PII S1095-0397(00)00051-0

Molecular Imaging and Biology
Vol. 4, No. 1, 11–26. 2002

1536-1632/02 $–see front matter

1999 ICP DISTINGUISHED SCIENTIST AWARD

The History of Positron Emission Tomography

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The history of Positron Emission Tomography (PET) is rich in technological achievements and advancements. The advancements that have benchmarked PET progress are the result of key components that include human intellect and passion for PET technology, relentless persuasion of key political forces to eliminate the barriers precluding PET usage, tireless efforts to raise awareness about PET and a crucial network of support throughout the PET community.

This article sets forth a timeline of significant events that have contributed to the development of PET as it is known today. It introduces the earliest physicist and physician, for instance, who were responsible for the first medical applications for positron emitting radioisotopes using a simple brain probe that utilized coincidence to localize brain tumors. Additionally, it identifies landmark technological achievements that have helped pave the way to modern PET. This study includes historical accounts surrounding the use of the first human PET tomograph, discovery of the Bismuth Germanate (BGO) scintillator, development of the Fluorodeoxyglucose (FDG) PET method, the design of the first PET medical cyclotron with automated chemistry and operated by a PC and a technologist, Food and Drug Administration's approval of FDG, HCFA reimbursement, and the capacity of Lutetium Oxyorthosilicate (LSO) to produce a revolutionary advance in PET scanners.

The main thrust of this article is to recognize via a timeline of PET accomplishments the noteworthy work of scientists, physicians and others who have been key players in various aspects of the continuous activity to move PET technology forward from invention to research, and to become a major clinical imaging modality. (Mol Imag Biol 2002;4:11–26) © 2001 Elsevier Science Inc. All rights reserved.

Key Words: PET; Positron; Tomography.

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 10 of the most important events that have shaped modern PET.

Early Medical Applications for the Positron

The first medical applications for the positron were made and reported by Sweet at Massachusetts General Hospital (MGH) in 1951.[1] This was a simple brain probe that utilized coincidence to localize brain tumors. Gordon L. Brownell (Figure 1) along with William Sweet (Figure 2) and the physics group at MGH developed and built this first brain probe using 2 opposing sodium iodide (NaI(Tl)) detectors. In the same year, Wrenn et al. described and published studies using annihilation for localizing brain tumors in *Science*.[2] These 2 independent papers represent the first attempts to record positron data for use in a medical application.

In the early 1960s, Kuhl and Edwards[3] were among the earliest pioneers to develop image reconstruction techniques for single photon tomography. Although this algorithm was not a true computed tomography (CT) approach, it did employ the principle of superimposition of backprojections. About a decade later Chesler[4–6] of the MGH physics group was developing the filtered backprojection technique. This occurred at about the same time as the first clinical trial for x-ray CT was published by Ambrose[7] with the x-ray CT developed by Hounsfield.[8] However, unbeknownst to the field of medical imaging, Cormack[9] had published pa-

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Figure 1. Gordon L. Brownell.

Figure 3. Terry Jones.

pers in the mid 60s 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 backprojection 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 in 1972 to 1974 on a technique for imaging metabolism and blood flow with Oxygen-15 (O-15). Prior to the work at MGH, Terry Jones worked with Michael E. Phelps, Edward Hoffman and Michel TerPogossian at Washington University.

In 1973, Roberston[10] 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 70s. 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 proper reconstructed images because it employed lead collimators, limited sampling, and did not provide for attenuation correction. This tomograph did, however, use a proper Fourier-based image reconstruction algorithm.

The Beginning of Modern Positron Emission Tomography (1973)

Event #1

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. These four individuals that assisted Phelps and Hoffman in building the first successful PET tomograph continue to be actively involved in developing PET tomographs 28 years later.

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 recon-

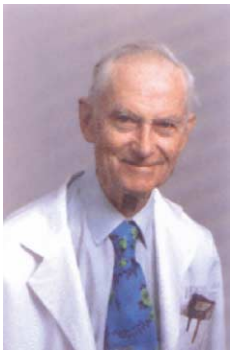

Figure 2. William H. Sweet.

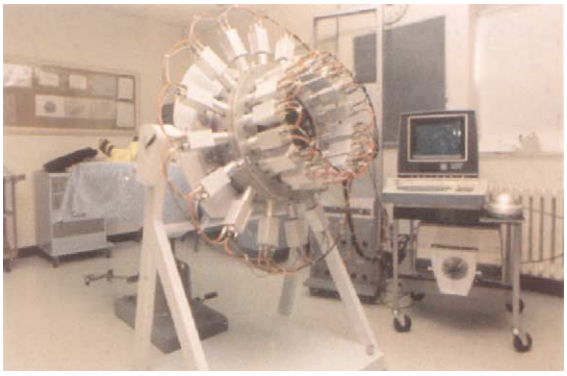

Figure 4. 32-detector circular array.

Figure 5. PET scanners developed by Phelps and his team. Left, PETT II, middle, PETT II 1/2; right, PETT III.

struction 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 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 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 colleagues[11] (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) and colleagues at Washington University 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 2 more detectors than PETT 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 and display. 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 Fluorine 18 (F-18) bone scans from this tomograph represented the first published human PET images using the filtered backprojection algorithm (Figure 8).[12,13]

"Event #1" clearly marks the beginning of modern PET development. It is also interesting to note that the PETT II and PET III had detector arrays of 24 and 48 circular detectors with a diameter of 50mm. These detector arrays are modest compared with today's most advanced tomograph, the High Resolution Research Tomograph (HRRT),[14] that has approximately 120,000

Figure 6. Michael E. Phelps.

Figure 7. Ed Hoffman.

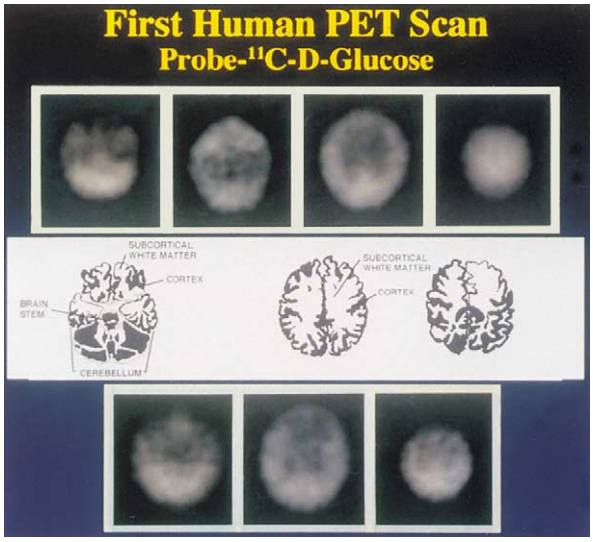

Figure 8. The first published human PET images using the filtered backprojection algorithm.

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 2500 to 5000.

Following the PET III development, the first commercial PET Scanner (Figure 9) was designed at EG&G ORTEC in collaboration with Phelps and Hoffman as a commercial version of PETT III. This tomograph was trade named ECAT II with the acronym meaning ECAT, Emission Computed Axial Tomograph used a total of 96 NaI(Tl) crystals with a diameter of 3.75cm, 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 Y2001). This was the first commercial PET scanner and it provided a means for the establishment of worldwide PET research programs. The first ECAT was delivered to University of California, Los Angeles, (UCLA) in 1976 with the arrival of Phelps and Hoffman at UCLA.

Cho et al.[15] at UCLA conceived one of the first ring tomographs that employed a proper image reconstruction algorithm. Eriksson, who was with Cho at UCLA, returned to Stockholm in 1977 to begin designing a commercial tomograph for Scanditronix. A few years later, Scanditronix became a viable competitor of EG&G ORTEC and especially in research centers in Europe during the early 1980s. At the same time, Derenzo and Budinger were building a circular PET scanner at the DOE Lawrence Berkeley Laboratory.[16]

Discovery of BGO Scintillator

Event #2 (1977–1978)

The detector material used in PET is the determining factor in the sensitivity, the image resolution and the

Figure 9. The first commercial PET Scanner, designed at EG&G ORTEC, the ECAT II; delivered to UCLA.

count rate capability. The only detector of choice in the mid-70s was NaI(Tl), which was difficult to manufacture because of its hygroscopic nature. Also, the NaI(Tl) scintillator has a 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 the PET, the crystal had not been evaluated as a scintillation detector. Weber at University of California, Berkeley, was the first to study the luminescence of BGO.[17] Nester and Huang[18] were the first to characterize the scintillation properties of BGO in 1975. The characteristics of BGO compared to NaI(Tl) are summarized in a table (Figure 10).

The first evaluation of BGO for use in PET was performed by Cho and Farukhi[19] and Derenzo.[20] The first actual tomograph constructed that employed BGO (Figure 11) 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 600 BGO-based PET tomographs have been produced since the first introduction.

Parameter (* at 511 keV)	NaI(T1)	BGO	LSO
Effective Atomic Number	51	75	66
Density (gm/cc)	3.67	7.13	7.4
Decay Time (ns)	230	300	48
Light Output [NaI(T1) = 100]	100	15	75

Figure 10. The characteristics of BGO and LSO compared with that of NaI(Tl).

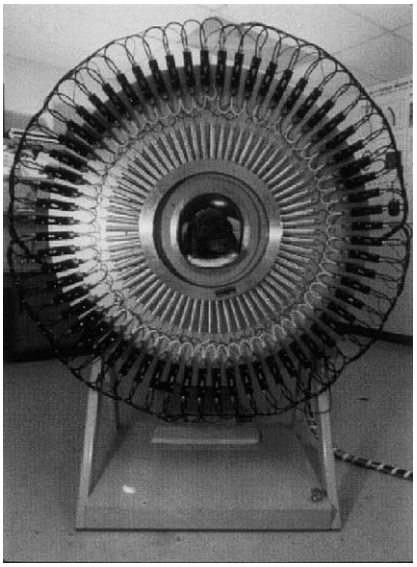

Figure 11. The first actual tomograph constructed that employed BGO, which was designed in 1978.

In 1978, approximately 2 years after the ECAT II was introduced, The Cyclotron Corporation (TCC) developed a tomograph based on the design of Brownell at MGH.[21] This tomograph had 2 large opposing NaI(Tl) detector heads composed of arrays of individual detectors that rotated around the subject. Only 2 or 3 of these scanners were sold before TCC replaced it with a BGO-based brain tomograph. Only 1 of the BGO systems was built and it was placed at Memorial Sloan Kettering in New York. Because of BGO contribution to the modern PET tomograph, the discovery of this 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. ORTEC and TCC were the first of the 2 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.

Figure 12. Lou Sokoloff.

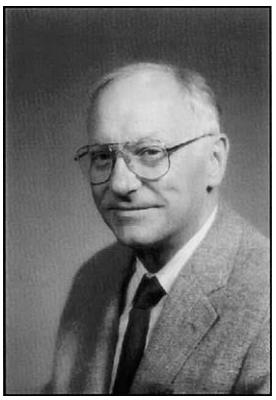

Figure 13. Al Wolf.

FDG Synthesized

Event #3 (1976–1980)

The first PET III images were obtained at Washington University using ^{11}C-glucose, O-15 water and N-13 ammonia for blood flow O-15 oxygen for oxygen utilization, and F-18 fluoride for bone scans. However, the most successful molecular imaging probe was derived from the ^{14}C-deoxyglucose developed by Sokoloff et al. for autoradiography to determine the cerebral glucose utilization rate in the rat.[22] According to Lou Sokoloff (Figure 12), he and Martin Reivich from the University of Pennsylvania attended a wine-tasting event and the subject of an ^{18}F-tagged deoxyglucose 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 (Figure 13) and Joanna Fowler (Figure 14). Wolf and Fowler's group synthesized the first FDG.[23]

Figure 14. Joanna Fowler.

Figure 15. George Hendry.

Figure 17. Lewis Carroll.

A single patient was injected with FDG at the University of Pennsylvania and imaged with the Mark IV single photon emission tomograph by Kuhl, Alavi, Reivich, Sokoloff, Phelps and Hoffman (with FDG flown from Brookhaven). The first PET imaging with FDG was performed by Phelps et al.,[24] who had moved to UCLA. They used the ECAT II that had been delivered to UCLA in December 1976 from EG&G ORTEC. The Sokoloff tracer kinetic model was adopted and rate constants for FDG measured by UCLA and the University of Pennsylvania groups.[24,25]

The development of the FDG PET method is coined "Event #3" in the evolution of modern PET. Hamacher et al.[26] 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.

Development of the First PET Medical Cyclotron and Automated Chemistry—Invention of the "Electronic Generators"

Event #4 (1984–1986)

In early 1984 The Cyclotron Corporation (TCC) was purchased by CTI. A team led by George Hendry (Figure 15) at TCC included Fred Ramsey (Figure 16), Lewis Carroll (Figure 17), and Maria Straatmaan. The basic design specifications for PET was completed in late-1985. The first of these mini-cyclotrons, the Radiopharmaceutical 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 Phelps. With this initial gift, Nickles raised the remainder of the necessary funds.

Figure 16. Fred Ramsey.

The first RDS (Figure 18) was an 11MeV, negative ion, proton cyclotron that had 4 target ports. The beam could be split and extracted simultaneously on 2 of the ports. The RDS could produce ^{18}F, ^{11}C gases, ^{15}O water and ^{15}O gases, and $^{13}NH_3$. 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 postdoctoral student working with Jorge Barrio (Figure 19), and Nagichettiar Satyamurthy (Figure 20) of UCLA, also joined the RDS team. Bruce Wieland developed the first high-yield miniaturized targets. Barrio et al. at UCLA developed the first automated chemistry module for synthesizing FDG, as well as other molecular probes.[27] The RDS, containing the automated synthesis technology, was controlled by an IBM PC (the first IBM PC was introduced in 1981). The team demonstrated that a sin-

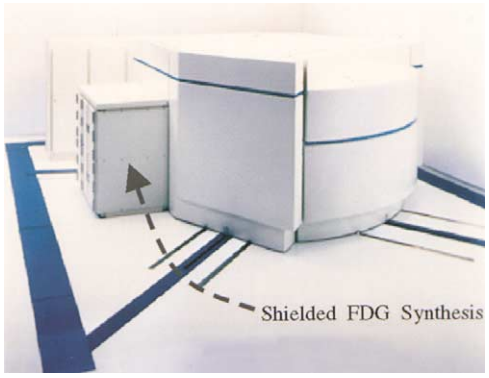

Figure 18. The first RDS: an 11MeV, negative ion, proton cyclotron with 4 target ports and automated chemistry technology.

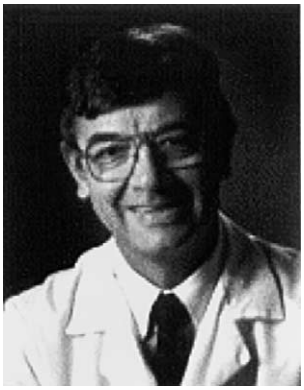

Figure 19. Jorge Barrio.

Figure 20. Nagichettiar Satyamurthy.

gle technician could operate the RDS and synthesize FDG on a routine basis. Although the RDS was initially controversial, it became the standard in the field and produced the new concept of "electronic generators" for the routine production of radiopharmaceuticals. Today, among the 60 or so PET radiopharmacies in the world, the typical site requires only 3 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 and research.

Presently, a number of companies provide small cyclotrons with various forms of automated chemistry for producing molecular imaging probes, such as General Electric, Scanditronix, IBA, and EBCO. Additionally, most companies sell automated chemistry modules for PET without the cyclotron. An excellent review of the cyclotrons and automated chemistry technologies is provided by Satyamurthy et al.[28] The development of the first "electronic generator" for automated production of PET molecular imaging probes is coined "Event #4" in the evolution of modern PET technology.

The Block Detector

Event #5 (1984–1985)

In 1984, Scanditronix designed a tomograph using 2 crystals on a single photomultiplier. One of the crystals was BGO and the second crystal was gadolinum orthosilicate (GSO).[29] The 2 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 small number of photomultiplier tubes. Burnham et al. at MGH developed a technique where individual small scintillator detectors were placed on a circular lightguide with photomultipliers placed on the opposite side of the lightguide (Figure 21).[30] Charlie Burnham demonstrated that by taking the ratio of 2 adjacent photomultiplier signals, the scintillator that detected the gamma ray could be identified. This technique is very similar to the Anger Camera concept, except it is performed on the circular lightguide.[31]

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" detector (Figure 22) was conceived as a means to simplify the Burnham detector and to make it easier to manufacture.[32,33]

The majority of dedicated tomographs built since 1985 have used some form of the Block detector. This invention has made possible high-resolution and high efficiency 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 4 photomultipliers or 8 crystals per photomultiplier. The latest tomograph uses 144 crystals per photomultiplier.[34]

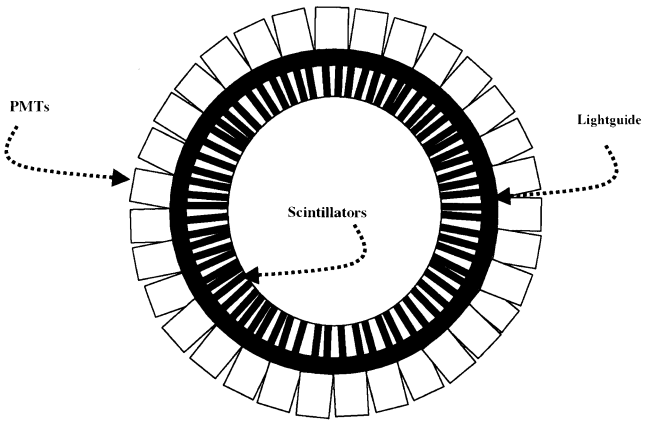

Figure 21. Scintillators on a circular lightguide, photomultipliers placed on the opposite side of the lightguide, as developed by researchers at MGH.

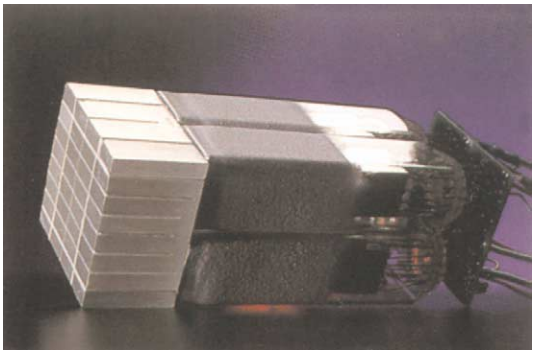

Figure 22. The "Block" detector.

Figure 23. H.R. Schelbert.

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 dominant commercial tomograph during the late 1970s and provided the growth of worldwide PET programs. 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 of visual stimulation that appeared on the cover of *Science* in March 1981. This study demonstrated the first brain mapping of normal cerebral function with FDG and initiated the field of brain mapping with PET, MRI and SPECT.

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 3 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 (^{82}RB) with an automated infusion system, the Posicam was promoted almost entirely as the scanner of choice for fast ^{82}RB cardiac studies. Very soon after introduction, the Posicam was converted to a non time-of-flight scanner using the BGO block detector approach.

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, Ursala, were producing septa for the ECAT tomographs. Shortly after discontinuing that business, Gerd designed a 6 sided NaI(Tl) based tomograph and in the 1990s began selling that tomograph through General Electric. Recently, ADAC purchased the UGM Co. and is marketing a version of the tomograph as the C-PET. Muehllehner has made a significant contribution to PET technology.

Cardiac Viability

Event #6 (1985–1990)

Schelbert (Figure 23), Schwaiger and Phelps along with their colleagues developed and validated the match/mismatch principle for determining cardiac viability (Figure 24) with N-13 Ammonia being used for blood flow and FDG for glucose metabolism.[35,36] For several years, cardiac tissue viability was the focus of clinical PET. During the later part of the 1980s, most PET centers were attempting to perform a 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.

Major Imaging Companies Enter PET

Event #7 (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 2 companies decide to establish a joint-venture entity, CTI PET System, Inc., to develop, manufacture, and market the PET equipment. Siemens would 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. Subsequently, CTI formed PETNet that began the establishment of a worldwide network of PET radiopharmacies. This concept removed the requirements of PET imaging centers having on-site cyclotron and allowed them to focus on imaging patients with PET radiopharmaceuticals delivered by commercial radiopharmacies.

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. Shortly after the acquisition of Scanditronix's tomograph business, GE began designing its own PET tomograph that would be produced in the United States. The cyclotron design and manufacturing remained in Sweden. GE also developed automated chemistry technology and integrated it with their cyclotron systems with central control to provide another commercial source of "electronic generators" for PET.

The entrance of the 2 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 2 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" and the 1990s marked the beginning of PET as a clinical service.

Formation of Institute for Clinical PET (ICP) and the First Whole-body Oncology Image

Event #8 (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 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, 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.[37] This was based upon the well established principle in cancer biology that glucose utilization is increased many fold in malignant tumors.

In 1991, at the second ICP meeting, Phelps presented the first whole-body oncology images (Figure 25) obtained by using a technique developed by Dahlbom, Hoffman and Phelps.[38] This started whole-body PET imaging 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 cancer applications, along with cardiac applications and epilepsy, formed the basis of the Food and Drug Administration's (FDA) approval of FDG and the Medicare reimbursement. 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.

FDA Reform Bill and Health Care Financing Administration (HCFA) Reimbursement For PET

Event #9 (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 26) 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 provide a more efficient process for approval of PET radiopharmaceuticals. After the FDA Reform Bill was passed, HCFA announced the first government reimbursement for PET in January 1998 for lung cancer and cardiovascular disease. In March of 1999 HCFA expanded coverage to include restricted indications in colorectal cancer, melanoma, and lymphoma. At the time a new

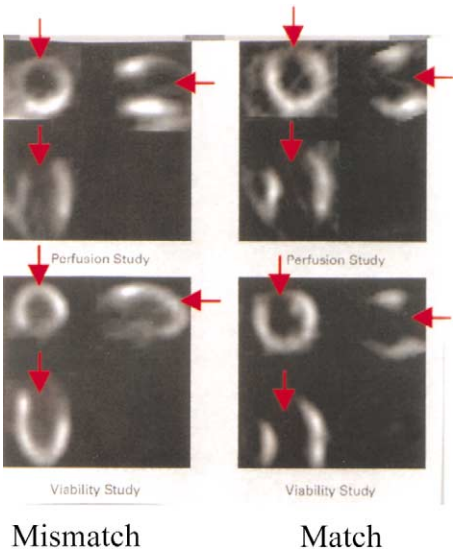

Figure 24. The match/mismatch principle for determining cardiac viability.

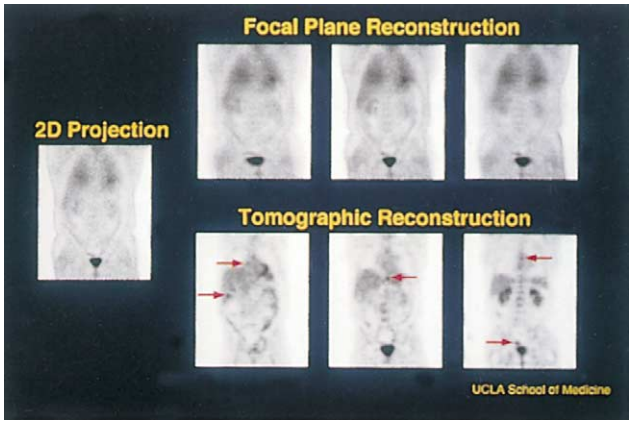

Figure 25. The first whole-body oncology images. Top: focal plane tomography that provided limited separation of image planes and identification of tumors. Bottom: true reconstructed longitudinal tomographic images of same patients as above. Tumors (arrows) are now readily apparent.

relationship was being established with the FDA through an ICP/SNM group led by Jorge Barrio, leading to FDA broad approval for FDG in all cancers and cardiovascular disease in March 2000. FDA approval for 13N-ammonia as a myocardial blood flow agent and 18F-fluoride as a bone imaging agent was also obtained. Subsequently, in December 2000, HCFA expanded coverage to the broad use of PET in lung, colorectal, head and neck, and esophageal cancers, as well as melanoma and lymphoma. Coverage also included cardiovascular disease and epilepsy (Figure 27).

The two people who contributed the most to this effort were Michael E. Phelps and Senator Ted Stevens from Alaska (Figure 28). Stevens became a close friend of Phelps after being introduced by a mutual friend, Norton Simon, a wealthy entrepreneur in southern California, in 1981. Stevens became acquainted with the PET program through Phelps and the relationship resulted in a lasting friendship. Senator Stevens and his legislative assistant, Liz Connell, have been relentless in pursuing the FDA approval and HCFA reimbursement for PET. Stevens tells the story of when he first came to UCLA to learn about PET. "I arrived at UCLA at 4 p.m. and had to give a talk at the Veterans of Foreign Wars (VFW) at 6 p.m. I became so involved with PET and Phelps' passion for it, that the next time I looked at my watch it was 7 p.m. and I had missed my talk at the VFW and was never invited back." Phelps' friendship with Stevens provided an opportunity to demonstrate the power of PET to one of the most influential people in the United States.

Senator Stevens was joined by several other key political figures to fight for PET reimbursement. Senator Ted Kennedy of Massachusetts and Senator Bill Frist of Tennessee 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 16,000 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 have encouraged a significant growth in clinical PET and is coined "Event #9" in the development of modern clinical PET.

Lutetium Oxyorthosilicate (LSO) and Future PET

Event #10 (1990–2001)

Although BGO has served the PET community since its discovery and was used in the fabrication of most PET tomographs for 2 decades, LSO has the capability to revolutionize PET imaging. BGO is very dense but has only 15% of the light output of NaI(Tl) and has a relatively slow light decay time of 300 nsec. LSO has a slightly greater density, slightly lower effective atomic number, and has 5 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 10) over BGO.

LSO was discovered and the first crystals were grown

Clinton Signs FDA Reform Bill

President Clinton showed his support for revitalization of the U.S. Food and Drug Administration (FDA) on 21 November 1997 by signing the FDA Modernization Act of 1997, which aims to improve many of the agency's processes. A Congressional conference had passed the bill by voice vote on 9 November after lengthy discussions concerning the resolution of some of the bill's provisions (see November AAMI News). The signed legislation comes after years of efforts by Congress to streamline FDA's processes. Among its many provisions, the joint bill encourages FDA reliance on national and international consensus standards in regulatory approval processes; allows the agency to use private, third-party service organizations to perform premarket reviews; and mandates that FDA harmonize regulations with other nations' regulatory agencies.

"The legislation enables FDA to use national and international standards as a basis for regulatory compliance," explains Don Barth, regulatory staff manager at Hewlett-Packard. Using standards to establish device safety will make FDA's review processes more efficient. The agency has already issued a draft guidance for the use of the International Electrotechnical Commission 60601 series of standards to satisfy premarket review requirements.

Also, FDA will be empowered to use independent service organizations to review 510(k) applications for Class II devices, excluding devices that are "permanently implantable, life-supporting, life-sustaining, or for which clinical data are required," according to a recent FDA memo. This provision addresses declining resources in the FDA and aims to supplement FDA's scientific expertise.

In addition, the bill requires FDA to coordinate with regulatory organizations in other nations to develop a plan of mutual recognition of good manufacturing practices (GMP). "Most manufacturers derive revenues from international shipments," says Barth, who adds that manufacturers must operate in a global marketplace. Western Europe and Japan are areas where FDA is likely to focus harmonization efforts, says Barth.

"This is by far the single largest legislative victory the medical device industry has ever achieved," said Jeffrey Kimbell, executive director of the Medical Device Manufacturers Association, in a recent statement. "This is the first time in the 21 years of medical device regulation that a piece of legislation is not adding but relieving some of the unnecessary regulatory burdens that have faced this industry."

For a copy of the recent bill, visit the Library of Congress legislation website at thomas.loc.gov; reference document number 105-399.

Figure 26. The FDA Reform Bill passed Congress and President Clinton signed the Bill into law in 1997. As part of the Bill, the FDA approved FDG as a radiopharmaceutical.

MEDICARE NEWS

FOR IMMEDIATE RELEASE
Monday, March 8, 1999
Contact: HCFA Press Office (202) 690-6145

POSITRON EMISSION TOMOGRAPHY (PET) SCAN COVERAGE EXPANDED

Following an expedited review of scientific information presented at a January town hall meeting, the Health Care Financing Administration (HCFA) today announced a national decision to cover additional uses of positron emission tomography (PET) scans to diagnose and manage certain cancers in Medicare beneficiaries.

Medicare already covers PET scanning for the diagnostic evaluation of solitary pulmonary nodules and for staging non-small cell lung cancer. Three new oncology indications will now be covered: detection and localization of recurrent colorectal cancer with rising carcinoembryonic antigen known as CEA; staging and characterization of both Hodgkins and non-Hodgkins lymphoma in place of a gallium scan or lymphangiogram; and identification of metastases in melanoma recurrence in place of gallium studies.

The Jan. 20-21 town hall meeting held by HCFA brought together clinical experts, consumer advocates, medical equipment manufacturers and others to discuss the use of PET scanning for the evaluation and management of head and neck, brain and colorectal cancers; melanoma; and lymphoma. HCFA staff have been working collaboratively with interested parties to review scientific information about oncology indications for PET scanning since 1997.

"The town hall meeting was an excellent way to obtain the latest information about the effectiveness of PET scanning as a diagnostic and management tool for oncology patients," said Mitchell Burken, M.D., a medical officer in the Coverage and Analysis Group within HCFA's Office of Clinical Standards and Quality. "We will continue to review information presented at the meeting about other potential oncology indications for PET, but we believe that these three indications have obvious clinical utility and wanted to take immediate steps to begin initiating Medicare coverage."

PET is a non-invasive imaging procedure that assesses metabolic activity in different parts of the body. A positron camera is used to produce cross-sectional images of the body by detecting radioactivity from a radioactive tracer substance injected into the patient.

"As scientific evidence becomes available showing the effectiveness of new technologies, HCFA wants to act as quickly as possible to make sure Medicare beneficiaries have access to safe and effective new technologies," said Jeffrey Kang, M.D.,

Figure 27. HCFA announced the first government reimbursement for PET in 1998 for lung cancer and cardiovascular disease, and in 1999 expanded coverage to include colorectal cancer, melanoma, and lymphoma.

Figure 28. Michael E. Phelps (left) and Senator Ted Stevens of Alaska.

Figure 30. The initial LSO factory.

in the period of 1989–1992, with patents issued to Melcher (Figure 29)[39,40] of Schlumberger Technology Corporation.[41] CTI obtained the rights to these patents in 1995 and began a rather difficult development process. Melcher joined CTI that same year to lead the LSO development.

An early discouragement occurred in the reported limited availability and high cost of the rare earth element, lutetium. 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 University of Tennessee, lutetium refinement was perfected and made very cost effective. Today the start-up material cost and availability is almost equal to that of BGO. Shown in Figure 30, is the initial LSO factory with a resulting cylinder of LSO crystal and lutetium raw material (brown) and refined material (white) shown in Figure 31.

The first LSO PET tomograph was designed and fabricated by Cherry et al. of UCLA,[42] the microPET. The microPET tomograph (Figure 32) 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 30 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 (Figure 33) has approximately 120,000 discrete LSO crystals and exhibits a uniform cubic resolution over the volume of the brain of approximately 2.5mm FWHM.[14]

A combination LSO and NaI(Tl) tomograph for PET and SPECT (Figure 34) was delivered to the Free University of Amsterdam in March 2000.[34] This tomograph is capable of performing PET scanning comparable to dedicated PET tomographs and is capable of performing state-of-the-art SPECT. The first whole-body LSO PET scanner, the Accel, was delivered to the Northern California PET Center in April 2001 (Figure 35).

Tomographs using LSO promise to be dominant in PET during the early 2000s with patient through-

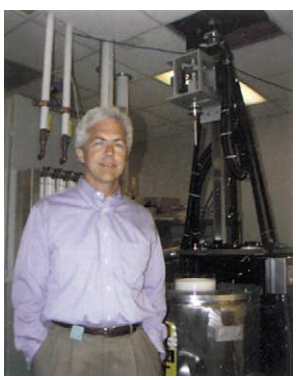

Figure 29. Charles Melcher.

Figure 31. Cylinder of LSO crystal and lutetium raw material (brown) and refined material (white).

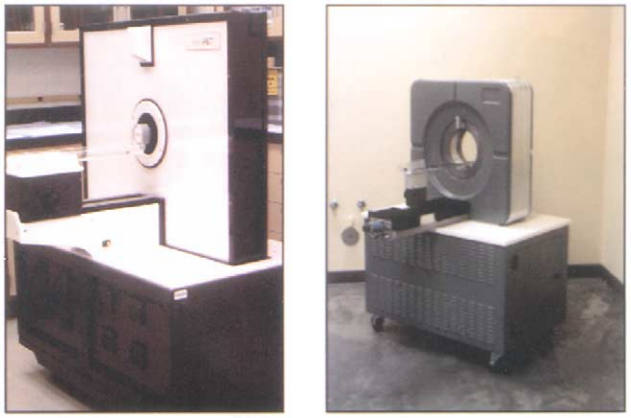

Figure 32. The microPET tomograph, designed for small animals, at left and the first commercial version on the right.

Figure 34. A combination LSO and NaI(Tl) tomograph for PET and SPECT.

put improvements of a factor of 5 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 or 4mm resolution scans in 10 minutes or less. 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 20th century, but did not make a significant impact on our society until 30 to 40 years later. Also, one might consider the history of the transistor (Figure 36). The transistor was invented in 1925 by Lilienfield, but 25 years passed before the Bell Laboratory group made a practical device, and in the year 2001 our society thrives on telecommunications and the personal computer, both of which are totally dependant on the semiconductor device. Although it has been 27 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.[43]

Like PET, the invention and development of the transistor was accompanied by a number of unusual events. 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. However, 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 37, the number of transistors in an integrated circuit doubles

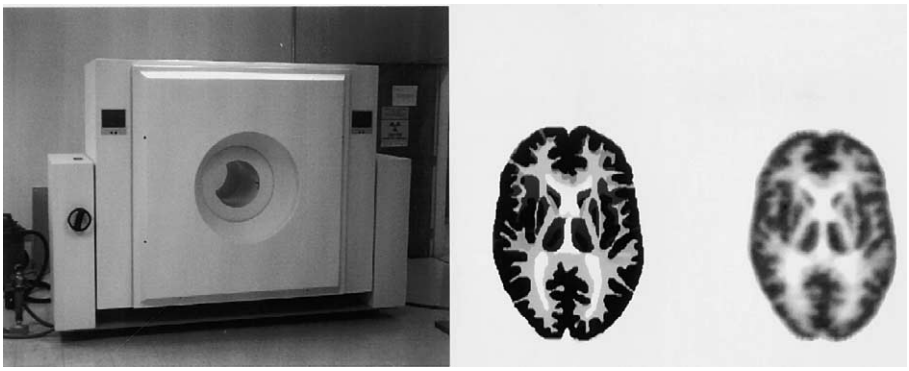

Figure 33. The HRRT brain tomograph. Middle: Hoffman Brain Phantom; Right: image of Hoffman Phantom with HRRT.

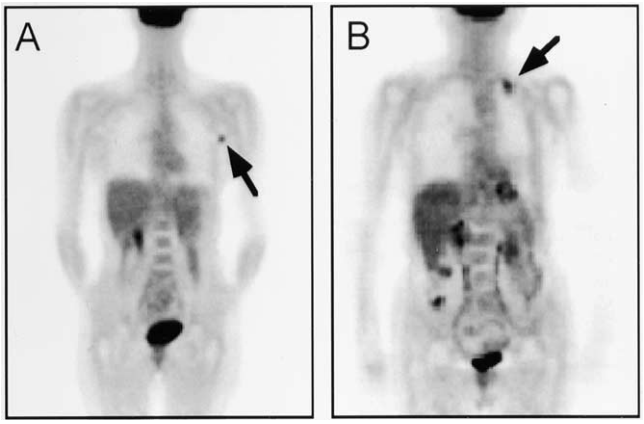

Figure 35. Images of patients using the LSO based ACCEL PET scanner. In each study, the emission and transmission data were collected in a total imaging time of 30 minutes after injection of 13m Ci of FDG. Left: 40 yr old female with primary breast cancer (arrow). Right: 78 yr old male with lung cancer (arrow). Courtesy of Dr. Peter Valk, Northern California PET Center.

every 18 months (Moore's Law). This had 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 2 years for the past 25 years (Nutt's Law, Figure 37). 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, but was made possible by Moore's Law.

Although not included in the Top 10 because of its early stage of development, PET/CT will become the next major advance in PET (Figure 38). This technology will improve diagnostic accuracy, provide surgery and radiation therapy planning and guided biopsies by merging the anatomy and the biology of disease into a single procedure (Figure 39). Fast, low-noise attenuation correction from the CT component will also improve and speed-up the PET component. CTI/Siemens and GE have produced the first commercial systems. Phillips (ADAC) has one under development.

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

Field Effect Transistor patented by Lilienfield	**1925**
Transistor first built by Brattain, Bardeen	**1947**
Nobel Prize - Shockley, Brattain, Bardeen	**1956**
First Integrated Circuit Kilby, Texas Instruments, Noyce, Fairchild	**1960**
First Personal Computer (IBM and Apple)	**1981**

Figure 36. The history of the transistor.

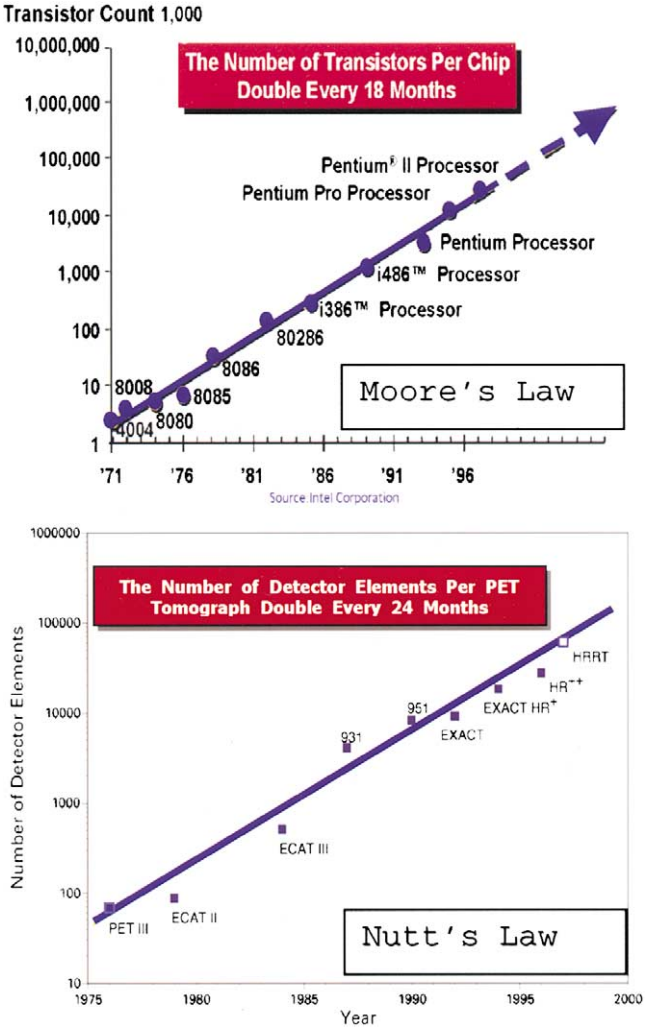

Figure 37. The number of transistors in an integrated circuit doubles every 18 months (Moore's Law). The number of individual crystals in a PET tomograph has doubled approximately every 2 years for the past 25 years (Nutt's Law).

Figure 38. Photograph of a commercial PET/CT scanner.

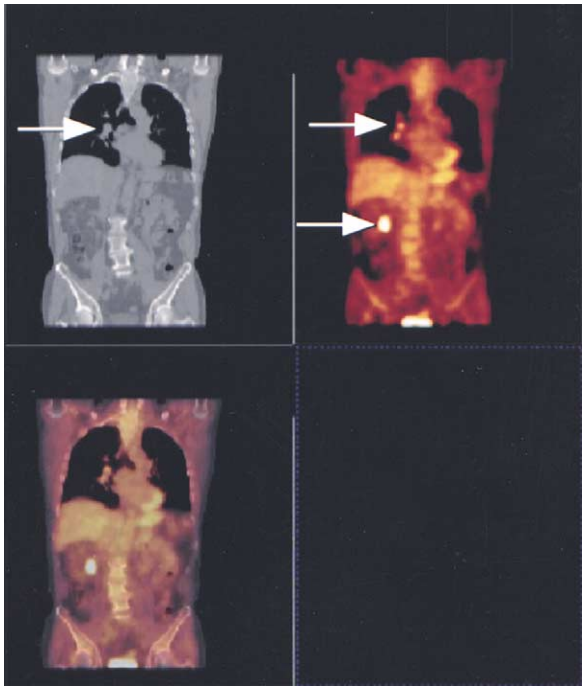

Figure 39. Image of a PET/CT study in a 65 yr old male. Study time was 40 minutes with injection of 10m Ci FDG. Primary tumor is in right lung with metastases in colon (arrows). Coronal, sagittal and transverse views are shown: CT (top left), PET (top right) and fusion of PET and CT (bottom). Courtesy of the University of Tennessee.

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 9 of the 10 top events in PET development. Phelps not only invented 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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