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.

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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 "disdain 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 ennumerate 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

more importantly to the public and their political leaders in order to create a clear understanding of how basic and applied science can be translated into better health care and perhaps even to the prevention of disease. The scientific orientation of modern medicine, the regulatory and cost-containment climate, and indeed the complexity of the technology itself will prevent excessive application of PET to the care of the sick. Has the vigorous promotion of MRI been detrimental? I think not.

Clinical investigations employing PET can come about only if the facilities and resources are available to conduct them. A down-playing of clinical applications of PET may prevent other institutions from doing what is now being done in the very institution with which Powers and Raichle are associated. Evens, Siegel, and Ter-Pogossian at Washington University are in the process of using private funds to establish a PET center dedicated to clinical applications of PET. Such controlled clinical studies are usually not possible under the aegis of the scientifically-oriented research pioneered by the National Institute of Nervous and Communicative Disorders and Stroke (NINCDS).

The article by Fox to which Powers and Raichle refer is not, in my opinion adequate evidence of a PET backlash, but an illustration of the unfortunate competitiveness in modern biomedical science resulting from a limitation of resources. Studies of the energy metabolism of brain work has been a major accomplishment of PET and should be a companion, rather than a competitor, to similar studies of phosphoenergetics by NMR. Some view PET and NMR as competing technologies rather than as two fantastic new eyes with which we can begin to understand brain chemistry in a way that may help solve some of the problems of nervous and mental disease.

The mathematical model for the measurement of glucose metabolism, questioned in the Fox article, has been adequately justified by a subsequent publication in the same journal by Sokoloff who answered the objections to the model that were raised. In the case of neuroreceptors, we have also developed a mathematical model that permits calculation of dopamine receptor density in the brain that yields results similar to those obtained in the study of the human brain at autopsy. (Our model has been accepted for publication in the April issue of *J Cereb Blood Flow Metab.*) Thus, the measurement of neuroreceptors in man has "been perfected to the point where accurate quantitative measurements can be made." Measurements of the effects of drugs, such as haloperidol or other neuroleptics may provide the psychiatrist with a way to monitor the specific effects of these powerful drugs on the brain. We can't be sure PET measurements can help individualize chemical treatment of brain disease but it is clearly worth trying to find out.

There is enough evidence for the usefulness of PET studies in clinical medicine to warrant extensive clinical research. PET helps to select brain biopsy sites, assess the aggressiveness of brain tumors, and to select patients for surgical therapy of epilepsy. What we need are PET centers oriented toward clinical research and feasibility testing. Within the next five to ten years, most University medical centers will have both PET and MRI. It is time for those decision makers who have chosen MRI *instead* of PET to realize that this is tying one hand behind one's back.

While I agree with Powers and Raichle that funds to support clinical applications *should* follow carefully conducted research studies, such things don't automatically happen. People make things happen. Pessimism, skepticism, and nihilism could undermine energies and inhibit growth.

Henry N. Wagner, Jr.
The Johns Hopkins Medical Institutions
Baltimore, Maryland

Comparison of "Direct" and "Indirect" Radionuclide Cystography

TO THE EDITOR: We were interested to read the recent paper by Bower et al. (*1*) since, like them, we feel that a comparison of the "direct" and "indirect" methods of radionuclide cystography would be of value. We were disappointed to find that the authors have misinterpreted their own results and misrepresented the findings of one of our own papers (*2*).

Bower's paper is flawed both in an inadequate experimental design and in a failure to provide any statistical analysis of their results. An application of McNemar's test (*3*) shows that there is no statistical difference ($p = 0.5$) between the number of refluxing ureters seen with the two techniques. Of equal importance, however, is whether a ureter is correctly reported as refluxing. The approach taken by Bower is to define as genuine those ureters whose kidneys are either shown to be scarred on IVU, had reduced glomerular filtration, had reflux on an x-ray cystogram or had reflux on the direct radionuclide cystogram. First we would question the suitability of using the direct cystogram as part of a "gold standard" which is testing the effectiveness of the direct cystogram. Certainly it ensures a specificity of 100% for this technique!

Secondly, cystoscopy is about as near as one can get to a "gold standard," allowing the detection of the abnormal ureteric orifices which are liable to reflux (*4*). Bower and colleagues have completely ignored this information in their assessment.

The most important principle underlying the management of patients suspected of having vesicoureteric reflux is the preservation of renal function. Recently, Winter and colleagues (*5*) have compared medical and surgical management of children with vesicoureteric reflux. They found no significant difference in outcomes between the two but they did find that in only half the cases did the ureters of pyelonephritic kidneys show reflux. This emphasizes the importance of having a test which measures renal function and not just the number, shape, and size of scars. As we have emphasized in our previous work (*2,6*) the indirect radionuclide technique allows renal function, gross renal anatomy, ureteric orifice competence (*7*), and reflux to be assessed in a test which requires only a single intravenous injection. The dismissal by Bower of the hazards and difficulties of catheterizing children is, in our opinion and that of others (*8,9*), unreasonable.

The results in Bower's paper do not show direct cystography to be "better" than the indirect and for the reasons given above we feel it to be a much less satisfactory technique. It may of course give "more confidence about the exclusion of reflux"