

THE INTERNATIONAL STATE OF PET

HAILED BY SOME AS AN innovative diagnostic imaging tool that will revolutionize the detection of disease, and berated by others as an expensive luxury that will only exacerbate the skyrocketing cost of health care, positron emission tomography (PET) has begun to escape its confinement in the research laboratory to enter the realm of clinical medical practice. However, the advancement of PET programs, in the United States and the rest of the world, continues to be tempered by concerns over its exorbitant cost and its technical complexity. While the status of PET programs varies from country to country, they all face the same problems, to various degrees, as the American program.

Currently, according to the Institute for Clinical PET, there are about 60 operating PET centers in the U.S., and 10-15 more are scheduled to initiate operations in the next 8 months. Outside the U.S., about 40-45 PET programs have been set up. The majority of them are located in Western Europe and Japan (see map, p. 31N).

Britain

Established in 1979, the Medical Research Council's (MRC) Cyclotron Unit, Hammersmith Hospital, London, was Britain's first PET facility. "There are also PET scanners in use in Royal Marsden Hospital in London and also one in a hospital in Aberdeen, Scotland," says Terence J. Spinks, PhD, staff physicist at Hammersmith. In addition, he notes that two more PET programs will be instituted later this year in Greater London-area hospitals.

The MRC Cyclotron Unit, says Dr. Spinks, routinely produces oxygen-15 (^{15}O), fluorine-18 (^{18}F) fluorodeoxyglucose (^{18}F FDG), ^{18}F -labeled-fluorodopa, "and other agents used primarily in cerebral imaging studies, since the focus of our research work is in the field of neuroscience."

Dr. Spinks notes that "The main obstacle to establishing a PET program in Britain was, of course, the cost. Although Hammersmith Hospital had a history of using radioisotopes in medicine prior to the development of PET, it was initially difficult to obtain sufficient interest from the funding authorities, which in Britain, is the government's Medical Research Council."

Addressing the issue of PET's usefulness, Dr. Spinks notes that "PET's ability to label an enormous number of biological compounds, its very high resolution and accuracy, and its ability to monitor the behavior and circulation of drugs in the body makes it an invaluable tool in the investigation of organ function and metabolism." Dr. Spinks affirms, "I believe that PET is gaining wider acceptance as a research tool among the neuroscience community in Britain, although the radiologic professions are still largely unfamiliar with it."

According to Dr. Spinks, the issue of recruiting qualified personnel to operate PET centers is not nearly as problematic as it is in the U.S. "We do not face a serious shortage of qualified people to work at PET centers simply because we have so few facilities here compared to the States. And although our staff members come from a wide range of specialties—physics, oncology, neurology, cardiology—without previous experience in nuclear medicine procedures per se, they learn on the job." While Dr. Spinks is optimistic about PET's future growth in Britain, he cautions, "Its clinical value will have to expand in order to justify its use, and currently, PET is almost exclusively an instrument of research in Britain."

"I see the future role of PET as falling somewhere between the research and clinical areas — not limited to either function," comments Terry Jones, PhD, assistant director of the MRC Cyclotron Unit. "PET will provide a fantastic teaching tool for future medical students

in order to help them to think in more quantitative functional terms."

Belgium

PET technology, however, is not limited to the larger countries. The small nation of Belgium is well advanced in its PET program as evidenced by the existence of five PET institutions. "The first PET facilities in Belgium were installed in the late 1970s at the University of Ghent and the University of Liège. Subsequently, PET programs emerged in Louvain-la-Neuve, Brussels and Leuven," says Christian Michel, PhD, senior physicist, laboratory of positron tomography, Catholic University of Louvain, in Louvain-la-Neuve. Plans for a sixth PET facility at Vrije Universiteit Brussels are also in the works.

Dr. Michel's facility was founded in 1985 with the sole purpose of providing research opportunities. "No private enterprise was able to finance the PET project here, thus we had to persuade the government to provide the funding." The newest PET center in Belgium — at Catholic University of Louvain — was established in the late 1980s, more than ten years after its plans were initially drawn up. Comments Alfons M. Verbruggen, PhD, laboratory of radiopharmaceutical chemistry, University Hospital Gasthuisberg, Leuven, "Cost is always a factor in retarding the installation of PET centers."

According to Dr. Michel, the Louvain PET facility routinely produces such radiopharmaceuticals as ^{15}O , carbon-11 (^{11}C)-labeled-acetate, ^{11}C -labeled-palmitate, ^{11}C -labeled-thymidine, ^{18}F FDG, and nitrogen-13 (^{13}N)-ammonia. "The radiochemistry group here is developing targetry for isotope production and automated radiopharmaceutical syntheses," he says. "Our biomedical program consists of studies in neurology, neurophysiology, neuropsychiatry, cardiology, hepatology, and hematology."

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Dr. Michel says that although a PET center requires only a few key scientific personnel — that is, physicists, radiochemists, and engineers — it is difficult to find people with nuclear medicine expertise. “Consequently, we have to recruit scientists with general qualifications and train them at our facility,” he says. Dr. Verbruggen adds that “all PET centers in Belgium follow the same policy: to send one or more of their own researchers to a PET facility in the U.S., for example, The Johns Hopkins Medical Institutions or the University of California at Los Angeles, in order to acquire experience and expertise.”

Concerning the future of PET in Belgium, Dr. Verbruggen tempers his enthusiasm with concern about PET’s future clinical applicability and burdensome cost. “In theory, PET permits the quantification of biochemical processes unlike SPECT, but it remains for me an open question whether the extra clinically useful information obtained by this technique is really worth the enormous cost. In my opinion PET will remain mainly a research tool.”

Moreover, in Belgium, Dr. Verbruggen explains, “Since January 1991, reimbursement of the cost for selected types of clinical PET investigations — notably epilepsy and heart studies — has been established by the government.” Dr. Verbruggen maintains that due to this new reimbursement policy, “the number of clinical PET studies will likely increase in Belgium.” He also adds that PET sites in Belgium “will remain centers of research, combined with a limited number of clinical studies.”

Sweden

“Sweden currently has two PET facilities, one at the Karolinska Institute in Stockholm and our facility in Uppsala, which will be getting a new scanner in May,” says Bengt Langstrom, PhD, professor of chemistry and director of the Uppsala University PET Center. “PET arrived in Sweden about ten years ago, and has up to now served strictly a re-

search function. However, the trend now is for PET to move toward more clinical and diagnostic roles. When our new facility in Uppsala is unveiled in spring, we foresee one third of our activities devoted to clinical responsibilities.”

Dr. Langstrom is confident that PET will undergo tremendous growth in Sweden. “Its potential is great, and at some Swedish universities there already exist programs for chemists and physicists to direct their careers towards PET.”

Dr. Langstrom maintains that the much ballyhooed issue of PET’s high cost obscures the benefits that can be accrued from it. “If you only look at the cost you forget that PET’s capability of functional imaging can provide great medical and scientific advancements. There are no viable alternatives to what PET can do. I believe its cost — which is not really that outrageous when compared to SPECT [single-photon emission computed tomography] or MRI [magnetic resonance imaging] — will be offset by its ultimate clinical and diagnostic value.” Dr. Langstrom adds that the Uppsala facility, unlike most PET centers around the world, is being funded largely (75%) by private and corporate donations. “Also, to generate revenue, we expect to produce 30 to 40 different radiopharmaceuticals for commercial buyers.”

Germany

Also moving ahead in its PET program is Germany. The oldest PET center there is the Deutsches Krebsforschungszentrum (DKFZ), in Heidelberg, founded in 1964 as a national research center in basic and applied cancer research. In collaboration with hospitals at the University of Heidelberg, the DKFZ facility routinely produces such familiar positron-emitters as ^{11}C and ^{13}N , as well as the ^{18}F -labeled agents, which have very important oncologic applications. The clinical program at DKFZ, which focuses exclusively on cancer studies, includes investigations into the differentiation of recurrent colorectal tumors from scar, the preoperative staging of bronchogenic carcinomas, the evaluation of regional chemotherapy in patients

with liver metastases, and the evaluation of the therapeutic effects of radiation therapy in recurrent colorectal carcinomas.

Another prominent German PET facility is the Abteilung Nuklearmesstechnik und Strahlenschutz, Medizinische Hochschule, in Hannover. Kurt Jordan, PhD, director of this center, has developed a computer program that simulates PET hardware. The objective of this project was to predict the performance of a complete tomograph through the use of a flexible computer-controlled hardware for mechanical simulation.

Italy

The PET program in Southern Europe is dominated by Italy. “There are currently three operating PET centers in Italy,” says Riccardo Guzzardi, MD, CNR Istituto di Fisiologia Clinica, Pisa. “Aside from our facility here, there are programs running in Milano and Napoli, and two others are in construction in Veneto and Genova.”

In operation since 1985, the PET program in Pisa faced “bureaucratic obstacles” — namely, satisfying the government regulations of radiation safety and the issue of cost — to its installation, according to Dr. Guzzardi. “The government seems to have realized the need for PET in this country, as manifested by the approval of these other facilities these past few years,” says Dr. Guzzardi. “There is quite a supportive climate for PET, despite its high cost. In fact, a committee of the government’s Ministry of Health is developing a protocol to establish guidelines for the installation of PET centers in Italian research institutions and hospitals.”

As in the U.S., Dr. Guzzardi remarks, “We also have a problem of recruiting qualified people to work at PET centers. Italian universities that educate physicists and chemists do not provide any specialized training in nuclear medicine. This requires that the PET facilities serve educational functions themselves.”

Dr. Guzzardi claims that no other imaging modality can remotely compete

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with PET. "Even if SPECT can provide comparable resolution to PET, you must remember that SPECT only provides qualitative data, not quantitative." Dr. Guzzardi says he believes that with the Italian Ministry of Health's continued encouragement, PET has a solid future in Italy, "especially as PET's clinical applications increase."

Role of the EEC

Two years ago the European Economic Community (EEC) established its Concerted Action on PET Investigations Program, designed to promote interaction between the various PET centers scattered throughout Europe. "Sponsored and funded entirely by the EEC, the purpose of this initiative was to foster an exchange of information between the various PET facilities in Europe in order to arrive at standardized performance criteria for PET and standardized methodologies and protocol," says a British radiochemist involved with the EEC. "Since each PET center has its own particular protocols and different equipment, this kind of continual informational exchange can ultimately facilitate the progress of PET." The EEC holds several meetings yearly in which PET experts from all over Europe meet to share and discuss methodology, instrumentation, and scientific output derived from PET studies. "It is very important for European PET centers not to duplicate research projects. We do not want to waste our time reinventing the wheel," says Dr. Langstrom. "These EEC meetings serve to prevent that, and that in turn, decreases the cost of running these facilities."

Canada

While the North American PET program is dominated by the U.S., the Canadians have also secured a firm foothold into the technology. "There are currently three PET centers operating in Canada," says Mike Adam, PhD, head of the radiochemistry group, TRIUMF

PET laboratory, University of British Columbia, Vancouver. "Two others are scheduled to open this year and next." Aside from the TRIUMF facility — which concentrates exclusively on neurological research investigations — the other Canadian PET centers are located at the McConnell Brain Imaging Center, Montreal Neurological Institute, Montreal, Quebec and McMaster University Hospital, Hamilton, Ontario. "Another PET facility in Canada will be established this year at the Clark Institute of Psychiatry in Toronto," adds Albert Gjedde, PhD, director of the Positron Imaging Laboratories, Montreal Neurological Institute.

"The Montreal Neurological Institute got into the PET program quite early with the acquisition of brain PET cameras in the late 1960s," explains Dr. Gjedde. "Since PET's initial application was in brain research, Canadian PET institutions have exclusively devoted their activities to cerebral studies. PET studies of the brain are five to ten years ahead of any other organ. There has not yet been strong interest in pursuing other types of PET studies in Canada."

Dr. Adam explains that while the Canadian federal government — through research grants provided by the Medical Research Council (MRC)— has generously funded the existing PET program in Canada, "the future expansion of PET in this country will most likely have to rely upon funding from provincial governments and private commercial interests. The high cost of PET limits how many facilities can operate in this country." Nevertheless, Dr. Adam believes the Canadian government encourages the future growth of PET, as evidenced by a recent 5-year, \$6.1-million [Canadian] research grant awarded to TRIUMF. "It was one of the largest scientific research grants ever disbursed in Canada," he notes. The PET group in Montreal, adds Dr. Gjedde, "also enjoys MRC support to the tune of \$1.25 million [Canadian] per year."

"I think the PET program will proceed slowly but steadily and its progress will be guided by financial considerations,"

says Dr. Adam. "Furthermore, I anticipate that the cost of PET will eventually decrease as manufacturers develop less expensive cyclotrons and radiopharmacies find cheaper ways to produce and distribute the radioisotopes." Dr. Gjedde cautions that existing and future PET institutions "will have to defend their existence by virtue of their research, not their diagnostic capabilities. Making sense of PET images is an extraordinary, multi-disciplinary effort depending more than anything upon the state of neuroscience. For this reason, justified diagnostic uses of PET will be very slow in coming."

Japan and Australia

Across the Pacific, PET has firmly established itself in Japan, while Australia has recently entered the field. The PET program in Japan has blossomed in the past decade to 19 operating centers, with two more to be instituted this year, according to Hiroyuki Hattori, PhD, director and general manager of Shimadzu Medical Systems, Inc., Gardena, California. "The majority of these centers are associated with university hospitals, and they recruit their employees from those same institutions."

Dr. Hattori explains that reimbursement is the most formidable issue facing the Japanese PET program. "The government classifies PET as a high-tech diagnostic procedure and pays for most of its cost under the auspices of the Ministry of Health," says Dr. Hattori. "However, hospitals and clinics must apply for approval of these payments and it can be a cumbersome process. Only large hospitals and research institutions can afford PET systems; they are completely out of reach of the smaller institutions and private clinics."

The introduction of PET technology into Australia is being undertaken by two facilities: Austin Hospital, University of Melbourne, in Heidelberg, and the Royal Prince Alfred Hospital in Sydney.

The nascent PET program in Australia has been guided by financial considera-

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Financing

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CREIGHTON UNIVERSITY MEDICAL CENTER, has been operating a free-standing PET center for 14 months. During this time, the center has performed 922 scans in 555 patients. Creighton set up the Center for Metabolic Imaging as an adjunct to structural imaging in patient diagnosis and has endeavored to bring PET applications with proven efficacy into daily clinical practice. The main indications for PET have been assessment of myocardial viability prior to intervention, the evaluation of brain tumors prior and during treatment, the evaluation of various forms of dementia, and the study of patients with focal epilepsy refractory to medical treatment. The patient mix has been as follows:

Cardiac Indications	50.4%
Oncologic Indications	22.6%
Psychiatric Indications	18.5%
Neurologic Indications	8.5%

Those planning to set up a PET Center should consider the need to satisfy all the relevant regulatory aspects involved, including certificate-of-need requirements and other state and federal laws. At this time, it is crucial that a PET center benefit from competitive financing (grants, donations, educational bonds, etc.). Finally, it is very important to find a suitable contractor to tackle the challenging and sophisticated specifications of a clinical PET center. Since Creighton built one of the first free-standing clinical PET centers with both a cyclotron

and a scanner, its planners had to deal with a lot of unknowns. Special needs for ancillary equipment were often overlooked. These problems may no longer exist for planners of PET centers. In our case, significant additional equipment was required that was not properly budgeted for, including additional air conditioning, surge protectors, hot cells, etc.

The equipment the Creighton PET center uses has worked almost flawlessly for the last 14 months. The personnel requirements are relatively low and include a director (PhD radiochemist), 1½ full-time technologists, 1 full-time cyclotron operator, 1½ full-time cardiac nurses, 1 secretary, and 1 nuclear medicine physician (this count does not include people assigned full-time to PET research).

The Creighton PET facility has exceeded its targets for PET volume in the first year and has created charges in excess of \$1.2 million. The revenues from charges are slightly below projections and are currently at about 35%. As you know, Medicare/Medicaid will not reimburse for PET studies. Most third-party carriers honor all or part of the PET charges, and some of our revenues were forthcoming through hospital contracts for inpatients.

The total cost of establishing a PET center was around \$5 million, with cost overruns amounting to about \$300,000, mainly in non-scheduled ancillary equipment and cost overrun for the building.

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tions, according to John McKay, MD, director of nuclear medicine, Austin Hospital. "The [start-up] cost and [operating] costs for our facility are being covered by federal and state government grants and corporate contributions. The plans for this PET center were on the drawing boards as early as 1978, and it took over ten years to get constructed." Dr. McKay is confident that PET will flourish in Australia. He also indicates that Australian PET facilities will for a while have to recruit some qualified personnel from overseas, while its own PET

program gets off the ground. "We recently advertised for a senior radiochemist for our newly installed minicyclotron, and the response has been tremendous. Candidates are apparently attracted to Australia." Dr. McKay points out also that "we are currently training personnel overseas as extensive links are being forged with overseas institutions." Dr. McKay adds that despite Australia's geographic remoteness, "Our research and clinical facilities are up to par with Europe and the United States, and our PET program shall eventually reflect that."

While the long-term efficacy and utili-

ty of PET continues to be debated by scientists and government officials throughout the world, manufacturers of PET scanners and cyclotrons are trying to reduce the cost by simplifying the circuitry, reducing the number of parts, and encouraging the establishment of centralized radiopharmacies, which can provide short-lived radioisotopes to various facilities. While PET supporters do not deny the substantial financial burdens of PET, they singularly point to its excellent diagnostic and clinical potential as a justification that countervails its other liabilities.

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