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A HISTORY OF POSITRON IMAGING

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The development of positron imaging covered many decades and included contributions by many individuals. Indeed, the unique challenges involved in the detection of annihilation radiation and the subsequent processing of such data into an image format suitable for detection of disease or study of physiological processes has attracted the attention of many outstanding physicists, chemists, biologists and physicians. A thorough review of all of these developments would be beyond the scope of this brief history. However, it is useful to describe some of the early developments in this field dating back to the early 1950's. Although it is true in many fields, it is still disconcerting to find that important developments are placed in a time period that is years or even decades after the initial work.

Keywords: *history, tomography, positron imaging, PET*

First Positron Imaging Device - 1950

The first application of positron annihilation radiation for medical imaging is well documented. In a discussion with William Sweet, then the Chief of the Neurosurgical Service at the Massachusetts General Hospital (MGH), in the early part of 1950, I made several suggestions to improve the quality of nuclear images for the detection of brain tumors and other brain diseases. In particular, I suggested that the use of annihilation radiation following positron emission might improve the quality of brain images by increasing sensitivity and resolution. The Physics Research Laboratory (PRL) at MGH had just been established under my direction and, with support from the Neurosurgical Service, a simple positron scanner using two opposed sodium iodide detectors was designed and built within six months. Imaging of patients with suspected brain tumors was commenced almost immediately. The results were sufficiently encouraging that an addendum including results on positron imaging was included in a paper by Sweet on brain tumor localization. The paper was then in press in the New England Journal of Medicine and together with the addendum appeared in December of 1951 [47]. During the same year, a paper by Wrenn, Good and Handler [53] described independent studies on annihilation radiation detection. These authors went on to illustrious careers - Philip Handler became the President of the American Academy of Science - but did not publish further on this topic.

Despite the relatively crude nature of this imaging instrument, the brain images were markedly better than those obtained by other imaging devices. It also contained several features that were incorporated into future positron imaging devices. Data were obtained by translation of two opposed detectors using coincidence detection with mechanical motion in two dimensions and a printing mechanism to form a two-dimensional image of the positron source. This was our first attempt to record three-dimensional data in positron detection. An article published in 1953 described this device and included preliminary results (Brownell and Sweet 1953 [8]).

First Clinical Positron Imaging Device - 1952

The success of our prototype positron scanner led us to develop a scanner designed specifically for brain imaging (Figure 1). This instrument followed the general concepts of the instrument build in 1950 but included many refinements. It produced both a coincidence scan as well as an unbalance scan. The unbalance of the two detectors was used to create an unbalance image using two symbols to record any unbalance in the single channel rates of the two detectors. The unbalance scan produced a low resolution image but was remarkable sensitive in determining whether a tumor existed, particularly if the tumor was to the right or left of midline of the brain. Figure 2 shows the two scans of a patient with recurring brain tumor.

First Multiple Detector Positron Imaging Device - 1962

Several versions of the single pair coincidence system were built including a commercial version. It was clear that increased sensitivity was required and a Hybrid Scanner (Figure 3) was developed in the mid 60's and re-

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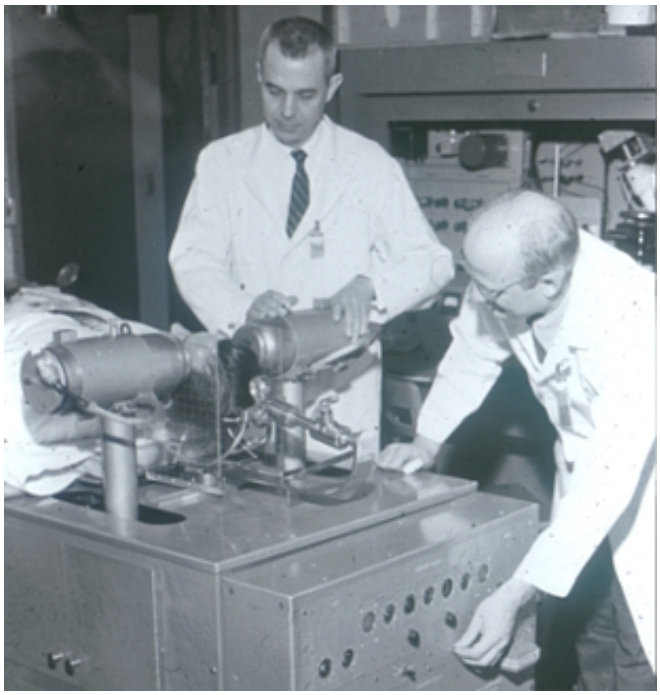

Figure 1: First clinical positron imaging device. Drs. Brownell (left) and Aronow are shown with scanner (1953).

sults published in 1968 [9]. This device used two rows of nine detectors each in coincidence with three detectors in the opposite row. The detector assembly translated in one direction so that a two dimensional image was formed. The scanner was designed specifically for brain imaging and served for that purpose in a clinical setting for nearly a decade. A unique feature of the scanner was that in addition to increased sensitivity, another form of three-dimensional image could be obtained by focusing on planes parallel to and lying between the two detector arrays. This feature proved to be a powerful addition to the scanner and permitted lesions to be imaged in two dimensions and their position to be estimated in the third dimension by selecting the plane with the sharpest image.

PC-I The First Tomographic Imaging Device and the First Computed Tomographic Imaging Device (PET): 1968-1971

The logical extension of positron instrumentation was a design using two 2-dimensional arrays. PC-I was the first instrument using this concept and was designed in 1968, completed in 1969 and reported in 1972 [11] [20]. The first applications of PC-I in tomographic mode as distinguished from the computed tomographic mode were

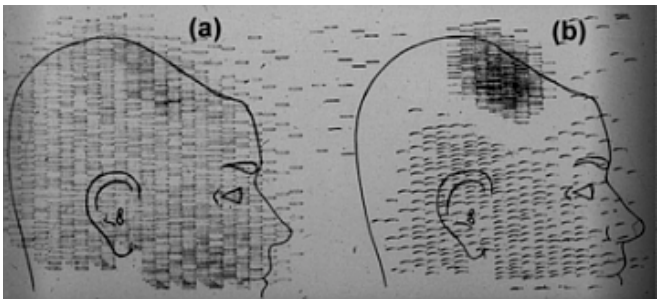

Figure 2: Coincidence and unbalance scans of patient with recurring brain tumor. Coincidence scan (a) of a patient showing recurrence of tumor under previous operation site, and unbalance scan (b) showing asymmetry to the left. (Reproduced from Brownell and Sweet 1953 [8]).

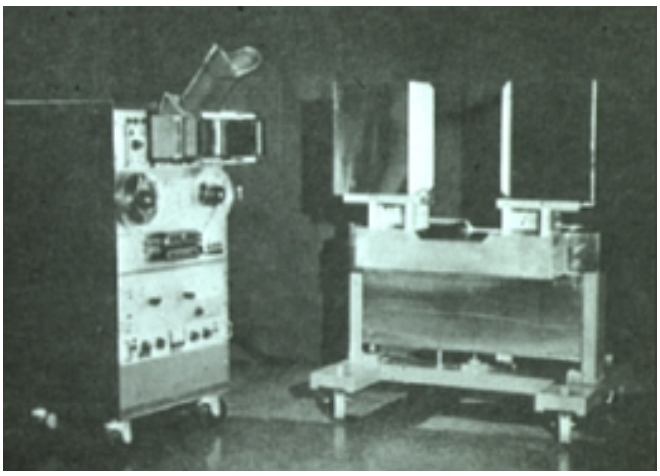

Figure 3: Hybrid Positron Scanner.

reported in 1970 (Brownell *et al* 1970 [10]). PC-I incorporated rotation and translation of the two detectorbanks and included interpolative motion of the detectors to improve sampling and image quality. PC-I could produce images on planes parallel to the detector planes or tomographic images on planes within the object. PC-I was not patented because it was disclosed in several papers but was covered by a US Atomic Energy Commission Record of Invention (S-40, 757) with date of inception as June 1968, completion in 1969 and first tests in May 1971 (Figure 4).

The original intent was to use PC-I to obtain focused images on planes parallel to the detector planes and tomographic images on transverse planes. The use of PC-I to obtain computed tomographic images or PET images evolved over this period of time.

In early 1970, David Chesler in our group at MGH conceived of filtered back projection. In the summer of 1970 he tested filtered back projection, including the effects of

Poisson noise, by computer simulation. On Veterans Day of 1970 he collected both emission and transmission data with a 'bench top scanner'. From this data he was able to produce three types of computed tomographic images: an emission image, a transmission image and an absorption-corrected emission image. Figure 5 illustrates the concept of filtered back projection and was presented by Chesler at the Meeting on Tomographic Imaging in Nuclear Medicine September 15-16, 1972. This development of filtered back projection was the first reconstruction of this type to be applied to PET and CT data. (Chesler 1971 [24], Chesler 1973 [25] (Figure 6) and Chesler *et al* 1973 [26] (Figure 7).) The original intent was to use PC-I to obtain focused images on planes parallel to the detector planes and tomographic images on transverse planes. The filtered back projection algorithm was immediately applied to data from PC-I and the subsequent computed tomographic images were dubbed PET images as an acronym for positron emission tomography. (Brownell and Burnham 1972 [11], Brownell and Burnham 1973 [12], and Brownell *et al* 1978 [16]). The excellent book by Steve Webb entitled "From the Watching of Shadows" [52] gives a well documented account of the development of X-ray CT as well as the early work in positron emission tomography (PET) and single photon computed emission tomography (SPECT) [39] [40]. Two names stand out in CT, Godfrey Houndsfield (Hounsfield 1973 [35]) and Allan Cormack (Cormack 1973 [29]), both of whom were recognized for their contributions by sharing the Nobel Prize. Houndsfield obtained his first patent in August of 1972 well after the first clinical trials at the Atkinson Morley Hospital in October 1971 (Ambrose 1973 [2]).

Figure 4: PC-I, the first tomographic PET imaging device.

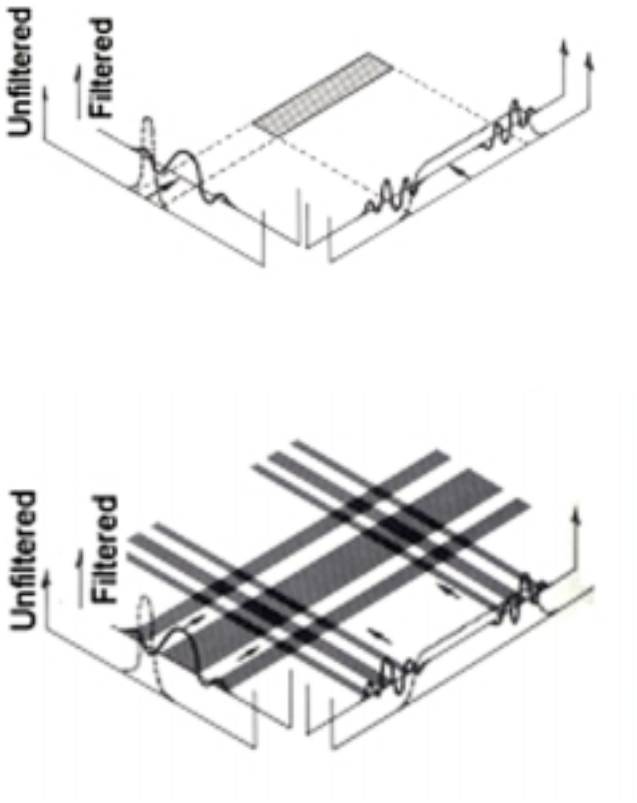

Figure 5: PET reconstruction techniques: (top) Original source distribution and measured projections, (bottom) Corrected tomography using filtered back projection. (Presented by David Chesler at the meeting of Tomographic Imaging in Nuclear Medicine, September 15–16, 1972 [25]).

PC-II and its Commercial Version

At the Physics Research Laboratory, an improved area sensing rotate-translate PET instrument, PC-II, was constructed 1971-1976 and the tomographic images obtained using PC-I and PC-II were widely disseminated at meetings and in publications (Figures 6–14) (Chesler *et al* 1973 [25] [26], Brownell *et al* 1974 [13], Chesler and Riederer 1975 [27], Correia *et al* 1976 [30], Brownell *et al* 1976 [14], Hoop *et al* 1976 [34], Brownell and Cochavi 1978 [15], Brownell *et al* 1983 [17]).

PC-I was the first device to obtain PET images and, together with PC-II, remained the only PET devices in use for animal and human imaging for almost a decade. A commercial version developed by The Cyclotron Corporation incorporated additional features (Figure 15). (EMI used an iterative algorithm for reconstruction of data from their original machines.) Among those contributing to the early studies were Saadia Cochavi, Wally Anluwalia, Bar-

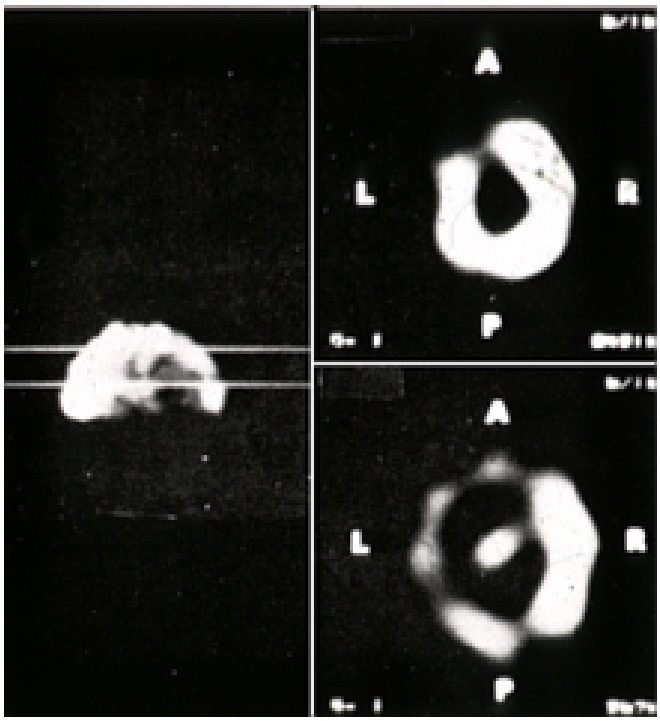

Figure 6: Brain study using PC-I and ^{68}Ga. Two lines on 2D-image show the levels of tomographic slices. A tumor is clearly observable in the lower transverse slice. Original images were presented by David Chesler at the Meeting on Tomographic Imaging in Nuclear Medicine, September 15-16, 1972.

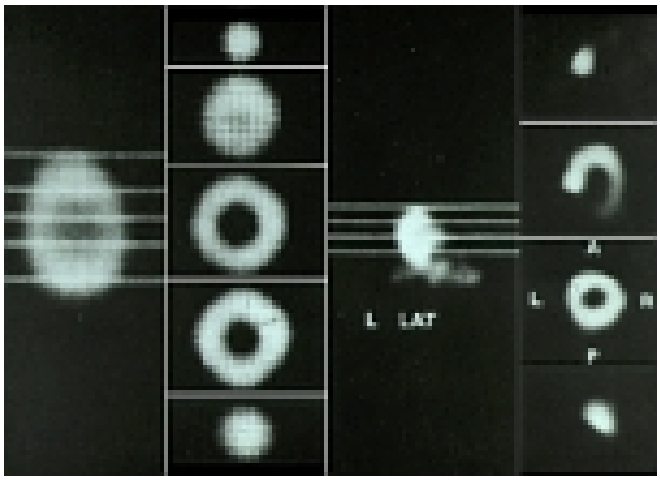

Figure 7: Lateral and tomographic images of the elliptical phantom (left) and the dog heart (right) using ^{68}Ga (Chesler 1973 [26]).

ney Hoop, John Correia and Nathaniel Alpert.

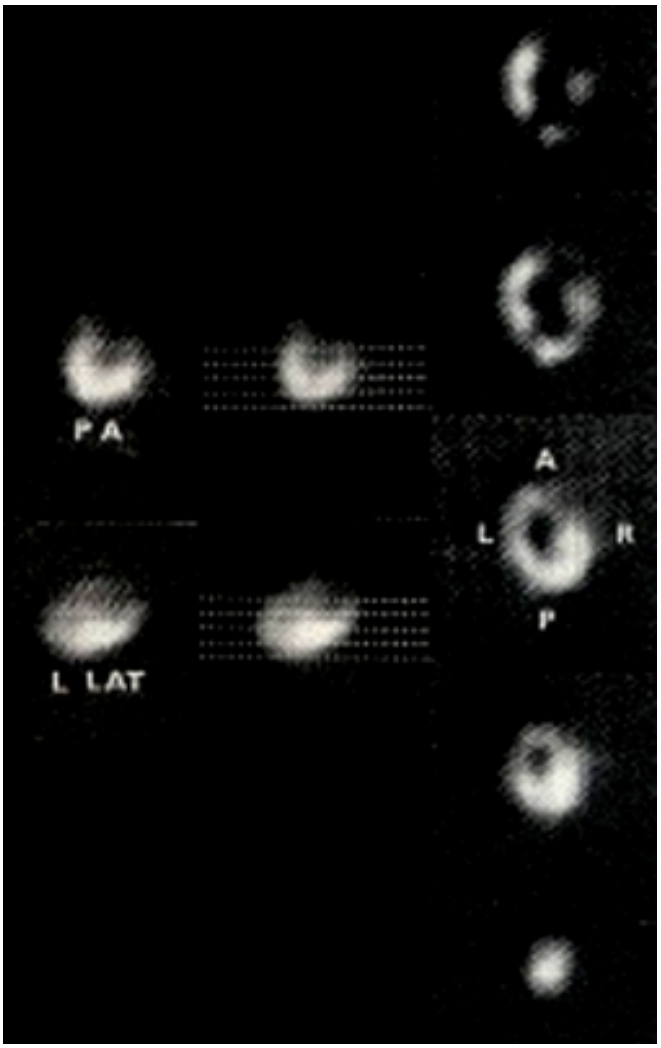

Figure 8: PA and left lateral images (left and center) and transverse section images (right) of ^{68}Ga infused into dog myocardium using PC-I.

Visit to Washington University - 1974

I was invited by Michael Ter-Pogossian to present our PET images in a talk given at Washington University in 1974. Over 50 PET images were shown relating to studies of blood flow, blood volume and oxygen metabolism in heart and lung in animals and man as well as PET images of lung function using ^{15}O and blood flow studies of brain and heart using $C^{15}O_2$, ^{13}N and ^{68}Ga and bone scans using ^{18}F. Some of these images are shown in Figures 6–10. It should be noted that ^{18}F-labeled 2-fluoro-2-deoxy-D-glucose was not available at this time.

Following the talk, the possibility of a single plane translate-rotate system was brought up and I pointed out

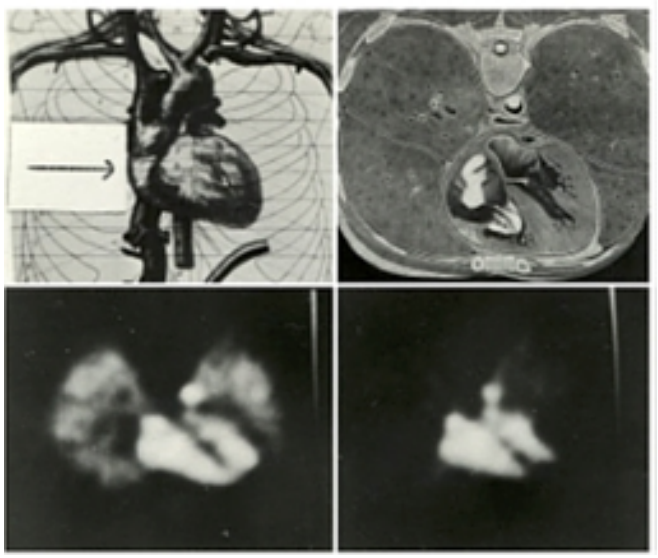

Figure 9: Top level: A-P anatomical illustration of heart and major vessels (left). Anatomical transverse section at the level shown in left. Lower level: Transverse section image of blood pool using inhalation of ^{11}CO corresponding the image on top right, uncorrected for absorption (left). Same as left with absorption correction (right).

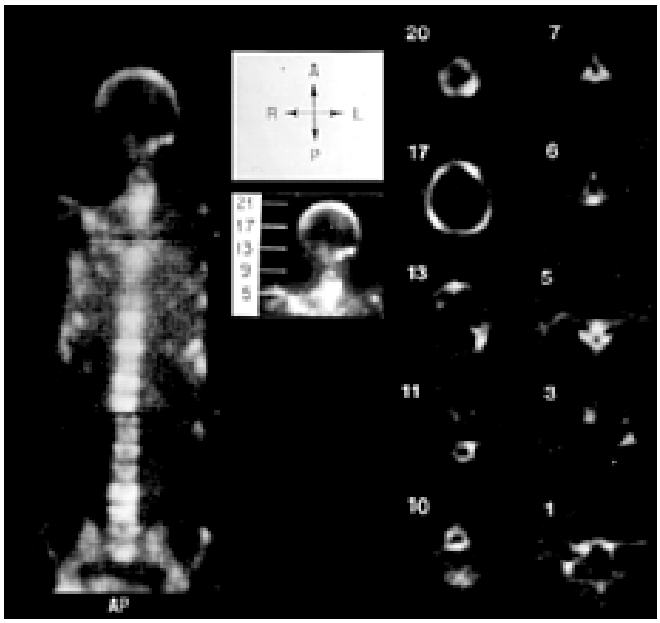

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Figure 10: ^{18}F (NaF) bone scan using PC-I. AP view shows multiple bone metastases in the pelvic area, the spine, the ribs, and the calvarium. The figure at the middle shows the levels where tomographic slices were reconstructed. Tomographic slices show better assessment of the location and size of the metastases.

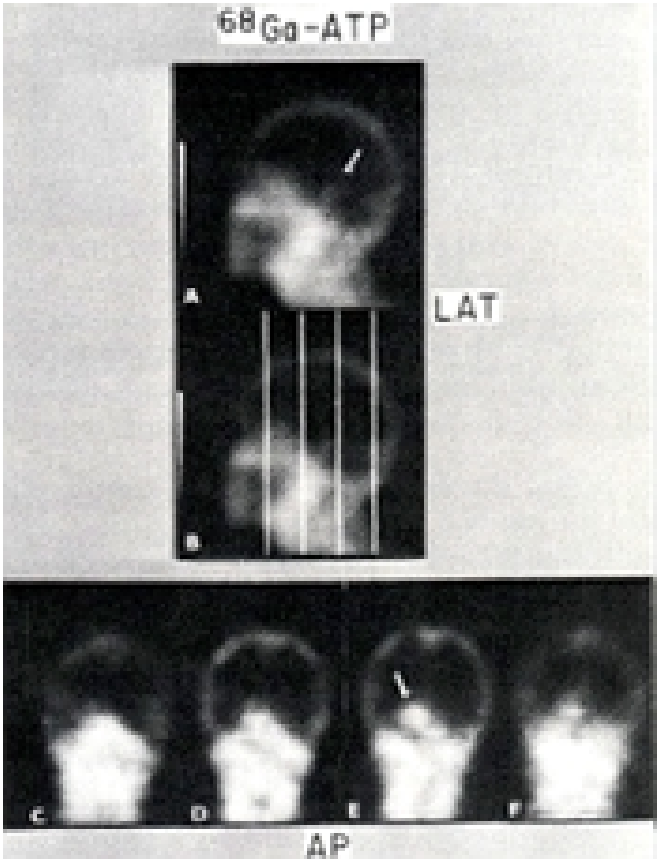

Figure 11: Brain study using $^{68}Ga-ATP$. Lower panel shows 4 tomographic coronal slices and the arrow points the tumor.

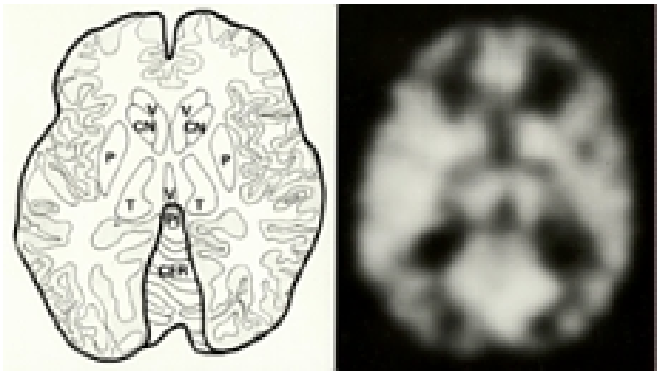

Figure 12: Brain study of the normal control patient using ^{18}F 2-fluoro-2-deoxy-D-glucose and PC-II.

that the data set resulting from the translation and rotation of the two banks of detectors of PC-I and PC-II was identical to that of the translation and rotation of a hexagonal array of detectors viewing one plane. This led in part to the development of a series of PETT instruments at Washington University (Ter-Pogossian *et al* [50])

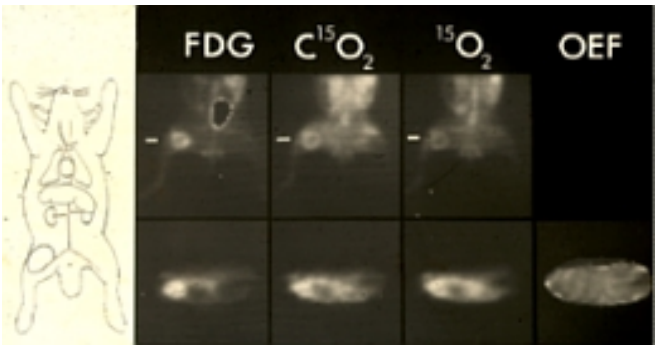

Figure 13: Study of glucose metabolism (^{18}F 2-fluoro-2-deoxy-D-glucose), blood flow (continuous inhalation of $C^{15}O_2$), oxygen metabolism (continuous inhalation of $C^{15}O_2$) and oxygen extraction fraction in a rabbit tumor model using PC-II.

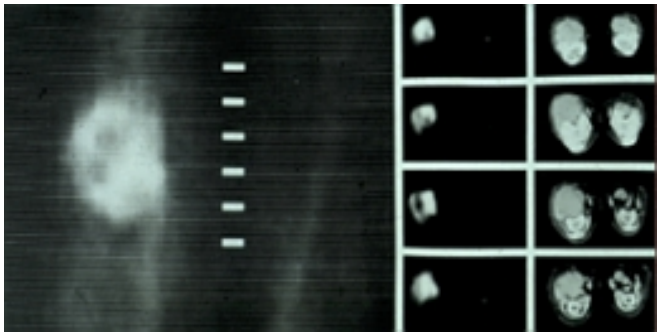

Figure 14: Blood flow study of soft tissue tumor in the left leg using PC-II and continuous inhalation of $C^{15}O_2$. Transverse slices are correlated with corresponding CT images.

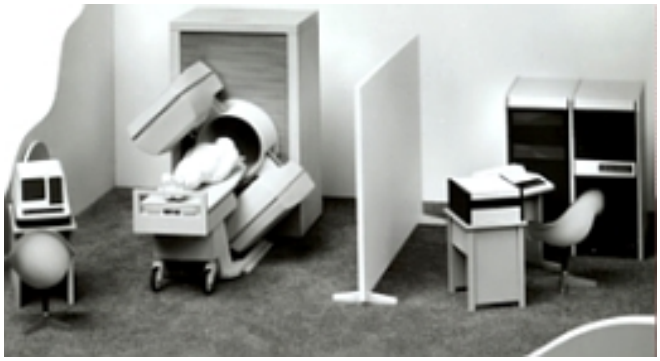

Figure 15: A commercial version of PC-II; The Cyclotron Corporation Positron Camera Model 4200.

and to the ECAT instruments (Hoffman *at al* [33]) developed by ORTEC, Inc, later CTI, Inc.

Radiopharmaceutical Development for PET Imaging

PET imaging was initially based on the use of ^{15}O labeled to O_2, CO and CO_2 primarily because the Allis Chalmers cyclotron in use initially at MGH and Washington University was a deuteron machine and was primarily used to producing ^{15}O. More powerful cyclotrons were available in government laboratories such as Brookhaven but it was not until the mid 70's that such cyclotrons became available to biomedical facilities and the full range of isotopes including ^{11}C, ^{13}N,^{15}O and ^{18}F became available to a wider audience.

Ter-Pogossian and Powers had demonstrated that ^{15}O labeled water could be used to measure blood flow in brain and other organs long before PET was developed (Ter-Pogossian and Powers 1958 [48] and Ter-Pogossian *et al* 1970 [49]). It should be mentioned that with the untimely death of Michael Ter-Pogossian the field lost a scientist of outstanding ability and integrity.

Oxygen-15 was and remains a very useful label for PET studies and became widely used at MGH for blood flow studies in brain and other organs (Ahluwalia *et al* 1973 [1], Brownell *et al* 1976 [14]). The application of labeled CO_2 to obtain equilibrium images of blood flow was applied successfully for imaging brain and heart in animals and man (Boucher *et al* 1976 [3]). The use of labeled O_2 together with CO_2 provided the basis for measuring regional oxygen metabolism. ^{15}O labeled CO provided a means of measuring regional blood volume (Brownell and Cochavi 1978 [15]). Models were developed to obtain quantitative regional values of these important parameters (Subramanyam *et al* 1978 [46]). The measurement of blood flow and blood volume has become a useful clinical and research tool. By use of these techniques, abnormalities in brain and other organs could be visualized. In addition, alterations in regional cerebral blood flow resulting from visual and other stimuli could be observed (Raichle et al 1973 [42]). More recently magnetic resonance imaging (MRI) has proven capable of observing blood flow and blood volume as well as cerebral metabolism.

It is interesting that one of the factors most responsible for the acceptance of positron imaging was the development of radiopharmaceuticals. In particular, the development of ^{18}F labeled 2-fluorodeoxy-D-glucose (2FDG) by the Brookhaven group under the direction of Al Wolf and Joanna Fowler was a major factor in expanding the scope of PET imaging [37]. The half-life of ^{18}F was nearly optimal for positron imaging and it was immediately obvious that 2FDG could give precise values of energy metabolism in brain, heart and other organs (Reivich *et al* 1979 [43]). Michael Phelps further extended the application of 2FDG [41] based on Sokoloff's autoradiographic studies using ^{14}C labeled deoxyglucose (Sokoloff

et al 1977 [45]). Recent developments in PET radiopharmaceuticals are based on Henry Wagner's pioneering work on imaging with receptors [51].

PCR-I and PCR-II: Ring and Cylinder PET Devices

It soon became clear to many of those involved in PET development that a circular or cylindrical array of detectors was the logical next step in PET instrumentation. Although many investigators took this approach, James Robertson (Robertson *et al* 1973 [44]) and Z.H. Cho (Cho *et al* 1975 [28]) were the first to propose a ring system. The only drawback was the limited sampling provided by these geometries and a number of techniques such as wobbling the array were proposed to increase sampling (Huesman *et al* 1983 [36]). A Donner ring was developed in Berkeley (Derenzo *et al* 1979 [31]) that used a large number of detectors individually coded to small phototubes. However, it was the development of analog coding by Charles Burnham of the PRL at MGH (Burnham *et al* 1981 [21] and 1985 [22]) that permitted the use of multiple small detectors identified by a smaller number of phototubes. The concept was applied to ring and cylindrical arrays to produce high resolution PET images without motion. This led to the development of two PET systems at MGH, PCR-I (Brownell *et al* 1985 [18]) (Figure 16) and PCR-II (Burnham *et al* 1988 [23], Brownell *et al* 1989 [19]) (Figure 17). PCR-I used a ring design while PCR-II used a cylindridal design. PCR-I has been in continuous use for sixteen years producing high resolution images in a variety of studies centered on the brain, heart and cancer in mice (Kallinowski *et al* 1991 [38]), rats (Brownell *et al* 1991 [4], Brownell *et al* 1998a [5]) (Figure 18), rabbits (Figure 19), dogs (Figure 20) and primates (Hantraye *et al* 1992 [32], Brownell *et al* 1998b [6] and 1999 [7]) (Figure 21). The single ring limitation of PCR-I has been overcome by use of a computer-controlled table and imaging a volume source in a step-and-shoot mode utilizing table motion as axial axis. This enables processing of transverse and sagittal slices in addition to coronal slices. The outcome of studies conducted with PCR-I led to world wide interest in developing special PET scanners for small animals.

The history of PET has been one of continuous improvement in resolution and sensitivity. Figure 22 shows improvement of resolution and sensitivity of the positron imaging devices developed at the Physics Research Laboratory over the last five decades. The future of PET imaging is bright. New geometries are being studied especially to develop organ specific imaging devices, new detector materials are being developed and techniques for reconstruction are improving. However, perhaps the most important need for further utilization of PET imaging is the development of new radiopharmaceuticals and quantitation procedures necessary to yield useful physiological data.

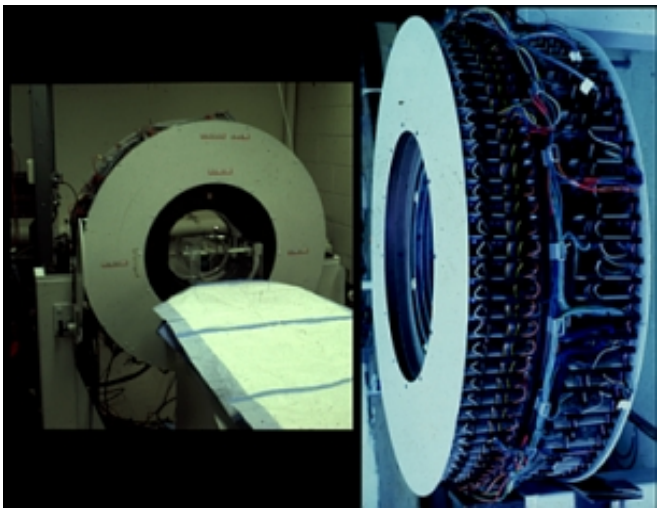

Figure 16: PCR-I, a single ring positron emission tomograph using analog coding. Tomograph with cot and computer (left) and the electronic assembly (right).

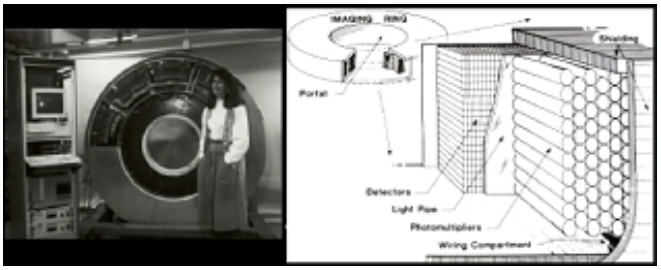

Figure 17: PCR-II, a cylindrical positron emission tomograph.

Acknowledgements

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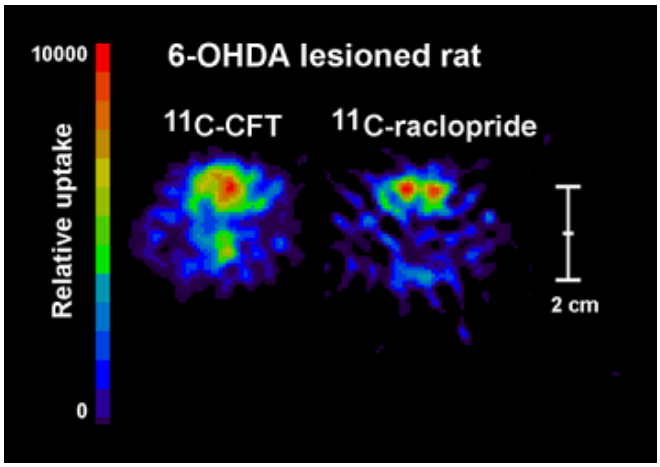

Figure 18: Study of dopamine transporters with $^{11}C - CFT$ and dopamine D_2-receptors using $^{11}C-$raclopride in a $6 - OHDA$ lesioned (left striatum) rat brain using PCR-I. Note the decreased accumulation of $^{11}C - CFT$ and increased accumulation of $^{11}C-$raclopride in the lesioned striatum (supersensitivity).

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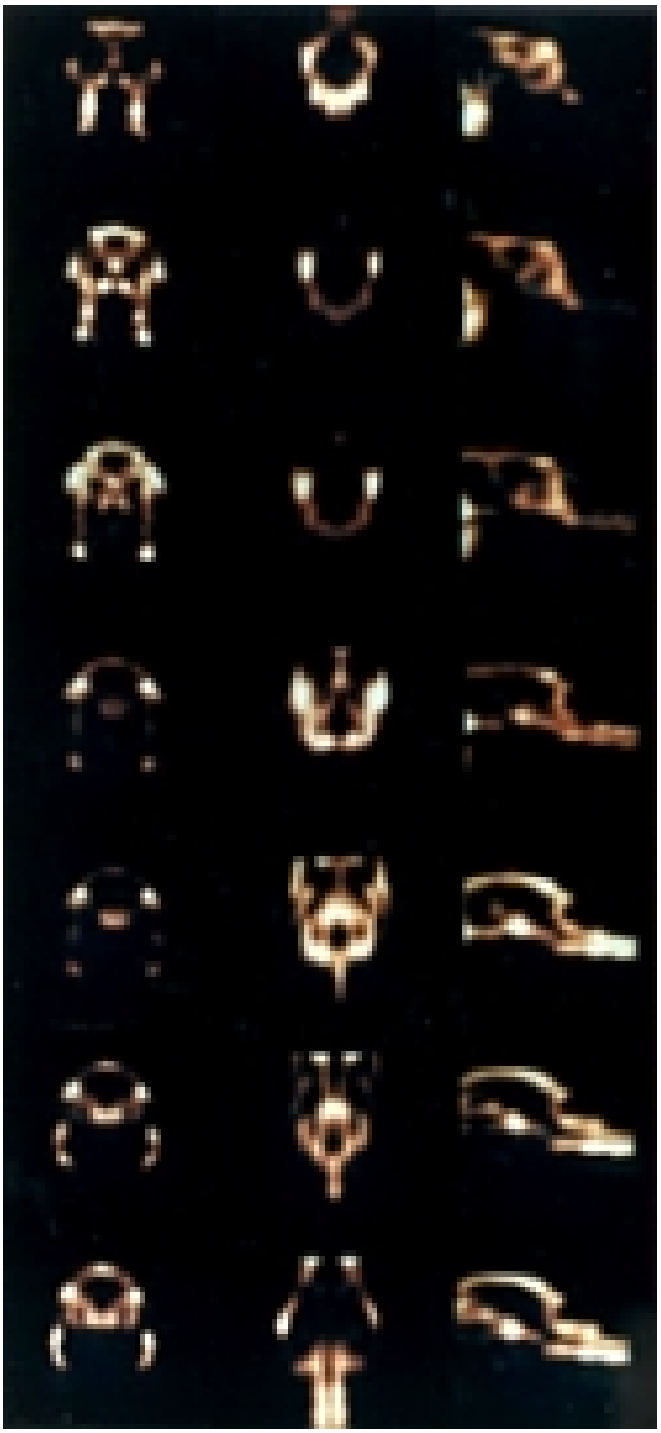

Figure 19: Bone study of a rabbit skull using ^{18}F and PCR-I. Coronal slices on the left, transverse slices at the middle and sagittal slices on the left.

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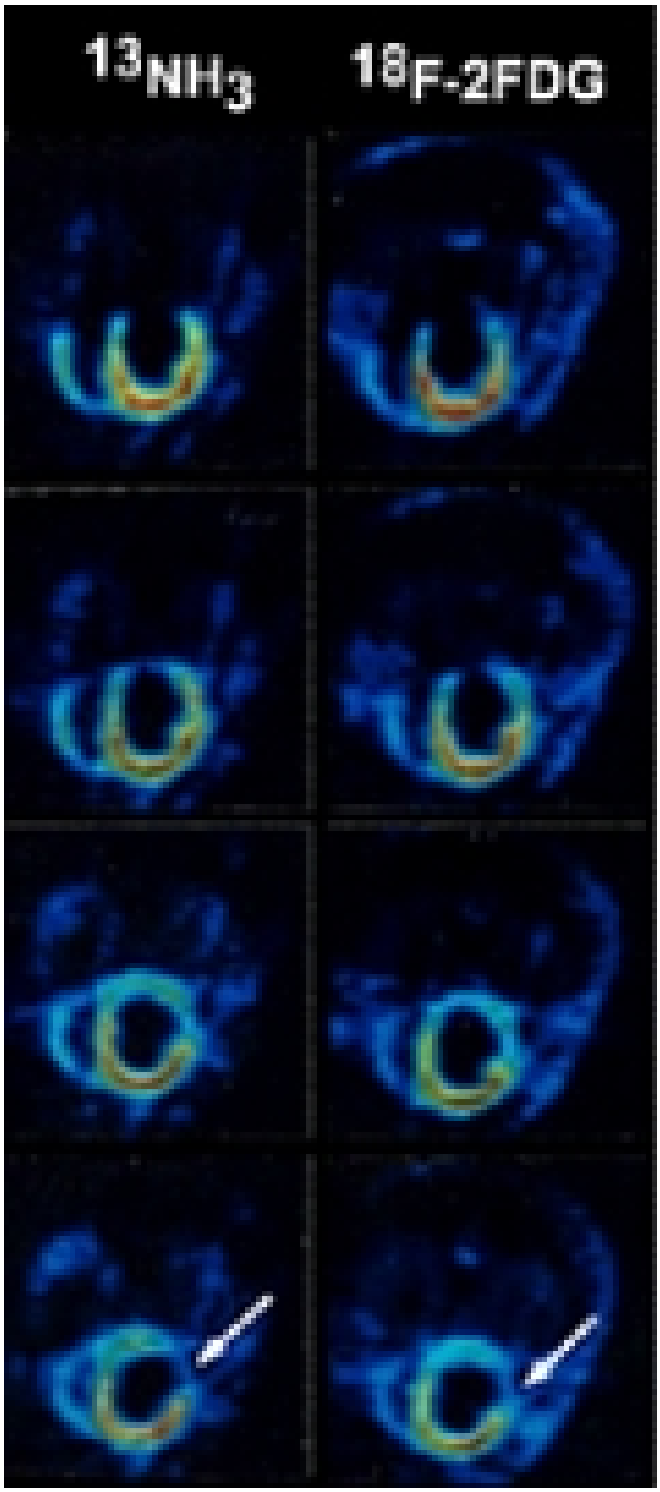

Figure 20: Gated studies of blood flow ($^{13}NH_3$) and glucose metabolism (^{18}F 2FDG) in infarcted dog heart using PCR-I.

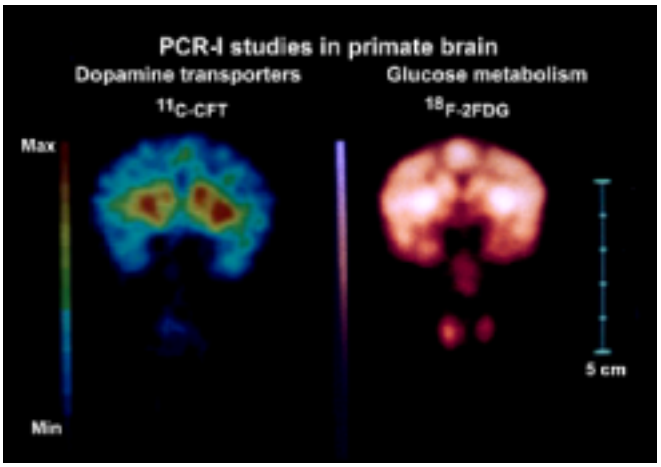

Figure 21: Study of dopamine transporters with $^{11}C-CFT$ and glucose metabolism with ^{18}F 2FDG in a primate brain using PCR-I.

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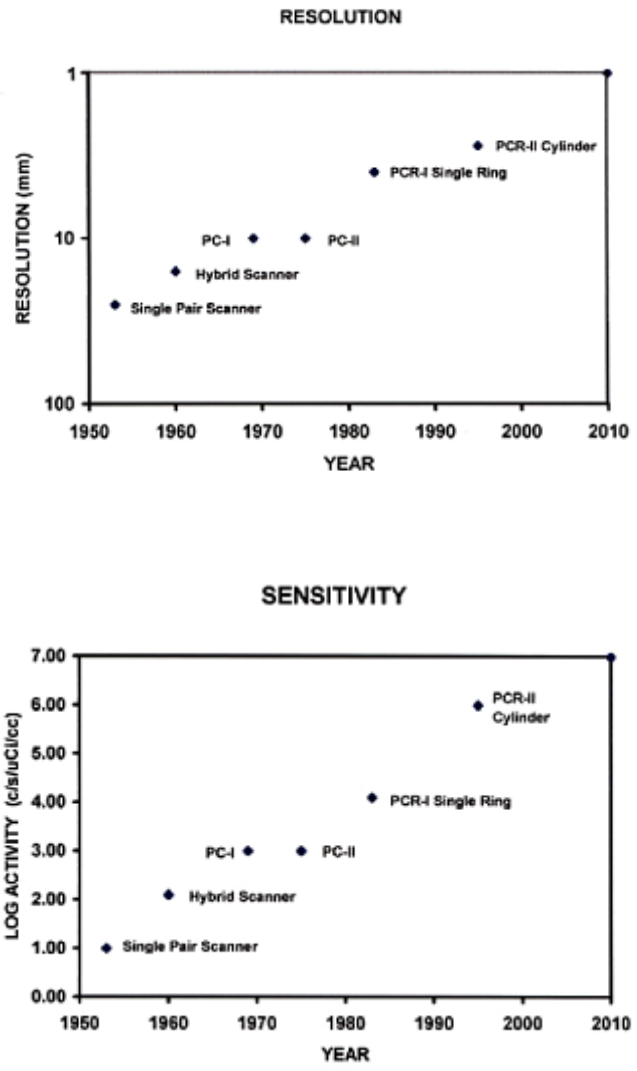

Figure 22: Improvement in resolution (top) and sensitivity (bottom) of MGH positron imaging systems.

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