SPECIAL CONTRIBUTION

A Brief History of Positron Emission Tomography

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"The true delight is in the finding out, rather than in the knowing." —Issac Asimov

Shortly before the time of this writing, Michael Ter-Pogossian, PhD, passed away at the age of 71. He was considered by many to be the father of PET and is best known for experiments beginning in the 1950s, which led to the development of PET as a practical diagnostic tool (Fig. 1). In my research of the literature for this article, Dr. Ter-Pogossian's name appeared frequently on many of the landmark publications and I have drawn heavily from his work as a historian and scientist. His death is a great loss to the nuclear medicine community. It is with his achievements in mind, as well as the achievements of many other outstanding scientists, that I have written this article. I have tried to be as accurate as possible in my documentation of events as well as in my interpretation of their significance. I trust that the reader will gain as much as I have from this endeavor.
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PET is a nuclear medicine procedure which takes advantage of the unique signal produced by the annihilation of a positron and an electron yielding two photons of 511 keV traveling in nearly opposite directions. If the two photons are detected in coincidence, the origin of the event is known to lie within a well define cylinder between the detectors. This electronic collimation eliminates the necessity for absorbing type collimators present on single-photon imaging devices, resulting in some distinct advantages: (a) higher contrast and resolution, (b) detection sensitivity independent of the depth of the activity in tissue, and (c) the ability to correct for the attenuation of the radiation signal. Contemporary PET cameras consist of a series of detector rings which produce tomographic images by reconstructing the distribution of radioactivity from measurements taken at different angles, similar to that used in computerized axial tomographic (CT) imaging.

In addition to the physical characteristic mentioned above, many positron emitting radionuclides exhibit chemical proper-

ties that are useful for the study of physiologic processes. The most widely used radionuclides in PET are cyclotron produced such as ^{18}F, ^{11}C, ^{15}O and ^{13}N with half-lives of 109.8, 20.0, 2.0. and 10.0 min, respectively. These are isotopes of elements that are abundantly present in nature and can be incorporated into the organic compounds without significantly altering their structural or biological properties. For example, ^{11}C can be incorporated into acetate or palmitate and will be metabolized by the myocardium in the same manner as the unlabeled natural substrate (1). Also, ^{82}Rb is widely used as a myocardial flow agent and is available through a generator infusion system.

HISTORY

The history of PET started shortly after the moment of creation, the Big Bang. Cosmologists hypothesize that all matter in the universe was contracted into an infinitely small space called a singularity and then exploded producing an enormous fireball at a temperature of 100 billion K. During the very early stages ($t = 10^{-2}$ sec) of this cosmic fireball, the universe was dominated by a great density of energy in the form of radiation. The density was so great that there was an energy equivalent of an electron-positron pair in a volume of space corresponding to the size of electron-positron pair. Newly created beta particles would immediately annihilate creating gamma radiation after the equivalence of energy and matter formula, $E = mc^2$. The energy state was continually alternating from electromagnetic radiation to electrons, positrons and back again to radiation. Not until the universe had expanded, ($t = 4$ min) and hence cooled was it possible for the heavier particles, protons and neutron to exist (2). From this boiling sea of nuclear reactions emerged positrons, electrons and the annihilation radiation signal used by today's PET systems.

The development of PET in more modern times took place in phases as a result of advances in physics, mathematics, chemistry, computer science and fundamental biology. Most of these advances were accomplished independently but drove the progress of the other. There were three significant phases in which important advances were made (3).
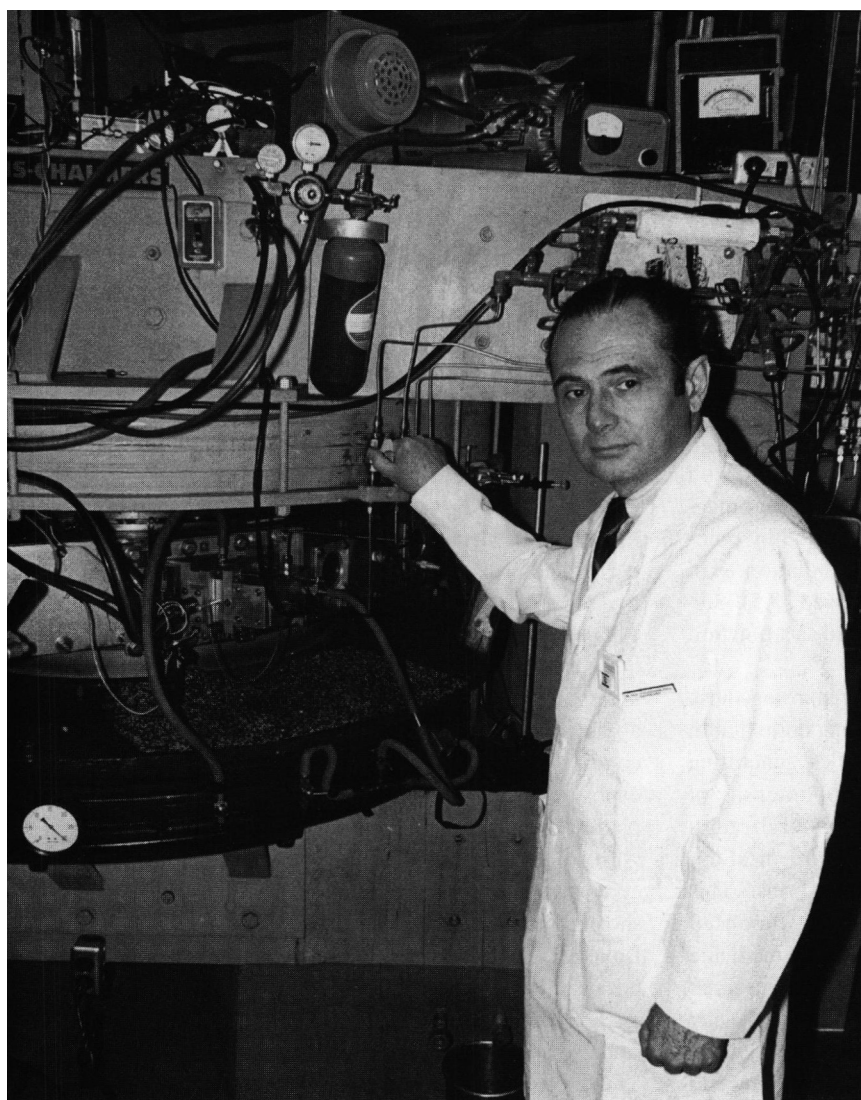
FIGURE 1. Michel M. Ter-Pogossian in the late 1960s. Dr. Ter-Pogossian was a member of the Institute of Medicine of the National Academy of Sciences. During his career he was a recipient of both the SNM Paul C. Aebersold Award for outstanding achievement in basic science in nuclear medicine and the Hevesy Nuclear Medicine Pioneer Award. (Photograph courtesy of the Mallinckrodt Institute of Radiology, Washington University Medical School, St. Louis, MO).

Phase one, late 1920s to the late 1940s: The discovery of the positron and artificial radiation, invention of the cyclotron, recognition that the radionuclides ^{11}C, ^{13}N, ^{15}O as well as ^{18}F were important for the tracing of important biochemical pathways and lastly, invention of the scintillation detector.

Phase two, mid-1950s to the early 1970s: The first installation of a cyclotron in a medical center, use of ^{15}O in biomedical studies, development of single-photon tomography, development of different types of positron scanning devices and development of CT using x-rays.

Phase three, mid 1970s to the present: The development of a positron detection tomograph that incorporated the fundamental features of modern day PET systems, the synthesis of the numerous PET compounds including, 2-[^{18}F]fluoro-2-deoxy-D-glucose and the evolution of the self shielded negative-ion cyclotron for medical uses.

PHASE ONE

In 1929, the physicist Paul Dirac published a paper titled, "A Theory of Electrons and Protons," in which he found two solutions to the equation he was working with that described the behavior of the electron (4). One solution corresponded to the electron, which carried a negative charge and one to a then unknown particle carrying a positive charge. Dirac thought that this positive charge might represent the proton. However, he argued against ignoring the unwanted solution to the equation and stated, " Further, in the accurate quantum theory in which the electromagnetic field also is subjected to quantum laws, transitions can take place in which the energy of the electron changes from a positive to a negative value even in the absence of any external field, the surplus energy, at least 2 mc^2 .... " He also noted that the laws of conservation of energy and momentum would require at least two light-quanta to be simultaneously formed (4).

Other physicists doubted Dirac's calculations were telling them anything significant about nature and thus ignored the unwanted solution (2). This may be explained, in simplicity, by the example of a quadratic equation which ends up with the square root of a number, one being positive and one negative. For example the square root of 9 is both +3 and −3 as each

multiplied times itself equals 9. It was not until 1932 that the concept of the positron was postulated by Carl Anderson while studying cosmic ray interactions with a cloud chamber (5). While investigating the influence of a magnetic field on the trails left by cosmic rays, Anderson found some trails were bent by exactly the same amount but in the opposite path of the electron. This was of great significance to him, as only a particle with the identical mass but opposite charge of an electron could act in such a way. Anderson called these particles antielectrons or positrons which was then confirmed to be the same particles predicted by Dirac's equation. This novel piece of work earned Anderson his Nobel Prize and in 1933 Dirac and Erwin Schrödinger received the prize for the prediction of this new particle.

In 1934, Irene Curie and Frederick Joliot were credited with the discovery that three elements, aluminum, boron and magnesium, when bombarded by alpha particles emitted by polonium, continued to be sources of penetrating radiation even after the alpha particle sources had been removed (3,5). Significantly, the intensity of this radiation decreased as a function of time.

Marie Curie made the following statement regarding these newly discovered radio-elements: "One could only hope that in the future one could obtain by means of tubes generating accelerated particles radio-elements of which the intensity of the radiation would be comparable to that of natural radio-elements. These new substances could then have medical applications and also probably other practical applications." This statement was prophetic as the use of artificially produced radio-elements has formed the foundation of nuclear medicine and proved to be an important tool in biomedical research (3,5). It is interesting to note that one of the first artificially produced radionuclides was ^{13}N which was generated by the nuclear reaction $^{10}B + {}^{4}He = {}^{13}N + {}^{1}n^{1}$. This radionuclide which decays with the emission of positrons, is commonly used today in the form, $[^{13}N]NH_3$ as a myocardial perfusion agent.

Motivated by the discovery of this new phenomena, investigators at the University of California in Berkeley used their recently developed cyclotron to produce artificial radionuclides in quantities meaningful to the performance of biological experiments. The cyclotron was developed by Ernest O. Lawrence while at Berkeley between 1930 and 1936 with the intent of transmuting elements. At the time there wasn't any thought given to the production of radionuclides. Ironically, it was only after the news of Irene Curie's and Frederic Joliot's findings that the Berkeley group realized that the transmutations produced by the accelerations of ions in their cyclotron often produced radioactive substances (3).

While numerous radionuclides were produced by the Berkeley positive-ion cyclotron, it was ^{11}C, ^{13}N and ^{18}F that received most of the recognition as useful radio-markers for biological studies. In 1939, researchers at the University of California published a preliminary report on the reduction of carbon dioxide by green plants, particularly sunflower, barley and wheat using the radionuclide ^{11}C (6). This work was extended in 1940 to green alga, *Chlorella pyrenoidosa*, which was more suited to the quantitative experimentation of photosynthesis.

The group allowed the plants to grow in an atmosphere of $[^{11}C] CO_2$ in the presence and absence of light. They were able to demonstrate that a reversible carboxylation reaction was the initial step of photosynthesis. Ruben's group also used ^{13}N to study nitrogen fixation by nonlegumenous plants. Cramer and Kristiakowsky labeled ^{11}C to lactic acid to study the synthesis of liver glycogen (7). Fluorine-18 was used to study the absorption of fluorides in dentine enamel and bone by Volker et al. (8) and the secretion of intravenously injected fluorine in the saliva of cats by Willis (9).

Possibly the first use of positron-emitting radionuclides in humans was by Tobias, Lawrence, Roughton, Root and Gregersen in 1945 (10). This group used ^{11}C labeled to carbon monoxide to study its fate in man. Several subjects inhaled $[^{11}C] CO$ followed by the inhalation of 100% oxygen. The exhaled $[^{11}C] CO_2$ was collected in soda lime while at the same time measurements over the thigh, chest, spleen and liver were performed using a Geiger-Muller counter. The results showed that most of the radioactivity was recovered in the subjects exhaled breath indicating that carbon monoxide uptake in the body is reversible. It is interesting to note that these experiments not only had a theoretical significance but a practical application as World War II was being waged and there was concern about the possible deleterious effects of prolonged exposure to carbon monoxide by soldiers working in tanks, planes, cargo ships, submarines etc.

In spite of the intense activity to produce radionuclides in cyclotrons, there was skepticism regarding the usefulness of the shorter half-lived ^{13}N and ^{15}O as tracers. In "Isotope Tracers in Biology", Kamen states, "Because of its short half-life and because it must be produced by a (d,n) reaction involving the installation like a cyclotron, ^{13}N is too restricted in application to be considered of importance as a tracer for nitrogen." (11). Kamen went on to say, "No radioactive isotope of oxygen is sufficient long lived to be useful in tracer work." E.L. Dougherty confirmed this feeling and wrote in "Isotopic Tracers in Nuclear Radiation" that ^{13}N was not a promising agent despite excellent cyclotron yields as it had very limited biological applications and he thought even less of the usefulness of ^{15}O because of its 2-min half-life (12).

There was only a limited use of ^{11}C, ^{13}N, ^{15}O and ^{18}F during the mid 1940s to the early 1950s, perhaps because the discovery of ^{14}C offered a more flexible label than ^{11}C for biological experiments (3). Other radionuclides such as ^{131}I became available with the development of the nuclear reactor during the Manhattan project, and interest shifted in that direction. This marked the end of the first phase in PET's history as the use of short lived cyclotron-produced radionuclides was considered impractical for biomedical research (3).

It is of historical significance to note the G-M counter was the predominant instrument used for the external detection of gamma rays. This device was relatively insensitive to the detection of higher energy gamma photons and would have been unsuitable for the detection of 511 keV photons. Fortunately, the groundwork for a better detector was accomplished at the turn of the century by Ernest Rutherford who visually counted the scintillations produced by interactions of alpha particles

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with zinc sulfite crystals. Heinz Kallman reported in 1948 that photomultiplier tubes could detect these scintillations individually and amplify them for electronic counting. By 1949 Cassen, Curtis and Reed reported the use of calcium tungstate as a detector for higher energy gamma photons (13). The resulting development of the scintillation detector during this period was crucial for the later advancement of dual- and single-photon cameras.

PHASE TWO

By 1950 there was renewed interest in the use of short-lived cyclotron produced radionuclides mainly because of the work started by Ter-Pogossian and co-workers at Washington University in St. Louis. Initially, the group used ^{15}O for the study of oxygen tension in malignant neoplasms in mice using autoradiographic techniques (3,14). This effort led to the utilization of ^{15}O-labeled oxygen and other radioactive gases for respiratory and cerebral metabolic studies. Their results were promising enough to lead to the installation of a cyclotron at the Washington University Medical Center during the early 1960s. The cyclotron was installed specifically for the production of short-lived radionuclides for in vivo metabolic studies. The early experiments performed by Ter-Pogossian motivated researchers at Hammersmith Hospital in London to also work with short-lived radionuclides produced by their cyclotron, the first to be commissioned, (1955) in a medical center (3). Later, other centers such as Massachusetts General Hospital in Boston and the Sloan Kettering Institute in New York installed small cyclotrons dedicated to the production of the short-lived, positron emitting radionuclides. Older existing cyclotrons at the University of California at Berkley and at Ohio State University were also being used for this purpose. This activity was driven by the recognition that the majority of the metabolic processes important to sustaining life, occur within a short enough time interval to be traced by the short-lived radionuclides. Additionally, chemists became interested in labeling important physiologic molecules with these nuclides and developed rapid procedures to synthesize the compounds (3).

It is of interest to note that in 1966, Ter-Pogossian and Wagner published an article in *Nucleonics* titled, "A new look at the cyclotron for making short-lived isotopes" (15). The authors argued that, short-lived isotopes had the optimum half-life, decay characteristics and chemical properties needed for medical and biochemical research. Additionally, they promoted the cyclotron as being cost effective with the flexibility to produce isotopes in large quantities. The joint effort by these two noted scientists was indicative of the activity and excitement surrounding not only nuclear medicine but the promise of PET during this time period. This early work by Wagner and Ter-Pogossian helped the evolution and proliferation of the more practical negative-ion cyclotron so important to the future of PET.

Several investigators exploited the distinct advantages inherent to the detection of annihilation radiation over single photon imaging. In 1951 Wren, Good and Handler first reported on the possible use of opposing thallium-activated sodium

iodide detectors, (NaI(Tl)) for the localization of ^{64}Cu-phthalocyanime in brain tumors (16). Wren hypothesized that, because it was known that two quanta emerged simultaneously and in opposite directions, (to within precision of 1/137 radian), if the two quanta could be counted in coincidence, the source of the activity must lie somewhere along a straight line joining the detectors. From experiments comparing single photon to dual-photon detection he concluded: "Thus, it appears possible to more accurately delimit point sources, and hence extended sources with the technique of coincidence counting of annihilation pairs." Brownell and Sweet had been working independently on the same problem. In 1953 they reported on a positron scanner also designed for the localization of brain tumors (17). This device consisted of two sodium iodide detectors mounted collinearly on an adjustable platform which moved in a rectilinear fashion. A printing mechanism recorded the coincidence counting rate on carbonized paper. Brownell thought there were few light element, positron emitting isotopes, with appropriate half-lives. He listed as the most suitable: ^{48}Va, ^{52}Mn, ^{64}Cu, ^{74}As and ^{84}Rb. All of these had half-lives on the order of days or weeks with the exception of ^{64}Cu. His thinking was logical as the equipment being developed at the time, although using coincidence detection for collimation, lacked sufficient sensitivity to satisfactorily image the short half-lived, physiologic nuclides.

In an attempt to improve sensitivity and resolution, different designs of positron cameras were developed. In 1962, Rankowitz et al. designed a positron scanner which consisted of a ring of scintillation detectors (18). The system imaged transverse tomographic distributions for the localization of brain tumors. Although the system was limited by under-sampling and the lack of attenuation correction, it did demonstrate the advantages of electronic collimation and its application to tomographic imaging. Kuhl and Edwards reported in 1963 on the development of a tomographic scanner designed to image single photon gamma ray emitters (19). Their early work clearly demonstrated the advantages of tomographic imaging and they concluded, "With section radioisotope scanning, the images of the body structures should be more clearly defined, and more useful information should be obtained from the study of the liver, brain, thyroid gland and other organs." Even though Kuhl and Edwards' work is linked primarily to single photon systems, their efforts also promoted the usefulness of tomography for dual-photon systems.

Anger and Gottschalk also reported in 1963 on the design of a positron camera for brain tumor imaging (20). The system used an 11.5 inch diameter sodium iodide crystal with an opposing compound coincidence detector consisting of 19, 1.75 in. crystals. No collimators or mechanical scanning motion was required and the large crystal permitted the entire brain to be encompassed in one image. The authors reported that the system provided high sensitivity (500 dots per min per μCi), and sharp focus within a predetermined plane. Importantly, the sensitivity was approximately 20 times the average rate per μCi than ^{203}Hg, when used with a 19-hole focused collimator under identical conditions. The system was used to image brain

tumor concentrations of ^{68}Ga labeled EDT and was the first application of coincidence detection using a gamma camera.

In 1970 Burham, Aronow and Brownell developed a hybrid positron scanner which used an array of nine crystal pair detectors arranged in columns and moved in a rectilinear fashion. Data was stored on magnetic tape and replayed into an oscilloscope for a timed camera exposure to generate the resultant image (21). The device was intended primarily for brain imaging but was envisioned as the first in a series of multidetector instruments for positron scintigraphy of various organs. The authors stated, "We hope that these devices will greatly advance the application of the short-lived nuclides (e.g., ^{15}O, ^{13}N, ^{11}C), with half-lives from 2–20 min." This represented a shift away from the their original position that, only the longer-lived radionuclides mentioned earlier were of potential use. Ter-Pogossian's successful work using oxyhemoglobin labeled with [15]O may have provided the motivation for their change in attitude (3,22). In spite of the short half-life of [15]O (120 sec), Ter-Pogossian and his co-workers demonstrated that regional cerebral oxygen utilization could be reliably measured with external counting devices and stated, "In fact, the short half-life of this label is considered desirable because, in many instances it can be administered in large quantities affording good counting statistics with relatively low exposure of the patient to radiation."

During the early 1970s Ambrose and Hounsfield described a technique in which radiograph transmission measurements were acquired through the head at multiple angles (23). From these measurements, absorption values of the tissue density within the head were calculated by a computer and displayed as a series of tomographic slices. By obtaining the absolute values of the tissue's absorption coefficients, tissues of similar density could be separated increasing the sensitivity for the detection of soft tissue abnormalities by approximately two orders of magnitude. The first computerized transaxial tomograph was introduced by EMI Company of England and was of great significance to Radiology and helped to propel PET into its third phase.

PHASE THREE

Instrumentation and radiochemistry characterized the two tracts of rapid development during this period. Advancements built on the momentum generated during the late 1960s and early 1970s. Initially, developments in PET instrumentation were of the greatest significance. These developments were motivated by the recognition that, the positron signal proved to have numerous advantages over conventional radiation, especially for tomographic imaging. Furthermore, as mentioned above, the short-lived radionuclides were confirmed to be important tracers for the study of many physiologic processes.

Between 1972 and 1973 the Washington University group of Phelps, Hoffman, Mullani and Ter-Pogossian built a device, (dubbed PETT II), which used annihilation coincidence detection to generate reconstructed transaxial tomographs (24). The unit consisted of a hexagonal array of 24 NaI (Tl) detectors mounted on a horizontal support. Examined objects were

placed on a computer-controlled turntable at the center of and perpendicular to the plane of the hexangle. Measurements for attenuation correction were made by placing a thin plastic ring filled with ^{64}Cu around the object. Tomographic images were reconstructed using a Fourier-based approach developed at Washington University, rather than the algebraic base method used on the early CT scanners. Phantom and animal studies demonstrated that this device provided: (a) high spatial resolution that was solely a function of the exposed detector diameter; (b) resolution and sensitivity that were essentially depth independent; and (c) attenuation correction in the reconstructed image that was simple and accurate. Even though the PETT II had humble beginnings, initially constructed in Mullani's garage (Mullani N, *personal communication*, 1996) it proved to be the foundation for the evolution of PET tomographs.

By 1975 the prototypical PET (II) was expanded to the clinically applicable PET (III) whole-body camera reported by Ter-Pogossian et al. (25). It consisted of 48 NaI (Tl) detectors placed in a hexagonal array with eight detectors on a side. The detector assembly scanned simultaneously in linear and rotational directions for the necessary linear and angular sampling of data. Data were reconstructed by a convolution based algorithm to generate cross-sectional images of the radionuclide distribution. As its name implies, the detection field of view was large enough to accommodate any position of the human body. The unit exhibited sufficient detection efficiencies to complete scans in 2–4 min with 500,000–2,000,000 counts collected from 10–15 mCi of injected material. This capability was important for the imaging of ^{11}C, ^{13}N, [15]O labeled compounds. PET (III) was used extensively for both patient and animal studies at Washington University and later at Brookhaven National Laboratory.

The PET II and III instruments incorporated the fundamental features of modern PET imaging devices. Success was based in part on the contributions of noted scientists working in the field of both single- (Budinger and Gullberg, Keys and Simon, Oppenheim and Harper, Todd-Pokropek, Kuhl and Edwards) and dual-photon instrumentation [Phelps, Mullani, Ter-Pogossian, Hoffman, Brownell, Chesler and Cho (26)]. The coincidental development of mini-computers contributed substantially to the success of the PET (III) as well as future PET and single photon imagers. These computers were cost effective, capable of solving the large computational problems associated with reconstruction tomography and essential to the advancement of PET instrumentation.

During the late 1970s and 1980s, advancements of PET cameras resulted in the following designs:

1. A system with a single ring of NaI(Tl) detectors was developed by Cho, Chan and Eriksson (27). This design was eventually expanded to multiple rings using the more efficient crystal, bismuth germanate oxide (BGO) reported on by Cho and Farukhi (28). BGO represented a significant improvement over NaI(Tl) because (a) it had twice the density allowing smaller crystal size, (b) it had a

comparable scintillation decay constant, (c) it was relatively inert and hydroscopic and (d) it had three times the detection efficiency.

2. Mullani, Ter-Pogossian and co-workers investigated and constructed ring detectors using the faster scintillating crystal, cesium fluoride and a time-of-flight detection scheme (29,30). These systems were designed specifically for fast dynamic studies of the brain and heart using the short half-lived ^{15}O and ^{82}Rb, respectively. Please see Appendix A for a further explanation of this technique.

3. In 1976, Muehllehner, Buchin and Dudek introduced a system which used two opposing Anger gamma cameras for the coincidence detection of positron emitters (31). Their design consisted of one inch thick NaI(Tl) crystals shielded by a set of thin absorbers (1.27 mm lead and 0.76 mm tin) intended to transmit most of the 511 keV signal while filtering out the scatter radiation from the patient. Projection data was obtained by rotating the detectors around the object. Their system had the advantage of a large axial field of view and a lower cost as compared to the ring design which used multiple small detectors. However, the sensitivity of this design was limited by the necessity for angular rotation.

The evolution of PET system geometry can be characterized by three basic designs: (a) planar, (b) polygonal and (c) stacked circular rings. Typical of PET's history, there were many other contributors who share credit for the success of these designs, including Derenzo (32), Lecomte (33) and Burnham (34). Today the most commonly found systems use either hexagonal or circular geometry with small BGO detectors and emphasize high resolution.

Contemporary systems have evolved to provide (a) spatial resolutions of 4–5 mm, (b) large axial fields of view (greater than 15 cm) and (c) three-dimensional imaging capabilities. Three-dimensional imaging refers to the ability to retract the lead septa housed between detector banks so that all detectors are in coincidence with every detector in all planes of the imaging system. Although dramatically improving sensitivity, this "wide open" imaging strategy also increases the acceptance of scatter and random events adding to the image noise. In spite of this, three-dimensional imaging has demonstrated usefulness in low count studies. These elegant instruments are the end result of many other unmentioned contributors from the related fields of mathematics, computer science, engineering and physics. The future may see PET tomographs that reach the theoretical limit of resolution (approximately 2 mm), provide even better sensitivity and, as temporal resolution improves, incorporate time-of-flight information.

As the progress of PET cameras accelerated so did the complimentary applications of PET radiochemistry and biology. During this period, chemists had become motivated to rapidly label increasingly complex molecules. In 1980, Ter-Pogossian, Raichle and Sobel published an article in Scientific American (35) in which they listed 30 compounds labeled with either ^{15}O, ^{11}C, ^{13}N or ^{18}F. Today that list has expanded to several hundred. Probably the most widely used compound to

be synthesized was [^{18}F]FDG, an analog of glucose. Fluorine-18-FDG is transported to tissue and phosphorylated to FDG-6-phosphate in a similar fashion as deoxyglucose or glucose. However, unlike glucose it is trapped as FDG-6-phosphate. This compound resulted from the development of [^{14}C]deoxyglucose (DG) and was extensively used by Louis Sokoloff and others to study the energy metabolism of the brain. In 1978, Ido et al. (36) first successfully synthesized [^{18}F]FDG and since that time much refinement of the process has been accomplished. Fluorine-18-FDG is now routinely synthesized using the "black-box" technology developed by Padgett (37). There has been much interest in using ^{18}F as a label for it is readily produced in cyclotrons, has a reasonably long half-life and possesses properties that are compatible for monitoring many biological processes. Today, over 100 radiopharmaceuticals have been synthesized using ^{18}F.

Sokoloff and his co-workers not only validated [^{14}C]DG as a marker for cerebral glucose metabolism, but in 1977 also developed a comprehensive mathematical model for the measurement of cerebral glucose metabolic rate using [^{14}C]DG (38). Since PET provides unique capabilities for the noninvasive quantification of biological processes, it was natural for Phelps and his colleagues in 1979 to extend the principles established by Sokoloff to the measurement of cerebral glucose metabolic rate in humans using PET and [^{18}F]FDG (39). The subsequent validation of this model by Phelps allowed for the accurate, in vivo quantification of glucose metabolism using PET technology. At the present time, additional mathematical models have been developed for use with other compounds for applications such as receptor imaging.

An important catalyst to the progress of PET radiochemistry and instrumentation was the coincidental evolution of the cyclotron from the large, high energy, multiparticle, positive-ion to the smaller, more practical, lower energy, single particle, negative-ion type. See Appendix B for an explanation on how the cyclotron works. Early cyclotrons were able to accelerate multiple particles such as, protons (^1H), deuterons (^2H), tritron (^3H) and alpha particles (^4H) up to energies ranging from 15 to 40 MeV. This capability allowed for the production of both the short- and longer-lived radionuclides and, as mentioned earlier, these early cyclotrons were the first to be installed in a medical center. As interest in using the physiologic radionuclides, ^{15}O, ^{13}N, ^{11}C and ^{18}F grew it was recognized that accelerators designed to produce these positron rich isotopes could be constructed, installed and operated at a lower cost. Between 1986 and 1987 CTI Corporation of Knoxville, TN introduced the first cyclotron designed specifically for the production of PET isotopes. These 11-MeV, negative-ion, proton-only units had the following advantages over positive-ion systems:

1. They could be self-shielded and conveniently placed whereas the older units, because of high-radiation levels, needed to be in a room (usually below ground level), with up to 2-meter thick concrete walls.
2. The installation and operating costs were greatly reduced.

3. Serviceability was increased due to the substantially lower radioactivation of their internal parts.
4. They were controlled by PC technology and could be operated by a qualified technologist.

Currently the trend is for even smaller and less expensive cyclotrons. For instance, in 1995, CTI introduced their new "deep valley" design which requires only a single unshielded room, reduced power consumption (67% of their older unit), boasts of a graphic interface providing even more convenient operator control and cost about 40% less to purchase (Odeh N, *personal communication*, 1996). The success of these negative-ion cyclotrons has provided more affordable access to the physiologic radionuclides and will most likely continue to be instrumental to the proliferation of PET centers.

CONCLUSION

PET's inherent strengths, which have been enjoyed by the scientific community, have not been fully recognized by the general medical community as being essential to the health care system. An uncertain future for PET has resulted. This uncertainty can be linked to the following:

1. In most cases, PET requires the presence of an onsite cyclotron.
2. The modern PET tomograph although elegant, is expensive.
3. Third-party reimbursement for clinical studies is not fully actualized
4. There are other competitive nuclear medicine procedures that provide similar information.

These points have not diminished the importance of PET but have merely served to slow its growth. Despite these obstacles, there continues to be strong scientific and clinical interest in PET. At the 1996 SNM Annual Meeting, for example, there were 150 presentations involving [18F]FDG, with 88 presentations in oncology, 49 in neuroscience and 23 in cardiology (40). Other radiopharmaceuticals have shown promise for oncological uses including, [11C]methionine, [18F]fluoroestrodiol and [18F]fluoromisonidazole (41). Work by Gambhir and his colleagues (42) has demonstrated the potential cost-effectiveness of PET. They found that when both [18F]FDG and CT studies were performed for the staging and management of non-small-cell lung carcinoma, there was a saving of $1154 without loss of life expectancy.

The vibrant interest in [18F]FDG has helped to motivate industry to produce Anger-type gamma cameras with coincidence detection capabilities. Two systems are currently on the market and will potentially provide greater access to PET technology by the general nuclear medicine community. This fact coupled with a *regional* cyclotron approach to the distribution of [18F]FDG and other 18F-labeled radiopharmaceuticals, may well serve as the engine which helps drive PET into its fourth phase, a clinically accepted imaging modality.

APPENDIX A

Time-of-flight (TOF) systems take advantage of the fact that if the difference between the arrival times of the two annihilation photons can be measured, then the spatial localization of the event can be estimated. This constrained estimation negates the necessity to spread the localization of the positron source over the entire coincidence line between the detectors improving the signal to noise ratio (43). Since TOF requires very fast temporal resolution, 600–800 psec compared to 5–20 nsec for conventional systems they have the additional advantage of reducing contributions due to random events. This capability is valuable for studies involving very high counting rates.

APPENDIX B

Cyclotrons take advantage of the fact that a charged particle moving at a constant velocity in a plane perpendicular to a homogeneous magnetic field will describe a circle. The radius of the circle is given by:

$$R = mcv/qB.$$

Where m = particle's mass, c = speed of light, v = particle's velocity, q = particle's charge and B = the strength of the magnetic field. In the cyclotron there is a continuous production of ions (charged particles) at a central point located between the two poles of a strong magnet. Between the poles and in a plane perpendicular to the magnet are two hollow box-shaped metal electrodes called dees, which have a high oscillating potential and reside in an evacuated chamber. The ions are attracted or repelled by the dees based on their overall charge. For each transit through the dees, the ions are accelerated, gain velocity and consequently the curved path they follow increases in radius. When the ions reach their maximum energy, just inside the circumference of the dees, they are deflected from their orbits by various means on a path through the beam line and towards the target (43). In the case of a negative ion (a proton with two electrons) cyclotron, the electrons are stripped off by passing them through an electrically charged carbon foil. The result is a proton beam which is then directed toward target material, normally a liquid or gas which undergoes nuclear transformation to create the positron emitting radionuclide.

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