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Michael A. Steiner

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PET – The history Behind the Technology
College Scholars Senior Project

Michael A. Steiner
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Committee Members:
Dr. George Kabalka
Dr. Gary T. Smith
Raymond Trotta

Brief Overview

Positron Emission Tomography, commonly known by the acronym PET, is a branch of nuclear medicine that has come to be an important imaging diagnostic in the medical field. PET relies on the use of radioactive isotopes to visualize physiological processes of the body. An isotope of an element has the same number of protons as its counterpart but differs in the number of neutrons. The difference in neutrons gives the isotope a different mass number and can also provide instability to the element or molecule derived from the isotope.

There are two fundamental differences between traditional nuclear medicine and PET. First, the radiotracers that are utilized in PET emit positrons. Also, there is difference in the process by which data is acquired and reconstructed into an image. Radioactive isotopes, often called radiopharmaceuticals or radiotracers, must be developed that mimic some function of the body. In PET, most radiotracers are labeled with the biogenic radionuclides including oxygen-15, nitrogen-13, carbon-11, and fluorine-18. Fluorine-18 labeled glucose analogue has become the most important in modern PET studies (Maisey et al. 3). Production of these radionuclides all requires the use of a cyclotron, which must be near the testing center due to the short half-lives of the tracers.

Because they emit positrons, the isotopes can be followed throughout the body by special cameras. A positron is the antimatter particle of the electron; it has the same mass but opposite charge. Detection of the isotope depends upon the release of photons of pure energy after the annihilation of a positron from an injected radiopharmaceutical and

an electron of the body. The photons are released in opposite directions (180 degrees apart) and are detected in coincidence. Coincidence detection eliminates the need of a collimater, which increases sensitivity. After detection, sophisticated computer technology is necessary to construct useful images for trained physicians to make diagnosis.

The Beginning

The use of radioactive elements in biological studies was limited before 1932 because only naturally occurring isotopes were available. In 1919, Ernest Rutherford at the Cavendish Laboratory in Cambridge, England placed an alpha emitting radium source in a container with oxygen gas. Alpha particles struck a zinc sulfide screen and produced scintillations, pinpoints of light, which could be counted by watching the screen through a microscope. Then, Rutherford put enough silver foil between the radium and the zinc sulfide screen so the particles were blocked and no scintillations were produced. However, when he replaced oxygen with nitrogen, the scintillations reappeared even in the presence of the silver foil. He later proved that the particles that were able to penetrate the silver were not x-rays but protons. He deduced that the alpha particles joined with a nitrogen nucleus and ejected a proton to produce oxygen (Eisenberg 409).

Rutherford had converted one familiar element into another familiar element. In addition, isotopes of common elements were also created from such bombardment reactions. Radium had limitations as a source for nuclear bombardment. At the Cavendish, Rutherford's group discovered that naturally occurring alpha particles induce more transmutations the faster they travel (Heilbron et al. Ch. 1). A new source was needed, and thus the race for particle accelerators began.

The Cyclotron

In 1927, Rutherford appealed the Royal Society of London to fulfill his wish for a copious supply of projectiles more energetic than natural alpha and beta particles (Heilbron and Seidel 49). First, the traditional x-ray tube was used with very high voltages in an attempt to accelerate particles. While many others tried to find ways of reaching high voltages, John Cockcroft kept his focus on the goal of making particles with energies sufficient to penetrate nuclei (Heilbron and Seidel 67). Cockcroft followed calculations made earlier by George Gamow and decided that protons would be better agents for acceleration than alpha particles. In 1932, John D. Cockcroft and Ernest T.S. Walton built a high-voltage transformer type of accelerator capable of producing protons with sufficient energy to bring about a nuclear transformation. With this accelerator, lithium could capture a proton to become Beryllium, which split into two helium nuclei with two protons each (Eisenberg 411).

The cyclotron made possible the resonant acceleration of protons and other particles. Inside, ions spiral out from the center of an evacuated shallow drum, suffering a kick each time they cross a gap between electrodes (later known as dees) arranged along the diameter of the drum. Between "kicks," the particles maintain a circular orbit by the presence of a magnetic field (Heilbron and Seidel 80). Max Steenbeck conceived the idea as a doctoral student at the University of Kiel in 1927 but was dissuaded by his professors due to the impracticality of the cost (Heilbron and Seidel 82). In 1927, Rolf Wideroe described experiments based on the cyclotron equation and the transformer principle. However, Wideroe did not succeed in holding electrons to circular orbits within the evacuated glass doughnut in which he tried to accelerate them (Heilbron and

Seidel 73). Wideroe remarked, "The theory of the stabilizing forces acting on the orbit had not yet been developed sufficiently" (Heilbron and Seidel 74). On January 5, 1929 Leo Szilard filed for a patent on the cyclotron, which he constructed on paper only. Ernest Lawrence thought he could correct the fault in Wideroe's design, which did not make sufficient provision for axial focusing, with extra coils to create a field that could drive errant electrons back to their orbital plane. On June 10, 1931, Lawrence tried and failed, but he was to persist and succeed.

Later in 1931, Ernest Lawrence had developed the cyclotron, a circular accelerator, at the University of California Radiation Laboratory. Instead of using high voltage for the initial acceleration, the cyclotron employed a magnetic field and a series of accelerators to achieve high-energy particles with lower voltages. Lawrence and his graduate student M. Stanley Livingston built the first successful cyclotron, which accelerated hydrogen ions to an energy of 80,000 electron volts. The particles that managed to reach full energy and fall into the collecting cup 4.5 centimeters from the center of the machine made no fewer than 40 turns (Heilbron et al. Ch.1). The main problem with Lawrence's early cyclotron was keeping the particles from the walls of the dee during the many revolutions necessary for acceleration. After working out many of the specifics to improve their particle accelerator, Lawrence came to require a more powerful oscillator, a larger tank, and a bigger magnet. Lawrence acquired a huge, abandoned magnet yoke that had been used by the Federal Telegraph Company in an obsolete method of radio transmission. Through several approved grant requests, Lawrence was able to continue his work and research on the cyclotron despite the country's economy sinking into the Great Depression (Heilbron et al. Ch. 1).

The Chemical Foundation pledged $68,000 to Berkely for the construction of a "medical cyclotron" which was to be the special instrument of John Lawrence, Ernest's brother. By 1939, this sixty-inch cyclotron was accelerating 16 MeV deuterons about 1.5 meters (Heilbron et al. Ch. 2). Cyclotron development and refinement continued as less space was needed for faster accelerations and higher voltages.

The Positron

Meanwhile, Harold C. Urey, an American chemist, discovered deuterium, which is hydrogen with an additional neutron. Deuterium not only allowed the labeling of hydrogen containing molecules to be used as a tracer in living systems but it also provided a new particle to be accelerated. By the end of 1933, Lawrence's cyclotron could accelerate protons, deuterons, and alpha particles. In addition to the neutron being discovered in 1932 by James Chadwick, another important particle to the history of nuclear medicine, the positron was also discovered at about the same time (Heilbron et al. Ch.1). The discovery of the positron is often credited to Carl Anderson on August 2, 1932. However, Paul Dirac had proposed the concept by 1931. Dirac said, "... all, and not nearly all, of the negative energy states for electrons are occupied. A hole, if there were one, would be a new kind of particle, unknown to experimental physics, having the same mass and opposite charge to an electron" (Hanson 151). He also proposed that a positron could drop into an unoccupied state of negative energy causing the disappearance of the positron and electron, and energy would be released as radiation.

In 1932, Carl Anderson, under the guidance of Robert Millikan, was investigating cosmic rays at California Institute of Technology in Pasadena, California. Anderson built a large cloud chamber inside a large magnet for studying the momentum and charge of

particles. In addition, Anderson placed a six-millimeter lead plate across the middle of the chamber, which caused the particles to lose energy and to change the curvature of their tracks above and below the metal plate (Fraser 15). He took more than 1000 chamber pictures; fifteen of which showed a positive particle crossing the lead plate in the middle of the chamber. After determining that the mass of these particles was no more than $20m_e$, he concluded that he had seen particles of unit charge and of much less mass than the proton. Anderson called these particles, positrons (Fraser 14-15).

In 1933, Patrick Blackett and Giuseppe Occhialini confirmed that Dirac's proposed particle and Anderson's positron were the same particle in a paper titled, 'Some photographs of the tracks of penetrating radiation' (Hanson 159). By placing the cloud chamber apparatus between two Geiger-Muller counters, any ray passing through both of the counters must also pass through the illuminating part of the chamber. This setup allowed them to time the illumination of the particles to reveal high-energy particles from 500 out of 700 photographs (Hanson 160). Blackett and Occhialini found fourteen tracks, which were identified as positive electrons based on their curvature (Hanson 161). In addition to identifying the positively charged electron, they also hypothesized about the production of these particles from the collision of high-energy waves, which later became known as the theory of pair creation (Hanson 162).

Nuclear Physics

Fifteen years after Rutherford's experiment, Irene Curie, daughter of Pierre and Marie Curie, and her husband, Frederic Joliet conducted similar experiments but looked for positrons in addition to alpha particles, beta particles, and gamma rays to be emitted

during nuclear bombardment. They soon discovered that many light elements emitted positrons when bombarded by alpha particles from polonium. Later, it was found that aluminum, magnesium, and boron caused an emission of positrons that continued even after the polonium alpha source had been removed.

Joliet and Curie deduced that alpha bombardment of an aluminum nucleus resulted in the formation of an unstable phosphorus nucleus, with one neutron being emitted as radiation. This first artificially produced isotope had a half-life of 3.25 minutes and led to a race to produce additional radioactive isotopes. Lawrence and his students reproduced this study using artificial isotopes from the cyclotron within a half hour of reading about Curie's experiments in *Nature* (Heilbron et al. Ch. 2).

Lawrence's cyclotron was the most efficient source to produce large amounts of radioactive isotopes. It employed high-energy protons, deuterons, and other particles with much more intensity than natural sources such as polonium used by Curie. In Rome, Enrico Fermi's group showed that neutrons induced nuclear activity in practically all elements. Lawrence knew that his cyclotron could produce the best available source of neutrons by irradiating beryllium-9 with ten billionths of an ampere of accelerated deuterons. Using this artificially produced beam of neutrons, Lawrence confirmed Fermi's work, and set the standard for what was to dominate nuclear physics until WWII: the production of artificial isotopes by proton, neutron, deuteron, and alpha particle bombardment (Heilbron et al. Ch. 2).

In the summer of 1936, Lawrence gave Emilio Segre a sample of an unknown radioactive material that had accumulated on the molybdenum deflector strip of the 27-inch cyclotron. Segre and his group studied the sample at the University of Palermo and

in June of 1937 announced it to be the first man made element, technetium-99 (Heilbron et al Ch. 2). Technetium-99 is now used daily in nuclear medicine practices around the world.

The cyclotron made it possible to produce isotopes to meet specific needs. Soon, the demand for radioactive materials exceeded the capacity of the few medical cyclotrons. To solve this problem, the Oak Ridge Reactor, constructed during World War II for plutonium production, was modified for medical isotope production. This reactor could not manufacture the variety of isotopes as the cyclotron, but it could produce many types in very large quantities at a much-reduced cost (Eisenberg 413).

Nuclear Medicine

The availability of new artificially produced isotopes allowed a Hungarian-born physicist, George Hevesy to make clinical contributions to nuclear medicine from research techniques he had invented more than a decade earlier. Hevesy used naturally occurring isotopes that participated in biochemical and physiological processes in precisely the same manner as the element itself. Through experiments with beans and radioactive lead, Hevesy established principles of selective uptake and metabolic turnover. He also developed the biological half-life, which is the time it takes for one half of a dose of some administered substance to depart from the body (Eisenberg 414).

In 1926, Blumgart, Weiss, and Yens, while in Boston, performed the first tracer study in clinical medicine. They injected minute amounts of radium C into a vein in the right arm of a patient. They then measured the time that elapsed before the radioactive substance would affect a cloud chamber placed near the patient's left arm. This blood

circulation time ranged from 14 to 24 seconds in patients with normal circulation (Eisenberg 414).

In 1934, Hevesy and an associate drank small amounts of water labeled with deuterium instead of hydrogen, also known as heavy water. They then measured the amounts excreted in their urine. This experiment established water's biological half-life. Also, by measuring the ratio of heavy water to plain water in urine, they were able to determine the total volume of body water with which the heavy water had been diluted (Eisenberg 414).

With the Joliet-Curie discovery of 1934, Hevesy had more tools to uncover mysteries of biological functioning. The new phosphorus-30 isotope had such a short half-life that less than 1% remained after three hours. This problem was resolved at Fermi's laboratory in Rome. The bombardment of Beryllium nuclei by alpha particles from radium caused neutron emission that in turn could be used to bombard other nuclei. Among the isotopes produced by this technique was phosphorus-32 with a half-life of 14.3 days (Eisenberg 414).

In 1935, Hevesy and Chiewitz reported the first biological experiments using a new artificial radioisotope. They treated phosphorus-32 with nitric acid to produce phosphoric acid. They then treated a sodium compound with this radioactive phosphoric acid to produce labeled sodium phosphate. They fed this labeled compound to laboratory rats and made careful observations of the amount of radioactivity excreted in the urine and feces. The rats continued to excrete radioactive phosphorus many days after initially ingesting it. After autopsy, more than half of the remaining phosphorus was lodged in bones, a third was in muscles and fat, and the small remainder was in the liver and other

organs. This experiment allowed them to conclude that bone construction is a dynamic process involving the uptake of phosphorus (Eisenberg 415).

Joseph G. Hamilton and Robert S. Stone reported the first application of artificially produced radioisotopes to a clinical problem in 1936. They reviewed reports by Proescher and Almquest, who in 1943 had injected radium chloride into the veins of patients suffering from various diseases. They encountered numerous incidents of radium poisoning and bone tumors due to the radioactive element being deposited in the bone. Theoretically, sodium-24 should be much safer than the radium salts because sodium is not fixed in body tissues. Hamilton and Stone decided to make cautious clinical trials on patients with chronic leukemia. Although the radioactive sodium produced no clinical benefits, it did not produce any toxic effects, and the uptake, excretion, and course in the body was successfully traced (Eisenberg 415).

Following Hamilton and Stone's reports, Lawrence administered phosphorus-32 to a patient with chronic leukemia on December 24, 1936. Twenty years later the patient was still alive and well. In 1939, Lawrence and coworkers administered phosphorus-32 to patients with polycythemia vera which had remarkable results. The patients had a dramatic decrease in red blood cell count with clinical improvement and no objectionable side effects. By the late 1940s, initial reports appeared demonstrating the use of radioactive iodine to treat functioning thyroid carcinomas and their metastases (Eisenberg 415). Also, reports of cobalt-60 in cancer chemotherapy appeared (Heilbron et al. Ch. 2). The first gamma-emitting radioisotope to be commonly used was iodine-131. However, the emitted principal gamma ray was of such high energy (364 eV) that until 1949 it

could only be detected with a Geiger-Mueller tube. In addition, the gamma rays could only be detected at about 1% in the Geiger-Mueller tube (Eisenberg 416).

Instrumentation Develops

The earliest attempts at describing spatial distribution of activity levels in a patient were natural outgrowths of the "point measurements" for determining the radiation field around a needle. Moore pushed tiny Geiger tubes through needles directly into the brain for detecting injected phosphorus-32 diodfluorescein. Later studies used iodine-131 distributions mapped by taking Geiger counter measurements at multiple symmetrical, external counting positions. In 1950, Veall used a collimated Geiger-Mueller tube to map the isoresponse curve image of the thyroid gland. In 1952, Mayneord described a shielded Geiger counter for "point by point" counting for thyroid and distant metastases. Soon, hospitals started to use templates that fit over the neck and were marked off in 1-cm squares. A picture of the distribution of radioiodine in the thyroid was obtained by drawing isodose lines between points of equal count levels (Eisenberg 417).

In 1949, Benedict Cassen at the University of California made a major breakthrough in radioisotope detection by developing the scintillation scanner. The scanner used photomultiplier tubes that could detect scintillation from a solid crystal at its cathode and generate a large electrical pulse as output. Cassen developed a moving solid-state detector utilizing a calcium tungstate crystal coupled to a photomultiplier tube. With a single-hole lead collimater, he was able to obtain a resolution of about 0.25 inches (Eisenberg 417). Cassen easily located the thyroid gland in animals with no more than 10 μC_i of iodine-131. Soon, the sensitivity was increased so that the thyroid could be

completely mapped in humans with a dose of 1 μC_i and an examination time of one to one and a half hours (Eisenberg 418).

Initially the detector was moved by hand but later Cassen developed one that moved automatically called a rectilinear scanner. He coupled the output of the counter to an automatic pen, which moved in synch with the counter marking whenever scintillation occurred. Areas with large amounts of radioisotope appeared as dark regions on the paper. Cysts or tumors in the thyroid that did not take up radioactive iodine appeared as "cold spots" with little or no marking (Eisenberg 418).

In 1952, David Kuhl developed a variation of the scintillation scanner called the photoscan. His device coupled the output from the photomultiplier tube to a moving beam of light, the brightness of which was proportional to the number of scintillations in the face of the crystal. A sheet of x-ray film exposed to the moving light recorded point-for-point the amount of radioactivity emerging from the area scanned (Eisenberg 418). In 1957, Hal Anger developed a stationary area detector consisting of a sodium iodide crystal optically coupled to nineteen photomultiplier tubes (Eisenberg 419).

Positron Emitters Recognized

In the early 1950s, Gordon Brownwell and George Sweet were developing a different method of radionuclide scanning to enhance spatial resolution. Their technique involved the "coincidence counting" of the annihilation product between a positron and an electron (Eisenberg 420). In 1951, William H. Sweet reported the first medical applications of the positron at Massachusetts General Hospital (Sweet 875). Sweet received his first training in the use of radioactive isotopes in 1947 at the Biophysical Laboratory at Harvard Medical School (Sweet 875). During this training, Dr. Sweet and

his colleague, Dr. Bertram Selverstone, decided to search for an isotope to localize brain tumors (Sweet 875). They made progress in tumor detection with phosphorus-32 injected intravenously, but an invasive Geiger-Muller type detector was necessary to detect the beta radiation (Sweet 875). This method was only used during surgery of intracranial tumors (Brownwell and Sweet 40). These studies directed them to the use of potassium-42, which Gordon Brownwell proposed could allow for external localization through the intact skull by positron/electron annihilation radiation (Sweet 876).

In the same year, Wrenn, Good, and Handler published studies of positron annihilation for localizing brain tumors (Nutt 1). In this study, they discussed using simultaneous detection of the annihilation product photons to localize positron emission. They also discussed principles behind the earliest cameras in positron studies (Wrenn et al. 525). In 1953, Brownwell and Sweet reported on their progress since the preliminary reports of 1951. Sweet and a group of physicists developed a brain probe of two opposing scintillation counters utilizing sodium iodide crystals. Scintillation counters emit light when radiation passes through them. Photomultiplier tubes measure the amount of light emitted by the scintillation counters, which is proportional to the amount of radiation emitted. The patient's head was to be placed between the two detectors, and the circuitry was designed to detect the coincidence photons from the annihilation products. In addition to the crude design of the detection camera, these studies were also hindered by the short half-lives of the best positron emitting isotopes (Brownwell and Sweet 41). However, the idea of coincidence detection with mechanical motion in two dimensions used in these studies was the underlying principle of modern PET.

Brownwell and Sweet performed the initial studies with positron emitters by changing Polaroid films in rapid succession. Electronic formatters increased the rate of obtaining images and image quality. In 1965, Hal Anger built the first instrument capable of giving multiple images at different depths from a single scan of a patient. He called this machine the multiplane, longitudinal tomographic scanner (Eisenberg 421).

Tomography In Imaging

In 1917, Johann Radon worked out the mathematics of reconstructing a function from a set of projections. The Radon transform, as his decomposition of a function is now known, is the basis of computed tomography (Pineda online). In the late 1920s and early 1930s, several independent researchers tried to design techniques to image (using x-rays) the body from several different locations to produce diagnostically useful images (Webb 14). However, all of these designs were flawed except one called tomography proposed by Gustave Grossman in 1935 (Webb 35). Tomography is a superficially complicated arrangement with the x-ray tube and detector attached to a rigid pendulum but "...in such a manner that, regardless of the orientation of the pendulum, the detector always remains parallel to the plane of the cut" (Webb 31-32). Although Grossman's idea was fundamentally sound, analogue devices never worked due to blurring of the images.

Although he was not working on the problem of medical imaging, Bracewell made large contributions to the development of tomographic imaging. In 1956, Bracewell showed that two-dimensional maps of structures in the radio sky were derivable from one-dimensional linear radiotelescope measurements (Webb 184). In 1967, Bracewell and Riddle produced a mathematical algorithm, which did not require

the computation of Fourier transforms. Fourier transforms deal with function reconstruction, and at the time required much longer for computers to calculate (Webb 184). Although it was unknown to the field of medical imaging, Allan Cormack had published papers in the mid 1960s, in which he demonstrated a bench top x-ray computerized tomography scanner. His scanner had proper image reconstruction based on the work of Johann Radon (Nutt 1). In the early 1970s, Godfrey Hounsfield directed a project to combine x-ray and digital computer technology. This effort gave birth to computerized tomography (Pineda online).

Tomography and Positron Studies

Several versions of the positron detector with two opposing scintillation counters were built after the initial studies in the 1950s by Brownwell and Sweet. However, it soon became clear that a greater sensitivity was needed to produce useful images (Brownwell online). In 1963, David Kuhl and Roy Edwards proposed a method of discriminating an image from its background in radioisotope scanning, "by separation of images of radioactivity according to their depths in the body" (Kuhl and Edwards 653). To be known later as single photon emission computed tomography (SPECT), their technique coupled a transverse section-imaging device to produce transaxial tomography using single gamma rays from radionuclides (Eisenberg 421). By moving a pair of opposed collimated detectors in angular increments around the patient, they were able to obtain a series of tangential scans (421). Multiple projections were interpreted on photographic paper (Eisenberg 422). Although their technique was not a true computed tomography approach, it did employ the principle of superimposition of back projections (Nutt 1).

Brownwell and others reported the development of a Hybrid Scanner in the mid 1960s (Brownwell et. al. 1968). The Hybrid Scanner had two rows of nine detectors each in coincidence with three detectors in the opposite row. This scanner produced a two-dimensional image and was constructed specifically for brain imaging (Brownwell et. al. 1968). By focusing on planes parallel to and lying between the two detector arrays, this scanner also allowed for a three-dimensional estimated location of a lesion (Brownwell online)

In 1973, James Robertson of Brookhaven National Laboratory built the first ring tomograph, which consisted of 32 detectors. However, he was unable to obtain true reconstructed cross sectional images due to limited sampling, lack of attenuation correction, and lack of a proper image reconstruction algorithm. Eventually, this detector was transferred to the Montreal Neurological Institute where Chris Thompson, Lucas Yamato, and Ernst Myer completed the development in the mid to late 1970s (Nutt 2). Also, in 1973, Michael E. Phelps built the first PET tomograph, known as PETT I, at Washington University (Nutt 2). Phelps named the machine PETT for Positron Emission Transaxial Tomography (Nutt 3). The "transaxial" was later dropped because the machine could reconstruct images in more than just this plane (Nutt 3). Limited sampling, attenuation problems, and bad collimators also hindered the PETT I from producing successful transverse back projected images. However, the PETT I employed a proper Fourier based image reconstruction algorithm (Nutt 2).

By the summer of 1973, Phelps and Edward J. Hoffman of Washington University were planning the construction of the PETT II with a group at EG&G ORTEC in Oak Ridge, Tennessee. EG&G ORTEC was the leading supplier of nuclear research

instrumentation at this time (Nutt 2). In their first meeting, Phelps and Hoffman proposed a hexagonal array of 24 NaI(Tl) detectors with coincidence detection, attenuation correction, and image reconstruction using a proper filtered back projection algorithm (Nutt 3). The EG&G ORTEC group consisted of James Kelly Milam, Charles W. Williams, Terry D. Douglas, and Ronald Nutt (Nutt 2). This group provided expertise in detectors and coincidence electronics, as well as provided Nuclear Instrumentation Modules electronics (Nutt 3). Construction of PETT II began in December 1973, and the first scans were produced in January 1974. PETT II ½ was constructed one month later, which featured a computer-controlled table to allow for automatic rotation of phantoms and animals to provide a fully sampled data set (Nutt 3). Initial studies from these two machines allowed Phelps and his team to establish the mathematics and physics of PET and to perform imaging of blood flow and metabolism in animals (Nutt 3).

Modern PET Develops

During the latter part of 1974, Phelps and Hoffman continued to refine their machine with PETT III, which consisted of 48 NaI(Tl) detectors. PET III was designed for human studies and was a hexagonal array with excellent sampling by a combination of linear movement of detectors and a 60-degree rotation of the gantry (Nutt 3). PET III also had computers for controlling the motion of the detectors, gantry and bed, and for performing image reconstruction (Nutt 4). "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" (Nutt 4).

With experience from PETT III, Phelps and Hoffman in collaboration with EG&G ORTEC designed the first commercial PET scanner ECAT II, an acronym for

Emission Computed Axial Tomograph (Nutt 4). Selling for about $600,000 in 1978, ECAT II employed 96 3.75 cm NaI(Tl) crystals and a PDP-11 computer with 32 Kb of memory (Nutt 4). The first ECAT scanner went to UCLA in 1976 its chief developers, Phelps and Hoffman (Nutt 5). While at UCLA, Z.H. Cho, J.K. Chan, and L. Erikkson reported the development of a circular ring transverse axial camera in 1976 (Cho et al. 614). The system consisted of 64 two cm diameter NaI(Tl) crystals arranged in a circular array (614). In 1977, Derenzo and his colleagues at Berkely reported the construction of a 280 crystal ring arrangement also using NaI(Tl) crystals (Derenzo et al. 544).

There were some difficulties with use of NaI(Tl) as the detector for PET. First, its hygroscopic nature made it difficult to manufacture. In addition, its low density limited the efficiency for detecting the high-energy 511 KeV gamma rays from the annihilation reactions (Nutt 5). Unknown to the early pioneers of PET, Bismuth-Germanate (BGO) is very dense and has a high effective atomic number. In 1973, Weber published reports of the luminescence of BGO. Nester and Huang followed in 1975 by characterizing the scintillation properties of BGO and suggesting its potential in PET studies. Nester and Huang characterized BGO as mechanically and chemically durable, nonhygroscopic, and "pure" as a scintillator (Nestor and Huang 71). By 1978, Chris Thompson and his group at the Montreal Neurological Institute designed the first PET scanner with BGO (Nutt 6). EG&G ORTEC produced the first commercial PET scanner using BGO, called the NeuroEcat, later that year (Nutt 6).

In 1978, The Cyclotron Corporation built scanners based on the Brownwell design with two large opposing NaI(Tl) detector heads composed of arrays of individual detectors that rotated around the subject (Nutt 6). However, they soon made the switch to

BGO. The Cyclotron Corporation and Scanditronix were the principle suppliers of cyclotrons for research during the late 1970s. By 1981, Scanditronix had begun building tomographs with the introduction of a BGO scintillator scanner based on the design of Eriksson (Nutt 6).

Radionuclides (FDG)

The first PET III images were obtained at Washington University using caron-11 glucose, oxygen-15 water, and nitrogen-13 ammonia (Nutt 6). In the early 1970s, Louis Sokoloff from the National Institute of Health (NIH) and Martin Reivich from the University of Pennsylvania had shown that beta-emitting carbon-14 deoxyglucose could be used to map brain metabolism in rats (Alavi). They showed that deoxyglucose crossed the blood-brain barrier and is phosphorylated by the hexokinase system to deoxyglucose-6-phosphate, very similarly to glucose (Alavi). This function made labeled glucose a very valuable molecule in studies of mapping regional function in the brain and other organs (Alavi). Because carbon-14 is a beta-emitting isotope, they assessed its distribution using autoradiography. This technique exposes slices of the brain to radiographic films to reveal the beta particles emitted for a period of time.

In 1973, Martin Reivich, David Kuhl, and Abass Alavi proposed using deoxyglucose for in-vivo physiologic studies. At a meeting of investigators from Brookhaven National Laboratory (BNL) and the University of Pennsylvania, Al Wolf suggested fluorine-18 rather than carbon-11 to be pursued as the appropriate label (Alavi). His reasons for this preference were the relatively long half-life and the low positron energy of the isotope. Dr. Tatsuo Ido later joined these researchers, and he published the first paper describing the synthesis of FDG. By 1975, FDG was

successfully synthesized at BNL. Soon after successful synthesis, an Investigational New Drug Application was filed with the FDA in order to continue toward the use of FDG in human studies (Alavi).

As the research of FDG synthesis at BNL progressed, investigators at Penn had assembled had assembled a set of high-energy collimators to equip the Mark IV scanner to be able to image 511 KeV gamma rays from positron annihilation. By 1976, researchers from both Penn and BNL were planning the first human studies to be conducted at BNL. In August of 1976, two normal volunteers were given a dose of FDG, which was shown to concentrate in the brain by detecting only one of the two coincident rays from the annihilation reaction (Alavi). Image quality was poor, but the investigators had achieved their goal. In addition, a whole body image of the subjects was obtained using a dual head Ohio-Nuclear Scanner, which was equipped with high-energy collimators for srontium-85 bone studies (Alavi).

Also during this time, Michel Ter-Pogossian directed a group consisting of Michael Phelps and Edward Hoffman at Washington University, which developed the first successful Positron Emission Tomography machine (Alavi). Phelps, Huang, Hoffman, and Kuhl obtained the first PET images with FDG at UCLA (Nutt 7). They used the ECAT II and employed the Sokoloff tracer kinetic model to measure rate constants for FDG. In Germany, Hamacher, Coenen, and Stocklin developed a more efficient synthesis of FDG using a nucleophilic reaction, which continues to be the preferred method of synthesis today (Nutt 7).

Based on observations made by Warburg in the 1930s, Som and his group at BNL were able to show a substantial concentration of FDG in tumor models in animals. Dr.

Dichiro and colleagues at NIH were later able to investigate metabolic activities of brain tumors in humans (email Abass). The degree of FDG uptake correlated with the severity of the tumor and became used as a predictor of diagnosis (Alavi). By the mid 1980s, FDG-PET testing was noted as being a better indicator than contrast-enhanced CT and MRI in differentiating recurrent tumors from radiation necrosis (Alavi). Throughout the 1980s, whole body PET imaging was validated, and by the early 1990s, it became known as an effective modality (Alavi).

Cyclotrons and Modern PET

In the early 1980s, George Hendry of The Cyclotron Corporation (TCC) led a team that included Fred Ramsey, Lewis Carroll, and Maria Straatmaan (Nutt 8). In 1983, The Cyclotron Corporation was unable to continue operations due to financial problems (Nutt 12). CTI contracted with the Bankruptcy Court in order to finish two of the 40 MeV, negative ion cyclotrons designated for neutron cancer therapy and a 30 MeV for Ed Coleman of Duke University (Nutt 12). In 1985, CTI bought The Cyclotron Corporation and assigned George Hendry a team to design a dedicated, self-shielded, negative ion cyclotron for use in the hospital environment (Nutt 12). The first of these mini-cyclotrons, Radioisotope Delivery System (RDS112) was delivered to Jerry Nickles at the University of Wisconsin in 1986. RDS112 was an 11 MeV, negative ion, proton cyclotron that had four target ports (Nutt 8). The ion beam could be split and extracted simultaneously on two of the ports. The RDS could make fluorine-18, carbon-11 gases, oxygen-15 water, oxygen-15 gases, and nitrogen-13 ammonia (Nutt 8).

Bruce Wieland joined the RDS team as the target designer in 1985 (Nutt 8). Henry Padgett, a Ph.D. postdoctoral student working with Jorge Barrio and Nagichettiar

Satyamurthy of UCLA, also joined the RDS team. Wieland developed the first high yield miniaturized targets. Barrio, Padgett, and Satyamurthy developed the first automated chemistry module for synthesizing FDG; it was controlled by an IBM personal computer (Nutt 9). Currently, there are several companies that provide small cyclotrons with automated chemistry for producing medical imaging radiotracers (Nutt 8). These companies include General Electric, Scanditronix, IBA, and EBCO (Nutt 9).

Cyclotrons designed for modern PET facilities accelerate negative ions (usually H^-), which are produced, by an ion source at the center of the two dees. An accelerating voltage is applied and the negative ions move back and forth between the dees. A strong magnetic field applied at right angles to the plane of the dees keeps the ion in a circular path, which increases in diameter over time. Two electrons are stripped from the H^- as they eventually pass through a thin carbon stripping foil located at the edge of the dees (Maisey et al. 5). The remaining H^+ are directed by the magnetic field to a target material where a nuclear reaction is to occur. Relatively low energies are needed for PET facilities with a maximum of 11 MeV sufficient to produce adequate yields of common radionuclides (Maisey et al. 7).

Fine Tuning

In 1984, Scanditronix designed a tomograph with one BGO crystal and one Gadolinum Orthosilate (GSO) crystal on the same photomultiplier (Nutt 9). With different scintillation times, the crystal producing the decay event could not identified, and this technique encouraged a search for optical multiplexing schemes that would permit the use of several small scintillator pixels on the same photomultiplier (Nutt 9).

At MGH, Burnham, Brownwell, and others developed a tomograph very similar in concept to the Anger camera (Nutt 10). Its design had scintillators placed on a circular lightguide with photomultipliers on the opposite side (Nutt 9). Charlie Burnham showed that taking the ratio of two adjacent photomultiplier signals, the scintillator that detected the gamma ray could be identified (Nutt 10).

In 1984, Mike Casey and Ronald Nutt visited MGH from CTI and decided that the Burnham detector would be difficult and expensive to manufacture (Nutt 10). However, they were able to simplify the design with thirty-two crystals for four photomultipliers, which they called the Block Detector (Nutt 10). Since 1985, nearly all dedicated tomographs are based on this technique from the Block Detector (Nutt 10). Todays detectors use up to 144 crystals per photomultiplier (Nutt 10).

Commercialization

Scanditronix and EG&G ORTEC were the only major suppliers of PET tomographs during the early 1980s (Nutt 11). By 1984, EG&G ORTEC had decided to extend its ECAT business to a new company called Computer Technology and Imaging (CTI) (Nutt 11). Michael Phelps and part of his team from Washington University and Mike Crabtree, EG&G ORTEC's ECAT Product Manager, were the principal founders of CTI (Nutt 11). The commercial commitment to PET began as twenty-two engineers and technicians from EG&G ORTEC joined CTI in the spring of 1984 (Nutt 11).

Also during this time (1983-1984), Nazar Mullani, Lance Gould, and others from the University of Texas, formed Positron Corporation and introduced the a time-of-flight tomograph, the Posicam, which used barium fluoride as the scintillation detector (Nutt 11). The Posicam was noted for having a very fast data collection time and was sold

primarily to researchers interested in cardiac imaging (Nutt 11). Later, CTI and Squibb introduced rubidium-82 with an automated infusion system, and the Posicam's barium fluoride scintillation detector was replaced with BGO (Nutt 11).

In 1986, Siemens began distributing CTI PET tomographs with RDS cyclotrons (Nutt 13). In 1987, Siemens and CTI entered a joint venture to develop, manufacture, and market PET equipment (Nutt 13). They called this entity, CTI PET Systems, Inc. (Nutt 13). This relationship continued through the 1990s with CTI later purchasing the RDS cyclotron from the joint entity (Nutt 13).

The use of PET changed from more research based to clinical applications as General Electric (GE) entered this field of imaging. GE purchased the tomograph business from Scanditronix as they entered the PET industry in 1986 (Nutt 13). GE designed its own PET tomograph that was manufactured in the USA, and also developed automated chemistry with cyclotron systems with central control (Nutt 13).

Practical Applications

Cancer, becoming more and more prevalent, is one of the areas that PET's use has become extremely valuable. The most effective way to cure many cancers is through surgical excision. However, many cancer patients show extremely low survival rates after surgery because the cancer has spread to other regions of the body. One of PET's most significant contributions to health care is in the area of reducing unnecessary surgeries (Maisey et al. 36). Not only can PET reduce the cost of avoiding these unsuccessful surgeries but it also provides a method of monitoring metabolic response to treatments such as chemotherapy and radiation therapy (Maisey et al. 36). Through these

alternative treatments and PET monitoring, physicians can make better decisions as to when and if a patient should go for operation.

In the field of oncology, the metabolic information obtained from PET complements much of the anatomical information obtained from CT and MRI. PET can distinguish metabolically active tissue from scar tissue. Through the use of different radiopharmaceuticals, PET has the potential to assess the function of different tissues. Also, PET has the ability to provide quantitative measurements of metabolic activity. PET has the ability to detect change in a mass before there is a detectable change in size. Also, detection in PET scanning is dependent on the intensity of the signal rather than the size of the mass (Maisey et al. 37). All of this complementary information obtained from PET is increasing the accuracy of diagnosis and the effectiveness and efficiency of treatment.

In addition to an elevated glucose metabolism, many amino acids and DNA precursors are overtransported and overutilized by cancers (Maisey et al. 42). However, other than FDG, carbon-11 L-methionine is the only agent extensively applied to clinical cancer imaging (42). This tracer has been used in brain tumor imaging, head and neck cancer imaging, lymphomas, and lung cancers (42). As research in tumor physiology continues, PET tracers can be developed for specific cancers improving the accuracy of diagnosis.

PET has also come to be an important diagnostic in the field of cardiology. Coronary artery disease is an increasingly common problem and is placing rising demands on healthcare resources. Patients with ventricular failure often undergo expensive, unsuccessful revascularization procedures. However, with PET imaging,

physicians can make better decisions as to the possible benefits that patients with impaired left ventricular function can gain through revascularization, medical therapy, or transplantation (Maisey et al. 301).

The amount of hibernating myocardium is the most important determinant for functional recovery following revascularization. The amount of hibernating myocardium correlates inversely with prognosis. PET flow and metabolism studies are becoming a standard as to determining the amount of hibernating myocardium (Maisey et al. 301). PET's uses extend beyond cardiology and oncology. As more and more tracers are developed that mimic the physiology of the body, physicians will be able to acquire more information about a number of health questions.

Conclusion

From the discovery of the positron to the development of computed tomography, Positron Emission Tomography has developed through a number of different disciplines. Years of discoveries, observations, and experiments have all contributed to PET's development. PET has already made a profound impact on cancer and cardiology diagnosis, and it seems to becoming more useful at a rapid rate. As computers become more powerful and more radiotracers are developed, the potential for diagnosis using PET seems almost limitless.

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