Medical Technology Assessment Determined by Science and Economics

CLINICAL PET: WHAT ARE THE ISSUES?

"Can the scientific proof of PET's ability to provide new information, reduce risks or costs, and enhance the medical treatment of patients be determined without its widespread clinical application? The answer, unequivocally, is no. Only with the opportunity to test the potential capabilities of PET will the true measure of its success or failure be known."

In this issue, William J. Powers, MD, Marcus E. Raichle, MD, and Henry N. Wagner, Jr., MD, explore the pros and cons of promoting the clinical use of positron emission computed tomography (PET) in the Letters to the Editor section (see pages 1501-1502). Since this dialogue began with the Scientific Highlights of The Society of Nuclear Medicine's Annual Meeting, published in the July 1985 Newsline, *we invited other investigators active in PET research to comment on the debate.*

What is the clinical potential of PET in the future practice of medicine? This question underscores the dialogue between Drs. Powers and Raichle (*1*) and Dr. Wagner (*2*). While it may seem like a straightforward and well-defined question, it raises the more general issue of how clinical procedures are developed, assessed, and released for use in the medical community. These complex issues must be considered in terms of the criteria used to define the complicated and ever-changing requirements of the medical care system, particularly in its present economic turmoil.

The establishment of a clinical procedure typically involves at least four phases:

(a) basic research where the fundamental principles and precision of a technique are determined (primarily funded by public agencies and private foundations);

(b) clinical research where the ability to separate normal from abnormal tissue is explored (typically funded by the same sources that support basic research);

(c) clinical trials where the sensitivity and specificity of a technique are determined (typically subsidized by fee-for-service arrangements, the commercial sector and, to a lesser degree, the public sector); and

(d) clinical utility determinations where the impact of the procedure on mortality, morbidity, and medical economics is assessed.

With these stages in mind, let us consider the basis for a clinically useful test. A successful clinical procedure must, first and foremost, be sound in principle. These principles are developed and evaluated by experiments directed at defining the fundamental relationships that underlie the procedure. Experiments are carried out under tightly controlled conditions and employ many different methodologies to measure the variables of these relationships. Secondly, the test must be precise; the results must be reproducible and must be performed with a high degree of quality control. Lastly, the test must provide more accurate or unique information about disease, reduce medical costs, enhance patient care, or reduce patient risk.

PET criteria

How does PET fare with respect to these criteria? The scientific basis for PET is the application of the principles of computed tomography and tracer kinetic methods to measure physiologic, biochemical, pharmacokinetic, and hemodynamic processes (*3-12*). The principles underlying such measurements are well founded in the basic science laboratory where radioassays are used throughout the entire spectrum of biologic sciences. In contrast to PET, other imaging techniques, such as conventional radiology, ultrasound, nuclear medicine planar imaging, x-ray computed tomography (CT), and nuclear magnetic resonance imaging (NMRI), were implemented clinically before the biophysical and biologic principles that result in the image were, or are still not, well understood.

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Empirical relationships are commonly used to establish much of the technique's value. While such empirical relationships can be extremely valuable in the clinical setting, they frequently add little to the understanding of a disease process. For example, one may say that cerebral edema is associated with decreased x-ray attenuation values in x-ray CT or altered signal intensities with NMRI. These changes are not specific to edema. More importantly, however, what does this test result tell us of the biology of the tissue?

PET has indicated that edema in the brain can have a direct impact on specific physiologic processes: it can reduce blood flow and oxidative respiration (*3–5*). Ischemic diseases typically are detected at later stages by identification of resultant tissue damage (usually an irreversible component) or vessel occlusion by conventional radiologic imaging techniques. By definition, however, ischemia is a state in which supply (blood flow) is insufficient to meet demand (metabolism)—parameters directly measured by PET. In other words, the results from PET are expressed in biologic terms derived from the tracer kinetic measurements with biologically active compounds. The x-ray CT and NMRI results are expressed in physical terms since these techniques result from the application of basic physical principles to biologic systems. Biologic changes do underlie alterations seen by x-ray CT and NMRI. The ambiguities that result, however, from the immense array of chemical constituents contributing to the signal deny specific association.

Precision and reproducibility

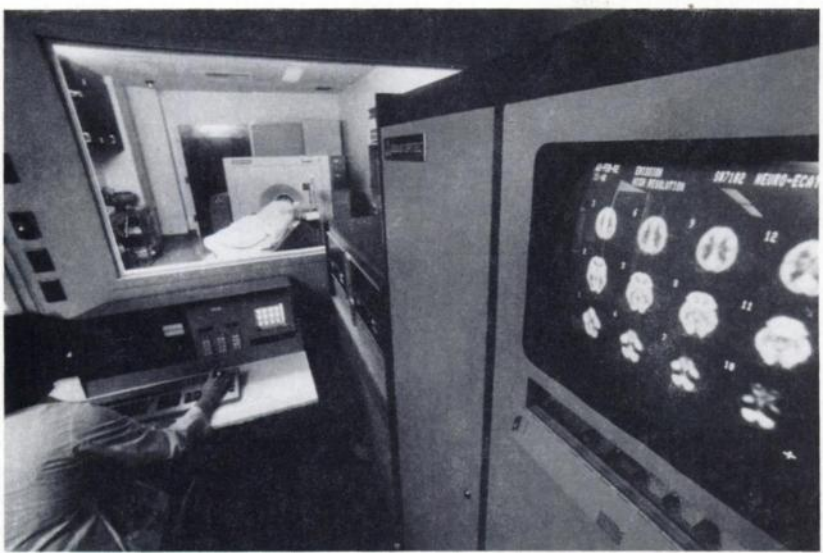
How reproducible and precise are PET studies? Basic research at over 50 centers throughout the world, including extensive studies of normal subjects over the last 10 years, document PET's ability to provide consistent and reproducible results in a research environment (*3–16*). The wealth of information and the number of normal and abnormal subjects studied with PET far exceeds those for other techniques prior to their introduction into the clinical arena.

How can the clinical utility of PET be determined? In order to judge PET's capacity to provide new information, reduce patient costs or risks, or enhance patient care, we need to examine the criteria used for clinical utility testing.

Consider the following question. *Can you identify any clinical procedure, no matter how trivial, that has been scientifically proven to be clinically useful, and to have a positive impact on mortality, morbidity, and medical economics prior to its application in general patient populations?* We cannot, and the reason is simple.

A basic paradox is inherent in clinical utility testing. In order to determine the very important variables needed to establish the efficacy of a clinical test, one needs to apply the test to large patient populations by undertaking clinical trials and utility testing. Therefore, the very information needed to *prove* the utility of the test *prior* to its application can only be obtained *through* its application.

Clinical trials and utility testing require a broader study design than basic research. The study approach is less controlled and more constrained in the scope of investigational interventions. The nature of clinical problems addressed is also less clearly defined than that in basic research because of our limited knowledge of the mechanisms of human disease, the heterogeneity of its manifestations, and the vagaries of clinical classifications. Since clinical utility testing requires large populations, research funding typically cannot—and presently will not—support such undertakings. Therefore, it must be done in the clinical environment.



"Basic research at over 50 centers throughout the world document PET's ability to provide consistent and reproducible results." **(Dan McCoy/Rainbow)**

Research vs. clinical medicine

The objectives and criteria for judging significance and success are different for research and clinical medicine. In the former, one seeks new knowledge about the underlying mechanisms and principles of a disease process; the "scientific method" guides the experimental design and

methods of assessment. The latter uses the resultant knowledge and techniques to detect the presence of disease in the general population, select therapies, and predict outcomes as efficiently and safely as possible. Empirical techniques, with scientific methods to analyze significance, are the hallmark of these approaches.

Although research and clinical medicine are related (the latter commonly being an outgrowth of the former) they remain distinct entities. Through the full gamut of present-day diagnostic tests, from the physical examination itself to the application of NMR principles to imaging, no test has proven scientifically valid or unequivocally useful, by the criteria listed above, prior to its application in populations larger than research studies can provide.

Economics and science

What, then, is required of PET to perform well in the difficult and competitive clinical environment imposed by today's economic and scientific standards? Consider one of the most fundamental issues in the study of human disease—the question of whether tissue is alive or dead. This basic question goes largely unanswered by bedside, laboratory, or imaging approaches. The basis of such a determination is physiologic and biochemical rather than anatomic.

What technique is better suited than PET in basic principles to answer such a question? Lest we consider this question trivial, consider its implications. What is the value, in terms of therapeutic implications, of determining the viability of a segment of the myocardium, a portion of the cerebral cortex, a tumor previously treated and possibly recurring, or an ischemic extremity in need of amputation or revascularization? If PET can answer this one basic question, its ability to fulfill the criteria necessary to satisfy today's demanding scientific and economic constraints will be realized. In our opinion it can.

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Although the general issue of tissue viability is a sufficient reason to justify PET's application in general clinical populations, more specific examples are easily found.

The elimination of invasive or unnecessary tests, or ineffective therapies, can certainly result from PET's application to neurologic and cardiovascular disease. Examples are found in the basic research literature on coronary artery disease, epilepsy, and dementias (*3–11, 14–17*). Information provided by PET could enhance therapy and reduce risk by excluding patients, for example, who would unnecessarily undergo revascularization procedures. Evidence for this potential use comes from the PET studies of patients with acute and chronic ischemic heart disease (*14–16*). Similar evidence is found in the PET literature associated with extracranial-intracranial bypass procedures (*3–11,13,17*).

By eliminating unnecessary surgery for nonviable tissue, health care would realize substantial reductions in cost and risk. Research studies with PET indicate that possibly as many as half of the $7 billion/year coronary artery bypasses will be without benefit in terms of improving segmental and global cardiac function (*16*). PET can also provide more objective selection criteria for surgery versus medical therapies (*14–15*).

Similarly, biochemical and pharmacologic measurements with PET offer the potential for improving subcategorization of patient populations and refining the selection process for the use of drugs (*14–17*).

Lastly, when diseases are examined early in their course, patient evaluation is typically on an outpatient basis. PET, as a noninvasive study, limits risks with attendant morbidity and mortality, and therefore is well suited as a screening procedure.

PET investigations have concentrated on the brain and heart because of the interests of those investigators who initiated and applied PET technology to human disease. Because PET provides an examination of biologic processes that are ubiquitous and fundamental to all human disease, however, its applicability can be generalized throughout the body.

Criticisms of PET

It seems clear, therefore, that PET is not only fundamentally sound, and has undergone extensive testing in normals to determine reproducibility and separation of healthy tissue from abnormal states, but it also has a tremendous capacity for providing new and previously unobtainable information about normal and pathologic processes in the human body. *Why, then, has PET not gone the way of other diagnostic tests with a more rapid dissemination into clinical trials?* To understand this situation, it would be valuable to address a number of the more common criticisms of PET in regard to its clinical use.

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It is sometimes stated that PET is too complicated because it involves physicists, chemists, biochemists, pharmacologists, computer scientists, biomathematicians, engineers, radiologists, cardiologists, neurologists, oncologists, etc. Although this notion is true, it applies to the professional constituency of the field—not the people who would carry out the resultant clinical procedures. One could also say, for example, that clinicians could not carry out conventional nuclear medicine procedures because nuclear medicine consists of this same professional constituency.

Over the last decade, a professional constituency has developed that will continually expand PET's capabilities. This in good part is based upon the existence of an enormous number of biochemical assays in the biologic sciences that can be continually transferred to patient settings via PET.

Where is the cost problem?

"PET is too expensive!" according to some critics. One part of this argument is the tomograph, but it really is not the determining issue. Tomographic imaging devices for PET, SPECT and x-ray CT, produced for a clinical market, are all expected to fall in a similar price range (*12,17*).

There are many factors that affect price within the free enterprise system, and it is not the purpose of this discussion to examine them. However, consider x-ray CT, which has gone through four generations of technical improvement over the last 10 years while the scanners have only increased modestly in cost and charges have remained almost constant—a rare event in medicine, and consumer goods in general, in the last decade.

So where is the cost problem? It is in the supply of labeled compounds. Is this real or artificial? At this time it is probably both. A cyclotron-based system with supplies, personnel, renovations, and overhead can be competitive in cost, and, in fact, advantageous in cost over an eight-year annualized depreciation schedule when compared with the routine purchase of labeled compounds (*17,18*). This analysis is a "model," however, and not a reality because at present there is no technologist-oriented and simplified minicyclotron-based system that supplies positron-labeled compounds for a truly clinical setting. This system must not be confused with small "medical cyclotrons" which exist in a number of commercial systems. We are referring to a system that provides labeled compounds (not isotopes) under good and guaranteed commercial practice, consistent with the professional quality control of nuclear medicine.

Such systems are under development and are benefitting from research now carried out in laboratories throughout the world. This research is providing new approaches to targetry, delivery line, and synthesis technologies required to produce positron-labeled compounds in high yield and purity with ever-increasing simplicity. However, it is *not* required that this system be achieved for all positron-labeled compounds before such an approach can begin. Today it is needed only for those positron-labeled compounds for which there are procedures to support the clinical enterprise. In fact, there are so many positron-labeled compounds (over 200 at present), and the number is so rapidly growing, that this is an open-ended objective (*3,5*).

When such a system is developed so that we no longer refer to it as a "minicyclotron" or "medical cyclotron," but rather as a generator system for producing labeled compounds, it will meet this practical requirement of PET in a clinical setting. It is not a question of whether it *can* be achieved (because we know it can) but whether it *will* be. Even the present cost projections for such a system (from $500,000 to $1 million) are not sufficient to deny the clinical success of PET when put into perspective with annualized expenditures. This cost, added to other expenditures for carrying out PET studies, would indicate procedure charges of $400 to $1,500 per study, depending primarily on throughput (demand and value of the study) (*17,18*). These estimated charges, the implications of PET procedures for medical decision-making, and the cost factors resulting from a diagnosis, are not restricting factors; in fact, they give favorable indications for the type of information provided with PET.

Critical issue

So what is the critical issue? It is clear that a practical stumbling block stands in the way of testing the clinical hypothesis presented here. How can one move to the next tier by the dissemination of PET to a number of clinical (not clinical research) environments if there is no "clinical positron generator system"?

Cyclotron technology inspired the beginning of nuclear medicine. Today, cyclotron technology lies at the heart of nuclear medicine and represents the future of this specialty (*12*). It is unlikely that the long-term goals and vitality of nuclear medicine can be achieved by always relying on the "magic bullet" concept of technetium-99m-labeled compounds. All other radioisotopes used in nuclear medicine are produced from a cyclotron. Research involving accelerator technologies, therefore, should not be put aside as some foreign factor in nuclear medicine.

We should also keep in mind the fundamental principle of technology development: The greater the development effort, the simpler, cheaper, and more effective the resultant solution.

There are, of course, alternatives that some would propose to the mini-

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cyclotron-based technology for PET, including the use of conventional generator approaches such as with strontium-82/rubidium-82 and germanium-68/gallium-68. All of these alternatives can potentially play a role as this field evolves.

The carbon-11, oxygen-15, nitrogen-13, and fluorine-18-labeled compounds, however, are too valuable to be put aside. These radioisotopes form the fabric that connects in vivo radionuclide procedures to the biologic sciences. They are the only radioactive forms of the natural elements that can be detected externally. These radioisotopes can directly provide labeled versions of compounds for which a tremendous body of knowledge relating to biologic behavior and assay techniques exists. These radioisotopes provide labeled compounds for which issues of safety and approval for human use are resolved by mainly satisfying quality control requirements. These labeled compounds will not require *de novo* development as is so commonly the case with our conventional nuclear medicine radioisotopes that often result in labeled compounds with unknown or unpredictable biologic properties. As we move more from body functions to body chemistry, it becomes increasingly more difficult to produce labeled compounds that retain specific biologic properties.

For example, one does not have to measure and prove the biologic properties of amino and fatty acids labeled with carbon-11 instead of carbon-12 and given in pico- or nanomole amounts. Drugs and analogs of substrates are typically selected that have been extensively investigated in the biologic and clinical sciences and are labeled to produce the identical compound, thus retaining the knowledge of the compound's properties. Additionally, such compounds are produced on-site, which avoids shipping problems, and they reduce concerns of radioactive waste disposal and contamination because of their short half-lives.

> "The rationale for resisting PET's dissemination does not rest on any difficulties with the technology's basic principles or lack of confidence in its ultimate capacities."

PET has a very large research base, established not only through over 50 PET centers operational worldwide, but also through the vast application of tracer kinetic methods in the basic sciences with analogous labeled compounds. This research base combined with the clinical information available to date indicates a number of target areas where, in a controlled setting, clinical application and utility testing should begin. These target areas include epilepsy, coronary artery disease, cerebrovascular disease, neoplastic disorders, and dementia.

It would be justifiable and prudent to be less aggressive in the application of PET in areas where either basic research or initial clinical research is not as advanced. However, these less advanced areas, in terms of disease categories and processes that can be measured, represent the broad application and growth potential of PET.

We must accept the fact that PET is based upon sound principles. No one in medicine would deny the tremendous value and specificity that local, noninvasive, biochemical examinations of patients could provide categorically (independent of any particular technology) since all diseases have a biochemical basis and origin, and all therapies are directed at correcting, retarding, or supplementing that biologic abnormality.

The PET research community continues to establish new methods, new data, and new ideas in specific PET approaches for performing analytic biochemical assays. This occurs as an inherent part of the investigators' search for more refined and diverse tools to probe the fundamental nature of processes in human health and disease. This work continually expands the number and scope of existing (and potential) approaches that can be simplified and later used to test the value of these PET-provided assays in medical care.

The major economic issue is not the cost of carrying out diagnostic procedures, but rather the cost of implementing the decisions that result in patient care. It is very likely that as the changing medical care system advances in its understanding of how to be more cost-efficient while maintaining medical care, it will progress from limiting diagnostic procedures to emphasizing those that can most effectively alter the course of the treatment. Techniques with high specificity (and also high sensitivity) should be favored in such a climate.

The rationale for resisting PET's dissemination does not rest on any difficulties with the technology's basic principles or any lack of confidence in its ultimate capacities—but rather on issues of practicality. Even economics cannot be viewed as the basis for the delay of PET's appearance in the clinical marketplace. Cost reductions realized through the early detection of disease, the avoidance of unnecessary surgery or other

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procedures, and the improved diagnostic, therapeutic, and prognostic capacities that PET should ultimately provide far outweigh the expenditures required for acquisition and maintenance of equipment. Although cost has played a role in the dissemination of comparable technologies such as x-ray CT and NMRI, it has not denied them access to the proving grounds of medical care. These technologies have benefitted from a commercial supply-driven approach while PET has developed through a demand-side evolution by investigators who believe in its value.

Is PET sound both in fundamental principles and its potential to enhance the study of human biology and disease? The answer, unequivocally, is yes. Can the scientific proof of PET's ability to provide new information, reduce risks or costs, and enhance the medical treatment of patients be determined without its widespread clinical application? The answer, unequivocally, is no. Only with the opportunity to test the potential capabilities of PET will the true measure of its success or failure be known.

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Michael E. Phelps, PhD (seated at the President's left), joined US President Ronald Reagan and senior vice president of research and development from IBM, AT&T, Westinghouse, and Entel, as well as the chairman of computer sciences at Carnegie-Melon, at a White House luncheon last March. Also in attendance were the honorable George A. Keyworth, science advisor to the President, and Bernadine Healy Bulkley, MD, then deputy director, Office of Science and Technology Policy. The meeting was held to discuss national developments in high technology, including medical advances with PET. President Reagan also accepted a framed PET scan from Dr. Phelps, and expressed interest in PET's potential contribution to health care.