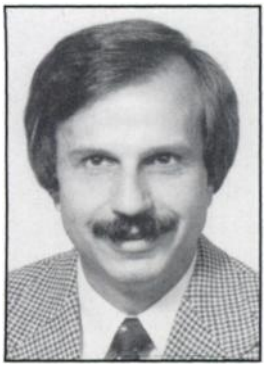
COMMENTARY

CLINICAL PET: A CHALLENGE FOR NUCLEAR MEDICINE

THE DEVELOPMENT IN THE LAST 20 YEARS that will have the most impact on the future of nuclear medicine is positron emission tomography (PET). PET was developed in the early 1970s in academic institutions, and its development continued within a few medical centers and small companies until the mid-1980s. The first PET centers were supported by research grants, and the initial studies determined the role of a large array of metabolically important radiopharmaceuticals in understanding disease processes. These studies documented PET's ability to quantify metabolism and perfusion in the brain and heart. PET's ability to provide this unique information *in vivo* made obvious the logical extension of the technique to clinical applications.



R. Edward Coleman, MD

PET is an ideal technique for achieving the diagnostic goals of nuclear medicine. PET permits quantification of chemistry *in vivo,* thereby providing information in humans analogous to that from autoradiography in animals. The availability of radionuclides of carbon, oxygen, nitrogen, and fluorine for imaging with PET provides the opportunity to label a large array of metabolically important substrates for studying disease processes. Generators available for the production of rubidium-82 (^{82}Rb) and gallium-68 provide additional radiopharmaceuticals for PET. Accordingly, many different physiologic processes can be assessed for both research and clinical purposes.

Despite these favorable attributes, PET has not gained widespread clinical acceptance for several reasons. PET is often considered a research modality because of the cost of the technology, the manpower-intensive requirements for some studies, the major emphasis on research topics, the absence of a policy for reimbursement by third-party payers, and uncertainty concerning the role of the Food and Drug Administration (FDA) in regulating radiopharmaceuticals for PET.

In addition, PET studies are expensive compared to most routine nuclear medicine studies. The cost of a PET scanner is approximately $2 million, and the cost of a cyclotron-radiopharmaceutical production system is also about $2 million. There are also extensive operating costs. For example, the cost of the strontium-82 parent for an ^{82}Rb generator is $25,000 per month.

Most clinical PET facilities are currently charging between $1,600 and $2,600 for diagnostic examinations, depending on their complexity. These charges are based on six to eight clinical studies per day, which is the number that a facility needs to perform to be profitable. In the proper clinical setting, the unique clinical information available from PET studies justifies these charges, which are only slightly greater than charges for some quantitative nuclear medicine studies, for example, exercise-redistribution thallium-201 imaging, or for some anatomic imaging studies, for example, magnetic resonance imaging (MRI) performed with or without contrast administration.

Reimbursement Issues

Reimbursement by third-party payers is the major issue that will determine the fate of clinical PET. The Health Care Financing Administration (HCFA), which administers Medicare, has referred the review of PET to the Office of Health Technology Assessment (OHTA). OHTA has reviewed PET for clinical applications and will send the results of its review to HCFA this year. OHTA and HCFA have determined that they will neither establish a reimbursement policy nor make the result of the OHTA review available until the radiopharmaceuticals used for PET are approved by the FDA.

Although several insurance companies are reimbursing for PET scans, few, if any, have a national policy for reimbursement. The Health Insurance Association of America (HIAA) represents most of the private insurance companies with the exception of Blue Cross/Blue Shield. The Medical Practice Assessment Unit of HIAA sponsored a meeting on the cardiac application of PET in November 1990. The expert panel, which consisted of physicians with specialty training in cardiology, nuclear medicine, radiology, and thoracic surgery, reached a consensus that PET provided unique information in certain clinical situations. A recommendation for reimbursement for defined cardiac indications is anticipated from some of the insurance companies who participated in the meeting. HIAA also sponsored a meeting on the neurologic applications of PET in March 1991.

Once a reimbursement policy is established, the insurance companies do not have a method for restricting the use of the technology to those indications approved for reimbursement. When one insurance company develops a national policy for reimbursement, this policy will influence other insurance com-

(continued on page 52N)

Coleman Commentary

(continued from page 42N)

panies. If several major insurance companies develop policies for PET reimbursement, these policies will influence the policy at HCFA. Furthermore, if HCFA establishes a policy for reimbursement for PET, this policy likely will greatly influence private insurance carriers. Because of these far-reaching ramifications of decisions to reimburse PET studies, the medical directors of several insurance companies have expressed concern about the proliferation of PET centers (there were approximately 60 in the United States as of February 1991), the cost of the studies, the quality of studies, and the credentials of persons performing and interpreting the studies.

PET Radiopharmaceuticals and the FDA

The potential impact of FDA regulatory actions regarding the clinical use of PET radiopharmaceuticals is another issue that will affect the fate of clinical PET. Although many of the initial research PET studies were performed under the aegis of an Investigational New Drug (IND), new PET centers that are doing research have been notified that they can perform studies with fluorine-18 (^{18}F) fluorodeoxyglucose (^{18}FDG), nitrogen-13 ammonia ($^{13}NH_3$), and oxygen-15 tracers under institutional authority (presumably with approval of a Radioactive Drug Research Committee) without filing an IND. Although the FDA is not requiring INDs for certain research studies with PET, FDA representatives have stated that clinical studies with PET radiopharmaceuticals require an approved New Drug Application (NDA). For clinical PET studies with an on-site cyclotron, the physician writes an order for a radiopharmaceutical, the radiopharmaceutical is prepared under the license of a physician or a radiopharmacist, and the study is performed. This radiopharmaceutical preparation and administration occurs on-site in the medical center. Since the radiopharmaceutical is not transported across state lines (that is, it is not introduced into interstate commerce), and since these studies are performed in the hospital under the practice of pharmacy/practice of medicine exemptions in the Food, Drug and Cosmetic Act, most clinical PET centers have detemined that an NDA is not needed for radiopharmaceuticals such as ^{18}FDG and are performing these studies under state authority. Representatives of the FDA have stated that they are aware of this clinical use of ^{18}FDG, but that they have no plans to alter the agency's regulatory posture at this time. However, if someone were to make an issue of the FDA jurisdiction, the FDA is willing to exert what it believes to be its authority to regulate the use of this special group of drugs. The Board of Pharmacy of the State of California and the leadership of The Society of Nuclear Medicine and the American College of Nuclear Physicians have written letters to the FDA stating their opinion that the FDA has no jurisdiction over the local use of PET radiopharmaceuticals. As yet, no definitive legal opinions regarding FDA jurisdiction have been rendered.

Regional distribution centers for PET radiopharmaceuticals are being developed. These centers plan to distribute primarily ^{18}FDG. This ability to distribute ^{18}F radiopharmaceuticals commercially was demonstrated in the late 1960s and early 1970s, when ^{18}F sodium fluoride was made available in most parts of the country for use as a bone-scanning agent. But, an NDA is needed for such interstate distribution of ^{18}FDG and other PET radiopharmaceuticals. In addition, HCFA requires an NDA for reimbursement. To assist radiopharmaceutical manufacturers and individual medical centers with their NDAs for ^{18}FDG, the Institute for Clinical PET, working in cooperation with the FDA, is developing a Drug Master File (DMF) for ^{18}FDG.

Clinical PET: The Challenge for Nuclear Medicine

Several issues need to be resolved before clinical PET will be available in hospitals other than major medical centers, but these issues are being addressed. The major instrument manufacturers involved in PET have made impressive improvements in the hardware and software of the tomograph. Cyclotrons and the necessary radiochemistry are becoming more and more automated, and the manpower needs of PET facilities have decreased with these improvements. The costs of the equipment will decrease as the needs of clinical systems become more well-defined and the number of systems sold increases. Data supporting the clinical applications of PET continue to be generated, and these data are convincing third-party payers to reimburse for PET. The extent of FDA jurisdiction over PET radiopharmaceuticals has yet to be determined, but representatives of the FDA have stated that the agency does not plan at this time to curtail the activities of centers doing clinical PET studies under local authority.

Clinical PET is important to the specialty of nuclear medicine. Clinical PET is the epitome of the application of the tracer method to medical diagnosis. The nuclear medicine community must keep current in the advances in PET technology and its clinical applications. PET technology is technology of nuclear medicine. If nuclear medicine does not demonstrate its interest in the development and application of PET, other specialties will make PET their own.

R. Edward Coleman, MD
Professor of Radiology
Director of Nuclear Medicine
Duke University Medical Center