The Origins of Positron Emission Tomography

Michel M. Ter-Pogossian

The development of positron emission tomography (PET) took place through the combination of the following recognitions: (1) a handful of short-lived, positron-emitting radionuclides, carbon-11, nitrogen-13, and oxygen-15, exhibit chemical properties that render them particularly suitable for the tracing of important physiological pathways, and (2) the radiation emitted as a result of the annihilation of positrons in matter exhibited physical properties that made it well-suited for nuclear medicine imaging, particularly for tomographic reconstruction. The scientific building blocks that were necessary for the structure of PET were contributed over a period of several decades by many investigators in physics, mathematics, chemistry, and fundamental biology.

POSITRON emission tomography (PET) is a nuclear medicine imaging modality that consists of the systemic administration to a subject of a radiopharmaceutical labeled with a positron-emitting radionuclide. Following administration, its distribution in the organ or structure under study is assessed as a function of time and space by (1) detecting the annihilation radiation resulting from the interaction of the positrons with matter, and (2) reconstructing the distribution of the radioactivity from a series of measurements taken at different angles, an approach very similar to that used in computed tomography (CT).

PET exhibits some specific characteristics that identifies it within the broader field of nuclear medicine imaging. The only nuclides used in PET decay by positron emission, and their presence in vivo is always detected through the use of the two annihilation radiation by the coincidence detection of the annihilation photons. These nuclides most generally exhibit chemical properties that render them particularly desirable in physiological studies. The radionuclides most widely used in PET are listed in Table 1. Note that oxygen, carbon, and nitrogen are atoms essential to most physiological processes, and fluorine has been found to be a useful analog in physiological tracing as well as an important marker as an intrinsic marker for fluorine. The images yielded by PET are usually displayed as tomographic sections.

The conceptual structure of PET consists of building blocks that were contributed by scientific investigations. These building blocks were generated during the history of artificial radioactivity, and the maturation process of PET has been slow.

Historically, the development of PET can be divided into three phases: (1) the application in physiological studies in the earlier days of artificial radioactivity of a small number of positron-emitting radionuclides; (2) the recognition that a certain number of short-lived, positron-emitting radionuclides exhibit properties that rendered them particularly useful in nuclear medicine physiological studies in spite of some of their shortcomings; and (3) the combined use of the previously mentioned positron-emitting radionuclides with the coincidence detection of the annihilation radiation and the tomographic reconstruction process from projections. On a time scale, the first period extends between the early 1930s to the late 1940s; the second period between the middle of the 1950s to the early 1970s; and the third period from the end of the second to the present (Fig 1).

FIRST PHASE

Before the discovery of artificial radioactivity, the use of radioactive tracers in biology and medicine was severely limited by the physical and chemical properties of naturally occurring radioelements. In 1934, Irene Curie and Frederic Joliot discovered that when exposed to irradiation by alpha particles emitted by polonium, some nuclides—such as aluminum, boron, and magnesium—emitted a penetrating radiation after the source of alpha rays was removed. The intensity of this penetrating radiation decreased as a function of time. It is interesting to note that nitrogen-13, generated by the nuclear reaction $^{10}B + {}^{4}He = {}^{13}N + {}^{1}n^{1}$, was among the very first artificially produced radionuclides. At the time, the half-life of ^{13}N

From Washington University, St Louis, MO.
Address reprint requests to Michel M. Ter-Pogossian, PhD, 510 S Kingshighway Blvd, Box 8131, St Louis, MO 63110.

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Table 1. The "Physiological" Radionuclides

Nuclide	Approximate Half-Life
^{11}C	20.4 min
^{13}N	10 min
^{15}O	120 s

was measured as approximately 14 minutes. The amount of artificially produced radionuclides was severely limited by the intensity of alpha particle fluxes available from naturally occurring radionuclides. The acceleration of ions by the cyclotron, which was developed at the University of California in Berkeley by Ernest O. Lawrence between 1930 and 1936, provided intense sources of accelerated positive ions, which permitted the generation and study of a very large number of artificially produced radioelements. It is a quirk of scientific investigation that, the cyclotron was developed with the purpose of transmutation of elements with no thought of producing artificial radioactivity, and that the discovery of Irene Curie and Frederic Joliot prompted the Berkeley group to note that the transmutations produced by their apparatus led often to radioactive substances.

The abundant availability of radioactive iso-

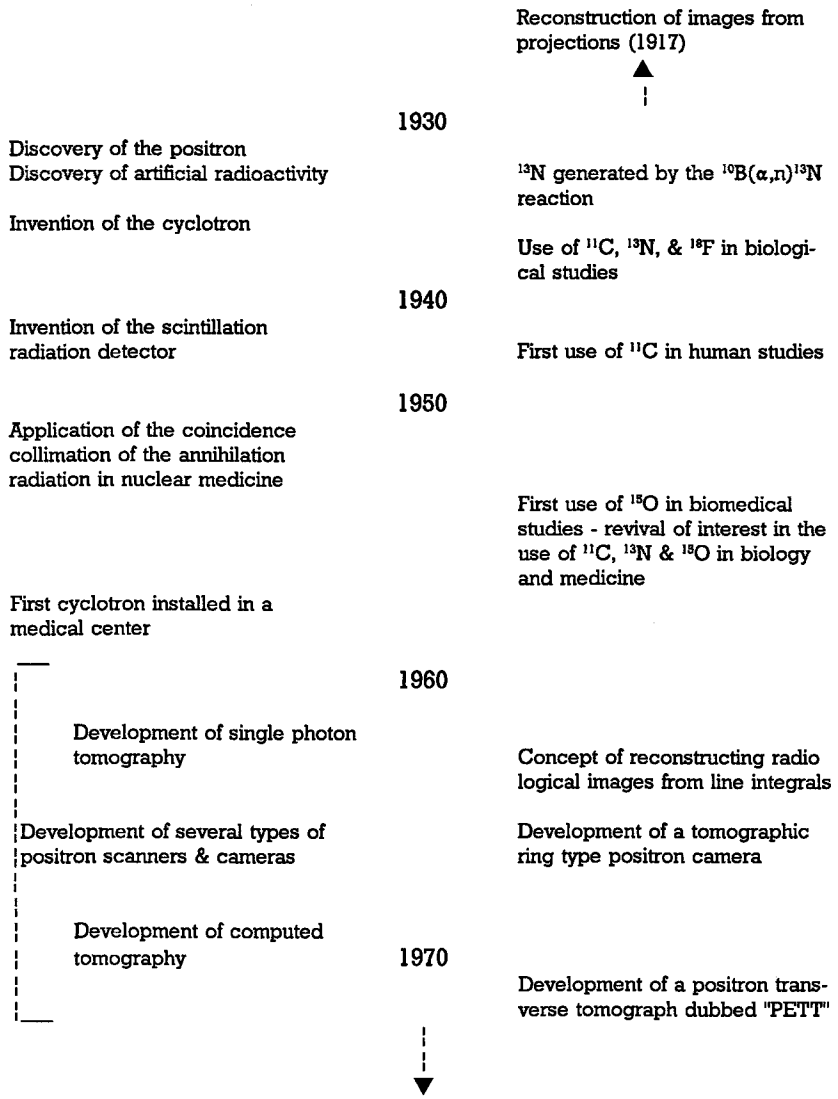

Fig 1. Milestones in the historical development of PET.

topes spread over most of the periodic table stimulated in Berkeley the interest not only in studying these substances but also in using many of them in biological research. In many instances, the interest of these early investigators focused on radionuclides whose physical properties were akin to physiological processes. Several of these radionuclides are those that have provided the foundation for positron emission tomography.

Shortly after the development of the cyclotron in Berkeley, the usefulness of carbon-11, (^{11}C), ^{13}N, and fluorine-18 (^{18}F) as radioactive tracers for biological studies was recognized. In the late 1930s and early 1940s, Kamen[2] used ^{11}C in the study of carbon dioxide use by plants, and Cramer and Kistiakowsky[3] used lactate acid labeled in the 1, 2, and 3 positions for metabolic studies. In the middle 1940s, Buchannan and Hastings[4] used ^{11}C in the study of intermediary metabolism. One of the very early studies, if not the first one, carried out in human subjects by means of ^{11}C was performed by Tobias et al,[5] who used ^{11}C-labeled carbon monoxide to study its activity in man. Ruben et al[6,7] reported on the use of ^{13}N in the study of nitrogen fixation by nonlegumenous plants. Fluorine-18 was used in the early 1940s by Volker et al[8] in the study of the absorption of fluorides by enameled dentine and bone, and by Wills[9] in studying the secretion of intravenously injected fluorine in the submaxillary gland saliva of the cat. In that early period, the investigators most active in using cyclotron-produced, short-lived radionuclides were skeptical of the possible usefulness as radioactive tracers of ^{13}N and oxygen-15 (^{15}O). In *Isotopic Tracers in Biology,*[2] Kamen states "because of its short half-life and because it must be produced by a d,n reaction involving an installation like the cyclotron, N-13 is too restricted in application to be considered of importance as a tracer for nitrogen." In the same reference, "No radioactive isotope of oxygen is sufficiently long-lived to be useful in tracer work." Elsworth C. Dougherty stated in *Isotopic Tracers and Nuclear Irradiations,*[10] "Nitrogen-13 may be made in the cyclotron by the reaction ^{12}C(d,n)^{13}N but it is not a promising agent despite excellent cyclotron yields. It has had very limited biological applications as a tracer." And, in the same reference, "The unstable species of longest half-life is oxygen-15 (126 seconds), this has not been employed for tracer work and does not offer much promise." It is clear now that these early assessments were unduly pessimistic.

Between the middle 1940s and the early 1950s, the interest in using ^{11}C, ^{13}N, and ^{18}F in biomedical studies dwindled, perhaps because the discovery of ^{14}C in 1940 by Kamen and Ruben provided a much more flexible label than ^{11}C for tracing organic compounds. Also, because of the availability of reactor-produced radioelements, the focus of in vivo tracer methodology shifted to other labels, particularly iodine-131. For practical purposes, short-lived, cyclotron-produced, positron-emitting radionuclides became inconsequential in biomedical research between the middle 1940s and the middle 1950s, thus ending the first phase of PET.

SECOND PHASE

In the middle 1950s, Ter-Pogossian and Powers[11] rekindled at Washington University an interest in using, in spite of their short half-lives, short-lived radionuclides for physiological studies. The early phase of this work consisted of using radioactive ^{15}O for the study by autoradiography of oxygen tension in malignant neoplasms. This pioneering effort in the use of ^{15}O led to the use of ^{15}O-labeled oxygen and other radioactive gases for respiratory and cerebral metabolic studies.[12] The short-lived radionuclides were generated in a cyclotron installed at Washington University in the early 1940s for the specific purpose of producing medically useful radionuclides. The results of the above investigations were sufficiently promising to lead in the early 1960s to the installation, with National Institutes of Health support, of a cyclotron in the Washington University Medical Center for the generation of short-lived radionuclides for use in in vivo metabolic studies. These early experiments stimulated active work with short-lived, cyclotron-produced radionuclides, particularly gases, at the Hammersmith Hospital in London, where the first cyclotron in a medical center had been commissioned in 1955 for the general purpose of providing radionuclides for nuclear medicine for radiation therapy and radiobiologic studies.

Encouraged by these early results in the decade following the 1960s, the scope of the use of these short-lived physiological radionuclides grew slowly at first. Their use then grew more rapidly in a number of centers, most notably at the Massachusetts General Hospital in Boston and the Sloan Kettering Institute in New York, where small cyclotrons dedicated to the production of short-lived, positron-emitting radionuclides were installed, and at Ohio State University and the University of California at Berkeley, where older, existing cyclotrons were used. Three early studies were of particular importance in the development of this new tool in biomedical research:

1. It was recognized that the majority of metabolic processes fundamentally important to life occur rapidly enough to be traced by means of the short-lived physiological radionuclides listed in Table 1.
2. A number of chemists became interested in the labeling of molecules of physiological importance with the above mentioned short-lived radionuclides. This interest led to the development of a number of rapid labeling procedures suitable for the incorporation of these short-lived labels into radiopharmaceuticals.
3. In the early days of the use of positron-emitting radionuclide labeling of radiopharmaceuticals, the annihilation radiation was considered to be less than optimal for its detection and collimation because of its relatively high energy of approximately 511 keV. However, during the period under discussion, it was demonstrated that the two annihilation photons traveling nearly colinearly offered substantial advantages in the collimation of this radiation.[13,14] This property of the annihilation radiation was found later to be particularly desirable in the tomographic reconstruction of the distribution of positron emitters. It is well recognized now that the annihilation radiation offers substantial advantages over single gamma ray photons for in vivo nuclear medicine imaging.

The advantages of detecting the annihilation radiation by the coincidence method were exploited by several investigators during that period.[14-16] Positron-emitting, short-lived radionuclides were used in a series of physiological studies including pulmonary, cerebral, and hepatic studies. In these early studies the annihilation radiation was detected by means of scanners, multiprobe systems (Fig 2), and cameras (Fig 3)[17-20] designed specifically for the detection of the annihilation radiation. In the early 1960s, Rankowitz et al[21] developed a positron scanner for the localization of brain tumors. The scanner consisted of a ring of scintillation radiation detectors designed for the coincidence collimation of the annihilation radiation. The system provided transverse tomographic sections of the distribution of positron-emitting radionuclides. Although the quality of the images obtained by this system was limited by sampling data and lack of attenuation correction, the design demonstrated the advantages that could be gained from the combined use of electronic collimation and tomographic imaging in mapping the distribution of positron emitters. In 1963, Kuhl and Edwards[22] developed a nuclear medicine tomographic imaging device designed for the imaging of nuclides decaying with the emission of gamma rays. This device, which was the ancestor of modern single photon emission computed tomography systems, clearly demonstrated the usefulness of the tomographic imaging in nuclear medicine. The advantages exhibited by positron-emitting radionuclides for nuclear medicine imaging were analyzed by several authors, including Chesler [23] and Cormack.[24] It became apparent at the time that for tomographic imaging, the annihilation radiation exhibited three major advantages over gamma rays: (1) the coincidence collimation of the annihilation radiation is a more efficient process than the collimation by absorption of gamma rays, (2) the coincidence detection of the annihilation photons allows a very accurate compensation for the attenuation of the radiation in tissues, and (3) the isoresponse curves for the coincidence detection of annihilation photons are nearly uniform.

THIRD PHASE

The numerous scientific investigations carried out before the early 1970s and pertaining to the use of a handful of positron-emitting radionuclides had by that period coalesced into a clearly perceivable pattern: The short-lived,

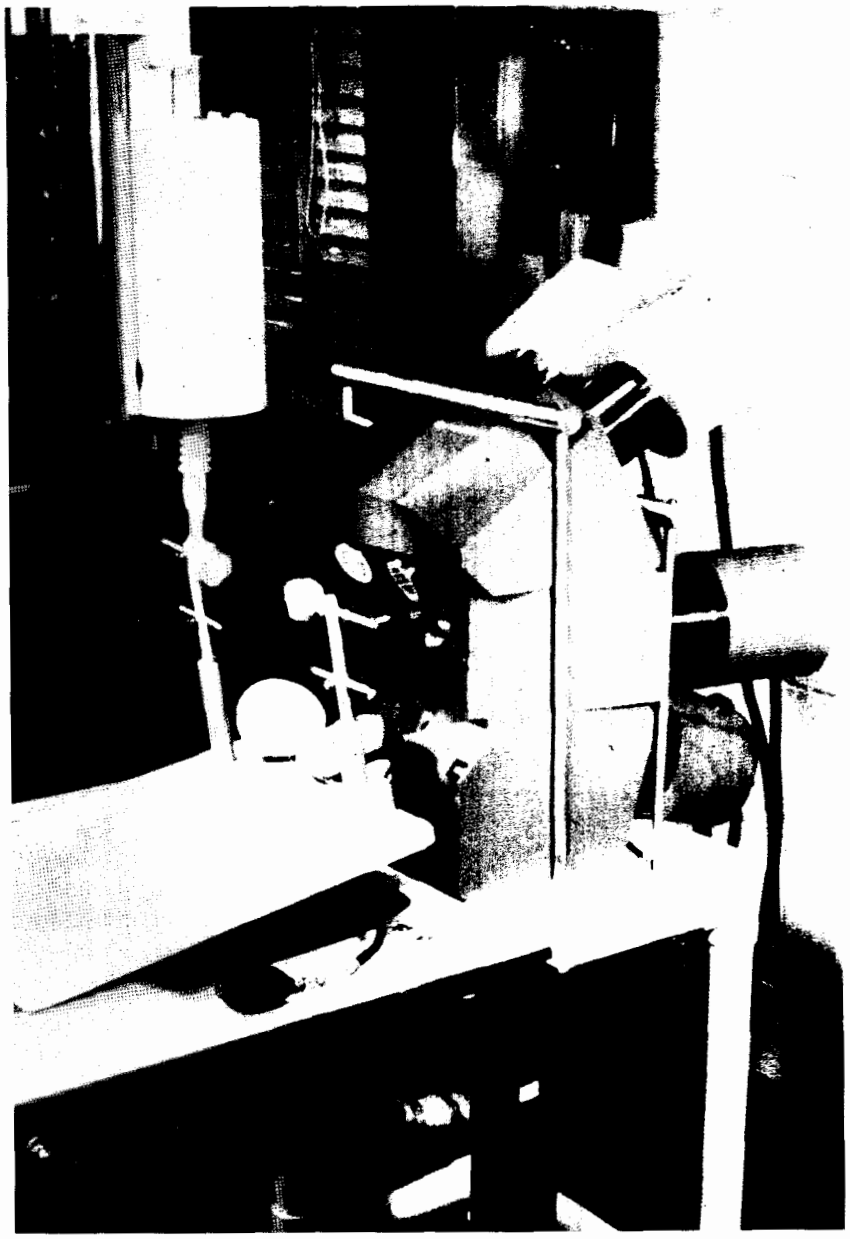

Fig 2. Array of six scintillation detectors fitted with converging collimators for the determination of regional cerebral blood flow and oxygen metabolism by means of ^{15}O.

positron-emitting radionuclides, ^{15}O, ^{11}C, ^{13}N, and ^{18}F, had been found to be useful tracers in physiological studies either difficult or impossible by any other means.[25,26] Oxygen-15, once considered useless as a physiological tracer, had proven to be a useful tracer for that element, which was used extensively, particularly in neurological studies.[27-29] Although short-lived, many of these labels had been incorporated into increasingly complex molecules, and the detection for in vivo studies of the annihilation radiation had been found not only less burdensome than more conventional gamma radiation, but it offered some features, particularly in tomographic imaging, unmatched by the detection of single photons.

In the early 1970s, the research group at Washington University, led by Ter-Pogossian, was faced with the need to develop an imaging device to expand this groups' long interest, since the middle 1950s, in using short-lived "physiological" radionuclides. After investigat-

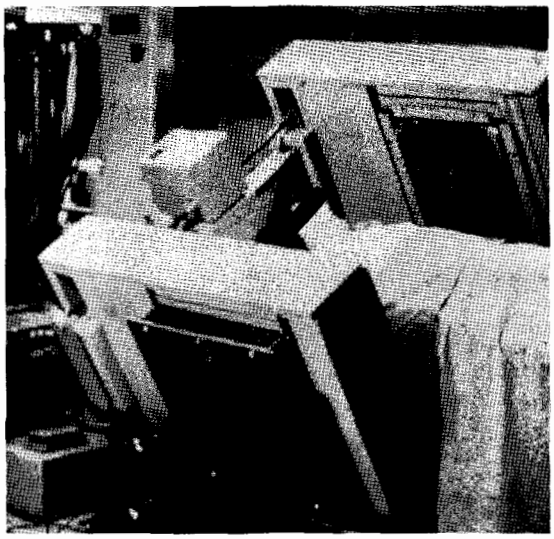

Fig 3. The Massachusetts General Hospital positron camera. (Reprinted courtesy of Gordon L. Brownell and the Physics Research Laboratory at Massachusetts General Hospital.)

ing various possible configurations, this group developed a positron emission transverse tomograph, which was dubbed PETT III.[30] PETT III was a very early version incorporating the fundamental features of modern PET devices. This system used coincidence electronic collimation of the annihilation radiation. The image reconstruction from projections was similar to that used by Hounsfield et al[31] and Cormack[32,33] for transmission CT. The motions in PET were designed to provide the necessary linear and angular samplings dictated by theory for the faithful reconstruction of the image. The attenuation of the annihilation radiation was compensated for by measuring that attenuation for each coincidence line by the use of a ring of positron emission activity. A clinical version of PETT III was used extensively in animal and patient studies at Washington University and later at Brookhaven National Laboratory. The physiological studies carried out with short-lived physiological radionuclides and tomographic reconstruction stimulated much interest in the modality, which by then was widely known as PET. Investigators from different disciplines focused their attention to the technical aspects of PET. Chemists became ambitious in labeling rapidly increasingly complex molecules. In 1980, a list of approximately 30 compounds labeled with short-lived, positron-emitting radionuclides was included in an article published in *Scientific American*.[34] Since that publication the list has increased to several hundred. The encouraging results obtained with the early PET tomographs stimulated the development of a large number of new architectures. These included an adaptation of the Massachusetts General Hospital camera for positron tomography, the use of Anger cameras for the same purpose, and several configurations using different size and numbers of detectors. It should be noted that in the majority of these efforts scintillation counters were used as radiation detectors. Although there has been some investigation of the use of different detectors, particularly multiwire proportional counters, so far only scintillation detectors have been found to be useful in PET physiological studies. In the same period, much effort was expended in understanding the mathematical aspects of PET image reconstruction, and several different reconstruction algorithms have been tested with increasing degrees of success. Perhaps most important in the development of PET was the general recognition by the biomedical community of the usefulness of this technique in the in vivo study of regional biochemical processes essential to life. An important facet of these physiological studies was the well-accepted recognition that the proper use of the data produced provided by PET requires its incorporation into a mathematical model derived, in most instances, from the known biochemistry of some of the pathways of the phenomenon under study.

This third phase in the development of PET can be regarded as the maturation of a new methodology during which the quality of the methodology was and is being continuously improved, while its usefulness is widely accepted.

The analysis of the historical development of PET reveals some interesting characteristics of that methodology. PET owes most of its strength to a serendipitous combination of physical and chemical properties. Had it not been for the chemical properties of the physiological radionuclides, it is probable that positron-emitting radionuclides would have played a minor role in nuclear medicine. Had these physiological radionuclides decayed through the emission of sin-

gle photon gamma rays rather than positrons, their collimation would have less inefficiency, and the tomographic reconstruction of their distribution would not have yielded the quantitative results and high contrast spatial and temporal resolution that has so enhanced the value of PET. The development of PET was entirely dependent on the separate developments of scientific concepts that in their early stages were pursued without any thought of their combined use. Thus, the application in biomedical research of physiological radionuclides was carried out for over two decades before the early 1970s without any thought of their imaging by a reconstructive tomographic process. The early work carried out in the coincidence detection of annihilation photons focused on the physical properties of this approach rather than on the desire to exploit the chemical properties of some positron-emitting radionuclides. The tomographic reconstruction from projections was developed with little thought to the chemical properties of short-lived, positron-emitting radionuclides or to the desirable features of the coincidence detection of the annihilation radiation. The development of PET consisted in bringing together the above properties and creating a new system using the desirable features of the all the components. Although it is not easy to identify which of the above components contributed most to the usefulness of PET as a biomedical tool, it is probable that the desirable chemical properties of a handful of positron-emitting radionuclides was the most important single concept in the birth of PET.

PRESENT STATUS AND PREDICTABLE FUTURE FOR PET

The development of PET to its present status as a useful research and clinical modality took much longer than the span of the same process of maturation for other imaging modalities such as magnetic resonance imaging (MRI) and CT. This slow acceptance of PET by the scientific community is due in major part to that facts that (1) PET evolved, as pointed out previously, from different disciplines, each contributing its development process, and (2) in most instances, PET requires the presence of a cyclotron and, often, complex chemistry in its operation. The latter factor has slowed down considerably the development of PET, and even today it represents a formidable barrier in its dissemination either for research or in clinical practice.

In spite of the long and difficult "gestation" period, PET has reached a level of maturity where its present position in science can be easily assessed, and its near future can be predicted with some degree of confidence. Today, the PET armamentarium can be regarded as mature technology. Several commercial companies offer cyclotrons specifically designed for PET studies that are relatively easy to operate, reliable, and competitively priced. Extensive progress has been made in the past two decades in developing practical labeling methods for PET radiopharmaceuticals. A number of automated systems, either single-purpose "black boxes" or programmable, robot-based systems, have been developed for the labeling of the most widely used radiopharmaceuticals. Highly advanced PET imaging devices providing good spatial resolution, ease of operation, and tolerable reliability are offered by several major companies.

The scientific literature dealing with PET-related research and applications clearly shows that PET provides a tool that allows us to probe physiological processes essential to life by means unavailable with any other technology. PET has also been found to be highly useful clinically in a series of determinations covering a large number of organs and diseases (Table 2). Although at this time there are less than 100 PET centers in the world, the number of publications in the nuclear medicine literature directly related to PET represents over 10% of the published articles in the nuclear medicine literature.

It is easy and safe to predict that in the near future the PET armamentarium will incrementally improve. Indeed, in addition to cyclotrons, which at this time are the preferred mode for the generation of PET radionuclides, several companies are working on the development of less expensive and easier-to-install accelerators (Fig 4). The performance of the apparatus needed for the labeling of PET radiopharmaceuticals is rapidly improving, and it is quite probable that many of the difficulties encountered with present systems will be overcome in the

Table 2. Some Clinical PET Applications (Established and Potential)

Application	Radiopharmaceutical	Description
Neurology/neurosurgery/psychiatry		
Dementia (Alzheimer's disease)	^{18}FDG, labeled $^{15}O_2$, $H_2{}^{15}O$	Display of areas of decreased activity
Epilepsy	^{18}FDG	Presurgery, replaces depth electrodes
Stroke	^{18}FDG, labeled $^{15}O_2$, $H_2{}^{15}O$	Display of decreased blood flow, tissue damage
Huntington's chorea	^{18}FDG, ^{11}C-N-methylspiperone	Diagnosis
Schizophrenia	^{18}FDG and other pharmaceuticals	Develop biochemical disease definition
Brain receptors	Multiple radiopharmaceuticals, [^{18}F]spiperone	Trace chemistry of brain receptors
Cardiology		
Myocardium viability	^{82}Rb, [^{13}N]ammonia, ^{18}FDG, [^{11}C]acetate	Determination of tissue viability before surgery
Stenosis/restenosis	[^{13}N]ammonia, ^{82}Rb	Early detection of occlusion-evaluation of postrevascularization
Early evaluation of high-risk patients	[^{13}N]ammonia, ^{82}Rb, ^{18}FDG, [^{11}C]acetate	Early detection of CAD-determinative test
Oncology		
Tumor evaluation	^{18}FDG, labeled $^{15}O_2$, $H_2{}^{15}O$, ^{82}Rb, among others	Distinguishes recurrence from necrosis *grading*
Tumor staging	^{18}FDG, labeled $^{15}O_2$, $H_2{}^{15}O$, and others	Dose uptake analysis allows real-time *staging*
Assessment of tumor extent	[^{18}F]estradiol	Identification of EP nodes and metastases

Abbreviations: FDG, fluorodeoxyglucose; H, hydrogen; Rb, rubidium; CAD, coronary artery disease; EP, xx.

near future. The present PET imaging devices provide images with a spatial resolution of approximately 5 mm. It has already been shown that much higher resolutions are possible,[34] and it is probable that the resolution of commercial PET devices also will be improved in the very near future. Perhaps what is particularly important in PET instrumentation is an improvement in sensitivity. Considerable efforts are presently being expanded to increase the solid angle of radiation acceptance of present PET devices. It is easy to predict considerable improvements in that area because the preliminary results obtained are highly encouraging. Industrial companies with suitable competence are becoming more interested in providing PET radiopharmaceuticals with a half-life sufficiently long (usually labeled with ^{18}F) to allow their shipment from a remote site of preparation to a hospital where they are to be used. Also, there is much work to be carried out in developing generator-produced radionuclides so as to minimize the need of on-site generation and labeling of PET pharmaceuticals.

As shown in Table 2, PET has been used for clinical applications as well as for research

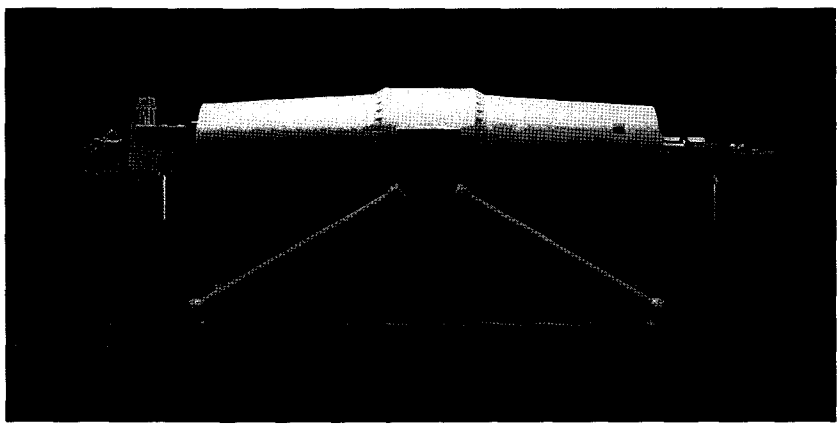

Fig 4. The 3.7-MeV Tandem Cascade Accelerator for PET. (*Reprinted courtesy of Science* Research Laboratory and Accelerator Applications Incorporated, Somerville, MA.)

purposes in a very broad spectrum of applications, and it will probably will continue to do so. Two areas, oncology and psychiatry, offer particularly challenging areas of development for PET. In oncology, PET has already been found to be useful in assessing the viability of tumors engaging the effect of therapy, be it radiation, chemical, or hormonal, in identifying the presence of metastases and in determining their receptor status. There are strong indications that the applications of PET in oncology will develop at a particularly fast rate. Another most promising possible use of PET is in the study of mental disease. Although a certain number of studies have already been carried out, these applications, at this time, are in their infancy, but they offer particularly exciting future possibilities because of PET's unmatched ability to trace in vivo and noninvasively some of the biochemical processes essential to cerebral function.

In closing, it might be useful to compare PET with other medical imaging procedures, such as CT, MRI, and magnetic resonance spectroscopy. It is unquestionable today that CT and MRI are clinically much more important tools than PET, perhaps with the exception of some specific cases in which PET provides information totally unavailable by CT or MRI. It is difficult to comment about the place of magnetic resonance spectroscopy because this modality is still in its infancy, and its future is difficult to predict. PET provides the ability to measure, in vivo, regionally, and noninvasively, a large number of physiological variables that are essential to normal organ functions because pathology derives from or affects normal physiological activities. At this time it appears that PET will contribute to clinical medicine through a better understanding of pathophysiology, and in some applications it will be used directly as a clinical diagnostic tool.

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