Medical Applications of Particle Physics: from the First Radiography to Hadrontherapy

Saverio Braccini

Albert Einstein Center for Fundamental Physics
LHEP – Laboratory for High Energy Physics
University of Bern, Switzerland

saverio.braccini@cern.ch

Outline

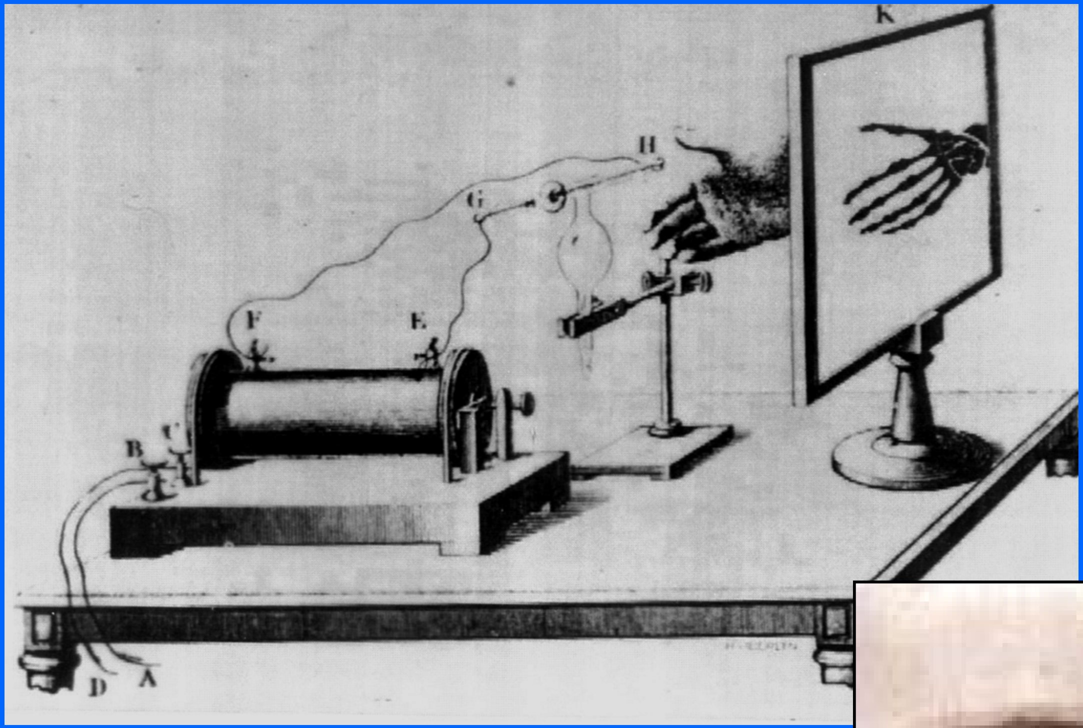
1. **Introduction: a historical overview**
   - Physics and medicine: two paths, many crossroads
   - The first radiography and the concept of dose
2. **Modern medical diagnostics**
3. **Particle accelerators for medicine**
4. **Conventional radiation therapy**
5. **Basic principles of hadrontherpy**
6. **Present and future of hadrontherapy**
7. **A tour in a hadrontherapy centre**
8. **Specific topics in hadrontherapy**

Fundamental research in particle physics and modern medicine

Two paths, many crossroads

- **November 1895 : discovery of X rays**

Wilhelm Conrad Röntgen



- **December 1895 : first radiography**

…the real first medical radiography…

Radiography of the hand of

Roentgent's wife Bertha

Important points:

- X-rays penetrate matter
- X-rays are differently absorbed by bone and muscle tissues
- Exposure time 15 minutes
- Exposure nowadays for a hand radiography:
  - 1/25 to 1/50 second
  - Dose: about <0.1 mSv (natural background 1-2 mSv/year)

Curiosities

- Roentgen convinced his wife to participate in an experiment
- Bertha was horrified and saw in the image a premonition of death

Basic units

- The physical dose absorbed by matter is measured in Gray
  - 1 Gy = 1 J / 1 Kg
  - Used in radiation therapy

- In radioprotection the dose equivalent is measured in Sievert
  - Dose Equivalent = (Physical dose) x Wr
  - Wr takes into account the biological effects of specific radiation

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

Basic units

- In radioprotection the effective dose is defined as
  - Effective dose = (Physical dose) x Wr x Wt
  - Wt takes into account the sensitivity to radiation of different organs for stochastic effects

Fattori di ponderazione tessutale per ottenere il passaggio dalla dose equivalente alla dose efficace (secondo ICRP 60/1990 o L.241/00)

Tessuto/Organo	Fattore di ponderazione tessutale **Wt** Icrp60
Gonadi	0,20
Colon	0,12
Esofago	0,05
Fegato	0,05
Mammella femminile	0,05
Midollo rosso	0,12
Pelle	0,01
Polmone	0,12
Stomaco	0,12
Superficie ossea	0,01
Tiroide	0,05
Vescica	0,05
Organi restanti	0,05

Dose equivalent and effective dose

- **Wr is a multiplicative factor to take into account the "biological effectiveness" of radiation**

- **Wt has a different meaning**
  - **Σ Wt = 1**
  - **If the dose is "full body" ➔ dose equivalent = effective dose**
  - **If the irradiation is not homogeneous (ex. The dose is given only to one organ) the effective dose represents the dose equivalent given to the full body which produces the same risk.**

- **Risk for stochastic effects:**

Annual limit for radio exposed workers

Annual effective dose (mSv)	10	20	30	50
Lifetime dose (Sv)	0.5	1.0	1.4	2.4
Probability of death linked to exposure (%)	1.8	3.6	5.3	8.6
Contribution of non-fatal cancers (%)	0.4	0.7	1.1	1.7
Contribution of hereditary effects (%)	0.4	0.7	1.1	1.7

Stochastic and deterministic effects of radiation

- **The cancer induction risk factor is estimated at 4% Sv-1 for a population of workers and at 5 % Sv-1 for the general population (children included!)**

- **The threshold dose of deterministic effects is situated at 0.5 Gy.**
- **Deterministic effects:**

Syndrome	Dose range (Gy)	Survival time (days)
Hematopoietic	3-5	30-60
Gastro-intestinal	5-15	10-20
Central nervous system	>50	1-5

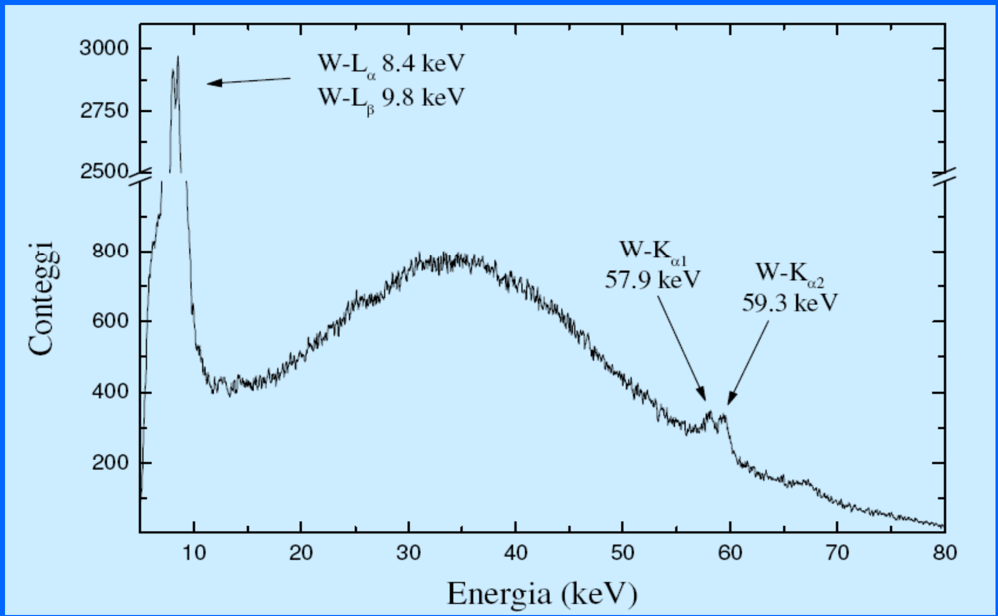
Dose (Gy)	Dose range (Gy)
3−5	Erythema and dry desquamation
20	Wet desquamation with blister formation
50	Skin necrosis

- **The aim of radiation therapy is to cure i.e. to produce deterministic effects**
- **The doses are therefore large (of the order of 60-80 Gy) and there are no limits for patients coming form laws on radiation protection**

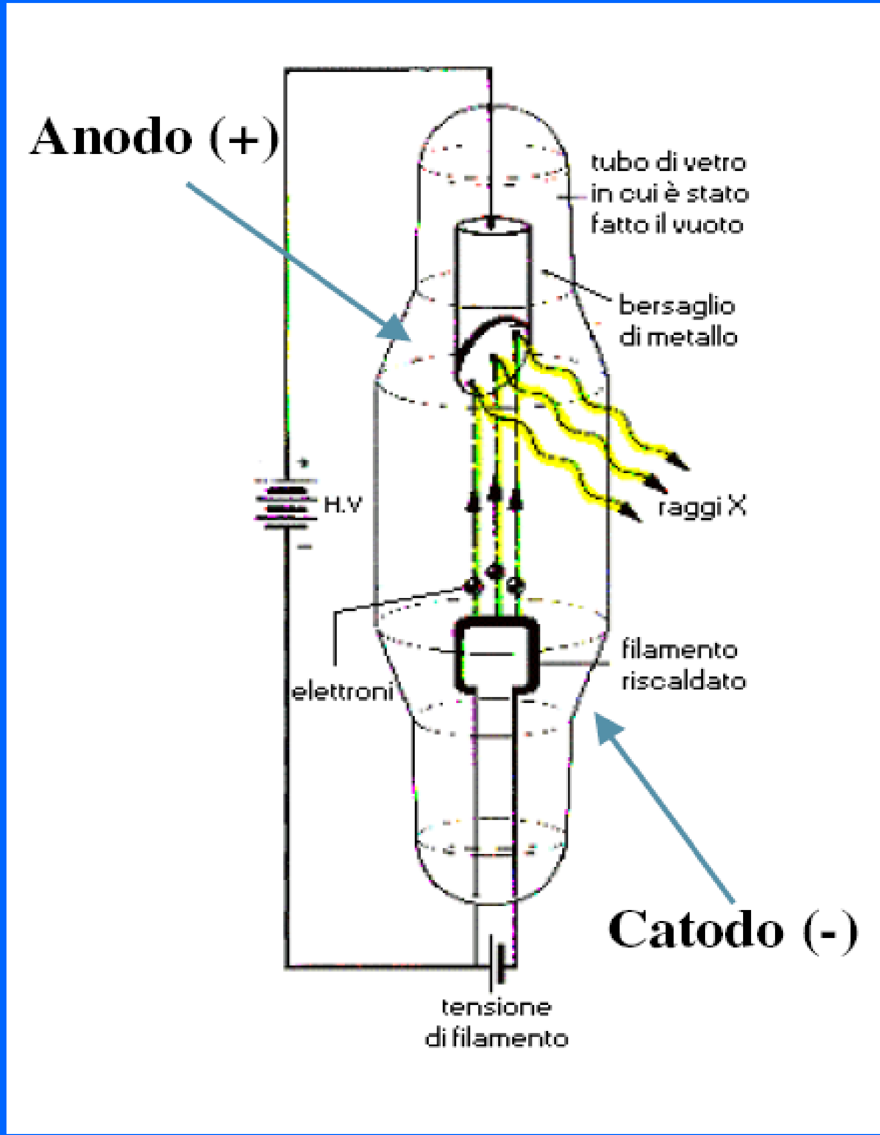
X-ray tube : accelerated electrons interact and radiate photons

=

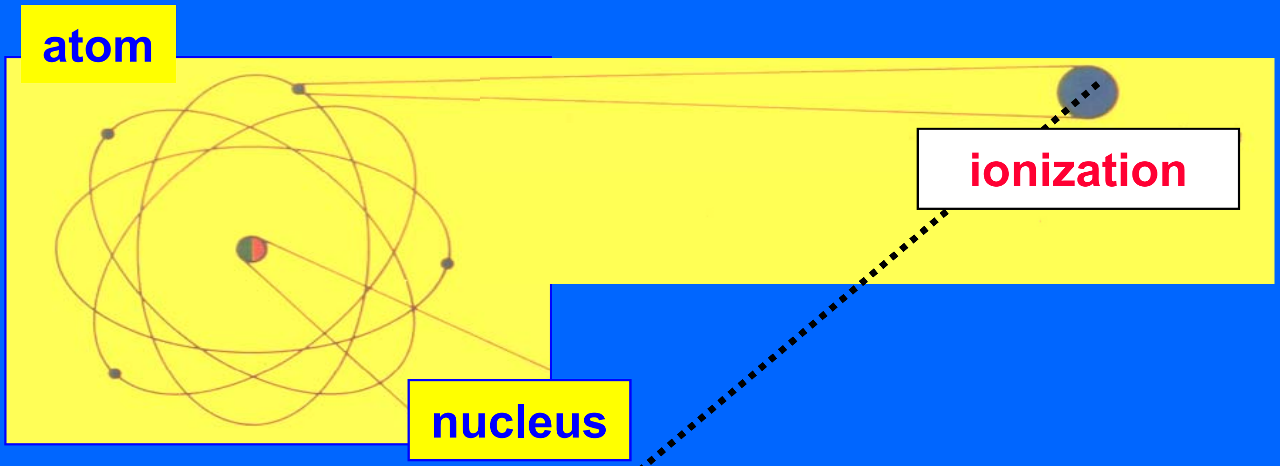
X-ray production



X-ray energy spectrum



Production of X and γ "quanta"



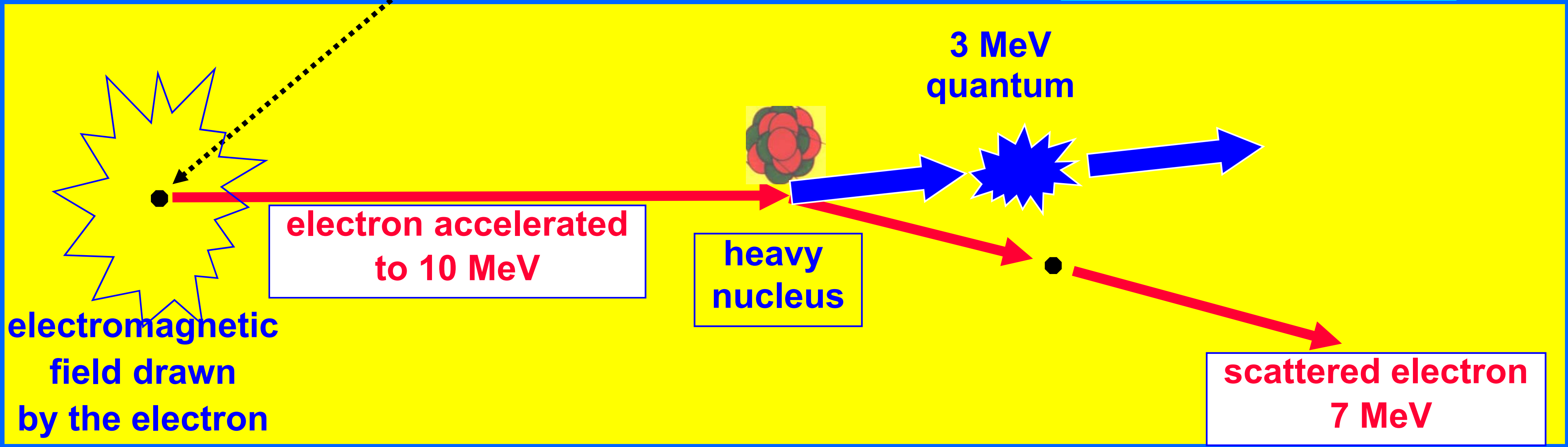
Physicists:

keV → X quanta

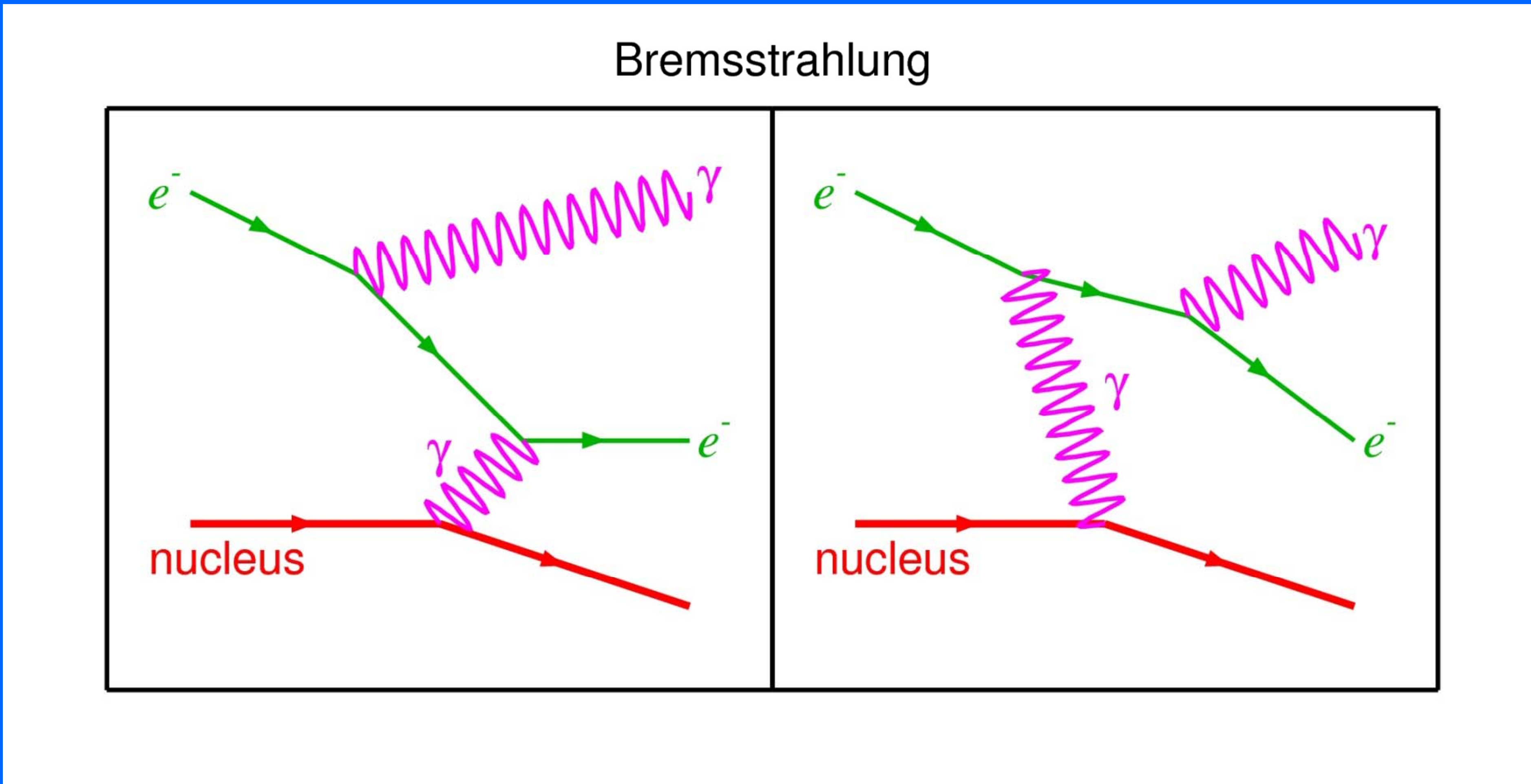
MeV → γ quanta

Medical doctors:

They are all X rays!



The physical process



X-rays interact with matter (material Z) through different mechanisms:

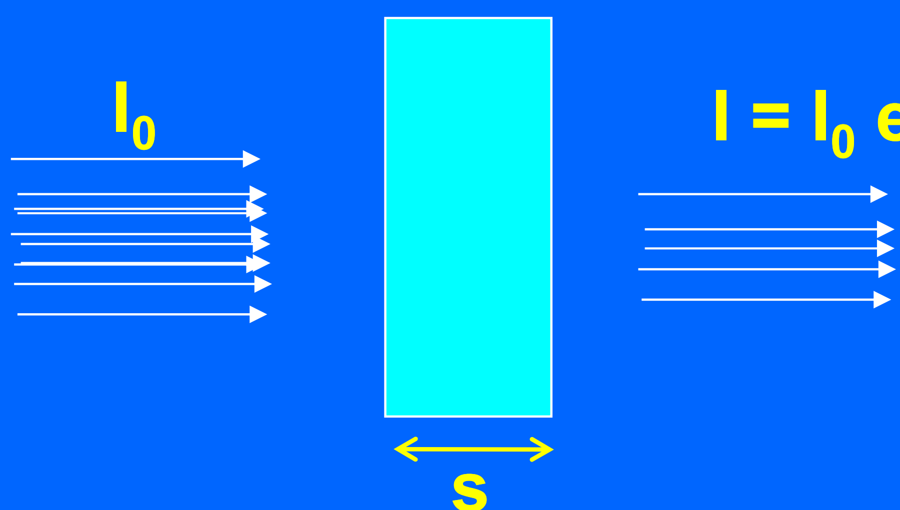
- **Photo-electric effect**
- **Compton effect**
- **Electron Positron pair production**

  (Threshold : 2 x 511 keV)

Probability

$$\propto \begin{cases} Z^4 \\ Z \\ Z^2 \end{cases}$$

What happens to a photon beam ?



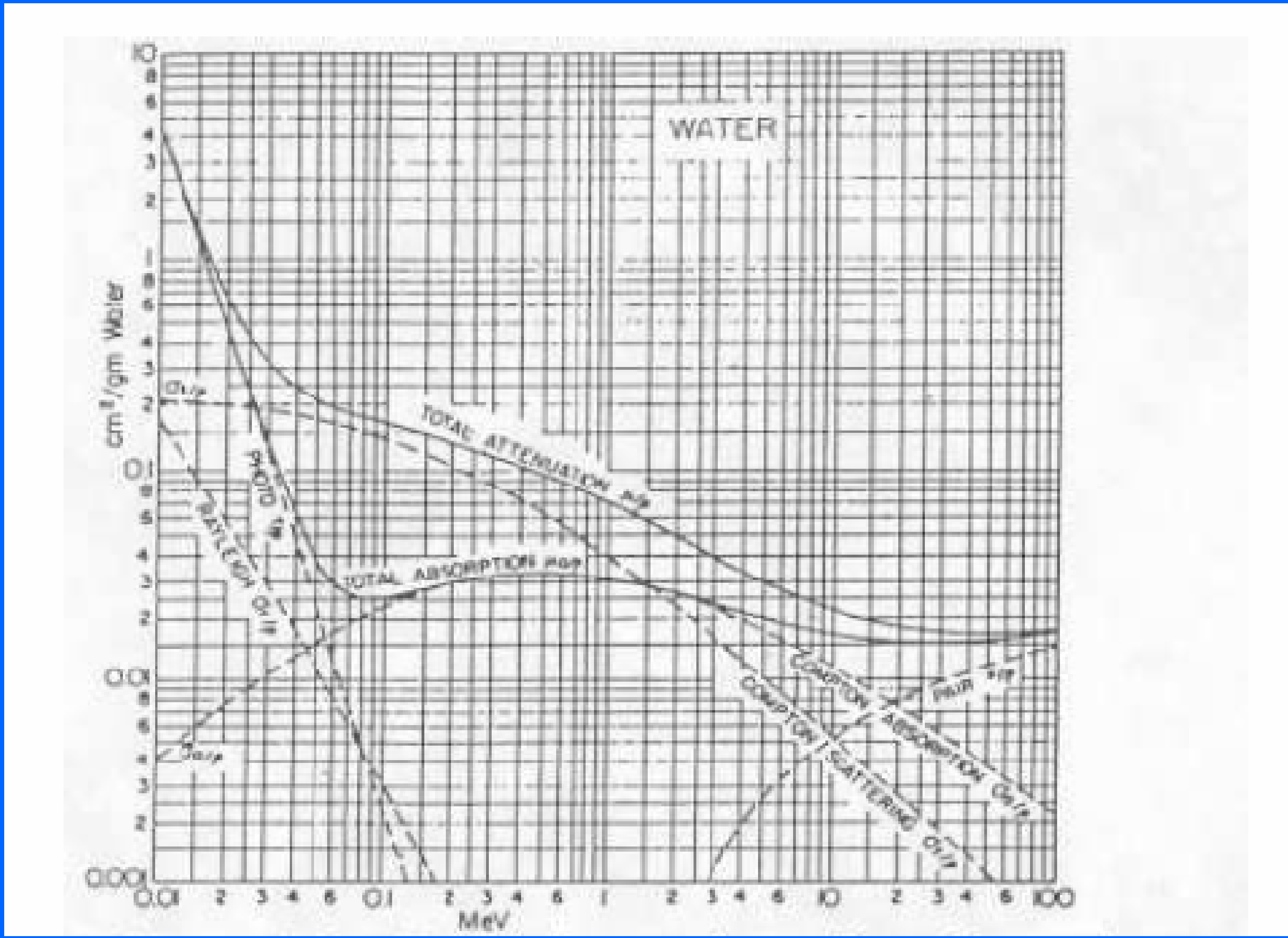
$$I = I_0 \, e^{-\mu s}$$

μ attenuation coefficient

Depends on:

- **The material (z)**
- **The density**
- **The energy of the photons**

The attenuation coefficient

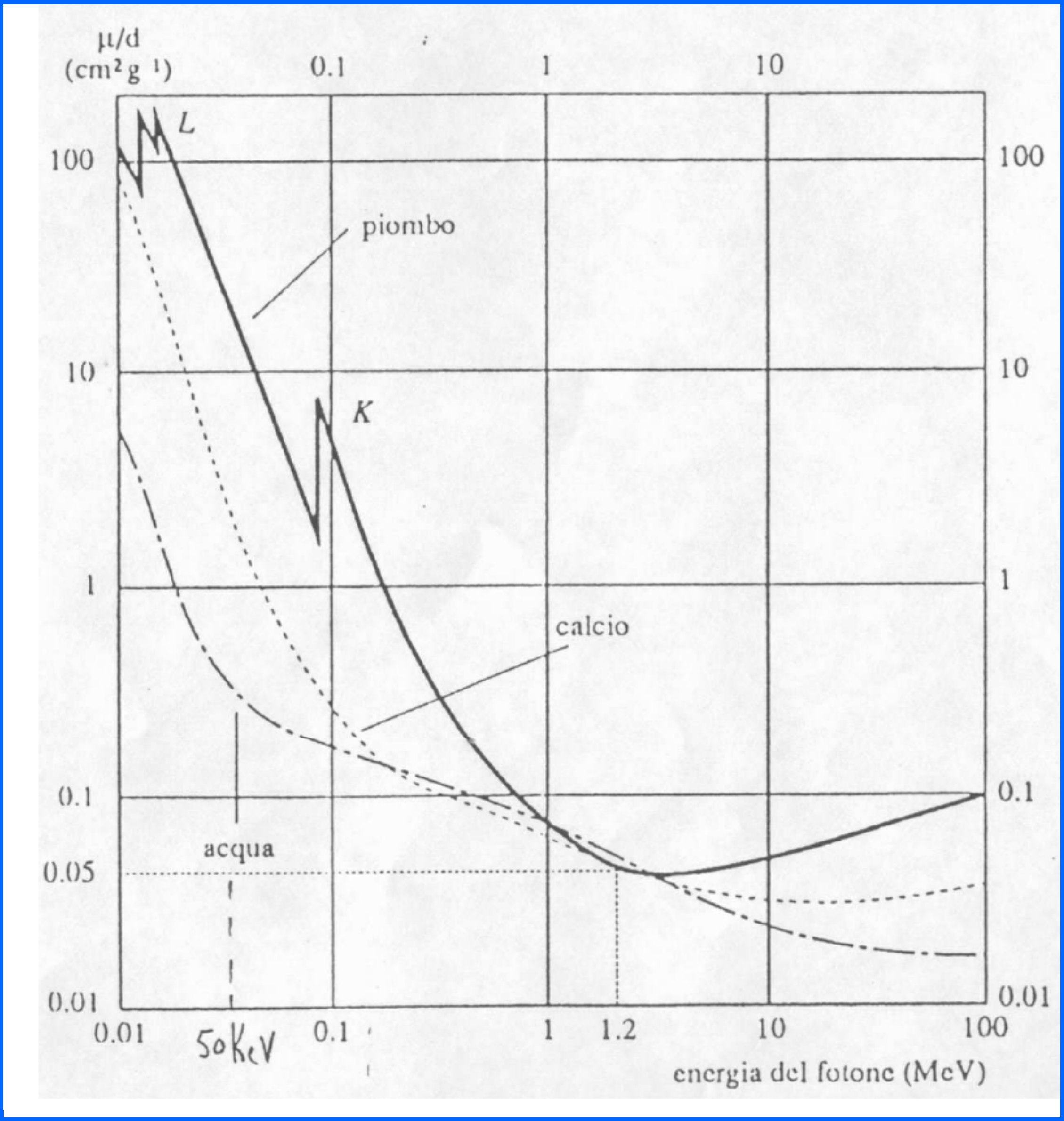


Why water?

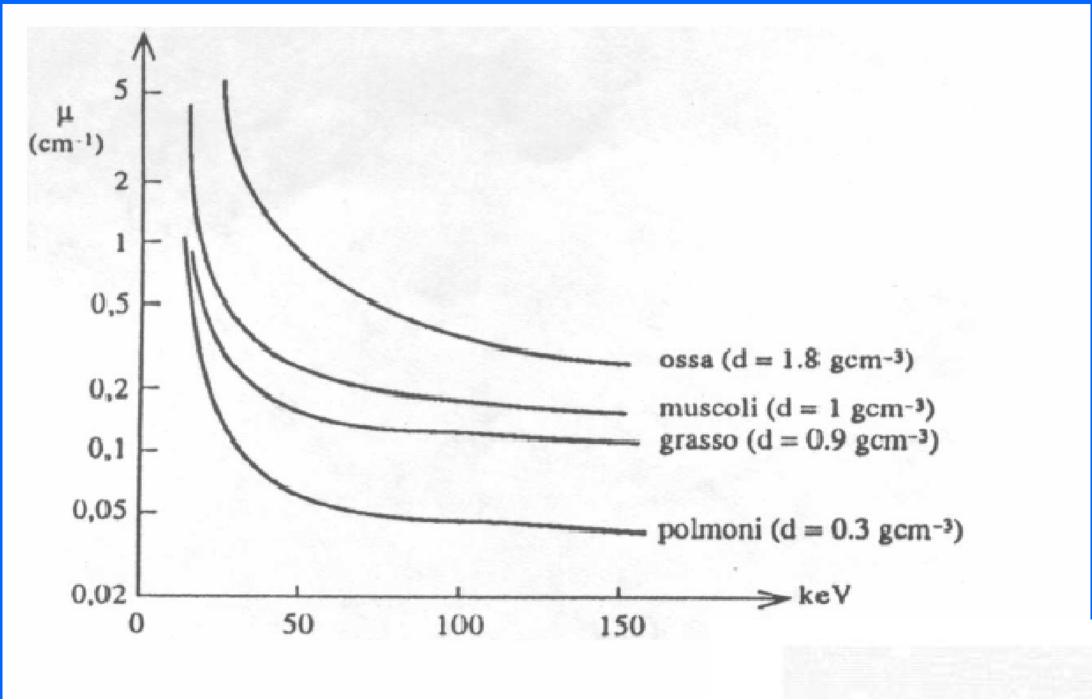
Water is the main component of tissues

"Water equivalent" a very used concept in medical applications

Water and other materials

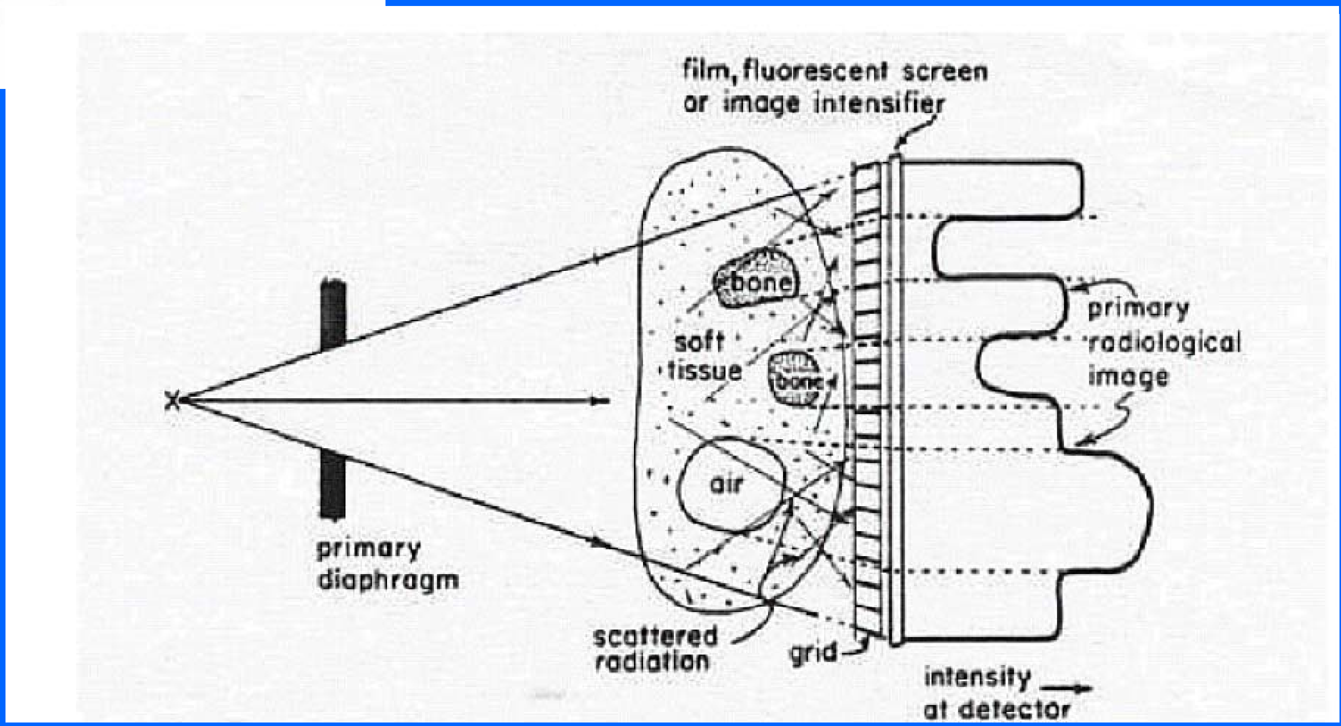


Let's get back to Roentgen



Many X-rays stop in the tissues

Dose to the patient!



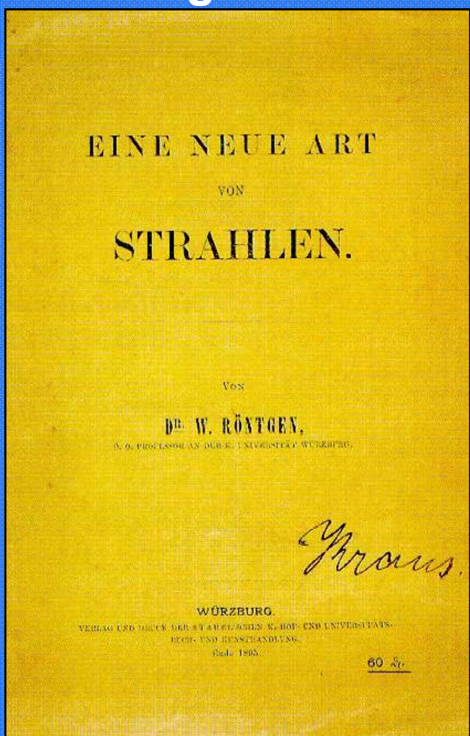
The beginning of modern physics and medical physics

Wilhelm Conrad Röntgen

1895 – starting date of four magnificent years in experimental physics

1895

discovery of X rays


EINE NEUE ART

VON

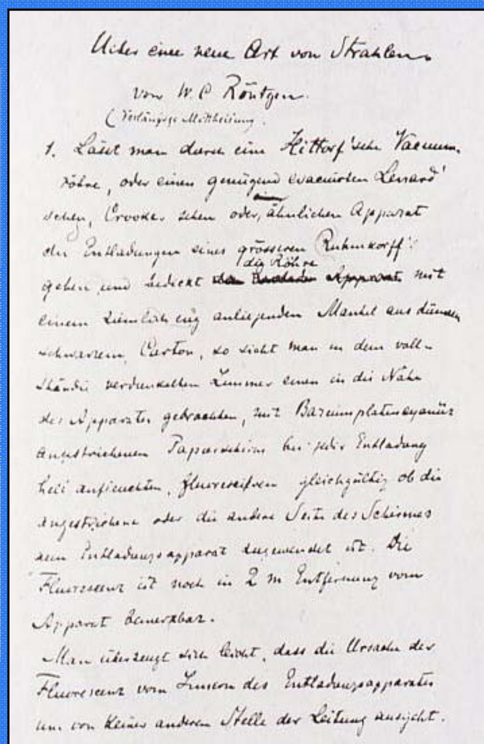
STRAHLEN.

VON

DR. W. RÖNTGEN,

WÜRZBURG.

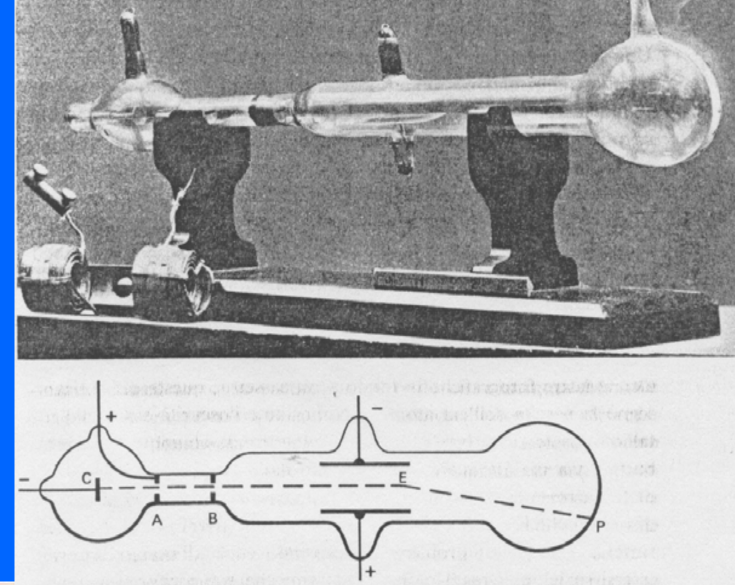
60 Pf.

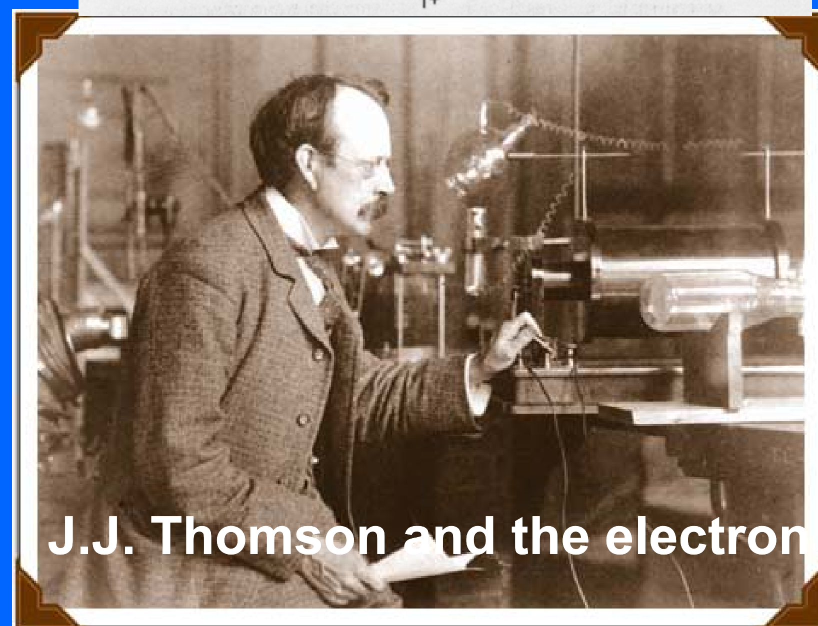

Ueber eine neue Art von Strahlen
von W. C. Röntgen
(Vorläufige Mittheilung)

1. Lässt man durch eine Hittorf'sche Vacuumröhre, oder einen genügend evacuirten Lenard'schen, Crookes'schen oder ähnlichen Apparat die Entladungen eines grösseren Ruhmkorff's gehen und bedeckt die Röhre mit einem ziemlich eng anliegenden Mantel aus dünnem, schwarzem Carton, so sieht man in dem vollständig verdunkelten Zimmer einen in die Nähe des Apparates gebrachten, mit Bariumplatincyanür angestrichenen Papierschirm bei jeder Entladung hell aufleuchten, fluoresciren, gleichgültig ob die angestrichene oder die andere Seite des Schirmes dem Entladungsapparat zugewendet ist. Die Fluorescenz ist noch in 2 m Entfernung vom Apparat bemerkbar.

Man überzeugt sich leicht, dass die Ursache der Fluorescenz vom Innern des Entladungsapparates und von keiner anderen Stelle der Leitung ausgeht.

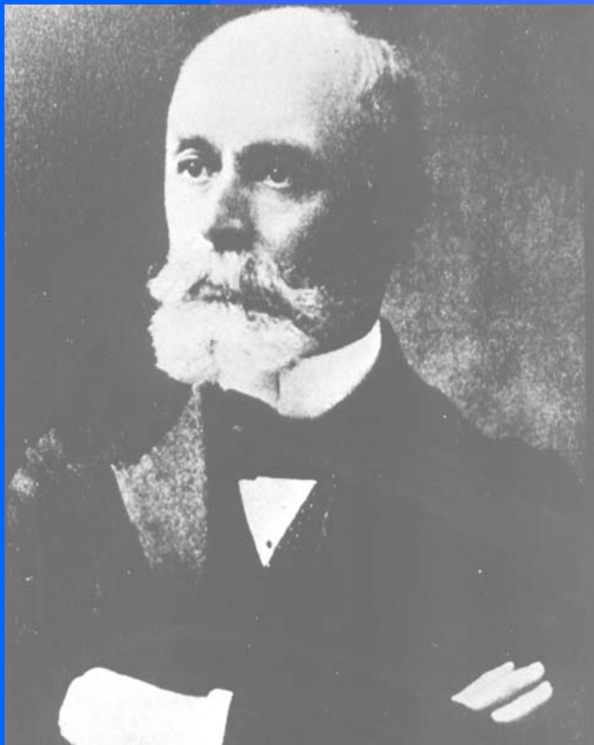
An accelerator of 1897





J.J. Thomson and the electron

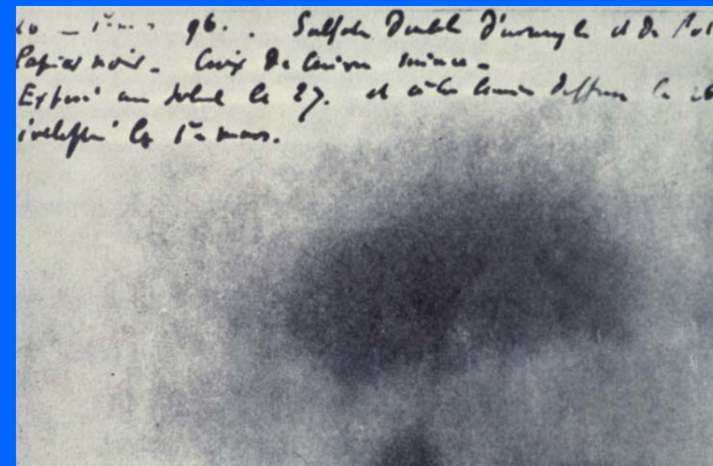
The beginning of modern physics and medical physics



Henri Becquerel
(1852-1908)

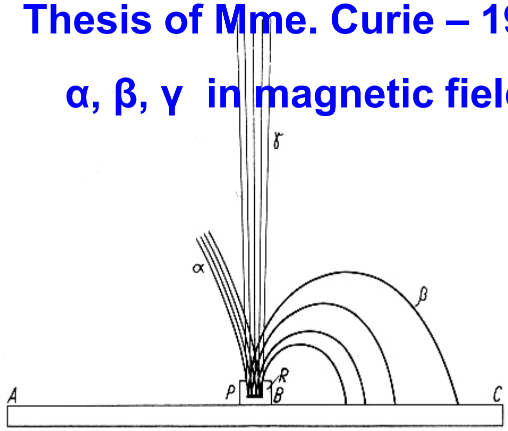
1896:

Discovery of natural radioactivity



Thesis of Mme. Curie – 1904

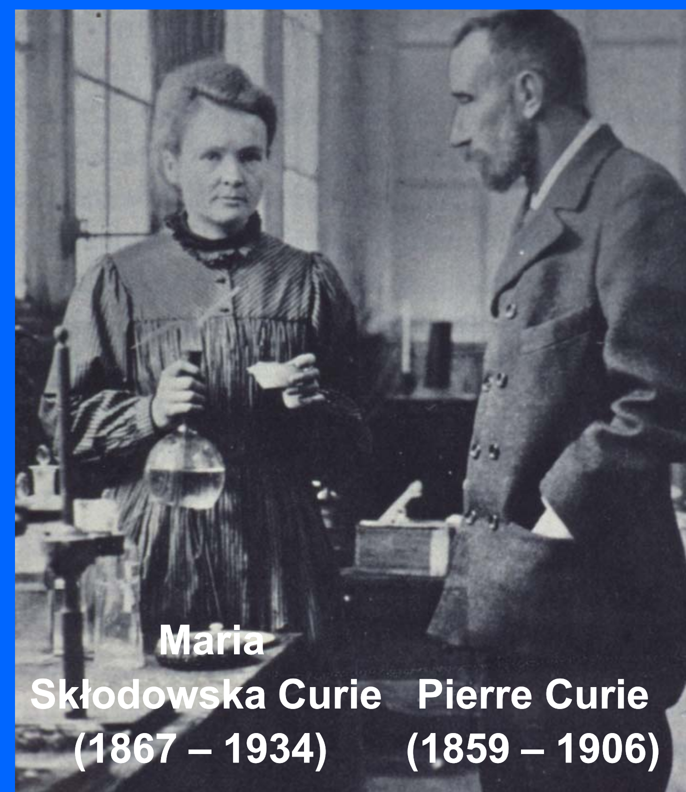
α, β, γ in magnetic field



About one hundred years ago

1898

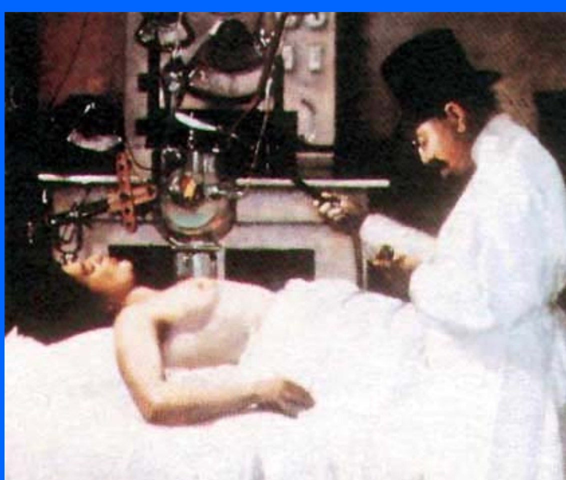
Discovery of radium



Maria Skłodowska Curie (1867 – 1934)   Pierre Curie (1859 – 1906)

Basic concept

Local control of the tumour



1908 : first attempts of skin cancer radiation therapy in France ("*Curiethérapie*")

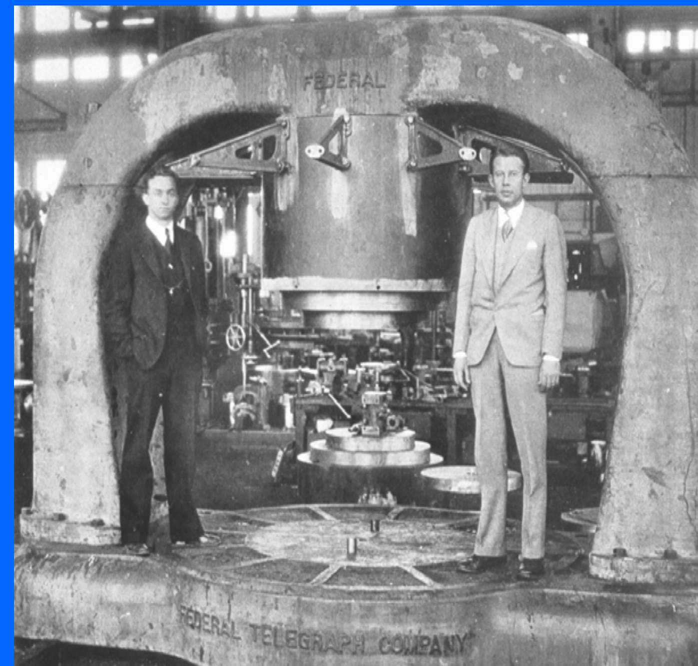
A big step forward…

…in physics and in

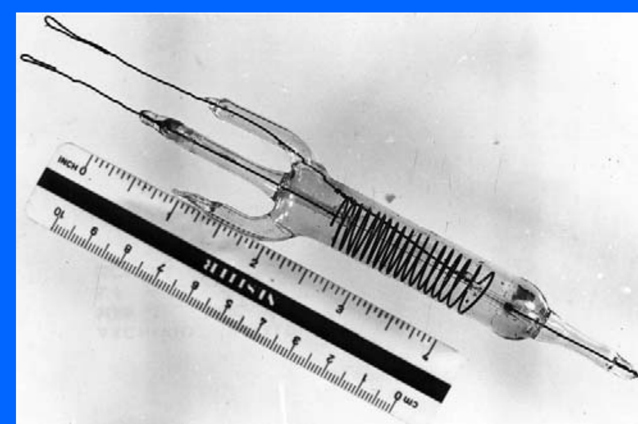
- Medical diagnostics
- Cancer radiation therapy

due to the development of three fundamental tools

- Particle accelerators
- Particle detectors
- Computers



M. S. Livingston and E. Lawrence
with the 25 inches cyclotron

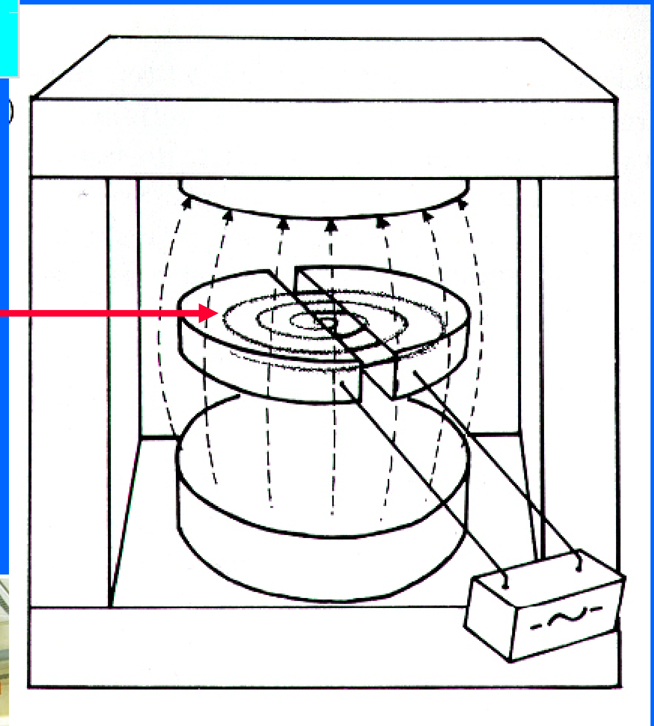


Geiger-Müller counter built by
E. Fermi and his group in Rome

1930: the beginning of four other magnificent years

1930: invention of the cyclotron

Spiral trajectory of an accelerated nucleus



Ernest Lawrence

(1901 – 1958)

A copy is on display at CERN Microcosm

The invention of the cyclotron

- Magnet of 9 inches = 22.8 cm
- Magnetic field of 15 000 gauss = 1.5 T

represent respectively the magnetic and optical anisotropies of the negative ion present in it. It is significant that the values for the three carbonates are practically the same, as are also the values for the two nitrates.

TABLE I.

Crystal	$(\chi_\perp - \chi_\parallel)\cdot 10^6$	$R_0 - R_e$
$CaCO_3$ (calcite)	4.1	2.94
$CaCO_3$ (aragonite)	4.1	2.41
$SrCO_3$	3.8	2.72
$NaNO_3$	4.7	4.83
KNO_3	4.8	4.32
$KClO_3$	−3.8	2.12

What is remarkable is whereas for the CO_3^{--} and NO_3^- ions the diamagnetic susceptibility along the axis of symmetry is numerically a *maximum*, in the case of the ClO_3^- ion it is numerically a *minimum* along its axis; although optically all the three ions behave similarly.

It may also be remarked that the values given in the table would suggest a positive magnetic double-refraction for the nitrate and carbonate ions in solution, and a negative value for the chlorate ion under the same conditions. Observations are available only for the nitrate ion and are in agreement with the above conclusion. (K. S. Kirshnan and C. V. Raman, Roy. Soc. Proc. **A115**, 549, 1927.) It would be interesting to confirm the negative magnetic double-refraction of the chlorate ion in solution.

K. S. KRISHNAN

Physics Laboratory,
Dacca University, India,
July 11, 1931.

The Production of High Speed Protons Without the Use of High Voltages

A method for the production of high speed protons without the use of high voltages was described before the meeting of the National Academy of Sciences last Semptember (Lawrence and Edlefson, Science **72**, 376–377, 1930). Later before the American Physical Society (Lawrence and Livingston, Phys. Rev **37**, 1707, 1931) results of a preliminary study of the practicability of this method were presented. In this preliminary experimental work 80,000-volt hydrogen molecule ions were successfully produced in a vacuum tube in which the maximum applied potential was less than 2,000 volts, and the conclusion of the experiments was that there are no serious difficulties in the way of producing 1,000,000-volts protons in this indirect manner.

This important conclusion has now been confirmed. A magnet having pole faces nine inches in diameter and producing a field of 15,000 gauss has recently been constructed and with its aid protons and hydrogen molecule ions having energies in excess of one half million volt-electrons have been produced.

The magnitudes of the high speed hydrogen ion currents turned out to be surprisingly large, being in excess of one-tenth of one microampere. The proton currents were about one-tenth this value.

The voltage amplification obtained in the present experiment was approximately one hundred. That is to say, about five thousand volts were applied to the tube for the production of five hundred thousand volt ions. This amplification was limited by the slit system used to select out the high speed ions, and can be greatly increased by better design of this part of the tube.

There can be little doubt that one million volt ions will be produced with intensities as great as here recorded when the present experimental tube is enlarged to make full use of the magnet. This alteration is now being carried out.

These experiments make it evident that with quite ordinary laboratory facilities proton beams having great enough energies for nuclear studies can be readily produced with intensities far exceeding the intensities of beams of alpha-particles from radioactive sources.

Possibly the most interesting consequence of these experiments is that it appears now that the production of 10,000,000-volt protons can be readily accomplished when a suitably larger magnet and high frequency oscillator are available. The importance of the production of protons of such speeds can hardly be overestimated and it is our hope that the necessary equipment for doing this will be made available to us.

We are very much indebted to the Federal Telegraph Company, through the courtesy of Dr. Leonard F. Fuller, Vice-president, for the loan of essential parts of the apparatus used in this work.

ERNEST O. LAWRENCE
M. STANLEY LIVINGSTON
University of California,
July 20, 1931.

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E. O. Lawrence and M. S. Livingston, Physical Review, 38 (1931) 834.

The Lawrence brothers

Ernst Lawrence and his brother John Lawrence at the control panel of the 60-inch (152 cm) cyclotron shortly.

The Lawrence brothers

John H. Lawrence made the first clinical therapeutic application of an artificial radionuclide when he used phosphorus-32 to treat leukemia. (1936)

- John Lawrence, brother of Ernest, was a medical doctor
- They were both working in Berkley
- First use of artificially produced isotopes for medical diagnostics and therapy
- Beginning of nuclear medicine

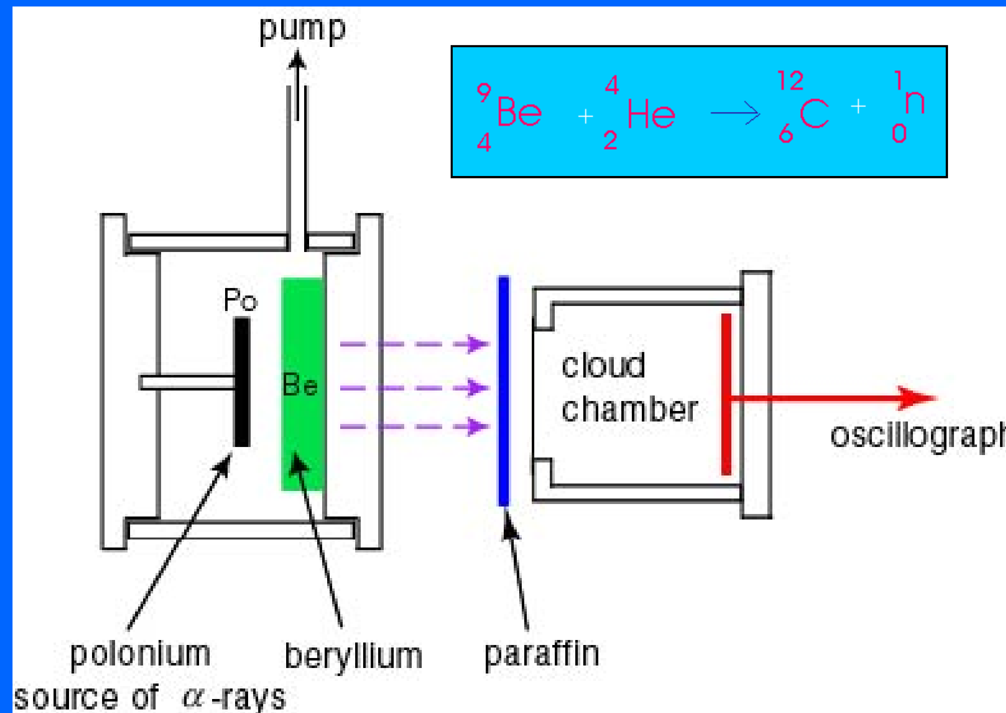
An interdisciplinary environment helps innovation!

Discovery of the neutron

1932

James Chadwick

(1891 – 1974)



Student of

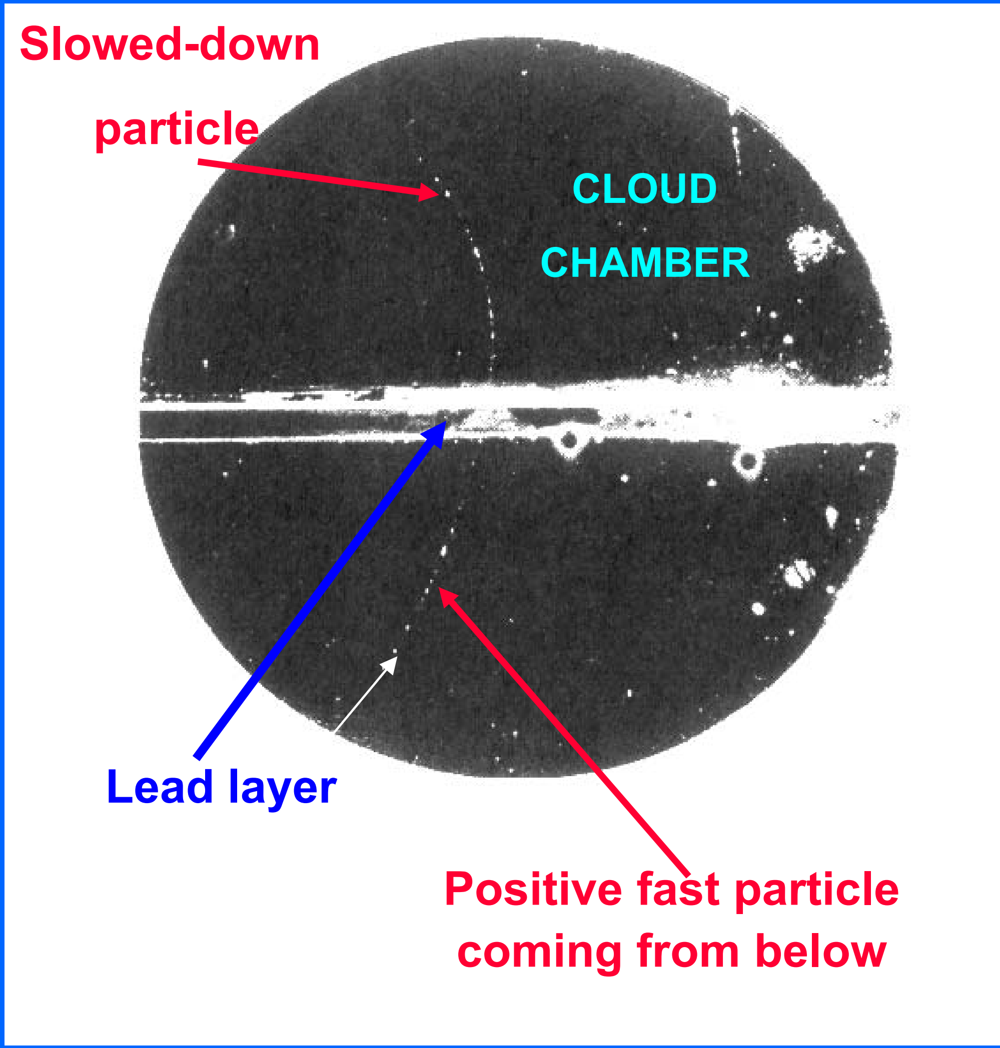
Ernest Rutherford

Neutrons are used today to

- Produce isotopes for medical diagnostics and therapy
- Cure some kind of cancer

Matter and antimatter...

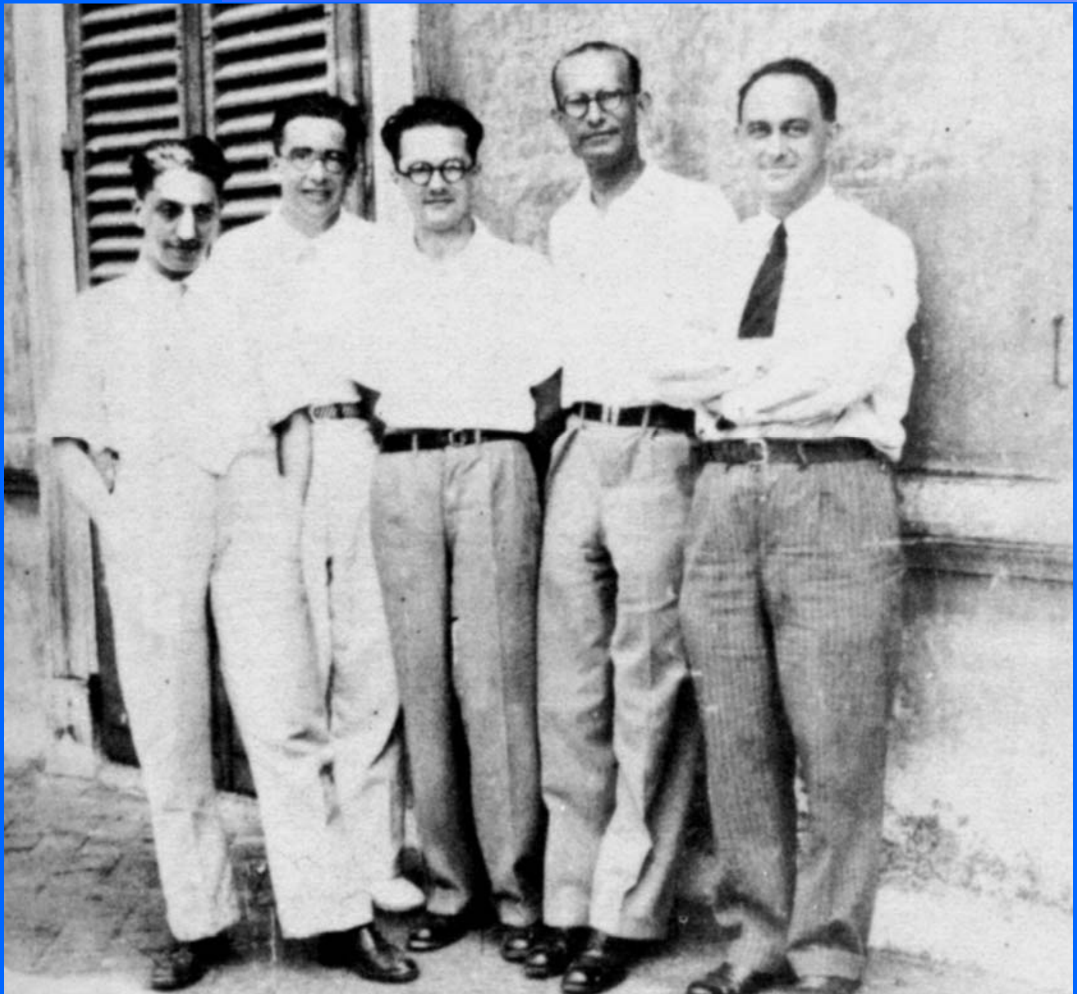
1932 – discovery of antimatter: the positron



Carl D. Anderson - Caltech

The positron is at the basis of Positron Emission Tomography (PET)

Discovery of the effectiveness of slow neutrons



O. D'Agostino E. Segrè E. Amaldi F. Rasetti E. Fermi

1934

First radioisotope of Iodine

among fifty new artificial species

RADIOATTIVITÀ « BETA » PROVOCATA DA BOMBARDAMENTO DI NEUTRONI. — III.

E. AMALDI, O. D'AGOSTINO, E. FERMI, F. RASETTI, E. SEGRÈ

« Ric. Scientifica », 5 (1), 452–453 (1934).

Sono state proseguite ed estese le esperienze di cui alle Note precedenti [1] coi risultati che ricordiamo appresso.

Idrogeno – Carbonio – Azoto – Ossigeno. – Non dànno effetto apprezzabile. Sono stati esaminati paraffina irradiata al solito modo per 15 ore con una sorgente di 220 mC, acqua irradiata per 14 ore con 670 mC e carbonato di guanidina irradiato per 14 ore con 500 mC.

Fluoro. – Il periodo del Fluoro è sensibilmente minore di quanto indicato precedentemente e cioè di pochi secondi.

Magnesio. – Il Magnesio ha due periodi, uno di circa 40 secondi e uno più lungo.

Alluminio. – Oltre al periodo di 12 minuti segnalato precedentemente ve ne è anche un altro dell'ordine di grandezza di un giorno. L'attività corrispondente a questo secondo periodo segue le reazioni chimiche caratteristiche del Sodio. Si tratta probabilmente di un Na^{24}.

Zolfo. – Il periodo dello S è assai lungo, certamente di molti giorni. L'attività si separa con le reazioni caratteristiche del Fosforo.

Cloro. – Si comporta analogamente allo S. Anche qui si può separare

corrispondente a questo secondo periodo segue le reazioni chimiche caratteristiche del Sodio. Si tratta probabilmente di un Na^{24}.

Zolfo. – Il periodo dello S è assai lungo, certamente di molti giorni. L'attività si separa con le reazioni caratteristiche del Fosforo.

Cloro. – Si comporta analogamente allo S. Anche qui si può separare
un principio attivo; probabilmente si tratta di un P^{32} identico a quello che si ricava dallo S.

Manganese. – Ha un effetto debole con un periodo di circa 15 minuti.

Cobalto. – Ha un effetto di 2 ore. Il principio attivo si comporta come Mn. Data l'identità di periodo e di comportamento chimico si tratta quasi certo di un Mn^{56} identico a quello che si forma irradiando il Fe.

Zinco. – Ha due periodi, uno di 6 minuti e uno assai più lungo.

Gallio. – Periodo 30 minuti.

Bromo. – Ha due periodi, uno di 30 minuti e l'altro di 6 ore. L'attività corrispondente al periodo lungo e probabilmente anche l'altra, seguono chimicamente il Br.

Palladio. – Periodo di alcune ore.

Jodio. – Periodo 30 minuti. L'attività segue chimicamente lo Jodio.

Praseodimio. – Ha due periodi. Uno di 5 minuti e l'altro più lungo.

Neodimio. – Periodo 55 minuti.

Samario. – Ha due periodi uno di 40 minuti e uno più lungo.

Oro. – Periodo dell'ordine di grandezza di 1 o 2 giorni.

Also for physicists, patents are important!

Discovery: Saturday 20 October (*)

Patent: Friday 26 October because of Orso Mario Corbino

> **"To obtain radioactive substances in quantities of <u>practical</u> importance"**

(*) A. De Gregorio : not on October 22!

REGNO D'ITALIA

MINISTERO DELLE CORPORAZIONI

UFFICIO DELLA PROPRIETÀ INTELLETTUALE

Attestato di Privativa Industriale

№ 324458

Nel Registro degli attestati di privativa industriale di questo Ufficio è stata regolarmente inscritta la domanda depositata, coi documenti voluti dalla legge, all'Ufficio stesso nel giorno ventisei del mese di ottobre 1934 alle ore 12,15 da
Fermi Enrico,
Amaldi Edoardo,
D'Agostino Oscar,
Pontecorvo Bruno,
Rasetti Franco,
Segrè Emilio
e Trabacchi Giulio Cesare
a Roma
per ottenere una privativa industriale per il trovato designato col titolo:

Metodo per accrescere il rendimento dei procedimenti per la produzione di radioattività artificiali mediante il bombardamento con neutroni.

Il presente attestato non garantisce che il trovato abbia i caratteri voluti dalla legge perchè la privativa sia valida ed efficace, e viene rilasciato senza esame preliminare del merito e della novità di esso

Roma, li -2 FEB 1935 Anno XIII

Il Direttore

Nei riferimenti al presente attestato richiamare soltanto il suindicato numero, adottando la dizione PRIVATIVA ITALIANA N. 324458

Istituto Superiore di Sanità - 1934

“Il tubo”

“Il tubo” – 1 MeV Cockcroft-Walton ion accelerator - 1938

Letter by D. Marotta to E. Fermi – 16.11.36

I nuovi orizzonti che ha aperto per la terapia dei tumori maligni la possibilità di fabbricare sostanze radioattive artificiali in quantità considerevoli mi fa pensare alla convenienza che l'Istituto di Sanità faccia il possibile per organizzare i mezzi tecnici per tali preparazioni. Prima però di prendere in considerazione il progetto proposto dal Capo del Labratorio di Fisica di questo Istituto desidererei avere il parere di Vostra Eccellenza.

The new vistas opened for tumour therapy by the possibility of producing large quantities of radioactive substances convince me that it is convenient for 'Istituto di Sanità' to procure the technical means for such productions. However , before considering the project proposed by the Chief of the Physics Laboratory (G. C. Trabacchi), I would like to have the opinion of Your Excellency.

Fermi and the use of radio isotopes in medicine

Lecture by Enrico Fermi at Istituto di Sanità Pubblica 29 .5.1938

PROSPETTIVE DI APPLICAZIONE DELLA RADIOATTIVITÀ ARTIFICIALE

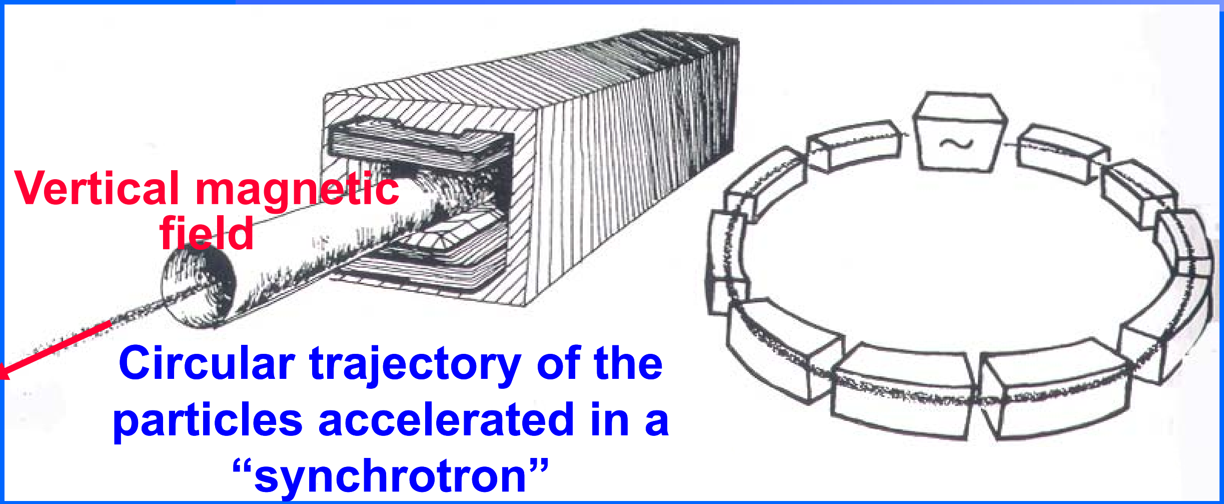
"It can be forseen WITHOUT DOUBTS that the (new) radioactive substances will find THERAPEUTICAL APPLICATIONS similar to the one of natural occurring radioactive substances.

Moreover and independently, the use of large quantities of radioactive substances will open, I HOPE, the way to many interesting studies in biology and chemistry through the use of radioelements as 'INDICATORS' "

È da prevedere senz'altro che le sostanze radioattive artificiali troveranno un impego terapeutico analogo a quello delle sostanze radioattive naturale.

Ma anche indipendentemente da queste possibilità , l'uso delle sostanze radioattive artificiali in quantità rilevanti renderà possibili, io spero, anche molte interessanti ricerche nel campo della biologia e della chimica, usando i radioelementi come " indicatori".

Four other crucial years: the synchrotron



1944

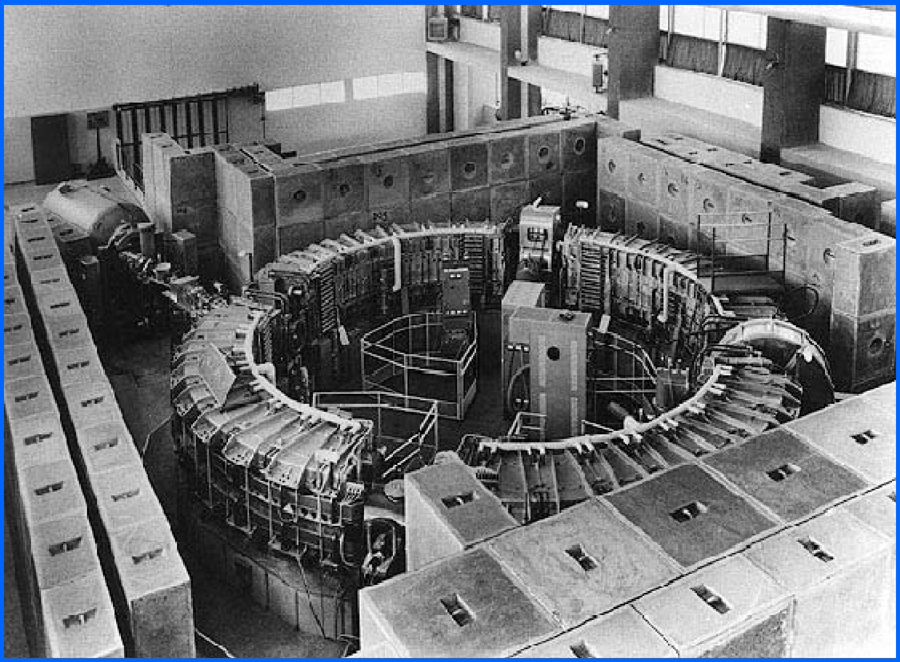
principle of phase stability

1 GeV electron synchrotron

Frascati - INFN - 1959

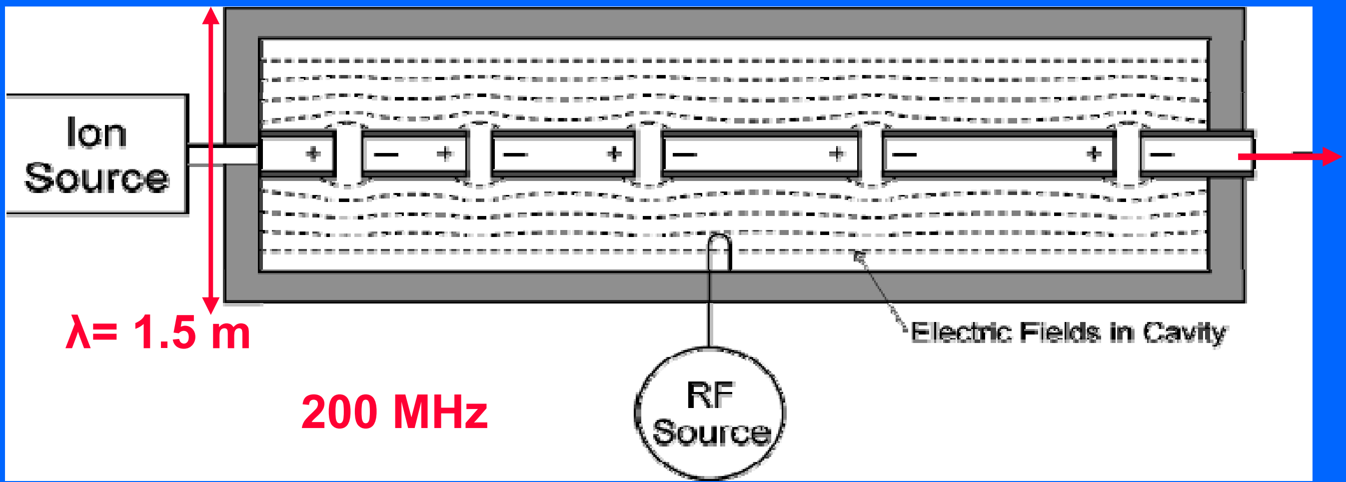
Veksler visits McMillan

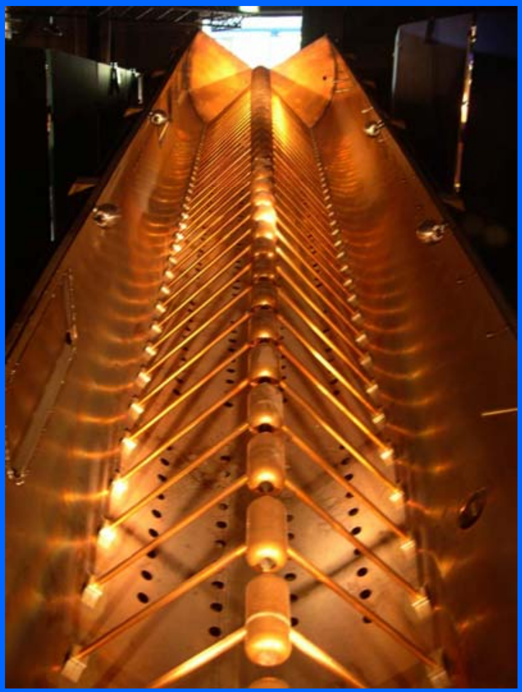
1959 - Berkeley



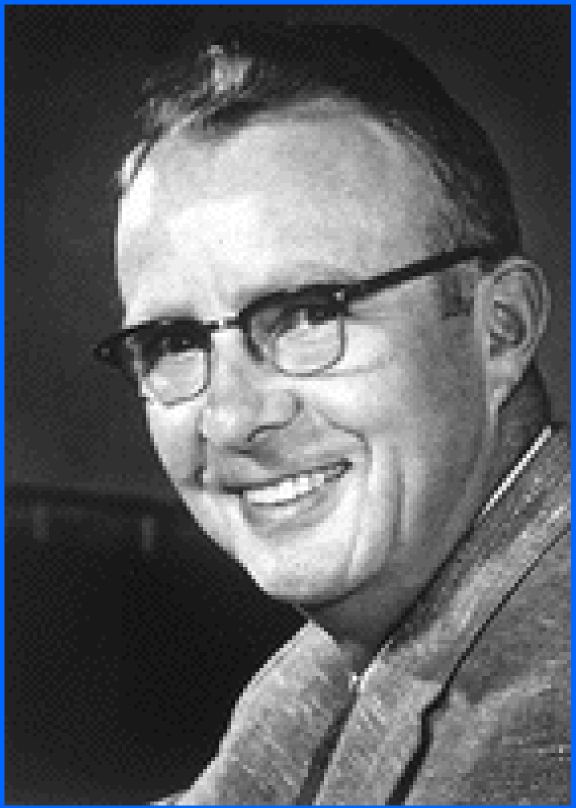
Radio-frequency linacs for protons and ions

Linear accelerator (linac)





100 MeV linac on display at CERN Microcosm

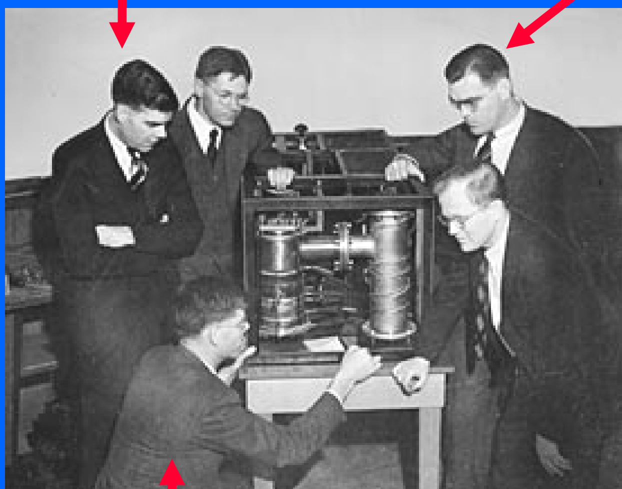


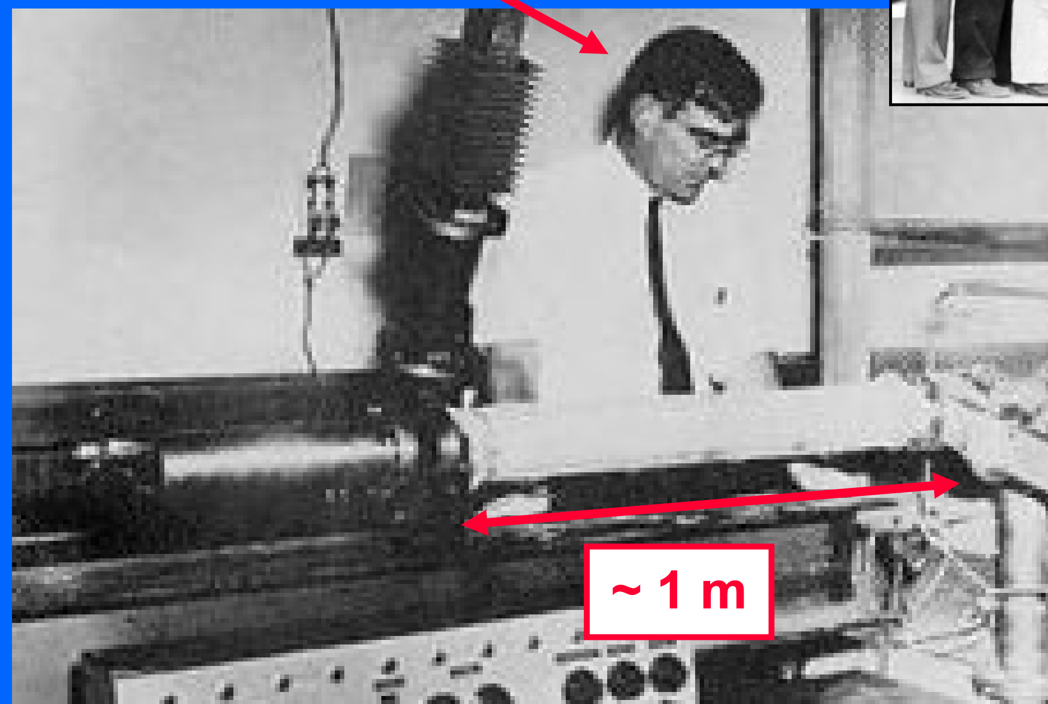
L. Alvarez

1946 – Drift Tube Linac

Sigurd Varian

William W. Hansen





Russell Varian

1939

Invention of the klystron

The electron linac is used today in hospital based conventional radiation therapy facilities

1947
first linac for electrons
4.5 MeV and 3 GHz

The beginning of CERN 50 years ago

Isidor Rabi

UNESCO talk in 1950

1952: Pierre Auger **Edoardo Amaldi**

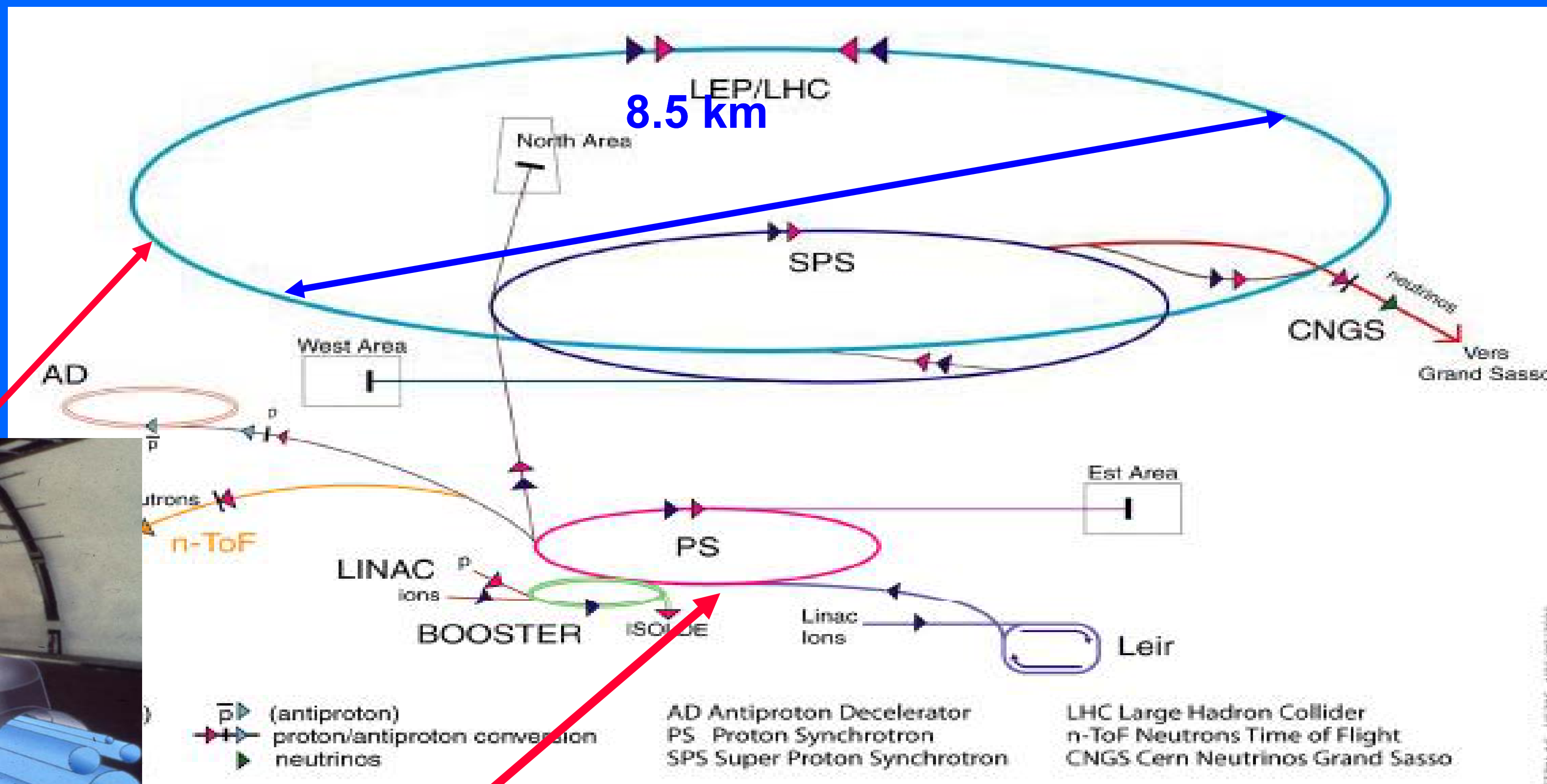
Secretary General

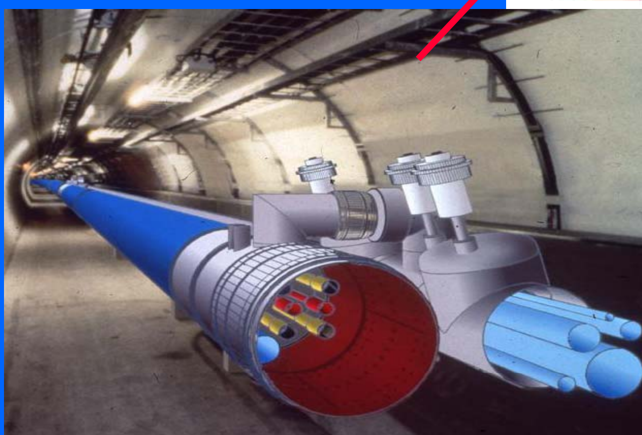
1952-54

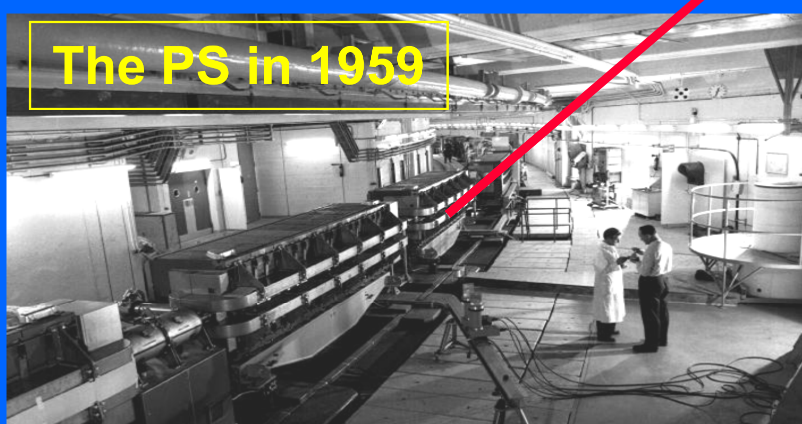
at the meeting that created the provisional CERN

At CERN we have linacs and strong-focusing synchrotrons

Large Hadron Collider (7+7) TeV







In 1952 the "strong-focusing" method invented at BNL (USA) was chosen for the CERN PS

Accelerators running in the world

CATEGORY OF ACCELERATORS	NUMBER IN USE (*)
High Energy acc. (E >1GeV)	~120
Synchrotron radiation sources	>100
Medical radioisotope production	~200
Radiotherapy accelerators	> 7500
Research acc. included biomedical research	~1000
Acc. for industrial processing and research	~1500
Ion implanters, surface modification	>7000
TOTAL	> 17500

$\left.\begin{array}{l}\sim 200 \\ >7500 \\ \sim 1000\end{array}\right\} 9000$

(*) W. Maciszewski and W. Scharf: Int. J. of Radiation Oncology, 2004

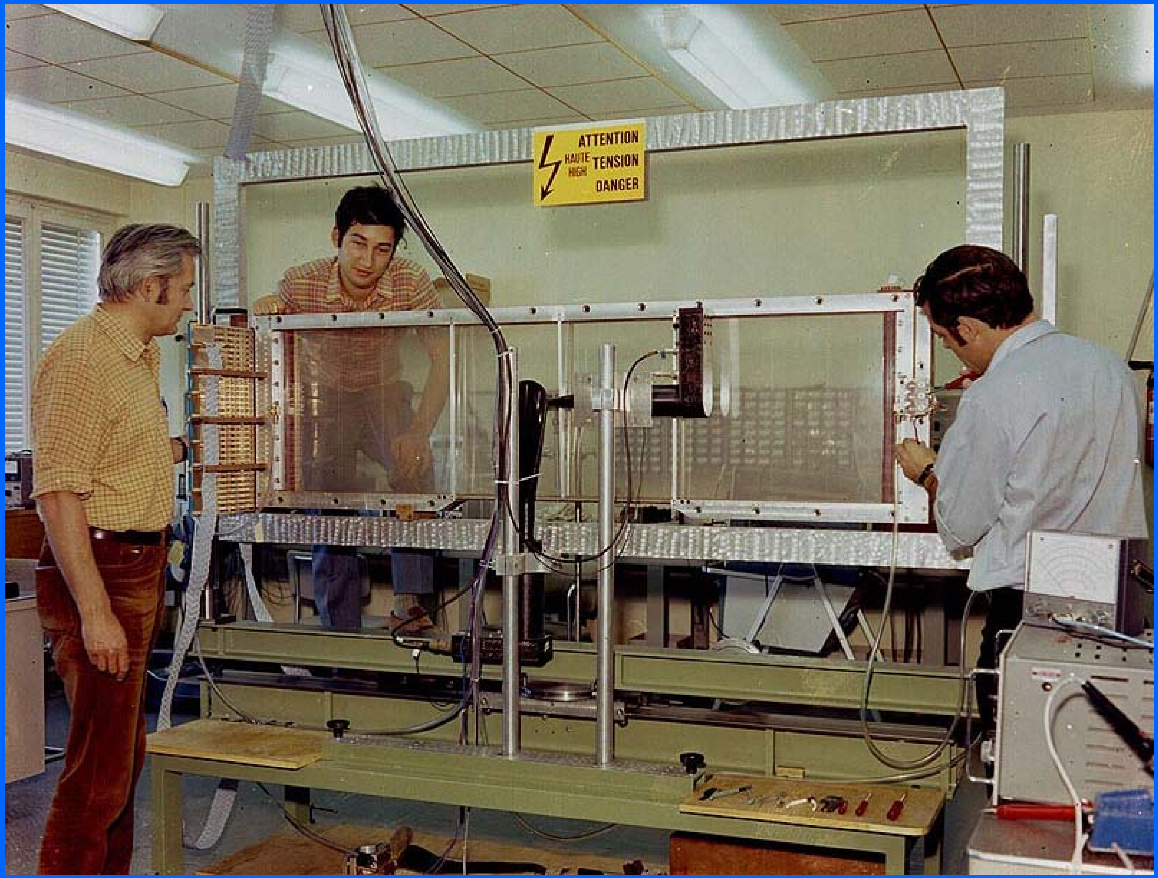
- **About half are used for bio-medical applications**

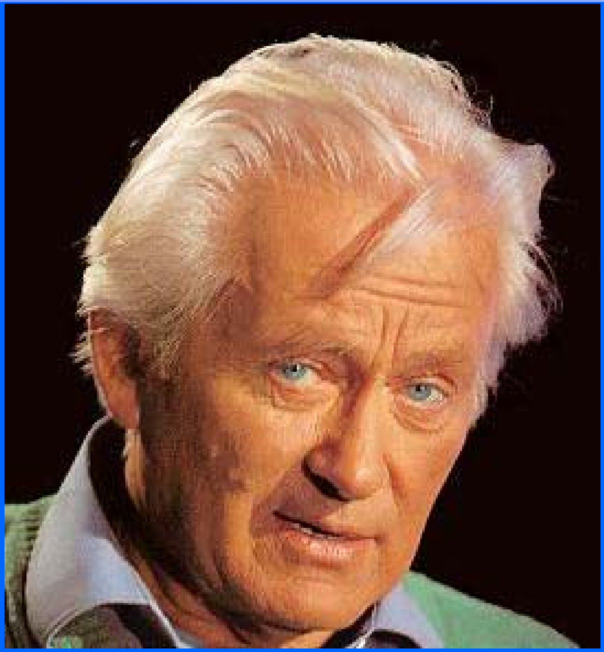
- They are the “eyes” of particle physicists

- A very impressive development in the last 100 years
  - From the Geiger counter to ATLAS and CMS at CERN!

- Crucial in many medical applications

One example: the multiwire proportional chamber



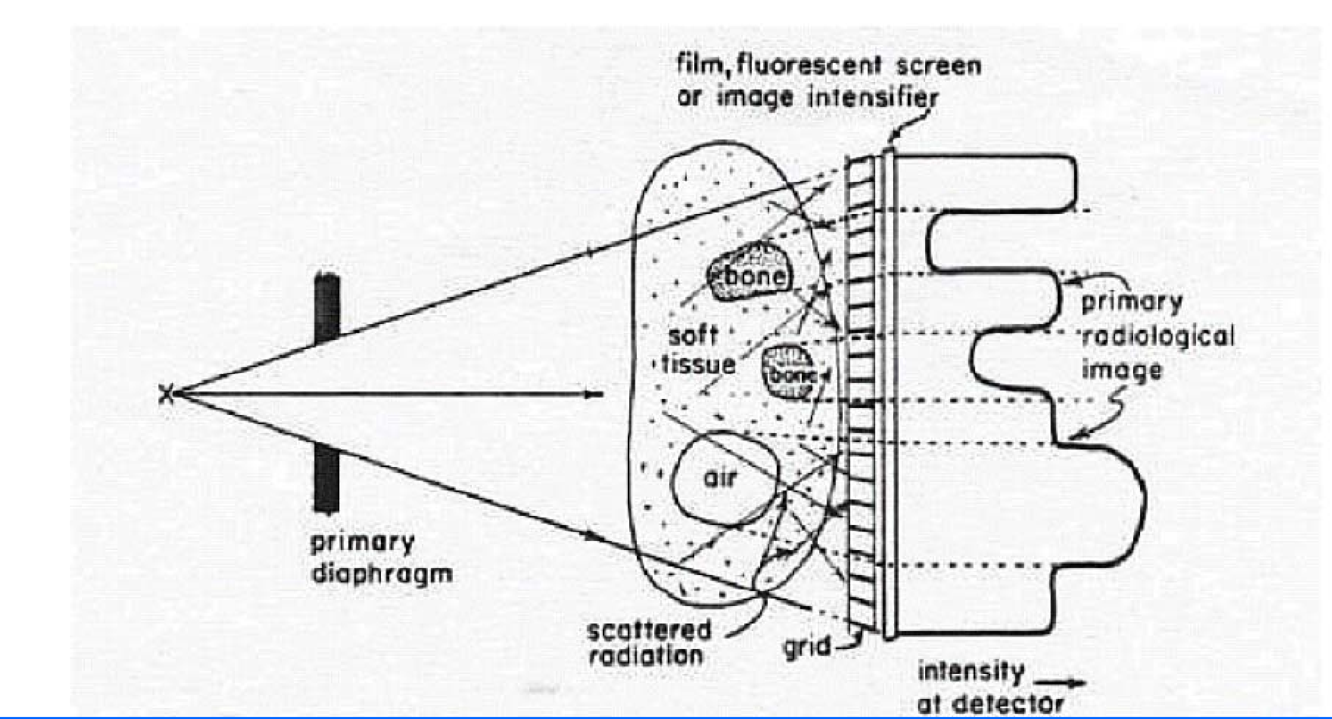


Georges Charpak, CERN physicist since 1959,

Nober prize 1992

- Invented in 1968, launched the era of fully electronic particle detection
- Used for biological research and could eventually replace photographic recording in applied radio-biology
- The increased recording speeds translate into faster scanning and lower body doses in medical diagnostic tools based on radiation or particle beams

Radiography and imaging with radiations



General features:

Sensitivity of the detector = less dose to the patient

Granularity of the detector = better image definition

Speed of the detector = detection of movements

End of part I