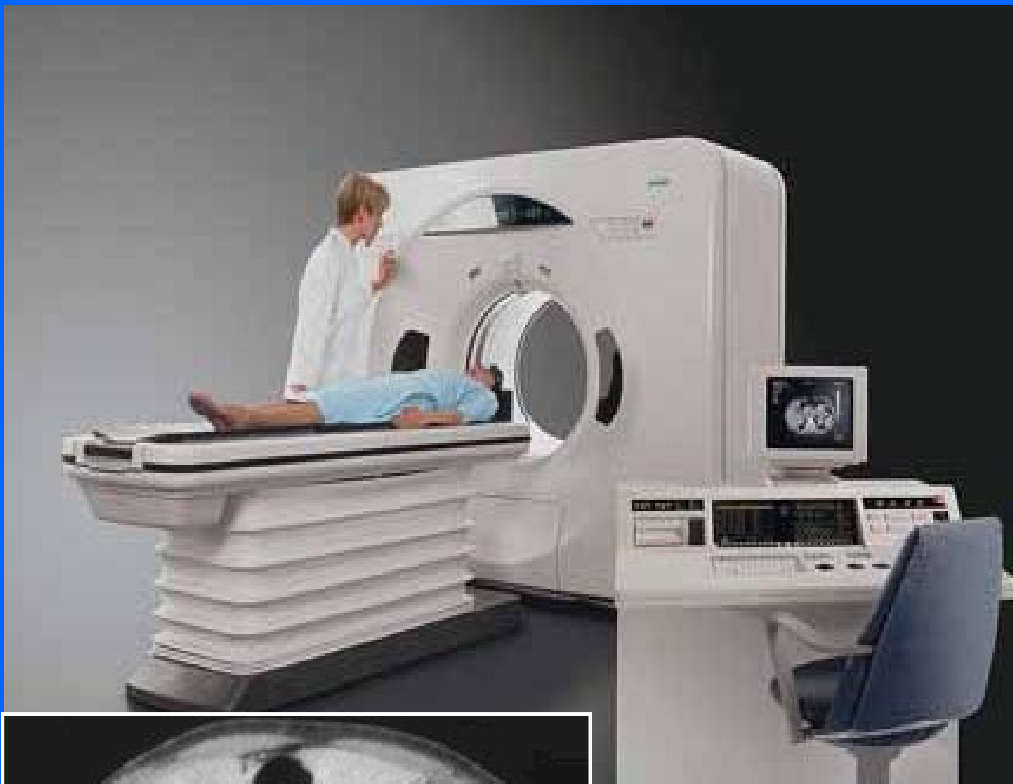
Outline

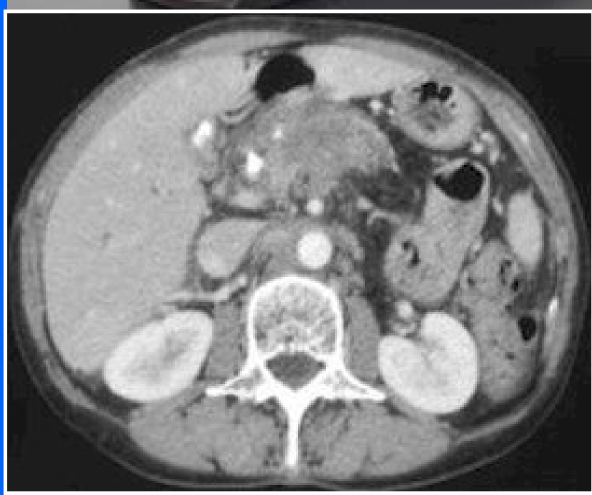
1. Introduction: a historical overview
2. Modern medical diagnostics
   - o CT, NMR, SPECT, PET
   - o 18-F production
   - o The SWAN project in Bern
3. Particle accelerators for medicine
4. Conventional radiation therapy
5. Basic principles of hadrontherpy
6. Present and future of hadrontherapy
7. A tour in a hadrontherapy centre
8. Specific topics in hadrontherapy

Medical imaging is essential in modern medicine

…and the high precision of hadrontherapy would be useless without it

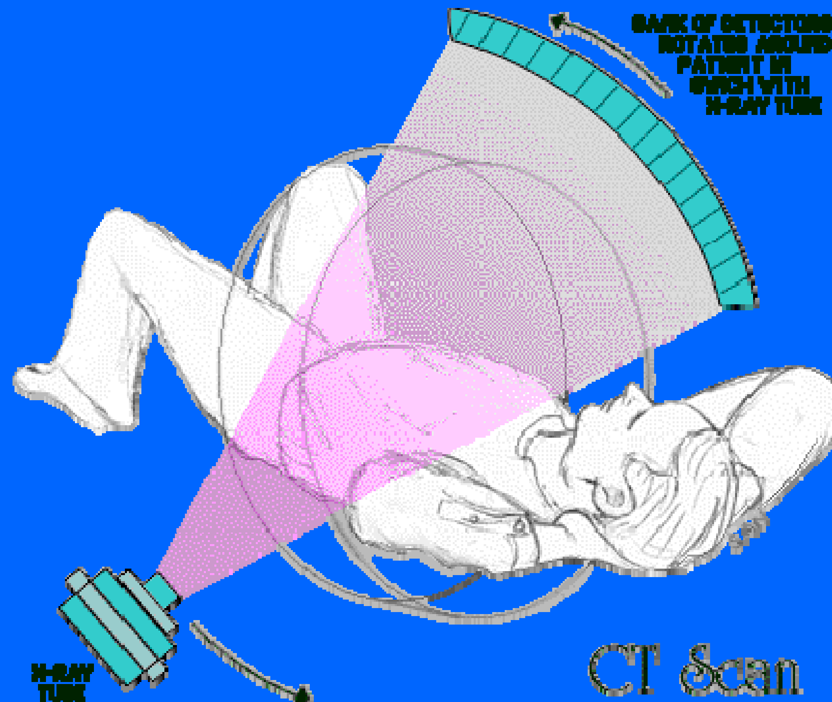
Diagnostics is essential!





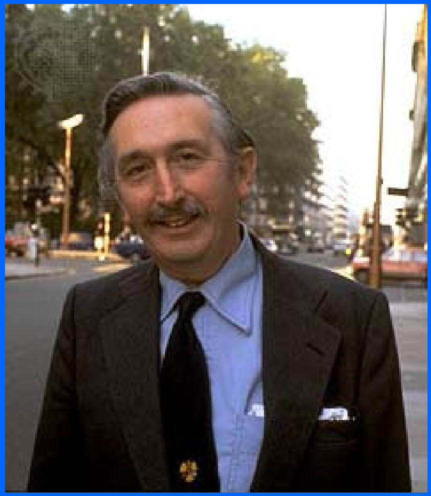
Abdomen

Computed Tomography (CT)



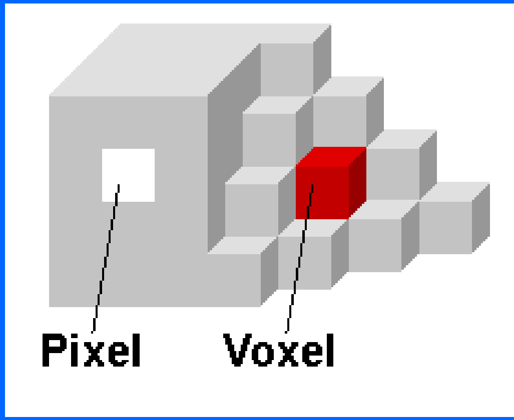
- **Measurement of the electron density**
- **Information on the morphology**

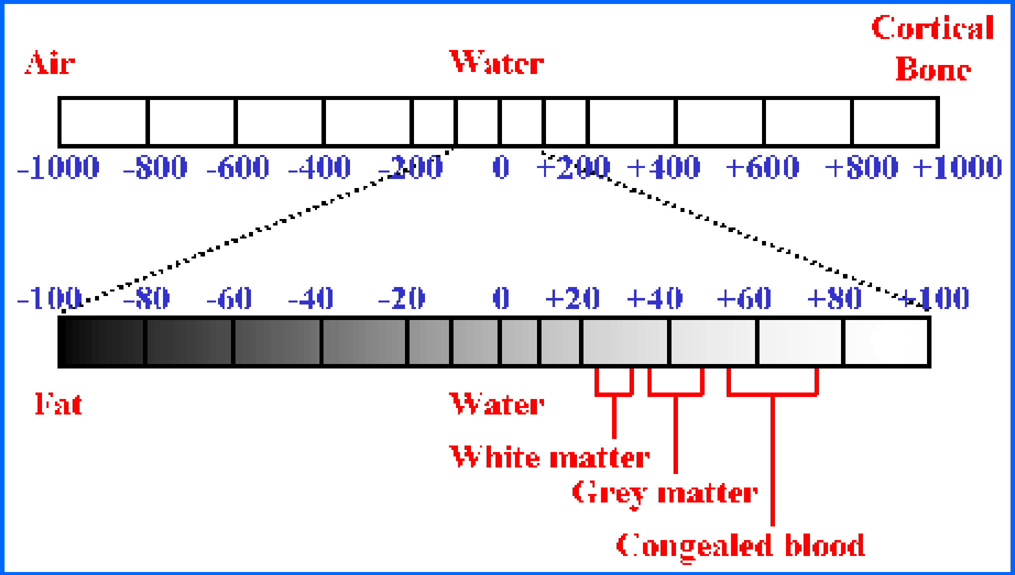
CT and Hounsfield numbers



G. Hounsfield

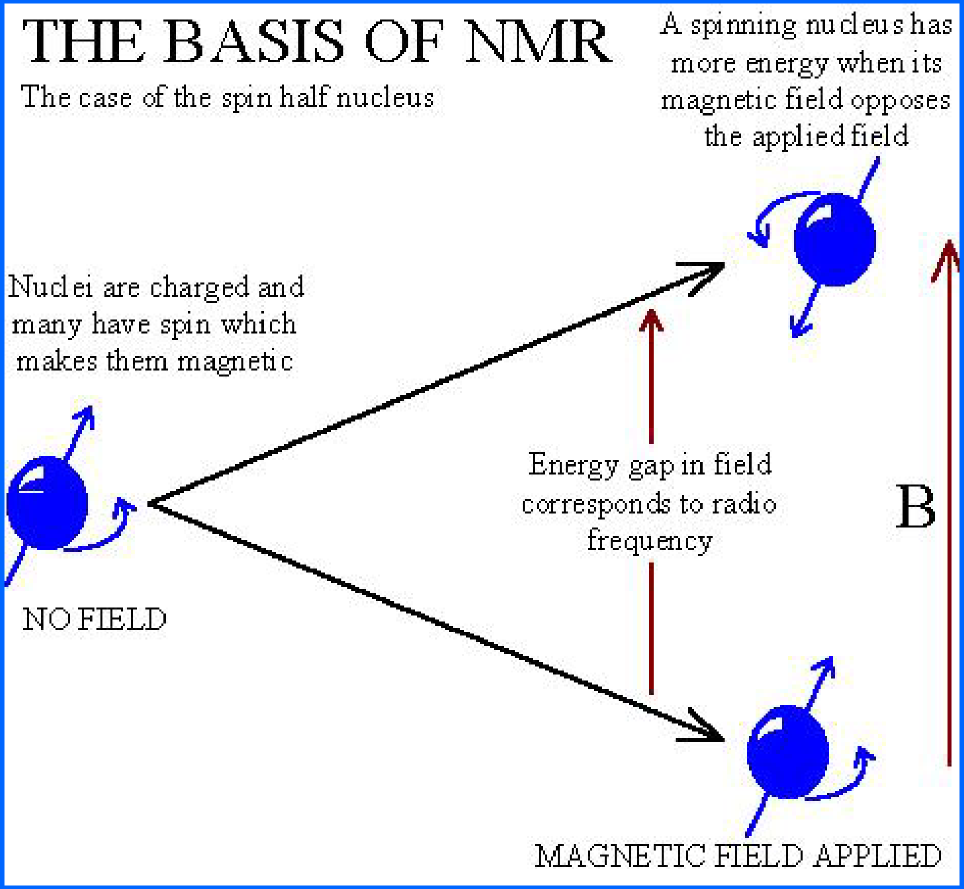
1979 Nobel Prize for Physiology or Medicine





Through the measurement of the attenuation coefficient in many directions and slices (i.e. many radiographies) the Hounsfield numbers are calculated for all the Voxels (=VOlume piXELS)

Nuclear Magnetic Resonance

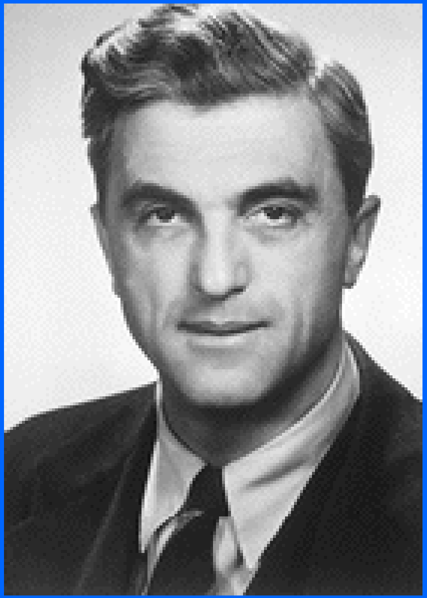


1938-1945

Felix Bloch and Edward Purcell

discover and study

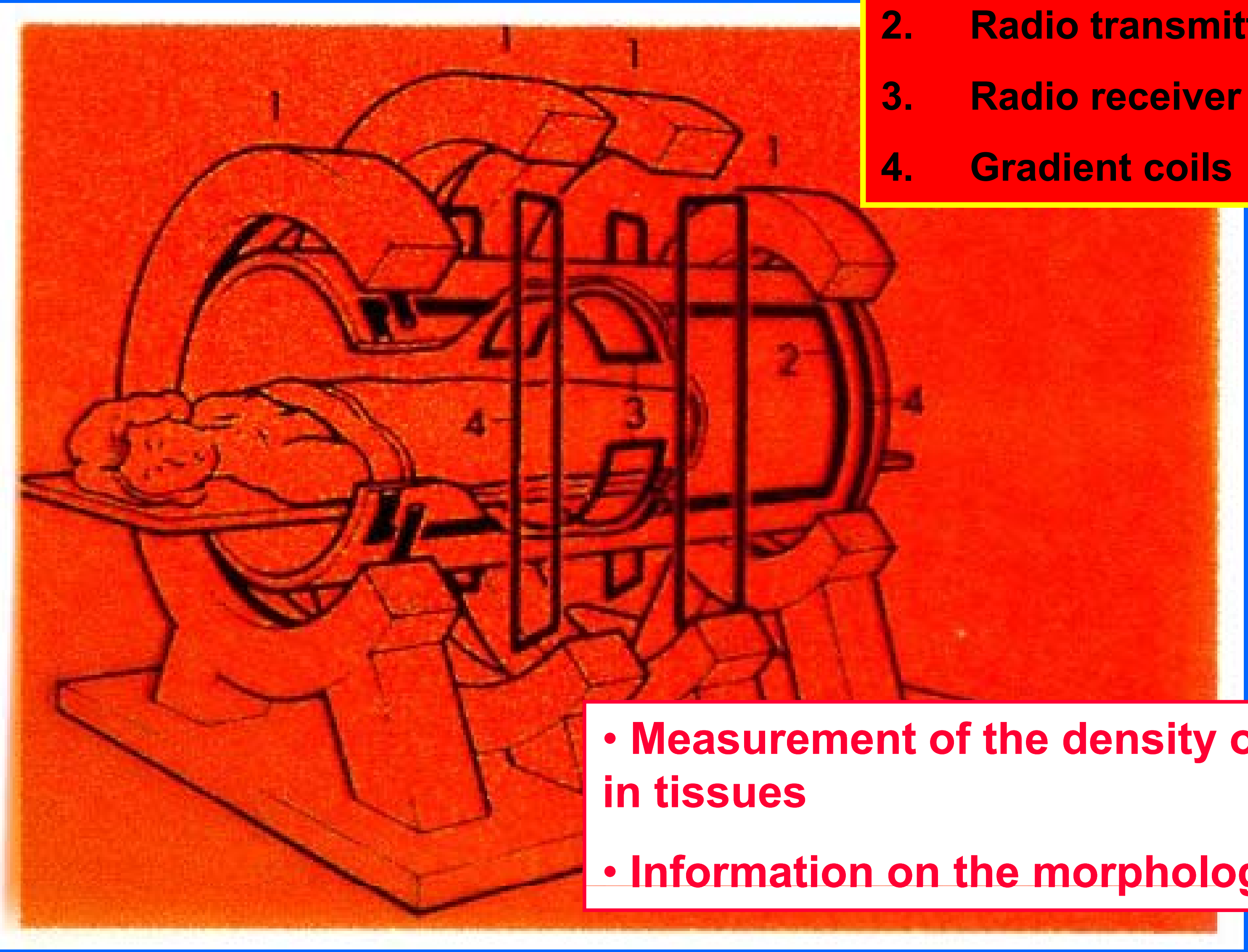
NMR



In 1954 Felix Bloch became

the first CERN Director General

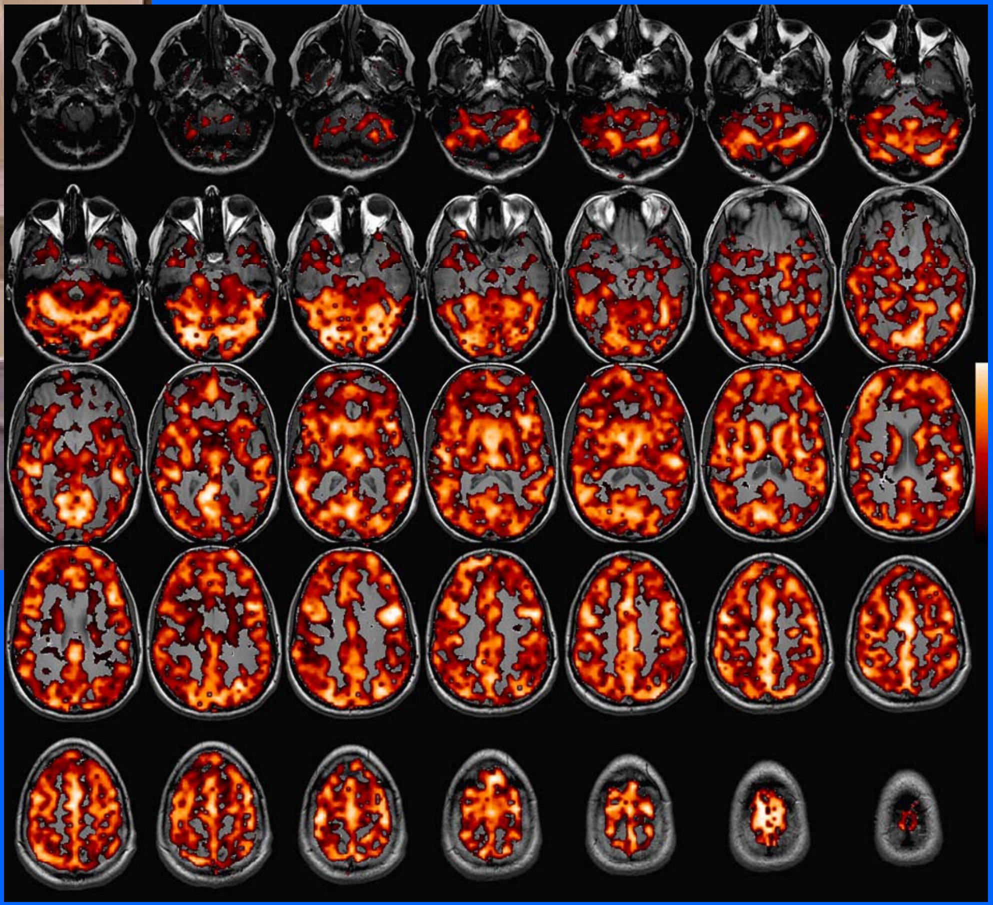
MRI = Magnetic Resonance Imaging



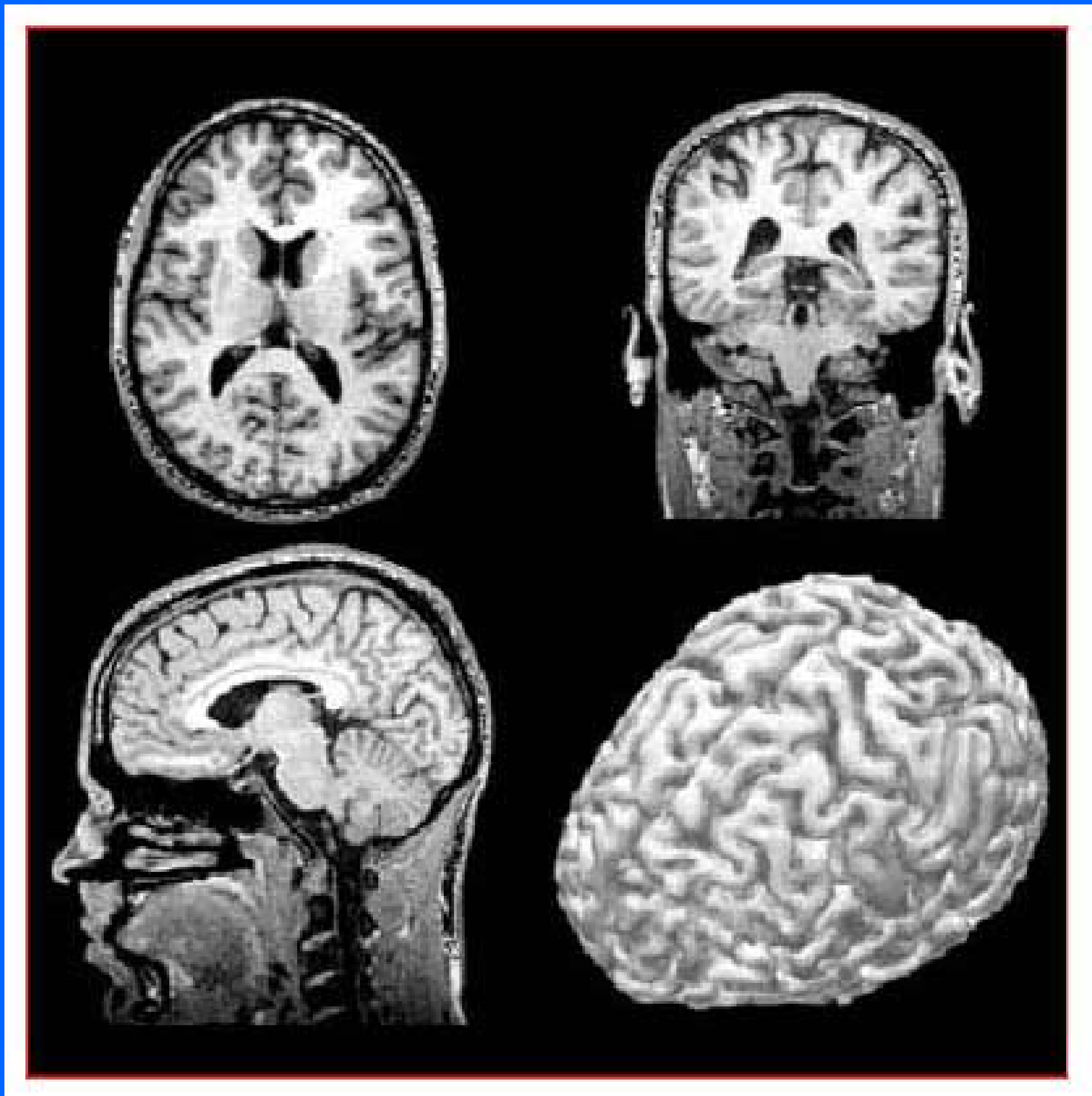
1. **Main magnet (0.5-1 T)**
2. **Radio transmitter coil**
3. **Radio receiver coil**
4. **Gradient coils**

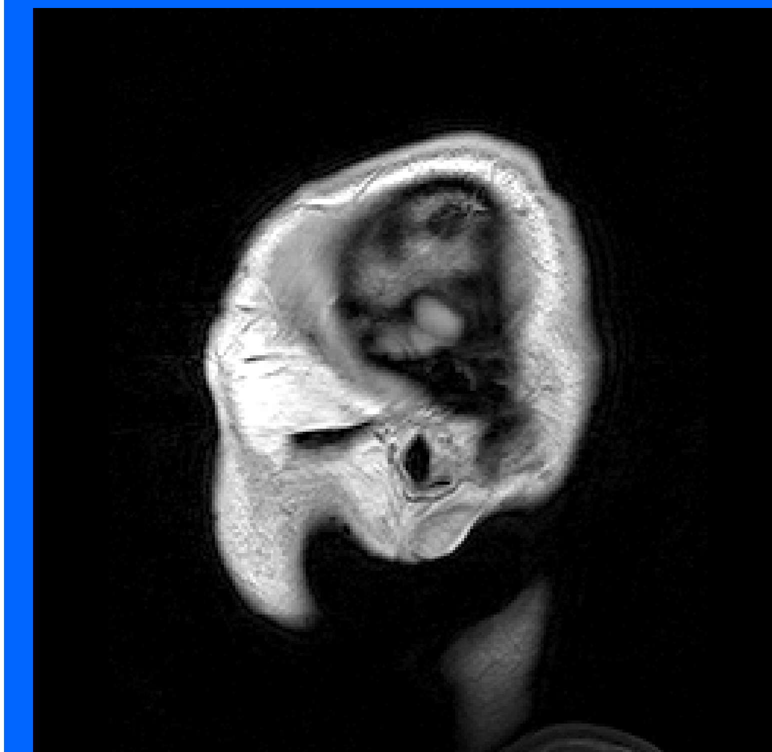
- **Measurement of the density of the protons (water) in tissues**
- **Information on the morphology**

A MRI scanner

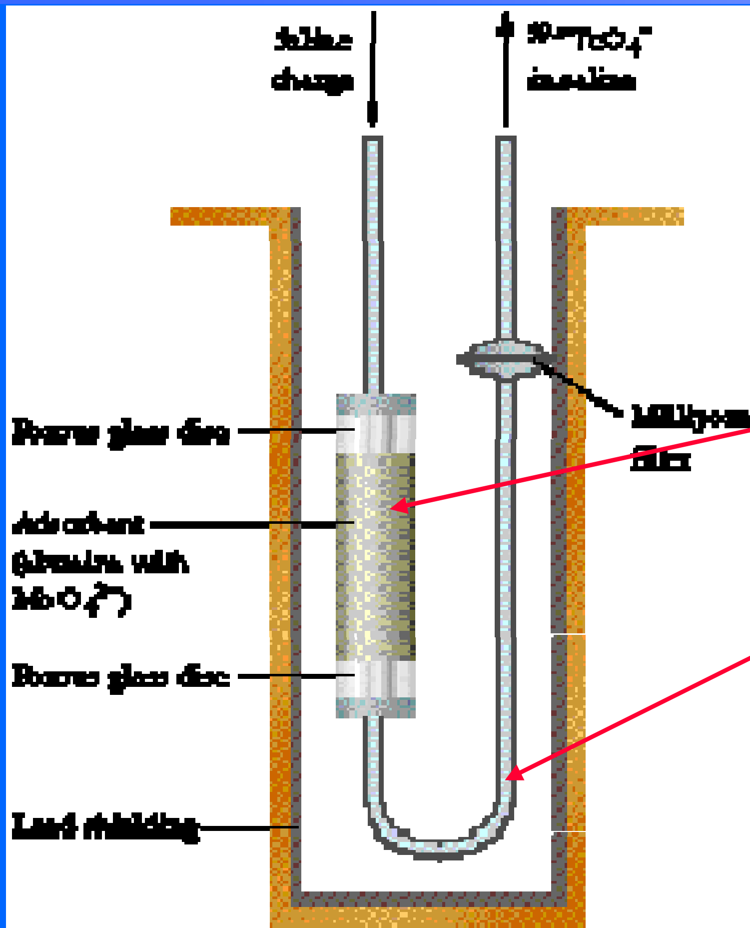


MRI morphological imaging





SPECT = Single Photon Emission Computer Tomography

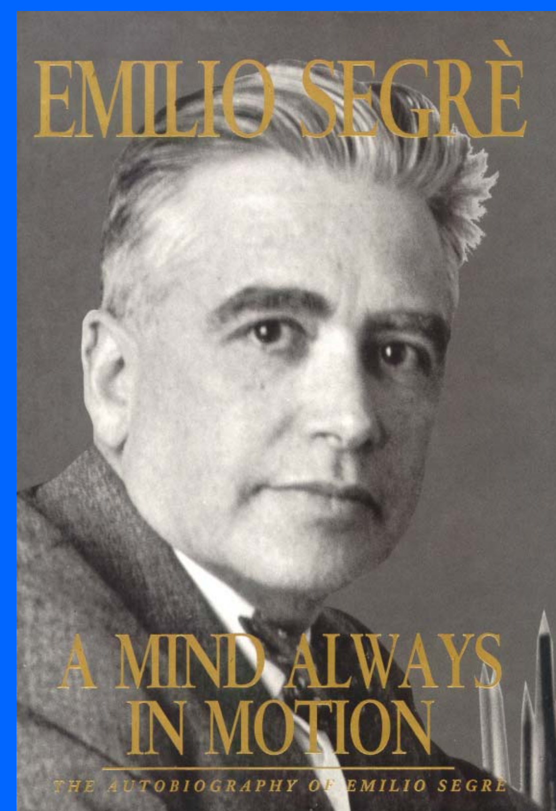


In reactors <u>slow neutrons</u> produce

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

$$^{99}Mo\ (66\ h) = {}^{99m}Tc\ (6\ h) + e^{-} + \overline{\nu}$$

gamma of 0.14 MeV



Emilio Segrè

1937: Discovery of element 43 "Technetium" ^{97}Tc(2.6 My)

1938: discovery of ^{99m}Tc with E. McMillan (m stands for metastable)

The molybdenum technetium generator

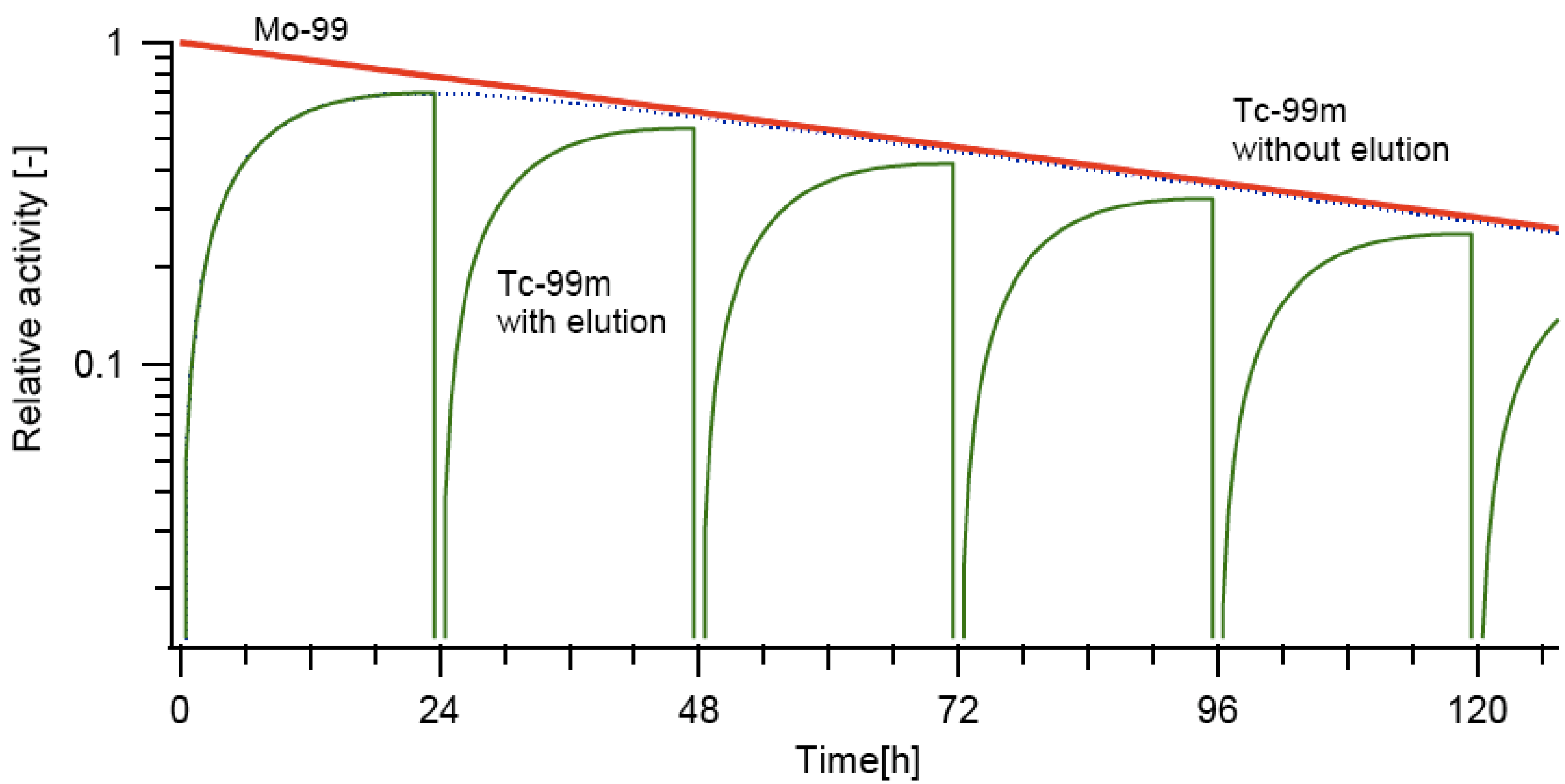
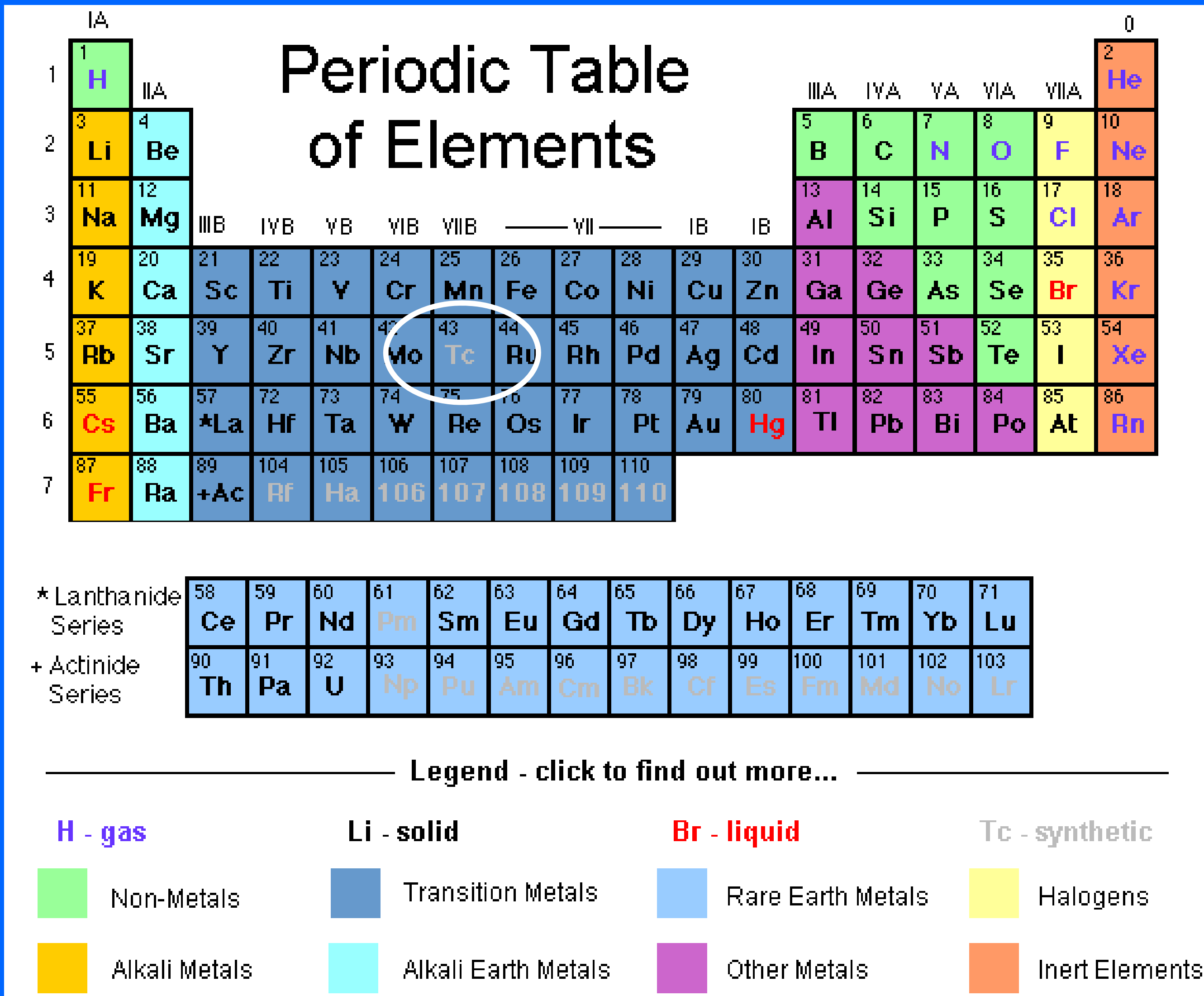


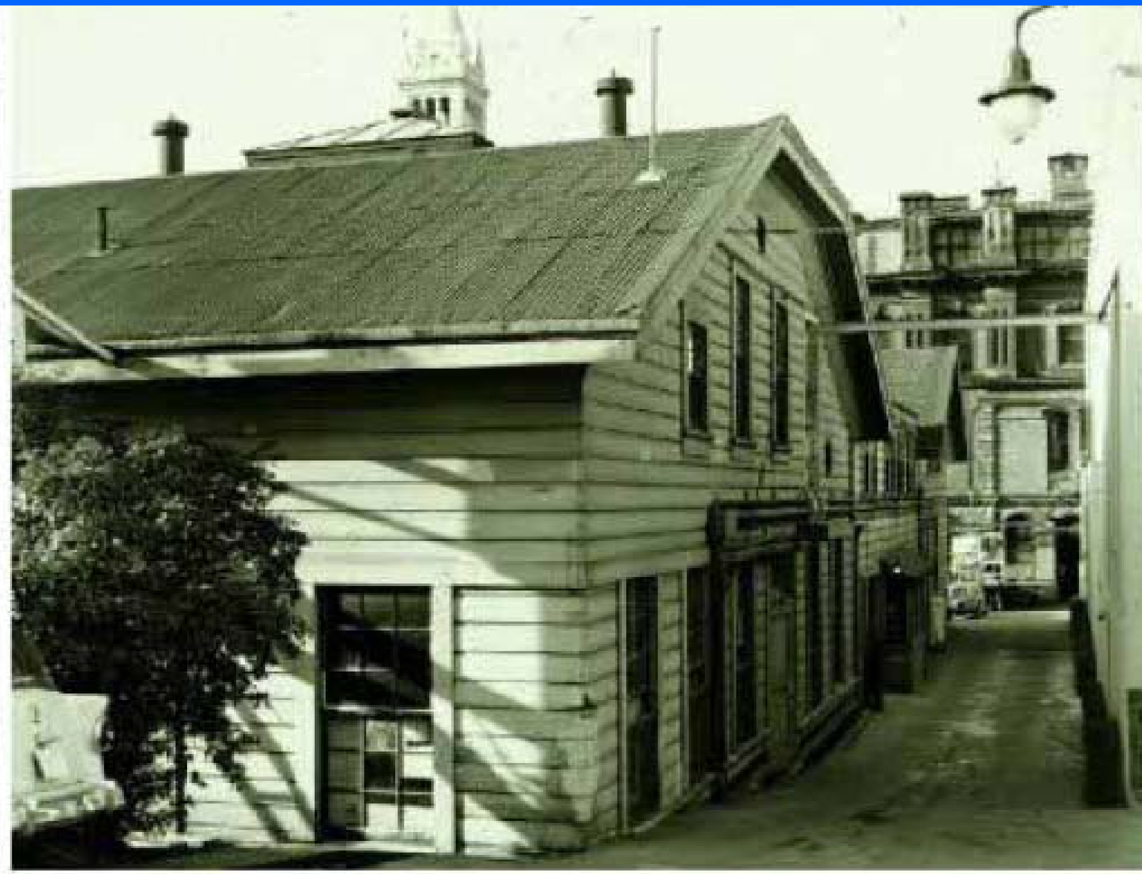
Figure 2.1: Functioning of an isotopic Tc-99m generator. The half-life of Mo-99 being greater than that of Tc-99m, the activity in Tc-99m increases, then decreases with the activity of the parent atoms. When a Tc-99m generator is functioning normally, we let its activity increase for 24 hours then we extract it (elution); the activity of the Tc-99m can then increase again in order to be used the next day.

The element 43



- The element 43 was missing
- In 1925 W. Noddack and I. Tacke announced the discovery of Rhenium (75) and Masurium (43)
- In 1934 Fermi and his group were bombarding "all" the elemnts with slow neutrons and Segrè was in charge of procuring the different elements
- …but asking for a sample of Masurium he was answerd "Numquam vidi"…

The discovery of technetium



The Rad Lab is officially established within the UC Physics Department with Lawrence as director; in Italy, Segrè examines an "invaluable gift" of material irradiated by the 27-inch cyclotron and discovers the first artificial element, later named technetium.

The discovery of technetium

- Lawrence was using deflectors for the cyclotron made of Molybdenum (42)
- Segrè thought : Molybdenum + proton… 42 + 1 = 43 !
- In February 1937 Segrè received a letter from Lawrence with some Molybdenum coming from the deflectors and…
- …the element 43 was identified with the help of a chemist (Carlo Perrier)
- The element 43 was called Technetium since it is the first element artificially produced (the most stable isotope has an half-life of 4.2 x 10^6 years)

SPECT scanner

85% of all nuclear medicine examinations use technetium produced by slow neutrons in reactors

• Measurement of the density the molecules which contain technetium

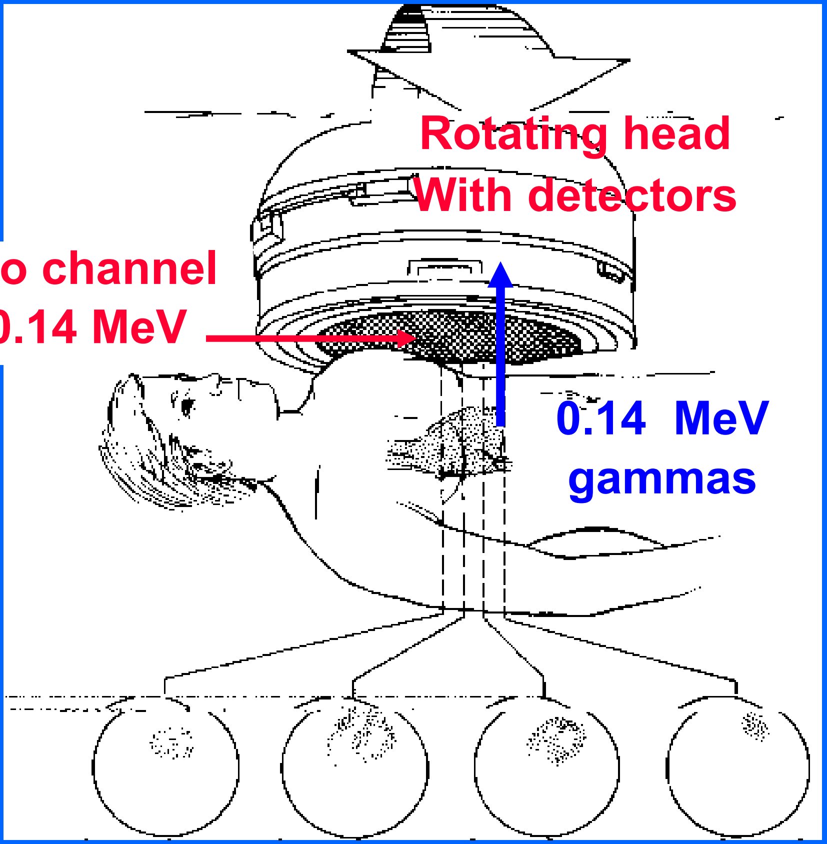
• Information on morphology and/or metabolism

… liver

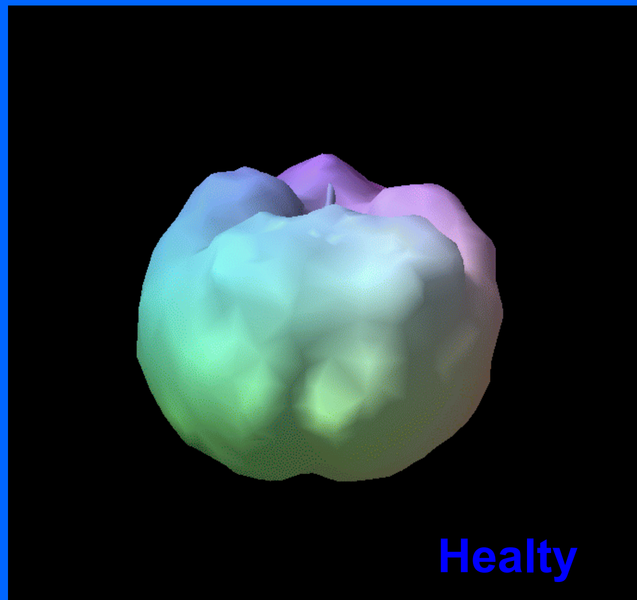
lungs

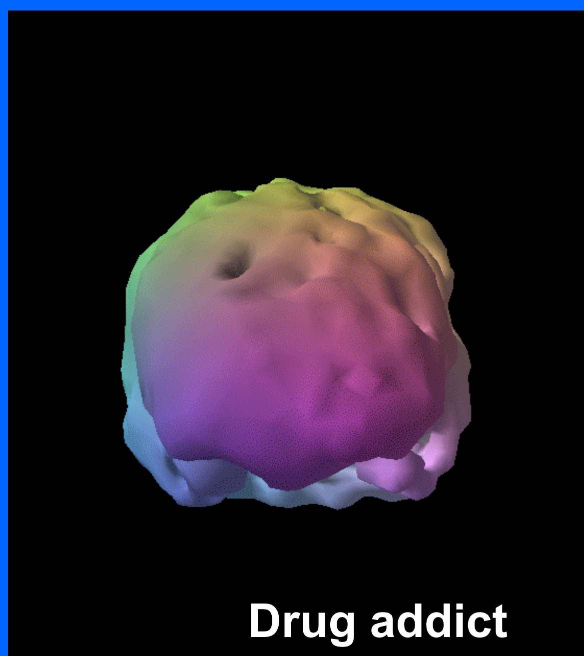
bones …

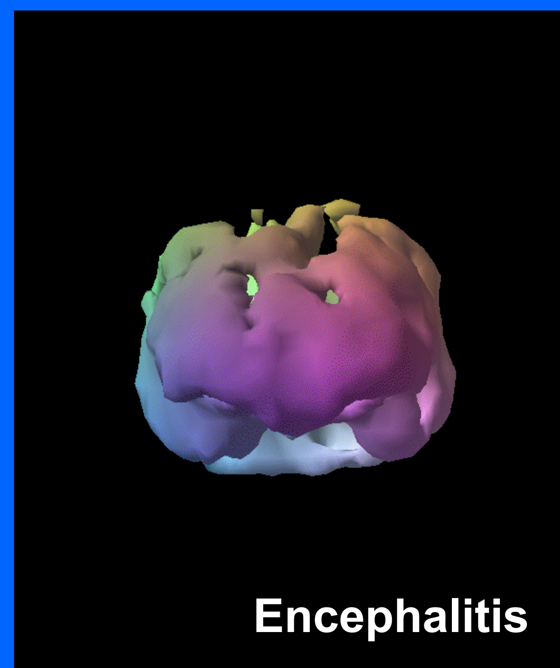
Lead collimators to channel the gammas of 0.14 MeV



SPECT images

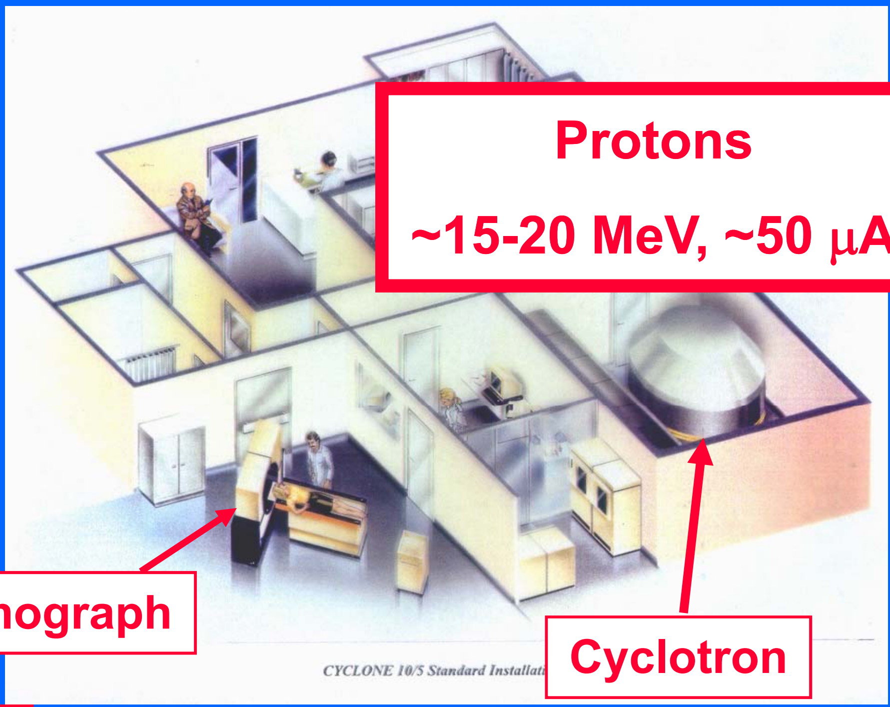






Positron Emission Tomography (PET)

- FDG with ^{18}F is the most used drug (half life 110 minutes)
- Measurement of the density of ^{18}F through back-to-back gamma detection
- Information on metabolism



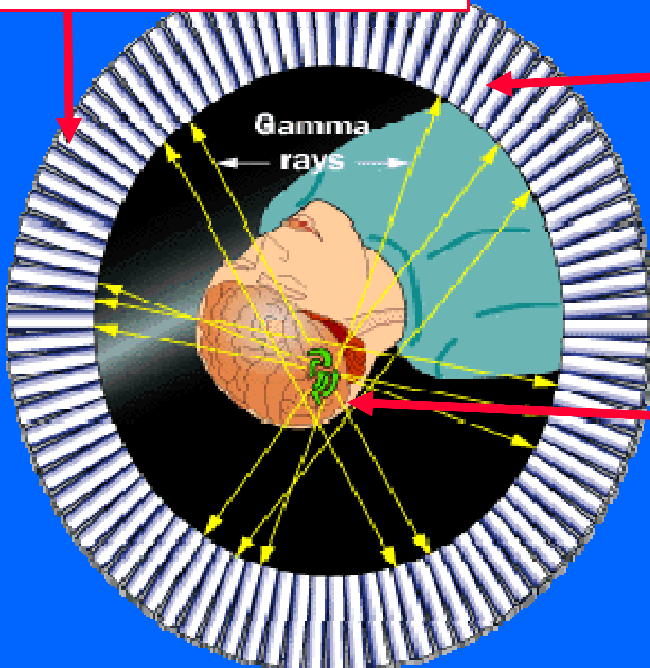
Protons

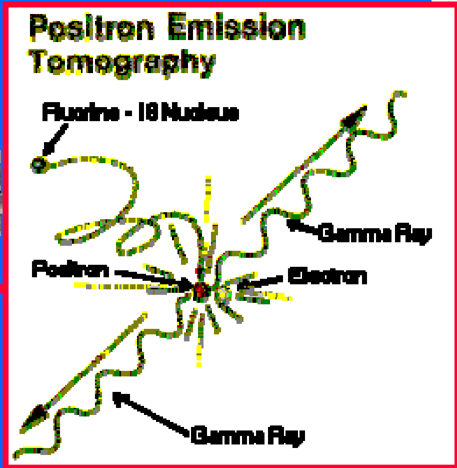
~15-20 MeV, ~50 μA

PET tomograph

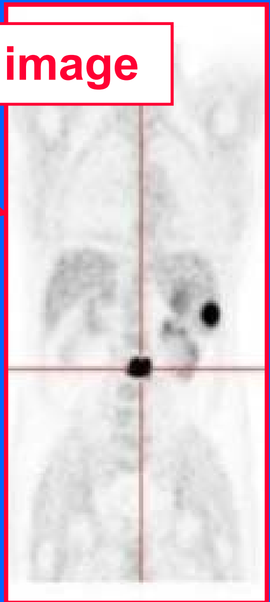
Cyclotron

Gamma ray detectors
(Ex. BGO crystals)





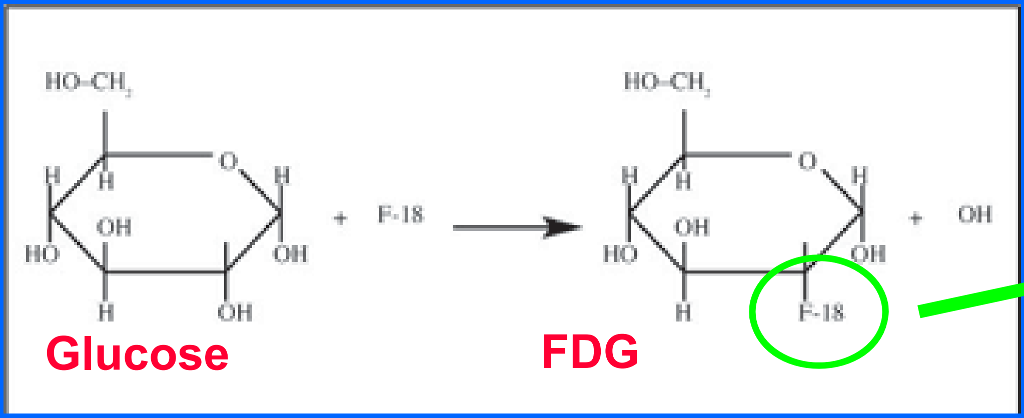
PET image

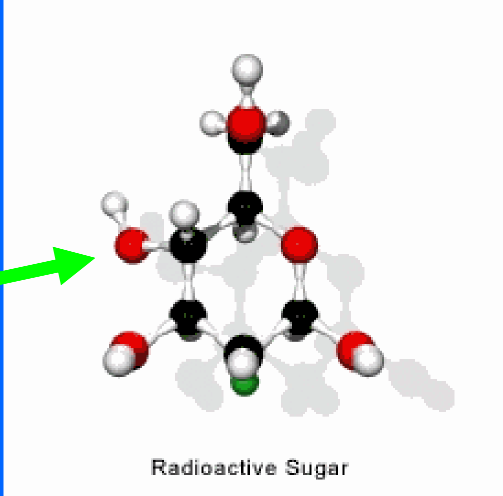


CT-PET

How does it work?

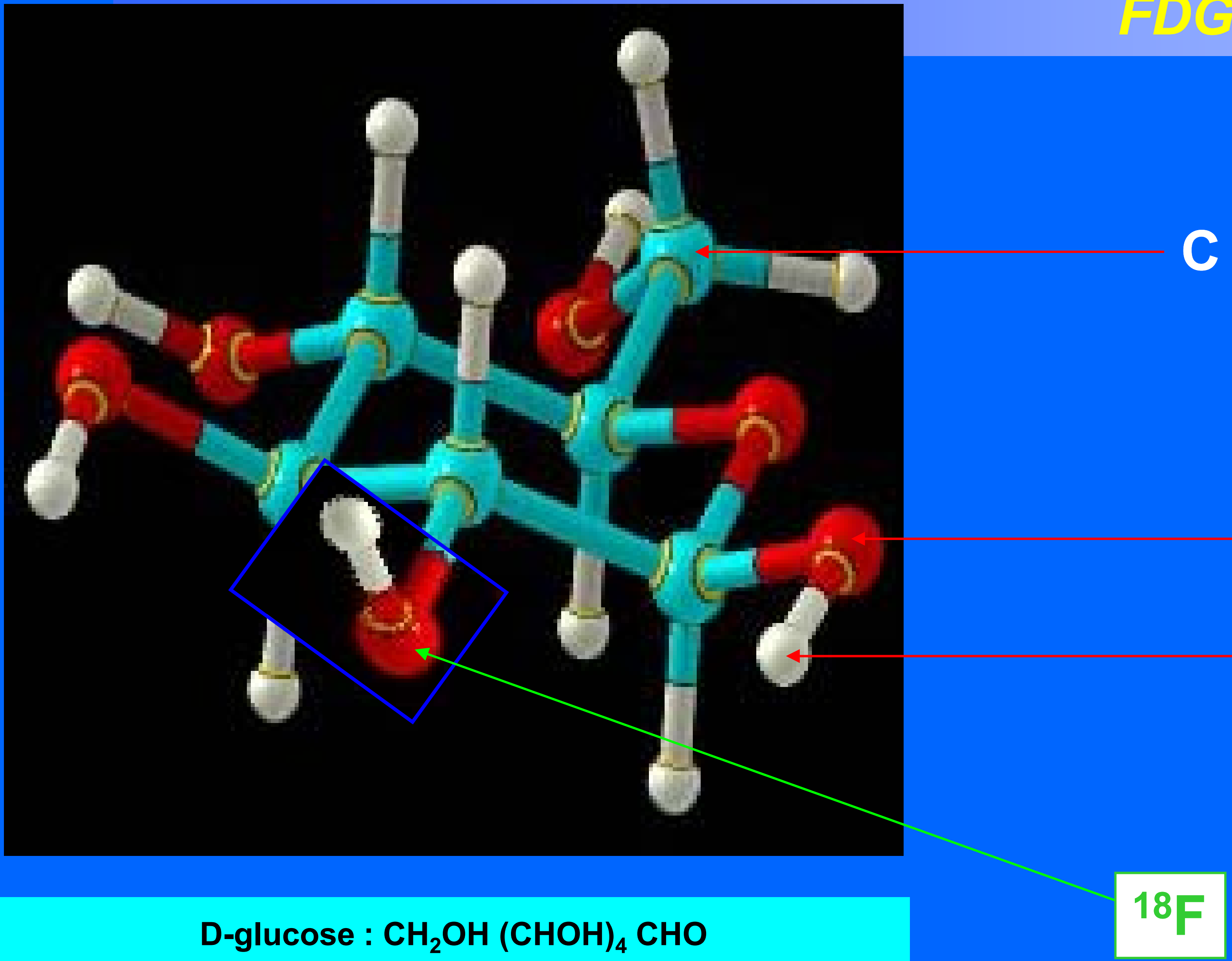
- $H_2{}^{18}O$ water is bombarded with protons to produce ^{18}F
- Fluoro-Deoxy-D-Glucose (FDG) is synthesized





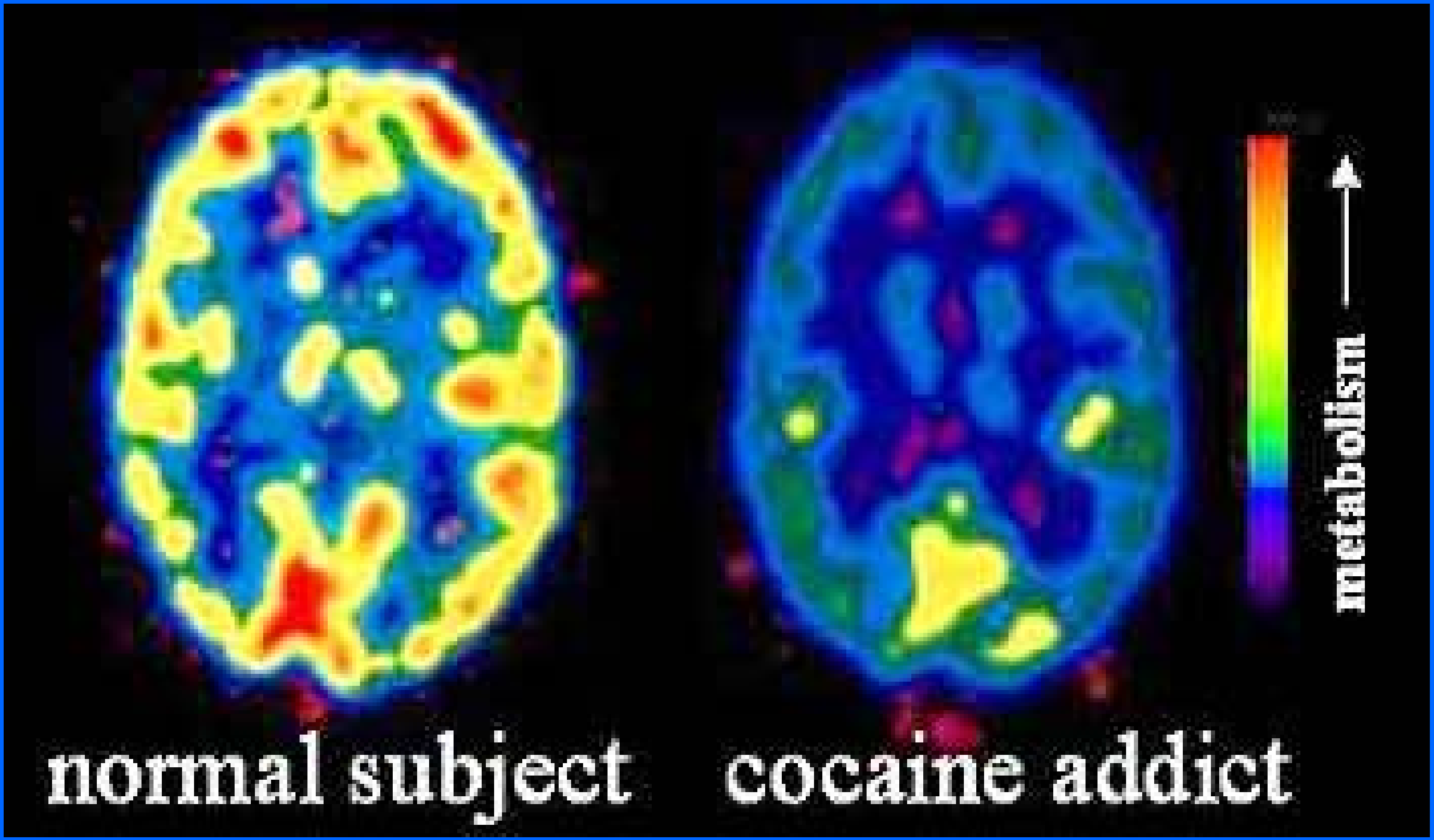
- FDG is transported to the hospital
- FDG is injected into the patient
- FDG is trapped in the cells that try to metabolize it
- Concentration builds up in proportion to the rate of glucose metabolism
- Tumors have a high rate of glucose metabolism and appear as “hot spots” in PET images

FDG synthesis



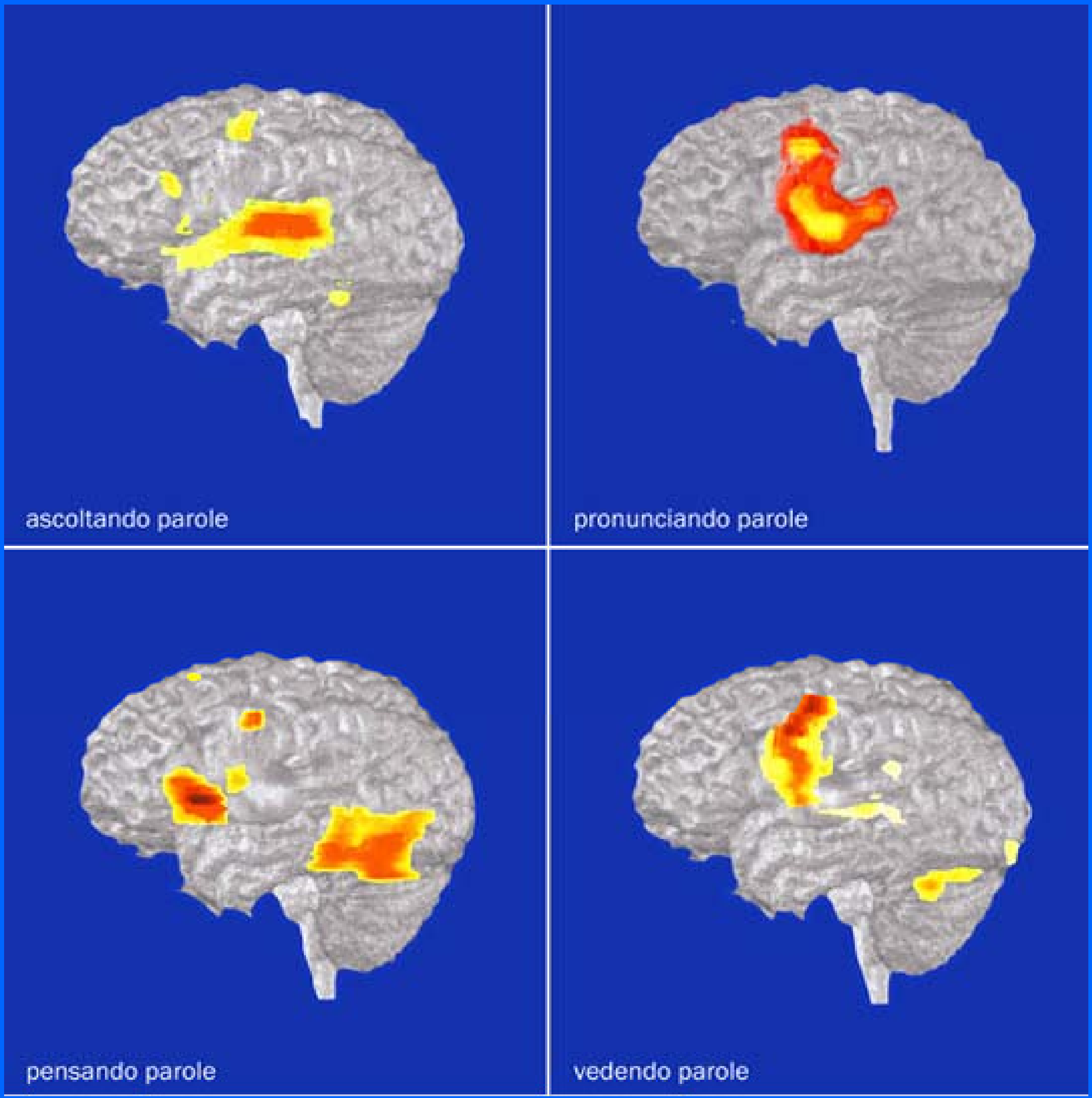
D-glucose : $CH_2OH\ (CHOH)_4\ CHO$

PET images (1)

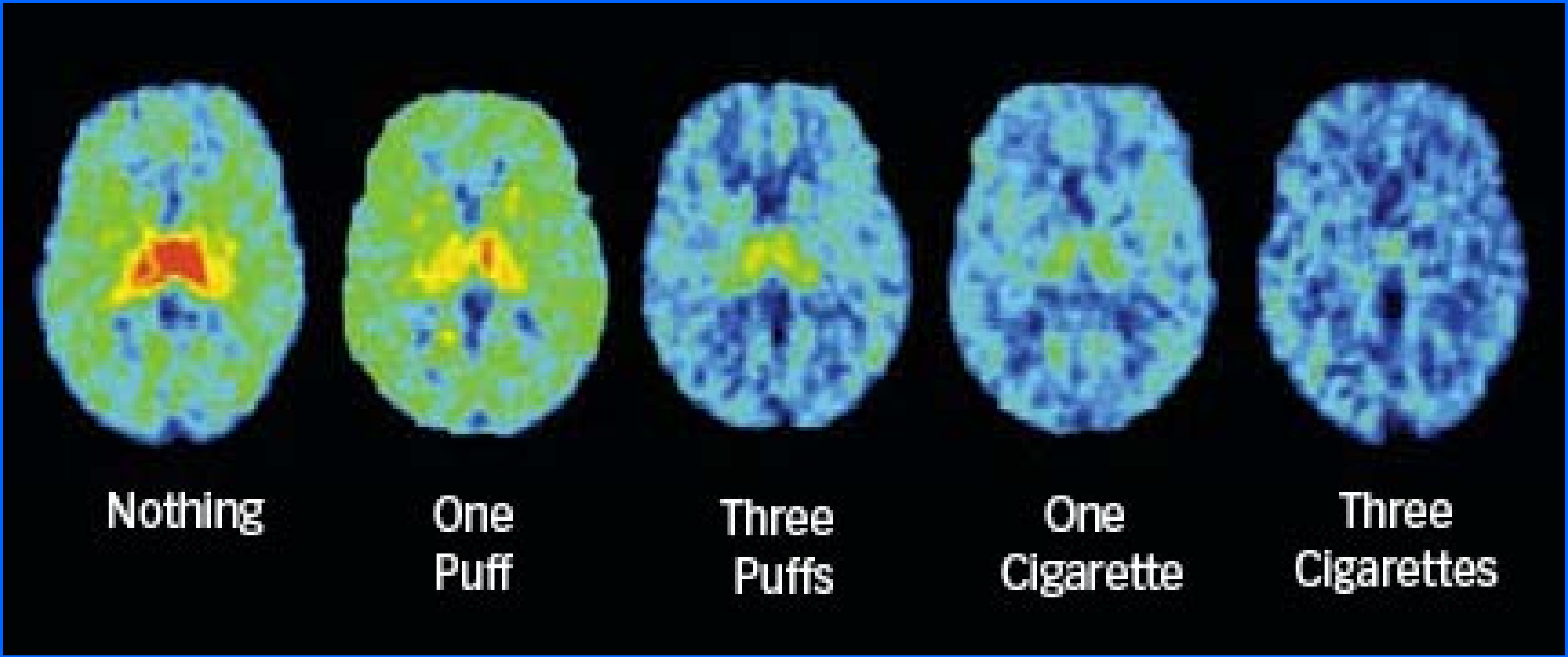


- 18FDG/PET images
- The cocaine addict has depressed metabolism !

PET images (2)


ascoltando parole
pronunciando parole
pensando parole
vedendo parole

PET images (3)

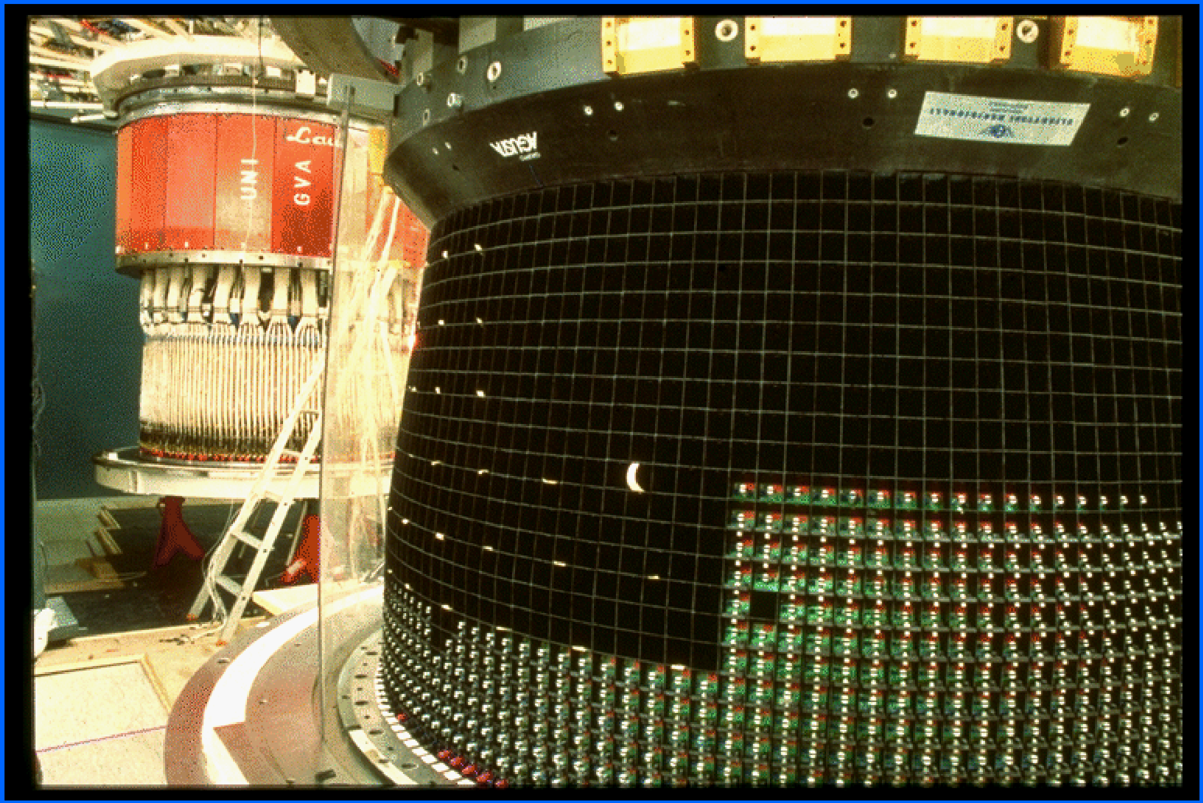


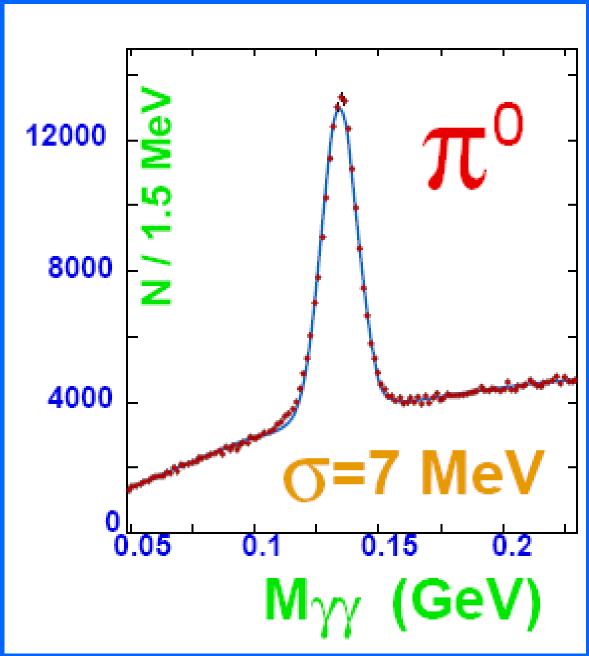
SMOKING SATURATES RECEPTORS As nicotine from a cigarette attaches to the α4β2*-nACh nicotinic receptors in the brain, it displaces a radiolabeled tracer (red and yellow indicate high levels of the tracer, green indicates intermediate levels, and blue indicates low levels). The nicotine from three puffs displaced 75 percent of the tracer from study participants' receptors, and the nicotine from three cigarettes, nearly all.

www.drugabuse.gov

The BGO calorimeter of the L3 experiment at LEP (CERN 1989-2000)

BGO crystals have been developed for detectors in particle physics

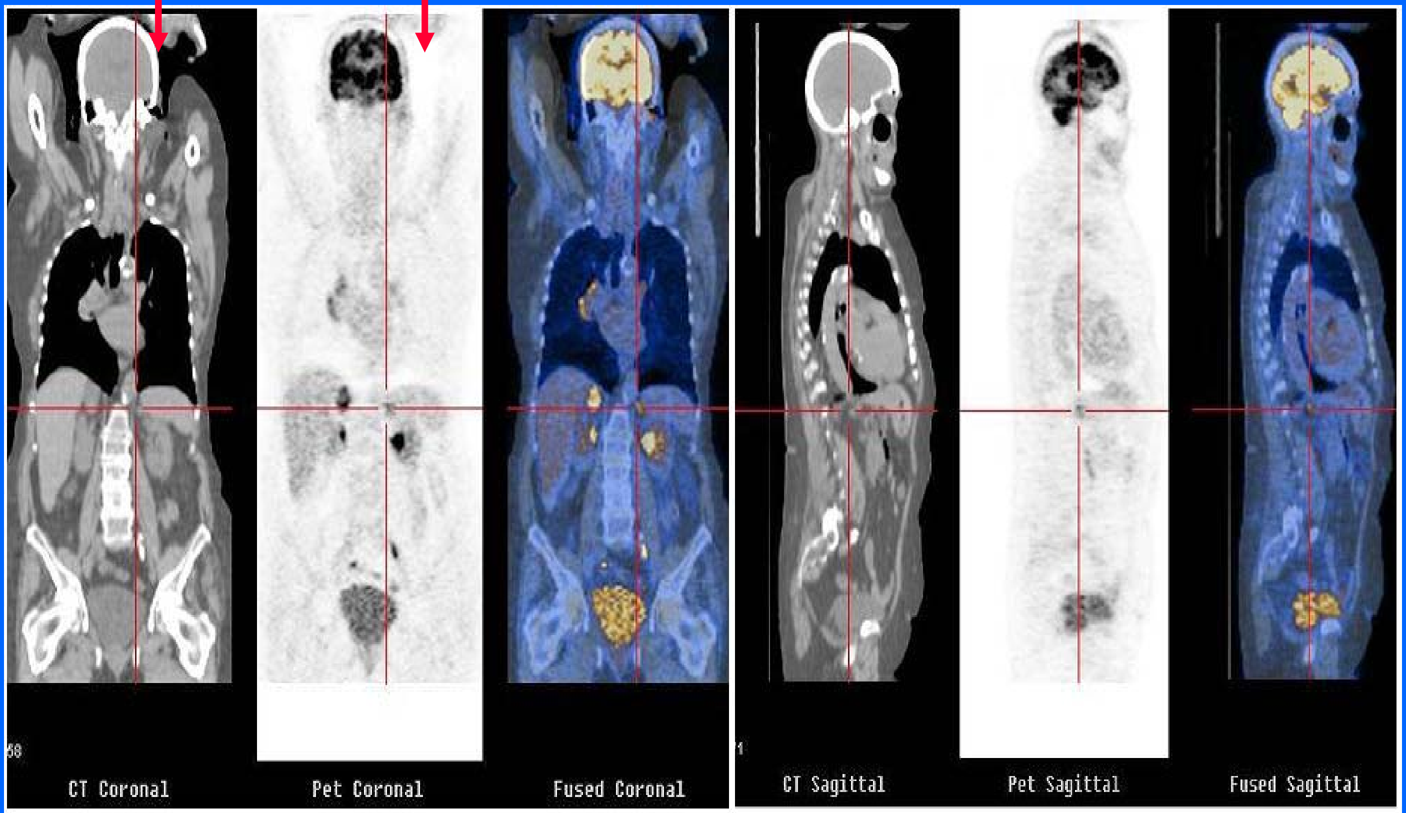




- 11000 BGO crystals
- Precise measurement of the energy deposited by the particles
- Almost 4 π coverage

The new diagnostics: CT/PET

morphology   metabolism



David Townsend

CERN: 1970-78

Uni Ginevra

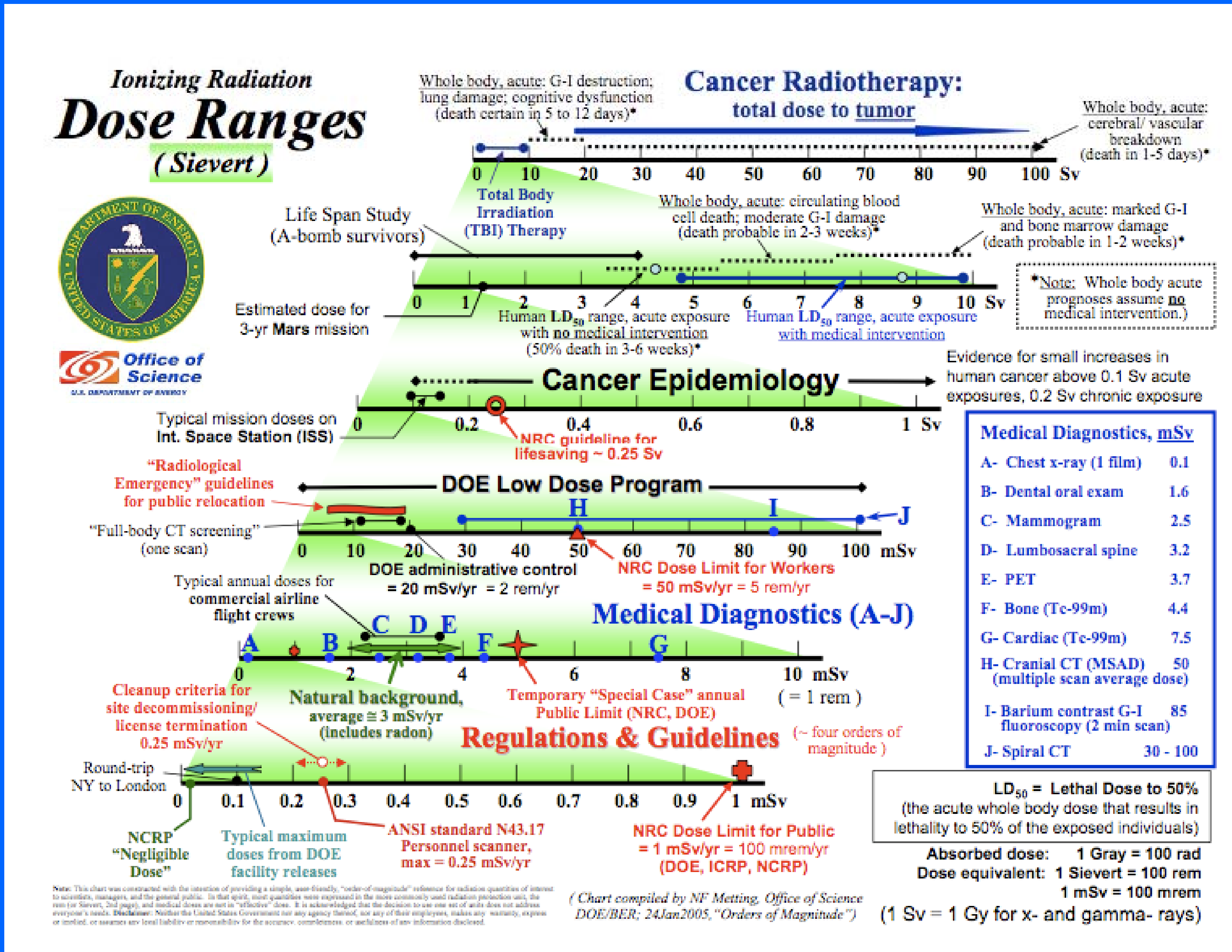
UPSM Pittsburgh

and

Ronald Nutt

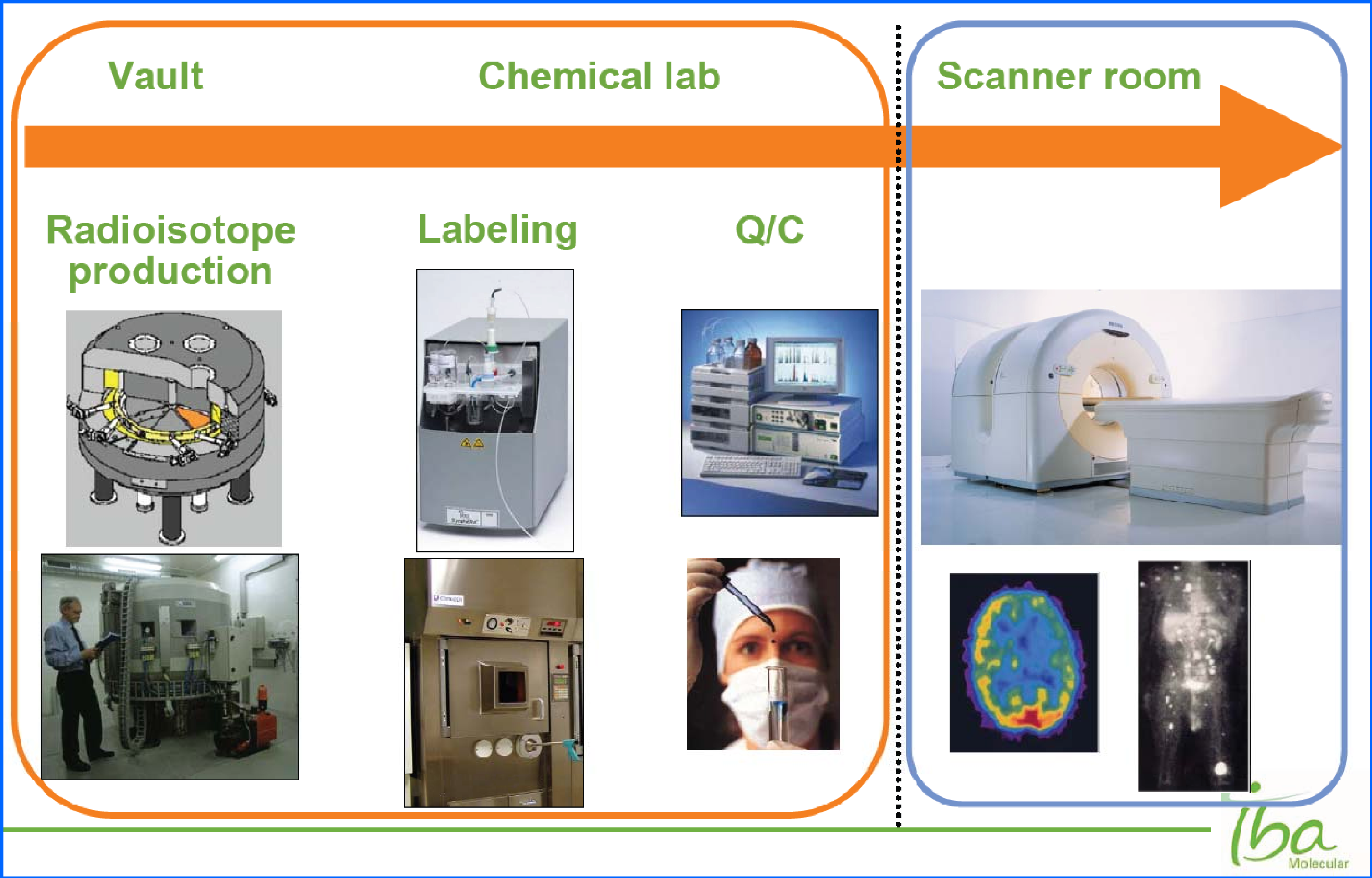
(CTS – CTI)

Doses in medical diagnostics



Exercise: the production of FDG for PET

The full FDG-PET chain



Courtesy IBA

Basic data

- 20 MeV proton beam (cyclotron)
- Current : 50 μA
- FWHM : about 15 mm
- Target : 99% 18-O enriched water
- Reaction : 18-O (p,n) 18-F

- Fluorine 18 : half-life $t_{1/2}$=110 min.
- Irradiation time 60 min.

- What is the value of the 18-F activity produced?

One TR19 cyclotron by the company ACSI

(Vancouver, Canada) is installed at the Policlinico Gemelli in Rome

It is daily used for FDG production

Courtesy

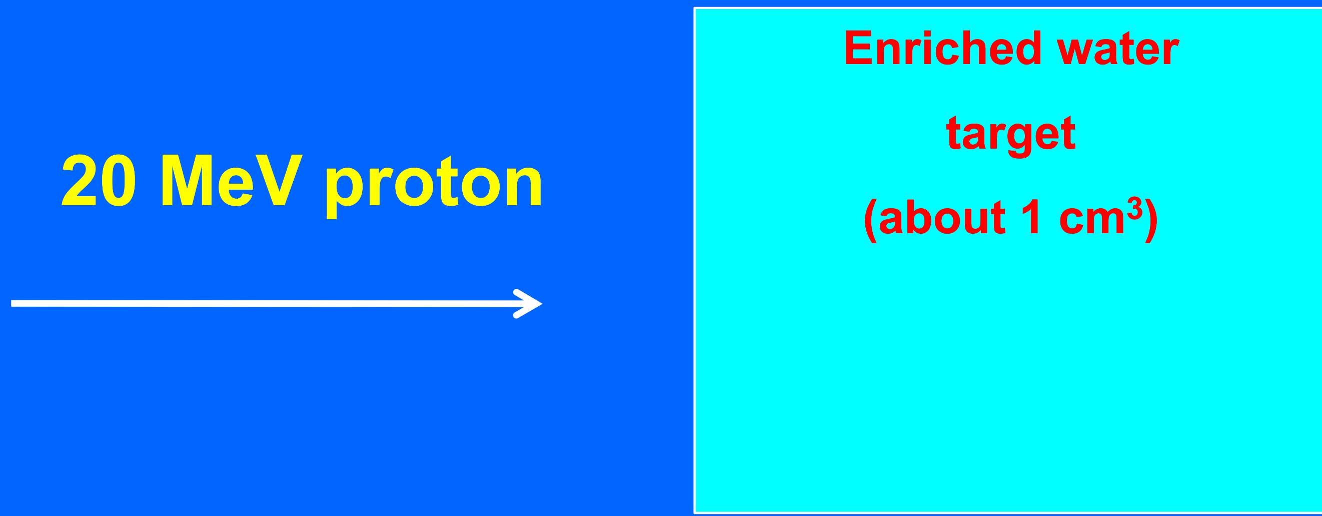
Pipes for cooling. Why?

Let's suppose that the beam completely stops in the target:

$$20\ \text{MeV} \times 50\ \mu\text{A} \times (1/e) = 1000\ \text{W}$$

1 cal = 4.18 J i.e. 1 cm^3 of water passes between 0 and 100 degrees

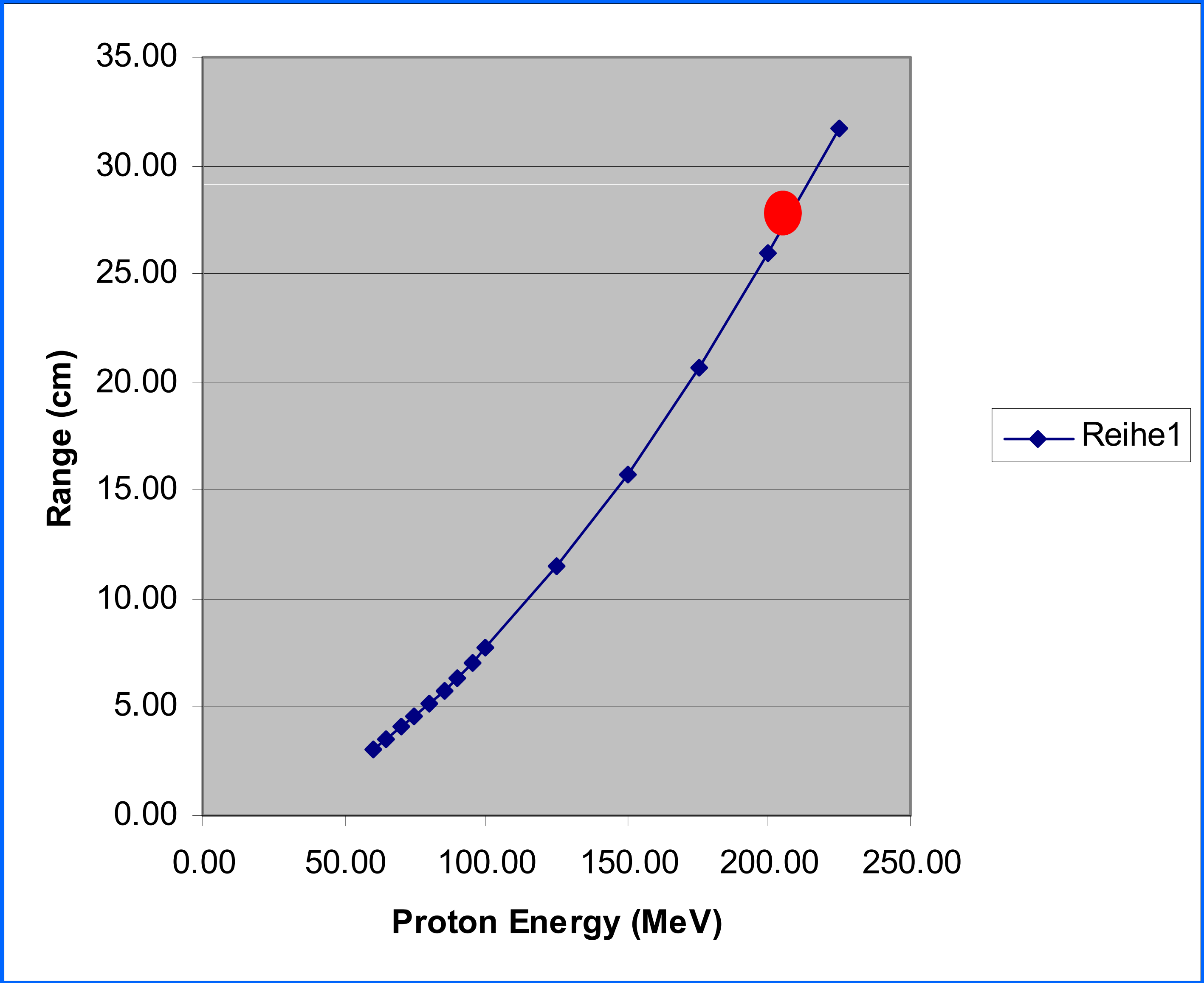
in less than 0.5 seconds !



- **Does the proton stop in water?**

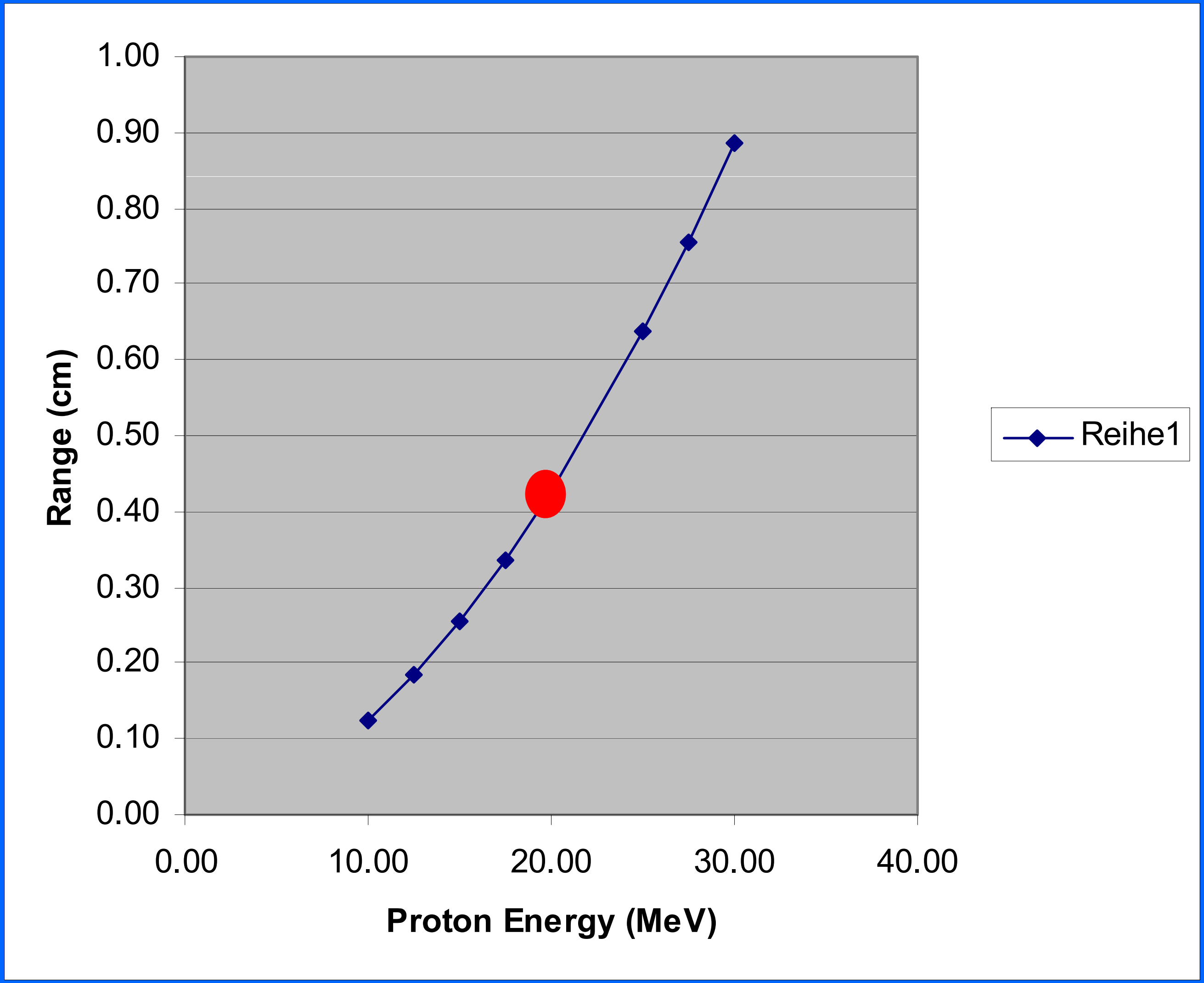
- **"Sometimes" the reaction 18-O (p,n) 18-F occurs. Probability?**

Range of the protons in water



Important to remember : 200 MeV → 27 cm

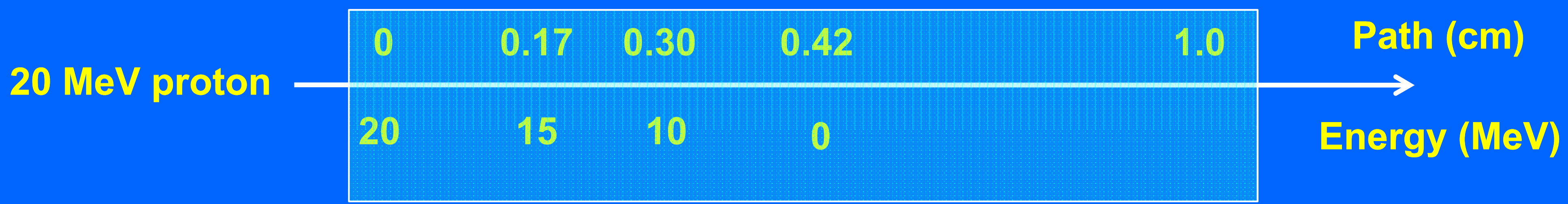
Range of protons in water



20 MeV → 0.4 cm – All protons stop in the target

Residual range

Energy (MeV)	Range (cm)
20	0.42
15	0.25
10	0.12
5	0.036



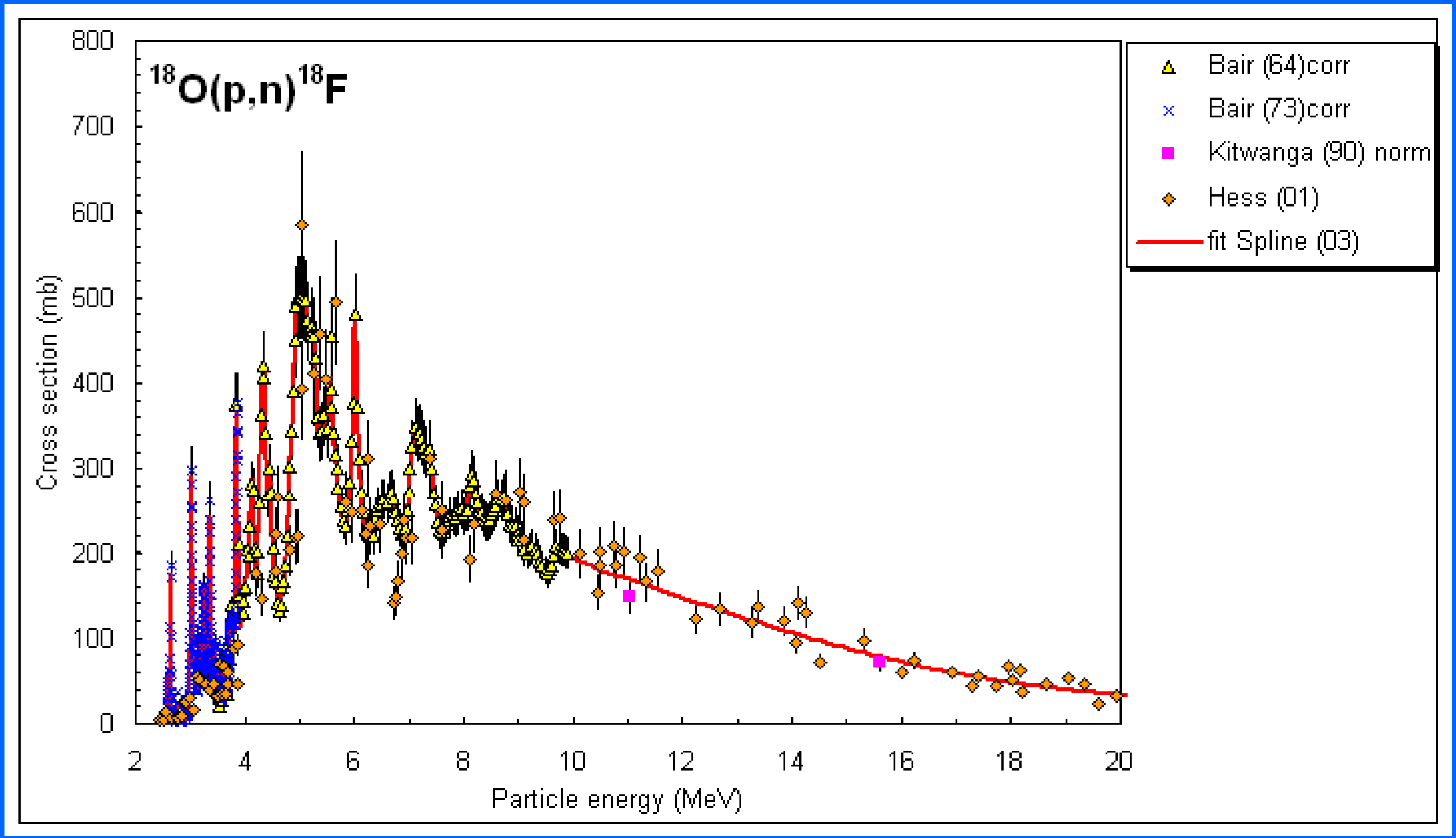
The reaction can take place in any point of the path

i.e. at different energies !

A useful link :

physics.nist.gov – NIST National Institute of Standards and technology

The cross section



For the exercise we will consider an average value of 100 mb for all the energies

(1 barn = 10^{-24} cm^2)

- How many 18-O targets are there?

  20 g (18+1+1) of enriched H2O contain N_0 molecules

  $\rightarrow$ 6.022 x 10^{23} / 20 $\rightarrow$ 3 x 10^{22} 18-O atoms/cm^3

- How many “bullets” per second?

  Current / charge of the proton

Calculations

$$N_R = \sigma \times \frac{I}{e} \times \frac{N_t}{V} \times L_t \times \Delta t$$

N_R	number of reactions i.e. number of 18-F nuclides produced
σ	cross section
I	beam current
e	charge of the electron
N_t	number of traget 18-O nuclei
V	volume of the target
L_t	thickness of the target ?
Δt	Irradiation time interval

Calculations

- Thickness of the target → range = 0.42 cm

Result 1

- In 60 minutes : $N_0 = 2 \times 10^{15}$ 18-F nuclei are produced

- Which is the corresponding activity?
- $N(t)=N_0 \times \exp(-t/\tau)$
- At t=0 the activity dN/dt is: N_0/τ
- F-18 : $t_{1/2}$ = 110 min → $\tau = t_{1/2} / \ln 2$ = 158 min = 9480 s
- Activity : A = 2×10^{11} Bq (Bq → Bequerel)
- 1 Ci = 3.7×10^{10} Bq (Ci → Curie)

Result 2

- The produced activity is about 6 Ci at the end of the irradiation

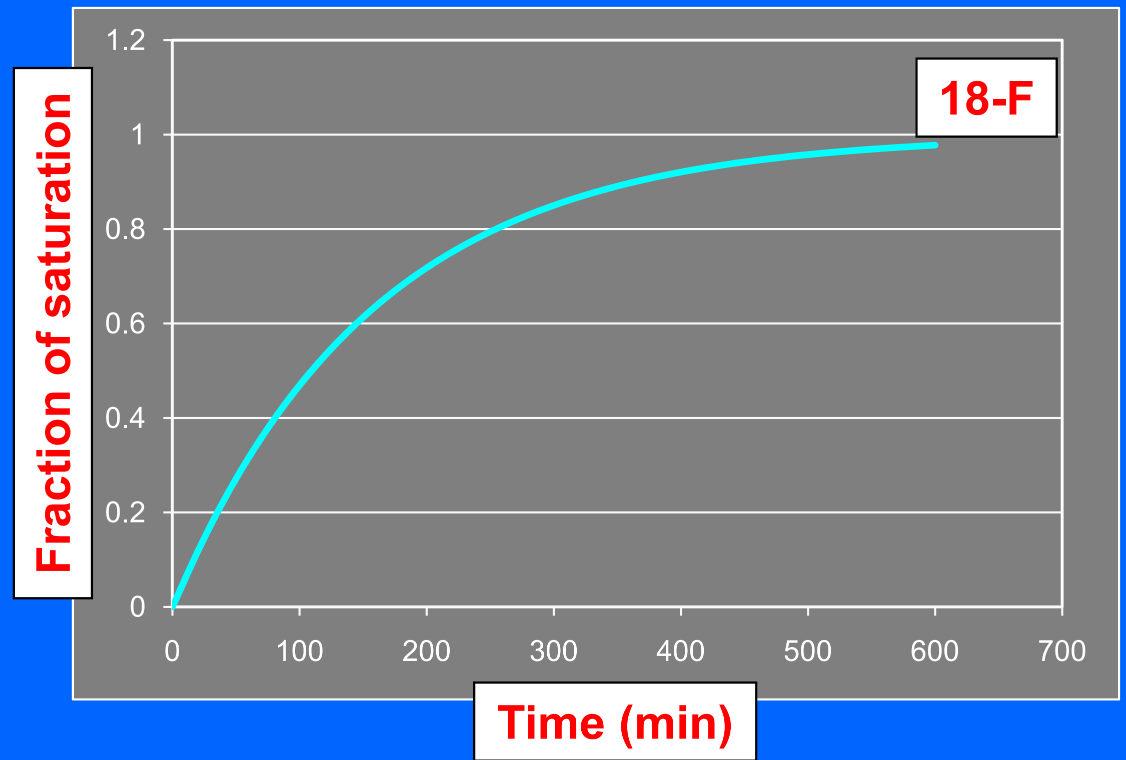
…but 18-F decays during irradiation

$$\Delta N = A \times \Delta t - N(t) \times \frac{\Delta t}{\tau}$$

Irradiation

Decay

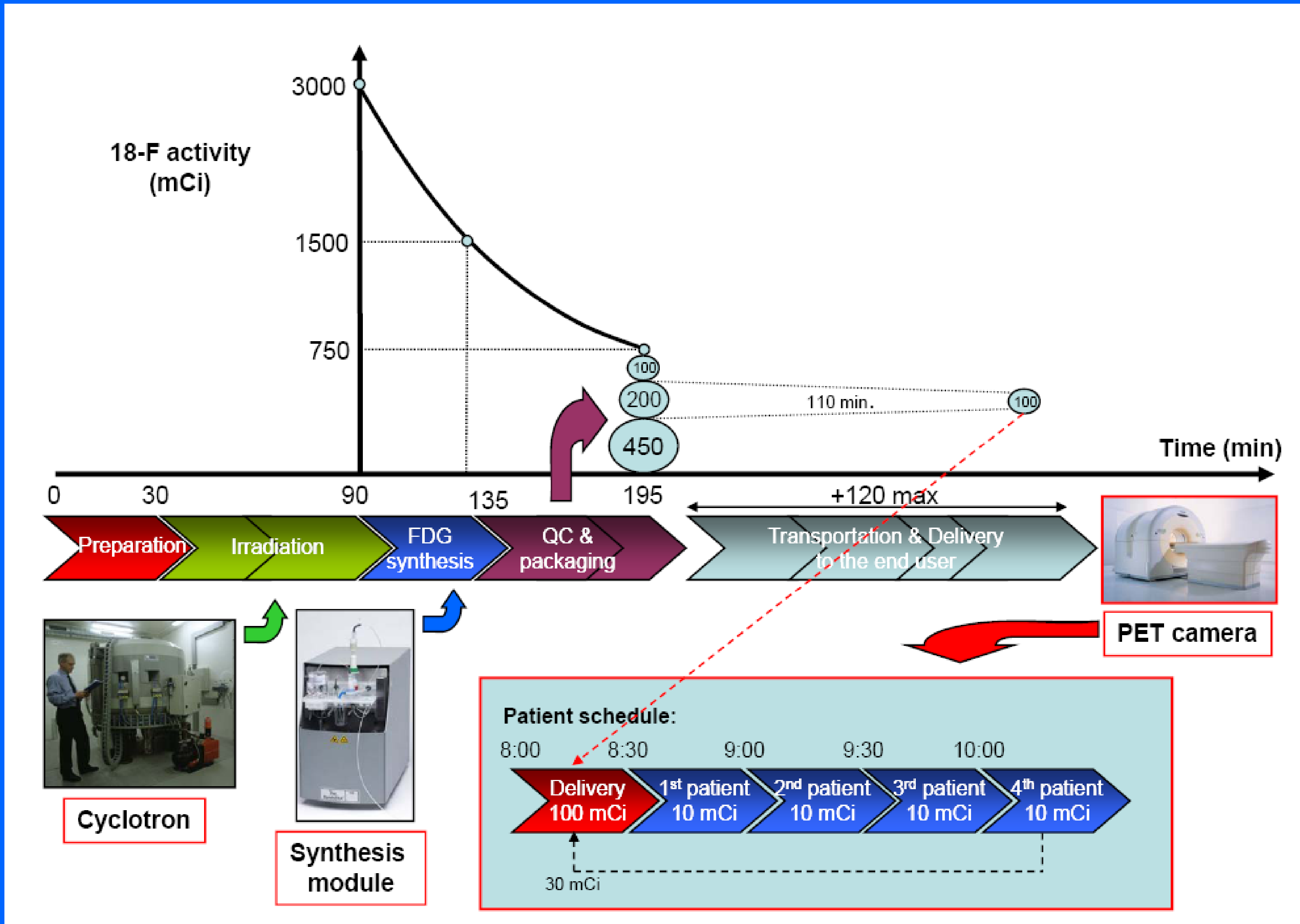
$$N(t) = A\tau \times (1 - e^{-t/\tau})$$



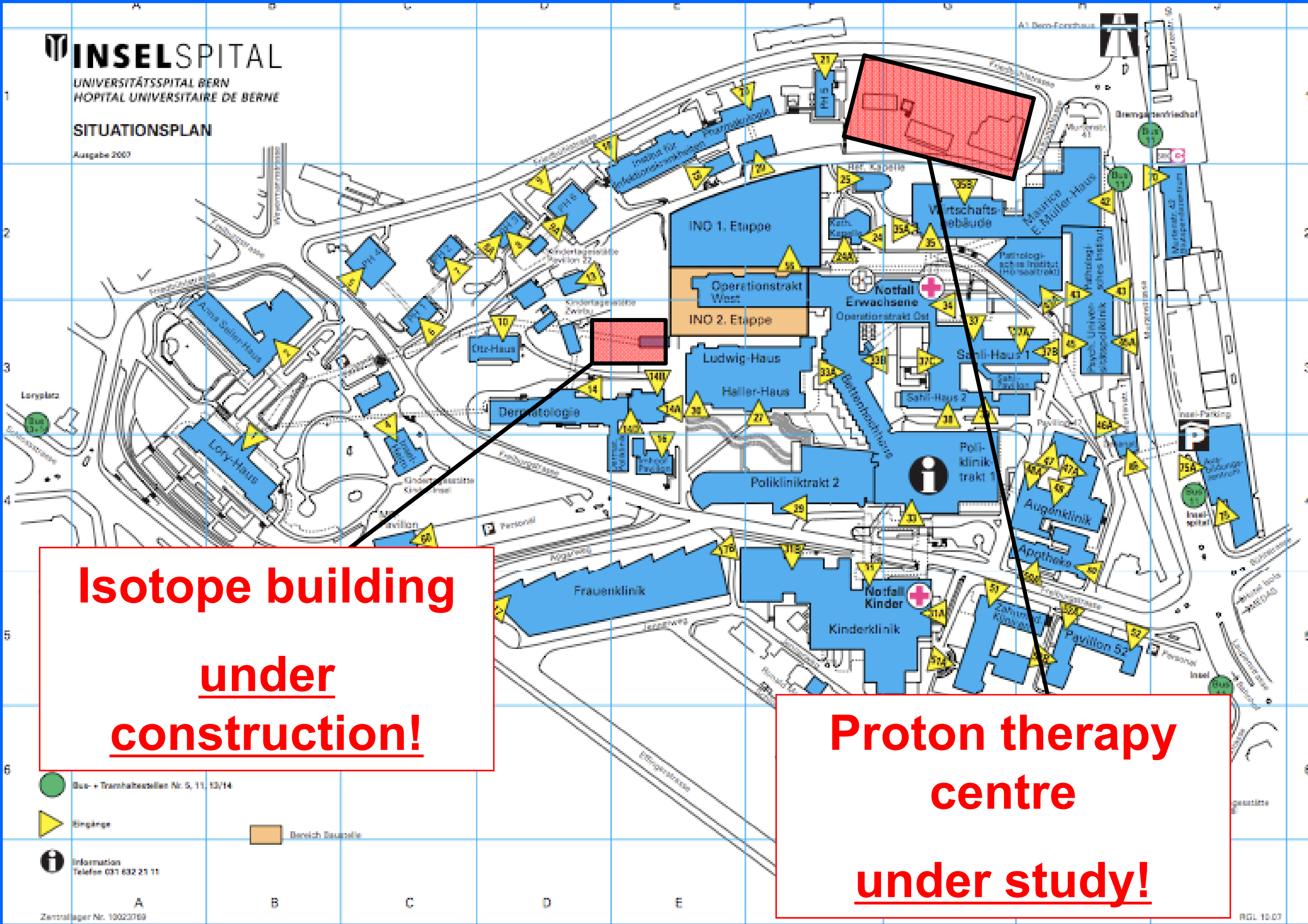
- If t<<τ the effect can be neglected
- If t>>τ saturation effect : production ~ decay
- For 18-F : the regime is far from saturation for t<120 min.

- Exercise – Taking this effect into account about 4.5 Ci of activity are produced in 60 min. irradiation

A realistic supply chain



The SWAN Project at the Inselspital in Bern



Isotope building

<u>under construction!</u>

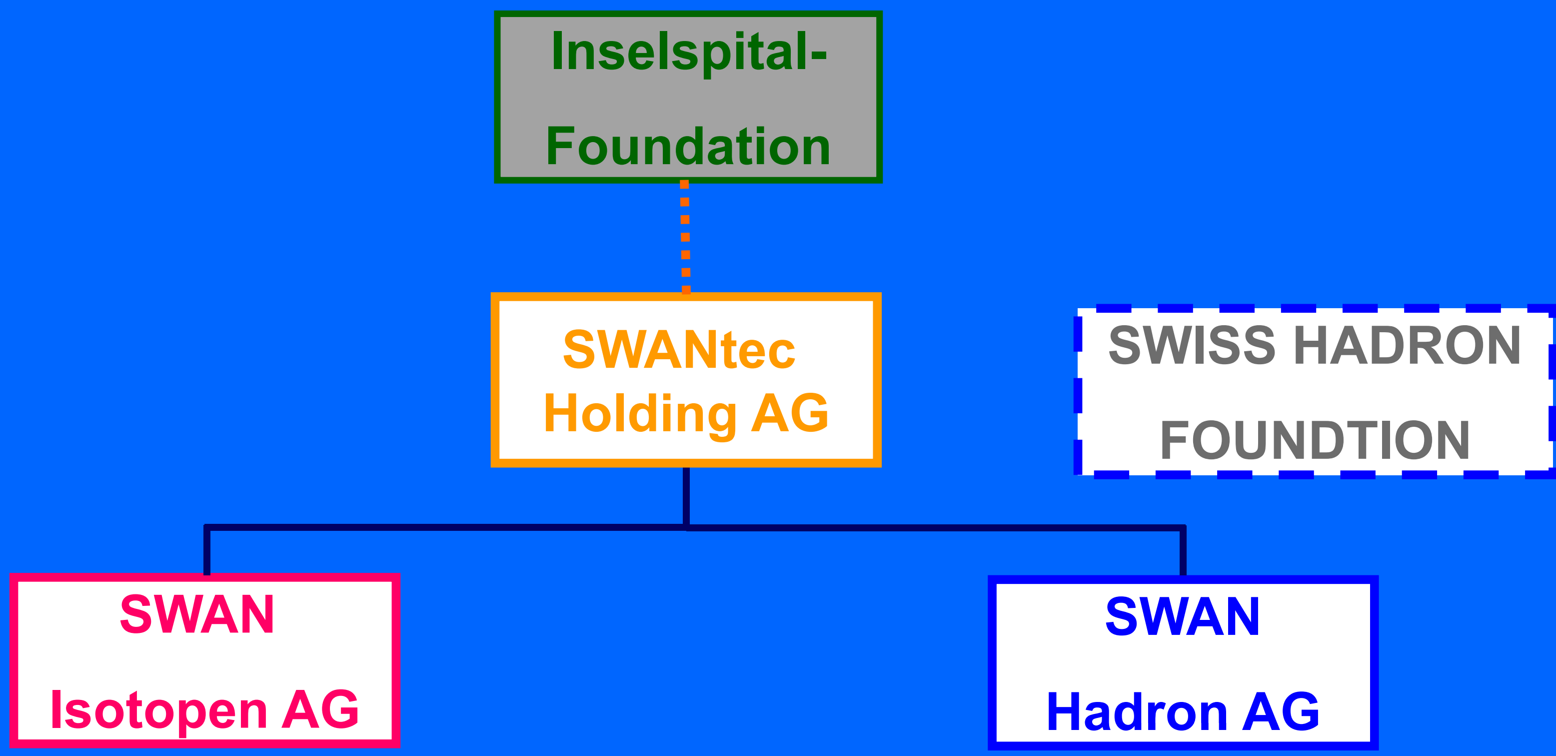
Proton therapy centre

<u>under study!</u>

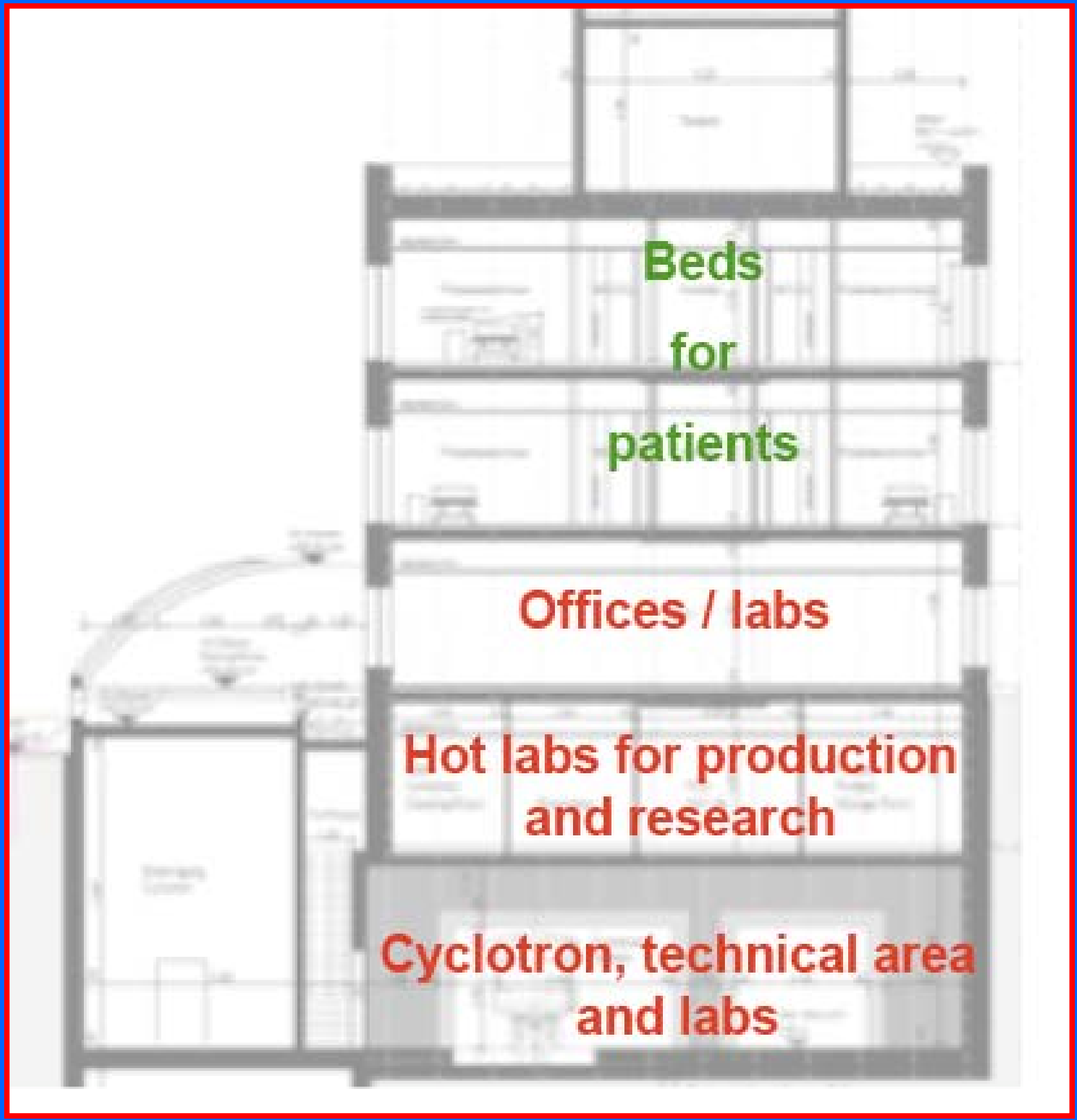
- Scope: constitute a combined centre for
  - Radioisotope production
  - Proton therapy
  - Research
- Short history
  - 2006/2007 first feasibility studies by Inselspital + Uni Bern
  - End 2007 approval and constitution of the main structure
  - 2008 detailed studies of the “Isotopen” part
  - 2009 start for the construction of the “Isotope building”
  - 2009 study for the implantation of the proton therapy centre
- Innovative structure involving public and private partners.
- Stakeholders:
  - Inselspital
  - University of Bern
  - Private investors

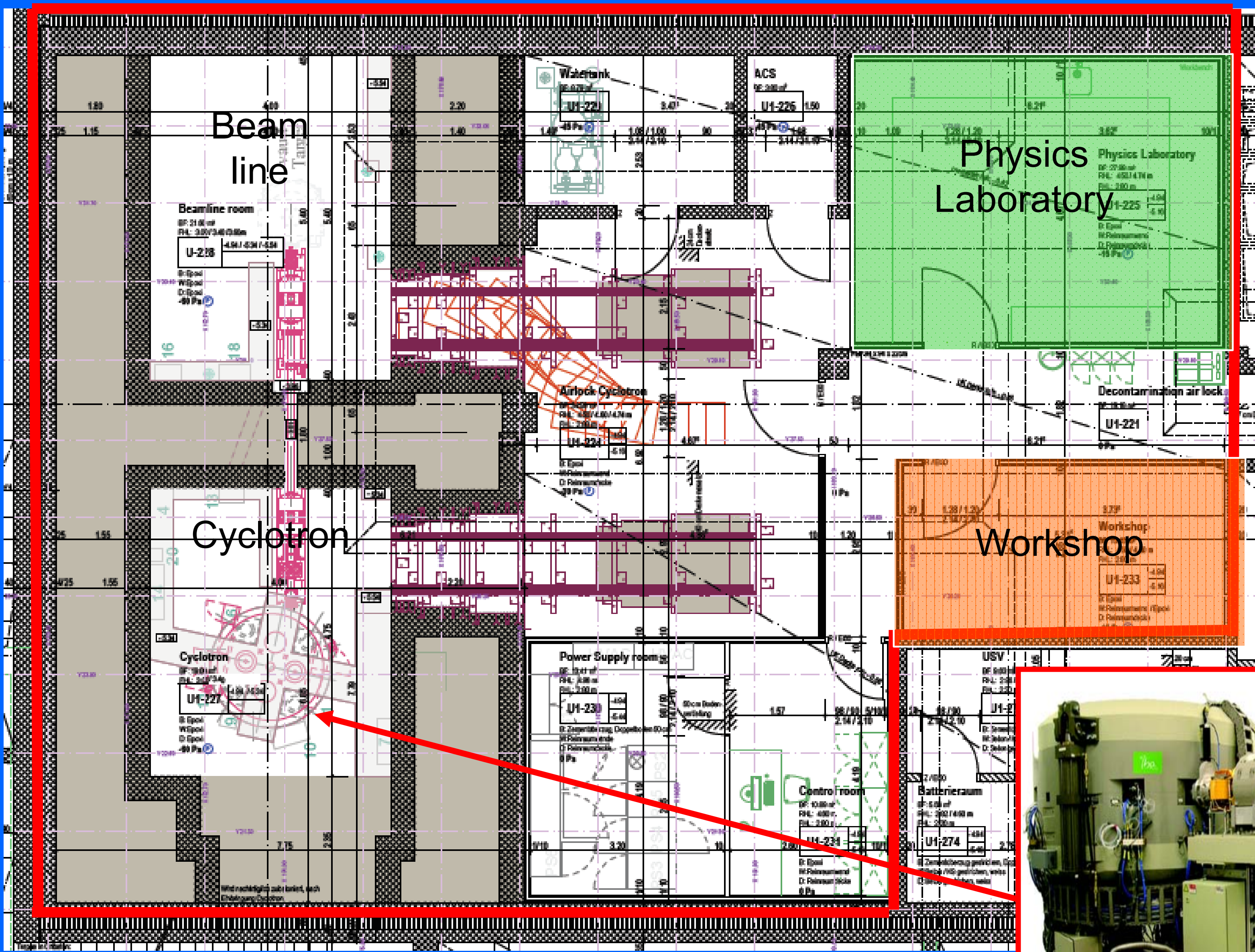
The swanTEC group

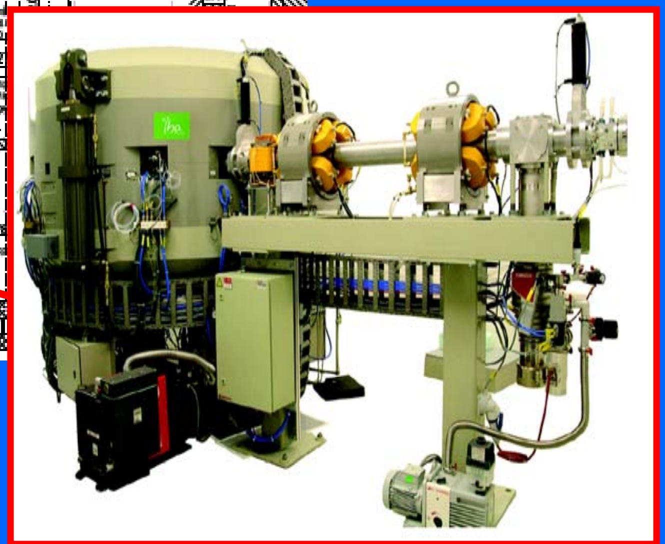
- SWAN stands for SWiss hAdroN
- Founded at the end of 2007
- Shareholders: Inselspital, University of Bern, private investors



Structure of the isotope building




Beam line
Physics Laboratory
Cyclotron
Workshop



Status of the construction (March 2010)

Many possible research activities

- **Fundamental physics**
  - **Positronium**

- **Particle detectors**
  - **Beam monitoring**
  - **Gamma-ray Resonant Absorption (GRA) related activities**
  - **Innovative detectors (tests, calibrations, etc.)**

- **Applied physics**
  - **PIXE (Proton Induced X-ray Emission)**
  - **PIGE (Proton Induced Gamma Emission)**
  - **PALS (Positron Annihilation Lifetime Spectroscopy)**
  - **TLA (Thin Layer Activation)**

- **Radiation bio-physics**

Many possible research activities

- **Targets**
- **Radiochemistry**
- **Clinical research**
  - **Oncology**
  - **Neurology**
  - **Cardiology**

Dedicated irradiation chamber in the beam line vault

(Picture from CNA, Sevile, Spain)

Radiation protection issues

- To screen 511 keV photons:
  - lead (about 10 cm) in hot cells
  - Lead: ρ=11.3 g/cm^3 ; $\mu\rho$=1.81 cm^{-1}; 10 cm ➔ Reduction factor = 1.4x10^{-8}
  - tungsten (about 5 cm) for transport containers

Hot cells host radiochemical modules

Transport container for the vials

Radiation protection issues

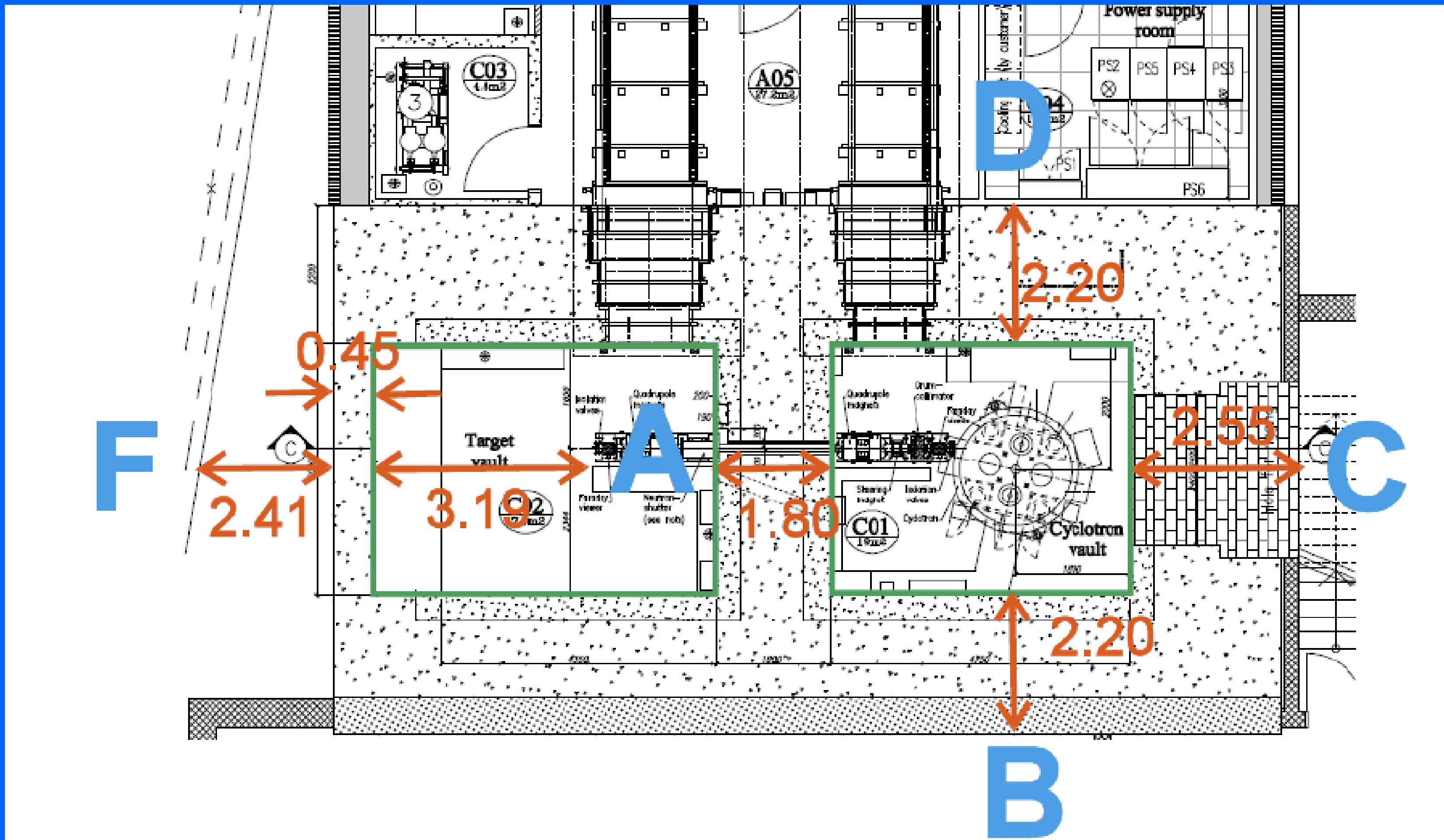
- **What about the cyclotron?**
- **The target is a very powerful neutron source!**
  - **p (18-O, 18-F) n**
  - **Neutrons are very dangerous (W in the range 10-20)**

Fattori di ponderazione della radiazione incidente per ottenere dalla dose assorbita (in Gy) il valore di dose equivalente (in Sv)

Tipo di radiazione	Fattore di ponderazione della radiazione (**Wr**)
Fotoni di tutte le energie ed elettroni	1
Neutroni di energia inferiore a 10 KeV	5
Neutroni tra 10 KeV e 100 KeV	10
Neutroni tra 100 KeV e 2 MeV	20
Neutroni tra 2 MeV e 20 MeV	10
Neutroni di energia maggiore di 10 MeV	5
Protoni	5
Particella alfa, nuclei pesanti	20

- **Neutrons become “thermal neutrons” and produce activation!**
  - **The choice of the materials is important!**

Shielding against neutrons



Shielding against neutrons

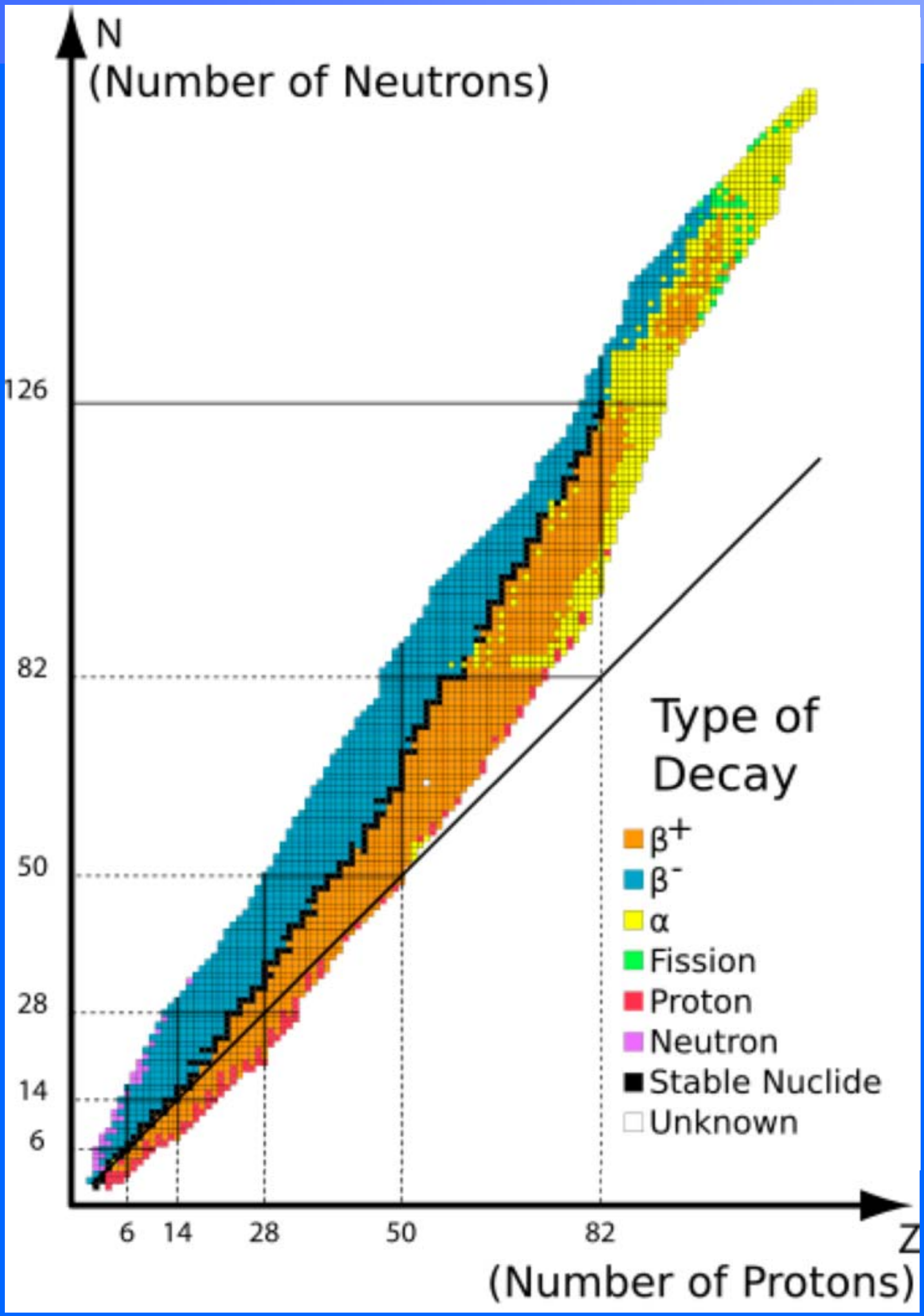
$$D = D_0 \left(\frac{d_0}{d_1}\right)^2 e^{-\frac{d_2}{\lambda}}$$

Tabelle 3: Schwächungslänge λ für Normalbeton für schnelle Neutronen.

λ [cm]	Quelle
17.02	Argonne National Laboratory, LS Note 116, 1988
15.7	NCRP51 F10 (1977), ($\rho = 2.35$ gcm^{-3})
13.8 – 15.7	< 50 MeV, IAEA Technical Report Series 188 Seite 189 ($\rho = 2.4$ gcm^{-3})
15.2	Concrete Radiation Shielding, Tabelle 10.24, M.F. Kaplan ($\rho = 2.2$ gcm^{-3})
5.9	$E_n = 2$ MeV, [3]

- **Concrete : λ=9.6 cm^{-1}; 200 cm ➔ Reduction factor = 9.2x10^{-10}**
- **Polyethilene : λ=4.17 cm^{-1}; 87 cm ➔ Reduction factor = 9.2x10^{-10}**

All this is possible thanks to artificially produced isotopes



The first table of isotopes comes from Rome!

TABELLE RIASSUNTIVE E BIBLIOGRAFIA DELLE TRASMUTAZIONI ARTIFICIALI

Nota di GIORGIO FEA (*)

Dato il grande sviluppo preso dallo studio delle trasmutazioni artificiali, sopratutto dopo l'impulso dato dalla scoperta della radioattività provocata, è parso utile, allo scrivente, riassumere in alcune tabelle sinottiche quanto è stato sin qui ottenuto dagli ormai moltissimi ricercatori, che si sono occupati dell'argomento.

Segue un'ampia bibliografia delle opere consultate per la compilazione delle tabelle stesse, e un quadro rappresentante, nel diagramma neutroni-protoni, quanto si conosce circa gli isotopi stabili e radioattivi.

Disposizione delle tabelle.

§ 1. Esse sono quattro, in corrispondenza dei quattro tipi di corpuscoli bombardanti considerati. e cioè:

1) Trasmutazioni ottenute con bombardamento di protoni e deutoni.
2) Trasmutazioni ottenute con bombardamento di nuclei d'elio.
3) Trasmutazioni ottenute con bombardamento di neutroni.
4) Trasmutazioni ottenute con bombardamento di fotoni.

Ciascuna tabella è divisa in otto colonne, nelle quali è riportato, salvo nella seconda parte della terza tabella, quanto segue:

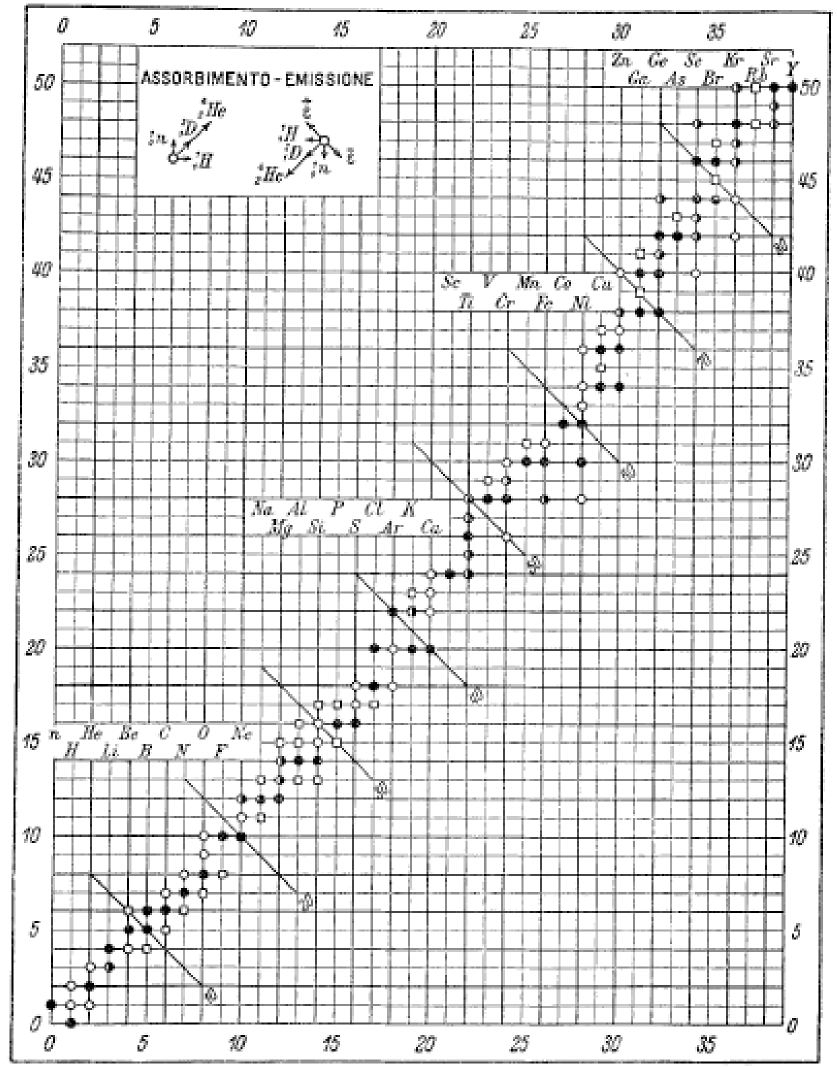
1) l'elemento bombardato, indicato col simbolo chimico e il numero atomico;

2) *a*: la energia del corpuscolo bombardante corrispondente ai dati energetici dei prodotti di trasmutazione riportati nella sesta colonna; questo dato ha importanza particolare per le trasmutazioni con nuclei d'elio, mentre può essere in generale trascurato nel caso di trasmutazioni con protoni e deutoni; perciò esso manca nella prima tabella.

b: in parentesi quadra e con segno > quella che da molti autori è data come energia minima per l'emissione dei corpuscoli indicati accanto in parentesi (se manca l'indicazione del corpuscolo il dato si riferisce alla

(*) Si presentano la bibliografia e le tabelle riassuntive di tutte le trasmutazioni artificiali studiate sino al Maggio 1935.

QUADRO PROTONI-NEUTRONI - I.



Georgio Fea. Il Nuovo Cimento 2 (1935) 368

End of part II