Advances Make It Easier, But Challenges Remain

CLINICAL PET: IS IT TIME TO TAKE THE PLUNGE?

"This is the most complicated imaging technology that there is. You have to have someone who understands the problems and is still willing to do it, plus enough money to get the thing going."

Positron emission tomography—PET—is unique. No other technology can image body chemistry with such sensitivity, so that the moment-to-moment change in concentration of a tracer in blood or tissue can be determined in absolute units. While other imaging approaches are better at showing anatomical detail, better at noninvasively "dissecting" a diseased organ, by revealing physiological function PET offers the hope that disease can be detected even before physical changes appear. The conditions that have been studied with PET—heart disease, schizophrenia, Alzheimer's disease, AIDS, epilepsy, Huntington's disease, cancer—include humankind's most devastating illnesses. Add to that list basic research into brain function, including drug and alcohol addiction, and it is easy to see why researchers and clinicians are so excited about PET.

But is PET ready for community hospitals? The preponderance of opinion seems to be that "clinical PET"—the routine application of positron emission tomography to the diagnosis of disease in an ordinary hospital setting, as opposed to its use in a research environment—is within the reach of many facilities. But even vigorous proponents of widespread clinical PET caution that effective use of this technology requires a substantial financial and administrative commitment to it and a thorough appreciation of the complexity involved.

Attempts Stalled

"The people who are promoting PET—manufacturers and a few individuals—make it seem like it's a very simple operation. It is more difficult than they would like you to believe," said Michael P. Kilbourn, PhD, associate professor of internal medicine at the University of Michigan in Ann Arbor. "I look at it as something that is very, very much more difficult than is often made out to be the case," said Stephen L. Bacharach, PhD, medical physicist at the National Institutes of Health, Bethesda, Maryland. "This is the most complicated imaging technology that there is," said Michael A. Wilson, MD, of the University of Wisconsin at Madison, whose research-oriented PET program is just getting started. "You have to have someone who understands the problems and is still willing to do it, plus enough money to get the thing going."

At times, attempts to establish or maintain PET facilities have stalled. Mount Sinai Medical Center in Miami Beach, Florida, has just closed down its PET center. "It was an old PET machine and we had to replace it, but we couldn't get the funding," said Ranjan Duara, MD, associate professor of radiology and neurology at the University of Miami School of Medicine. "We've installed a SPECT machine to replace the kind of activity we had been doing." Baylor University, Houston, Texas, which appears on lists of those with serious PET intentions, has abandoned its effort for the time being. "We were going to get it, but because of some financial problems we put it off until next year," said Satish Gopal Jhingran, MD, director of nuclear medicine at Methodist Hospital, Baylor's teaching affiliate. The process was halted just before the equipment order was to be placed.

Other facilities are successfully performing clinical work. The University of Tennessee Hospital in Knoxville has been applying PET and cyclotron-produced radiopharmaceuticals to routine patient care since early this year. "Is this an appropriate thing for a community hospital to consider?" asked Jeffrey Collmann, PhD, administrative director. "That's what we're here to model. . . . Our experience augers well for such people." North Shore University Hospital, Manhasset, New York, a community hospital affiliated with Cornell University, has begun examining patients at its center, and numerous other facilities, including William Beaumont Hospital, Royal Oak, Michigan, Creighton University (continued on page 1752)
(continued from page 1751) Medical Center, Omaha, Nebraska, and Mount Sinai Medical Center, New York City, are in the process of establishing centers of their own. Predictions are that the number of PET centers in North America could double by 1990.

Task Force Report

The clinical potential of PET is widely accepted. According to the report of the American College of Nuclear Physicians/Society of Nuclear Medicine Task Force on Clinical PET, to date there are at least three conditions that are amenable to PET's clinical application: coronary artery disease, epilepsy and brain tumors. PET perfusion imaging is more accurate than thallium scintigraphy for diagnosing and assessing coronary artery disease, the report said, and it can differentiate patients who will benefit from revascularization from those who will not. In surgical candidates with partial epilepsy, PET provides spatial localization of the seizure focus that complements other tests, such as the surface electroencephalogram, and can help eliminate the need for depth electrodes in about half of these cases. PET can also give important diagnostic and prognostic information in the management of patients with gliomas, and can distinguish tumor recurrence from radiation necrosis (1).

Apparantly no one knows exactly how many PET centers there are in the world; different investigators in the field report different tallies. This may be true for two reasons: the process of instituting cyclotron PET is such a long, drawn-out one that it is not always clear exactly when an institution deserves to be listed, and second, because there is so much activity that those who try to keep track find their data continually outdated. Stephen McQuarrie, MS, an academic staff member in the pharmacy department at the University of Alberta in Edmonton, Canada, is attempting to maintain a comprehensive worldwide database listing not only existing centers but also their equipment and the names of the facilities' users. His data, which were updated in September of 1987, show that there are 60 facilities worldwide that have at least one scanner (see map, pages 1754–1755).

Research Focus

Most of these facilities appear to be principally engaged in research. While some of the 1 centers in Japan are doing PET studies nearly every day, they usually select their patients in terms of a research protocol, according to Yoshiharu Yonekura, MD, of the department of nuclear medicine at Kyoto University. Clinical use would become more widespread if facilities were allowed to charge patients for the procedure. Dr. Yonekura noted, adding that the Japanese government is considering whether PET scans should be covered by insurance, as computed tomography and magnetic resonance imaging already are. An automatic system for radiopharmaceutical production has also entered clinical trials in Japan, and at least four more PET centers are in the planning stages. In Italy, the University of Milan installed a PET center in July and is just now beginning operations, which will include both research and clinical application, according to Ferruccio Fazio, MD, professor of internal medicine. In West Germany, PET is used primarily as a research instrument with limited routine clinical work, according to Franz Oberdorfer, PhD, a chemist and the academic leader of the radiochemistry group and radiopharmacy at the Institute of Radiology and Pathophysiology in Heidelberg. Like magnetic resonance, PET studies are paid for by the government in Germany, he said, in contrast to computed tomography (CT), which is established enough that it is covered by private insurance. At his institute, PET is used in oncology for energy metabolism studies of tumors in selected patients referred to the institute by physicians from a nearby university hospital.

At least one Middle East country, Saudi Arabia, is in the process of establishing a clinical PET center. Richard M. Lambrecht, PhD, chair of the radionuclide and cyclotron operations department at King Faisal Specialist Hospital and Research Center in Riyadh, said that his new center will examine patients with advanced cancer and other diseases found in developing countries. The technology will also be used for basic research.

Knoxville Experience

PET installations can take one of three forms: a PET scanner with an in-house cyclotron; a PET scanner using only generator-produced tracers, such as strontium-82/rubidium-82; or a PET scanner with generators augmented by regional distribution of fluorine-based radiopharmaceuticals, especially fluorodeoxyglucose (FDG). This latter option is available only in a few areas. Cost estimates range from about $1 million to $1.8 million for each scanner, plus $1 million to $2 million for a hospital-style cyclotron. In addition, there are the costs of facility renovations and operating costs, which can reach $1 million a year (1). Reports suggest these figures are underestimates, however. Howard Dworkin, MD, chief of nuclear medicine, anticipates a $6 million expenditure for cyclotron PET at his facility, William Beaumont Hospital in Royal Oak, Michigan, plus $1 million a year to operate the center. Others report needing at least $4 million for construction and equipment acquisition.

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Before spending such sums for its cyclotron PET installation, the 600-bed University of Tennessee Hospital contracted with a market research firm to perform its own market analysis, according to Karl Hubner, MD, director of nuclear medicine. The results were favorable, and the hospital spent close to $3.5 million for a cyclotron and one PET scanner. The center is a "clinical risk investment" that had to meet the same demands as magnetic resonance or computed tomography, and the money comes from the operating funds of the hospital, which is connected to the University of Tennessee but receives no funding from the school for clinical care. "There may be somebody else out there who did it this way, but to the best of our knowledge there isn't," said Dr. Collmann. Noted Dr. Hubner: "If we're not going to get reimbursed for PET studies, the administration has to be willing to take a significant financial loss."

The planning and writing of the certificate of need began in 1986, and the center became operational in January of 1988. It has one chemist, one half-time pharmacist, two nuclear medicine technologists, two nurses and two physicians who share responsibility for the center. They normally image a maximum of three patients or six studies per day, but have studied as many as five patients, two studies each, during a regular working day. (Additional hours of operation are precluded for lack of staff.)

Dr. Hubner has acquired only one software package from a vendor, and that for cerebral metabolism rate of glucose (FDG), but has hired a person to write software for absolute quantitation in cardiac studies. "In cardiology, with ammonia and FDG, I don't think you have to be quantitative to do good clinical work," Dr. Hubner pointed out. "If you want to

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Cities known to have at least one operating PET center with access to cyclotron-produced radiopharmaceuticals as of September 1987.

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be clinical you can't afford to spend eight hours post-processing on each case."

Other physicians and researchers agree. Giovanni di Chiro, MD, and Rodney A. Brooks, PhD, both of the National Institutes of Health, wrote recently that "it is time for PET to emerge from behind the veil of mathematics and models into the real world of clinical imaging" (2). Their point of view appears to have been very well received by many hospital-based PET users. Dr. di Chiro noted that in a just-published study of patients with glioma (3), the relative quantitative information available from PET was found to be sufficient.

For those facilities that need absolute quantitation, useful models exist for FDG and oxygen-15, but for nothing else, according to Alfred P. Wolf, PhD, director of the cyclotron-PET
program at Brookhaven National Laboratory, Upton, New York. For those who want to measure such things as receptor density, Dr. Wolf cautioned that “you’d have to have a lot of courage to buy somebody’s program and say, ‘I know what I’m doing.’”

Another kind of challenge Duke University Medical Center, Durham, North Carolina, has faced is radiation exposure, according to C. Craig Harris, MS, associate professor of radiology. “I’m having trouble getting my exposure down to less than 100 mR a month,” he said. “Our facility is not well designed in that respect.” For one thing, it lacks hot cells, relying instead upon such innovations as a free-standing, lead-lined garage for synthesis of FDG. But Mr. Harris notes that a well-designed lab won’t experience such difficulties. In addi-

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tion, Mr. Harris warns that “as with any new modality, when you’re beating the bushes for patients, some expectations are not realistic.”

North Shore

Another PET facility is at North Shore University Hospital. Although the 600-bed hospital is affiliated with Cornell University, it functions primarily as a community hospital with resources dedicated to research at its adjacent Boas-Marks Biomedical Research Building. It contracted for its equipment in 1986, but serious discussions began on the project as early as 1983, according to J. Robert Dahl, MS, the PET facility’s technical director. The first human study was performed in January of 1988, and the first FDG scan occurred in July.

In 1983, “we began talking, planning, plotting,” Mr. Dahl said. “Doing something like this has as much politics involved in it as any other palace revolution. This one was looked upon favorably; we were very lucky.”

The hospital has a 17 MeV proton, 8.2 MeV deuteron cyclotron, and one scanner that is intended primarily for research and is not expected to generate revenue. The cyclotron could support as many as six or seven PET instruments, Mr. Dahl said, and these additional units would be used clinically.

Site Visits

To prepare for the acquisition, Mr. Dahl and Donald Margouleff, MD, chief of nuclear medicine, visited six facilities, one of them twice. The hospital’s research administrator, Andrew Szilagyi, strongly supported the acquisition because he felt PET had come of age. “Timing was the biggest factor;” he said. “There had been sufficient work in certain areas where there could really be patient benefits.” While he agreed that PET technology is expensive, Mr. Szilagyi noted that “it’s expensive to do anything” in a hospital, be it equipping an up-to-date pediatric ward or acquiring PET. He added that few administrators attend scientific meetings, and charged that they are overly preoccupied with financial considerations. “These pressures of budgetary medicine are what create the problems,” he claimed. Excessive concern for cutting costs can lead health care providers to make decisions based on the price of a particular procedure rather than on what is best for the patient, he said.

In his talk during the PET symposium at the Society of Nuclear Medicine’s meeting in June, Dr. Dworkin pointed out that support from colleagues both inside and outside of the nuclear medicine department is crucial for successful implementation of a PET center. This was also a consideration at North Shore. “If you’re the proponent of something like this, your expectation has to be, should be, that this will be in competition with [your colleagues’] favorite endeavor,” noted Dr. Margouleff. “They are no less obligated to be a proponent of that than you are [of this]. You have to be prepared to accept that competition in a logical way, and ultimately, after everybody has presented his case, an institutional decision is made. Your obligation is to be a proponent and a spokesperson for this technology.”

Dr. Margouleff said that for the most part, his colleagues were receptive to his proposal, which he championed at every meeting and over every cup of coffee. “Everything new isn’t better. But I think in this hospital we have assembled a group of people who, by and large, are not into buggy-whip medicine. They’re not immersed in nostalgia.”

One problem such clinical users could face, Dr. Wolf pointed out, is that a physician may hear about a new PET compound at a meeting and then request that the hospital produce it immediately. Dr. Margouleff hopes to address this problem by requiring colleagues to do extensive background research, to become experts in all aspects of the compound, before bringing their requests to the center.

North Shore’s vendor supplied image manipulation, reconstruction and region-of-interest software, but specifically avoided offering a complete modeling package. “We opted for that,” said Mr. Dahl. “That was attractive to us because if you’re going to carry out studies, you have to understand what you’re doing. To understand what you’re doing, you have to get involved enough to write your own software.”

Rubidium Generators

As much of the expense and complexity of PET is attributed to the cyclotron, a number of facilities have opted to perform studies using rubidium-82 obtained from a strontium-82/rubidium-82 generator. But doing without a cyclotron has significant drawbacks. “With a rubidium generator, you’re restricting yourself to a very narrow range of things you can do. That’s OK for the heart, but the strontium/rubidium generator won’t tell you anything about receptors, and it won’t tell you anything about a lot of other things,” said Dr. Wolf. Henry Wagner, MD, director of nuclear medicine at Johns Hopkins Medical Institutions, Baltimore, Maryland, agrees, adding that he believes community hospitals would be ill-advised either to take on the challenge of the cyclotron or to stick with rubidium alone. He concedes, however, that “rubidium would not be a bad place to start” for facilities anticipating delivery of cyclotron-produced compounds, particularly fluorine-18. It is also worth noting that Los Alamos National Laboratory and Brookhaven National Laboratory, the only sources of the strontium-82 for the genera-
tors, produce isotopes only some months of the year. In addition, new radiopharmaceuticals for single photon emission computed tomography are now under review and some believe these could supplant rubidium's usefulness as a heart tracer.

**Regional Fluorine-18**

Regional delivery of fluorine-18 would do much to encourage clinical PET, researchers agree. In fact, such deliveries were important to the initial development of the technique. "We were probably the first ever to transport fluorinated compounds for PET studies," said Dr. Wolf. "We transported to Washington and to Pennsylvania in the early days. The main hitch is not so much making the stuff and the half life, the main hitch is the route of transportation." Depending on how smooth the transportation system is, shipments are possible within 200 or 300 miles, he said. Brookhaven stopped shipping because of transportation difficulties—such things as pilots refusing to fly with radioactive material—and because those who benefited from the shipments have their own cyclotrons now. Cooperation between equipment manufacturers and radiopharmaceutical companies for regional shipment of FDG would do much to encourage the clinical use of PET, as would reimbursement for the studies (see box, page 1753).

The shortage of personnel trained in PET is another serious problem, exacerbated by the absence of radiochemistry courses in many chemistry departments. Dr. Wolf said that four people, including ideally an electrical engineer and at least one PhD-level chemist, are usually required to operate and maintain a cyclotron, with another set of technically trained personnel available to use the PET scanner. While it may be possible to get by with fewer people with less experience, that could create problems if something should go awry. "You have to have people who are critical enough to know that something doesn't make sense," noted Joanna Fowler, PhD, senior chemist at Brookhaven National Laboratory.

Obtaining such people is difficult. "There is no pool of trained people to take," said Dr. Wolf, "so what happens? They spend their time raiding. This is happening in all the new PET centers that are opening up. They just raid the established centers like ours, Washington University, UCLA, and they hire away the people at huge salaries to set their centers up. Now of course that works, but it means that places like ours, and Wash U primarily, serve as training centers for people that feed out into the PET system. . . . You get kind of tired starting over and over again." Because the demand for such people may already outstrip the supply, it may be some time before the personnel shortage is eased.

**Statistical Base**

Future developments in PET can be expected to make it accessible to a far wider range of facilities than is currently the case. For now, before taking on the benefits and challenges of PET, community hospitals need to work hard to educate themselves. "Some of them have a good feel for what is required; others are just wandering around and come up with the most absurd ideas of what you can do," said Dr. Wolf. "You know what's bad about that? It's not that [they're] wasting a lot of money and doing something really stupid, it's that if people like that get into the business and make a mess of it, it will reflect on the rest of us." He added that "PET never really will be proven, one way or the other, until it gets into hospitals where they just grind out eight to 10 patients a day, and we get a big statistical base."

Existing installations may be the best source of information. "Find out who's got it and using it in the fashion you want to use it," advised Dr. Bacharach. "I'm afraid that some of the hospitals that are getting into it now are getting into it strictly on the basis of what they're told by the commercial companies. We think that's a mistake," added Dr. Wolf.

**It's Going to Happen**

When they make these visits, prospective PET owners should be clear in their intentions. "If these places would come around to people like us or Wash U and tell us what it is they want to do, then we can give them a very accurate idea—that's easy to do," said Dr. Wolf. "What is not easy to do is when somebody comes to us and says, 'I want to set up a PET cyclotron facility.' That's like saying I want to build a car. But once you know what the parameters are of what these people want to do, then it's very easy to tell them what they're going to need."

Perhaps in a few years, PET studies will be as common as CT scans are today. "It's going to happen," said R. Edward Coleman, MD, director of nuclear medicine at Duke University Medical Center, about widespread clinical PET. "There's such powerful information available that it can't help but happen."

Karla Harby

**References**

