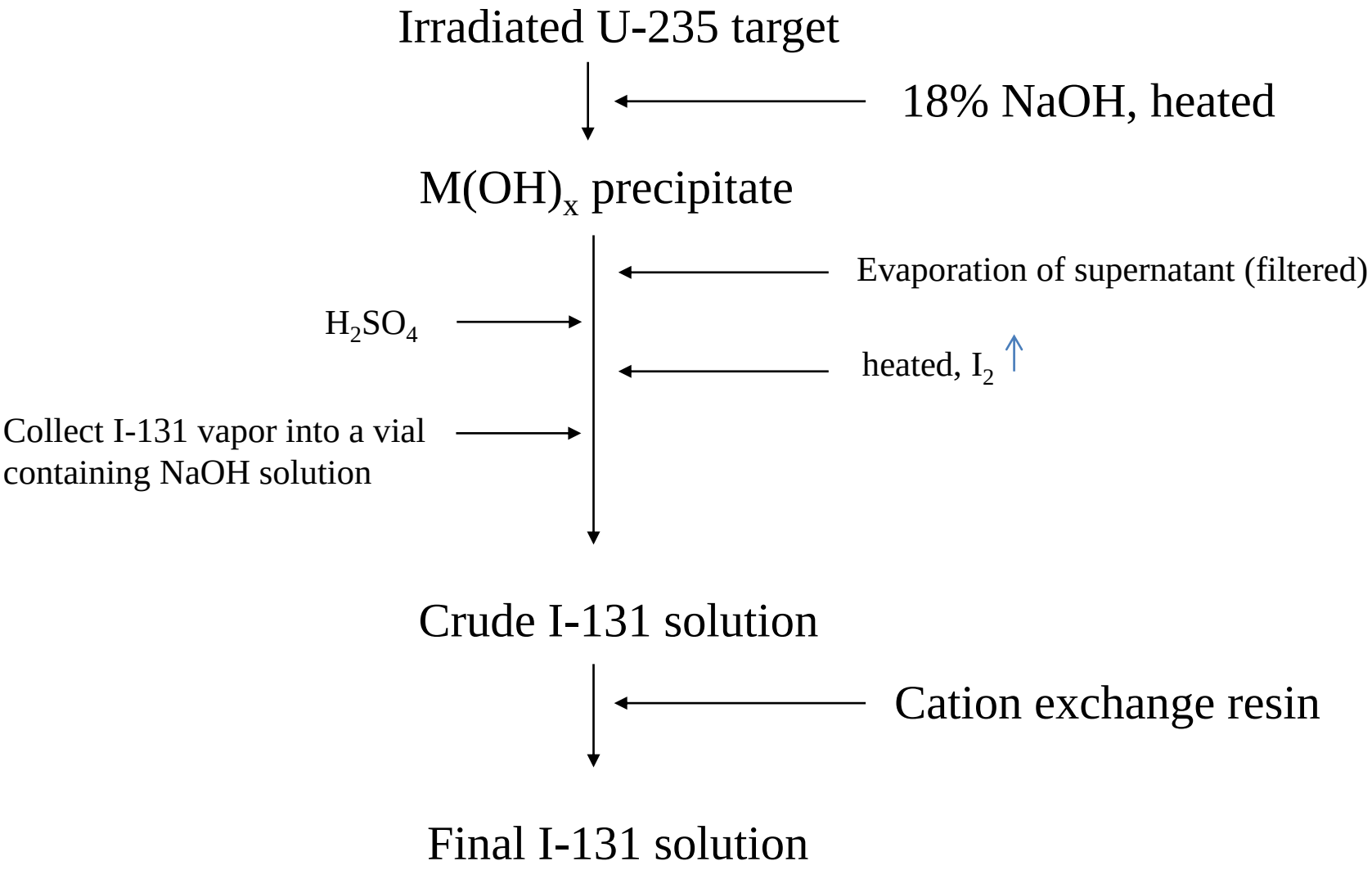
$$\rightarrow ^{156}_{62}\mathrm{Sm} + ^{77}_{30}\mathrm{Zn} + 3^{1}_{0}\mathrm{n}$$

Nuclear Power Plant

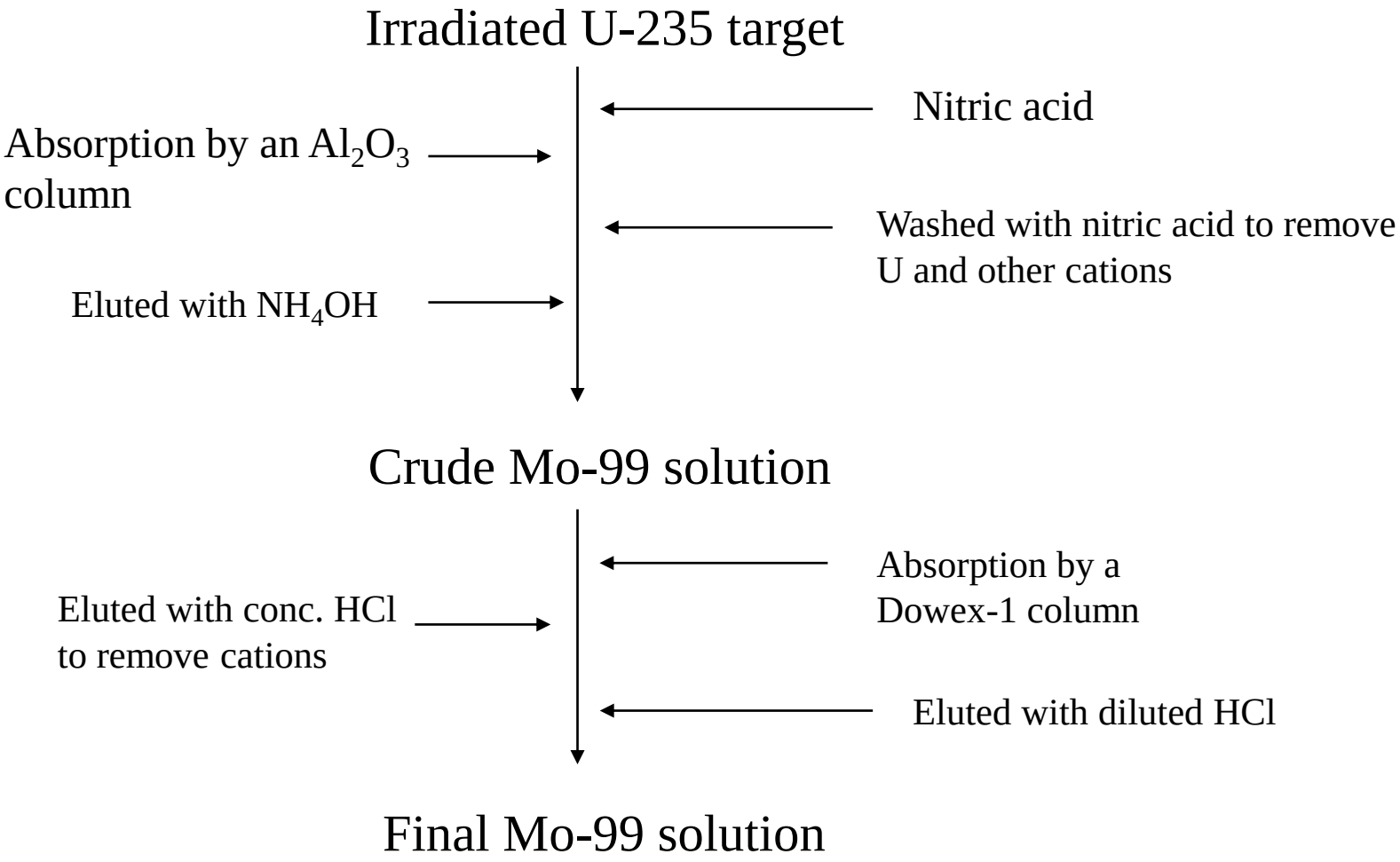


廠別	核能一廠	核能二廠	核能三廠	核能四廠
位置	台北縣石門鄉	台北縣萬里鄉	屏東縣恆春鎮	台北縣貢寮鄉
商業運轉日期	#1 67年12月	#1 70年12月	#1 73年7月	#1 95年7月
	#2 68年 7月	#2 72年03月	#2 74年5月	#2 96年5月
裝置容量	636千瓩*2	985千瓩*2	951千瓩*2	1,375千瓩*2
反應器類型	輕水式反應器（沸水式）	輕水式反應器（沸水式）	輕水式反應器（壓水式）	輕水式反應器（沸水式）

Reactor Produced Radionuclides – iodine-131



Reactor Produced Radionuclides – Molybdenum-99



Radionuclide Generators

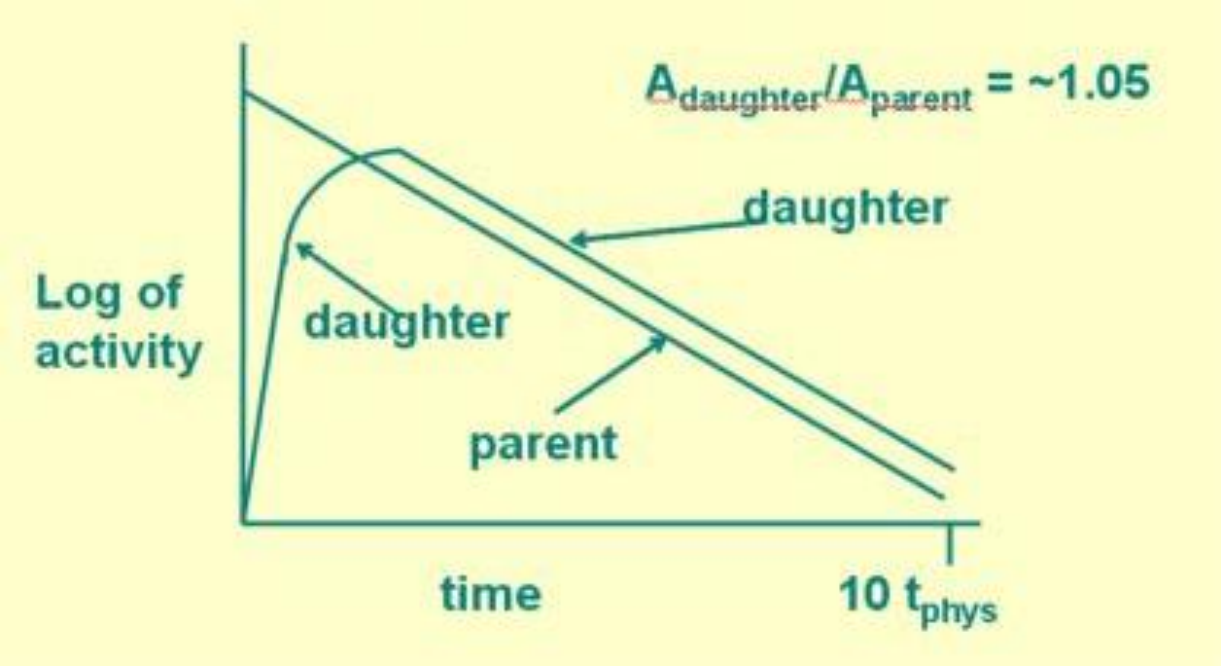
- The column is filled with adsorbent material such as cation- or anion-exchange resin, alumina, and zirconia, on which the parent nuclide is adsorbed.

- The daughter radionuclide grows as a result of the decay of the parent until either a transient or a secular equilibrium is reached within several half-lives of the daughter, after which the daughter appears to decay with the same half-live as the parent.

- Because there are differences in chemical properties, the daughter activity is eluted in a carrier-free state with an appropriate solvent, leaving the parent on the column.

Growth of Radioactive Products in a Decay Chain

- The ratio of the daughter atoms to the parent atoms becomes constant after several half-lives of the daughter have passed.
- The activity of the daughter is greater than that of the parent when transient equilibrium is achieved.

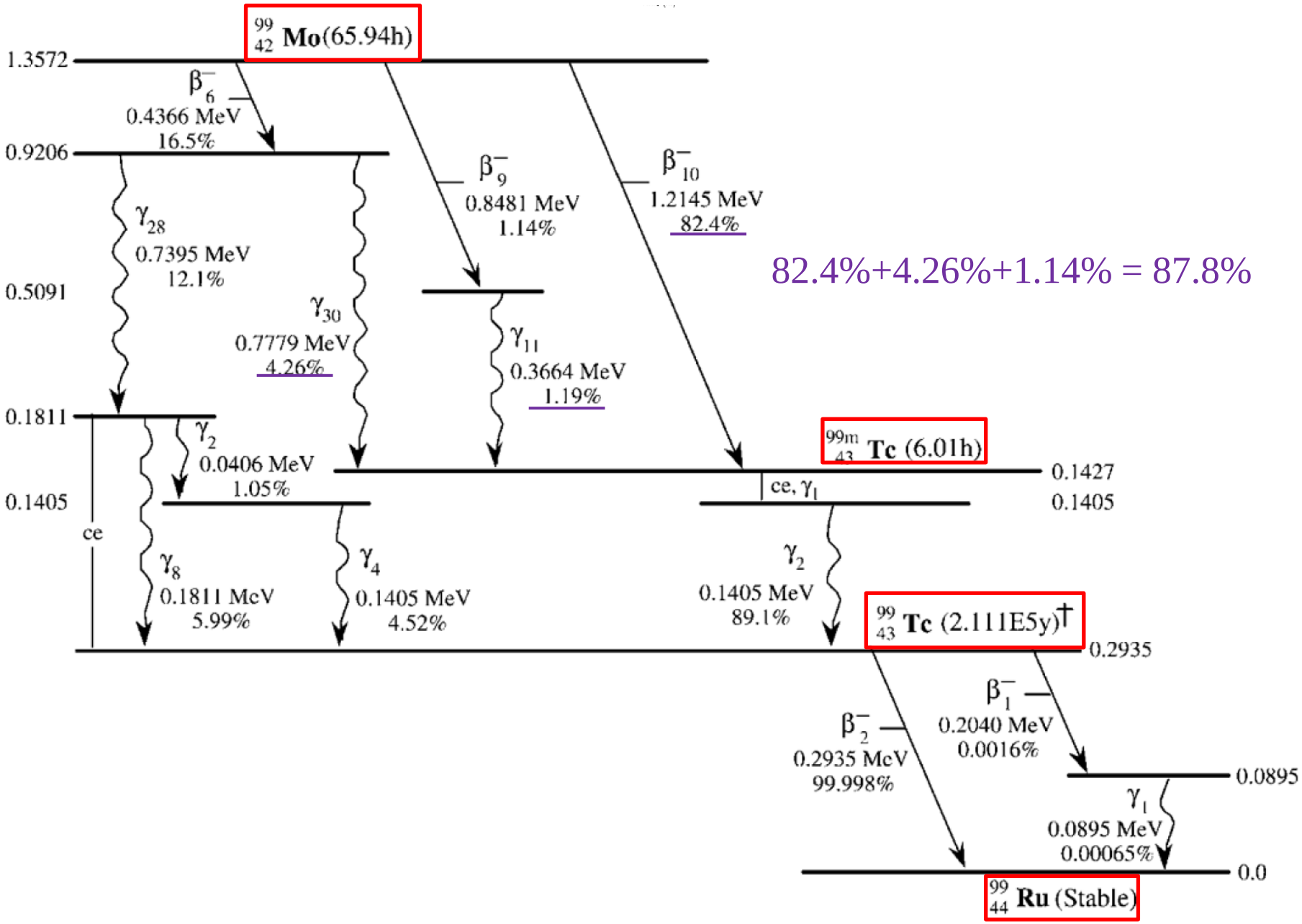


Radionuclide Generators

TABLE 5.1. Several generator systems useful in nuclear medicine

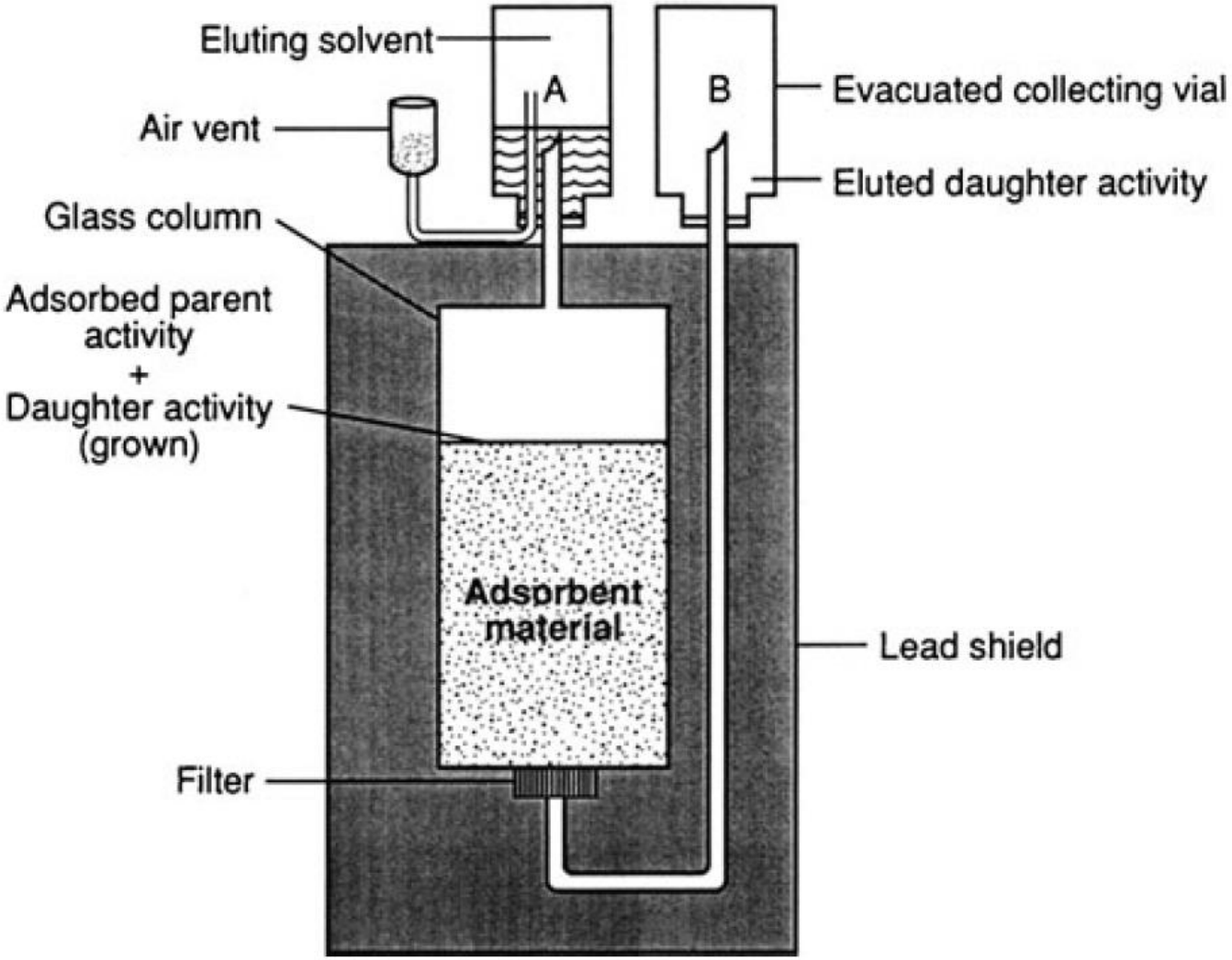
Parent	Parent $t_{1/2}$	Nuclear reaction	Daughter	Daughter $t_{1/2}$	Mode of daughter decay	Principal photon energy (keV) (% abundance)	Column	Eluant
^{99}Mo	66 h	Fission, ^{98}Mo(n, γ)	^{99m}Tc	6 h	IT	140 (90)	Al_2O_3	0 9% NaCl
^{68}Ge	271 days	^{69}Ga(p, 2n)	^{68}Ga	68 min	β^+	511 (178)	Al_2O_3	0 005 *M* EDTA
							SnO_2	1 *N* HCl
^{62}Zn	9 3 h	^{63}Cu(p, 2n)	^{62}Cu	9 7 min	β^+	511 (194)	Dowex 1X8	2 *N* HCl
^{81}Rb	4 6 h	^{79}Br(α, 2n)	^{81m}Kr	13 s	IT	190 (67)	BioRad AG 50	Water or air
^{82}Sr	25 5 days	^{85}Rb(p, 4n)	^{82}Rb	75 s	β^+	511 (190)	SnO_2	0 9% NaCl
^{90}Sr	28 6 years	Fission	^{90}Y	64 1 h	β^-	–	Dowex 50	0 03 *M* EDTA

Data from Browne E, Firestone RB Table of Radioactive Isotopes 1st ed New York Wiley; 1986
IT isomeric transition



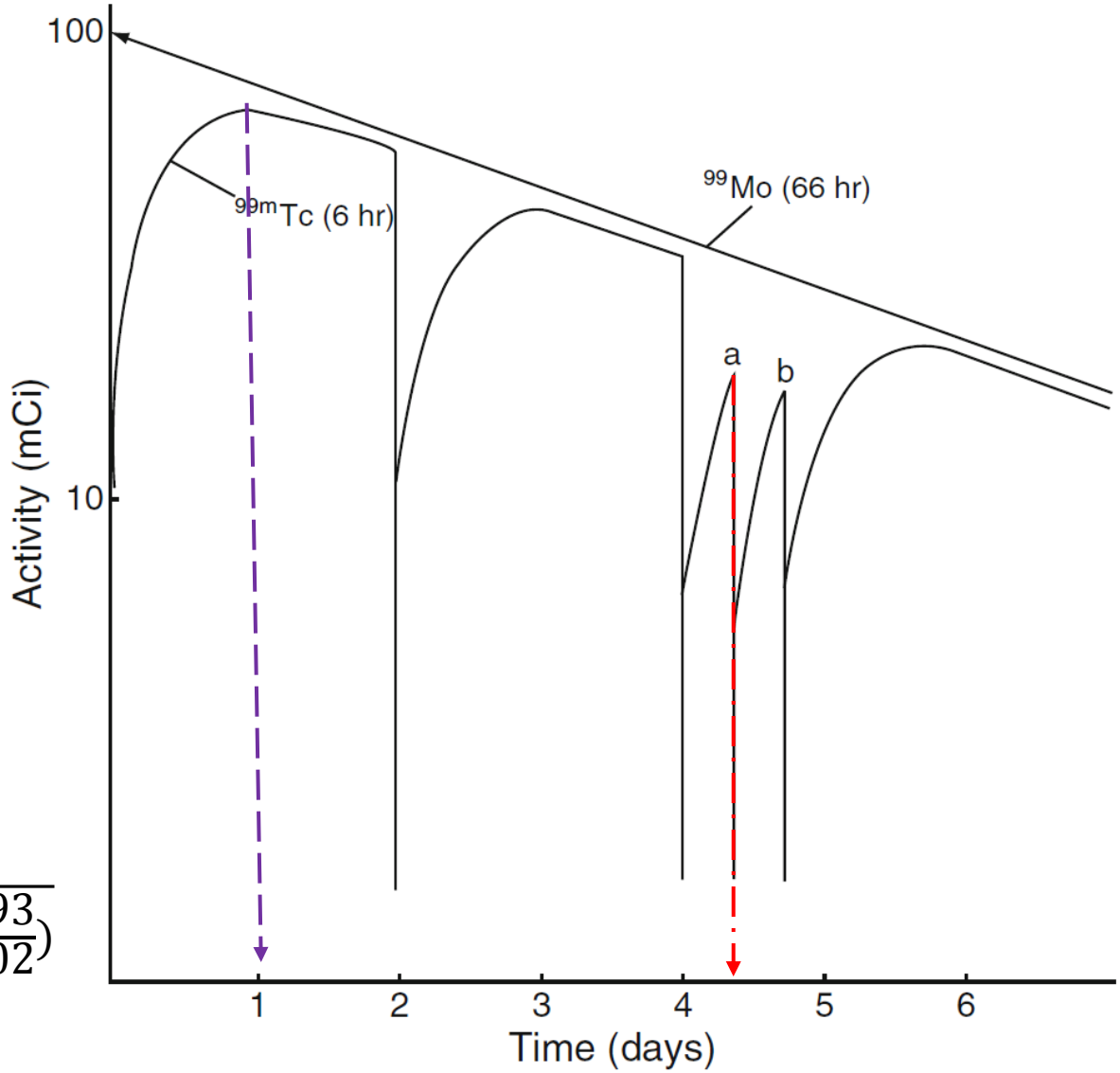
82.4%+4.26%+1.14% = 87.8%

^{99}Mo-^{99m}Tc Generator - Solid Column Generator



^{99}Mo-^{99m}Tc Generator - Solid Column Generator

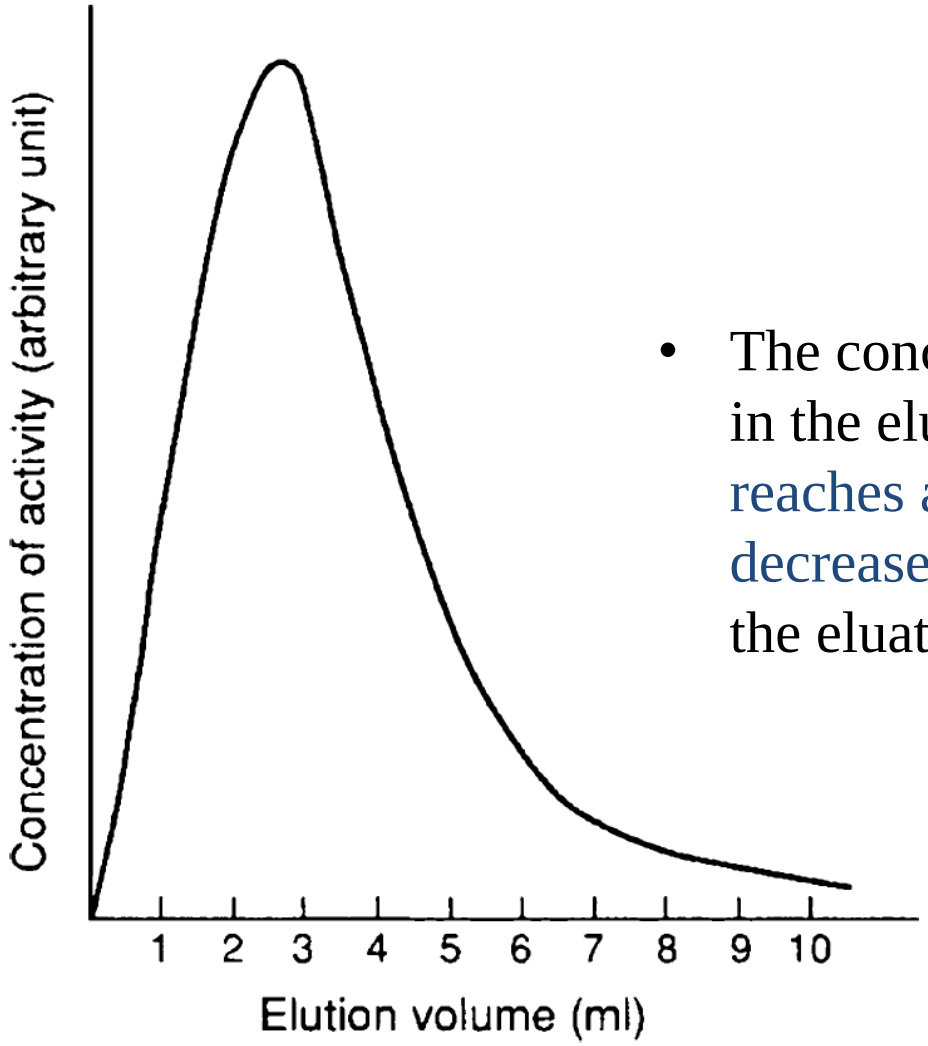
^{99}Mo-^{99m}Tc Generator - Solid Column Generator



$$t = \frac{\ln(\frac{\lambda_B}{\lambda_A})}{(\lambda_B - \lambda_A)} = \frac{\ln(\frac{66.02}{6.02})}{(\frac{0.693}{6.02} - \frac{0.693}{66.02})}$$

$$= 22.91 \text{ hr}$$

^{99}Mo-^{99m}Tc Generator - Solid Column Generator



- The concentration of ^{99m}Tc activity in the eluate initially increases, then reaches a maximum, and finally decreases with increasing volume of the eluate

^{99}Mo-^{99m}Tc Generator - Solid Column Generator

The ^{99m}Tc content in the Tc-eluate is given by the mole fraction (F) of ^{99m}Tc expressed as follows:

$$F = \frac{N_A}{N_A + N_B}$$

where N_A and N_B are the number of atoms of ^{99m}Tc and ^{99}Tc, respectively.

$$F = \frac{0.87\ \lambda_A\ (e^{-\lambda_A t} - e^{-\lambda_B t})}{(\lambda_B - \lambda_A)\ (1 - e^{-\lambda_A t})}$$

$$N_{(total)} = \frac{^{99m}\text{Tc activity}}{0.1155 \times F}$$

^{99}Mo-^{99m}Tc Generator - Solid Column Generator

TABLE 5.2 Mole fractions of ^{99m}Tc in Tc eluate at different times after elution

Days after elution	Hours after elution							
	0	3	6	9	12	15	18	21
0		0.7346	0.6254	0.5366	0.4641	0.4044	0.3550	0.3138
1	0.2791	0.2498	0.2249	0.2035	0.1851	0.1691	0.1551	0.1428
2	0.1319	0.1222	0.1136	0.1059	0.0990	0.0927	0.0869	0.0817
3	0.0770	0.0726	0.0686	0.0649	0.0614	0.0583	0.0553	0.0526
4	0.0500	0.0476	0.0454	0.0432	0.0413	0.0394	0.0377	0.0360

^{99}Mo-^{99m}Tc Generator - Quality Control

^{99}Mo breakthrough

- This is ^{99}Mo contamination in the ^{99m}Tc-eluate and originates from the small quantity of ^{99}Mo that may be eluted with ^{99m}Tc. The US Pharmacopeia (USP 32) limit [also the Nuclear Regulatory Commission (NRC) limit] is 0.15 μCi ^{99}Mo/mCi (0.15 kBq/MBq) ^{99m}Tc at the time of administration.

- The ^{99}Mo contamination is measured by detecting 740-keV and 780-keV photons of ^{99}Mo in a dose calibrator or a NaI(Tl) detector coupled to a pulse height analyzer.

- The eluate vial is placed in a lead pot (about 6-mm thick) to stop all 140-keV photons from ^{99m}Tc and to count only 740-keV and 780-keV photons from ^{99}Mo.

^{99}Mo-^{99m}Tc Generator - Quality Control

- Molybdenum-99 along with ^{98}Mo (from the molybdenum target) can also be detected by adding phenylhydrazine to the eluate and observing the color change due to the Mo-phenylhydrazine complex by the use of a colorimeter.

- The A_{Mo}/A_{Tc} ratio increases with time because ^{99}Mo ($t_{1/2}$ = 66 h) decays more slowly than ^{99m}Tc ($t_{1/2}$ = 6 h). The time at which the A_{Mo}/A_{Tc} ratio will exceed 0.15 can be calculated by

$$0.15 = \frac{(A_{Mo})_0 e^{\ 0.0105t}}{(A_{Tc})_0 e^{\ 0.1155t}}$$

$$t = \frac{-\ln[(A_{Mo})_0/(A_{Tc})_0]}{0.105} - 18.07$$

- $^{99m}TcO_4^-$ obtained from the Moly generator has an expiration period of 12 h for clinical use.

^{99}Mo-^{99m}Tc Generator - Quality Control

Other Radionuclide contamination

- In generators using fission-produced molybdenum, a number of extraneous activities such as those of ^{103}Ru, ^{132}Te, ^{131}I, ^{99}Zr, ^{124}Sb, ^{134}Cs, ^{89}Sr, ^{90}Sr, and ^{86}Rb may remain in the eluate as contaminants.

- The USP 32 limits of these radionuclides in ^{99m}Tc eluate are ^{131}I: 0.05 μCi/mCi (0.05 Bq/kBq) ^{99m}Tc; ^{103}Ru: 0.05 μCi/mCi (0.05 Bq/kBq) ^{99m}Tc; ^{89}Sr: 0.0006 μCi/mCi (0.0006 Bq/kBq) ^{99m}Tc; ^{90}Sr: 0.00006 μCi/mCi (0.00006 Bq/kBq) ^{99m}Tc; other β^- and γ-emitting radionuclides: not more than 0.01% of all activity at the time of administration; gross α-particle impurity: not more than 0.001 nCi/mCi (0.001 Bq/MBq) ^{99m}Tc.

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- These contaminants can be checked by a multichannel pulse height analyzer after allowing ^{99m}Tc, ^{99}Mo, and other relatively short-lived radionuclides to decay completely. Usually these tests are performed by the manufacturer.

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Aluminum Breakthrough

- The aluminum contamination originates from the alumina bed of the generator.
- The presence of aluminum in the ^{99m}Tc-eluate interferes with the preparation of ^{99m}Tc-sulfur colloid; particularly phosphate buffer in colloid preparations tends to precipitate with excessive aluminum.
- It also interferes with the labeling of red blood cells with ^{99m}Tc, causing their agglutination. The USP 32 limit is 10 μg Al/ml ^{99m}Tc for fission-produced ^{99}Mo
- The presence of aluminum can be detected by the colorimetric method using aurin tricarboxylic acid or methyl orange, and can be quantitated by comparison with a standard solution of aluminum.

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pH

- The pH of the eluate should be between 4.5 and 7.5; this can be checked quantitatively with a pH meter or qualitatively with pH paper. The actual pH of the ^{99m}Tc-eluate from the generator is about 5.5. The pH of the 99mTc solution obtained by methyl ethyl ketone extraction is slightly higher (~6–7).


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