PET: The New Focus of Nuclear Medicine?

TO THE EDITOR: We were pleased to read Dr. Henry Wagner's enthusiastic espousal of positron emission tomography (PET) as the new focus of nuclear medicine (1). As neurologists who have used PET to study a variety of physiologic and pathologic conditions of the human brain, we have long believed that the quantitative regional measurements of cerebral physiology provided by PET will prove useful in the management of patients with neurological disease. However, we also believe that it is premature to advocate the "wide scale" clinical application of PET. In our opinion the data currently available are not sufficient to prove the clinical usefulness of PET except in a few special circumstances. Furthermore, we are somewhat apprehensive that vigorous promotion of the clinical utility of PET without solid scientific clinical research to back up such claims may prove deleterious. A "PET backlash" has already developed in the scientific community (2) among those who perceive that PET research has consumed much money but yielded little new information about cerebral physiology and pathophysiology. We are concerned that this backlash may worsen and spread to the spheres of clinical practice, third-party carriers, hospital administration, and government regulatory agencies if claims of the clinical utility of PET are made prematurely and without adequate supporting data.

Up until this time the primary use of cerebral PET studies has been for clinical research. The value of PET as a research tool stems from its ability to provide accurate measurements of regional radioactivity of positron-emitting radiotracers in the brain. These measurements can be converted, with appropriate mathematical models, to provide regional measurements of cerebral physiology. The usefulness of PET in research depends on the accuracy of these measurements. Since each mathematical model contains assumptions about radiotracer behavior that may or may not be valid, each PET method should ideally be validated by comparison with another method for measuring the same variable. This has been done for PET measurements of cerebral blood flow and metabolism (3,4). Newer methods, such as those aimed at measurements of protein synthesis or receptor binding, are extremely complex and have yet to be perfected to the point where accurate quantitative measurements of physiologically relevant variables can be made.

The requirements for clinical utility are different from those for clinical research. Quantitative accuracy, although desirable, is not really necessary. The ultimate clinical utility of any diagnostic procedure is measured by its ability to reduce morbidity and mortality or expense. This can be accomplished by providing information previously unavailable or by replacing more expensive or hazardous procedures. In spite of the enthusiasm that it has generated, there is little evidence currently available to show that PET studies of the brain fulfill these criteria except under certain special circumstances.

Some evidence for the clinical utility of PET comes from DICHTO and his colleagues who have demonstrated, in a small series of patients, that FDG scans are useful for differentiating radiation necrosis from recurrent brain tumor, a differentiation that often required biopsy in the past (5). Although these findings will be a useful addition to patient care if confirmed, the occurrence of this diagnostic problem is, fortunately, rare. The value of PET in the diagnosis of epilepsy remains to be proven. Epilepsy is primarily a clinical diagnosis based on a careful history and supported by electroencephalographic data. The finding of focal areas of brain hypometabolism with PET is nonspecific and can be due to a variety of nonepileptogenic processes (6). The documentation of focal hypermetabolism by PET during a clinical spell is physiologically interesting but too cumbersome to replace clinical observation or EEG as means to determine if the spell is a seizure. Research by the UCLA group has helped to define the role of PET in surgical therapy for intractable seizures. The findings of a hypometabolic focus in a location that correlates with the seizure focus determined by surface EEG has obviated the need for placing depth electrodes in the brain of some patients (7). While this approach clearly demonstrates clinical value, it must be remembered that surgical therapy for epilepsy is performed in a small number of patients in a few specialized centers and that depth electrode recordings are not always necessary.

The role of PET in the differential diagnosis of dementia and the identification of patients with Alzheimer's disease has been the object of a number of clinical studies. To our knowledge, all of these studies have used as their gold standard the clinical diagnosis of Alzheimer's disease made by a trained neurologist aided by conventional laboratory tests. Similarly, patients with multi-infarct dementia (8) and depression in these studies have also been diagnosed by conventional criteria. There is really no need for a diagnostic test that can merely replicate the clinical diagnosis and it is unlikely that PET will replace the neurologist as primary diagnostian. A neurological consultant is just as fast, cheaper, involves no ionizing radiation, and, as an extra bonus, can provide advice on how to treat the patient. There is, certainly, a need for a way to diagnose early Alzheimer's disease at a time when symptoms are mild and the distinction from other conditions such as depression is difficult. PET is potentially useful in this area and studies are ongoing. Its sensitivity and specificity remain to be proven.

Studies of subjects at risk for Huntington's disease have demonstrated decreased FDG uptake in the caudate nuclei before the onset of clinical symptoms (9). The suggestion has been made that this might be useful in identifying asymptomatic at-risk subjects who will develop the disease. The ethical questions involved here are formidable especially if there is any chance of false-positive or false-negative results. Even so, Huntington's disease is rare and unlikely to create a large demand for PET studies. Furthermore, the fully developed disease is easily diagnosed by history, neurological examination, and CT scan.

The recent development of positron-emitting neuroreceptor ligands has opened up the possibility for imaging neuroreceptors in vivo in a variety of pathologic conditions. While these studies have the potential to increase our understanding of pathophysiology and neuropharmacology, their value in the diagnosis and treatment of patients with movement disorders such as Parkinsonism and psychiatric diseases such as schizophrenia is problematic. While PET may provide elegant pictures of receptors ligand binding in untreated patients and show changes with drug treatment, it is important to remember that
these diagnoses can usually be made clinically and that the clinical response of the patient is the most important measure of drug efficacy.

The application of PET to clinical cerebrovascular disease has great appeal. Although PET studies have added to our understanding of pathophysiology of stroke, translation of these findings to improvements in the diagnosis and treatment of patients has not been accomplished. The diagnosis of cerebral infarction can be made with great accuracy in the patient who suffers the abrupt onset of a focal neurological deficit and has a normal CT. The demonstration of an area of decreased blood flow or metabolism at a time when the CT is normal provides little additional information and is merely confirmatory. The absence of a flow-metabolism deficit does not rule out cerebral infarction since small lesions below the resolution of PET can cause major clinical deficits. The value of PET in the choice of therapy for patients with cerebrovascular disease shows great promise but is, as yet, unproven. Research in our laboratory and in others have suggested that PET can differentiate viable from non-viable tissue early in the course of ischemic stroke(10). Confirmation of these important findings will require studies of the effect of surgical or pharmacologic revascularization in these patients. Studies of patients with transient ischemic attacks have demonstrated that it is possible to differentiate those patients with normal cerebral perfusion pressure and blood flow from those with hemodynamically compromised cerebral circulation by PET(10). While it is tempting to conclude that this information can be used to choose medical or surgical therapy more rationally, it remains to be shown that these two groups of patients have a different prognosis and respond differently to therapy.

The quantitative regional accuracy of radioactivity measurement with PET combined with the wide variety of radiotracers that can be synthesized and the use of ever more sophisticated mathematical models provide a fertile ground for further clinical research. At this time, however, the clinical usefulness of PET in all but a small number of specific situations remains unsupported by solid, scientific data. We urge caution in advocating the widespread clinical application of this technology until such data exists. Premature claims about the clinical usefulness of PET, if they cannot be supported, could lead to a “backlash” that would be detrimental to the overall development and application of this valuable new technology. When carefully conducted research studies are available that show the value of PET in reducing morbidity and mortality or expense, widespread clinical application of PET and the funds to support it are sure to follow rapidly.

References


William J. Powers
Marcus E. Raichle
Washington University School of Medicine
St. Louis, Missouri

REPLY: The issues related to the clinical application of positron emission tomography (PET) involve both science and politics. One of the reasons why PET is not more widely used today clinically is that up to now those involved in PET research have devoted their efforts primarily to increasing our understanding of the chemistry of the living human brain. Their "dismay for the mundane" applications of PET to the solution of problems such as brain tumor treatment has been in sharp contrast to the actions of the advocates of other imaging technologies, including magnetic resonance imaging. Despite the de-emphasis of patient studies, the number of clinical investigations with PET is still increasing in number and warrants emphasis on the clinical role of PET. Enormous amounts of money are being spent today to establish magnetic resonance imaging (MRI) centers, financed primarily by institutional and private funds, which make possible not only basic and clinical research, but also the application of MRI imaging to patient care. The same thing is happening to a far lesser degree in the case of PET. One reason is that the more abstract, chemically-oriented, lower resolution images of PET do not evoke the same "shock of recognition" that the anatomically-familiar images of MRI produce in the minds of practicing physicians and the public. The "go-slow" approach that Powers and Raichle seem to advocate tends to perpetuate the widespread view, held even by some of the most respected professionals in nuclear medicine, that PET will never be more than an exceedingly complex and expensive technology, never more than an elitist research tool, and never translatable into better care of patients. Many forces today limit the transfer of high technology into medical practice, forces so apparent that it is not necessary to enumerate them. To counterbalance these forces, it is necessary for scientists to present their findings and accomplishments to practicing physicians, funding agencies, regulatory and other governmental agencies, and