

## THE HISTORY OF PET

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### Introduction

The development of Positron Emission Tomography (PET) has attracted many strong personalities, great scientists, physicians and businessmen, many of whom have dedicated their entire lives to this technology. The history of PET is dynamic and is marked by many significant technological advances. In fact, volumes of books would be required to record the history of PET development. The purpose of this article is to identify ten of the most important events that have shaped modern PET.

### Early Medical Applications

The first medical applications for the positron were made and reported by William H. Sweet at Massachusetts General Hospital (MGH) in 1951. This was a simple brain probe that utilized coincidence to localize brain tumors. Gordon L. Brownell (Figure 1) along with William H. Sweet (Figure 2) and the physics group at MGH developed and built the first brain probe using two opposing Sodium Iodide (NaI(Tl)) detectors. In the same year, Wrenn, Good and Handler described and published studies of positron annihilation for localizing brain tumors in Science<sup>2</sup>. These two independent papers represent the first attempts to record positron data for use in a medical application.

In the early 1960's, Kuhl and Edwards<sup>3</sup> were among the earliest pioneers to develop image reconstruction techniques for single photon tomography. Although this algorithm was not a true computed tomography approach, it did employ the principle of superimposition of back projections. About a decade later Chesler<sup>4,5,6</sup> of the MGH physics group was developing the filtered back projection technique. This occurred at about the same time as the first clinical trial for x-ray CT was published by Ambrose<sup>7</sup> with the x-ray CT developed by Hounsfield<sup>8</sup>. However, unbeknownst to the field of medical imaging, Cormack<sup>9</sup> had published papers in the mid 60's in which he demonstrated a bench top x-ray CT scanner with proper image reconstruction based on the Radon equations. In 1979, Hounsfield and Cormack were awarded the Nobel Prize in recognition of their development of x-ray CT. Chesler's filtered back projection technique was clearly developed in the same time frame as the iterative technique used by Hounsfield and Cormack.

Terry Jones (Figure 3), while on sabbatical from the Hammersmith Hospital, worked with the MGH group from 1972 to 1974 on a technique for imaging metabolism and blood flow with Oxygen-15. Prior to his work at MGH, Terry Jones worked with Michael E. Phelps at Washington University.



In 1973, James Robertson<sup>10</sup> of Brookhaven National Laboratory built the first ring tomograph, 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. This 32-detector circular array (Figure 4) was eventually transferred to Montreal Neurological Institute where Chris Thompson, Lucas Yamato and Ernst Myer completed the development in the mid to late 70's. Also in 1973, Michael E. Phelps built the first PET tomograph, known as PETT I, at Washington University. Like the Brookhaven efforts, this first attempt by Phelps was unsuccessful in producing transverse back projected images because it employed bad collimators, limited sampling and did not provide for attenuation correction. This tomograph did, however, use a proper Fourier based image reconstruction algorithm.

### **Event # 1: The Beginning of Modern Positron Emission Tomography (1973)**

In the summer of 1973, Mike Phelps and Ed Hoffman of Washington University journeyed to Oak Ridge, TN, to discuss the building of PETT II with a group at EG&G ORTEC. At the time, EG&G ORTEC was a spin-off company of the Oak Ridge National Laboratory and was the leading supplier of nuclear research instrumentation. The group at EG&G ORTEC included James Kelly Milam, Charles W. Williams, Terry D. Douglass and Ronald Nutt. Four of the original EG&G ORTEC Team that assisted Phelps in building the first successful PET tomograph continue to be actively involved in the PET community today.

In the first meeting at EG&G ORTEC in Oak Ridge, 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. The EG&G ORTEC group 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. Later he reduced the name to PET because transaxial was not the only plane in which images could be reconstructed. The construction of PETT II began in December of 1973 and the first scans were taken in January 1974.

PETT II  $\frac{1}{2}$  was constructed a month later. This tomograph had a hole cut in the center of the board holding the detectors with a computer-controlled table installed underneath the detector array to allow automatic rotation of phantoms and animals to provide a fully sampled data set. In PETT II, the phantom had to be rotated by hand. PETT II and PETT II  $\frac{1}{2}$  were used to establish the mathematics and physics of PET, as well as to perform imaging of blood flow and metabolism in animals. The principles of PET, as we know them today, were published from studies on these tomographs developed by Phelps and his team<sup>11</sup> (Figure 5) and are coined "Event #1" in the development of modern PET.



### First Human PET Tomograph (1974)

Mike Phelps (Figure 6) and Ed Hoffman (Figure 7) constructed PET III for human studies during the latter part of 1974. PET III was composed of 48 NaI(Tl) detectors, or a factor of two more detectors than PET II. This system was a hexagonal array with excellent sampling by a combination linear movement of detectors and a 60-degree rotation of the gantry. The system had its own computer for controlling the motion of the detectors, gantry and bed, as well as performing image reconstruction. Nizar Mullani is credited for developing the coincidence logic while EG&G ORTEC designed the electronics. The first images of blood flow, oxygen and glucose metabolism and F-18 bone scans from this tomograph represented the first published human PET images using the filtered back projection algorithm<sup>12,13</sup> (Figure 8).

Event #1 clearly marks the beginning of modern PET development. It is also interesting to note that the PET II and PET III had detector arrays of 24 and 48 circular detectors with a diameter of 50mm. These detector arrays are small compared with today's most advanced tomograph, the HRRT14, which has approximately 120,000 detector elements measuring 2mm by 2mm. This represents a decrease in detector size of 25 or area of individual detector elements of 625 and an increase in number of detectors of more than a factor of 2,500 to 5,000.

Following the PET III development, the first commercial PET Scanner was designed at EG&G ORTEC in collaboration with Phelps and Hoffman. This tomograph was trade named ECAT II with the acronym ECAT, meaning Emission Computed Axial Tomograph. This tomograph used a total of 96 3.75cm NaI(Tl) crystals, had a PDP-11 computer with 32Kbytes of memory for a console and sold for approximately \$600,000 in 1978 (this translates to more than \$2,000,000 in Y2000). This was the first commercial PET scanner, and it provided a means for the establishment of worldwide PET programs.

### Event #2: Discovery Of BGO Scintillator (1977 – 1978)

The detector material used in PET influences the sensitivity, the image resolution, and the count rates or patient throughput. The only detector of choice in the mid 1970s was NaI(Tl), which was difficult to manufacture because of its hygroscopic nature. Also, the NaI(Tl) scintillator has low density and effective atomic number that limits the efficiency for the high energy, 511KeV gamma ray. NaI(Tl), on the other hand, has a high light yield and reasonably fast decay time to provide good coincidence time resolution. A crystal known as Bismuth-Germanate (BGO) is very dense and has a high effective atomic number, but in the early days of PET, the crystal had not been evaluated as a scintillation detector. Weber<sup>17</sup> at University of California, Berkeley, was the first to study the luminescence of BGO. Nester and Huang<sup>18</sup> were the first to characterize the scintillation properties of BGO in 1975, and found that it was an excellent crystal for PET. The characteristics of BGO compared to NaI(Tl) are summarized below (Figure 10). The



first evaluation of BGO for use in PET was performed by Cho<sup>19</sup>, et al and Derenzo<sup>20</sup>, et al. The first actual tomograph constructed that employed BGO

\*\*Eriksson remains a Professor at University of Stockholm, but lives most of the time in Knoxville, TN, and is a Detector Scientist working with LSO detectors at CTI, Inc.

A tomograph was designed in 1978 by Chris Thompson and his group at the Montreal Neurological Institute. In that same year, EG&G ORTEC produced the NeuroECAT, the first commercial tomograph to use BGO. Approximately 300 BGO-based PET tomographs have been produced since the first introduction.

In 1978, approximately two years after the ECAT II was introduced, The Cyclotron Corporation (TCC) developed a tomograph based on the design of Brownell at MGH<sup>21</sup>. This tomograph had two large opposing NaI(Tl) detector heads composed of arrays of individual detectors that rotated around the subject. Only two or three of these scanners were sold before TCC replaced it with a BGO-based brain tomograph. Only one of the BGO systems was built and it was placed at Memorial Sloan Kettering, N.Y. Because of BGO contribution to the modern PET tomograph, the discovery of the dense PET scintillator is coined "Event #2" in the development of modern PET.

During the late 1970s, TCC and Scanditronix were the principal suppliers of large cyclotrons for research. TCC was the first of the two companies to build a PET scanner, but shortly afterwards, in 1981, Scanditronix introduced a commercial tomograph based on BGO scintillator material after the design of Eriksson.

### **Event #3: FDG Synthesized (1978 – 1980)**

The first PET III images were obtained at Washington University using an <sup>11</sup>Cglucose, <sup>15</sup>O water and <sup>13</sup>N ammonia for blood flow and <sup>15</sup>O for oxygen metabolism. However, the most successful molecular imaging probe was derived from the <sup>14</sup>C-deoxyglucose, used by Lou Sokoloff, Reivich<sup>22</sup> and colleagues who used Autoradiography to determine the cerebral glucose utilization rate in the rat.

According to Lou Sokoloff, he and Mark Reivich had attended a wine-tasting event and the subject of an <sup>18</sup>F-tagged glucose for PET came up in their discussion. Both men agreed that the most appropriate group to perform the chemistry was the Brookhaven group, so they telephoned Al Wolf and Joanna Fowler. Wolf and Fowler's group<sup>23</sup> synthesized the first FDG.

A patient was injected with FDG at the University of Pennsylvania and imaged with the Mark IV single photon emission tomograph developed by Kuhl, Alavi, Reivich, Phelps, Hoffman and the Brookhaven group (the FDG was flown in from Brookhaven). The first PET imaging with FDG was performed by Phelps, Huang, Hoffman and Kuhl<sup>24</sup>, who had

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moved to UCLA. They used the ECAT II that had been delivered to UCLA in December 1976 by EG&G ORTEC. The Sokoloff tracer kinetic model was adopted and rate constants for FDG were measured by UCLA and the University of Pennsylvania groups.<sup>24,25</sup>

The development of the FDG PET method is coined "Event #3" in the evolution of modern PET. Hamacher, Coenen and Stocklin<sup>26</sup> at Jülich in Germany later developed a new synthesis method for FDG using a nucleophilic reaction (F-18 ion) which has become the synthesis of choice for FDG today.

#### **Event #4: Development Of The First PET Medical Cyclotron & Automated Chemistry (1984 – 1986)**

In early 1984, the team led by George Hendry at The Cyclotron Corporation (TCC) included Fred Ramsey (Figure 16), Lewis Carroll (Figure 17) and Maria Straatmaan. The basic cyclotron design was completed in late-1985, after The Cyclotron Corporation was purchased by CTI, Inc. The first, of these mini-cyclotrons, the Radioisotope Delivery System (RDS112) was delivered to Jerry Nickles at University of Wisconsin in 1986. Interestingly, the funds for Nickles were partially provided by Norton Simon and had been arranged by Mike Phelps. With this initial gift, Nickles raised the remainder of the necessary funds.

The first RDS (Figure 18) was an 11MeV, negative ion, proton cyclotron that had four target ports. The beam could be split and extracted simultaneously on two of the 18F ports. The RDS would make  $^{11}\text{C}$  gases,  $^{15}\text{O}$  water and  $^{15}\text{O}$  gases and  $^{13}\text{NH}_3$ . The RDS was shielded for neutrons and gammas such that outside the room the radiation field was less than 2mr/hr.

In 1985 Bruce Wieland joined the RDS team as the target designer and Henry Padgett, a Ph.D. Postdoctoral student working with Jorge Barrio (Figure 19) and Nagichettiar Satyamurthy of UCLA, also joined with the RDS team. Bruce Wieland developed the first high yield miniaturized targets. Satyamurthy, Barrio and Padgett at UCLA developed the first automated chemistry module for synthesizing FDG, as well as other molecular probes<sup>27</sup>. The RDS, along with the automated synthesis, was controlled by an IBM PC (the first IBM PC was introduced in 1981). The team demonstrated that a single technician could operate the RDS and synthesize FDG on a routine basis. This concept was initially criticized by many professionals in the PET industry at the time. Today, among the twenty or so PET radiopharmacies in the world, the typical site requires only three people to perform the production, chemistry, quality assurance and business management for local distribution of FDG. This technology provides an electronic means for automated production of PET molecular probes and is the base technology for PET radiopharmacies to meet the needs for PET clinical service.



Presently, a number of companies provide cyclotrons with various forms of automated chemistry for producing molecular imaging probes, such as General Electric, Siemens, and IBA. Additionally, several companies sell automated chemistry modules for PET without the cyclotron. An excellent review of the cyclotrons and automated chemistry technologies is provided by Satyamurthy<sup>28</sup>. The development of the first PET medical cyclotron and automated FDG synthesis is coined "Event #4" in the evolution of modern PET technology.

### **Event #5: The Block Detector(1984 – 1985)**

In 1984, Scanditronix designed a tomograph<sup>29</sup> using two crystals on a single photomultiplier. One of the crystals was BGO and the second crystal was Gadolinium Orthosilicate (GSO). The two scintillators had different scintillation decay times, so that by measuring the decay, the crystal producing the event could be identified. A few of these tomographs were produced but, more importantly, this technique encouraged a search for optical multiplexing schemes that would permit the use of many small scintillator pixels on a single photomultiplier. Burnham, Brownell and colleagues<sup>30</sup> at MGH developed a technique where scintillators were placed on a circular lightguide with photomultipliers placed on the opposite side of the lightguide (Figure 21). Charlie Burnham demonstrated that by taking the ratio of two adjacent photomultiplier signals, the scintillator that detected the gamma ray could be identified. This technique is very similar to the Anger Camera<sup>31</sup> concept, except it is performed on the circular lightguide lightguide. Mike Casey and Ronald Nutt, from CTI, visited MGH in 1984 and concluded that although this was a promising technique, it probably would be difficult and expensive to manufacture. The "Block"<sup>32,33</sup> detector (Figure 22) was conceived as a means to simplify the Burnham detector and to make it easier to manufacture.

Almost all dedicated tomographs built since 1985 have used some form of the Block detector. This invention has made possible high-resolution PET tomographs at a much-reduced cost and is coined "Event #5" in the evolution of PET technology. The first Block detector had 32 crystals for four photomultipliers or 8 crystals per photomultiplier. The latest tomograph uses 144 crystals per photomultiplier<sup>34</sup>.

Formation of CTI, Inc., Positron Corporation, PET Electronics and UGM 1980 – 1985  
 During the period of the early 1980s, Scanditronix and EG&G ORTEC were the only major suppliers of PET tomographs. The EG&G ORTEC ECAT II was the dominate commercial tomograph during the late 1970s. The Scanditronix PC384 and the NeuroECAT with BGO detectors later became the leaders in PET brain research. The first significant recognition of this new era in brain imaging was a publication by Phelps, Kuhl and Mazziotta in Science, with images shown on the front cover of Science in March 1981, showing the first brain mapping of normal cerebral function with FDG PET.

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In 1983 and 1984, EG&G ORTEC decided to spin-off its ECAT business to Computer Technology and Imaging, Inc. (CTI), a startup company founded by three of the individuals who had helped Phelps construct the first tomographs at Washington University. Mike Phelps was also a founder of CTI that would be solely committed to PET. The fifth principal was EG&G ORTEC's ECAT Product Manager, Mike Crabtree. Twenty-two engineers and technicians from EG&G ORTEC joined CTI in the early spring of 1984. This was the beginning of a major commercial commitment to PET.

In this time frame, 1983 through 1984, Nazar Mullani (who had been in Phelps' original Washington University group), Lance Gould and others from the University of Texas, formed Positron Corporation and introduced a new time-of flight tomograph, the Posicam, using Barium Fluoride (BaF) as the scintillation detector. The Posicam was reported to have very fast data collection and was sold primarily to researchers interested in cardiac imaging. Later, after Squibb and CTI introduced Rubidium 82 (82RB) with an automated infusion system, the Posicam was promoted almost entirely as the scanner of choice for fast 82RB cardiac studies. Very soon after introduction, the Posicam was converted to a non time-of flight scanner using BGO as the detector material.

Also, in the early 1980s, the late Michael Ter-Pogossian from Washington University started PET Electronics, Inc. to build the BaF time-of-flight scanner that had been designed by his team at Washington University. This company had very limited commercial success and managed to build several time-of-flight tomographs, most of which were used at Washington University before the company's closure.

In 1985 Gerd Muehllehner, and his wife, Ursula, were producing septa for the ECAT tomographs. Shortly after discontinuing that business, Gerd designed a NaI(Tl) based tomograph and in the 1990s began selling that tomograph through General Electric.

In 1983, The Cyclotron Corporation experienced financial difficulties and was not able to continue operation. CTI, Inc. contracted with the Bankruptcy Court to finish building two of the large 40MeV, negative ion cyclotrons that were designated for use in neutron cancer therapy and a 30MeV cyclotron for Ed Coleman at Duke. In 1985, CTI purchased The Cyclotron Corporation and directed George Hendry and a small selected team of that company to design a dedicated, self-shielded, negative ion cyclotron that could operate in a hospital environment (See Event #4).

#### **Event #6: Cardiac Viability(1985 – 1990)**

Schelbert (Figure 23), Schwaiger and Phelps (Figure 24), along with their colleagues developed and validated<sup>35,36</sup> the match/mismatch principle for determining cardiac viability (Figure 25) with N-13 Ammonia being used for blood flow and FDG for glucose metabolism. For several years, cardiac tissue viability was the focus of clinical PET.

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During the later part of the 1980s, most

PET centers were attempting to perform cardiac clinical PET (with no Medicare reimbursement) along with the government sponsored research. The promise of this new and unique cardiac disease diagnosis kept many PET enthusiasts excited during the 1980s. This occurred at the same time of tremendous growth in nuclear cardiology in general. The development of cardiac viability proved to be very important in the process of making clinical PET a reality and therefore is coined "Event #6" in the evolution of modern PET. Although the diagnosis of difficult cardiac cases continues to be important in clinical PET, the use of PET for diagnosis and management of cancer treatment has become the focus of clinical PET in the 1990s.

### **Event #7: Major Imaging Companies Enter PET (1987 – 1990)**

In 1986, Siemens began to distribute the CTI PET tomographs along with the RDS cyclotrons. In 1987, serious discussions occurred between CTI and Siemens about Siemens acquiring CTI. Instead of a purchase of CTI, the two companies decided to establish a joint venture entity, CTI PET Systems, Inc., to develop, manufacture and market the PET equipment. Siemens would continue to distribute the products, including selling and servicing the equipment worldwide. The CTI and Siemens relationship continued through the 1990s with CTI pursuing the FDG distribution and later buying back the RDS cyclotron assets from the joint venture entity.

In 1990, General Electric (GE) purchased the tomograph business from Scanditronix and began selling PET tomographs. Later, GE also purchased the cyclotron business from Scanditronix. Almost none of the Scanditronix personnel were moved from Sweden to the USA when the tomograph business was acquired from Scanditronix. Shortly after the acquisition of Scanditronix's tomograph business, General Electric began designing its own PET tomograph that would be produced in the USA. The cyclotron design and manufacturing remained in Sweden. GE also developed automated chemistry technology and integrated it with its cyclotron systems with central control.

The entrance of the two largest medical imaging companies into PET served to further validate this new imaging technology for clinical applications. Until this time, most applications in PET were research oriented. The entrance of the two major imaging companies initiated a time of commercial focus on developing and supplying PET products for clinical service. The entrance of the major medical imaging companies to the PET market is coined "Event #7" in the evolution of modern PET.

### **Event #8: Formation of Institute for Clinical PET (ICP) and the First Whole-body Oncology Image (1990 – 1991)**

In 1990, ICP was formed by Mike Phelps and Ben Ambruster as a not-for-profit organization that would bring together academia, industry and advocacy groups to

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educate the public, Congress and professional groups about the value of clinical PET. During this time, cardiac viability and detection of coronary artery disease remained the greatest hope for clinical PET. During the 1980s, several researchers were studying tumor uptake of FDG and other radiopharmaceuticals. Di Chiro and others<sup>37</sup>, during the late 1970s and early 1980s, demonstrated that cerebral tumors could be detected and that the degree of malignancy was proportional to the FDG uptake.

In 1991, at the second ICP meeting, Phelps presented the first whole-body oncology images (Figure 26) obtained by using a technique developed by himself, Hoffman and Dahlbom. This started the evolution to detect primary and metastatic disease, differentiate benign from malignant lesions and assess therapeutic responses by being able to image all organs of the body in a single examination. These applications, starting with cardiac applications, formed one basis of the Food and Drug Administration's (FDA) approval of FDG and the Medicare reimbursement of several oncology indications. The development of whole-body PET imaging along with the vast amount of clinical research in PET imaging has been very important in the development of modern clinical PET and is coined "Event #8" in the development of modern PET.

### **Event #9: FDA Reform Bill and Health Care Financing Administration (HCFA) Reimbursement For PET(1997 – 1998)**

After repeated attempts to convince the FDA to approve FDG as a radiopharmaceutical for cardiac viability and cancer diagnosis, the ICP, spearheaded by Phelps of UCLA and Coleman of Duke University, began efforts to require the FDA to approve FDG as a radiopharmaceutical for the purpose of Medicare reimbursement. Prior to this effort, HCFA used the fact that the FDA had not approved FDG as a reason not to provide reimbursement. In the Fall of 1997, the FDA Reform Bill (Figure 28) passed Congress and President Clinton signed the Bill into law. As part of this Bill, in legislation sponsored by Senator Stevens, the FDA was required to approve FDG as a radiopharmaceutical. After the FDA Reform Bill was passed, HCFA announced the first government reimbursement for PET in January 1998 for lung cancer and cardiovascular disease, and in March of 1999 expanded coverage to include colorectal cancer, melanoma and lymphoma.

The two people who contributed the most to this effort were Michael E. Phelps and Senator Ted Stevens from Alaska. Ted Stevens is an influential Senator as Chairman of the Senate Appropriations Committee, who became a close friend of Phelps' after being introduced by a mutual friend, Norton Simon, a wealthy entrepreneur in southern California, in 1981. Ted Stevens became acquainted with the PET program through Mike Phelps and the relationship resulted in a lasting friendship until Senator Stevens's death in 2010. Senator Stevens, as Chairman of the Senate Appropriations Committee, and his Legislative Assistant, Liz Connell were relentless in pursuing FDA approval and HCFA reimbursement for PET. Stevens told the story of when he first came to UCLA to learn



about PET. Stevens arrived at UCLA at 4pm and had to give a talk at the Veterans of Foreign Wars (VFW) at 6pm. He became so involved with PET and Phelps' passion for it, that the next time he looked at his watch it was 7pm and he had missed his talk at the VFW and says they never invited him back. Phelps' friendship with Stevens provided an opportunity to demonstrate the power of PET to one of the most important people in the United States.

Senator Stevens was joined by several other key political figures to fight for PET reimbursement. Senator Frist of Tennessee and Senator Ted Kennedy of Massachusetts' joined with Senator Stevens to accomplish this important step in the History of PET. On June 23, 2000, a group from UCLA that included

Sam Gambhir, Johannes Czernin, Dan Silverman, Judy Schimmer and Mike Phelps, as well as Ed Coleman of Duke, submitted to HCFA a 4000-page document containing data from over 17,000 patients for broad coverage in cancer, heart disease and neurological disorders. As mentioned before, many other people in the PET community joined in the fight for PET including: Peter Valk of Northern California PET Center; Jenny Keppler of ICP; Kim Pierce of UCLA; Ruth Tesar of PETNet; Peter Conti of USC; Terry Douglass of CTI; Steve Larson of Memorial Sloan Kettering and a host of others. FDA drug approval and HCFA reimbursement has encouraged a significant growth in clinical PET and is coined "Event #9" in the development of modern clinical PET.

#### **Event #10: Lutetium Oxyorthosilicate (LSO) and Future PET (1990 – 2000)**

Although BGO has served the PET community since its discovery and was used in the fabrication of most PET tomographs for two decades, LSO has the potential to revolutionize PET imaging. BGO is very dense but has only fifteen percent of the light output of NaI(Tl) and has a relatively slow light decay time of 300nsec. LSO has a slightly greater density, slightly lower effective atomic number and has five times more light output than BGO. Also, the light output of LSO has 7.5 times faster decay than BGO. This LSO performance results in a combination speed and light output improvement of 37.5 (Figure 31) over BGO.

LSO was discovered and the first crystals were grown in the period of 1989-1992, with patents<sup>38,39</sup> issued to Charles Melcher (Figure 32) of Schlumberger Technology Corporation<sup>40</sup>. CTI obtained the rights to these patents in 1995 and began a rather difficult development process. Charles Melcher joined CTI that same year to lead the LSO development.

An early discouragement occurred in the reported availability of the rare earth element, Lutetium, and the cost of that base LSO element. There were no commercial applications of Lutetium except for PET detectors. In 1995, the price of refined Lutetium was in the range of \$6,000 to \$12,000 per kilogram and the availability was only in research



quantities (a few grams). Through the efforts of Mark Andreaco, of CTI, and George Schweitzer, of the Chemistry Department at the University of Tennessee, Lutetium refinement was perfected and made very cost effective. Today the start material cost and availability is almost equal to that of BGO. Shown below is a picture of the initial LSO factory (Figure 33), a resulting cylinder of LSO crystal, Lutetium raw material (brown) and refined material (white) (Figure 34).

The first LSO PET tomograph was designed and fabricated by Simon Cherry of UCLA41, the microPET. The microPET tomograph (Figure 35) was designed for small animals and demonstrated 1.6mm cubic resolution. A commercial version of the microPET was developed by Concorde MicroSystems, Inc. and approximately twenty of these tomographs have been ordered by academic programs and pharmaceutical companies for the study of the mammalian biology of disease in small animals, as well as for the development of molecular imaging probes and drugs.

The first human LSO tomograph was delivered to the Max Planck Institute, Köln, Germany, in February of 1999. The HRRT brain tomograph<sup>14</sup> (Figure 36) has approximately 120,000 discrete LSO crystals and exhibits a uniform cubic resolution over the volume of the brain of approximately 2.5mm FWHM.

A combination LSO and NaI(Tl) tomograph<sup>34</sup> for PET and SPECT (Figure 37) was delivered to the Free University of Amsterdam in March 2000. This tomograph is capable of performing PET scanning comparable to dedicated PET tomographs and is capable of performing state-of-the-art SPECT.

Tomographs using LSO promise to be dominant in PET during the early 2000s with patient throughput improvements of a factor of five or greater and with no increase in cost over existing BGO tomographs. LSO has very near ideal performance characteristics for PET and will make practical 2mm resolution tomographs that will image the torso in less than thirty minutes. The discovery of LSO will be important for future developments of PET and is coined "Event #10" in the development of modern PET.

## Conclusions

The automobile was invented around the turn of the twentieth century, but did not make a significant impact on our society until thirty to forty years later. Also, one might consider the history of the transistor (Figure 38). The transistor was invented in 1925 by Lilienfield, but twenty-five years passed before the Bell Laboratory group made a practical device, and in the year 2000, our society thrives on telecommunications and the personal computer, both of which are totally dependant on the semiconductor device. Although it has been approximately thirty years since the beginning of modern PET, this is a relatively short time compared to the development of many of our current



technologies. Molecular imaging with PET marked the time of moving from structural imaging to a time of imaging the biological basis of cellular function and its failure in disease. The merger of modern biology and medicine into molecular medicine played a significant role in making the unique information provided by PET important in the care of patients. The engagement of biology and the pharmaceutical industry will contribute greatly to the further evolution of PET, as well as bring together molecular diagnostics and molecular therapies<sup>42</sup>.

Like PET, the individuals receiving much of the credit for the technology were not always the real inventors. Shockley was a distant contributor to the real invention of the transistor. He did not believe in the first transistor demonstration enough to be present when Brattain and Bardeen presented the first transistor oscillator circuit to upper management of Bell Labs on Christmas Eve, 1947. The three would later (1956) be awarded the Nobel Prize for their invention of the transistor. For Shockley, his contribution was a thorough theoretical treatment of the semiconductor junction after the invention of the transistor. As shown in Figure 39, the number of transistors in an integrated circuit doubles every 18 months (Moore's Law). This has been the driving force behind the computer revolution since the early 1980s. Likewise, the number of individual crystals in a PET tomograph has doubled approximately every two years for the past 25 years (Nutt's Law). The data set for PET, which is measured by the square of the number of detector elements, has grown faster than the expansion of the number of transistors in integrated circuits.

Hundreds of individuals, from Brownell to Melcher, have made significant contributions to PET development over the past 25 to 30 years. One individual, whose contribution stands clearly above all others, is Michael E. Phelps. Not only did he invent the PET tomograph that produced the first published PET images, but he has also been the moving force behind at least nine of the ten top events in PET development. Michael E. Phelps d modern PET, but he also has been a passionate and inspiring father to this technology and all those involved in it through its infancy and adolescent stages. Moreover, Phelps continues to foster the development as PET takes its position with CT and MRI as a major clinical imaging modality. If molecular medicine becomes as significant as many believe, PET as the molecular imaging technology of molecular medicine, may very well exceed the incredible success and contributions made by CT and MRI.

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## References:

1. Sweet W.H.; "The use of nuclear disintegration in diagnosis and treatment of brain tumors"; *New England Journal of Medicine*, 1951; 245:875-878.
2. Wrenn Jr. F.R., Good M.L., and Handler P.; "The use of positron emitting radioisotopes for localization of brain tumors"; *Science*, 1951; 113:525-527.
3. Kuhl D.; Edwards, R.; Image separation radioisotope scanning. *Radiology* 1963, 80:653-661.
4. Chesler D.A.; "three-dimensional activity distribution from multiple positron scintigraphs"; *Journal of Nuclear Medicine*; 1971, 12:347-348.
5. Chesler D.A.; "Positron tomography and three-dimensional reconstruction technique" in *Tomographic Imaging in Nuclear Medicine*, ed. Freedman GS., The Society of Nuclear Medicine: New York. 1973, pp.176-183.
6. Chesler D.A., Hoop Jr. B., and Brownell G.L.; "Transverse section imaging of myocardium with  $^{13}\text{NH}_4$ ", *Journal of Nuclear Medicine*; 1973, 14:623.
7. Ambrose J.; "Computerized transverse axial scanning (tomography): Part 2. Clinical application", *British Journal of Radiology*; 1973, 46:1023-1047.
8. Hounsfield G.N.; "Computerized transverse axial scanning (tomography). Part I: Description of system. Part II: Clinical applications", *British Journal of Radiology*; 1973, 46:1016-1022.
9. Cormack A.M.; "Representation of a function by its line integrals, with some radiological applications, *J. Appl. Phys.*; 1963, 34:2722-2727; (also) Cormack A.M.: Reconstruction densities from their projections, with applications in radiological physics", *Physics in Medicine and Biology* 1973, 18:195-207.
10. Robertson J.S., Marr R.B., Rosenblum M., Radeka V., and Yamamoto Y.L.. "32-Crystal positron transverse section detector", in *Tomographic Imaging in Nuclear Medicine*, Freedman GS, Editor. The Society of Nuclear Medicine; New York; 1973, pp.142-153.
11. Phelps M.E., Hoffman E.J., Mullani N.A., Ter-Pogossian M., "Application of Annihilation Coincidence Detection to Transaxial Reconstructed Tomography", *Journal of Nuclear Medicine*; 1975, 16:210-215.
12. Phelps M.E., Hoffman E., Mullani N., Higgins C., Ter-Pogossian M.; "Design considerations for a positron emission transaxial tomograph (PET III)." *I.E.E.E. Trans. Biomed. Eng.*; 1976, NS-23:516-522; .
13. Hoffman E., Phelps M., Mullani N., Higgins C., Ter-Pogossian M.; Design and performance characteristics of a whole body transaxial tomograph. *J. Nucl. Med.*; 1976; 493-503.
14. Schmand M., Eriksson L., Casey M.E., Andreaco M.S., Melcher C., Wienhard K., Flugge G., Nutt R.; "Performance results of a new DOI detector block for high resolution PET – LSO research tomograph HRRT." *I.E.E.E. Trans. Nucl. Sci.*; December 1998; 45 (6):3000-3006.
15. Cho Z.H., Chan J.K., and Eriksson L.; "Circular ring transverse axial positron camera for 3-dimensional reconstruction of radionuclide distribution." *IEEE. Trans. Nucl. Sci.*; 1976, NS-23:613-623.
16. Derenzo S., Budinger T., Cahoon J.; "High resolution computed tomography for positron emitters." *I.E.E.E. Trans. Nucl. Sci.*; 1977, NS-24:544-558.
17. Weber M.J., Monchamp R.R.; "Luminescence of  $\text{Bi}_4\text{Ge}_3\text{O}_{12}$  Spectral and decay properties." *J. Appl. Phys.*; 1973, 44:5495-5499.
18. Nester O.H. and Huang C.Y., "Bismuth Germanate: A high-z gamma-ray and charged particle detector." *I.E.E.E. Nucl. Sci.* 1975, NS-22:68
19. Cho Z.H., Farukhi M.; "BGO as a potential scintillation detector in positron cameras." *J. Nucl. Med.* 1977, 18:840-844.
20. Derenzo S.; "Monte Carlo calculations of the detection efficiency of arrays of  $\text{NaI}(\text{TI})$ , BGO, CsF, Ge, and plastic detectors for 511KeV photons." *I.E.E.E. Trans. Nucl. Sci.*, 1981, NS-28:131-136.
21. Brownell G.L., Burnham C.A., Chesler D.A., Correia J.A., Correll J.E., Hoop Jr. B., Parker J. and Subramanyam R.; "Transverse section imaging of radionuclide distribution in the heart, lung and brain"; *Reconstruction Tomography in Diagnostic Radiology and Nuclear Medicine*, 1977, pp.293-307.
22. Sokoloff L., Reivich M., Kennedy C., Des Rosiers M.H., Patlak C.S., Pettigrew K.D., Sakurada O. and Shinohara M.. "The [ $^{14}\text{C}$ ] Deoxyglucose Method for the Measurement of Cerebral Glucose Utilization: Theory, Procedure and Normal Values in the Conscious and Anesthetized Albino Rat". *Journal of Neurochemistry*, 1977, Vol. 28, pp.897-976.
23. Ido T., Wan C.N., Casella J.S. et al.; "Labeled 2-deoxy-D-glucose analogs: 18F labeled 2-deoxy-2-fluoro-D-glucose, 2-deoxy-2-fluoro-D-mannose and 14C-2deoxy-2-fluoro-D-glucose." *J. Labeled Compds. Radiopharmacol*, 1978:14:175183.
24. Phelps M.E., Huang S.C., Hoffman E.J., Selin C., Sokoloff L., and Kuhl D.E., "Tomographic measurement of local cerebral glucose metabolic rate in humans with [ $^{18}\text{F}$ ] 2-fluoro-2-deoxy-D-glucose: Validation of method", *Annals of Neurology*, 1979; 6:371-388.
25. Reivich M., Kuhl D., Wolf A., Greenberg J., Phelps M.E., Ido T., Casella V., Fowler J., Hoffman E., Alavi A., Som P. and Sokoloff L., "The [ $^{18}\text{F}$ ] fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man"; *Circular Research*, 1979, 44:127-137.



26. Hamacher K.; Coenen H.H. and Stocklin G. (1986) "Efficient stereospecific synthesis of no-carrier-added 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution." *J. Nucl. Med.* 27:235.
27. Padgett H.C., Schmidt D.G., Luxen A., Bida G.T., Satyamurthy N. and Barrio J.R. (1989) "Computer-controlled radiochemical synthesis: A chemistry process control unit for the automated production of radiopharmaceuticals." *Appl. Radiat. Isot.* Vol.40, No.5:433-445.
28. Satyamurthy N., Barrio JR., Phelps ME.; "Electronic generators for production of positron-emitter labeled radiopharmaceuticals: where would PET be without them?" *Clin. Positron Imaging*, 1999; 2:233-254.
29. Eriksson L., Bohm C., Kesselber M., Litton J-E, Bergstrom M, Blomquist G.A.; "A high resolution positron camera. In: Greitz T, Ingvar DH, Widen L., eds. *The metabolism of the human brain studied with positron emission tomography*"; New York: Raven Press, 1985, 33-46.
30. Burnham C.A., Bradshaw J., Kaufman D., Chesler D.A., and Brownell G.L.; "Positron source position sensing detector and electronics" in United States Patent, Patent number 4,531,058, July 23, 1985.
31. Anger, H.; "Gamma-ray and positron scintillation cameras." *Nucleonics* 1963, 21:56-59.
32. Casey M., Nutt R.; "A multislice two-dimensional BGO detector system for PET." *I.E.E.E., Trans. Nucl. Sci.*, 1986, NS-33:760-763.
33. Casey M, Nutt R., Douglass T.D.; "Two-dimensional photon counting position encoder system and process." U.S. Patents 4,743,764 & 4,749,863. May 10, 1988.
34. Schmand M., Dahlbom M., Eriksson L., Casey M.E., Andreaco M.S., Vagneur K., Phelps M.E., and Nutt R.; "Performance of a LSO/NaI(Tl) phoswich detector for a combined pet/spect imaging system." *J. Nucl. Med.*, 1998 39 (5):9P.
35. Schelbert H.R., Schwaiger M.; "PET Studies of the Heart. In: Phelps M, Mazziotta J and Schelbert H.R.; *Positron Emission Tomography and Autoradiography*"; 1986, Raven Press, New York.
36. Schwaiger M., Brunken R., Grover-McKay M., Krivokapich J., Child J., Tillisch J.H., Phelps M.E., and Schelbert H.R.. "Regional myocardial metabolism in patients with acute myocardial infarction assessed by positron emission tomography."; *Am Coll. Cardiol*; 1986, 8:800-808.
37. Di Chiro G., Oldfield E., Bairamian D., Brooks R.A., Patronas N.J., Mansi L., Kornblith P.L., Smith B.H., Sank V.J., and Margolin R.A.; (1985) "In vivo glucose utilization of tumors of the brain stem and spinal cord." In: *Positron Emission Tomography* (Edited by Greitz T, Ingvar D.H. & Widen L.); pp.351361. Raven Press, New York.
38. Melcher C.L.; "Lutetium Orthosilicate single crystal scintillator detector."; U.S. Patent 4,958,080, Sept. 18, 1990.
39. Melcher C.L.; "Lutetium Orthosilicate single crystal scintillator detector."; U.S. Patent 5,025,151, June 18, 1991.
40. Melcher C.L., and Schweitzer J.S.; "Cerium-doped lutetium oxyorthosilicate: a fast, efficient new scintillator."; *I.E.E.E. Trans. Nucl. Sci.*; 1992, 39 (4):502505
41. Cherry S.R., Shao Y., Silverman R.W., Chatziioannou A., Meadows K., Siegel S., Farguhar T., Young J., Jones, W.F., Newport D., Moyers C., Andreaco M., Paulus M., Binkley D., Nutt R., and Phelps M.E.; "MicroPET: a high resolution PET scanner for imaging small animals." *I.E.E.E. Trans. Nucl. Sci.*; 1977, 44:1161-1166.
42. Phelps M.E.; "PET: The merging of biology and imaging into molecular imaging." *J. Nucl. Med.*; 2000, 41:661-681.

