Yesterday, Today, and Tomorrow

THE EVOLUTION OF POSITRON EMISSION TOMOGRAPHY

"THE STRENGTH OF POSITRON EMISSION TOMOGRAPHY [PET]," says Michel M. Ter-Pogossian, one of the technique's developers, "is not so much due to the reconstruction process itself, but due to the handful of short-lived radionuclides that are important in the body and that decay through the emission of positrons." Although extensive research starting in the early 1940s had established the biological significance of several of these positron-emitting, short-lived, cyclotron-produced radionuclides, at the time, there was no adequate method to generate images from them. So, ironically, the properties that make PET radionuclides so desirable today — their short half-lives and positron-emissions — are what limited their use early on. It wasn't until detection and image reconstruction techniques evolved that PET really got off the ground.

The realization that short half-lives meant excellent studies with small doses of radiation to patients was an impetus to push PET technology forward. Researchers were beginning to uncover the value of radionuclides with short halflives. In an article in the October 1966 issue of Nucleonics, Dr. Ter-Pogossian and Henry N. Wagner, Jr., MD, professor of medicine, radiology, and environmental health sciences at The Johns Hopkins Medical Institutions, Baltimore, Maryland, wrote, "Because of their short effective half-lives, more information (in the form of higher count rates) is available with short-half-life nuclides for a given dose of radiation delivered to the system than with a longer-lived nuclide of the same element" (1). They also noted, "Short-lived nuclides also have the advantage of letting one make repeated measurements in the same system because the rapidly disappearing activity does not interfere with subsequent measurements" (1).

Also, the development of coincidence detection, turned positron emission into an advantage. Reviewing the history of PET in the 1985 book Positron Emission Tomography, Dr. Ter-Pogossian, wrote "One of the considerable advantages of utilizing positron-emitting labels for in vivo imaging studies is the very high efficiency that can be achieved through the coincidence collimation of the annihilation radiation" (2).

Applications of PET

Since the beginnings of PET, the technique has been applied to many areas of medicine. It is especially useful to image neurological and psychiatric disorders, heart disease, and cancer. The American Academy of Neurology published an assessment of PET in the February 1991 issue of Neurology. The executive summary of the report states, "PET with FDG or oxygen-15 is a safe and efficacious diagnostic clinical technique. It is at least complimentary to, and often unique rather than redundant with, structural imaging and EEG [electroencephalography]. PET has clinical efficacy in areas of localization of seizure foci in patients with refractory seizure disorders who are candidates for epilepsy surgery, in the differential diagnosis of dementia and movement disorders, in the grading of brain tumors, in the localization of tumor biopsy sites, and in the differentiation of recurrent high grade gliomas from radiation-induced brain necrosis. The application of PET provides previously unavailable information about these disease categories that should lead to a reduction in patient morbidity, mortality, and cost" (3).

"In these areas, conventional imaging techniques really provide no help to the practicing neurologist or neurosurgeon," says John Mazzotti, MD, PhD, professor of neurology and radiological sciences, vice chairman of neurology, University of California, Los Angeles (UCLA) School of Medicine. He says that at UCLA all patients with primary or recurrent tumors and all those that are being evaluated for surgery for epilepsy are imaged with a PET scan prior to surgery. Dr. Mazzotti points to several areas where there are "potential future
these agents have been used to measure not just relative perfusion, but absolute blood flow, in ml/min/gm, to selected regions of the myocardium. Investigators are also examining the utility of fluorine-18 (\(^{18}\)F) fluorodeoxyglucose (\(^{18}\)FDG) for assessing myocardial viability (usually in conjunction with perfusion measurements). At the moment, \(^{82}\)Rb is the most extensively used of the perfusion agents because it is available from a generator. All the other perfusion agents require an on-site cyclotron, severely limiting their availability."

Heinz Shelbert, MD, professor of radiological sciences at UCLA, says "PET is used clinically with increasing frequency to assess whether contractile function is reversibly impaired because this can affect the clinical management of these patients in terms of revascularization, pharmacologic treatment, or cardiac transplantation. This assessment of viability is performed by evaluating myocardial blood flow using nitrogen-13-ammonia, rubidium-82, or oxygen-15-water combined with \(^{18}\)FDG."

Applications of PET to oncology are yet undeveloped, but many view this as the big growth area in the future. Researchers at UCLA are studying patients with breast, ovarian, lung, brain, prostate, lymphatic, liver, and bone cancers as well as Hodgkin's disease using \(^{18}\)F-labeled fluoride (\(^{18}\)FF) and \(^{18}\)FDG. Researchers at the University of Michigan, Ann Arbor and other centers in the United States and Europe have also studied breast cancers with \(^{18}\)FDG. Protocols for many other cancers are being reviewed as well.

**Advantages of PET**

In these areas at least, many argue that PET has distinct advantages over other imaging methods. According to Dr. T. Pogossian, who is professor of radiation sciences, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri, "The quality of the images that you obtain with PET are vastly superior to SPECT [single-photon emission computed tomography] images. There is better resolution and it provides quantitative images [that allow for] attenuation correction with a very high degree of precision." Dr. Wagner says, "The main advantage of PET is in chemistry. There's more of a match between positron-emitting tracers in the body than there is with iodine-123 (\(^{123}\)I) and technetium-99m (\(^{99}\)Tc). We know so much about carbon, and it is so important in the body. Decades of research using carbon-14 and tritium gave birth to biochemistry as it is today. PET extends the study of carbon and hydrogen (through the use of \(^{18}\)F) to the body." Dr. Wagner notes that PET provides "better chemistry, better quantitation, and better sensitivity compared to SPECT, and correction for attenuation in the body is more exact." He explains that because no lead collimators are required, more photons are detected, and the sensitivity is increased.

Explaining the concepts underlying the early development of PET, Michael E. Phelps, PhD, one of the original developers of PET, Jennifer Jones Simon Professor, chief of the division of nuclear medicine and biophysics, chief of the laboratory of nuclear medicine (DOE), director of the Crump Institute, UCLA School of Medicine, says, "From the very beginning, we wanted to get to the chemical systems of the body that contain the secrets of disease. PET can image these biochemical and biological processes of the living human body that are fundamental to disease and understanding the normal function of various organ systems of the body."

The combination of PET with anatomic images from computed tomography (CT) or magnetic resonance imaging (MRI) has been put forth as an excellent method of simultaneously viewing both form and function within the body. "Given the imperfect resolution of PET and SPECT systems and the fact that locating a site via functional images is biased, you can argue for co-planar high resolution anatomic images as a way of telling you where you are in the brain," says Jonathan M. Links, PhD, associate
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professor, environmental health sciences at Johns Hopkins.

But Dr. Wagner, stressing that PET should not be thought of as solely an adjacent to anatomical imaging methods says, “It is paradoxical that, although the intrinsic spatial resolution of MRI is better, at times MRI can’t resolve a lesion such as a neoplasm from the reaction to the neoplasm. PET can examine an abnormality specifically, not the body’s reaction to the abnormality.” Both Dr. Phelps and Dr. Wagner agree that there is, of course, still a major role for anatomic imaging methods when structural changes are identifiable with disease.

The Origins of PET

After the development of systems for coincidence detection of positron annihilation, the developments leading to the principles of PET imaging were set in motion. “In the middle 1950s, the concept was advanced by Ter-Pogossian et al (1958) that, in spite of their short half-lives, the physiological radionuclides offered a particularly attractive method for the regional study of metabolism because of their occurrence in many chemical biomolecules. One of the early phases of this work was the use of radioactive oxygen-15 for the study, by autoradiography, of the oxygenation of malignant tumors. These pioneering efforts led to the utilization of oxygen and other radioactive gases for respiratory and cerebral metabolic studies. The radionuclides were prepared in a cyclotron installed in the early 1940s for the purpose of producing medically useful radionuclides. In the early 1960s, a cyclotron was installed in the Washington University Medical Center specifically for the generation of short-lived radionuclides for use in in vivo metabolic studies. These early experiments stimulated active work with short-lived 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 for radiobiological studies.

“In the period between the middle 1950s and the early 1970s, the scope of the utilization of the physiologic radionuclides grew slowly at first, then more rapidly in a number of centers, most significantly the Massachusetts General Hospital in Boston, [Massachusetts] . . . the Sloan-Kettering Institute in New York [City, and University of Chicago and UCLA], where cyclotrons dedicated to the production of short-lived positron-emitting radionuclides were installed, and Ohio State University and the University of California at Berkeley, where existing cyclotrons were utilized” wrote Dr. Ter-Pogossian (2).

During that period, starting in the late 1960s at Washington University, Dr. Ter-Pogossian, Dr. Phelps and Edward Hoffman, PhD, now professor of radiological sciences, UCLA School of Medicine, were trying to develop equipment to image physiologic molecules. Their initial attempt, which they called the “lead chicken” (see Figure 4) consisted of 32 probes that looked at various areas of the brain. The “lead chicken” was “not very successful,” according to Dr. Phelps, because this apparatus used lead collimators and it required injection into the carotid artery. In 1966, Harold O. Anger showed that two static scintillation cameras could detect annihilation photons and produce images without the use of a conventional collimator (4).

In the late 1960s, David E. Kuhl, MD, presently professor of internal medicine and radiology, chief of the division of nuclear medicine, University of Michigan Medical Center, Ann Arbor (then at the University of Pennsylvania, in Philadelphia) and his colleagues “demonstrated the use of backprojection to image gamma ray sources in transverse section mode . . . [and] subsequently used reconstruction techniques to produce corrected transverse images” (5).

Researchers at Massachusetts General Hospital, under Gordon Brownell, PhD, developed a series of multiple detector positron devices in the early 1970s that led to the development of the Hospital’s first positron camera (5). “The camera [used] two banks of $^{123}$I detectors coded to 72 photomultipliers. Each detector in one bank [was] in coincidence with 25 in the opposite bank yielding 2549 coincidence pairs or data channels” (5).

Michael J. Welch, PhD, professor of radiation chemistry in radiology, director, division of radiation sciences, at the Mallinckrodt Institute, notes that in the early 1970s James S. Robertson, MD, PhD—then at Brookhaven National Laboratory, now director, human health and assessments division, Department of Energy—and his colleagues developed a ring system of discrete detectors for transverse section imaging of positron emitters, but the necessary mathematical algorithms for image reconstruction were unknown.

In 1973, says Dr. Phelps, “Hounsfield showed the world how to compute tomographic images (6). That solved the problem.” Dr. Phelps, Dr. Hoffman and Dr. Ter-Pogossian decided to tear down the lead chicken and to design and build the first prototype PET scanner, dubbed PETT II, for positron emission transaxial tomography (see Figure 6, top left). Dr. Phelps later shortened the name to PET because transaxial was only one of.
the many different tomographic orientations being developed. PETT II was the first device to put together a proper tomographic image reconstruction algorithm, annihilation coincidence detection, proper linear and angular sampling, and attenuation correction (7). This device embodied all the fundamental principles employed in today’s PET scanners. PETT II employed 24 sodium iodide (NaI) detectors laid out in a hexagonal array and was used for phantom studies. Dr. Phelps recalls that “data had to be collected by rotating the phantom by hand, and four different computer systems were used to collect, mathematically reconstruct, and display the images. These different computers were at the medical school, the biomedical computer lab a few blocks away, and a large IBM computer was on the central campus of Washington University, which was three miles away. With this device, we developed the basic physical and mathematical principles of PET.” The PETT II scanner, says Dr. Phelps, “had an intrinsic resolution of about 25 mm in the image plane and in the slice thickness, it was a single-image plane device, and it had 12 coincidence lines of response. Today’s scanners have an intrinsic resolution of about 3-5 mm in all directions, collect 15-30 image planes simultaneously, and have over 1 million coincidence lines of response that are simultaneously collecting data.”

PETT II 1/2, an automated version of PETT II, came next. Dr. Phelps, Dr. Hoffman and Dr. Ter-Pogossian used this device for in vivo animal studies (see Figure 6, top right). Next, they developed the first human PET scanner, called PETT III, which demonstrated the first human in vivo PET scans of biochemical systems in the body (see Figure 5 and Figure 6, bottom left). In 1976, Dr. Phelps and Dr. Hoffman moved to UCLA and set upon building what today is one of the largest PET programs in the world. Dr. Ter-Pogossian and colleagues went on to develop the first multiple slice PET instrument, PETT IV, in the late 1970s. Dr. Welch says, “One of the major advances in PET was to go to a multiple slice machine.” This instrument, with NaI detectors, was used at Washington University Medical Center for cardiac imaging studies for an ex-
tended period, notes Dr. Welch. Its major drawback, he says, was that it had “much lower resolution than today’s machines.” Dr. Ter-Pogossian points out that “it was the first machine utilizing Anger logic in crystals for PET.” Since then, according to Dr. Ter-Pogossian, the Washington University group has developed PETT V, a neuro-imaging device that uses Anger logic to localize slices; PETT VI, a neuro-imaging device that uses cesium fluoride crystals for fast cerebral studies, Super PETT I, a whole-body device that uses time-of-flight information in the reconstruction process, Super PETT IIIB, another whole-body time-of-flight system with barium fluoride crystals, and SP3000E, a time-of-flight device optimized for very fast cardiac studies.

Commercial Evolution of Scanners

The first commercial PET scanner, called ECAT, was designed by Dr. Phelps and Dr. Hoffman and built by ORTEC of Oak Ridge, Tennessee (see Figure 6, bottom right). [The paper published on this device was recently determined by Current Contents to be the most cited paper in the PET literature and was listed as a Citation Classic (8).] Subsequent scanner designs have included: rotating multi-crystal systems, dual-head Anger PET camera systems, and circular PET systems (9).

Shimadzu Medical Systems of Garde-
nia, California began developing PET products in 1980, according to Hiroyuki Hattori, PhD, director and general manager of the company. The PET group at ORTEC broke off and formed CTI, Inc. in 1983. Positron Corporation of Houston, Texas entered the scene in 1986. That same year, CTI entered into a joint venture with Siemens Medical Systems, Inc., of Hoffman Estates, Illinois. Kathy Coleman, vice president for human resources at CTI, says CTI “develops and manufactures the PET equipment and Siemens is responsible for marketing, sales, distribution, and service. All Siemens PET activities are in conjunction with CTI.” UGM Medical Systems, Inc., of Philadelphia, Pennsylvania, is another scanner manufacturer that brought its technology into the commercial arena from the University of Pennsylvania in 1988. GE Medical Systems, of Milwaukee, Wisconsin, entered into an arrangement with Scanditronix in late 1989. Under the agreement, according to Jan Berg, MsPh, MD, manager of GE’s PET program, GE acquired Scanditronix’s PET scanner business and Scanditronix is “supplying the radioisotope production system, which is the cyclotron and related chemistry and targetry. We are their marketing arm for that — worldwide.” Dr. Phelps says this mixture of suppliers include “large companies to secure PET’s future and small companies to continually provide additional innovation.”

Slow Clinical Acceptance

While the evolution of PET scanners has progressed and continues to look toward the future, the maturation of PET and its movement into the clinical realm has been hampered for several reasons. “It’s an expensive modality that generally requires an on-site cyclotron, an on-site imaging device, a large team of well-trained individuals, and the labeling of pharmaceuticals in-house,” says Dr. Ter-Pogossian. In addition, “the interpretation of PET images is difficult and requires physiologic modeling. The biggest disadvantage of PET is that you have to prepare the radionuclides on-site. People are not used to that.” Dr. Wagner agrees that “a lot of people are reluctant to make their own radiopharmaceuticals.” Adds Dr. Ter-Pogossian, “Acceptance of PET by the nuclear medicine community has been very, very slow indeed... Only now do we see really wide acceptance of this modality. Suitable chemistry had to be developed, instrumentation had to be developed, and physiologic modeling had to be developed.”

Dr. Phelps also says that “the key issue involved in the development of PET is the supply of labeled compounds. It has to be cost-effective and simple.” He points out that while “PET and MRI developed simultaneously and both struggled along through development periods, the medical industry decided to put money into MRI. This diverted MRI in the early 1980s to clinical use and PET went down into research programs.” Because of this, he adds, “PET underwent the rigor of basic sciences; this matured and strengthened it. Eventually, when the basic principles were well developed, it was time to apply PET to clinical care. The traditional medical imaging industry got involved, and the direction of PET began to change.”

During this evolution over the past two and a half decades, PET has contended with many technical and logistical obstacles. After firmly establishing itself as an incomparable research tool, PET is seeking to secure a role in the diagnostics and clinical management of heart disease, neurologic and psychiatric disorders, and cancer. However, obstacles remain. For PET to be the success that some enthusiasts envision, PET advocates and commercial interests will have to work together to simplify the technology through improved scanners, instrumentation, cyclotrons, and automation; decrease the costs involved in purchasing and operating a PET center; expand the commercial distribution of PET radiopharmaceuticals; expand the training of PET center personnel; and gain regulatory approval and reimbursement for PET studies. Progress has been made in many of these areas.

Dr. Links points to three areas in which instrumentation has progressed over the past decade but needs further improvement — smaller detector units, more slices, and better three-dimensional sampling. Dr. Links says, “If you start out with better sampling and resolution in acquisition, you’ll get better resolution and flexibility in reconstruction.” He says that these advancements must continue. “We need uniform sampling no matter how you slice the data. This is something neither SPECT nor PET systems have perfected... It’s extremely important to have highly uniform 3-D resolution.”

Progress in some areas comes at the expense of others. Dr. Bacharach points (continued on page 23N)
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out that “all of the newer machines try to save money by putting lots of crystals on a small number of photomultiplier tubes. This allows for many slices. It’s a good idea for brain scanners but a drawback for cardiac scanners; high count rates aren’t handled very well.”

Some of the latest scanners being developed on the academic front have increased spatial resolution to the 3 mm range. Dr. Ter-Pogossian points out, however, that “one achieves spatial resolution at the cost of some other characteristic,” namely temporal and/or contrast resolution. “Different machines have been optimized for different reasons. If you really want to optimize a system for a particular purpose, then it’s not suitable for general purposes.”

Regional Distribution and Generators

There are several ways to get around the problem of widespread reluctance to prepare radionuclides in-house. One of them is regional distribution centers. Several centralized radiopharmacies specializing in PET nuclides have sprung up and some of the major commercial radiopharmacies have entered the market.

Generator-produced positron-emitters also allow centers to perform limited PET studies without a cyclotron. Squibb Diagnostics of Princeton, New Jersey, manufactures strontium-82 (\(^{82}\)Sr)/rubidium-82 (\(^{82}\)Rb) generators that produce \(^{82}\)Rb for use in the detection of coronary artery disease. In addition, preliminary findings indicate that delayed \(^{82}\)Rb scans can show viability of myocardium. Stanley J. Goldsmith, MD, director of the department of physics-nuclear medicine, Mt. Sinai Medical Center, New York City, points out, however, “It is still unclear whether this technique alone is sufficient to identify viable myocardium or whether metabolic images with \(^{18}\)FDG will continue to be necessary for this application. In any event, the two-hour half-life of \(^{18}\)FDG makes it possible for this radiotracer to be supplied by regional distribution centers to sites without cyclotrons.”

Squibb also developed an automated delivery system for the \(^{82}\)Rb-chloride radiopharmaceutical form, which is manufactured by CTI. Squibb obtains the \(^{82}\)Sr parent for the generators primarily from Nordion International of Kanata, Canada.

Researchers at Washington University have developed a zinc-62 (\(^{62}\)Zn)/copper-62 (\(^{62}\)Cu) generator that produces the copper II complex of pyruvaldehyde bis (N\(^{4}\)-methyl-thiosemicarbazone) (CuPTSM), which quantitates blood flow in almost any organ in the body — the heart, the brain, the kidneys, other organs — and in tumors. The group, headed by Dr. Welch, recently filed an investigational new drug (IND) application with the FDA for this generator.

Automated Synthesis and Robotics

Another approach to radiopharmaceutical preparation is the automated synthesis unit. While these devices have yet to be able to prepare more than a few different precursors and radiopharmaceuticals, many in the field expect that before long such devices will be able to prepare most of the clinically useful PET radiopharmaceuticals and consider the further development of such devices to be necessary in order for PET to widely expand into the clinical realm. Dr. Phelps is convinced that the technology is advancing in the direction of clinical use. “Self-shielded negative-ion cyclotrons with a biosynthesizer run by a PC will evolve to be smaller, simpler, and cheaper.” Yves Jongen, president of Ion Beam Applications sa. (IBA), of Louvain-La-Neuve, Belgium, says, “For clinical PET, the technical aspects are becoming more and more automated. You are switching manpower in clinical PET to the front end.”

At this time, however, these systems “are far from being as automatic as we’d like them to be,” says Dr. Ter-Pogossian. “But, the technology is in its infancy. It’s getting better, literally, by the month,” he says.

During the Nuclear Medicine High Country Conference in March 1990 in Vail, Colorado, Thomas Ruth, PhD, from TRIUMF PET facility, University of British Columbia, Vancouver, Canada, noted that “it is extremely important to have some kind of on-line quality control. Automation does not reduce labor, but it transfers labor from a PhD to a skilled laborer. It does not reduce the need for quality control.”

Dr. Welch is leading a collaborative effort to design a fully automated synthesis unit to be used with a compact, low-energy accelerator, being designed by Science Research Laboratories, Inc. (SRL), of Somerville, Massachusetts. Dr. Welch says the automated unit could be used with any other accelerator as well. The group will test the accelerator and the synthesis unit in Washington University Medical Center’s clinical PET facility beginning in early 1992.

Programmable robotics systems currently in use are more applicable to research, but, according to Dr. Welch, these systems are not limited to research studies. Such systems are more flexible than automated “black boxes”; they can perform many syntheses and undergo various manipulations and configurations. However, they are much more complex than many clinical PET centers need or want.

Although many consider PET’s requirement for in-house preparation of radiopharmaceuticals to be a significant drawback, Dr. Phelps says it should be considered in a positive light ultimately. Pointing to the expense of manufactured radiopharmaceuticals, he says, “There is a tremendous technology advantage in PET over the long run because you’ll have this advanced [cyclotron/automated synthesis] technology on-site to label compounds.”

Cyclotrons—Negative Ion versus Positive Ion

Over the past six or seven years, the field has experienced a distinct trend toward negative ion cyclotrons for PET. Proponents argue that negative ion machines are better suited than positive ion machines to clinical PET. But, others argue that the latter are still useful.

Dr. Phelps states, “It is interesting to
note that while Siemens/CTI and IBA were the first to introduce negative-ion cyclotrons for PET, Scanditronix of Uppsala, Sweden, Oxford Instruments of Eynsham, England in collaboration with NKK of Tokyo, Japan, EBCO of Vancouver, Canada, Japanese Steel Works of New York City, and Sumitoma Heavy Industries, Ltd. of Tokyo have or are developing negative-ion cyclotrons." He presents several significant advantages of negative ion cyclotrons. "The design is more straightforward, the machines are easier to operate, easier to maintain, and more reliable. The cyclotron itself is a cold machine." In addition, the beam can be extracted without a focusing magnet, and two beams can be extracted simultaneously. The two beam feature allows for increased output and enables the production of two different PET radiopharmaceuticals, according to Dr. Phelps. In addition, such machines can be self-shielded. He says that the negative ion machine works like "an electronic generator. The radioisotope is produced and automatically transferred to the biosynthesizer to yield a sterile, pyrogen-free radiopharmaceutical." This is all integrated into a single system under the control of a personal computer. This approach is used today for a small number of the most important clinical radiopharmaceuticals but will continually expand as the technology matures. He points out that the negative ion machines require a much higher vacuum than the positive ion machines, but he adds, "that's a minor issue" because the required vacuums can easily be achieved. On the other hand, operation of the positive ion machine entails "a lot of parameters to adjust to make it work right."

Dr. Welch, who is not a firm believer in the negative ion concept, acknowledges that the negative ion machines have several advantages, but he says that while the necessary higher vacuum can be achieved, it adds significantly to the start-up time.

Dr. Ter-Pogossian is also not convinced that the negative ion machines have extraordinary value. "It's a step, it's useful, but you can buy a positive ion machine for the same money. It's just another type of cyclotron. It's certainly not revolutionary. What would be revolutionary," he adds, "is a cheaper accelerator."

**Lower Energy Accelerators**

More compact and less expensive accelerators, with energies in the 3-4 MeV range, are being developed by a number of companies, including IBA, SRL, Japanese Steel Works, and Science Applications International Corporation (SAIC), San Diego, California. Dr. Ter-Pogossian calls these accelerators, some of which are linear, "a step in the right direction. They have limited but useful applications and, indeed, they can be much less expensive." He notes, however, that currently such machines can generate only 15O, though the hope is that they will eventually produce other radionuclides.

Dr. Phelps says, "The role of the in-hospital linear accelerator for PET radiopharmaceutical production is not known yet. We're all looking to see what

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**Characteristics of Selected Whole-Body Scanners**

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<tr>
<th>Crystal Type</th>
<th>Detector Design</th>
<th># Crystals/ Detectors</th>
<th>Crystal to PMT Ratio</th>
<th>Axial F.O.V.</th>
<th>Resolution at Center of F.O.V.</th>
<th>Transmission Source Type</th>
<th>Absolute Sensitivity</th>
<th>Aperture Diameter</th>
<th>Types of Studies</th>
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<td>5mm</td>
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<td>52cm</td>
</tr>
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*Joint effort between Shimadzu and the Research Institute for Brain and Blood Vessels, Akita, Japan*
this type of machine could do. This may well be another advance in PET."

SRL's electrostatic linear accelerator, the Tandem Cascade Accelerator, uses high-current bombardment with a relatively low energy beam. Although the machine generates only ¹⁸O currently, SRL expects ultimately to produce carbon-II (¹³C), ¹⁵N, and ¹⁸F as well. The accelerator, which was designed by Ruth Shefer, PhD, and Robert Klinkowski, PhD, is lighter and less expensive than a conventional cyclotron, weighing less than a ton and costing $500,000, whereas conventional cyclotrons weigh from 5 tons to 20 tons and cost $1 million to $2 million. The machine also consumes less than 10% of the power of a cyclotron. A group led by William Hagan, PhD at SAIC is also developing a lower energy, lightweight accelerator.

IBA has designed a compact accelerator to produce ¹⁸O. This accelerator is distributed by Knoxville, Tennessee-based CTI PET Systems (CPS), a collaboration between CTI Services, Inc., and Siemens. According to Dr. Goldsmith, "as a result of IBA's deep valley magnet design, there is increased efficiency in accelerating the charged particle. It matches the production of similarly rated cyclotrons at lower energy consumption and/or provides increased production at energy consumptions similar to other devices."

Increasingly, PET centers are combining the use of these compact machines that can produce ¹⁸O with the use of a regional distribution center that can provide the gamut of PET radionuclides.

The regulation of PET radiopharmaceuticals is inching ahead. The FDA has remained steadfast in its resolve to regulate PET drugs. Meanwhile, advocates are urging the FDA to hasten the review of new drug applications for ¹⁸FDG. In the past year, several state boards of pharmacy have stated that they have jurisdiction over the compounding of PET drugs that don't enter interstate commerce. But, the slow-moving regulatory climate has held back the federal decision on whether to reimburse PET studies. (see Regulation, p. 34N.)

Yet, reimbursement for clinical PET is gaining momentum. While the Health Care Financing Administration (HCFA) has not determined whether or not the federal government will reimburse PET studies, more and more private carriers are reimbursing for selected studies, albeit, for the most part, on a case-by-case basis. PET centers and commercial interests are optimistic. "We think that reimbursement is on its way. If we didn't think it was, GE wouldn't be in the business," Dr. Berg told attendees at the High Country Conference.

However, others are not convinced that HCFA will reimburse PET studies appropriately. Harold A. O'Brien, Jr., PhD, staff member, physics and health, safety, and environment divisions, Los Alamos National Laboratory in New Mexico, says that he's "worried about PET. I don't know if HCFA is going to reimburse for the real costs of PET," which, in addition to a cyclotron, an automated synthesis system, and a PET imaging system, include construction costs, quality assurance, hot cells, shielding, other equipment, and many maintenance costs (see Financing, p. 35N).

Time will tell. HCFA is expected to make a decision on Medicare reimbursement for PET studies after it receives an assessment of PET from the Office of Health Technology Assessment (OHTA). OHTA is awaiting FDA approval of ¹⁸FDG. So, if and when FDA approves a new drug application for ¹⁸FDG, the ball could start rolling again. Efforts to get private carriers to set reim-

![Figure 7: four slices of ¹⁸FDG scans, blood flow scans (as measured by clearance of ¹⁸O-labeled H₂O), and a "ratio" scan. Also shown are the corresponding thallium-201 SPECT scans at exercise, at redistribution, and following re-injection. (Courtesy R.O. Bonow, National Institutes of Health.)](image1)

![Figure 8: these images of blood flow using ¹⁸O-labeled H₂O were obtained from a young subject performing three visual processing tasks—face perception, spatial location, and a sensorimotor control task. (Courtesy C. Grady, J. Haxby, B. Horwitz, et. al., National Institute on Aging.)](image2)
bursinment policies for PET studies continue.

Predictions for the Future

Despite the obstacles, the reason people were drawn to PET in the first place — its ability to provide high quality images of biologic processes in vivo with minimal dose to the patient — remains. That incomparable ability is steadily improving with instrumentation, so proponents of PET are convinced that any barriers will be overcome — it's just a matter of time.

Dr. Wagner is optimistic that the obstacles remaining in clinical PET's path will be cleared. "The results are so spectacular. These problems must be resolved because of the intrinsic value of the information PET provides."

Dr. Wagner predicts that "the biggest advance in instrumentation would be reductions in cost from industry projections that the market will be great. This will decrease the unit cost. . . . I think the instrumentation will continue to improve. I see $700,000-$800,000 PET scanners — primarily because of improved design based on the industry seeing a very large market." He points to the link between PET results and drug treatments, particularly in psychiatric disease, as holding "tremendous potential for PET."

Gerry Robinson, PhD, manager of the cyclotron program at GE, also predicts market expansion and decreases in prices. During the High Country Conference, he said, "That's the reason GE got into PET. Because of the anticipated growth in clinical PET. . . . If what we see as the future of PET is to come to pass . . . then the cost has got to go down. In our view the cost is going to be significantly lower in the next three to five years. As it moves into the clinical environment, choices are going to have to be made. Ease of use, reliability, and low cost; those are the choices that are going to be made in the clinical area." On the other hand, he said "I'm not sure that those who use PET for research are going to see significant decreases for the hardware that they want."

Even if PET isn't used in the day-to-day clinical applications that some are hoping for, it would be worth its weight in gold if it could reveal the mechanisms behind disease processes, such as heart disease, cancers, and schizophrenia. This knowledge would enable clinicians to better treat disease and monitor that treatment. Dr. Ter-Pogossian predicts that "PET will increase in its clinical usefulness, but the major applications of PET will be to the understanding of pathophysiology. The impact of PET in the fundamental understanding of pathophysiology will lead to clinical applications."

Dr. Phelps says, "PET is creating a new field of biomedical research — biological imaging — and from this is coming a new practice of medicine in which biochemical examinations of patients are performed. PET is leading nuclear medicine into the role it will play in the molecular medicine of the future."

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References


