NAMP

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A Short History of Nuclear Medicine

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Virginia Commonwealth University MCV RPI

University of Notre Dame

Meet the Presenter…

Carolyn J Anderson, PhD

Dr. Anderson is Director of the Nuclear Molecular Imaging Lab at the University of Pittsburgh and Co-Director of the In Vivo Imaging Facility at the UPMC Hillman Cancer Center.

Research interests include the development and evaluation of novel radiometal-based radiopharmaceuticals for diagnostic imaging and targeted radiotherapy of cancer and other diseases. She has co-authored over 180 peer-reviewed and invited publications, mostly in the area of developing radiopharmaceuticals for oncological imaging and therapy.

A current focus of her research lab is in the development of imaging agents for up-regulated receptors on immune cells that are involved in inflammation related to lung diseases including tuberculosis, primary tumor growth and cancer metastasis.

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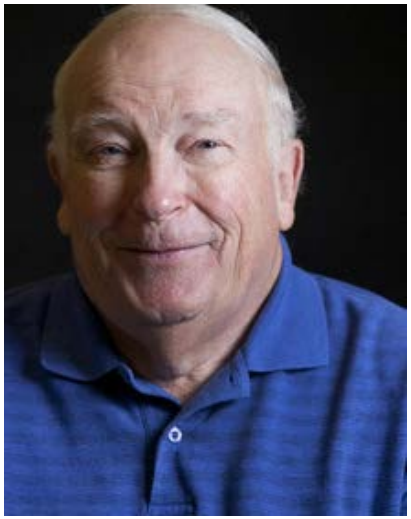
Acknowledgements



- Frank Kinard, PhD (1942-2013)
  - Professor, University of Charleston (41 years)
  - Director of the DOE San Jose State University Summer School in Nuclear Chemistry (15 years)
  - Amazing teacher of nuclear and radiochemistry (and generous with his teaching materials)

- David Schlyer, PhD (Brookhaven National Lab, Emeritus)
- Joanna Fowler, PhD (Brookhaven National Lab, Emeritus)

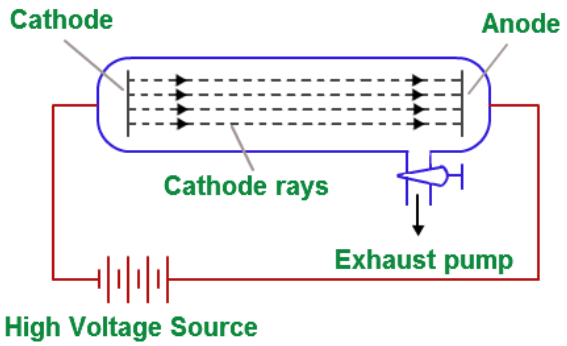
Origins of Nuclear Science

- 1895 – Discovery of x-rays by Wilhelm Conrad Roentgen
- Roentgen's initial discovery led to a rapid succession of other discoveries that, in a few short years, set the course of modern physics

State of Physics in 1895

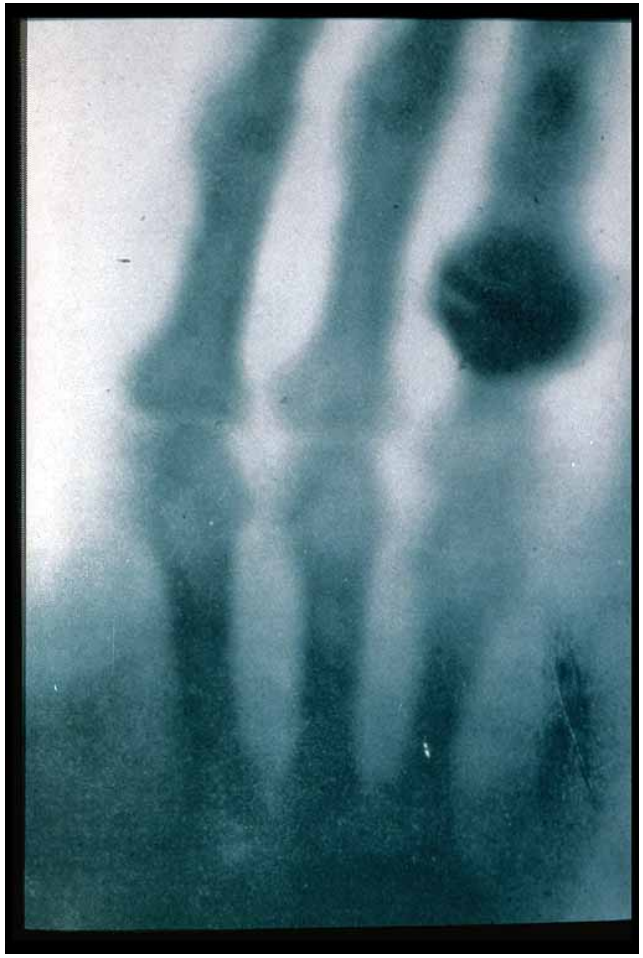
- Atomic theory of matter was not universally recognized, atomic and nuclear structure were hypothetical
- Electron not yet discovered
- Known that low pressure gases could conduct electricity, and at sufficiently low pressures will result in a visible discharge between electrodes

Wilhelm Conrad Röntgen (1845-1923)
1895: Discovered x-rays



- Röntgen had been working with Hittorf-Crookes tubes (similar to fluorescent light bulbs) to study cathode rays (*i.e.* electrons) (Univ of Würzburg).
- On November 8, 1895 he evacuated the tube of air and passed a high electric voltage through it.
- The tube, shielded with heavy black paper, caused fluorescence on a nearby table which he determined were caused by invisible rays originating from the partially evacuated tube.
- The rays (X-rays) penetrated the opaque black paper wrapped around the tube.
- Röntgen found the X-rays would pass through tissue, but not bones and other dense objects.

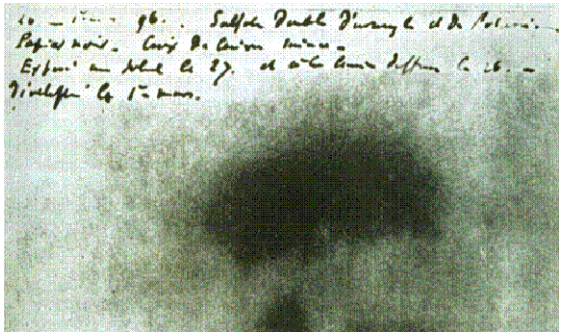
Roentgen's accidental discovery



- He noticed that a screen across the room was glowing
- When blocking the beam he could see his hand bones projected
- Spent several weeks experimenting on the new rays
- On Dec 28, 1895 gave report to local physics society "On the use of new rays"
- Presented hand X-ray of his wife (30 min exposure)
- **Röntgen had discovered X-rays. He was awarded the first Nobel Prize in physics in 1901**

Antoine Henri Becquerel (1852-1908)

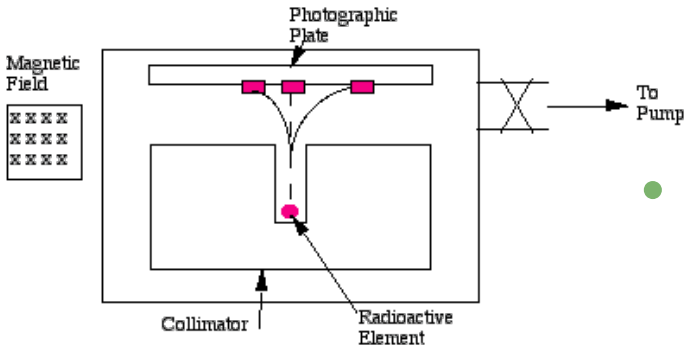
1896: discovered that uranium was radioactive



- Becquerel's early work (doctoral thesis) was on plane polarized light – the phosphorescence and absorbance of light by crystals
- Later on he was studying phosphorescence. He exposed $K_2UO_2(SO_4)_2 \cdot H_2O$ to sunlight and placed it on photographic plates wrapped in black paper
- When developed, the plates revealed an image of the uranium crystals
- Becquerel concluded "that the phosphorescent substance in question emits radiation which penetrates paper opaque to light."
- Initially he believed that the sun's energy was being absorbed by the uranium which then emitted X-rays

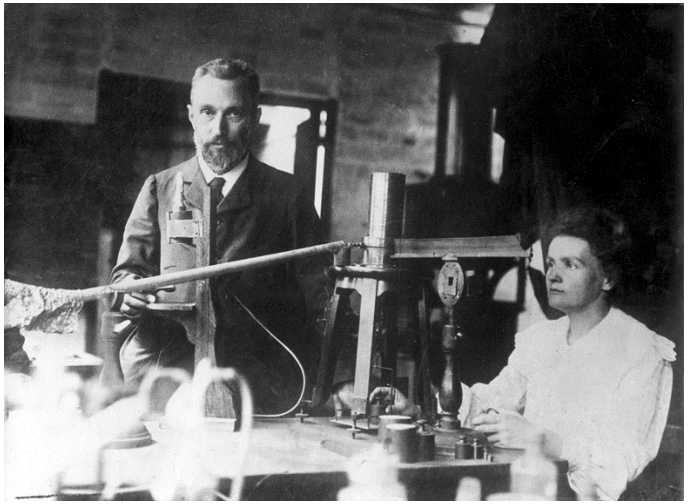
Antoine Henri Becquerel

1903: Nobel Prize in Physics



- The skies over Paris were overcast and the uranium-covered plates were returned to a drawer
- When he developed the photographic plates expecting only faint images, to his surprise, the images were clear and strong
- Becquerel had discovered radioactivity
- He later demonstrated that the radiation emitted by uranium shared certain characteristics with X-rays but, unlike X-rays, could be deflected by a magnetic field and therefore must consist of charged particles
- **For his discovery of radioactivity, Becquerel was awarded the 1903 Nobel Prize for physics**

Pierre (1859-1906) and Marie (1867-1934) Curie
1898: discovered new radioactive elements



- Although discovered by Becquerel, the term radioactivity was coined by Marie Curie
- After chemical extraction of uranium from the ore, she noted the residual material to be more "active" than the pure uranium
- She concluded that the ore contained, in addition to uranium, new elements that were also radioactive
- This led to the discoveries of the elements polonium, Po, and radium, Ra.
- **For their work on radioactivity, the Curies were awarded the 1903 Nobel Prize in physics**

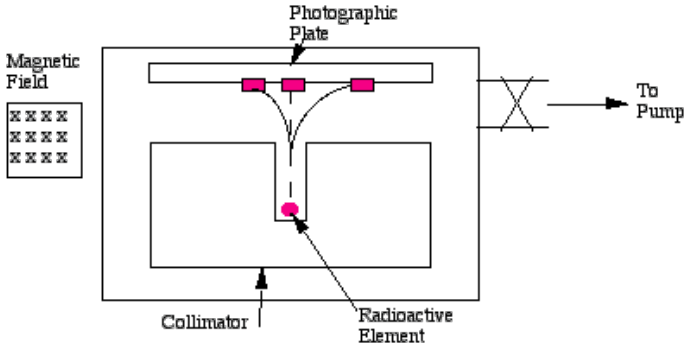
Marie Curie (1867-1934)
1911 (Nobel Prize in Chemistry)

- Pierre was killed while crossing a street in a rainstorm
- Pierre's teaching position at the Sorbonne was given to Marie
- Never before had a woman taught there in its 650 year history! Her first lecture began with the very sentence her husband had used to finish his last lecture

- **Marie was awarded the Nobel Prize in chemistry for her discoveries of radium and polonium, thus becoming the first person (male or female) to receive two Nobel Prizes**

Ernest Rutherford (1871-1937)

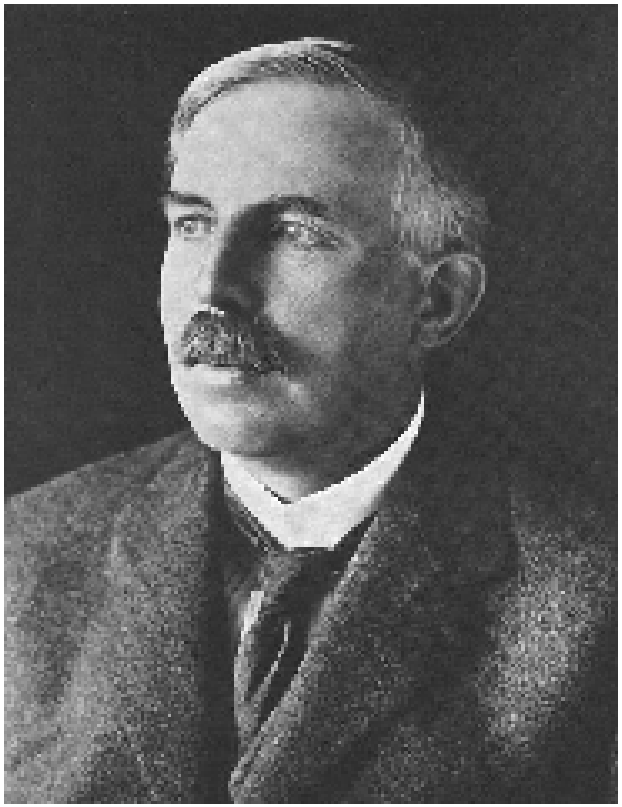
Studied properties of radioactive decay



- Rutherford named radioactive particles “alpha, beta and gamma”, and classified them by their ability to penetrate matter using a device similar to what Becquerel used
- He determined that alpha particles could be stopped by only a few centimeters of air and move more slowly compared to beta and gamma particles
- He showed that beta particles were negatively charged and could be stopped by a mm thick sheet of aluminum
- Gamma particles, with no charge, can penetrate large distances through material (several cm of lead or a meter of concrete)
- In 1907 he showed that alpha particles were $^{4}_{2}He$ nuclei

Ernest Rutherford (1871-1937)

1905: described equation to calculate radioactive decay



- The exponential equation used to calculate the decay of radioactive substances was first used for that purpose by Rutherford
- He was the first to describe the concepts of half-life and decay constant
- With Frederick Soddy at McGill University, Rutherford showed that elements such as uranium and thorium became different elements (*i.e.* transmuted) through the process of radioactive decay

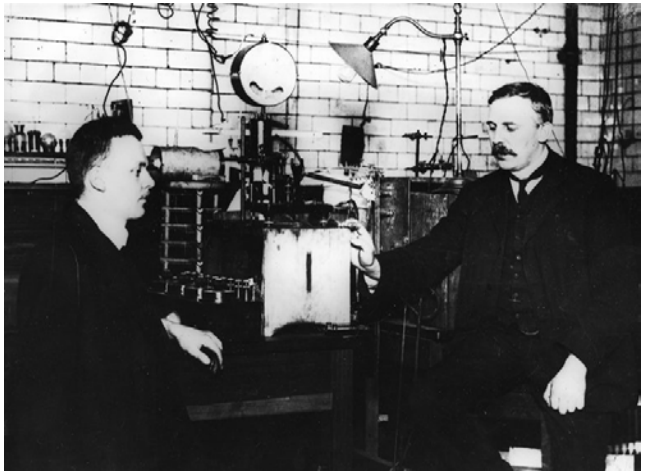
- **For this work, Rutherford won the 1908 Nobel Prize in chemistry**

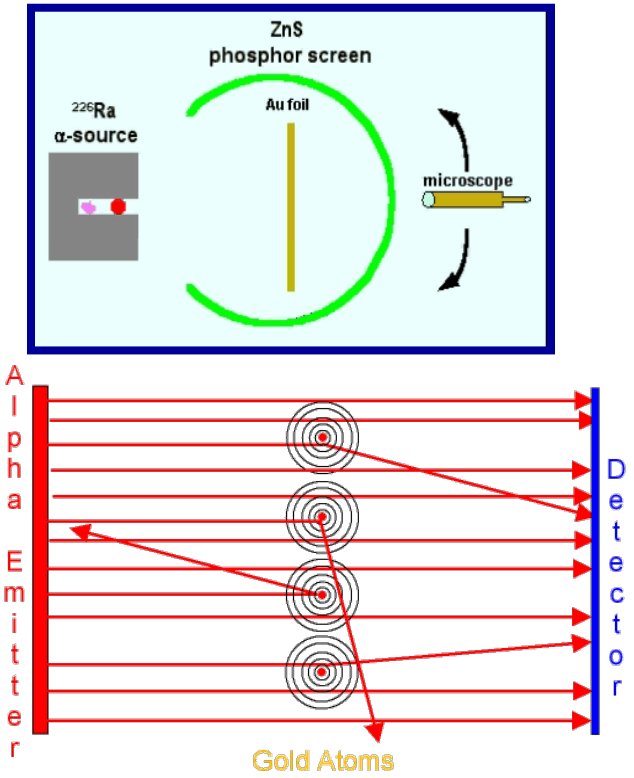
$$N_t = N_0 e^{-\lambda t}$$

Ernest Rutherford

1909: pioneered model of the atom

- In 1909 (University of Manchester) Rutherford, and his assistants, Hans Geiger and Ernest Marsden, bombarded a thin gold foil with alpha particles
- Although almost all of them went through the gold, one in eight thousand would "bounce" back.



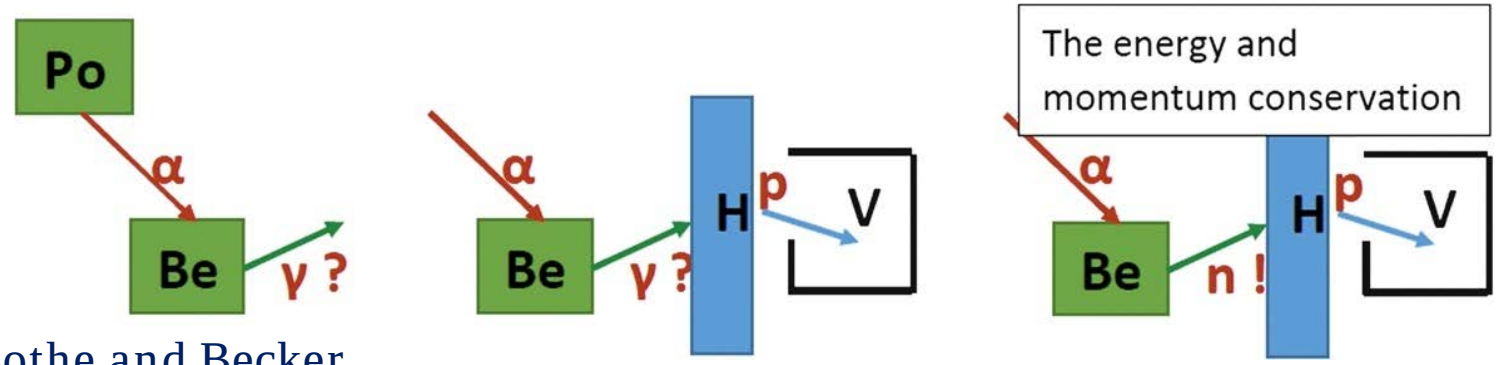


- Rutherford commented that it was "as if you fired a 15-inch naval shell at a piece of tissue paper and the shell came right back and hit you."
- **Rutherford concluded that the atom's mass must be concentrated in a small positively-charged nucleus while the electrons inhabit the farthest reaches of the atom**

Bothe and Becker Experiment[1]

[1]Nesvizhevsky, Villain, Comp Rend Phys 2017

- In 1930, Walther Bothe and Herbert Becker described an unusual gamma ray produced by bombarding Be metal with alpha particles
- Irène and Frédéric Joliot-Curie probed this further by placing H-containing material in front of detector and assumed a “new mode of interaction of radiation with matter”
- When Frédéric and Irène Joliot-Curie subsequently claimed that Bothe and Becker's "gamma rays" could eject high energy protons from paraffin, James Chadwick knew these were not gamma rays
- Chadwick recognized that the properties of this radiation were more consistent with what was expected of Rutherford's neutral particle, based on expected energies of an emitted photon vs neutron



Bothe and Becker

Joliot-Curies

Chadwick

James Chadwick (1881-1974)
1932: discovered the neutron

- Chadwick was the first to show that beta particles possess a range of energies up to some maximum value
- After being trapped in Germany when WW I broke out, Chadwick returned to England and joined forces with Ernest Rutherford
- Chadwick began a series of experiments to confirm Rutherford's speculation about a subatomic particle with no charge

James Chadwick

1935: Nobel Prize in Physics

- Chadwick proving the existence of the neutron earned him the 1935 Nobel Prize in physics.
- The neutron provided physicists with a superlative tool for investigating the atom, and a mechanism for producing a wide variety of new radioisotopes and permitted the initiation of nuclear chain reactions
- Discovery of the neutron was crucial to the understanding of fission of U-235 and the discovery of elements heavier than U
- Hans Bethe has referred to Chadwick's discovery as the historical beginning of nuclear physics

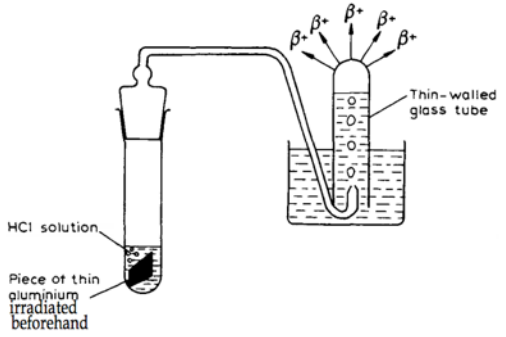
Jean Frédéric Joliot & Irène Curie

1935: Nobel Prize in Chemistry – discovery of artificial radioactivity

- The Joliot-Curies missed the discoveries of the neutron (James Chadwick) and the positron (Carl Anderson, Science, 1932)
- They bombarded a series of elements with alpha particles – of these only 3 elements produced artificial radioactivity
- The alpha bombardment of aluminum produced a positron-emitting radionuclide of phosphorous
- Bombarding boron, they were able to condense N-13 ($T_{1/2}$ = 10 min) into a separate vessel, proving they created a new radionuclide
- They produced the first artificial radionuclide AND were the first to experimentally confirm transmutation, the conversion of one element into another element!
- **This discovery the Joliot-Curies won the 1935 Nobel Prize for chemistry**

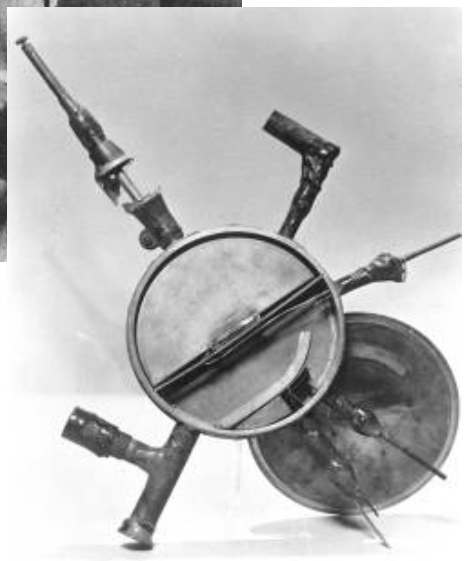
$$^{4}_{2}\mathrm{He} + ^{27}_{13}\mathrm{Al} \longrightarrow ^{1}_{0}\mathrm{n} + ^{30}_{15}\mathrm{P}$$

$$^{30}_{15}\mathrm{P} \xrightarrow{\beta^+} ^{30}_{14}\mathrm{Si}$$



Ernest O. Lawrence (1901-1958)

1932: Discovery of first cyclotron

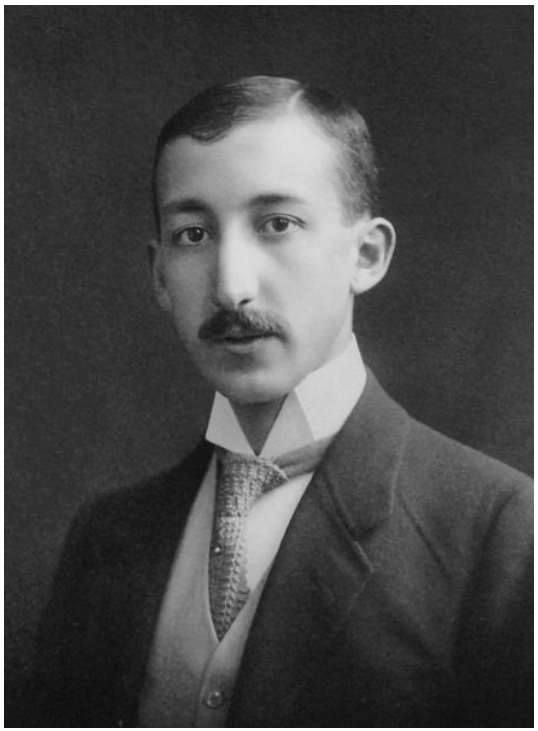


- Lawrence conceived the idea for the cyclotron in 1929
- His first machine, only 4.5" in diameter, accelerated protons to 80,000 eV. He later used improved versions of the cyclotron to investigate nuclear processes and to produce a variety of new and medically important isotopes
- He was also producing artificial radioactivity with the cyclotron, but at first failed to realize it because the same switch operated the cyclotron and the Geiger counter in the lab
- Lead to the discovery of I-131 and Tc-99m (with Segre and Seaborg)
- **Lawrence received the 1939 Nobel Prize in physics**

Seventh Solway Conference – 1933

Guerra et al. Phys Perspect 2012

George de Hevesy (1885-1966)
1909: first described radiotracer technique



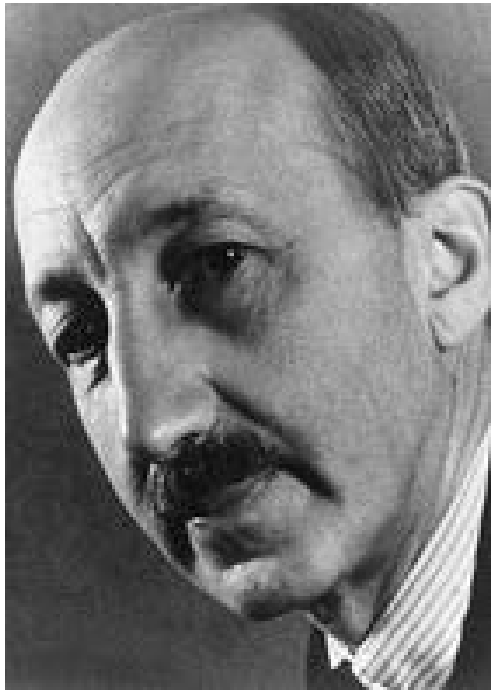
$^{238}_{92}U \rightarrow 7\alpha, 4\beta^- \rightarrow \boldsymbol{Ra\ D}\ (^{210}_{82}Pb)$

$PbCrO_4 \xrightarrow{K_{sp}} Pb^{2+} + CrO_4^{2-}$

- de Hevesy joined Rutherford's group at the University of Manchester investigating the radioactive properties of radium-D (^{210}Pb).
- The lead with which the radium-D was associated interfered with his analyses.
- Not realizing that radium-D was a radioactive form of lead, Rutherford erroneously thought it could be chemically isolated and told Hevesy "My boy, if you are worth your salt, you try to separate radium-D from all that lead".
- Out of his failure to complete that impossible task, Hevesy spiked pure Radium D to ordinary lead and studied the properties of lead
- He conceived the radiotracer technique by which radioisotopes could be used to investigate the behavior of stable atoms (a victory snatched from the jaws of defeat!)

George de Hevesy

Developed neutron activation analysis and discovered the element hafnium

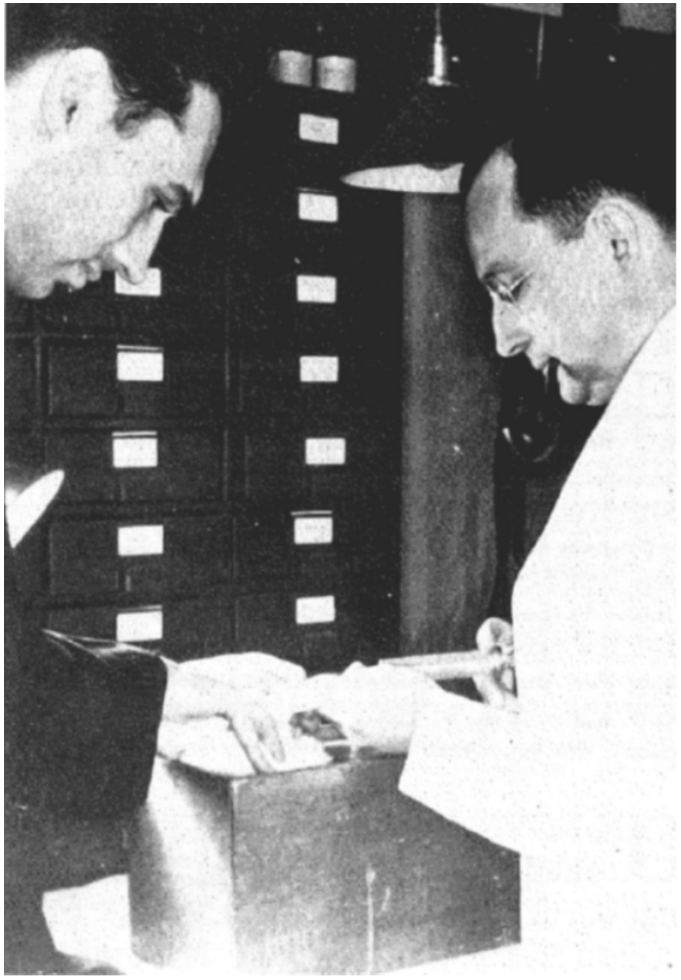


- Hevesy not only performed the first radiotracer studies on plants and animals, using both natural and artificial radionuclides, he also performed the first tracer studies employing stable nuclides by using deuterated water to measure the turnover of hydrogen in the body.
- In addition to these studies, which earned him the 1943 Nobel Prize in chemistry, Hevesy developed the technique of neutron activation analysis, perhaps the most powerful non-destructive technique for the elemental analysis of solid samples.
- Hevesy took the greatest pride in his discovery of the element hafnium. Hafnium played an important role in the organization of the periodic table.

Early work with radioiodine

Saul Hertz and Arthur Roberts

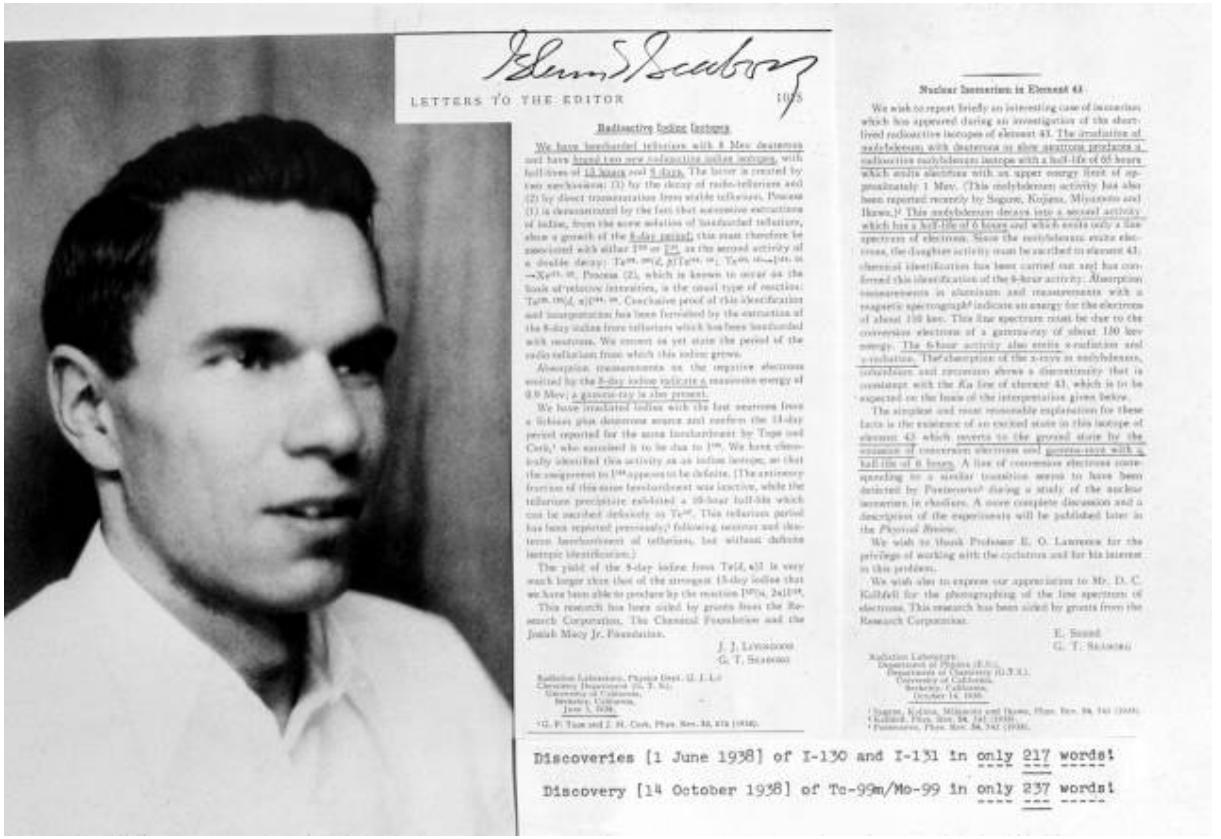
Fahey et al. EJNMMI Physics 2017



- Performed initial studies in rabbits at MGH with I-128 ($T_{1/2}$ = 25 min) in 1938
- The half-life of I-128 was too short; the team contacted Ernest Lawrence and his team at UC-Berkeley to produce I-131 ($T_{1/2}$ = 8 days)
- March 31, 1941, first patient treated with I-130/131 for thyroid disease
- Through 1943, 29 patients treated (20 of 29 were cured of hyperthyroidism)

Iodine-131 ($T_{1/2}$ = 8 d)

John Livingood and Seaborg in 1937 (published in 1938)



LETTERS TO THE EDITOR

Radioactive Iodine Isotopes

Nuclear Isomerism in Element 43

Discoveries [1 June 1938] of I-130 and I-131 in only 217 words!

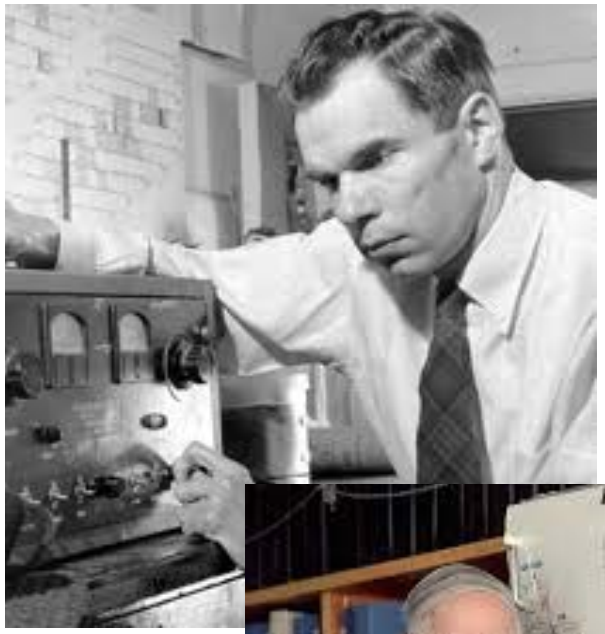
Discovery [14 October 1938] of Tc-99m/Mo-99 in only 237 words!

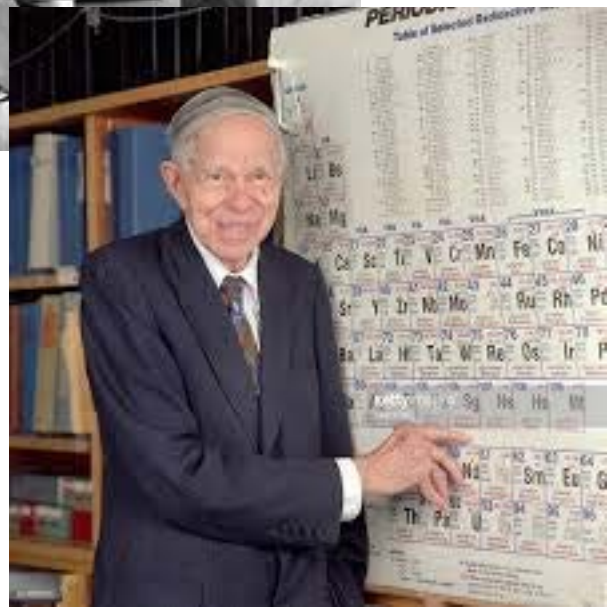
I-131 produced by bombarding Te with deuterons

Livingood and Seaborg at UC-Berkeley walking to mail their letter to the editor on discovery of I-131

Glenn Seaborg (1912-1999)

Discoverer of many transuranic and other elements





- Seaborg discovered (or co-discovered) the elements Pu, Am, Cm, Bk, Cf, Es, Fm, Md and No, as well as a wide variety of radionuclides including ^{131}I, ^{99m}Tc, ^{60}Co, ^{137}Cs, and ^{55}Fe
- He helped configure the periodic table as we now know it by placing the actinide series under the lanthanide series
- **For his discoveries of the transuranic elements and their chemistry, Seaborg was awarded the 1951 Nobel Prize in chemistry**
- **Element 106 (Sg) named after him**

Carbon-11 and Carbon-14

Kamen, M. "*Radiant Science, Dark Politics: A Memoir of the Nuclear Age*" 1985

Sam Ruben

Martin Kamen

Ruben was tragically killed in a phosgene accident in the lab in 1943

Kamen was accused of being a communist sympathizer/spy and was fired from UC-Berkeley in 1945. He was exonerated many year later and had an illustrious career

- Carbon-11 was first produced by Ernest Lawrence's team by bombarding boron oxide with deuterons
- Martin Kamen, Sam Ruben and I.L. Chaikoff used C-11 to study metabolism of carbohydrates by producing C-11 glucose by feeding $^{11}CO_2$ to plants undergoing photosynthesis
- Kamen and Ruben vigorously pursued producing C-14, which they expected to be longer-lived
- They ultimately prevailed, producing C-14 labeled $CaCO_3$ from bombardment of ammonium nitrate with slow neutrons
- **Discovery of C-14 a seminal moment in the history of radiochemistry and life sciences**

Manhattan Project (1942-1946)

Research and Development during WWII to develop the atomic bomb using fissile material – led by US with support from Canada and England

J. Robert Oppenheimer and Gen. Leslie Groves, Trinity Test Site, NM
First detonation of a nuclear weapon (18-20 kT yield) on July 16, 1945

Post WWII Nuclear and Radiochemistry

- Atomic Energy Commission founded in 1946 to promote peaceful uses of nuclear and radiochemistry
- In 1974 AEC was split into the Nuclear Regulatory Commission (NRC) and Energy Research and Development Administration (now called the Department of Energy (DOE))
- Many advances have occurred in the areas of nuclear energy, environmental science, national security and nuclear medicine
- Report by National Academy of Sciences (NAS) in 2012 reinforced the need to maintain a strong workforce in nuclear chemistry and radiochemistry

$^{99}Mo/^{99m}Tc$ Generator

- Element technetium (Tc-99) was discovered in 1937 by Perrier and Segre
- Segre went to Berkeley to work with Seaborg, and they discovered shorter-lived Tc-99m
- Patent for medical use of Tc-99m rejected (late 1950's)
- In the early 1960's, Beck found optimum detection energy for NaI crystals (gamma cameras) was 150 keV
- Paul Harper (U of Chicago) first demonstrated effectiveness of Tc-99m for imaging liver, brain and thyroid
- Mo-99 discovered as an impurity in Te-132 (used to produce I-132), and was then found to be parent of Tc-99m

Walter Tucker and Powell Richards, who was a staunch promoter of Tc-99m

99Mo/99mTc generator prepared by Tucker and Margaret Greene, 1958

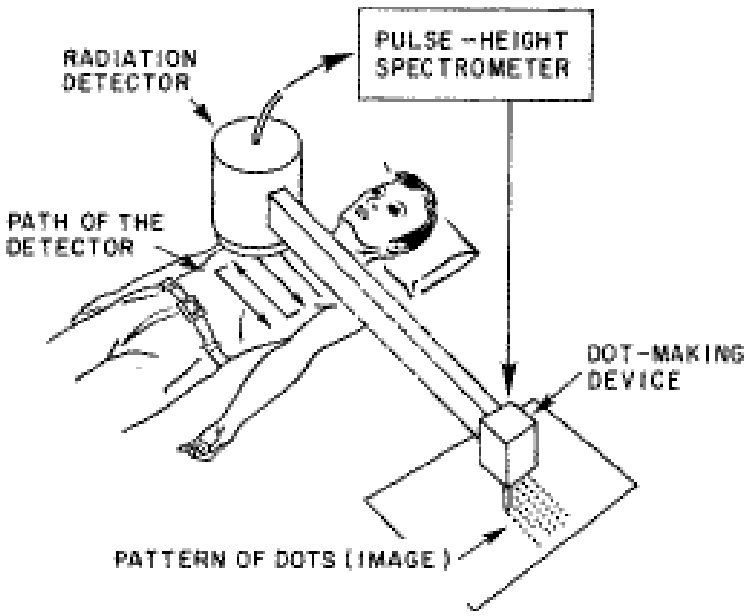
Nuclear Medicine Instrumentation

Hal Anger – gamma camera

- A pin-hole in lead was used to project a gamma ray image of the source distribution (1953)
- Image was projected onto a scintillating screen with photographic film behind it
- Although it was highly inefficient due to long exposure times and high radiation doses to patients, Hal Anger revolutionized the field of nuclear medicine with his development of the gamma camera
- He also developed the well counter, widely used in laboratory tests with small samples of radioactive materials

Nuclear Medicine Instrumentation

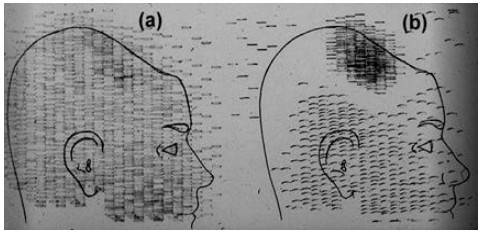
Benedict Cassen – rectilinear scanner

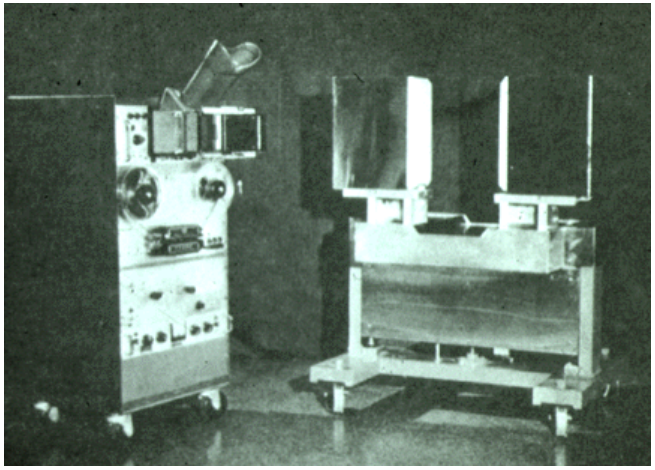


- Ben Classen improved this method in the **1950's** when he invented the rectilinear scanner
- This device produced planar images by mechanically scanning a detector in a raster-like pattern over the area of interest
- By today's standards, this technique required very long imaging times because of the sequential nature of the scanning

Nuclear Medicine Instrumentation

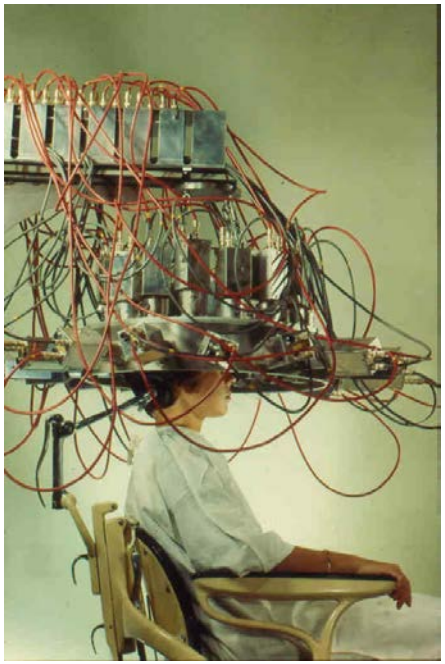
Gordon Brownell and William Sweet – positron detector

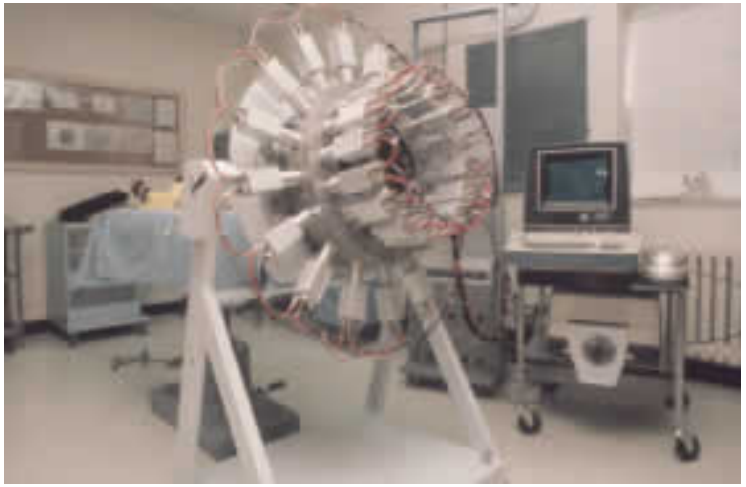




- In 1953, a multidetector instrument was developed by Brownell and Sweet for the localization of brain tumors with positron emitting radionuclides
- The device worked by moving the patient with respect to the detectors and having a pen make a mark on a sheet of paper whenever there was a coincident event
- **First device used with coincidence of 511 keV photons was planar PET (1959)**

Early ring detector PET scanners



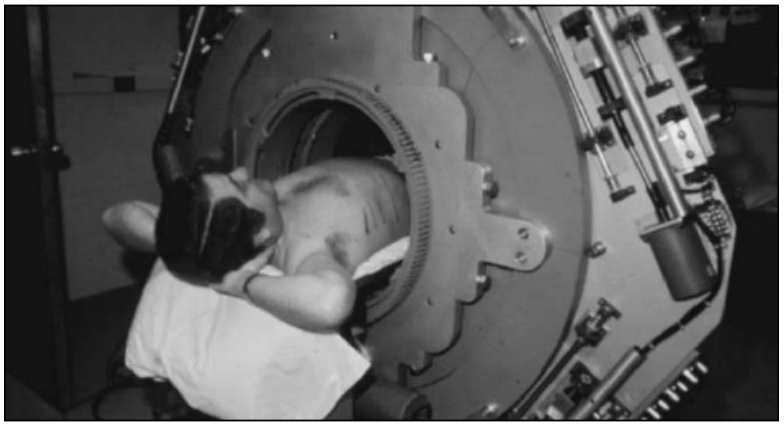


James Robertson of Brookhaven National Laboratory built the first ring tomograph (1963), but because of limited sampling, lack of attenuation correction and lack of a proper image reconstruction algorithm, was unable to obtain true reconstructed cross sectional images

First PET Scanner
Mike Phelps and Ed Hoffman

Phelps

Hoffman

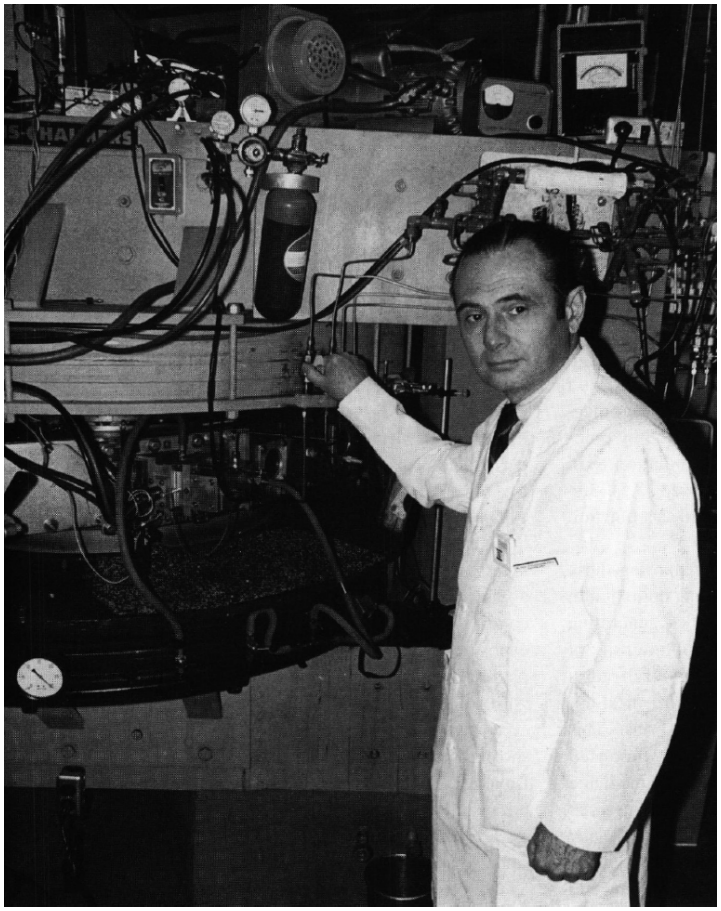


Henry Wagner in the scanner at Washington University, St. Louis 1974

- Phelps and Hoffman presented their design of a hexagonal array of 24 NaI(Tl) detectors with coincidence detection, attenuation correction and an image reconstruction using a proper filtered backprojection algorithm to the EG&G ORTEC group
- EG&G ORTEC provided expertise in detectors and coincidence electronics, as well as provided some Nuclear Instrumentation Modules (NIM) electronics.
- **Phelps had given the name "Positron Emission Transaxial Tomography" (PETT) to the first tomograph**

Early biomedical cyclotrons

dedicated to positron emitters for biomedical applications



Michel Ter Pogossian (WU-St. Louis)

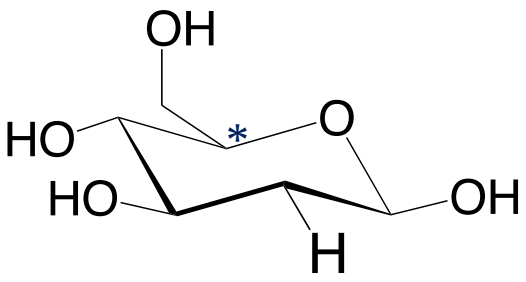
- Hammersmith Hospital – London installed a cyclotron in the medical center in 1955
- Washington University School of Medicine (St. Louis) installed a cyclotron in the early 1960's to focus on short-lived positron emitters for medical applications
- Mass General Hospital (Boston) and Sloan Kettering Institute in New York installed cyclotrons sometime later

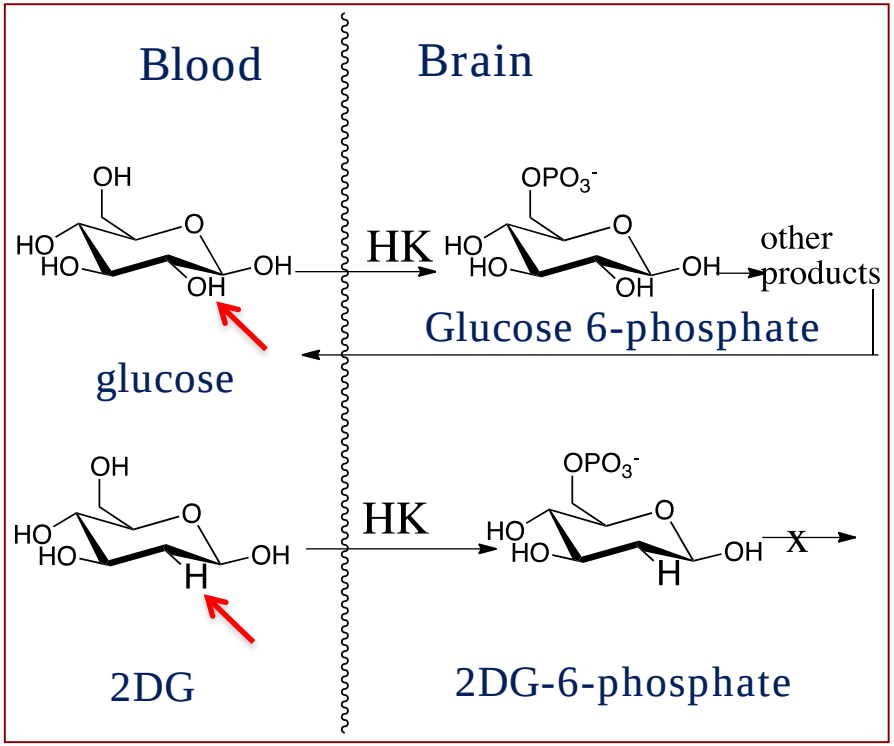
Discovery of FDG
Origins – Otto Warburg

- In 1931, Otto Warburg discovered that malignant cells show increased glucose metabolism compared with normal tissues

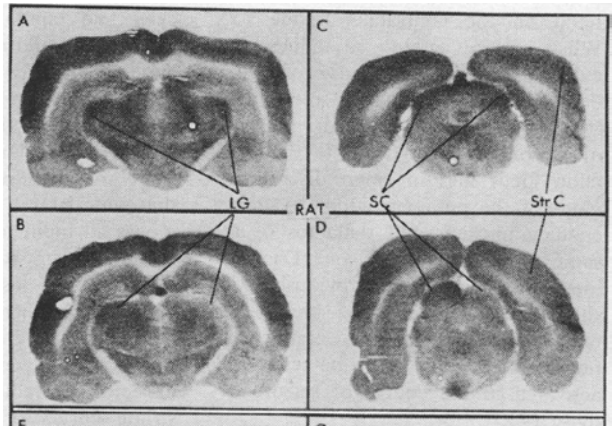
C-14-labeled 2-deoxyglucose (2DG)

Louis Sokoloff and Martin Reivich (Brookhaven National Lab)





Challenge– to label this with short half-life radionuclide



Kennedy C, Des Rosiers MH, Jehle JW, **Reivich M**, Sharpe F, **Sokoloff L**. Mapping of functional neural pathways by autoradiographic survey of local metabolic rate of (^{14}C)glucose. *Science*. 1975 Mar 7;187(4179):850-3.

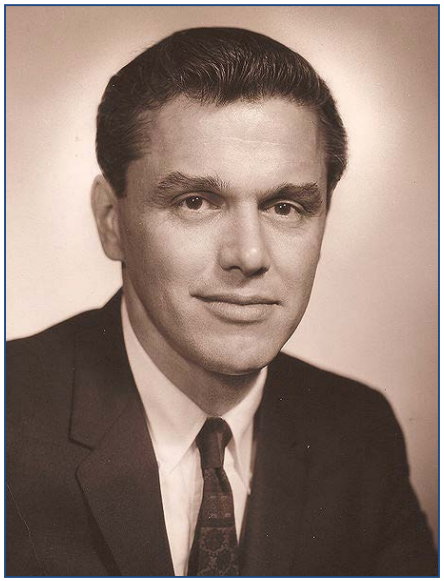
Short-lived PET radionuclides

Isotope	half-life
carbon-11	20.4 min
fluorine-18	110 min
nitrogen-13	10 min
oxygen-15	2 min

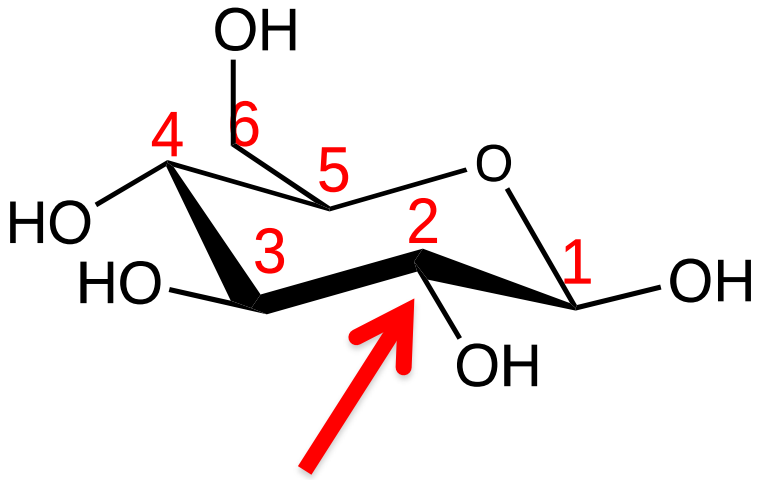
Requires the development of rapid, microscale synthetic methods

Where to label the 2-DG molecule?

Alberto Sols
1917-1989

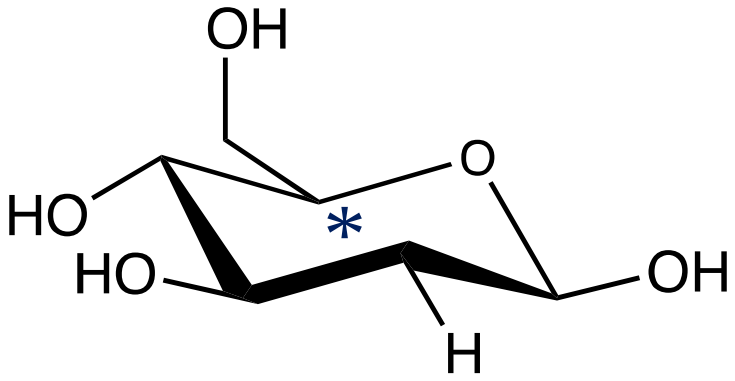


Robert
Crane
1919-2010

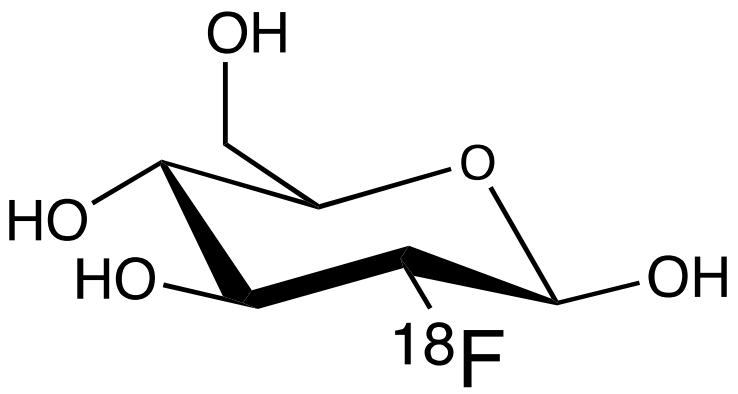


- Sols and Crane (1954): The C-2 –OH group on glucose is the only one that can be removed without affecting facilitated transport and phosphorylation by hexokinase. The C-2 -OH group is needed for active transport.
- ***"Removal of the OH on C-2 isolates the hexokinase reaction." (1954)***

^{18}FDG: Design and Synthesis



[^{14}C]2-deoxyglucose



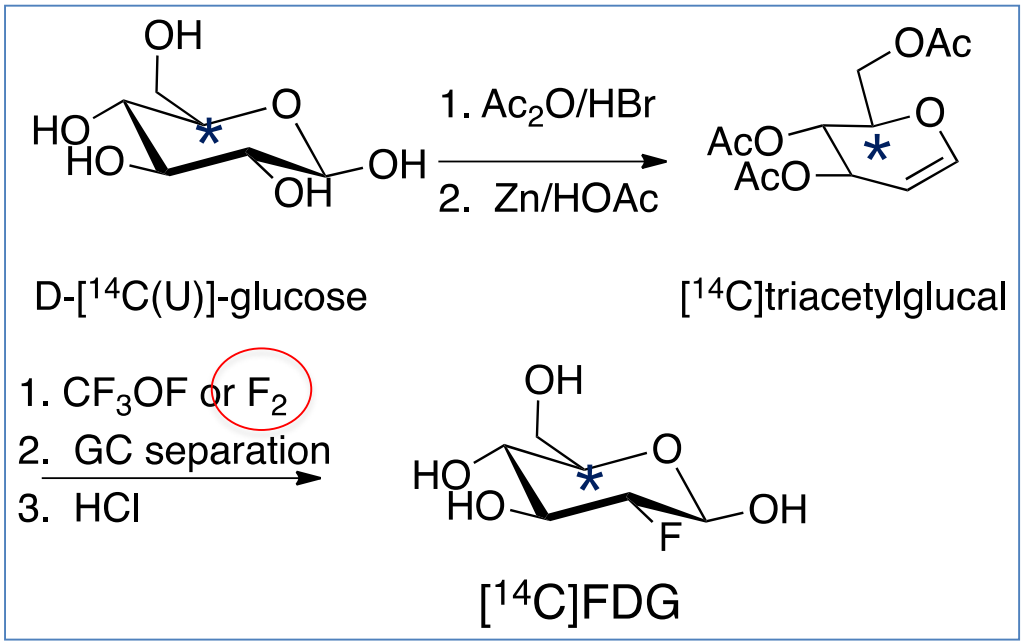
[^{18}F]Fluorodeoxyglucose (^{18}FDG)

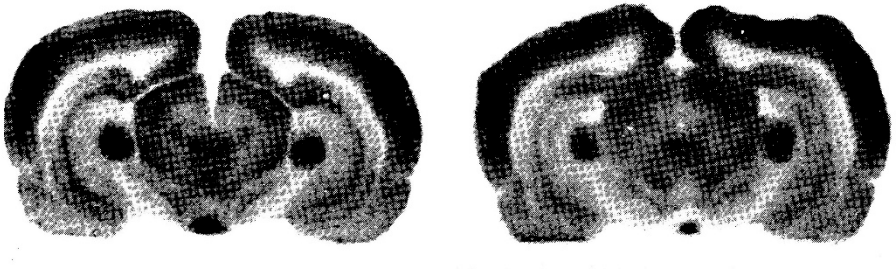
autoradiography in animals → **PET in humans**

^{18}F: $t_{1/2}$: 110 min; long enough to make it at BNL and send it to Philadelphia

Will ^{18}FDG behave like 2-DG?

Synthesis and comparison [^{14}C]FDG to [^{14}C]2-DG



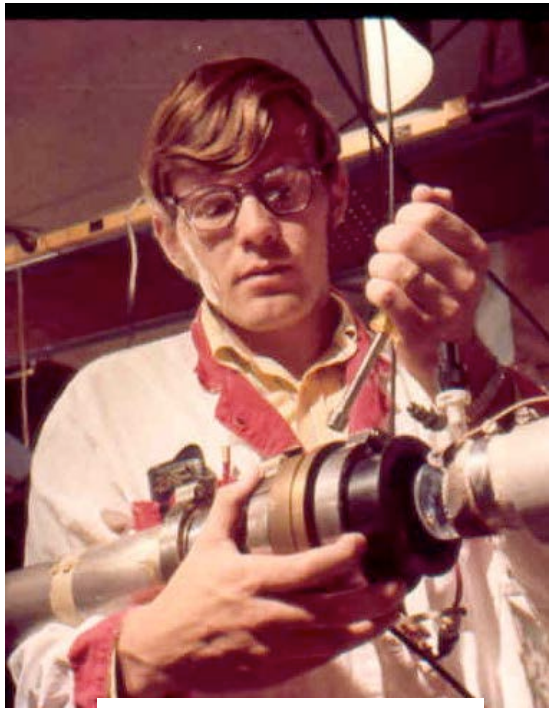


[^{14}C]2-DG [^{14}C]FDG

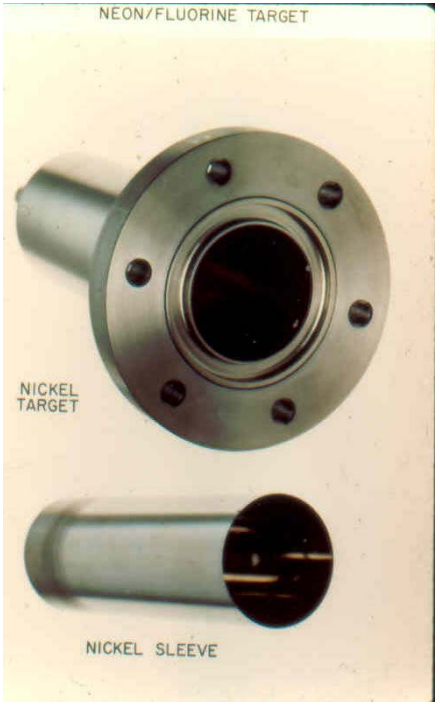
At the time Brookhaven's only reliable source of ^{18}F for chemistry was as elemental fluorine ($^{18}F]F_2$) which Lambrecht and Finn had developed in 1973

$^{20}Ne(d,\alpha)^{18}F \longrightarrow {}^{18}F + F_2\,(0.1\%)$ $[^{18}F]F_2$

Richard M. Lambrecht

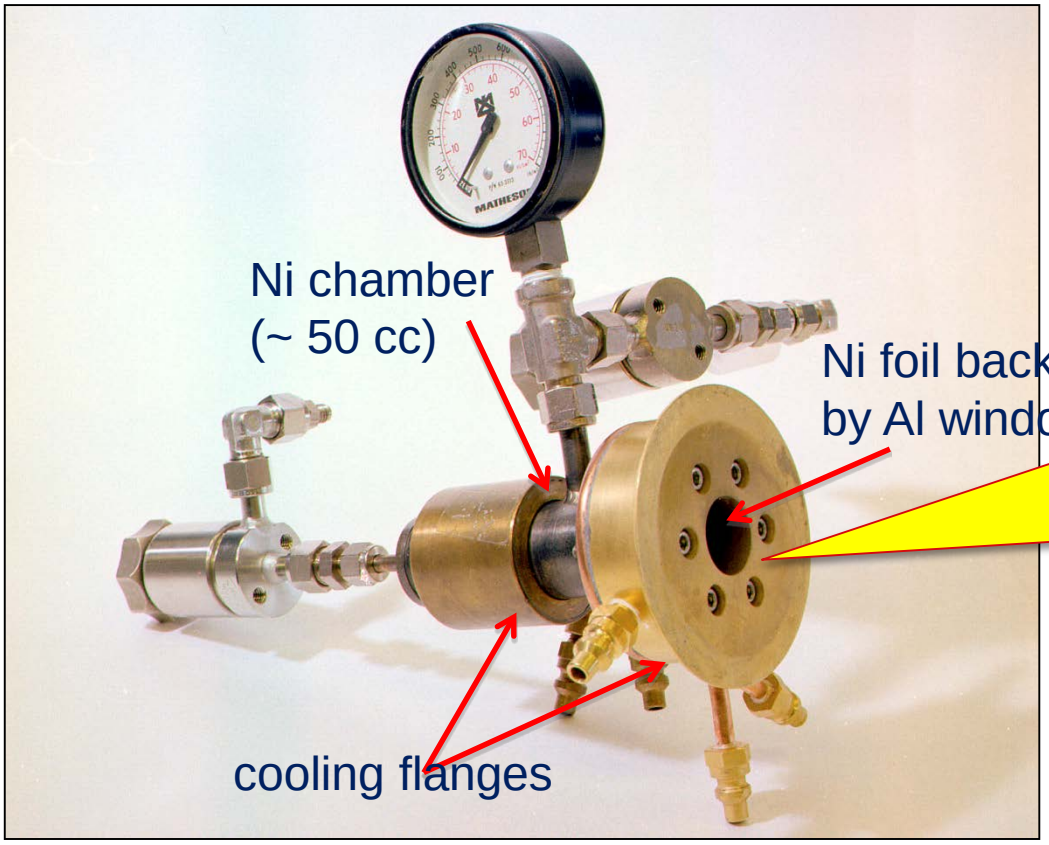


Ronald Finn



Fowler, Finn, Lambrecht and Wolf, The synthesis of 18 F-**5-fluorouraci,** J Nucl Med 14: 63-4, 1973

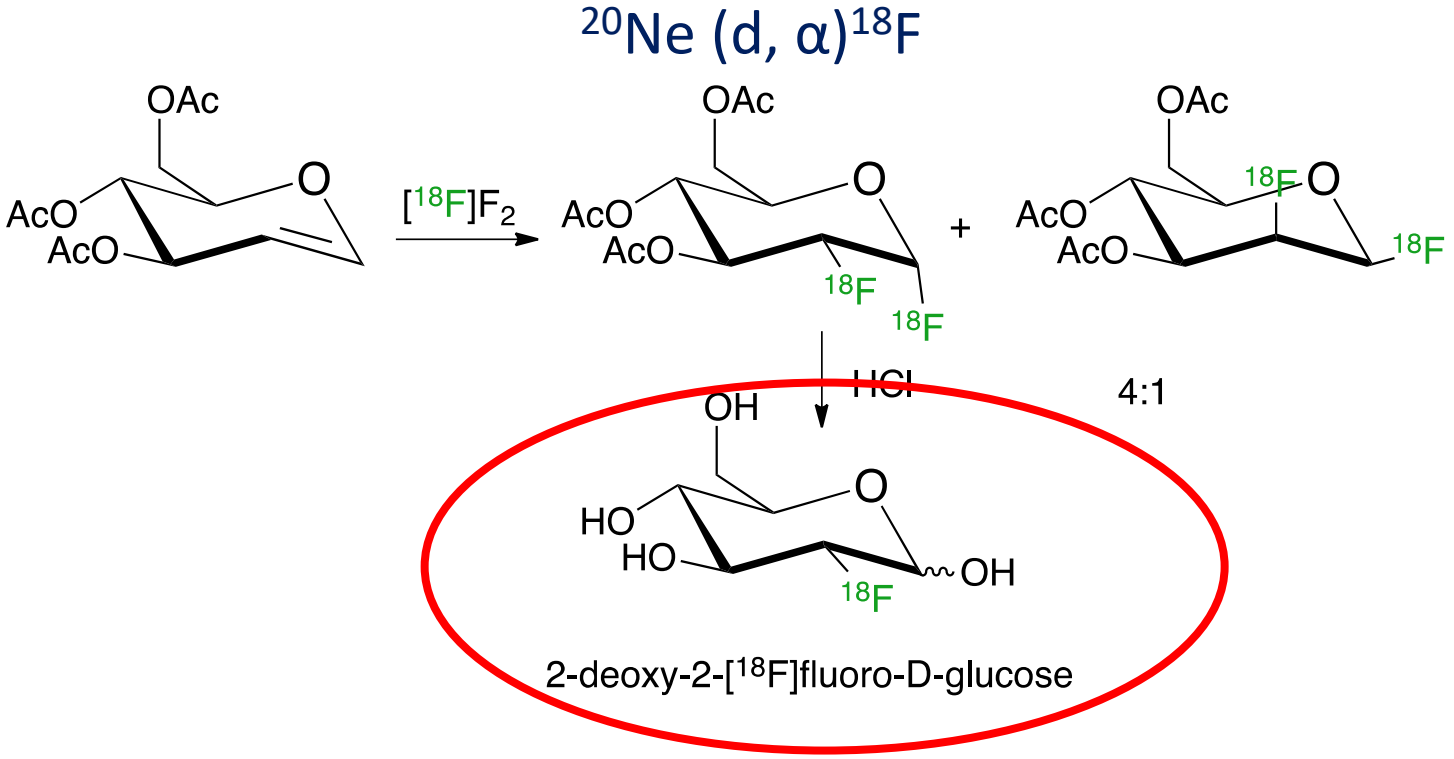
Challenge: to produce enough $[^{18}F]F_2$ to do the synthesis at BNL and send to Penn



Yield 600-800 mCi of $[^{18}F]F_2$ for a 2 hr beam

* Casella, Ido, Wolf, Fowler, MacGregor, Ruth, Anhydrous F-18 labeled elemental fluorine for radiopharmaceutical preparation, J. Nucl. Med. 21: 750, 1980

First ^{18}FDG Synthesis for Humans (1976)

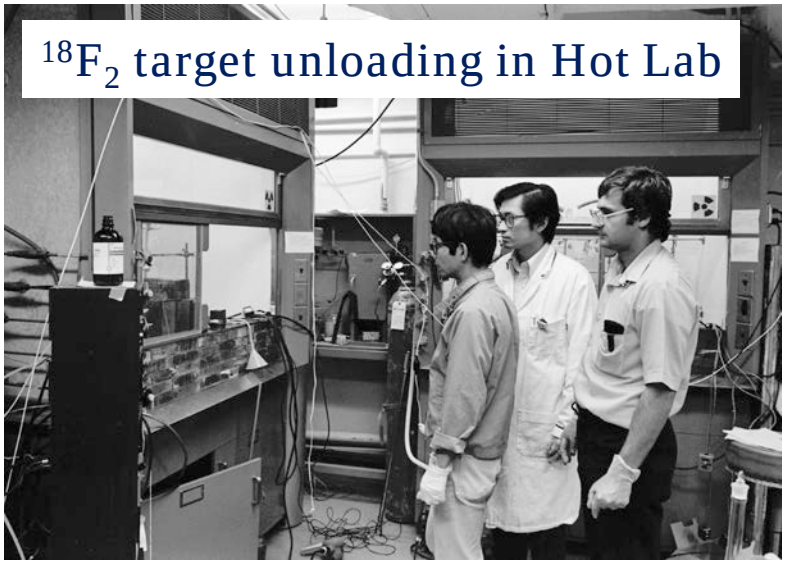


Synthesis time 2 hrs: enabled the first measures of glucose metabolism in the living human body; but yields were low (50% loss) and $^{18}F_2$ was hard to handle.

Brookhaven National Lab; August 17, 1976

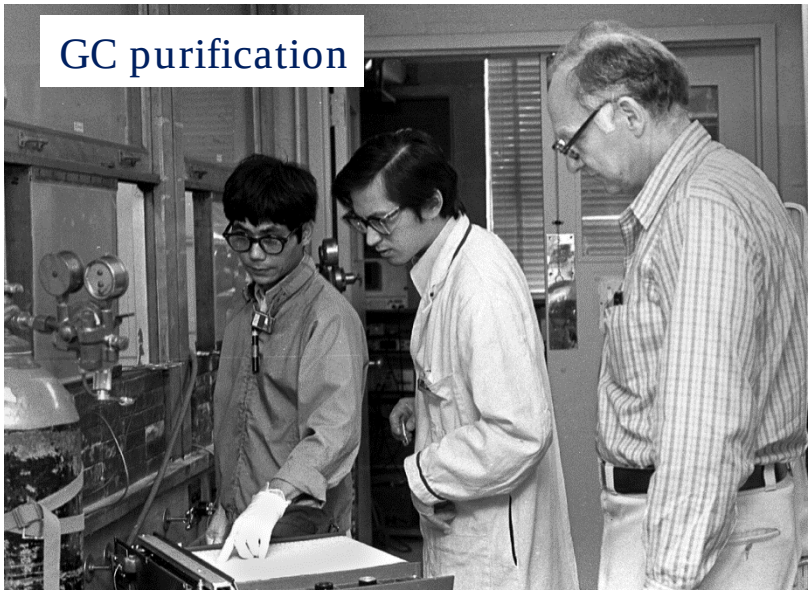
Tatsuo Ido mounts F_2 target

$^{18}F_2$ target unloading in Hot Lab

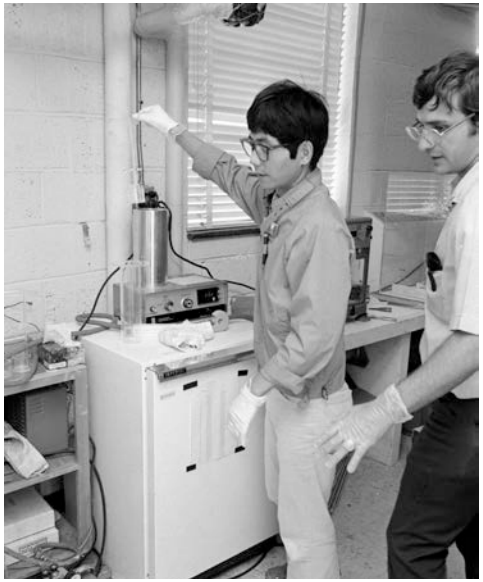


Crude product transfer

GC purification

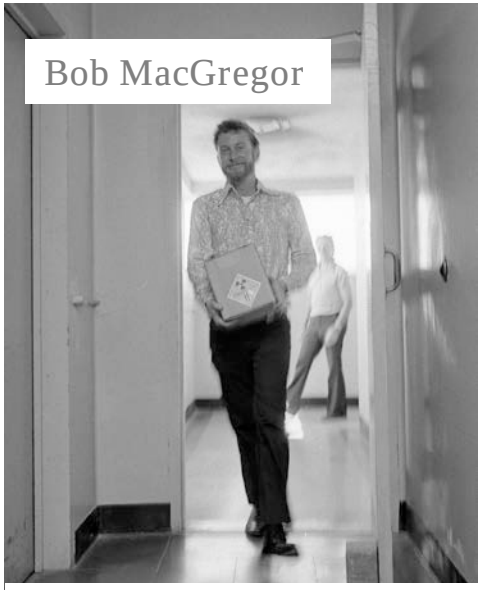


Brookhaven National Laboratory; August 17, 1976



^{18}FDG measurement

packaging



Bob MacGregor

^{18}FDG leaves hot lab

^{18}FDG leaves BNL

Brookhaven Calabro Airport

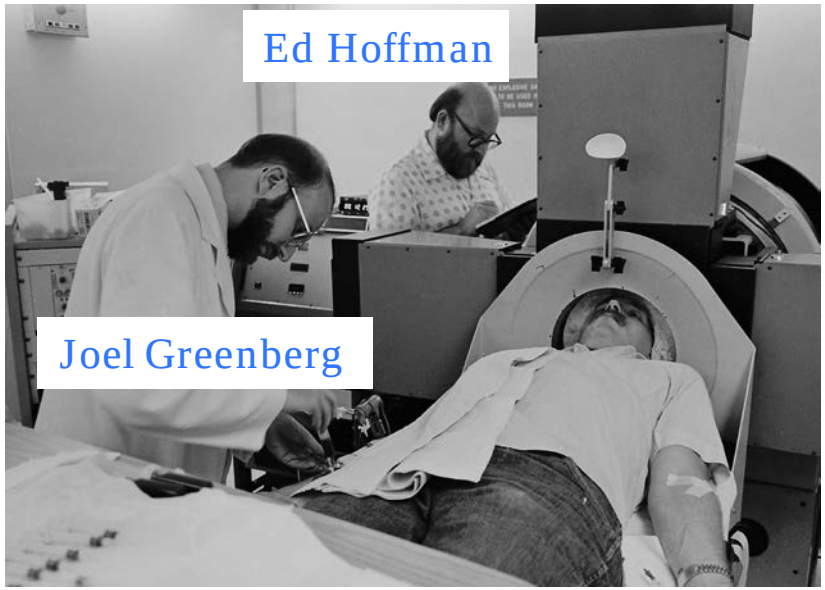
Philadelphia; August 17, 1976

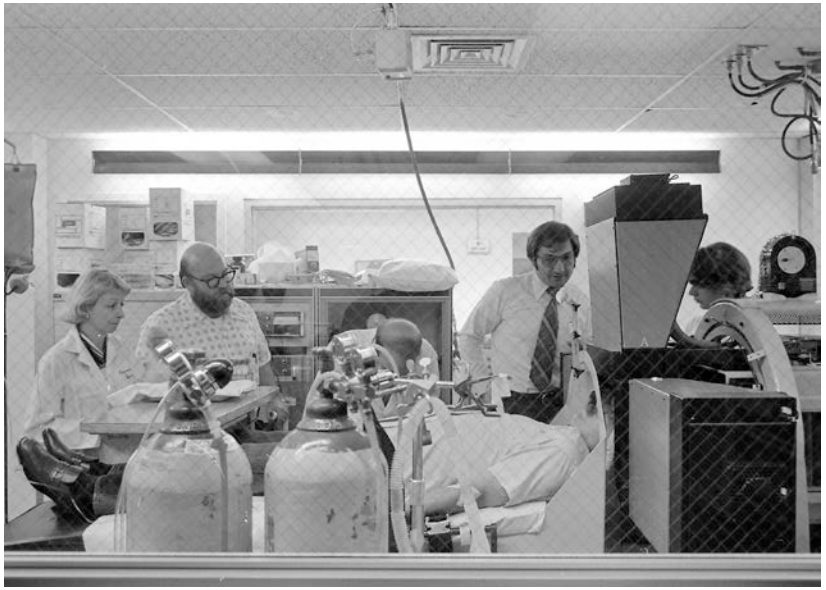

Philadelphia International Airport


^{18}FDG arrives in Philadelphia

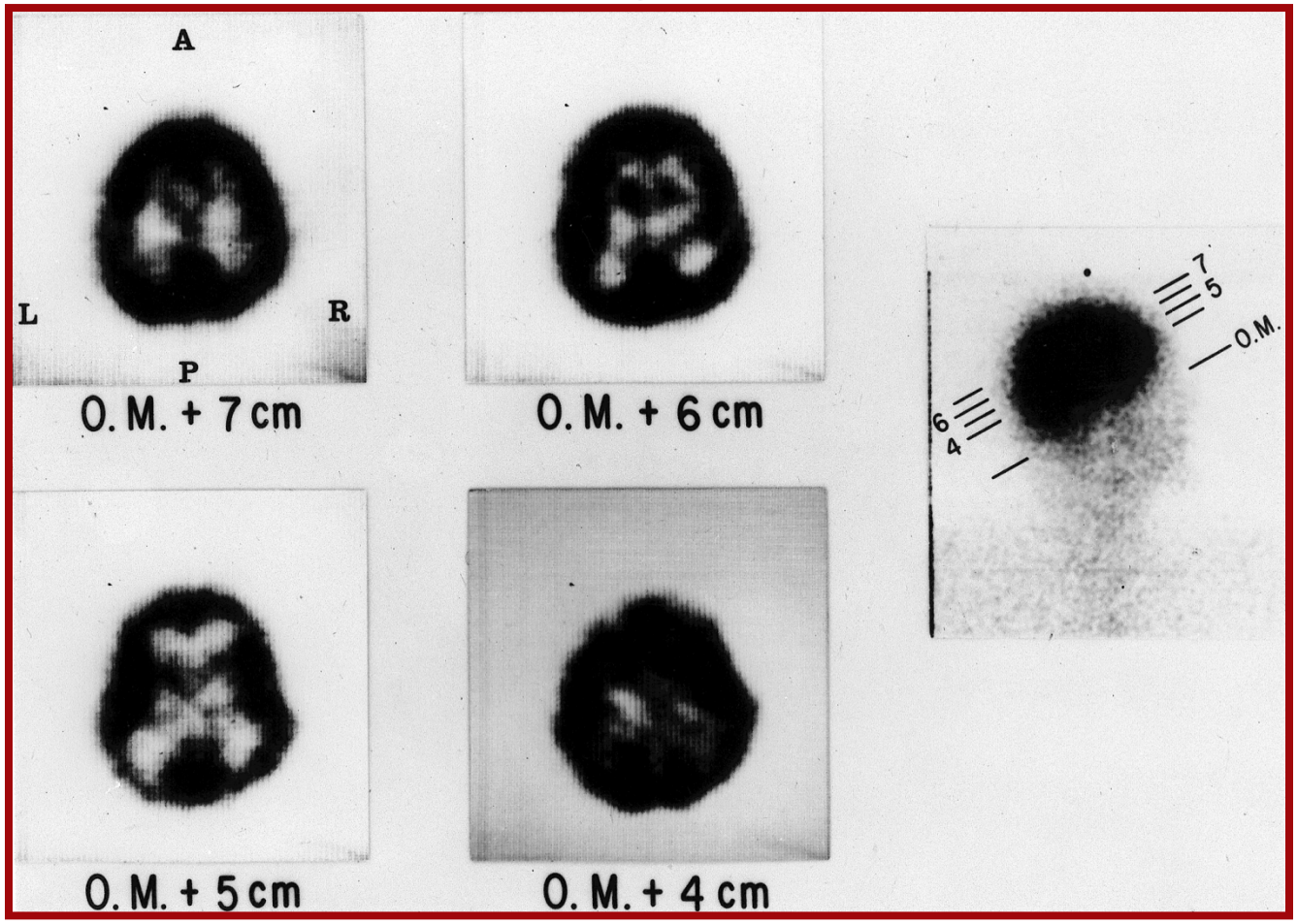

Arrival at Penn

Hospital University of Pennsylvania; August 17, 1976





First Brain images made on Dave Kuhl's Mark IV tomograph in 1976



Rates of glucose metabolism ranged from 10.27 mg/100 g/min in visual cortex to 3.80 mg/100 g/min in white matter.

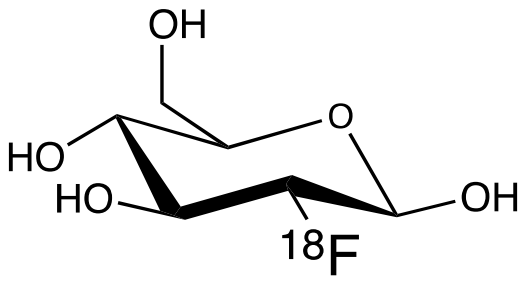
The [^{18}F]Fluorodeoxyglucose Method for the Measurement of Local Cerebral Glucose Utilization in Man

M. Reivich,[1] D. Kuhl,[2] A. Wolf,[3] J. Greenberg,[1] M. Phelps,[2] T. Ido,[3] V. Casella,[3]
J. Fowler, [3] E. Hoffman,[2] A. Alavi,[2] P. Som,[3] and L. Sokoloff[4]

range from 3.64 mg/100 g per minute in the corpus callosum to 4.22 in the occipital lobe. Average values for gray matter, white matter, and whole brain metabolic rates, calculated as a weighted average based on the approximate volume of each structure, are 8.05, 3.80, and 5.90 mg/100 g per minute, respectively. The value of 5.9 mg/100 g per minute compares favorably with values previously reported.

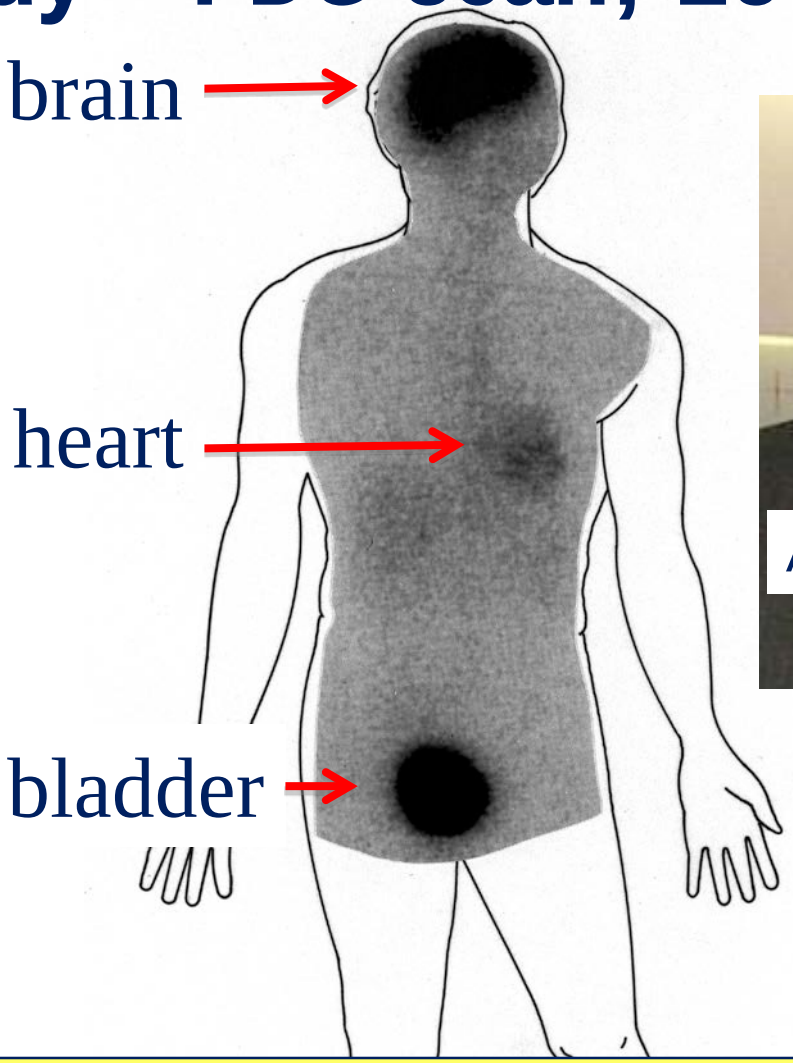
Circ Res 44: 127-137, 1979

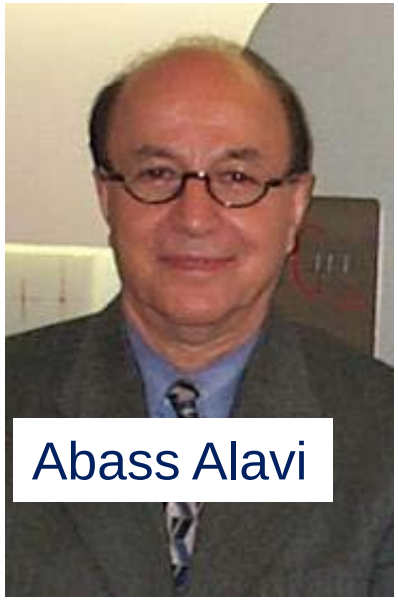
First Whole Body ^{18}FDG Scan, 1976



HK and facilitated transport does not require OH on C-2

glucose resorption (active transport) requires OH on C-2





The body background is low.

First Report of High ^{18}FDG Uptake in Tumors

Prantika Som
1942-2011

A Fluorinated Glucose Analog, 2-fluoro-2-deoxy-D-glucose (F-18): Nontoxic Tracer for Rapid Tumor Detection

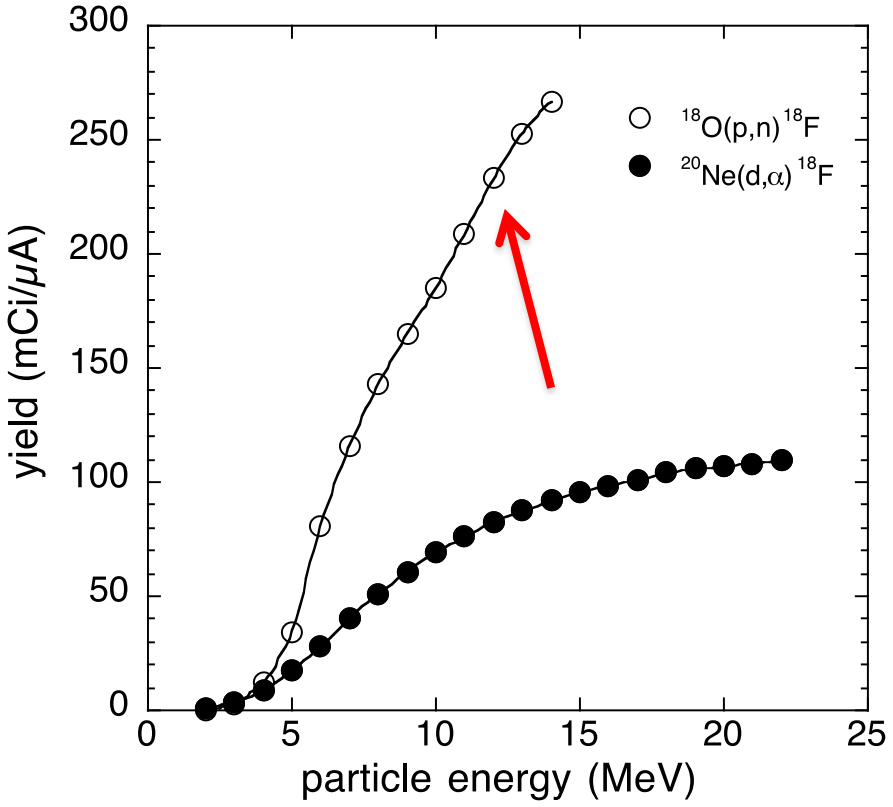
P. Som, H. L. Atkins, D. Bandoypadhyay, J. S. Fowler, R. R. MacGregor, K. Matsui, Z. H. Oster, D. F. Sacker, C. Y. Shiue, H. Turner, C-N. Wan, A. P. Wolf, and S. V. Zabinski

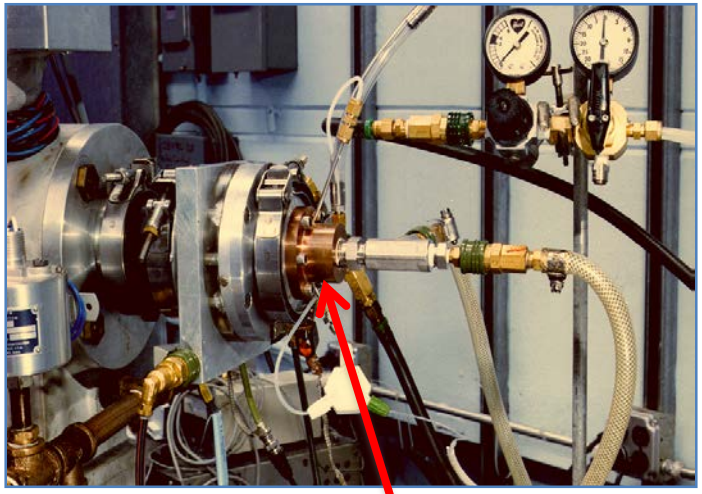
Brookhaven National Laboratory, Upton, New York

Rapid uptake of F-18 FDG was observed in a variety of transplanted and spontaneous tumors in animals. The tumor uptake reached a peak by 30 min and remained relatively constant up to 60 min, with a very slow wash-out of F-18 activity from the tumor thereafter. Tumor-to-normal tissue and tumor-to-blood ratios ranged from 2.10–9.15 and 2.61–17.82, respectively, depending on the type of tumor. A scintiscan of a seminoma in a dog showed very high uptake in the viable part and lack of uptake in the necrotic mass. Toxicological studies in mice using 1000 times human tracer dose (HTD) per wk for 3 wk and in dogs using 50 times HTD per wk for 3 wk did not show any evidence of acute or chronic toxicity.

J Nucl Med 21: 670–675, 1980

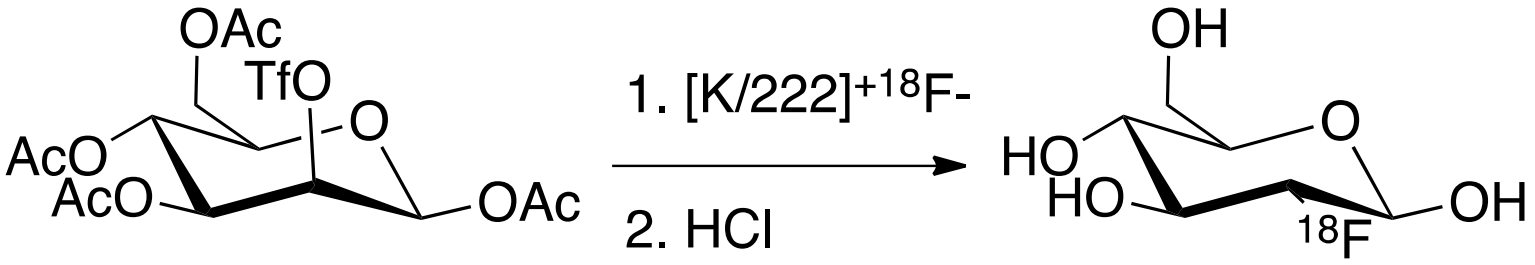
Ruth and Wolf publish high yield of ^{18}F via the $^{18}O(p,n)^{18}F$ reaction (1979)





Small volume (1 mL), 95% enriched water target ($H_2{}^{18}O$) (~$100/mL).

Hamacher's rapid synthesis of ^{18}FDG from [^{18}F]Fluoride in 1986 was a major milestone



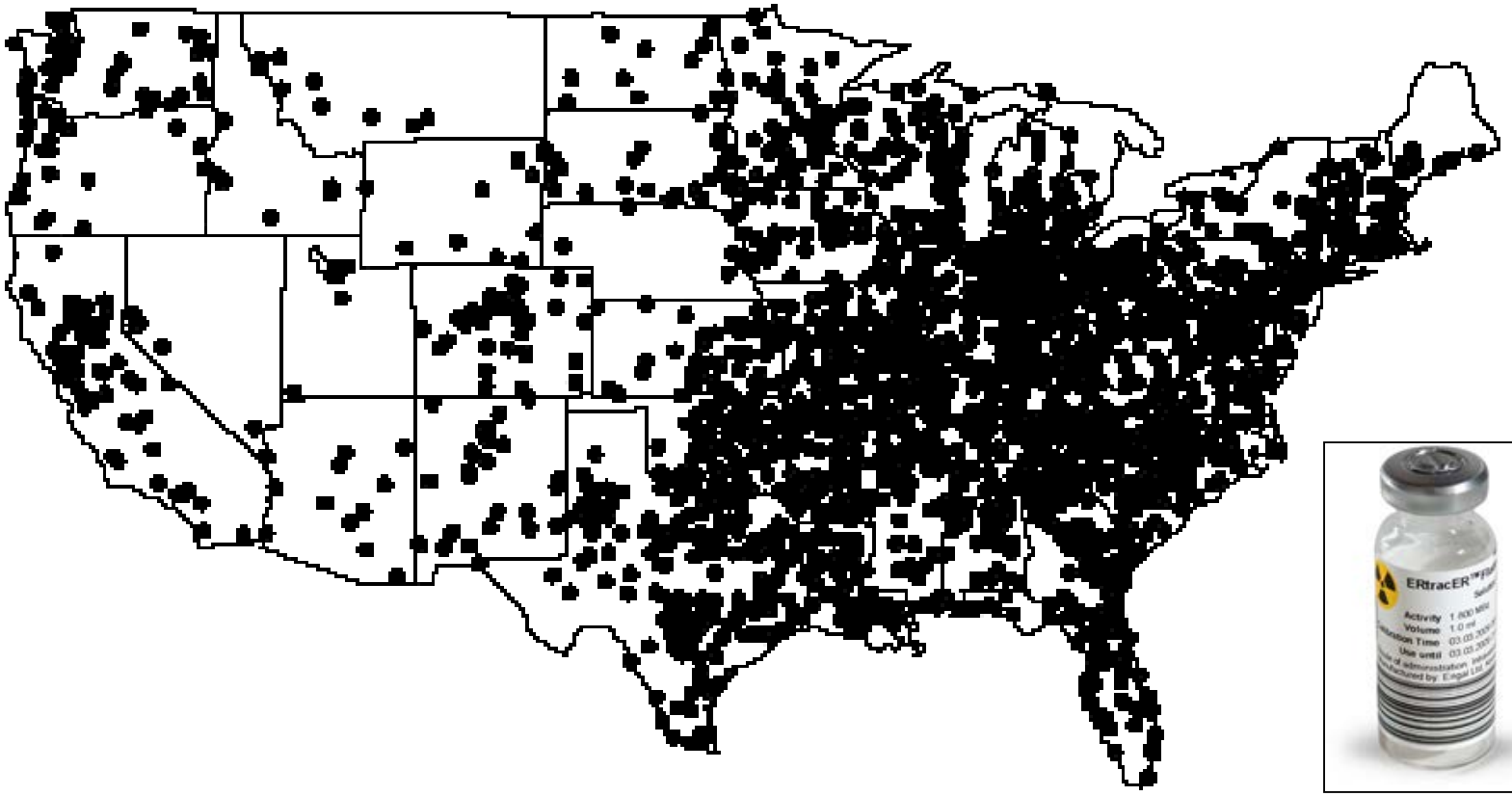
Mannose triflate

^{18}FDG

- 50% yield in 50 minutes
- no added F-19
- amenable to automation

The high yield synthesis of ^{18}FDG from ^{18}F-fluoride (Hamacher et al., 1986) stimulated the development of synthesis modules to automate the process and commercialize of production and distribution from regional centers worldwide

Clinical PET Centers in the USA in 2012



Map from M. Phelps

Summary

- The science surrounding the development of radiopharmaceuticals flourished in a relatively short time frame.
- The discovery of the X-ray in 1895 was quickly utilized in clinical practice and launched the discovery of natural and artificial radioactivity, which ultimately has had an enormous impact on human health.
- Although the ultimate goal of the Manhattan Project was the development of atomic weapons, the Atomic Energy Agency (now the Department of Energy) turned the science behind war into a means of diagnosing and treating disease.
- Accelerators and cyclotrons — and the technology behind them — first developed in the 1930s for physics experiments are now used to produce a plethora of radionuclides for medicine.
- Major advances in organic chemistry have been applied to quickly synthesizing radiotracers bearing short-lived radionuclides for PET imaging.
- **The science and technology behind radiopharmaceutical chemistry continues to grow, as new radiopharmaceuticals for cardiology, neurology, and oncology become approved for clinical use throughout the world**

References

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Questions??

Upcoming Webinars

- Radiopharmaceutical Series:
- Radiopharmaceutical Series:
- Radiopharmaceutical Series:

NAMP website http://www.wipp.energy.gov/namp/