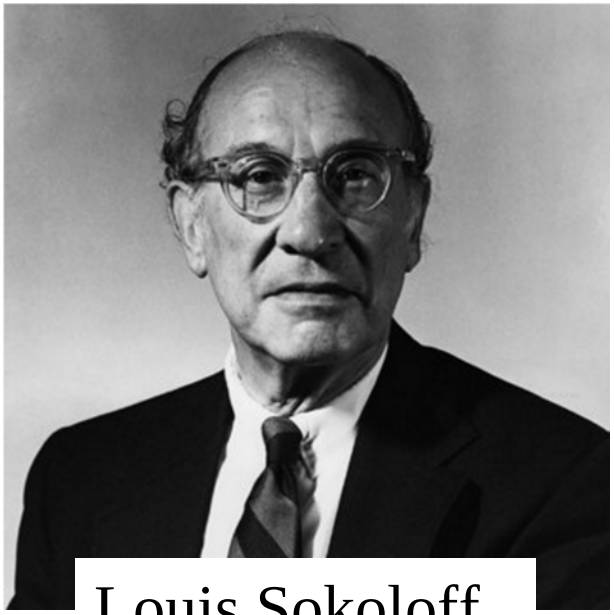
Working Against Time: Designing and Synthesizing ^{18}FDG for the First Human Studies in 1976

Joanna S. Fowler

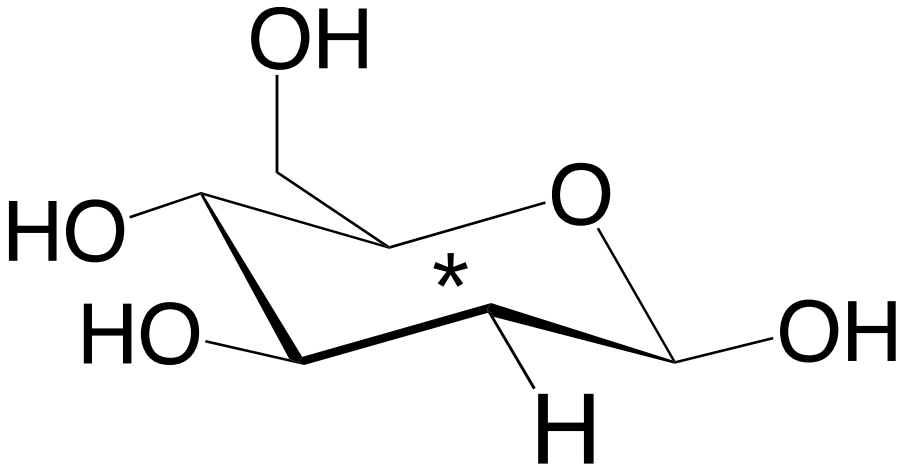
Brookhaven National Laboratory
National Institutes of Health

The ^{14}C-2-Deoxyglucose Method



Louis Sokoloff

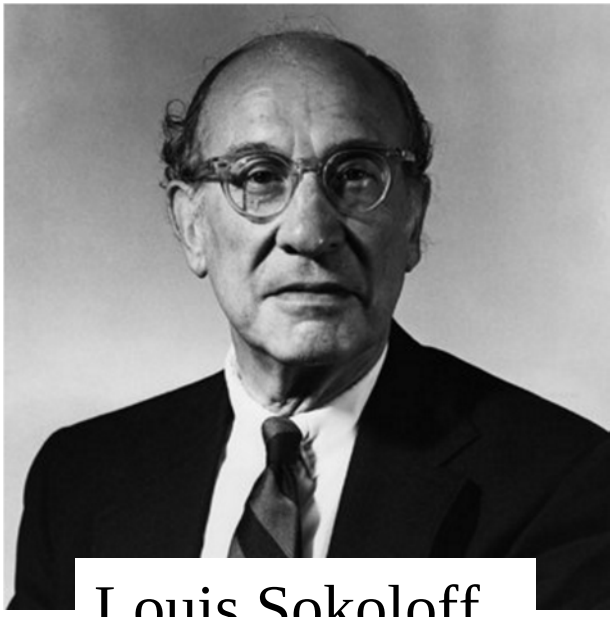
Martin Reivich



[U-^{14}C-2-deoxy-D-glucose]

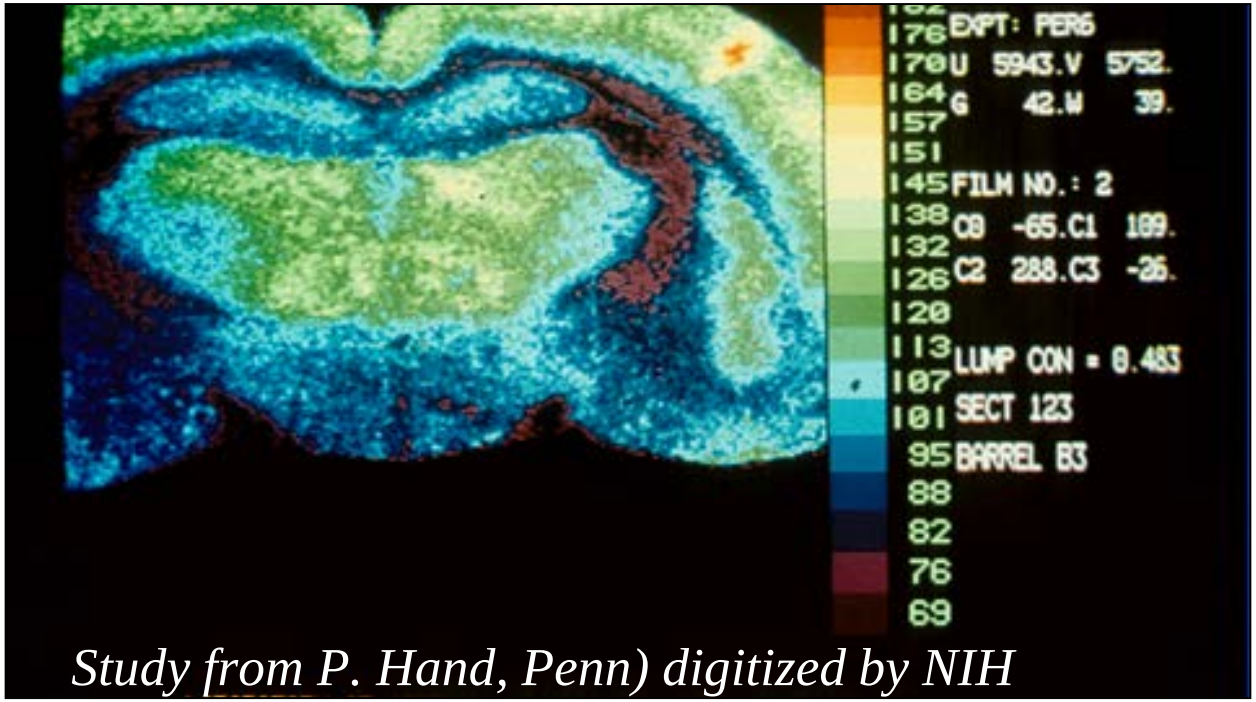
Kennedy C, Des Rosiers MH, Jehle JW, **Reivich M**, Sharpe F, **Sokoloff L**. Mapping of functional neural pathways by autoradiographic survey of local metabolic rate of (^{14}C)glucose. *Science*. 1975 Mar 7;187(4179):850-3.

The ^{14}C-2-Deoxyglucose Method



Louis Sokoloff

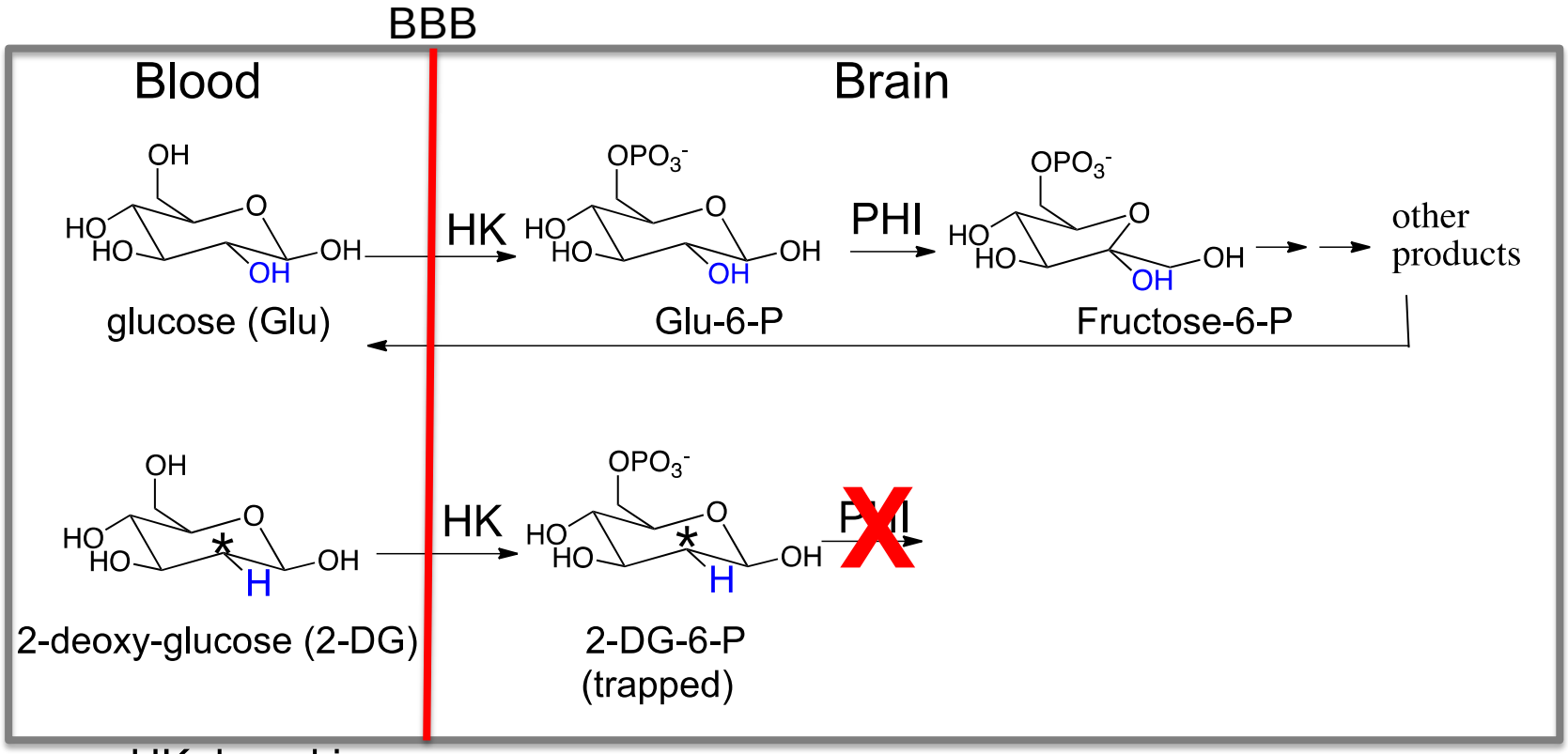
Martin Reivich



Study from P. Hand, Penn) digitized by NIH

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.

The ^{14}C-2-Deoxyglucose (2-DG) Method



HK: hexokinase
PHI:phosphohexose isomerase

Goal was to label the 2-DG molecule with a radioisotope that would maintain its properties; could be imaged in humans.

J Fowler

BROOKHAVEN NATIONAL LABORATORY
ASSOCIATED UNIVERSITIES, INC., UPTON, L.I., N.Y. 11973

DEPARTMENT OF CHEMISTRY

TELEPHONE: (516) 345- 2123

December 19, 1973

Subject: Meeting to discuss collaboration between the Nuclear Medicine Programs at BNL and U. of Pennsylvania.

Participants:

Abass Alavi, M.D.	Nuclear Medicine	HUP
Harold Atkins, M.D.	Nuclear Medicine	BNL
David Christman, Ph.D.	Chemistry	BNL
Joanna Fowler, Ph.D.	Chemistry	BNL
David Kuhl, M.D.	Nuclear Medicine	HUP
X Martin Reivich, M.D.	Neurology	HUP
Muni Staum, Ph.D.	Radiopharm. Chem.	HUP
Alfred Wolf, Ph.D.	Chemistry	BNL
Steven Nyary, M.D.	Neurology	HUP

Agenda: -Lunch- Berkner Hall, conf. room C

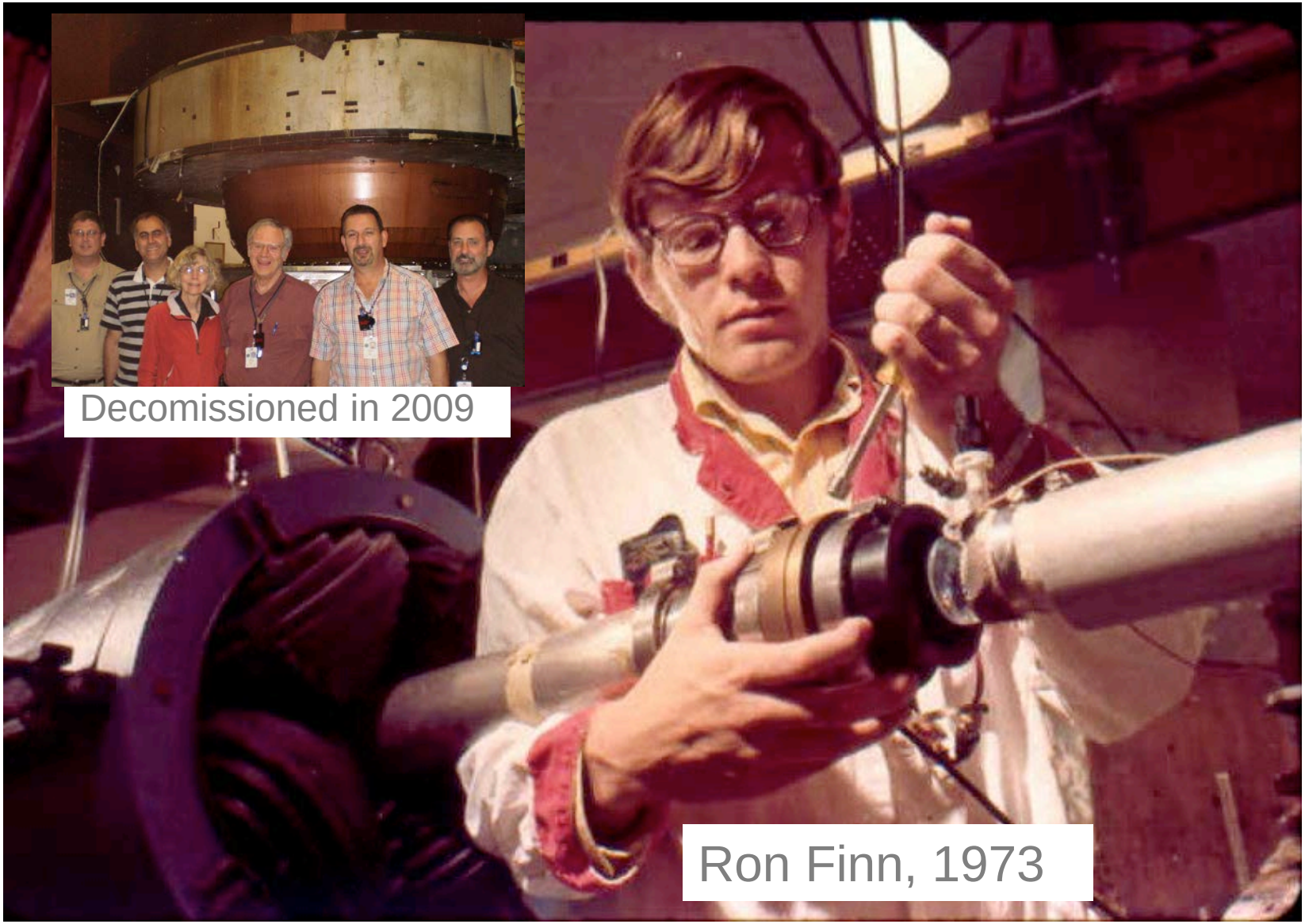
-Discussion of programs of mutual interest with emphasis on labeled carbohydrates for brain function studies.

Top row: Brian Gallagher, David Christman , David Schlyer, Tony Guzikowski, Toshi Hara, Bob MacGregor, Al Wolf, Betty Crawford, David Tang, Hernan Vera Ruiz

Bottom row: Richard M. Lambrecht, Joanna Fowler, David Lloyd, Chyng Shiue, Richard Ehrenkaufer, Bob Lade, Karin Karlstrom

Brookhaven 60 inch cyclotron

Decomissioned in 2009



Ron Finn, 1973

Short Lived PET Radioisotopes

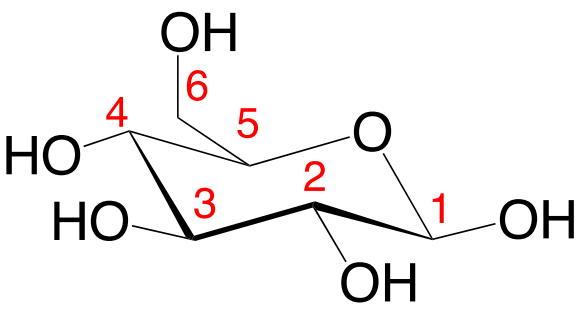
Isotope	Half-life
carbon-11	20.4 min
fluorine-18	110 min
nitrogen-13	10 min
oxygen-15	2 min

Fluorine-18's half life was potentially long enough to be incorporated into a radiotracer and transported from Upton, NY to Philadelphia for imaging on Mark IV.

Where should we label the 2-DG molecule?

Alberto Sols
1917-1989

Robert Crane
1919-2010



glucose

SUBSTRATE SPECIFICITY OF BRAIN HEXOKINASE*

By ALBERTO SOLS† and ROBERT K. CRANE

(From the Department of Biological Chemistry, Washington University School of Medicine, St. Louis, Missouri)

(Received for publication, February 8, 1954)

Where should we label the 2-DG molecule?

Alberto Sols
1917-1989

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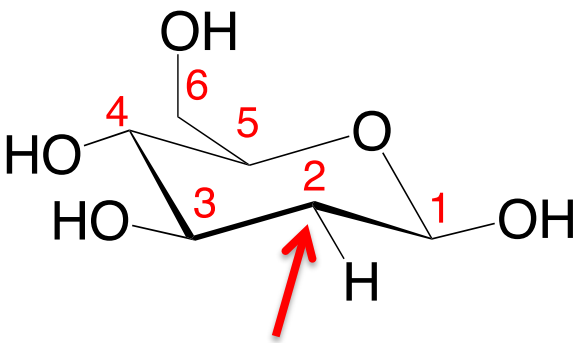
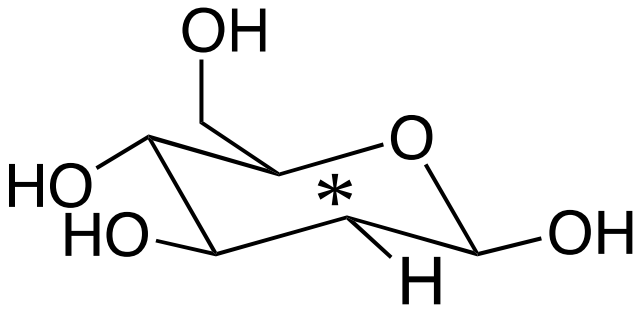
1919-2010



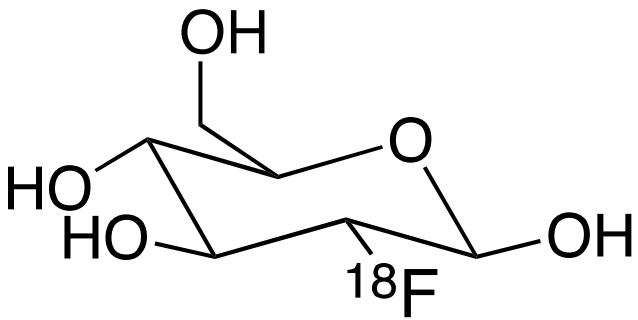
2-deoxy-glucose

"2-Deoxy-glucose possesses certain advantages over glucose as a substrate for experimental studies with crude preparations of brain an other tissue hexokinases. The phosphate ester formed from 2-deoxy-glucose is not inhibitory and it is not a substrate for either phosphohexose isomerase or glucose-6-phosphate dehydrogenase. <u>Thus the use of 2-deoxyglucose isolates the hexokinase reaction</u>." (J. Biological Chemistry 210: 581, 1954)

^{18}FDG: Design and Synthesis



[^{14}C]2-deoxyglucose



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

autoradiography in animals → **imaging in humans**

^{18}F: $t_{1/2}$ 110 min; had a long enough half-life to make it at BNL and ship it to Philadelphia.

Synthesis of Unlabeled FDG

From KHF_2 in 1969

CHEMICAL COMMUNICATIONS, 1969

Synthesis of 2-Deoxy-2-fluoro-D-glucose

By JOSEF PACÁK,* ZDENĚK TOČÍK, and MILOSLAV ČERNÝ

(*Department of Organic Chemistry, Charles University, Prague–Albertov, Czechoslovakia*)

From CF_3OF in 1970

Carbohydrate Research
Elsevier Publishing Company, Amsterdam
Printed in Belgium

FLUORINATED CARBOHYDRATES

PART III[1]. 2-DEOXY-2-FLUORO-D-GLUCOSE AND 2-DEOXY-2-FLUORO-D-MANNOSE*

J. ADAMSON**, A. B. FOSTER,

Chester Beatty Research Institute, Institute of Cancer Research: Royal Cancer Hospital, Fulham Road, London, S. W. 3 (Great Britain)

L. D. HALL, R. N. JOHNSON†,

Department of Chemistry, University of British Columbia, Vancouver 8, B. C. (Canada)

AND R. H. HESSE

Research Insitute for Medicine and Chemistry, Cambridge, Mass., 02142 (U.S.A.)

(Received June 1st, 1970; accepted for publication, June 22nd, 1970)

2-FDG but not 3 or 4-FDG was a good substrate for hexokinase

Biochem. J. (1972) **128**, 199–204
Printed in Great Britain

The Use of Deoxyfluoro-D-glucopyranoses and Related Compounds in a Study of Yeast Hexokinase Specificity

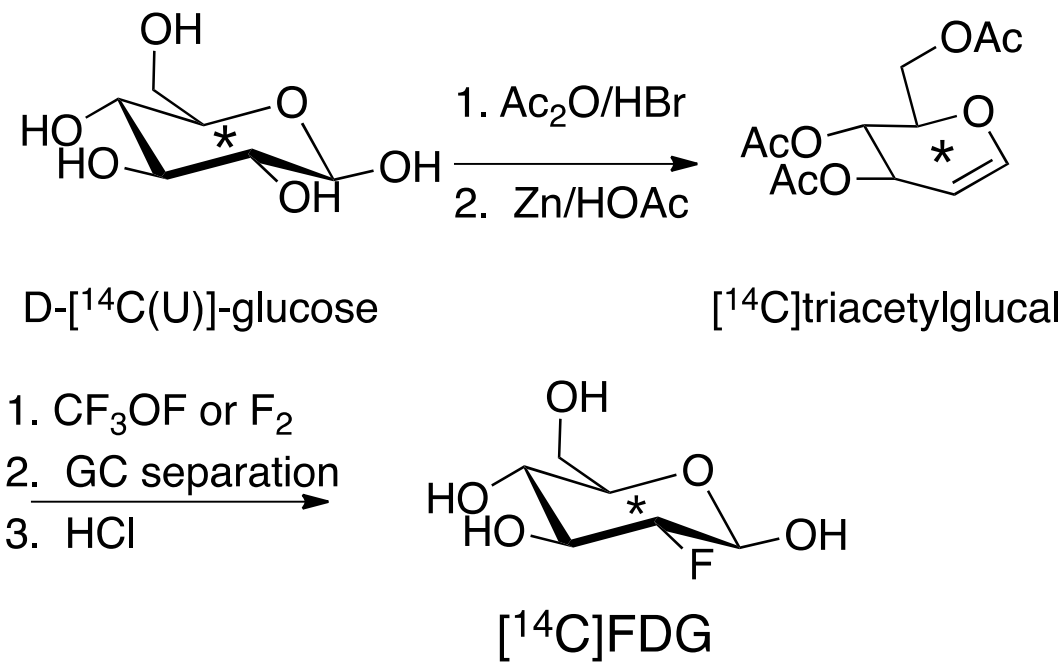
By E. M. BESSELL, A. B. FOSTER and J. H. WESTWOOD
Chester Beatty Research Institute, Institute of Cancer Research: Royal Cancer Hospital, Fulham Road, London S.W.3, U.K.

(*Received* 20 *December* 1971)

Compound	K_m (mM)	Relative $V_{max.}$	K_m $MgATP^{2-}$ (mM)	Calculated $\frac{K'_m}{K_m \text{ (glucose)}}$	Experimental $\frac{K'_m}{K_m \text{ (glucose)}}$
D-Glucose	0.17	1.00	0.20	1	1
2-Deoxy-D-*arabino*-hexose	0.59 ± 0.11	0.85	0.36 ± 0.11	—	—
2-Deoxy-2-fluoro-D-glucose	0.19 ± 0.03	0.50	0.26 ± 0.05	1.14	1.36 ± 0.37
2-Deoxy-2-fluoro-D-mannose	0.41 ± 0.05	0.85	0.66 ± 0.25	2.46	0.86 ± 0.75
2-Deoxy-2,2-difluoro-D-*arabino*-hexose	0.13 ± 0.02	0.53	0.21 ± 0.02	0.78	0.91 ± 0.47
3-Deoxy-3-fluoro-D-glucose	70 ± 30*	0.10	2.3 ± 0.3†	—	—
4-Deoxy-4-fluoro-D-glucose	84 ± 30*	0.10	1.9 ± 0.1‡	—	—
2-Chloro-2-deoxy-D-glucose	2.1 ± 0.6	0.54	0.97 ± 0.33	12.6	9 ± 10

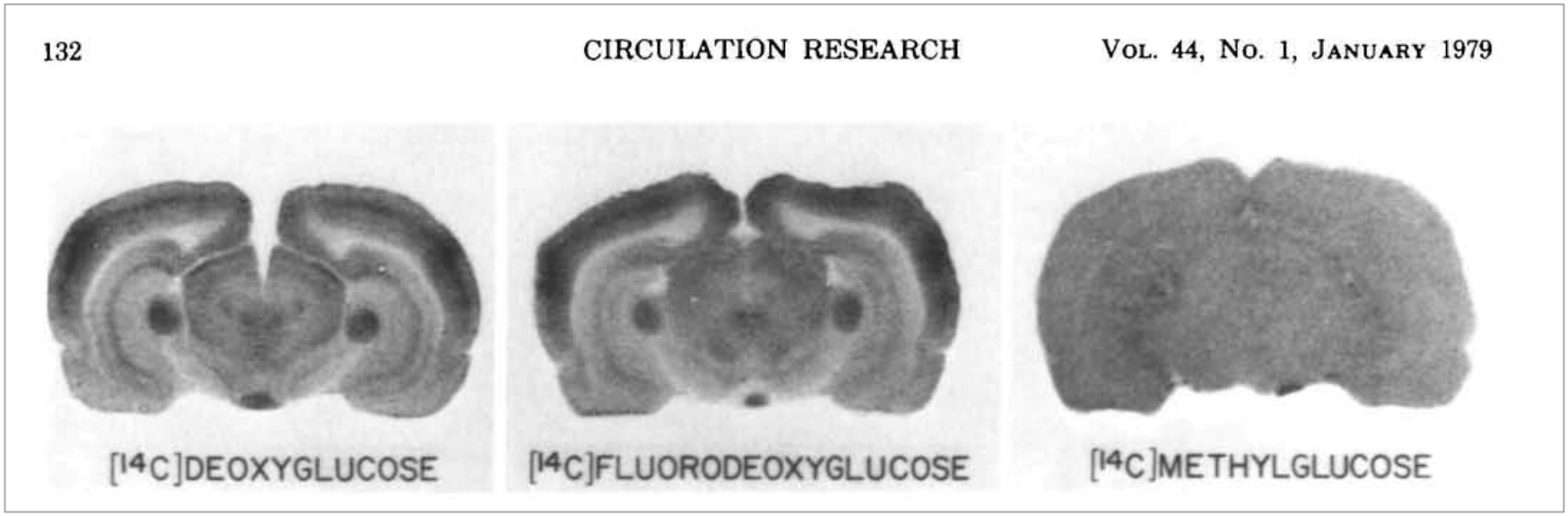
Sokoloff: "Will F substitution change its behavior in vivo?"

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



Ido T, Wan CN, Casella V, Fowler JS, Wolf AP, Reivich M, Kuhl D ., J. Labeled Cmpnds Radiopharm, XIV, 175, 1978

Will ^{18}FDG behave like [^{14}C]2-DG in vivo?



This supported the development of a rapid radiosynthesis of ^{18}FDG

The [^{18}F]fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man, M Reivich, D Kuhl, A Wolf, J Greenberg, M Phelps, T Ido, V Casella, J Fowler, E Hoffman, A Alavi, P Som and L Sokoloff Circulation Research 1979, 44:127-137

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 (J. Nucl Med 14; 63-4, 1973).

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

Richard M. Lambrecht

Ronald Finn

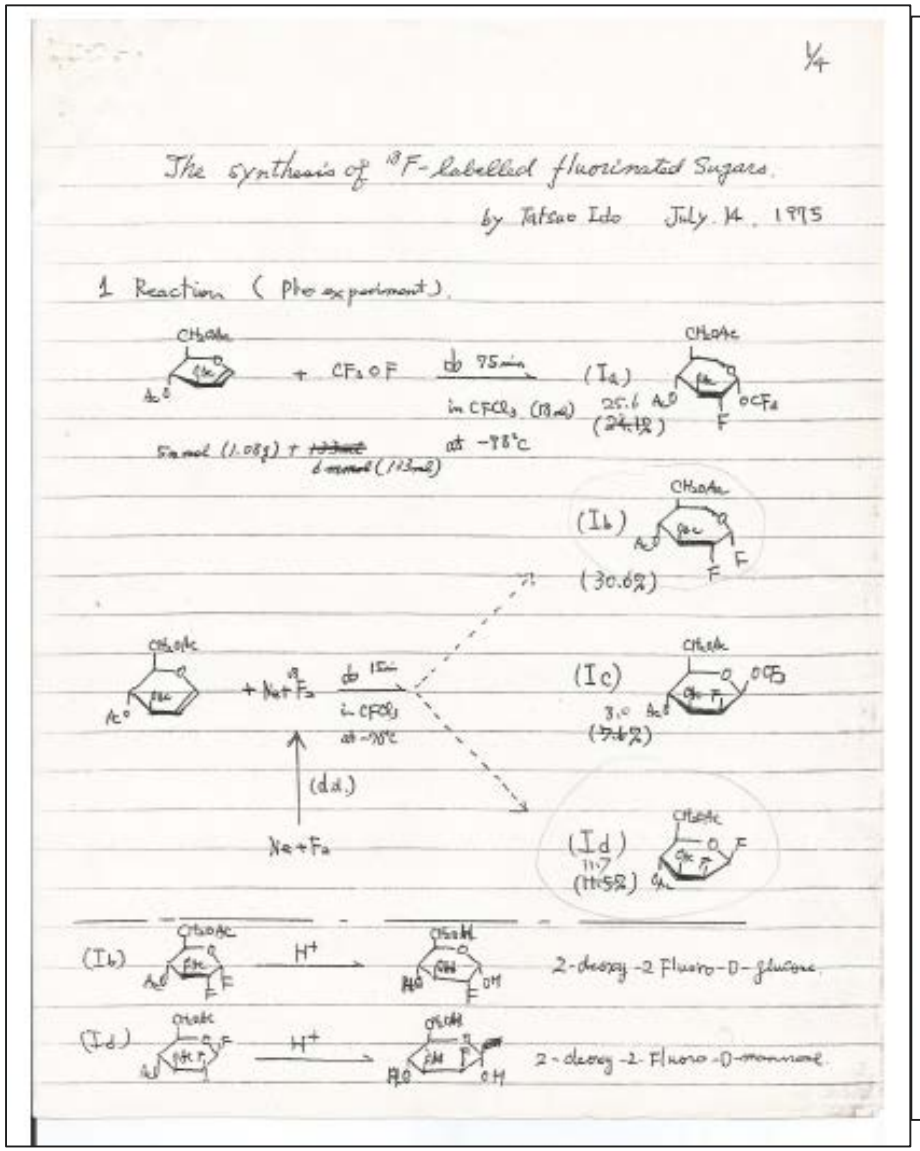
Ne/F_2 target

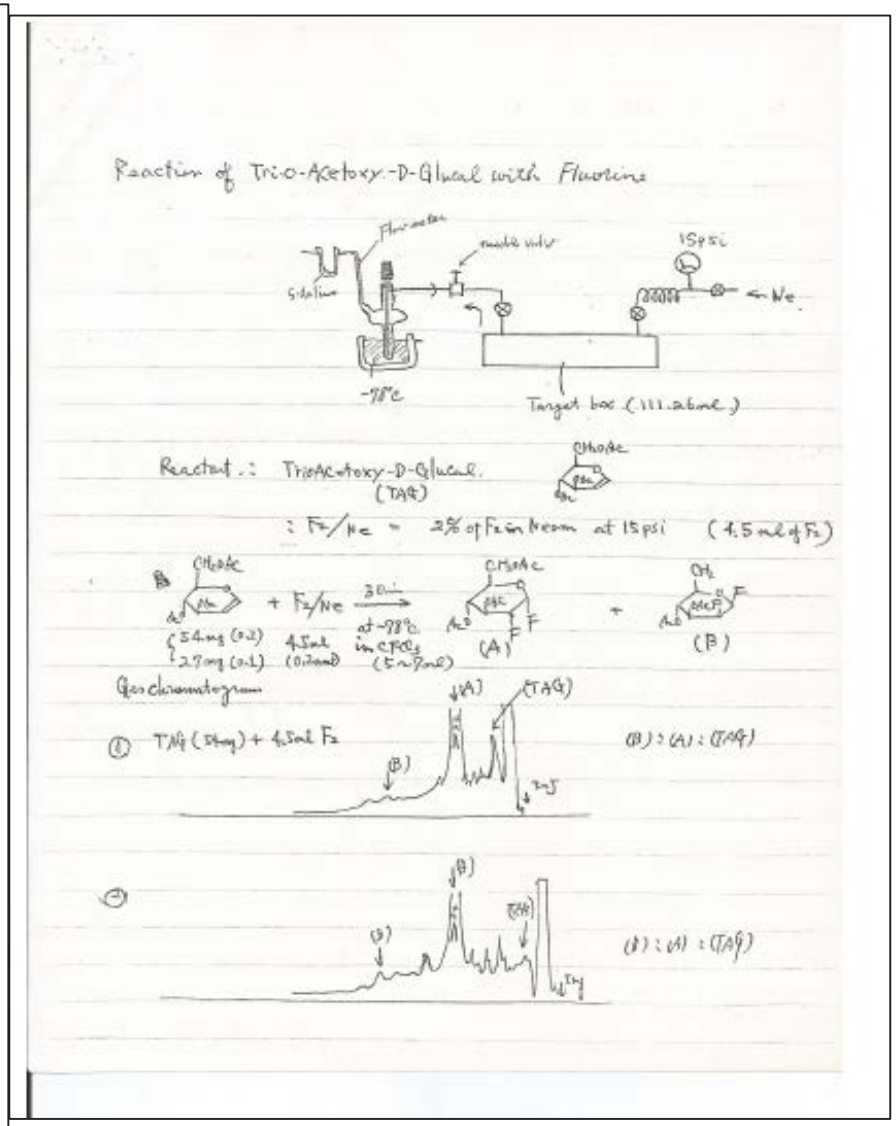
Tatsuo Ido, Chung Nan Wan and Vito Casella joined the Brookhaven group to work on $[^{18}F]F_2$ production and develop the ^{18}FDG synthesis

By 1975, the target was producing 600-800 mCi of $[^{18}F]F_2$

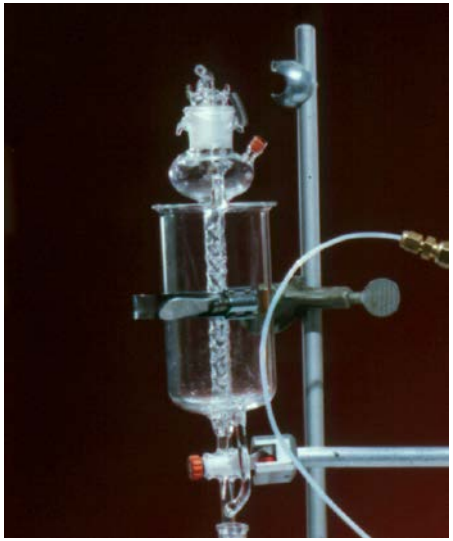
Casella, Ido, Wolf, Fowler, MacGregor, Ruth, Anhydrous F-18 labeled elemental fluorine for radiopharmaceutical preparation, J. Nucl. Med. 21: 750, 1980

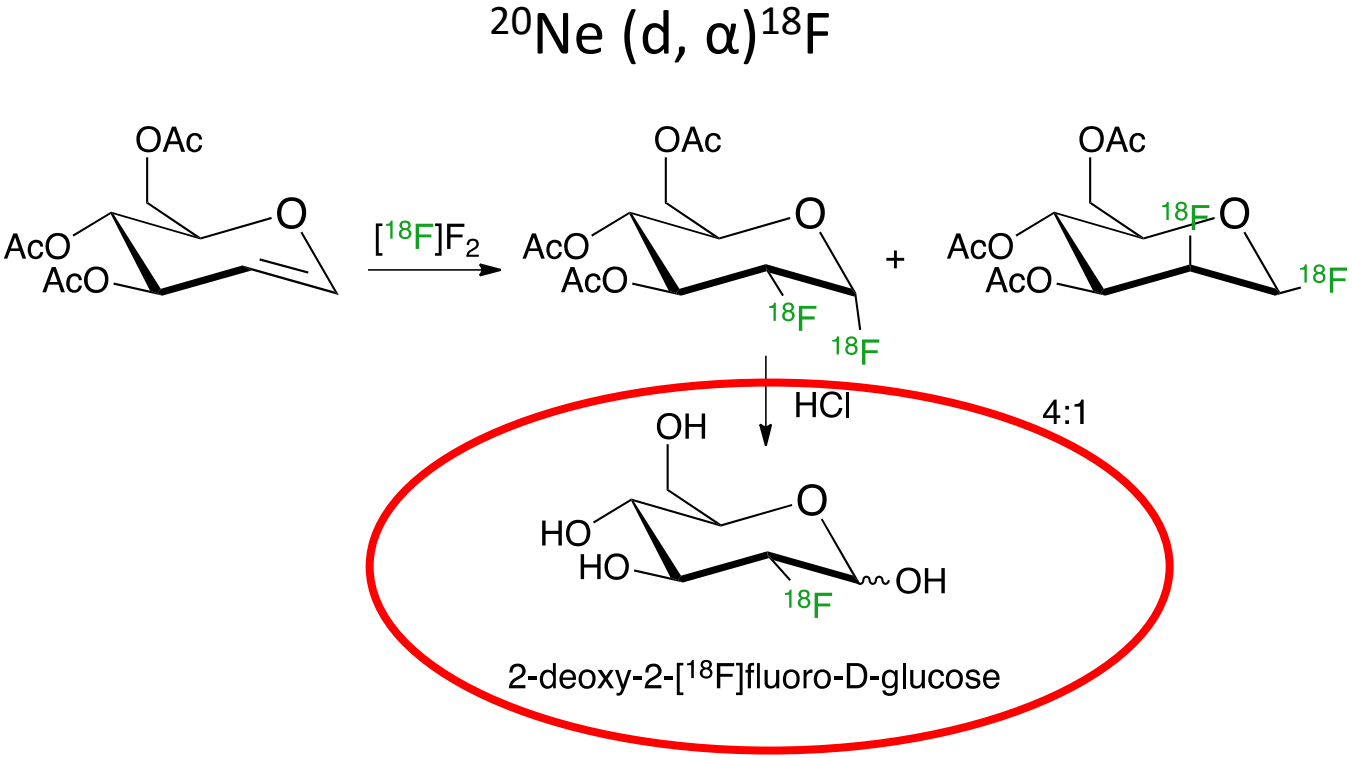
Tatsuo Ido's report and notebook (July 14, 1975): developing the radiosynthesis of ^{18}FDG





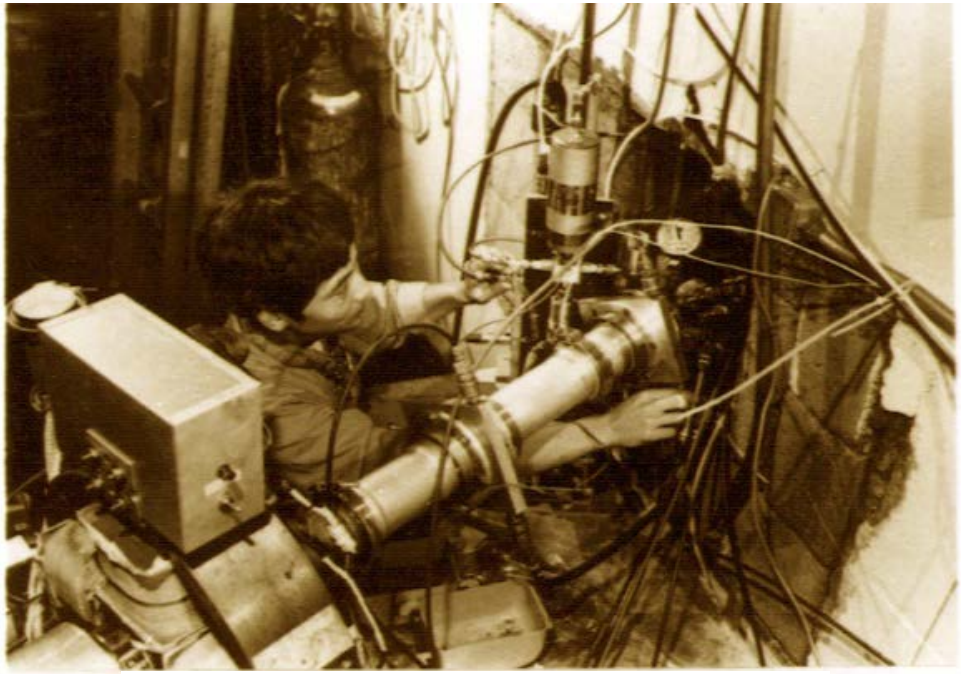
First ^{18}FDG Synthesis for Humans (1976)



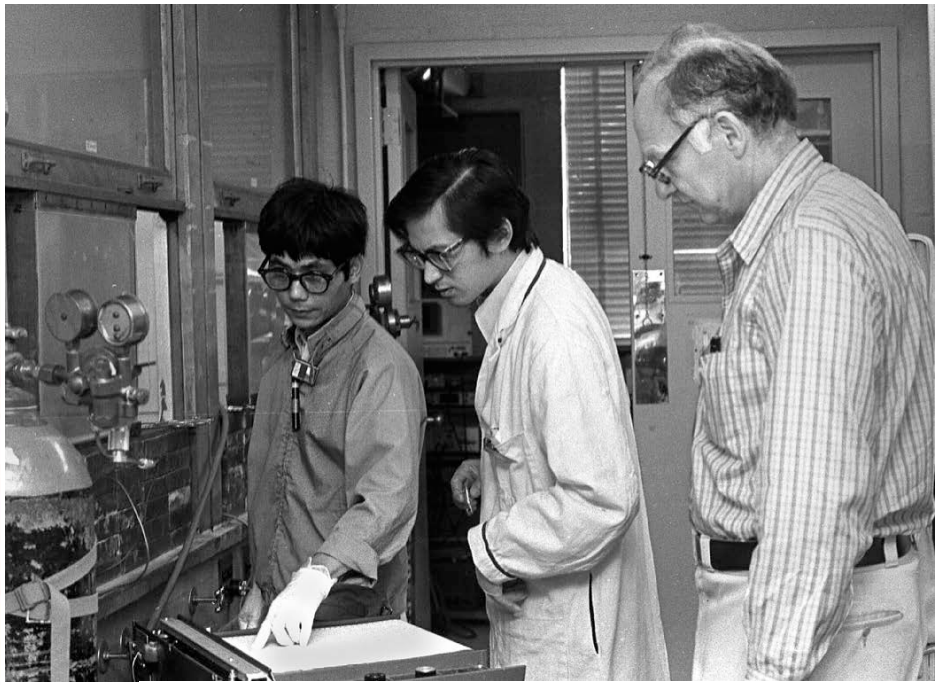


<u>Synthesis time 2 hr</u>: prepared according to a protocol that had been shown to produce a sterile, pyrogen free product.

Brookhaven National Lab; August 16, 1976

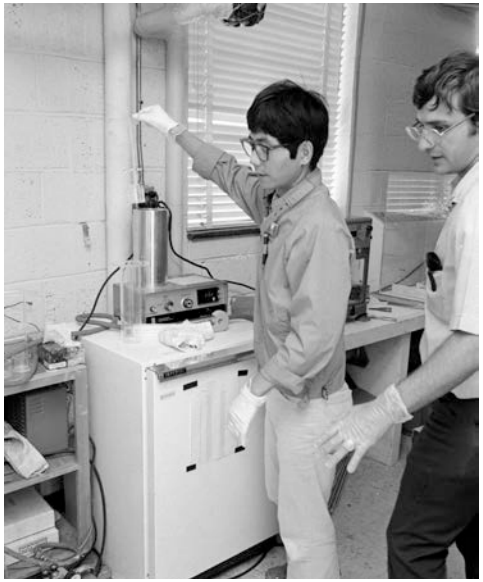


Tatsuo Ido mounts Ne/F_2 target



Tatsuo Ido CN Wan Al Wolf

Brookhaven National Laboratory; August 16, 1976



^{18}FDG measurement

packaging

Bob MacGregor

^{18}FDG leaves hot lab

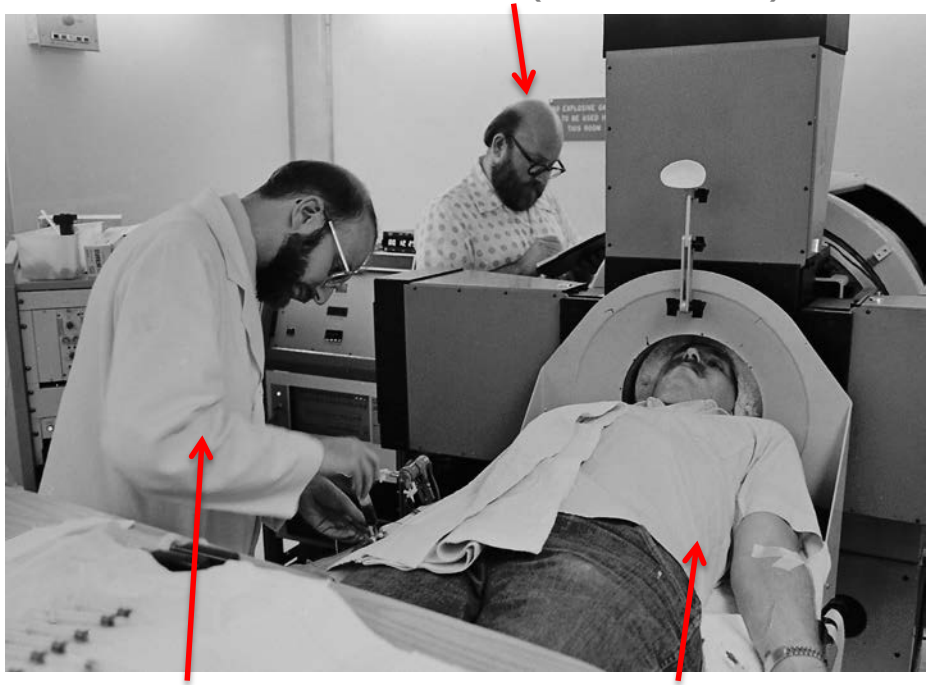
^{18}FDG leaves BNL

Brookhaven Calabro Airport

Philadelphia; August 16, 1976

Hospital University of Pennsylvania; August 16, 1976

Ed Hoffman (1944-2009)



Joel Greenberg

Volunteer in Mark IV

Dave Kuhl

Mike Phelps

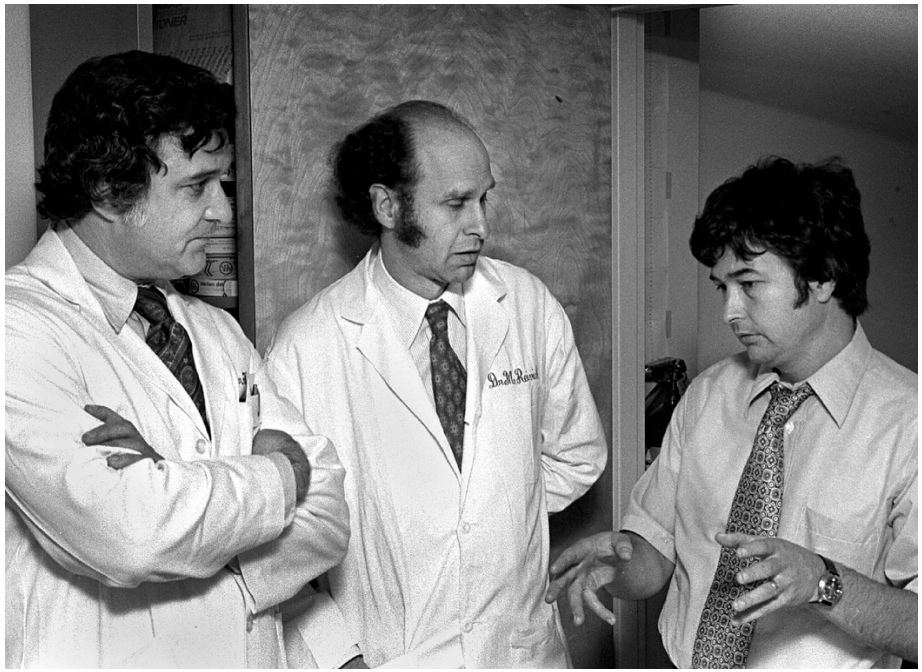
Martin Reivich

Angela Sylvestro

Joel Greenberg

Hospital University of Pennsylvania; August 16, 1976

Vito Casella Tatsuo Ido Dave Kuhl



Dave Kuhl Martin Reivich Mike Phelps

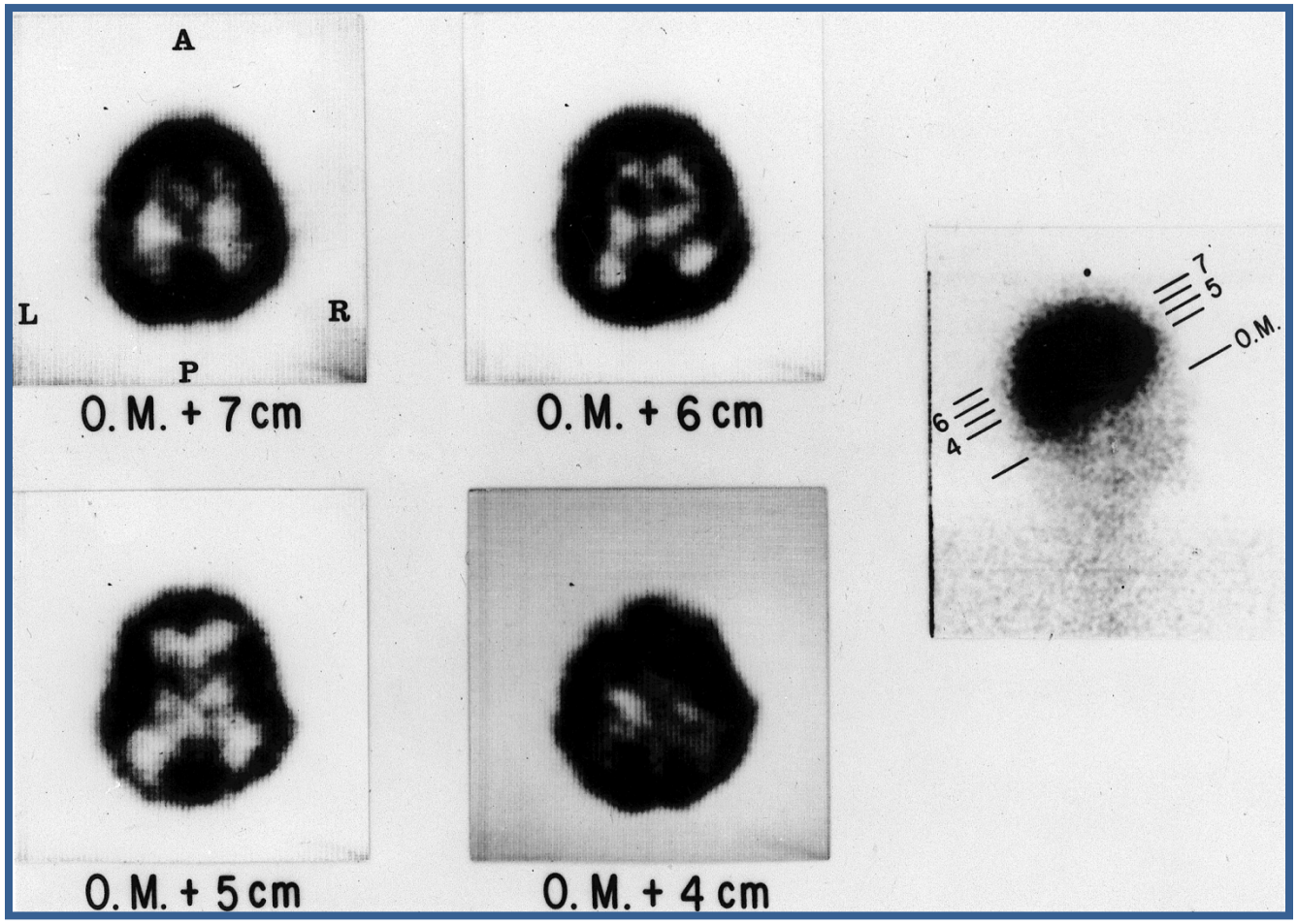
Hospital University of Pennsylvania; August 16, 1976

Vito Casella Tatsuo Ido Muni Staum

Hospital University of Pennsylvania; August 16, 1976

Martin Reivich David Kuhl

First Brain images made on Kuhl's Mark IV tomograph in August, 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]

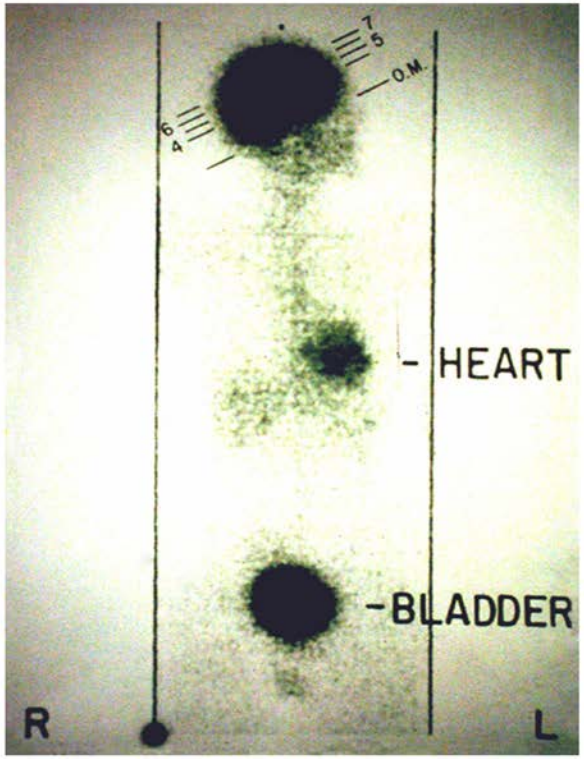
emission tomographic scanner. The method was used to measure local cerebral glucose consumption in two normal volunteers. The values in gray matter structures range from 5.79 mg/100 g per minute in the cerebellar cortex to 10.27 in the visual cortex, whereas, in white matter structures, the values range 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

The ^{18}FDG Method is quantitative

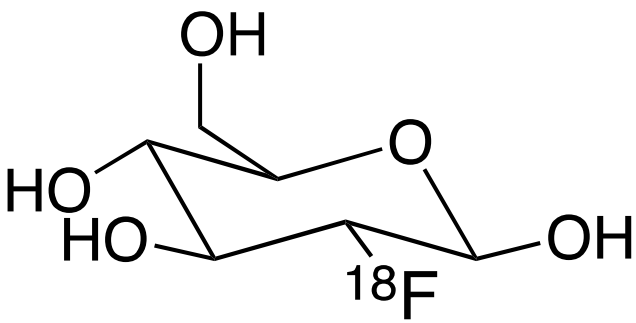
Operational equation for estimating glucose metabolic rate ($mg_{glucose}$/100 g_{brain}/min

$$R = \frac{C_T^*(T) - k_1^* e^{-(k_2^*+k_3^*)T} \int_0^T C_p^* e^{(k_2^*+k_3^*)t} dt}{\left[\frac{\lambda \cdot V_{max}^* \cdot K_m}{\phi \cdot V_{max} \cdot K_m^*}\right]\left[\int_0^T (C_p^*/C_p)dt - e^{-(k_2^*+k_3^*)T} \int_0^T (C_p^*/C_p) e^{(k_2^*+k_3^*)t} dt\right]}$$

Lumped constant: takes into account differences between 2-DG or ^{18}FDG and glucose

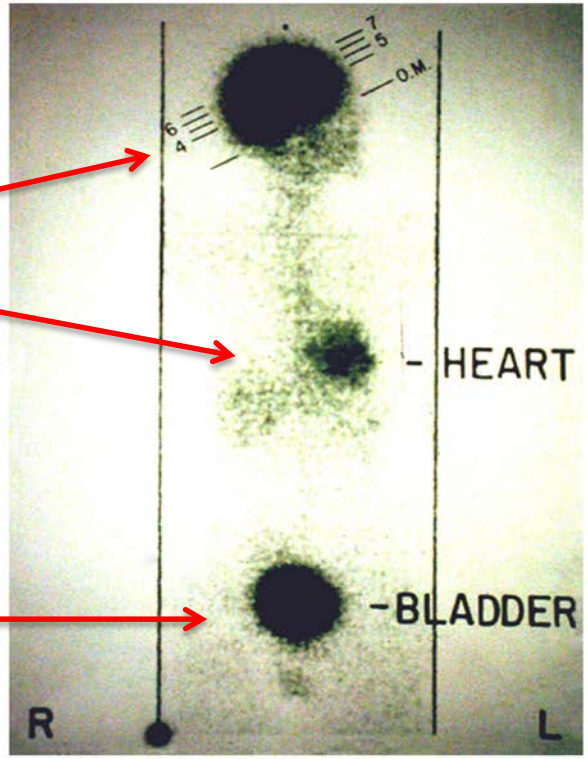


The first whole body human FDG scan was performed by
Abass Alavi
in August 1976 at University of Pennsylvania by employing a conventional rectilinear machine as the only option at the time.



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

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



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J Nucl Med 19: 1154–1161, 1978

Brian Gallagher

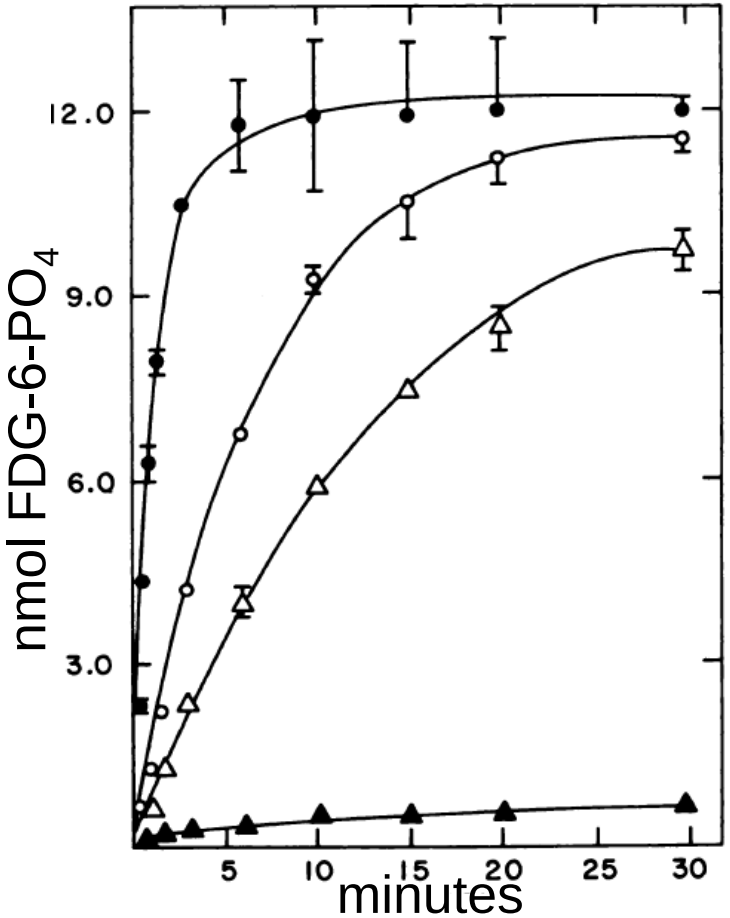
Metabolic Trapping as a Principle of Radiopharmaceutical Design: Some Factors Responsible for the Biodistribution of [^{18}F] 2-Deoxy-2-Fluoro-D-Glucose

Brian M. Gallagher, Joanna S. Fowler, Neal I. Gutterson, Robert R. MacGregor, Chung-Nan Wan, and Alfred P. Wolf

Brookhaven National Laboratory, Upton, New York

J Nucl Med 19: 1154–1161, 1978

Brian Gallagher



brain

heart ≅ kidney

lungs

liver

brain>heart≅kidney>lungs>>liver.

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.

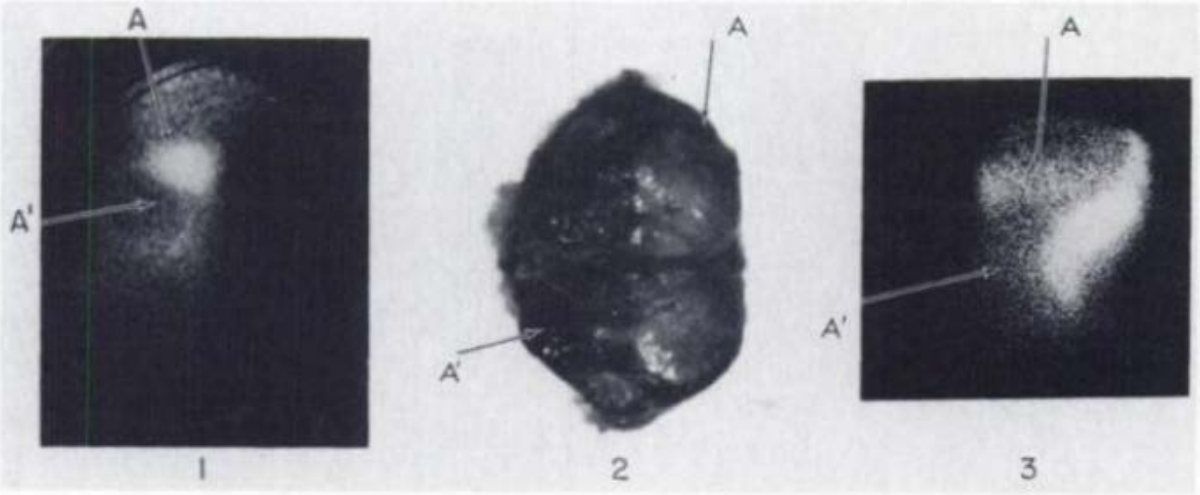
J Nucl Med 21: 670–675, 1980

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

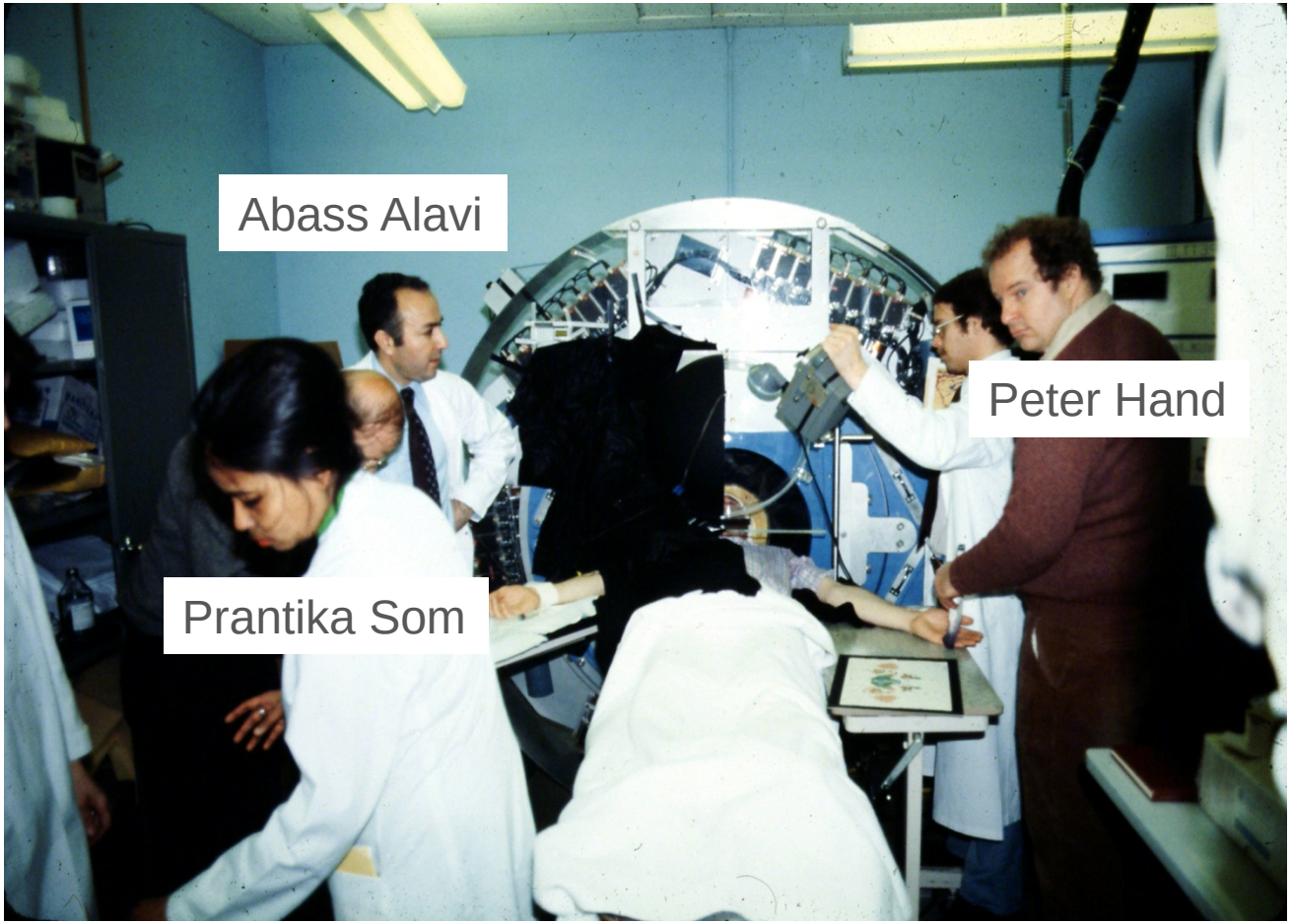
Prantika Som
1942-2011

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



In 1977 Brookhaven acquired PET III from Ter-Pogossian at Washington University and collaborations with Penn continued



A rapid synthesis of [^{11}C]2-DG was developed in 1980 by Bob MacGregor (1944-2009), Chyng Shiue and Robert Lade for serial studies on PET III using a subject as his/her own control.

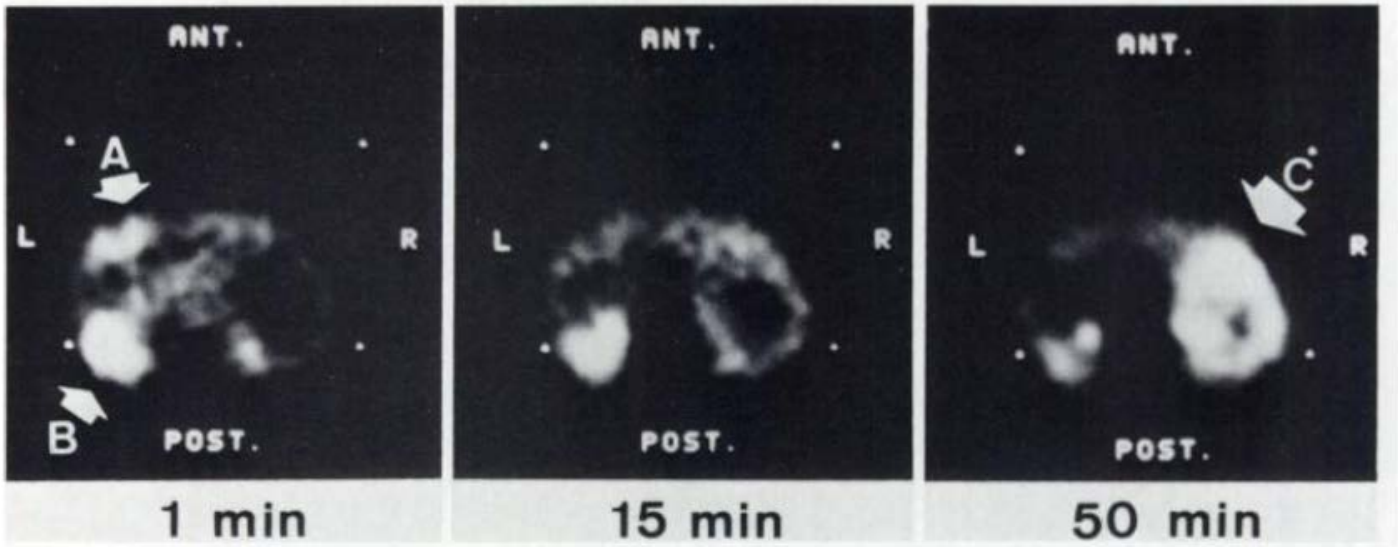
J Nucl Med 23: 1133–1137, 1982

Increased Accumulation of 2-Deoxy-2-[^{18}F]Fluoro-D-Glucose in Liver Metastases from Colon Carcinoma

Y. Yonekura, R. S. Benua, A. B. Brill, P. Som, S. D. J. Yeh, N. E. Kemeny, J. S. Fowler, R. R. MacGregor, R. Stamm, D. R. Christman, and A. P. Wolf

Brookhaven National Laboratory, Upton, New York, and Memorial Sloan-Kettering Cancer Center, New York, New York

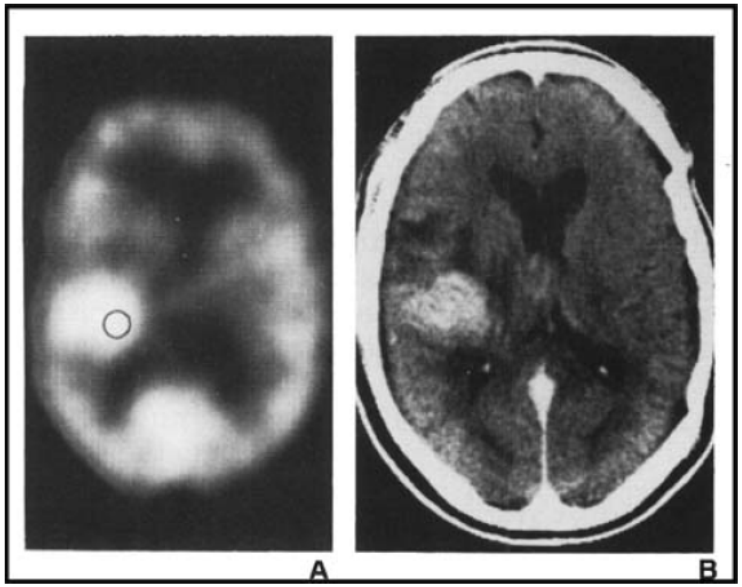
Yoshiharu Yonekura



NEUROLOGY (Ny) 1982;32:1323-9

Glucose utilization of cerebral gliomas measured by [^{18}F] fluorodeoxyglucose and positron emission tomography

Giovanni Di Chiro, M.D., Robert L. DeLaPaz, M.D., Rodney A. Brooks, Ph.D., Louis Sokoloff, M.D., Paul L. Kornblith, M.D., Barry H. Smith, M.D., Ph.D., Nicholas J. Patronas, M.D., Conrad V. Kufta, M.D., Robert M. Kessler, M.D., Gerald S. Johnston, M.D., Ronald G. Manning, Ph.D., and Alfred P. Wolf, Ph.D.

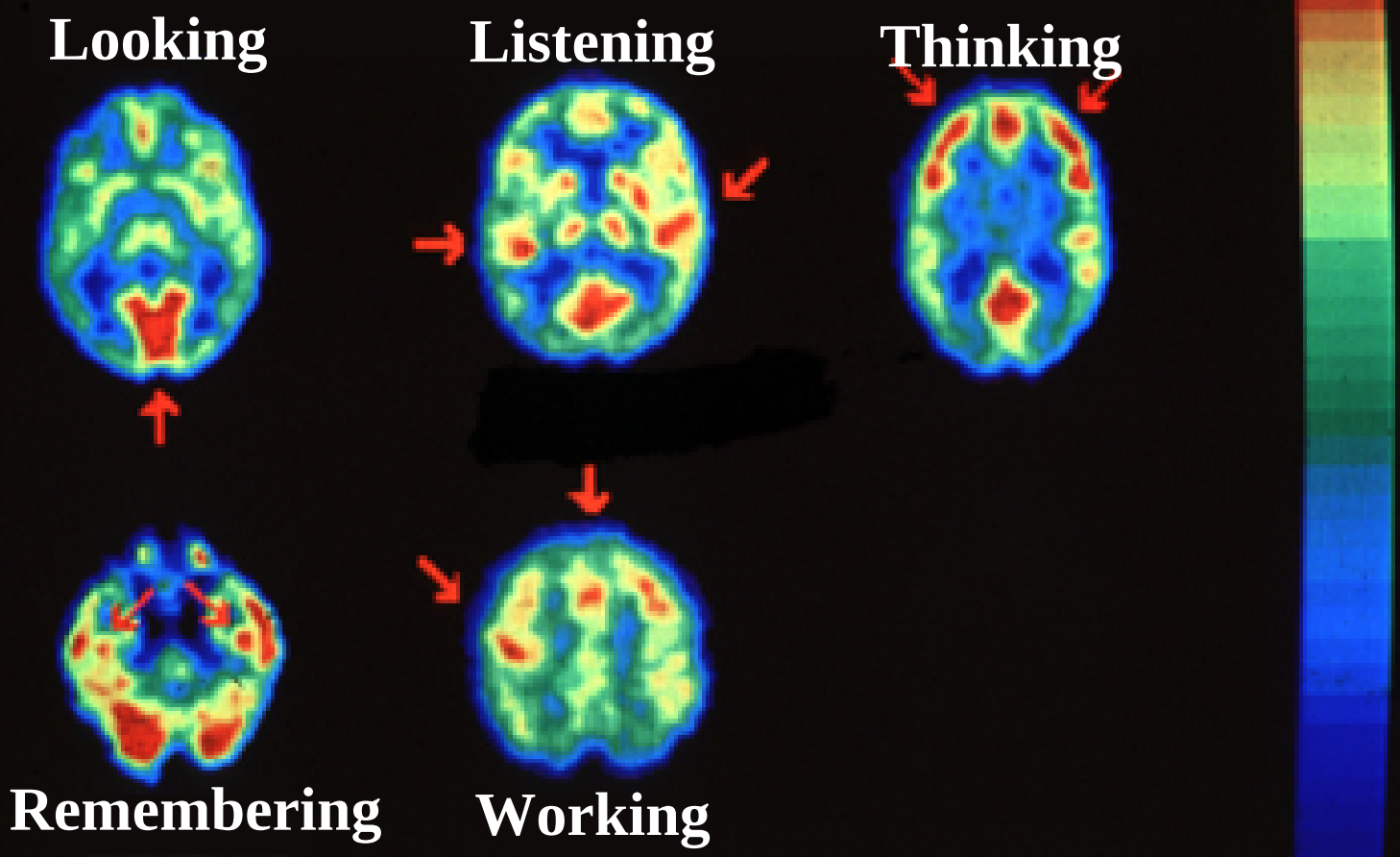


Some Early Human Studies with ^{18}FDG

- Normal Aging
- Neurologic disorders
- Psychiatric disorders
- Mapping brain activity
- Cerebrovascular disorders
- Brain development
- Myocardial viability
- Cancer
- inflammation

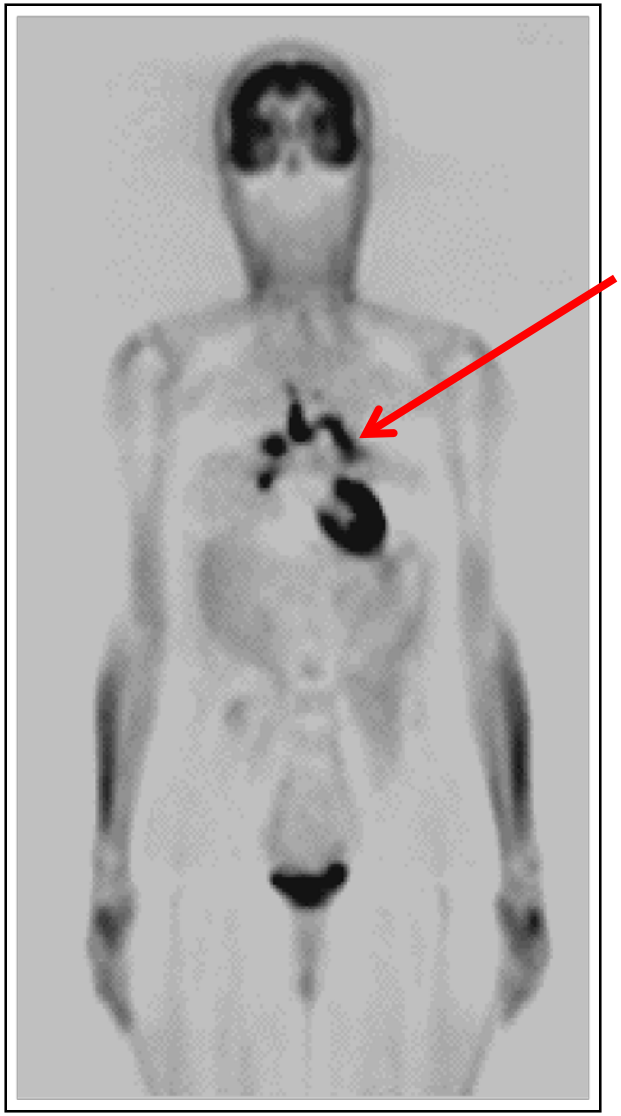
The Active Human Brain

PET Images of glucose metabolism (FDG) in performing tasks



Phelps, Kuhl, Mazziotta, Science, 1981

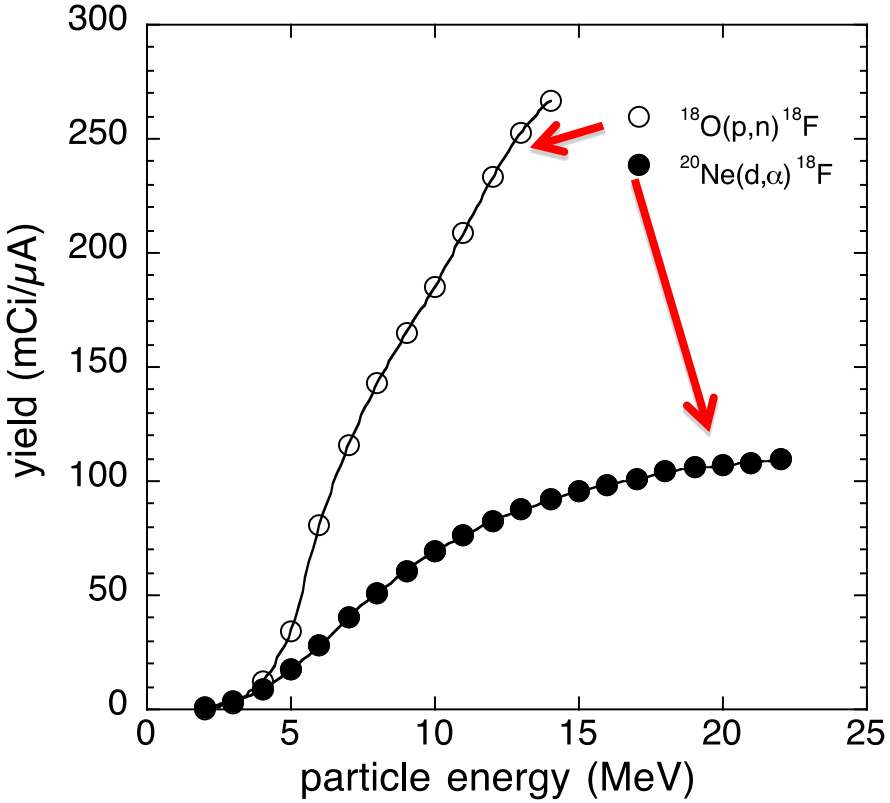
^{18}FDG and Cancer

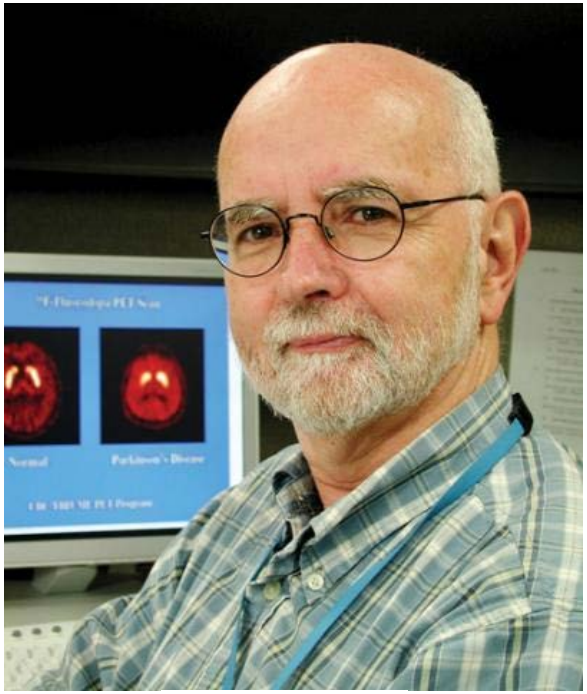


- Whole body ^{18}FDG-PET scan showing lung metastases from ovarian cancer (Phelps, UCLA)

- PET scans like this stimulated need for a high yield production of F-18 and ^{18}FDG for distribution to institutions without a cyclotron and chemists.

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

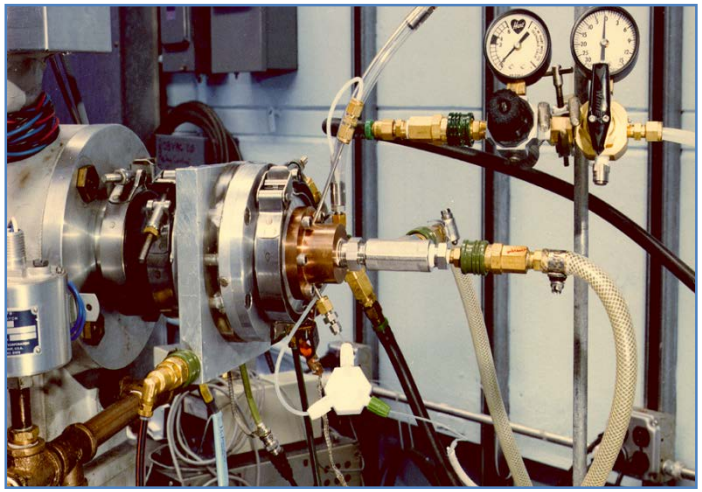


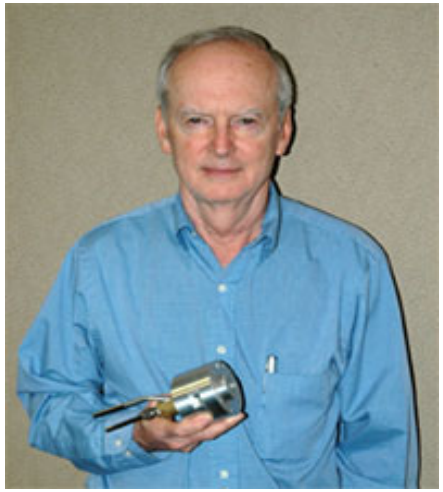


Tom Ruth

Ruth TJ, Wolf AP: Absolute cross sections for the production of ^{18}F via the $^{18}O(p,n)^{18}F$ reaction. Radiochim Acta 26:21-24, 1979

Small volume enriched water targets yielded large quantities of [^{18}F]fluoride via the ^{18}O(p,n)^{18}F reaction





Bruce Wieland

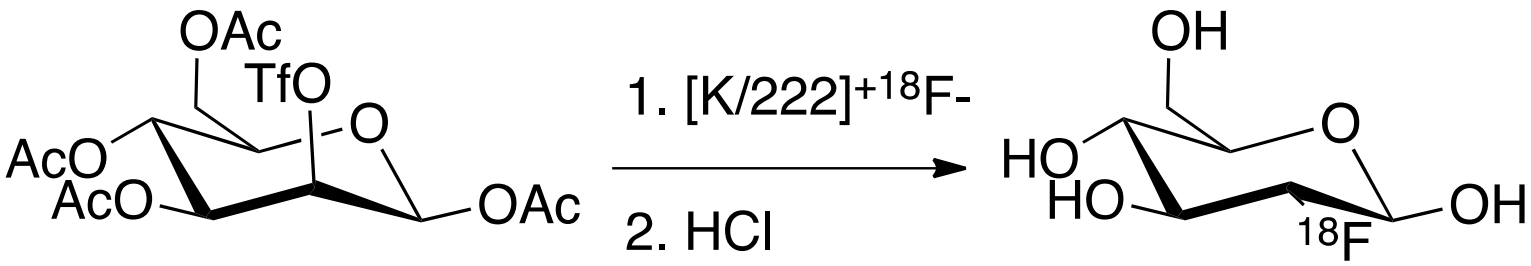
Dave Schlyer

- Small volume (1 mL), 95% enriched water target ($H_2{}^{18}O$) (~$100/mL) (Wieland)
- $H_2{}^{18}O$ could be recovered by anion exchange and reused

Schlyer DJ, Bastos MAV, Alexoff D, Wolf AP. *Separation of [^{18}F]fluoride from [^{18}O]water using anion exchange resin, IJARA. Part A. Applied Radiation and Isotopes 41: 531, 1990)*

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

Kurt Hamacher



Mannose triflate

^{18}FDG

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

Hamacher K, Coenen HH, Stöcklin G. Efficient stereospecific synthesis of no-carrier-added 2-[18F]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. J Nucl Med. 27, 235, 1986.

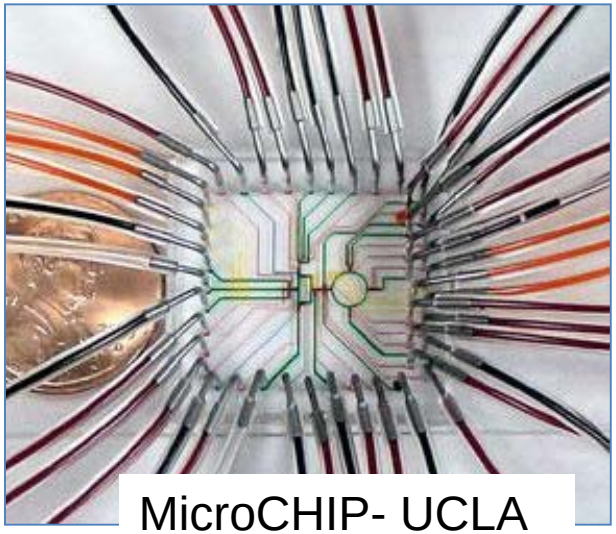
^{18}FDG Black Boxes

Tatsuo Ido first suggested FDG black boxes in 1980, Lake of the Ozarks meeting

Alexoff ^{18}FDG Box (~1986)

Siemens Explora FDG

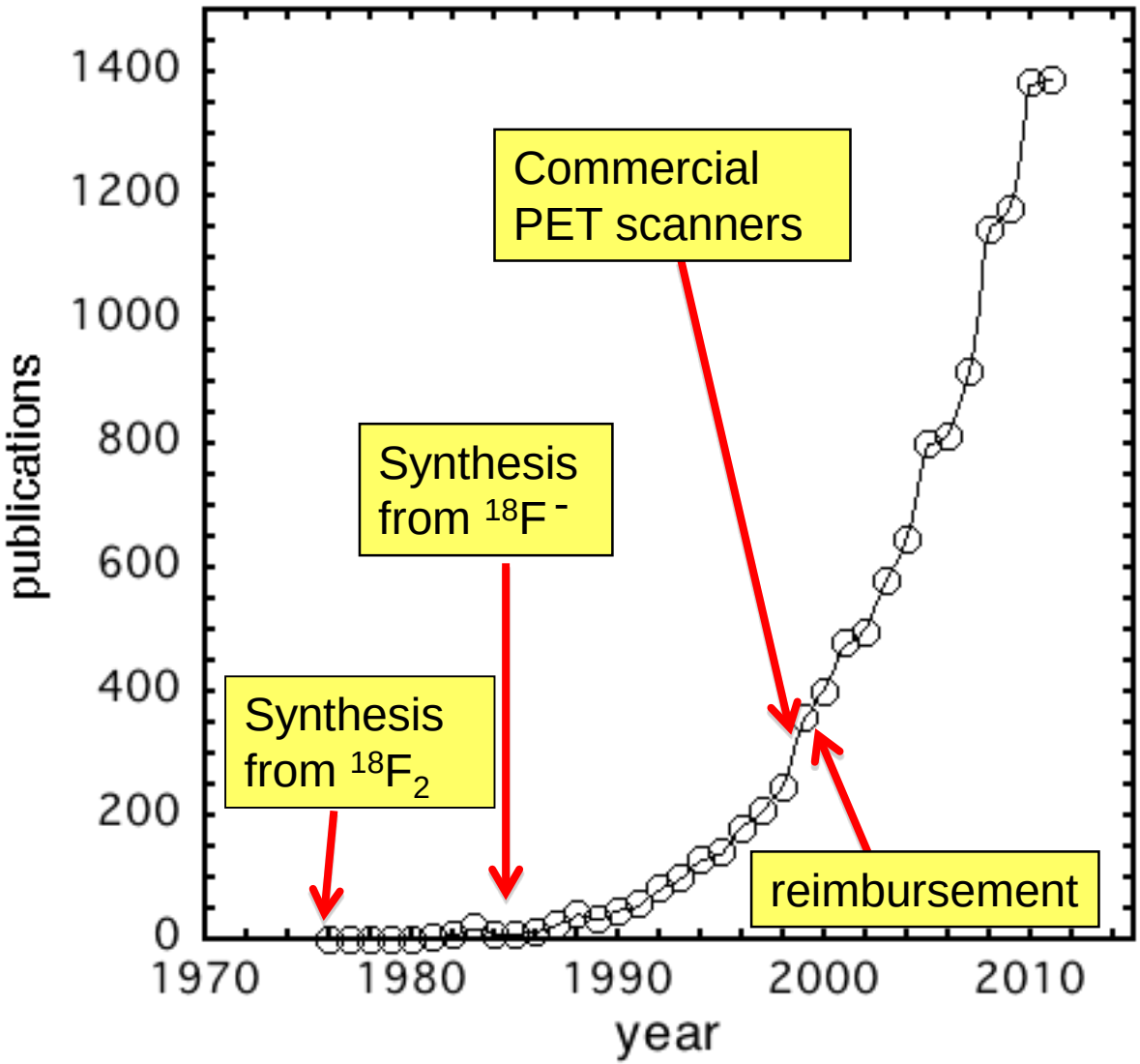
GE FASTlab



MicroCHIP- UCLA

There is a Commercial PET Radiopharmacy within a 100 miles of >98% of the patient beds of America (Slide from M. Phelps)

^{18}FDG publications: 1976-2012



Mike Phelps Ed Coleman

Spearheaded efforts to require the FDA to approve reimbursement for ^{18}FDG scans

In 2012, the NY Chapter of the American Chemical Society designated the Chemistry Department at Brookhaven National Laboratory as a Historic Chemical Landmark for the development of ^{18}FDG

https://www.bnl.gov/newsroom/news.php?a=23446

Why a rich country should support science

Louis Sokoloff: 1921-2015

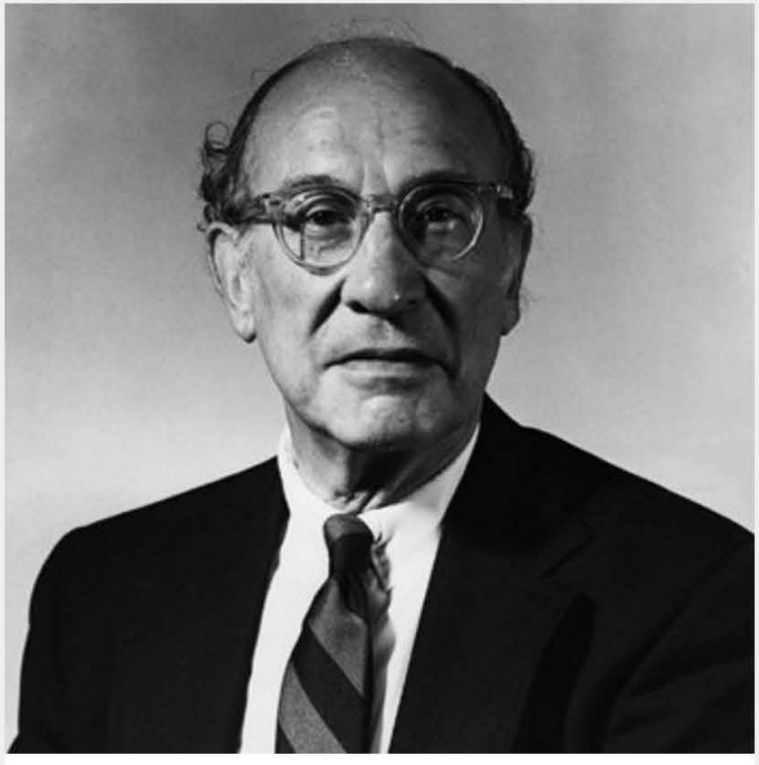
Acknowledgments

- Office of Science, U. S. DOE (1977-2016) and predecessor offices, ERDA (1974-1977) and AEC (1946-1974)
- National Institutes of Health
- SNMMI for providing a home for radiotracer chemistry

Brookhaven Group: 2013

1981 Albert Lasker Clinical Medical Research Award

[14C]Deoxyglucose method for measuring brain function



Louis Sokoloff

National Institute of Mental Health

"This is an unprecedented achievement that contributes to the basic understanding and diagnosis of brain diseases.

Dr. Sokoloff's brilliant contributions constitute a prime example of a bridge that leads from basic laboratory research to clinical application that can benefit literally millions of people everywhere."