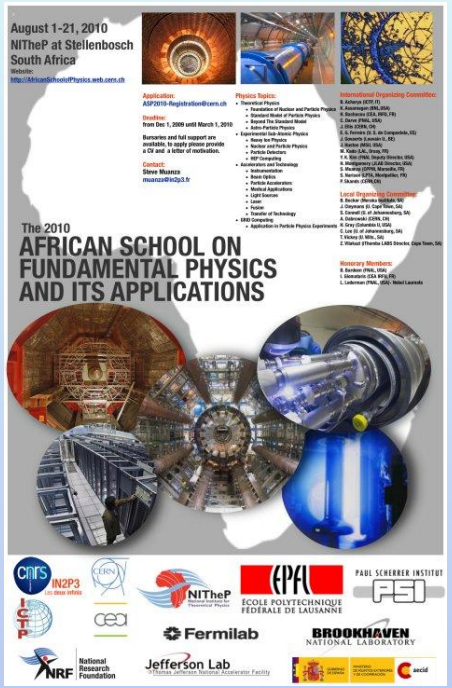
African School of Physics 2010



Radionuclide production

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Radionuclide production

The use of radionuclides in the physical and biological sciences can be broken down into three general categories:

- Radiotracers
- Imaging (95% of medical uses)
  - SPECT (^{99m}Tc, ^{201}Tl, ^{123}I)
  - PET (^{11}C, ^{13}N, ^{15}O, ^{18}F)
- Therapy (5% of medical uses)
  - Brachytherapy (^{103}Pd)
  - Targeted therapy (^{211}At, ^{213}Bi)

Relevant physical parameters (function of the application)

- Type of emission (α, β^+, β^-, γ)
- Energy of emission
- Half-life
- Radiation dose (essentially determined by the parameters above)

Radionuclides can be produced by

- **Nuclear reactors**
- **Particle accelerators (mainly cyclotrons)**

First practical application (as radiotracer)

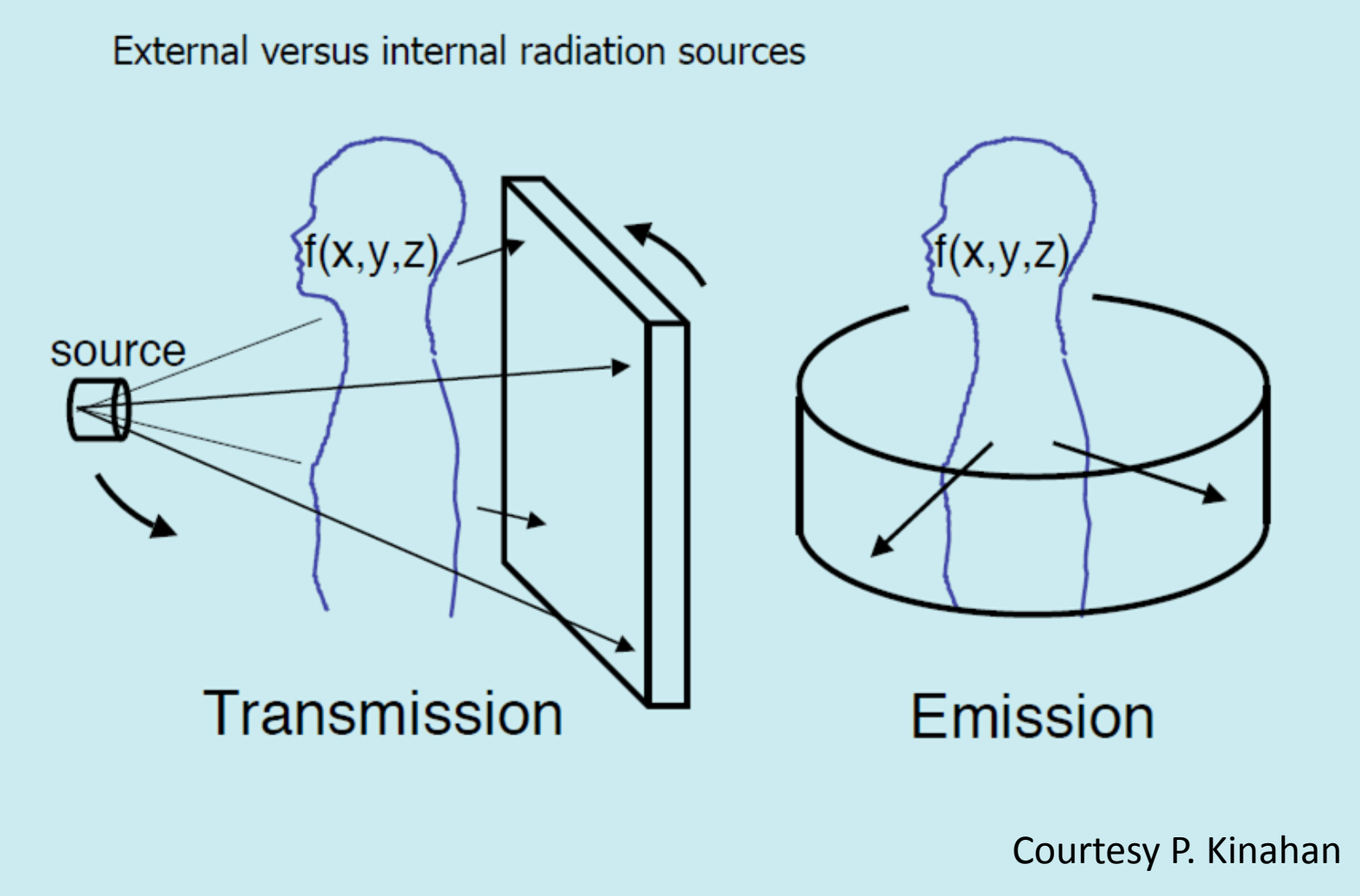
The **first practical application of a radioisotope** (as *radiotracer*) was made by G. de Hevesy (a young Hungarian student working with naturally radioactive materials) in Manchester in **1911** (99 years ago!)

In 1924 de Hevesy, who had become a physician, used radioactive isotopes of lead as tracers in bone studies.

Brief historical development

- 1932: the invention of the cyclotron by E. Lawrence makes it possible to produce radioactive isotopes of a number of biologically important elements
- 1937: Hamilton and Stone use radioactive sodium clinically
- 1938: Hertz, Roberts and Evans use radioactive iodine in the study of thyroid physiology
- 1939: J.H. Lawrence, Scott and Tuttle study leukemia with radioactive phosphorus
- 1940: Hamilton and Soley perform studies of iodine metabolism by the thyroid gland in situ by using radioiodine
- 1941: first medical cyclotron installed at Washington University, St Louis, for the production of radioactive isotopes of phosphorus, iron, arsenic and sulphur
- After WWII: following the development of the fission process, most radioisotopes of medical interest begin to be produced in nuclear reactors
- 1951: Cassen et al. develop the concept of the rectilinear scanner
- 1957: the $^{99}Mo/^{99m}Tc$ generator system is developed by the Brookhaven National Laboratory
- 1958: production of the first gamma camera by Anger, later modified to what is now known as the Anger scintillation camera, still in use today

Emission versus transmission imaging



Courtesy P. Kinahan

Fundamental decay equation

$$N(t) = N_0 e^{-\lambda t} \text{ or } A(t) = A(0) e^{-\lambda t}$$

where:

$N(t)$ = number of radioactive atoms at time t

$A(t)$ = activity at time t

N_0 = initial number of radioactive atoms at $t=0$

$A(0)$ = initial activity at $t=0$

e = base of natural logarithm = 2.71828…

λ = decay constant = $1/\tau = \ln 2/T_{1/2} = 0.693/T_{1/2}$

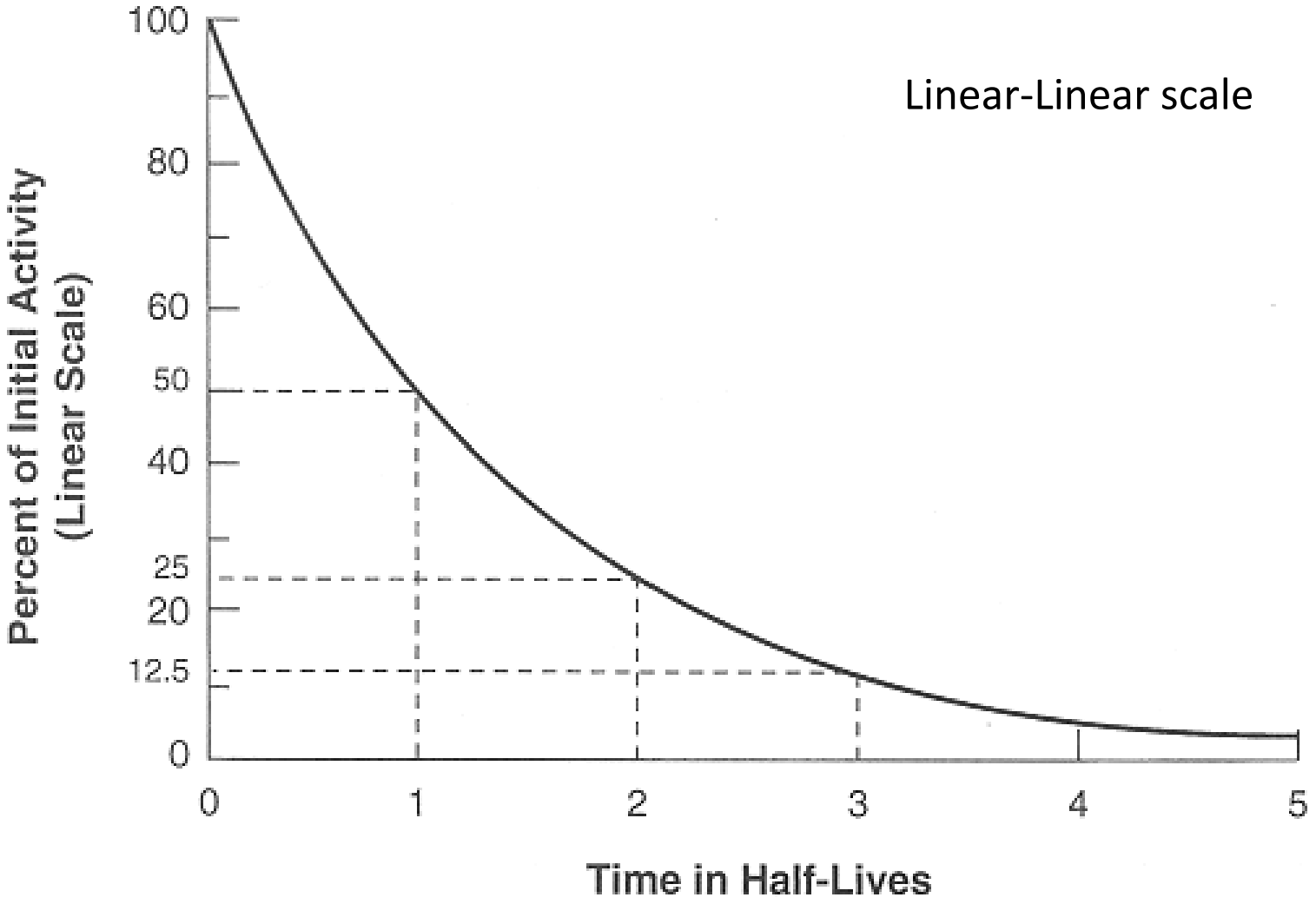
t = time

and remembering that:

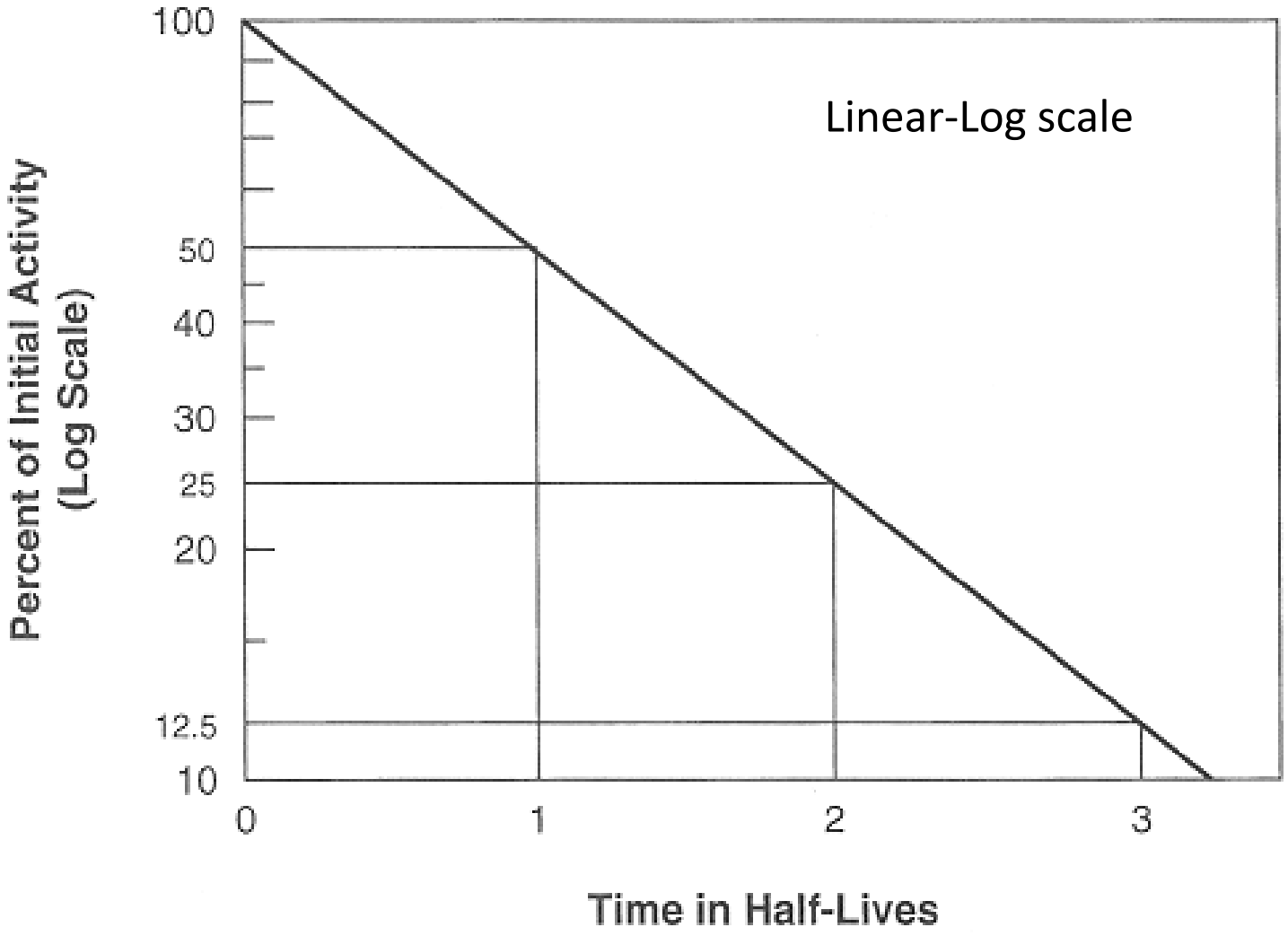
$-dN/dt = \lambda N$

$A = \lambda N$

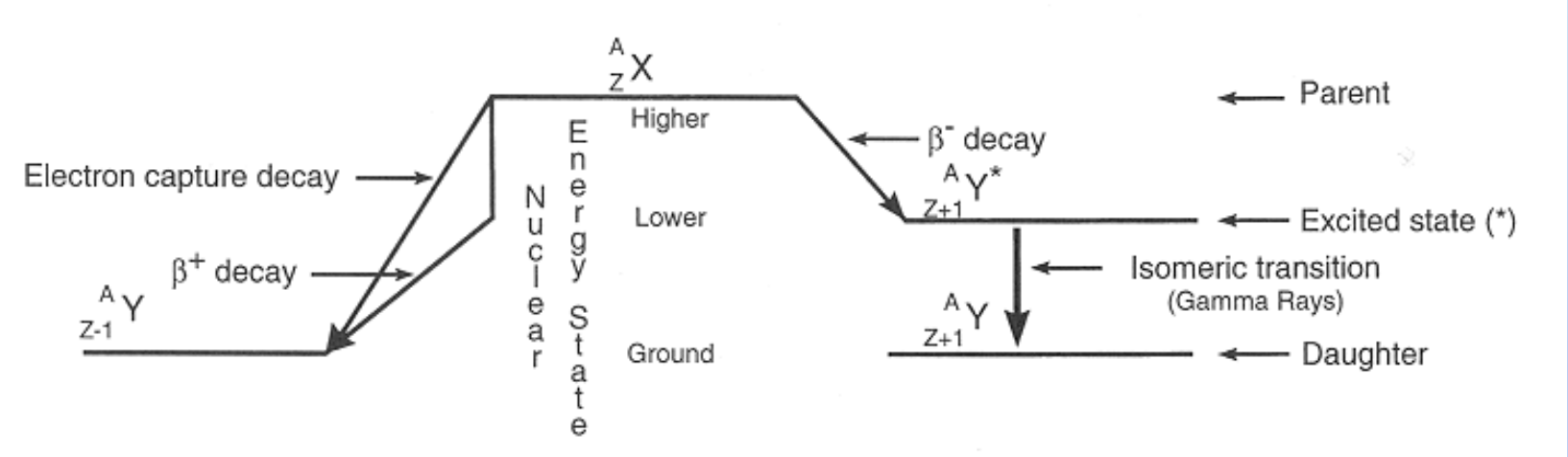
Fundamental decay equation



Fundamental decay equation

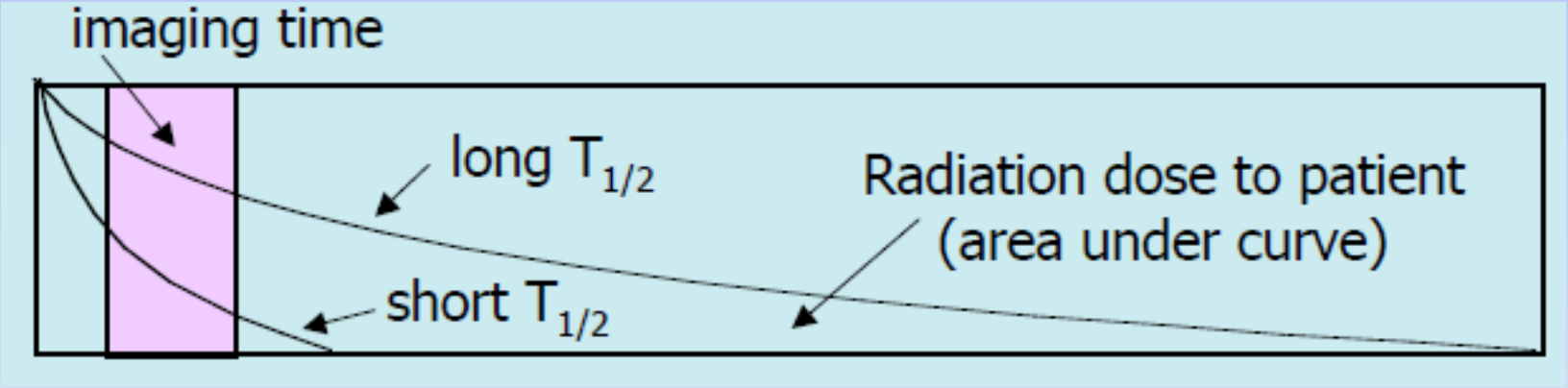


Generalized decay scheme



The “ideal” diagnostics radiopharmaceutical

a) Be readily available at a low cost
b) Be a pure gamma emitter, i.e. have no particle emission such as alphas and betas (these particles contribute radiation dose to the patient while not providing any diagnostic information)
c) Have a short effective biological half-life (so that it is eliminated from the body as quickly as possible)
d) Have a high target to non-target ratio so that the resulting image has a high contrast (the object has much more activity than the background)
e) Follow or be trapped by the metabolic process of interest



$$A(t) = A(0)e^{-t(\ln(2)/T_{1/2})}$$

Production methods

All radionuclides commonly administered to patients in nuclear medicine are artificially produced

Three production routes:

- (n, γ) reactions (**nuclear reactor**): the resulting nuclide has the same chemical properties as those of the target nuclide
- Fission (**nuclear reactor**) followed by separation
- Charged particle induced reaction (**cyclotron**): the resulting nucleus is usually that of a different element

Production methods

Characteristic	Production method			
	Cyclotron	Nuclear reactor (fission)	Nuclear reactor (neutron activation)	Radionuclide generator
Bombarding particle	Proton, deuteron, triton, alpha	Neutron	Neutron	Production by decay of parent
Product	Neutron poor	Neutron excess	Neutron excess	Neutron poor or excess
Typical decay pathway	Positron emission, electron capture	Beta-minus	Beta-minus	Several modes
Typically carrier free	Yes	Yes	No	Yes
High specific activity	Yes	Yes	No	Yes
Relative cost	High	Low	Low	Low (^{99m}Tc) High (^{81m}Kr)
Radionuclides for nuclear medicine applications	^{201}Tl, ^{123}I, ^{67}Ga, ^{111}In, ^{18}F, ^{15}O, ^{57}Co	^{99}Mo, ^{131}I, ^{133}Xe	^{32}P, ^{51}Cr, ^{125}I, ^{89}Sr, ^{153}Sm	^{99m}Tc, ^{81m}Kr, ^{68}Ga, ^{82}Rb

Reactor versus accelerator produced radionuclides

Reactor produced radionuclides

The fission process is a source of a number of widely used radioisotopes (^{90}Sr, ^{99}Mo, ^{131}I and ^{133}Xe)

Major drawbacks:

- large quantities of radioactive waste material generated
- large amounts of radionuclides produced, including other radioisotopes of the desired species (no carrier free, low specific activity)

Accelerator produced radionuclides

Advantages

- more favorable decay characteristics (particle emission, half-life, gamma rays, etc.) in comparison with reactor produced radioisotopes.
- high specific activities can be obtained through charged particle induced reactions, e.g. (p,xn) and (p,*a*), which result in the product being a different element than the target
- fewer radioisotopic impurities are produce by selecting the energy window for irradiation
- small amount of radioactive waste generated
- access to accelerators is much easier than to reactors

Major drawback: in some cases an enriched (and expensive) target material must be used

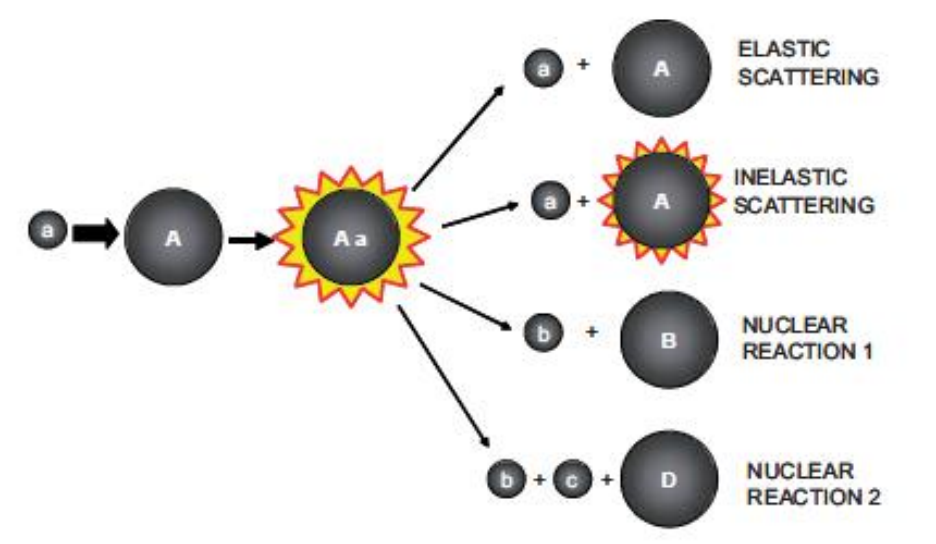
Accelerator production of radionuclides

- The binding energy of nucleons in the nucleus is 8 MeV on average
- If the energy of the incoming projectile is > 8 MeV, the resulting reaction will cause other particles to be ejected from the target nucleus
- By carefully selecting the target nucleus, the bombarding particle and its energy, it is possible to produce a specific radionuclide

The **specific activity** is a measure of the number of radioactive atoms or molecules as compared with the total number of those atoms or molecules present in the sample (Bq/g or Bq/mol). If the only atoms present in the sample are those of the radionuclide, then the sample is referred to as **carrier free**

The essential steps in accelerator r.n. production

1. Acceleration of charged particles in a cyclotron
2. Beam transport (*or not*) to the irradiation station via a transfer line
3. Irradiation of target (solid, liquid, gas) – *internal or external*
4. Nuclear reaction occurring in the target (e.g. $^{A}X_{Z}(p,n)^{A}Y_{z-1}$)
5. Target processing and material recovering
6. Labeling of radiopharmaceuticals and quality control



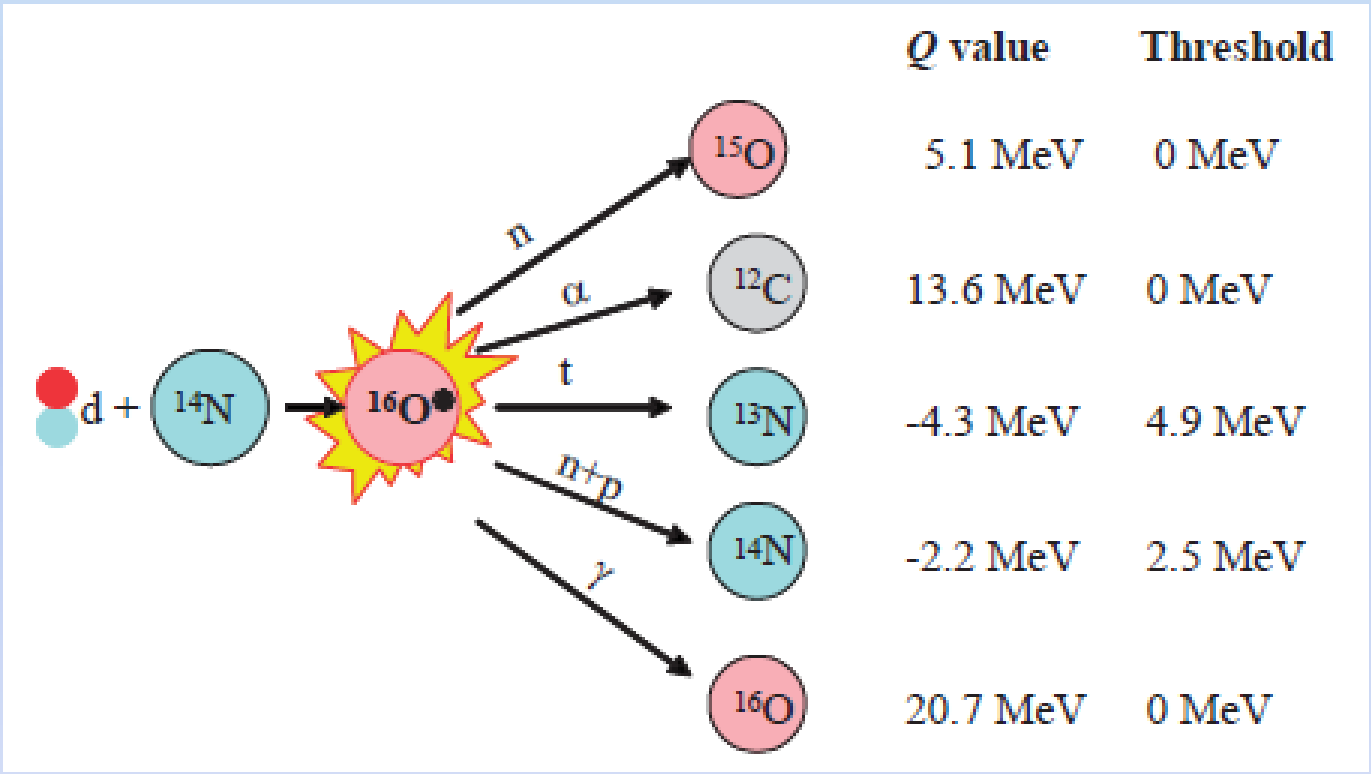
a = bombarding particle

b, c = emitted particles

A, B, D = nuclei

Example: d + $^{14}N \Rightarrow {}^{16}O^*$

Q values and thresholds of nuclear decomposition for the reaction of a deuteron with a ^{14}N nucleus after forming the compound nucleus ^{16}O



Production rate and cross section

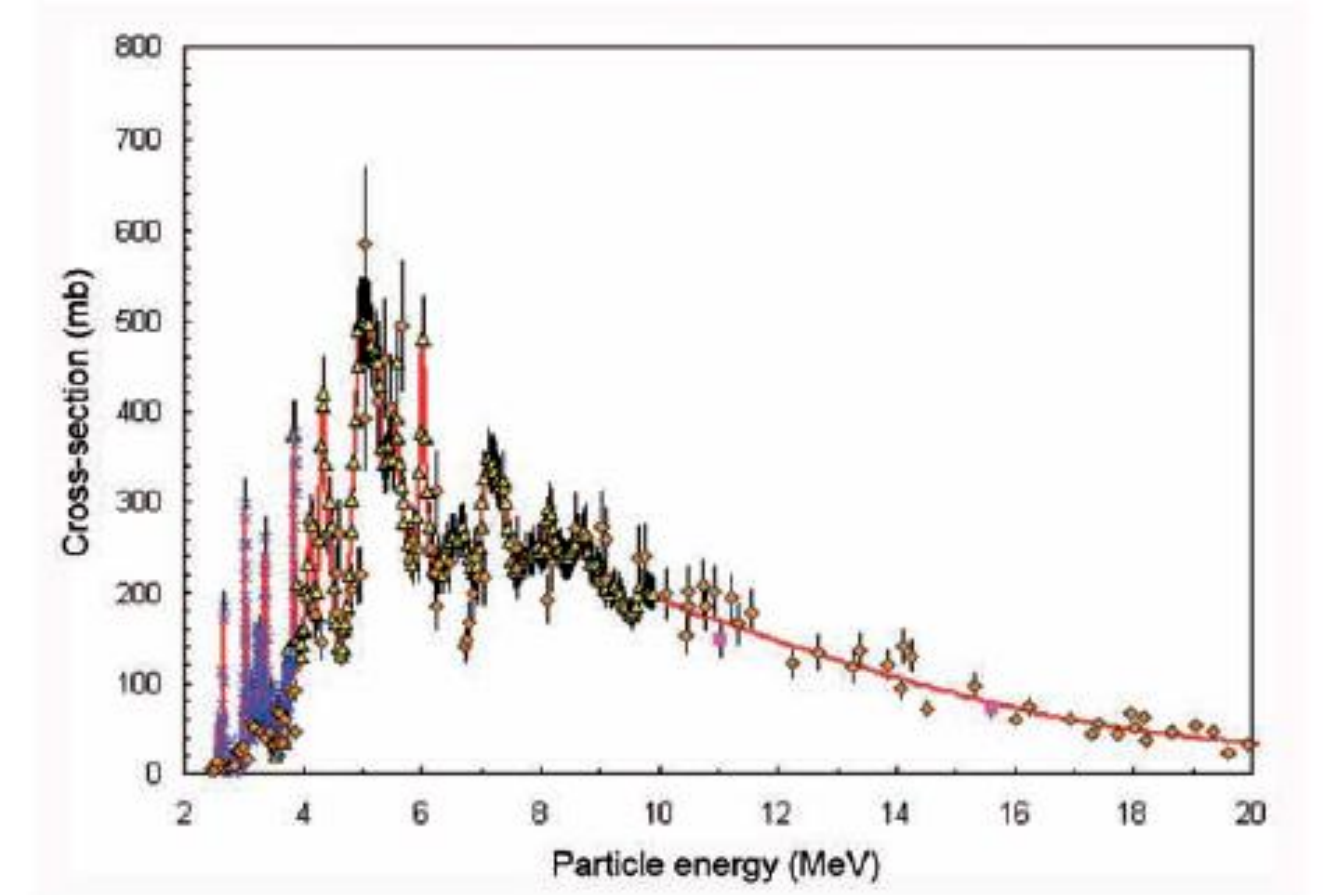
$$\frac{dn}{dt} = R = nI(1-e^{-\lambda t})\int_{Es}^{E0}\frac{\sigma(E)}{dE/dx}dE$$

R = the number of nuclei formed per second
n = the target thickness in nuclei per cm^2
I = incident particle flux per second (related to the beam current)
λ = decay constant = $(\ln 2)/T_{1/2}$
t = irradiation time in seconds
σ = reaction cross-section, or probability of interaction (cm^2), function of E
E = energy of the incident particles
x = distance travelled by the particle

and the integral is from the initial to final energy of the incident particle along its path

Energy dependence of the cross section σ

Excitation function of the $^{18}O(p,n)^{18}F$ reaction



Experimental measurement of cross section σ

$$R_i = Inx\sigma_i$$

where

R_i = number of processes of type i in the target per unit time
I = number of incident particles per unit time
n = number of target nuclei per cm^3 of target = **$\rho N_A/A$**
σ_i = cross-section for the specified process in cm^2
x = the target thickness in cm

and assuming that

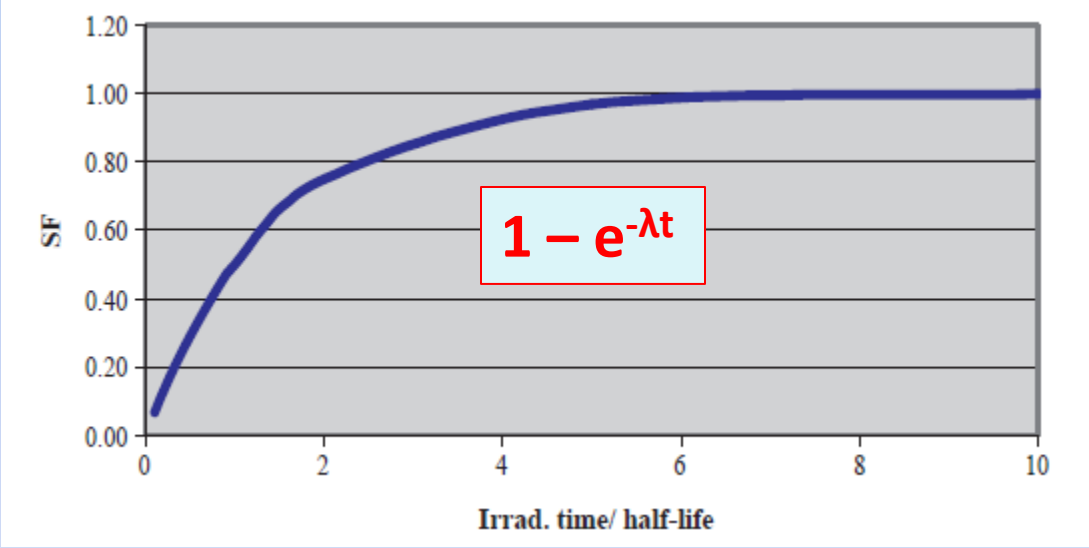
1. The beam current is constant over the course of the irradiation
2. The target nuclei are uniformly distributed in the target material
3. The cross-section is independent of energy over the energy range used

Saturation factor, SF = $1 - e^{-\lambda t}$

T_{irr} = 1 half-life results in a saturation of 50%
2 half-lives → 75%
3 half-lives → 90%

The practical production limits of a given radionuclide are determined by the half-life of the isotope, e.g.

^{15}O, $T_{1/2}$ = 2 minutes
^{18}F, $T_{1/2}$ = almost 2 hours



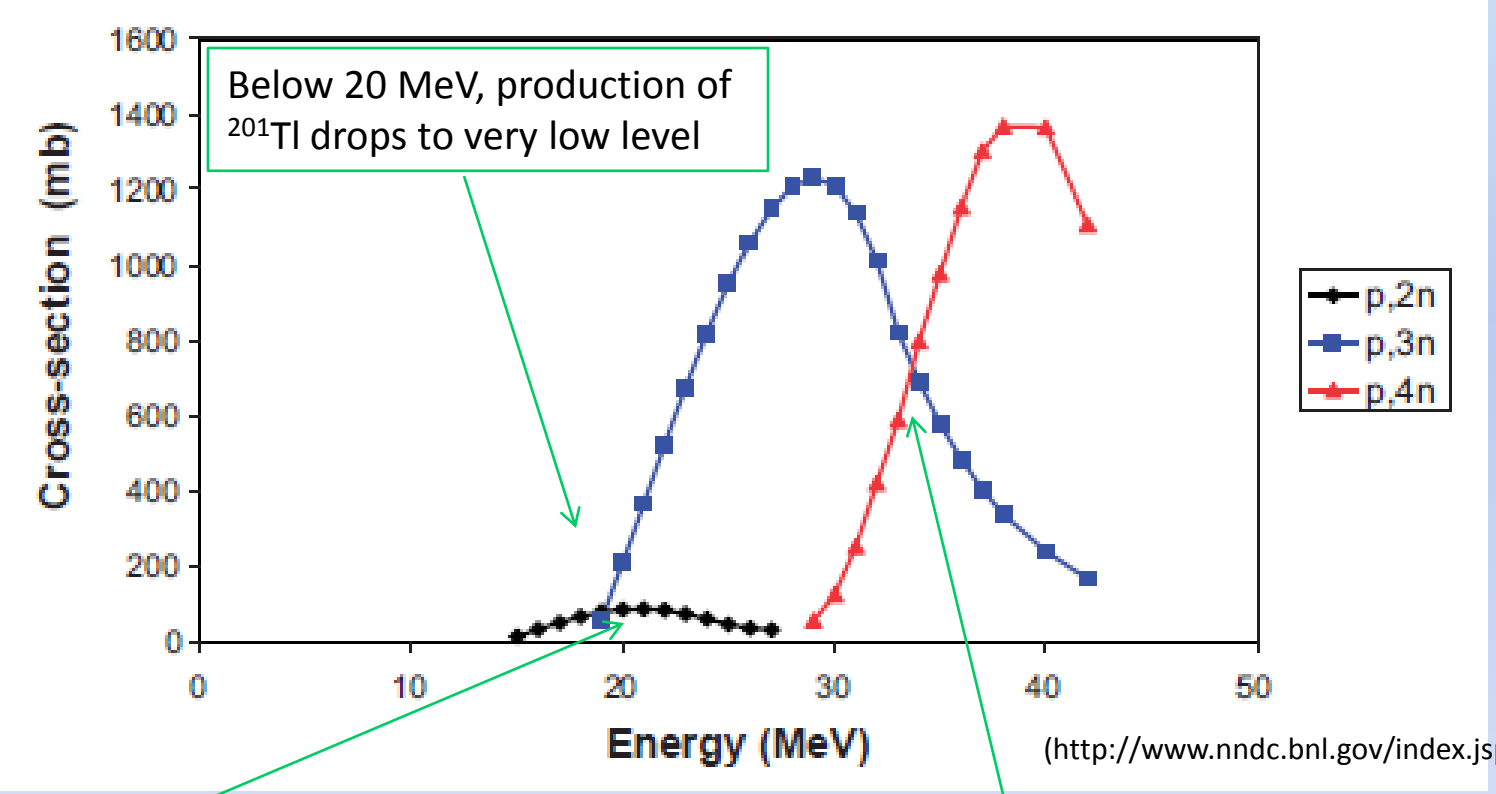
For ***long lived species***, the production rates are usually expressed in terms of integrated dose or total beam flux (*μA·h)*

Competing nuclear reactions, example of ^{201}Tl

The nuclear reaction used for production of ^{201}Tl is the ^{203}Tl(p,3n)^{201}Pb

^{201}Pb ($T_{1/2}$ = 9.33 h) ⟶ ^{201}Tl ($T_{1/2}$ = 76.03 h)

Cross-section versus energy plot for the ^{203}Tl(p,2n)^{202}Pb, ^{203}Tl(p,3n)^{201}Pb and ^{203}Tl(p,4n)^{200}Pb reactions



Targets

Internal (beam is not extracted from the cyclotron)
External (extracted beam + beam transport to target)

Simultaneous irradiation of more than one target (H^- cyclotrons)

The target can be

- **Solid**
- **Liquid**
- **Gaseous**

Principal constraints on gas targets

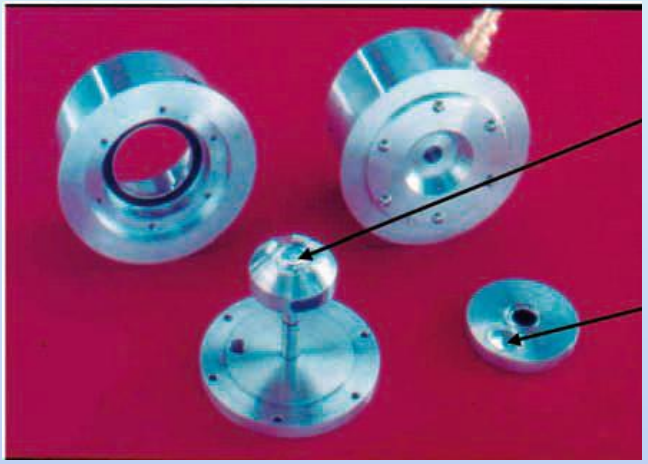
- removal of heat from the gas (gases are not very good heat conductors)
- the targets must be quite large in comparison with solid or liquid targets in order to hold the necessary amount of material.

Targets

^{18}O water target

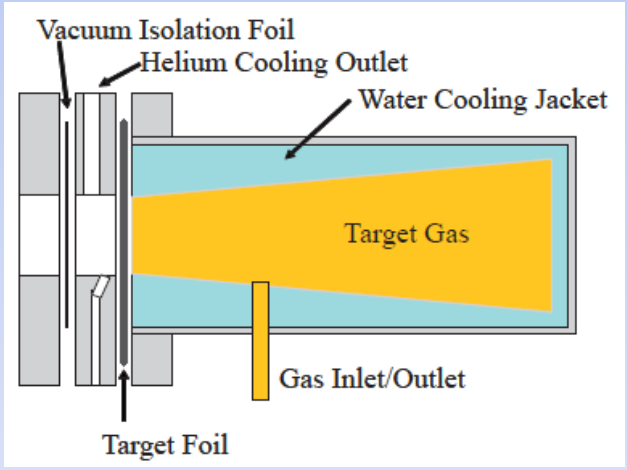
Liquid

Solid powder target used at BNL

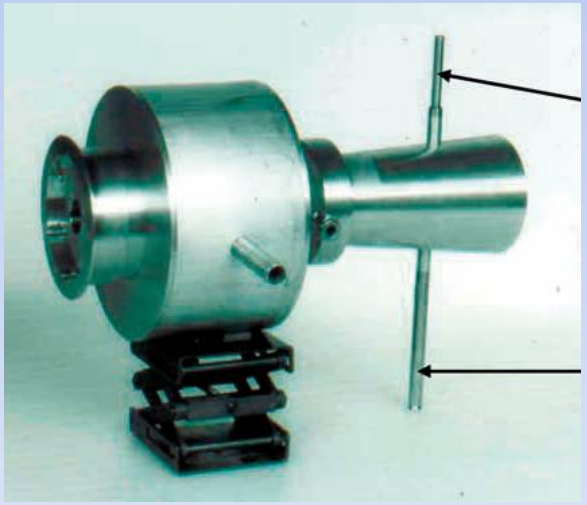


Solid

Gaseous



Gas target used for production of ^{123}I from ^{124}Xe



Targets

A major concern in target design is the generation and dissipation of heat during irradiation ⇒ target cooling

Efficient **target cooling**:

— ensures that the target material will remain in the target

— allows the target to be irradiated at higher beam currents, which in turn allows production of more radioisotopes in a given time

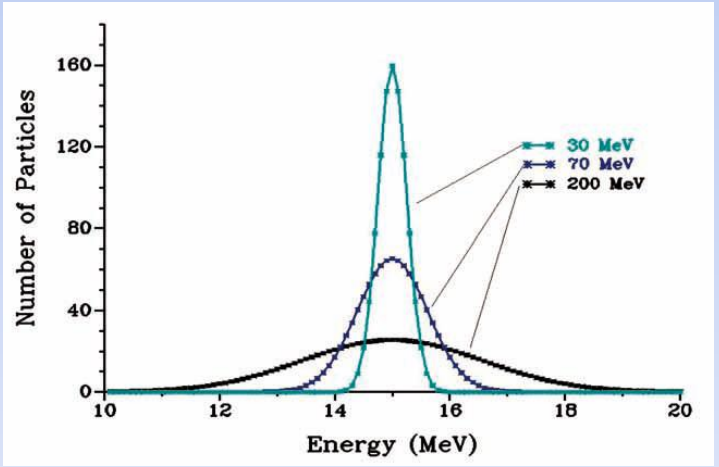
Factors to be considered in relation to **thermodynamics** include:

— Interactions of charged particles with matter

— Stopping power and ranges

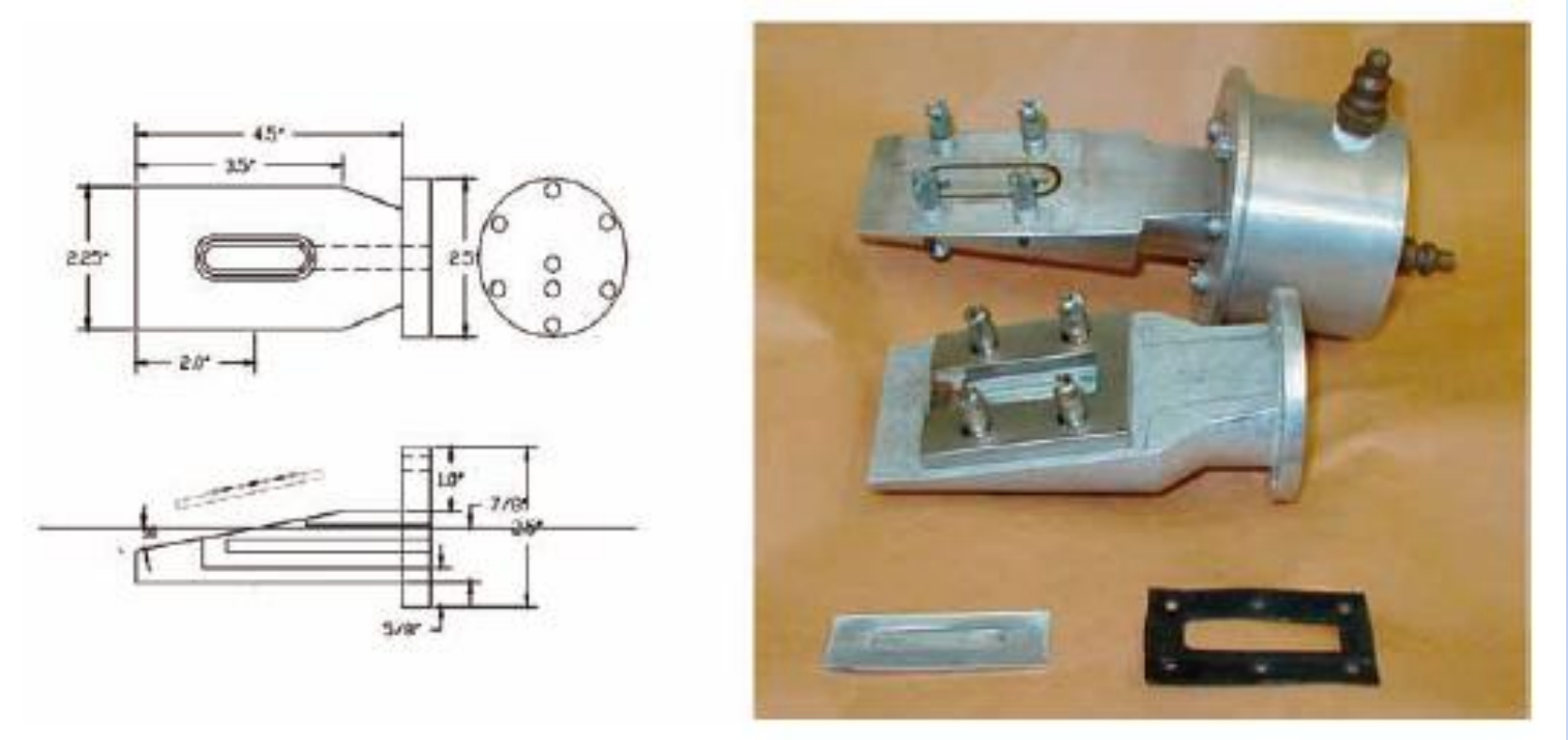
— Energy straggling

— Small angle multiple scattering



Distribution of beam energy when protons are degraded from an initial energy of 200, 70 or 30 MeV to a final energy of 15 MeV

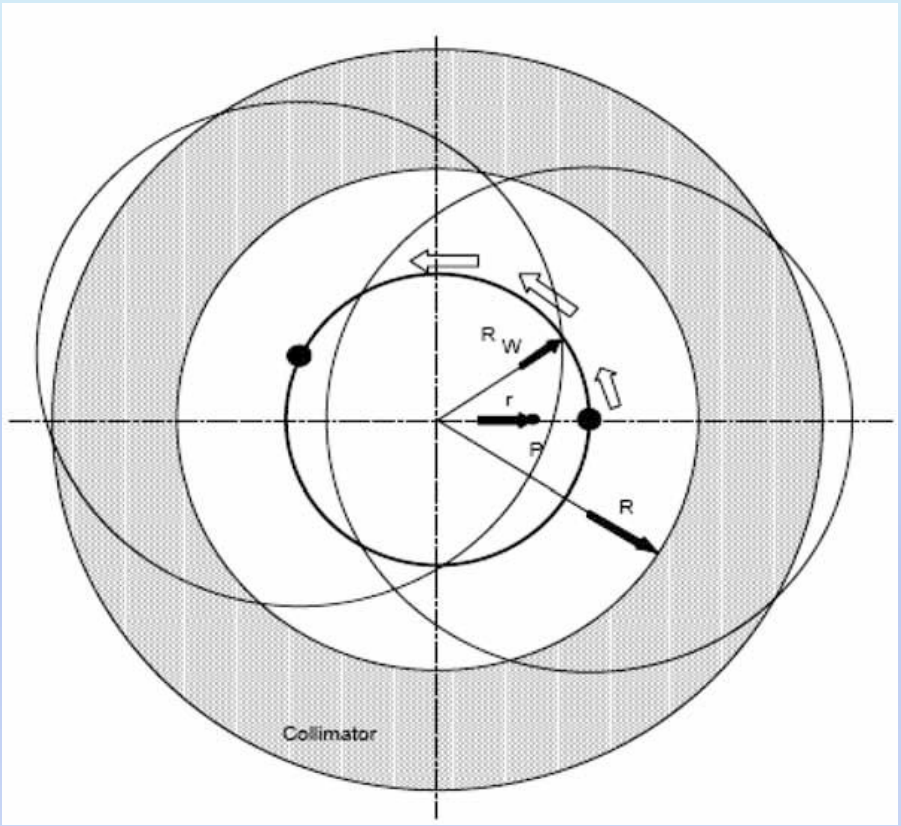
Inclined target for better heat dissipation

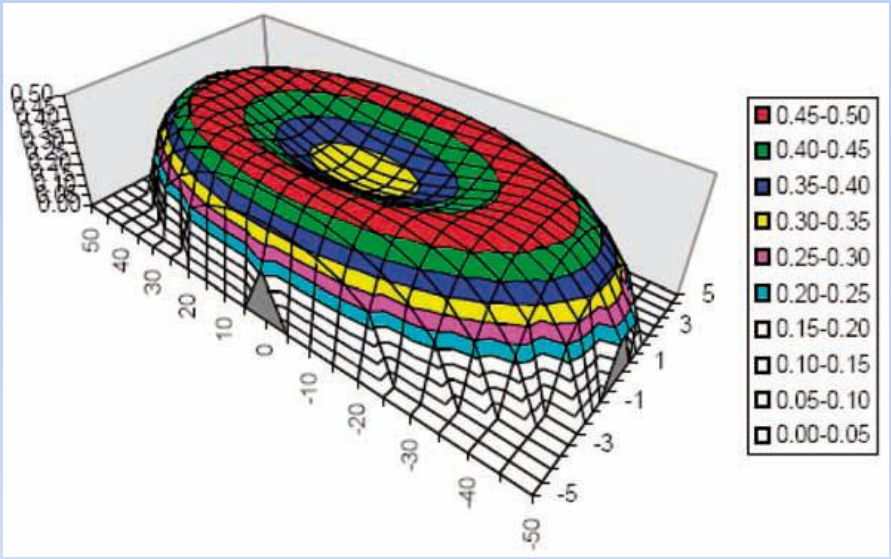


Example of an inclined plane external target used for solid materials either pressed or melted in the depression in the target plane

Circular wobbling of the beam during irradiation

R_w = radius of wobbler circle (mm)
R = radius of cylindrical collimator (mm)
r = distance

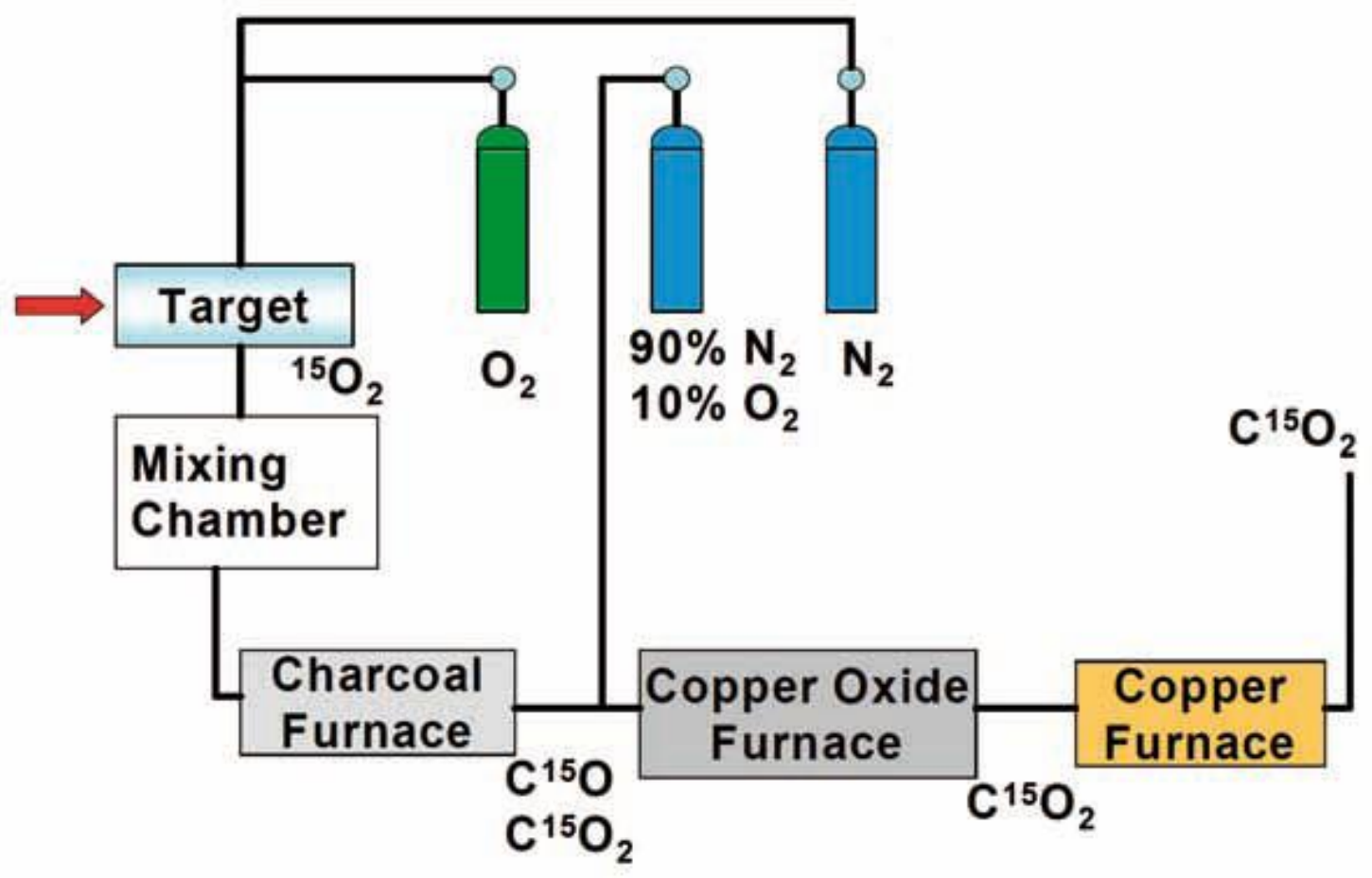




Current density distribution for a ‘wobbled’ beam

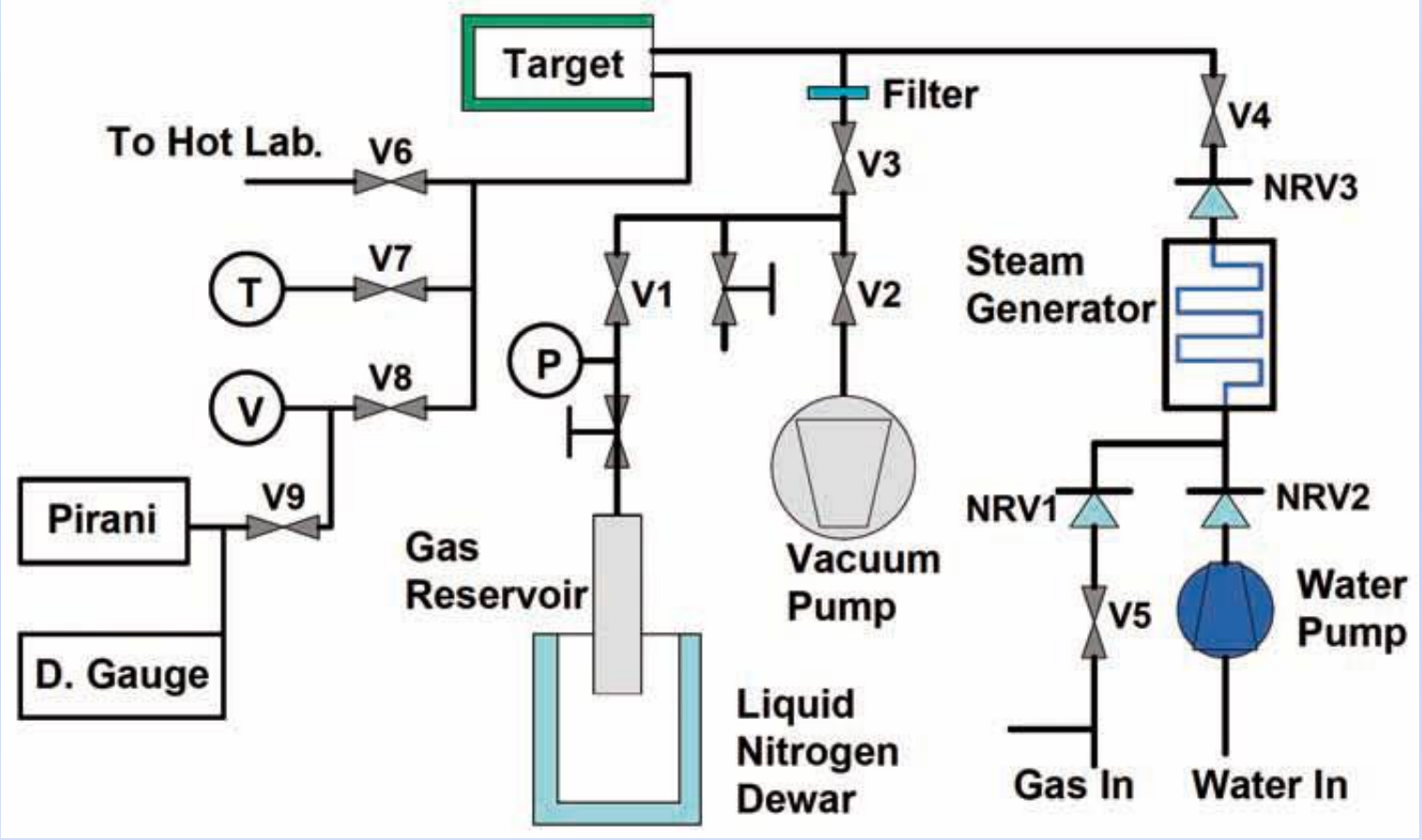
Target processing and material recovering

Schematic diagram of a processing system for the production of $[^{15}O]CO_2$



Target processing and material recovering

Example of a gas handling system for production of ^{81m}Kr. Vs and Ps are mechanical pressure gauges and NRVs are one way valves to prevent backflow

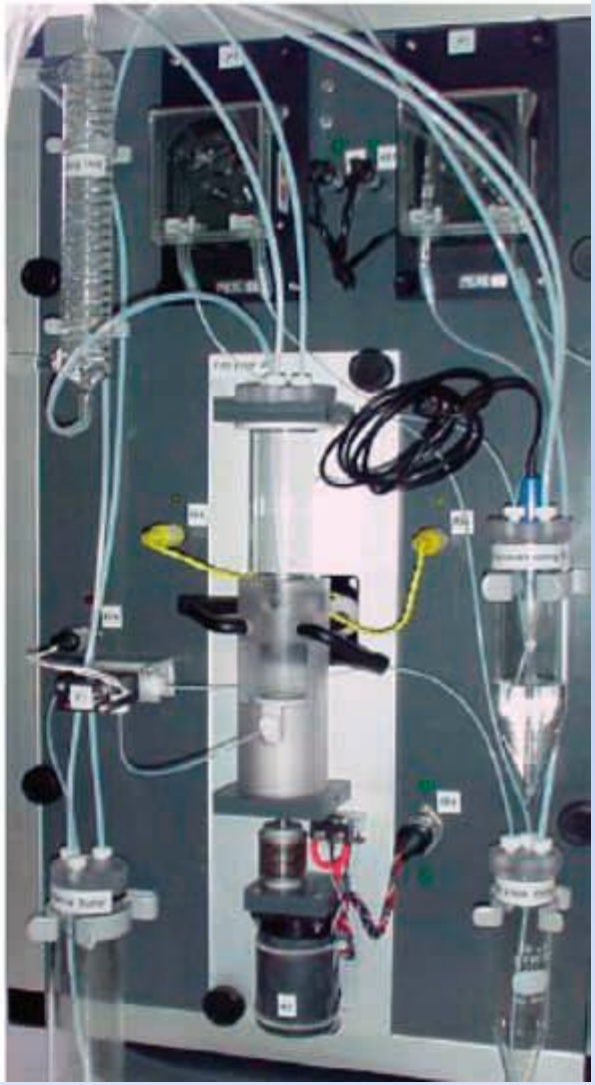


Target processing and material recovering

Manifolds used for: (a) precipitation of ^{201}Pb and (b) filtration of the final solution.

(a)

(b)



Most common radionuclides for medical use versus the proton energy required for their production

Proton energy (MeV)	Radionuclide easily produced
0 – 10	^{18}F, ^{15}O
11 – 16	^{11}C, ^{18}F, ^{13}N, ^{15}O, ^{22}Na, ^{48}V
17 – 30	^{124}I, ^{123}I, ^{67}Ga, ^{111}In, ^{11}C, ^{18}F, ^{13}N, ^{15}O, ^{22}Na, ^{48}V, ^{201}Tl
30+	^{124}I, ^{123}I, ^{67}Ga, ^{111}In, ^{11}C, ^{18}F, ^{13}N, ^{15}O, ^{82}Sr, ^{68}Ge, ^{22}Na, ^{48}V

Nuclear reactions employed to produce some commonly used imaging radionuclides (1)

Radionuclide	Use	Half-life	Reaction	Energy (MeV)
^{99m}Tc	SPECT imaging	6 h	^{100}Mo(p,2n)	30
^{123}I	SPECT imaging	13.1 h	^{124}Xe(p,n)^{123}Cs ^{124}Xe(p,pn)^{123}Xe ^{124}Xe(p,2pn)^{123}I ^{123}Te(p,n)^{123}I ^{124}Te(p,2n)^{123}I	27 15 25
^{201}Tl	SPECT imaging	73.1 h	^{203}Tl(p,3n)^{201}Pb $\rightarrow$ ^{201}Tl	29
^{11}C	PET imaging	20.3 min	^{14}N(p,α) ^{11}B(p,n)	11–19 10
^{13}N	PET imaging	9.97 min	^{16}O(p,α) ^{13}C(p,n)	19 11

Nuclear reactions employed to produce some commonly used imaging radionuclides (2)

Radionuclide	Use	Half-life	Reaction	Energy (MeV)
^{15}O	PET imaging	2.03 min	$^{15}N(p,n)$ $^{14}N(d,2n)$ $^{16}O(p,pn)$	11 6 > 26
^{18}F	PET imaging	110 min	$^{18}O(p,n)$ $^{20}Ne(d,\alpha)$ $^{nat}Ne(p,X)$	11-17 8-14 40
^{64}Cu	PET imaging and radiotherapy	12.7 h	$^{64}Ni(p,n)$ $^{68}Zn(p,\alpha n)$ $^{nat}Zn(d,\alpha xn)$ $^{nat}Zn(d,2pxn)$	15 30 19 19
^{124}I	PET imaging and radiotherapy	4.14 d	$^{124}Te(p,n)$ $^{125}Te(p,2n)$	13 25

Decay characteristics and max SA of some r.n.

Nuclide	Half-life (min)	Decay mode	Maximum SA (theoretical)
C-11	20.4	100% β^+	9220 Ci/μmol (341 TBq/μmol)
N-13	9.98	100% β^+	18 900 Ci/μmol (700 TBq/μmol)
O-15	2.03	100% β^+	91 730 Ci/μmol (3394 TBq/μmol)
F-18	109.8	97% β^+	1710 Ci/μmol (63.4 TBq/μmol)
Cu-62	9.74	99.7% β^+	19 310 Ci/μmol (714 TBq/μmol)
Ga-67	4696.8	100% EC	40 Ci/μmol (1.5 TBq/μmol)
Ga-68	68.0	89% β^+	2766 Ci/μmol (102 TBq/μmol)
Br-75	96.0	75.5% β^+	1960 Ci/μmol (73 TBq/μmol)
Rb-82	1.25	95.5% β^+	150 400 Ci/μmol (5565 TBq/μmol)
In-111	4048.8	100% EC	46 Ci/μmol (1.7 TBq/μmol)
I-122	3.62	75.8% β^+	51 950 Ci/μmol (1922 TBq/μmol)
I-123	793.4	100% EC	237 Ci/μmol (8.8 TBq/μmol)
I-124	6019.2	23.3% β^+	31 Ci/μmol (1.15 TBq/μmol)
Tl-201	4374.7	100% EC	42.6 Ci/μmol (1.58 TBq/μmol)

Radionuclides for therapy

- High LET decay products (Auger electrons, beta particles or alpha particles)
- Radionuclide linked to a biologically active molecule that can be directed to a tumour site
- Beta emitting radionuclides are neutron rich ⟹ they are in general produced in reactors
- Some of the radionuclides that have been proposed as possible radiotoxic tracers are:

Sc-47	Cu-64	Cu-67	Br-77	Y-90
Rh-105	Pd-103	Ag-111	I-124	Pr-142
Pm-149	Sm-153	Gd-159	Ho-166	Lu-177
Re-186/188	Ir-194	Pt-199	At-211	Bi-213

Radionuclides for therapy

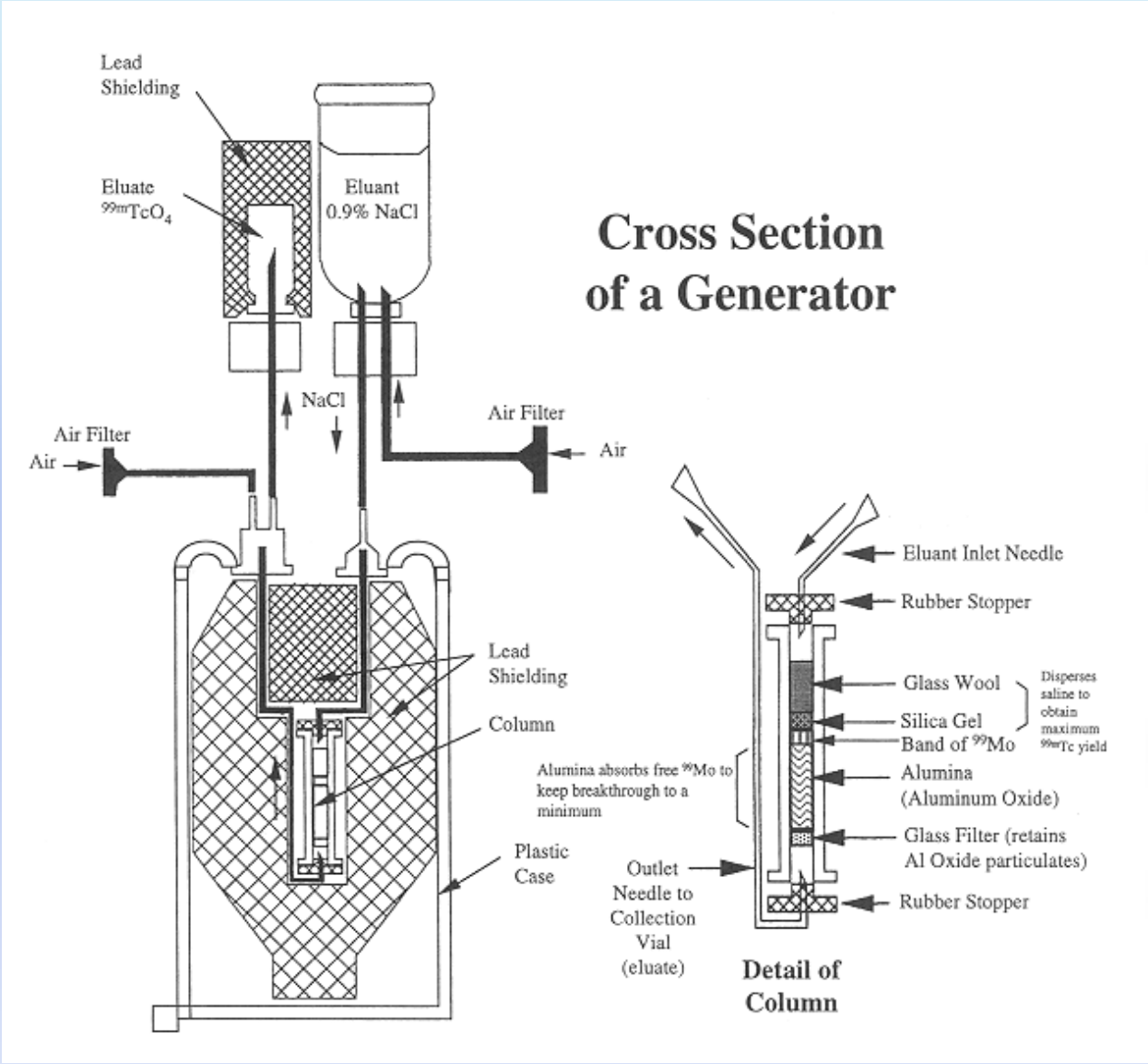
Charged particle production routes and decay modes for selected therapy isotopes

Radionuclide	Half-life	Decay mode	Reaction	Energy (MeV)
Br-77	2.4 d	Auger electrons	$^{75}As(\alpha, 2n)$	27
			$^{77}Se(p, n)$	13
			$^{78}Se(p, 2n)$	24
			$^{79,81}Br(p, xn)^{77}Kr$	45
			$^{nat}Mo(p, spall.)$	>200
Pd-103	17.5 d	Auger electrons	$^{103}Rh(p, n)$	19
			$^{nat}Ag(p, xn)$	>70
Re-186	90.6 h	β^-	$^{186}W(p, n)$	18
			$^{186}W(d, 2n)$	20
			$^{197}Au(p, spall.)$	>200
			$^{nat}Au(p, spall.)$	>200
			$^{nat}Ir(p, spall.)$	>200
At-211	7.2 h	α	$^{209}Bi(\alpha, 2n)$	28
			$^{209}Bi(^7Li, 5n)^{211}Rn$	60
			$^{232}Th(p, spall.)^{211}Rn$	>200

Radionuclide generators

- Technetium-99m (^{99m}Tc) has been the most important radionuclide used in nuclear medicine
- Short half-life (6 hours) makes it impractical to store even a weekly supply
- Supply problem overcome by obtaining parent ^{99}Mo, which has a longer half-life (67 hours) and continually produces ^{99m}Tc
- A system for holding the parent in such a way that the daughter can be easily separated for clinical use is called a *radionuclide generator*

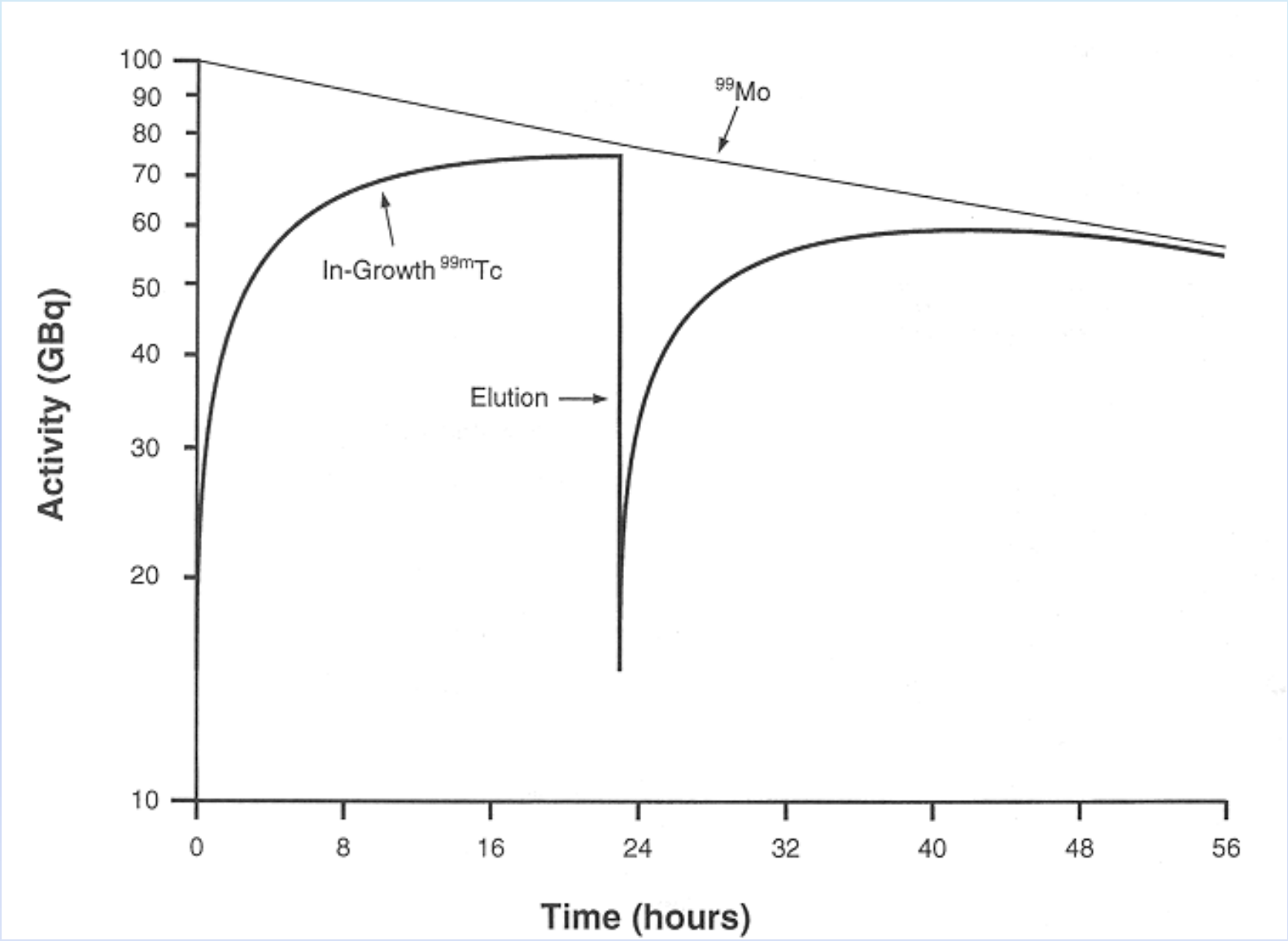
Radionuclide generators



Transient equilibrium

- Between elutions, the daughter (^{99m}Tc) builds up as the parent (^{99}Mo) continues to decay
- After approximately 23 hours the ^{99m}Tc activity reaches a maximum, at which time the production rate and the decay rate are equal and the parent and daughter are said to be in *transient equilibrium*
- Once transient equilibrium has been reached, the daughter activity decreases, with an apparent half-life equal to the half-life of the parent
- Transient equilibrium occurs when the half-life of the parent is greater than that of the daughter by a factor of about 10

Transient equilibrium



Radionuclide generators

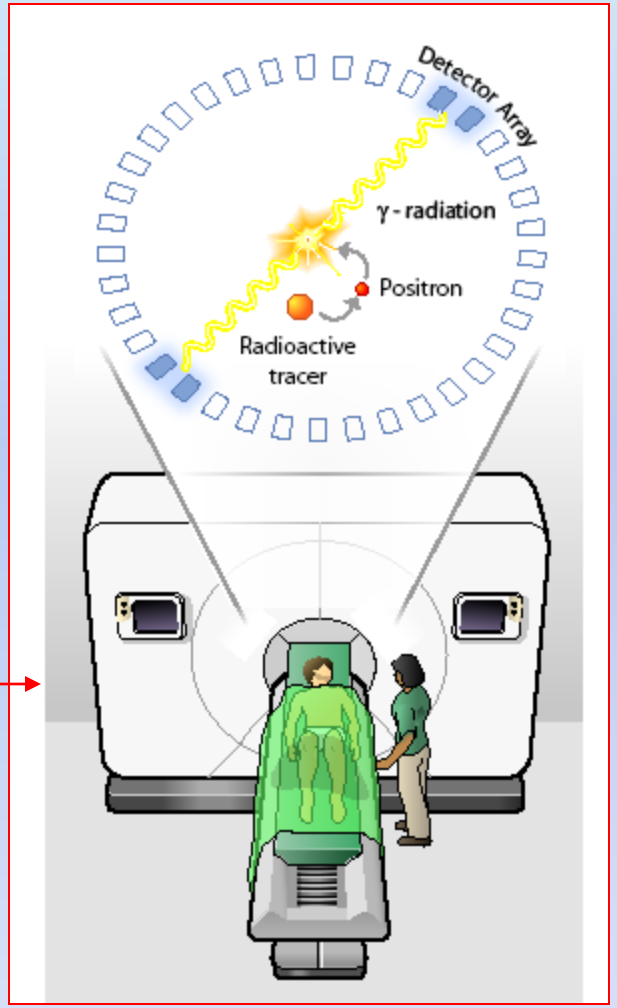
Parent	Decay mode → Half-life	Daughter	Time of maximal ingrowth (equilibrium)	Decay mode → Half-life	Decay product
Germanium 69 (^{69}Ge)	EC → 271 days	Gallium 68 (^{68}Ga)	~6.5 hr (S)	β^+, EC → 68 min	Zinc 68 (^{68}Zn), stable
Rubidium 81 (^{81}Rb)	β^+, EC → 4.5 hr	Krypton 81m (^{81m}Kr)	~80 sec (S)	IT → 13.5 sec	Krypton 81 ^{81}Kr[a]
Strontium 82 (^{82}St)	EC → 25.5 days	Rubidium 82 (^{82}Rb)	~7.5 min (S)	β^+ → 75 sec	Krypton 82 (^{82} Kr), stable
Molybdenum 99 (^{99}Mo)	β^- → 67 hr	Technetium 99m (^{99m}Tc)	~24 hr (T)	IT → 6 hr	Technetium 99 (^{99}Tc)[a]

Positron Emission Tomography (PET)

Cyclotron

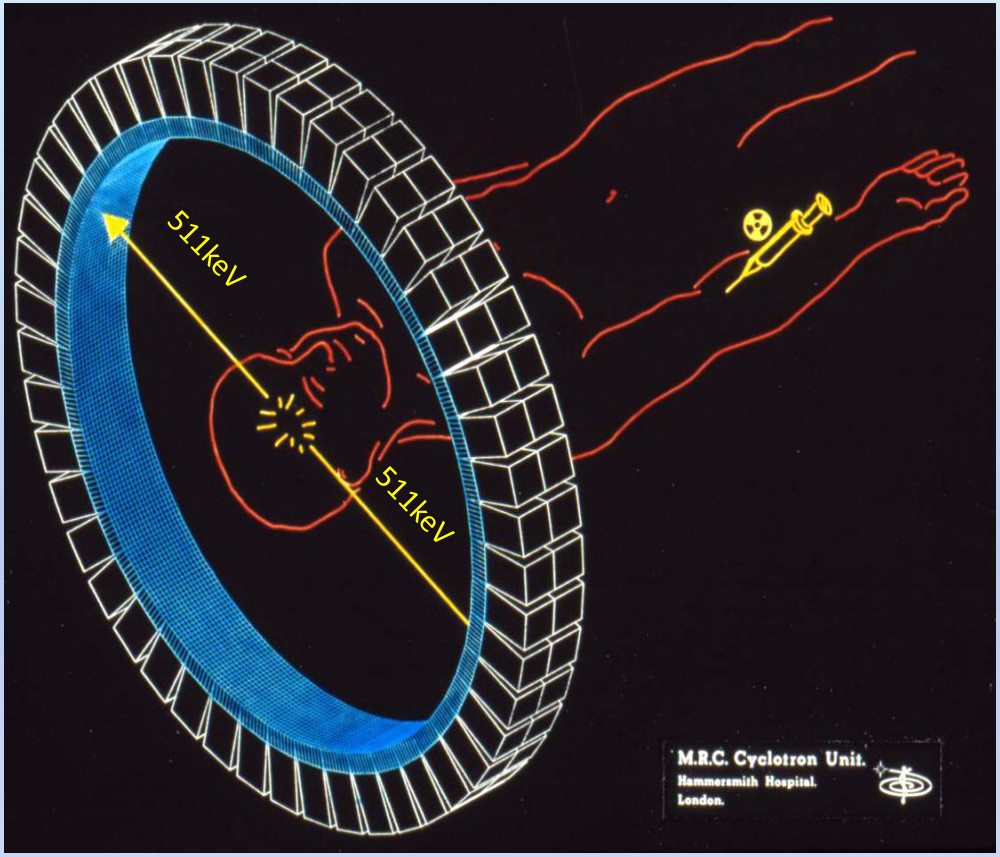
Radiochemistry

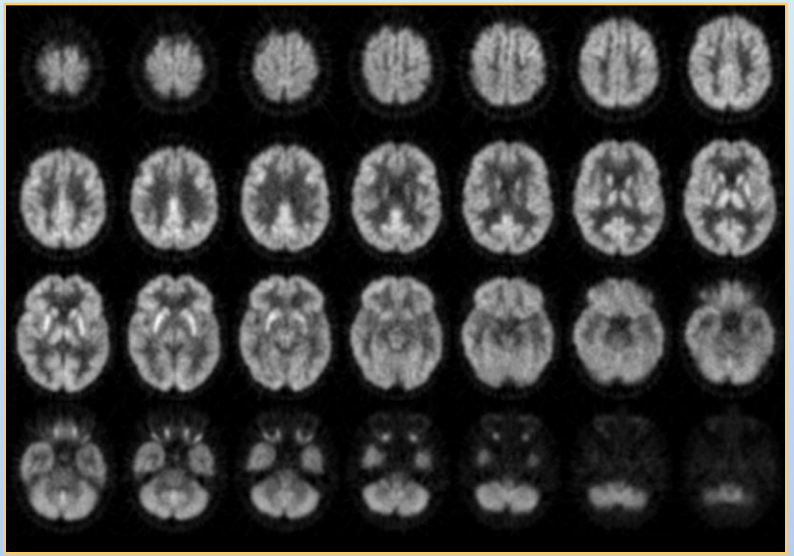
PET camera



J. Long, "The Science Creative Quarterly",scq.ubc.ca

Positron Emission Tomography (PET)





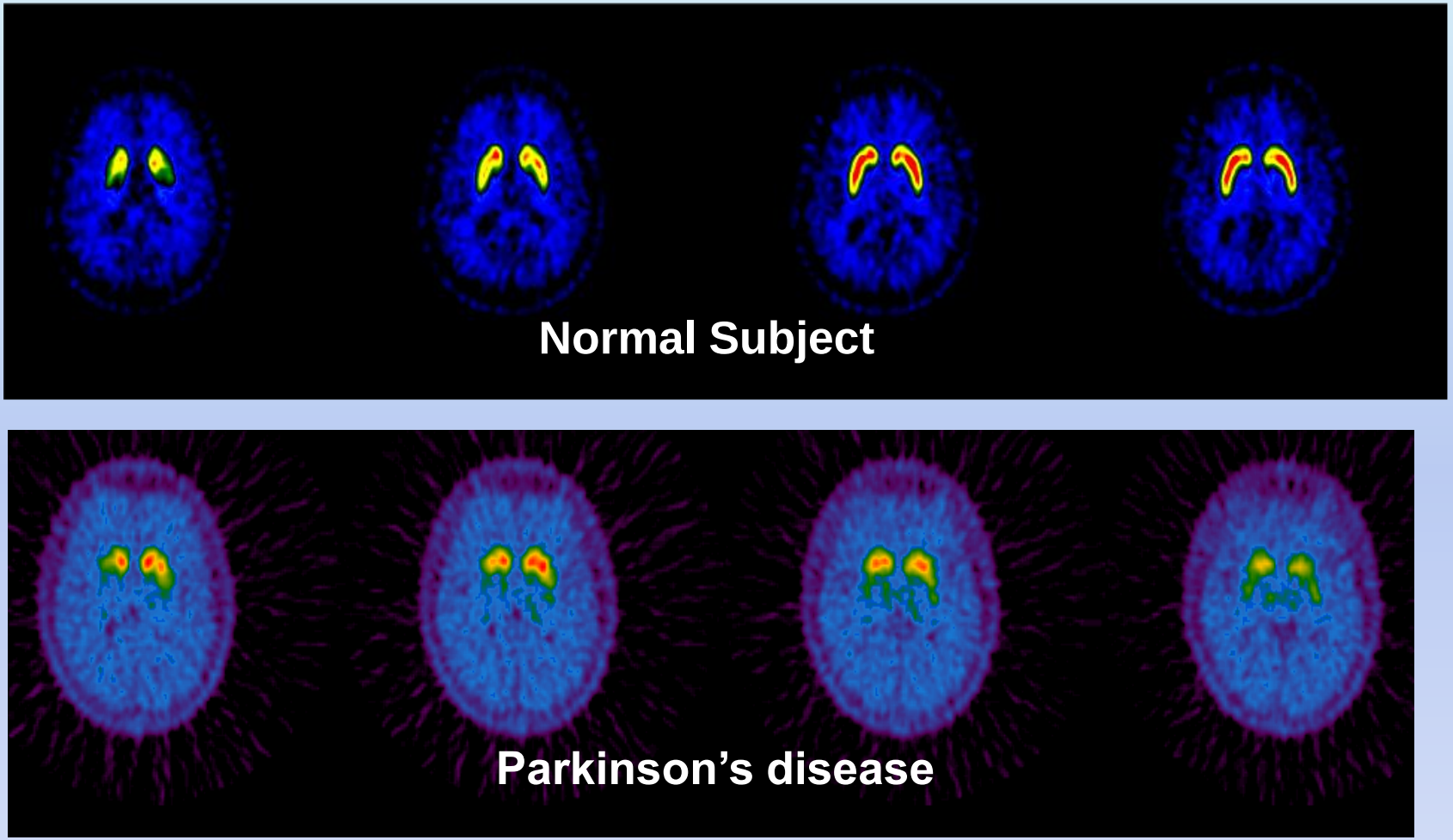
COVERAGE:
~ 15-20 cm

SPATIAL RESOLUTION:
~ 5 mm

SCAN TIME to cover an entire organ:
~ 5 min

CONTRAST RESOLUTION:
depends on the radiotracer

PET functional receptor imaging



[^{11}C] FE-CIT

Some textbooks

Cyclotron Produced Radionuclides: Principles and Practice, IAEA Technical Reports Series No. 465 (2008) (Downloadable from IAEA web site)

Targetry and Target Chemistry, Proceedings Publications, TRIUMF, Vancouver (http://trshare.triumf.ca/~buckley/wttc/proceedings.html)

CLARK, J.C., BUCKINGHAM, P.D., Short-Lived Radioactive Gases for Clinical Use, Butterworths, London (1975)