Clinical PET: Its Time Has Come

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Today's medical practice is yesterday's research. The bridge linking the two is technology assessment, which makes possible the acceptance or rejection of new technologies in the practice of medicine. Experience is the key determinant of effectiveness. If the information provided is not useful to the physician caring for the patient, the procedure will eventually fall by the wayside.

A technology can be efficacious when applied correctly by experts to appropriate patients on a routine basis. Usually, surveillance can establish effectiveness, while controlled clinical trials assess efficacy. In the case of diagnostic tests, an important criterion is whether the procedure provides the required information. The next question is the impact of information on the care of the patient by the responsible physician. Its assessment is based on knowledge about the specific patient before the procedure, the results of the procedure, and its effect on the care of the patient. J.S. Schwartz has formulated this hierarchy:

1. Technical capacity
2. Diagnostic accuracy
3. Diagnostic impact
4. Therapeutic impact
5. Patient outcome.

The Office of Health Technology Assessment (OHTA) evaluates the safety and effectiveness of new, unestablished technologies and makes recommendations for coverage under the Medicare program. The technology may be categorized by OHTA as established, unproven because of insufficient data, not effective, or outmoded. In most cases, the data are deemed insufficient to reach a satisfactory conclusion.

Randomized clinical trials can be used to compare diagnostic procedures, but they are used most often in assessing treatment. Unfortunately, comparative assessment presents diagnostic tests as being competitive, whereas their combined use can provide greater accuracy of diagnosis than individually. Replacing a test that is 80% accurate with one that is 90% accurate is less desirable than combining them to provide nearly 100% accuracy. Another frequently encountered problem is that a test, such as a lung scan or myocardial perfusion study, may not correlate highly with a more definitive test standard, such as an arteriogram, because the latter is only performed when the results of the nuclear medicine procedure are equivocal. Thus, the differences in results are exaggerated due to selection bias. This problem can be addressed by performing the arteriogram in all patients regardless of the results of the nuclear medicine procedure, but often this is not possible on ethical grounds, especially after the test has been in clinical use for a long period. There is also the problem of the accuracy of the "gold standard."

The first question with respect to a nuclear medicine procedure such as positron emission tomography (PET) is whether PET measures what it is intended to measure. The essence of PET is in vivo chemistry. The human body is made up of molecules, which are fundamental units in modern medicine, as well as the cell. Most physicians and some scientists in addition to the public view disease, such as cancer, as something foreign and invasive caused by a virus, chemical, or ionizing radiation entering the body. According to this view, cancer must be treated by surgical removal, destruction by radiation, or chemical poisoning. PET makes it possible to view such a disease not as a capricious invasion of the body, but as a failure of normal control processes; these processes can now be examined and quantified in normal persons and identified if deficient in patients with cancer. Accordingly, the treatment is to restore these deficient control mechanisms. For example, growth factors bind to cellular membrane receptors and activate the growth stimulatory process by small regulatory molecules, called second messengers. Eventually, the message to proliferate is signaled to the nucleus, which then divides. Growth inhibitory signals then prevent cellular proliferation from proceeding indefinitely. Elucidation of the biochemistry of these signal-transducing functions can be extended to living human beings with PET. Such studies of in vivo biochemistry can be used not only to detect disease, but also to plan its treatment and monitor the effectiveness of the treatment.

In many cases, the results of PET are expressed as a continuous variable, analogous to measurement of the

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patient's blood pressure. The information is then used to discriminate between patients with and without a particular disease, which requires a definitive means to characterize patients with a specific disease. In many cases of mental disease, such as depression or schizophrenia, the populations are defined by phenotype and are so heterogeneous that the test itself provides the best characterization of the population group; for example, those patients with elevated dopamine receptors.

PET procedures often provide results analogous to the measurement of serum hormone. After World War II, biochemistry was revolutionized by the introduction of carbon-14 and tritium as radioactive tracers. Most biochemistry today is still based on the continued use of these two tracers, but they cannot be used for in situ studies of living human beings. Their beta emissions cannot penetrate the body and be detected by external imaging devices. Other isotopes—carbon-11 and fluorine-18—make it possible to examine the chemistry of organs, or parts of organs, in the living human body. By means of mathematical models and appropriate measurements, the results can be expressed in absolute units of meters, kilograms, and seconds (the MKS system), or more simply in relative terms, such as the percentage of the administered dose of a radiotracer accumulated by a tumor. These nuclear medicine techniques define normal regional chemistry in normal persons, and provide a means of detecting deviations from the normal by statistical analysis. They provide "functional" or "biochemical" images of disease. When we can measure the rate of a chemical process in a region of the body, the possibility exists that there are at least two diseases, one in which the rate of the chemical process is abnormally slow, and another in which the process is abnormally fast.

In general, PET studies are of three types: (1) regional blood flow; (2) substrate metabolism; and (3) chemical "recognition sites," including receptors and enzymes.

PET goes far beyond simple detection of disease, providing information about prognosis and the planning and monitoring of treatment, as well as diagnosis. Diseases are not viewed only in terms of structure, but as process. As Koestler has said, what we call structures are slow processes of long duration. What we call functions are fast processes of short duration.

Sometimes we hear that new diagnostic techniques are continually being added to the practice of medicine, but that established techniques are never dropped. The fallacy of this belief is indicated by the fact that two imaging methods, pneumoencephalography and ventriculography, are today of historic interest only.

The accompanying articles in this special issue document how PET can examine biochemistry and distribution of disease in the brain and other organs, decrease surgical morbidity and complications, improve selection of the type of treatment, and provide an effective way to plan and monitor treatment. Characterization of disease on the basis of regional biochemistry, as well as histopathology, provides a new way to classify disease and a new approach to patient care. Disease is described in terms of molecular as well as cellular abnormalities. There are now enough clinical investigations to document how PET can be used in the context of a given patient's problems; how measuring the blood flow and bioenergetics of diseases, ranging from cancer to epilepsy, can help in the planning and monitoring of treatment. It is no longer adequate to characterize disease solely on the basis of histopathology. Molecular abnormalities can now be related to clinical symptoms, signs, and prognosis. Microscopic examination of biopsy tissue remains the best way to characterize cancer, and the best guide to prognosis and treatment, but requires removal of tissue from the body, which once removed is no longer living. PET makes it possible to extend the study of histopathology to the study of regional chemistry of living human beings. Enormous advances have been made in the clinical applications of PET, not only in detecting disease, but in determining benignancy or degree of malignancy. PET helps predict the course of disease and direct treatment. Other imaging methods, such as magnetic resonance imaging (MRI), reveal lesions only indirectly by portraying the effects of disease, such as edema, or by revealing distortion of normal structures by cancer.

MRI is an exquisite form of anatomical imaging that has the particular advantage of not involving ionizing radiation. PET reveals regional abnormalities in biochemistry, such as glucose, amino acid, or nucleoside metabolism. Spectroscopic images of phosphorus-containing compounds in the body have been obtained with magnetic resonance spectroscopy (MRS), but the technique continues to suffer from poor sensitivity and spatial resolution. NMR spectra of molecules containing naturally-occurring phosphorus-31 or administered fluorine-19 or carbon-13-labeles make it possible to measure molecular concentrations of important compounds, such as ATP, inorganic phosphorus or phosphocreatine, and to measure chemical reaction rates in different organs and lesions, but only in relatively large anatomic regions (centimeters), requiring long observation times (hours).

PET makes it possible to measure the utilization rate of substrates, such as sugars and fatty and amino acids, which supply energy, or nucleotides, which reflect DNA metabolism. PET provides pharmacokinetic and pharmacodynamic data concerning radiolabeled therapeutic agents.

PET is used to assess the effectiveness of surgery, radiation therapy, and chemotherapy, and can document the extent of disease and its progression or regression in response to different forms of treatment. Such data permit modifications of treatment sooner than can be determined by clinical response of patients or changes in size of lesions. Thus, treatment need no longer be based solely on clinical response, gross morphology of lesions, and histopathologic examination of biopsies. Biochemical characterization of disease with labeled tracers is becoming a new method for

classifying patients, and for planning and monitoring their treatment.

For example, an important characteristic of neoplastic tissue is its increased rate of cell division. Accumulation of thymidine into neoplasms is increased in the presence of increased DNA synthesis. Amino acid transport across tumor cell membranes has also been found to differentiate many malignant from nonmalignant tumors. In addition to membrane transport, protein synthesis can be examined if suitable mathematical modeling is used in data analysis. The accumulation of labled fluorodeoxyglucose can be used to measure both aerobic and anaerobic regional glucose utilization. Many malignant tumors have accelerated glycolysis compared with surrounding tissues.

In addition to measuring blood flow, blood volume, substrate incorporation, or DNA synthesis, PET can be used to measure the number and affinity of hormones and neuroreceptors. Estrogen receptors are increased in many breast tumors, in both the primary and metastatic sites. Dopamine receptors are often increased in pituitary adenomas. Measurement of the rate of fluorine-18-FDG uptake is helpful in determining the degree of malignancy of tumors. DiChiro and his associates at the National Institutes of Health in Bethesda first reported in 1982 the correlation of the rate of glucose utilization with the histologic grading of brain tumor malignancy, a good predictor of the patient's life expectancy. If the tumor has a low rate of metabolism and is in a particularly dangerous location from the standpoint of surgical therapy, the lesion may be followed with periodic reassessment for signs of increasing metabolism of the lesion. Assessment of tumor metabolism can be based on absolute glucose metabolism in the tumor or relative metabolism of the tumor compared with a corresponding region on the opposite side of the brain, or compared with global glucose metabolism. Both visual and objective criteria have been used to make these assessments. After treatment, measurement of metabolic activity of the tumor relative to normal brain helps to discriminate between persistence or recurrence of tumor and damage to normal brain tissue, such as that resulting from radiation necrosis. Similar studies of tumor recurrence are being carried out with fluorine-18-FDG in colorectal tumors.

Another substrate, carbon-11-methionine, is useful for delineating the boundaries of brain tumors and providing valuable information for the planning and performance of brain surgery, by permitting differentiation of metabolizing brain tumor from simple disruption of the blood-brain barrier.

Since the classical work of Claude Bernard, the body has been conceived as comprised of cells bathed in a sea of extracellular fluid. Communication among cells is to a large degree based on the existence of "recognition sites" that identify the sources of energy to be incorporated into the cells, or "messages" from other cells that determine the subsequent activity of the receptor cells.

How the human body recognizes foreign substances remains one of the most intriguing and important questions in biomedical science. The process seems to be a general phenomenon in which billions of specific molecules, some free in the blood and others attached to mobile cells, circulate until they encounter a stereospecific fit with another free or cell-bound molecule. After the encounter of the "key" with the "lock," the molecule binds to the stereospecific recognition site, whether the site is an enzyme, receptor, or antigen. A basic question is how we are able to tolerate our own molecules. Since 1950, it has been known that each of the trillion lymphocytes in the human body has specific receptors that identify specific antigens and then respond by proliferation, a process called the "clonal selection theory." These new cells then "attack" and eliminate the antigen from the body. The lymphocyte receptors include B cells that recognize unaltered antigens, and T cells, which bind by connecting proteins (MHC proteins) to smaller polypeptide chunks of the broken-down original antigen. The T cells include cytotoxic cells and "helper" cells. The cytotoxic lymphocytes release lymphokines, including interleukins and interferons. Not only tumor antigens, but damaged normal cells are recognized and dealt with in this way. Tolerance of self is believed to occur as a result of early exposure of immature lymphocytes that die after they encounter the antigens of normal cells. In essence, the lymphocytes that recognize "self" are filtered out early in life. It is now possible to label these B- and T-lymphocytes with antibodies or antibody fragments, labeled with technetium-99m. To date, technetium-99m-labeled anti-granulocyte antibodies have been used to visualize the normal distribution of granulocytes and their increased concentrations in infections.

One example of the use of PET to assess the presence of receptors in tumors is breast cancer. Fluorine-18 estradiol accumulation as determined by PET makes it possible to determine the treatment of a specific patient on the basis of the number of estrogen receptors. A tumor containing estrogen receptors is more likely to be treated successfully with estrogen-receptor blocking drugs, such as Tamoxifin, than cancers that do not contain estrogen receptors. The presence of progesterone receptors as well as estrogen receptors is the best prognostic sign. Radioactive tracers that bind to estrogen receptors make it possible to assess the status of the primary breast cancer and regional metastatic deposits. This is an excellent example of the new biochemical approach to the characterization of disease, directly related to prognosis and therapy.

Another example is the study of receptors in pituitary tumors. Using the dopamine receptor binding agent ^{11}C-N-methylspiperone, pituitary adenomas can be classified as to whether they possess dopamine receptors. If the tumors contain such receptors, they can be treated chemically rather than surgically, by administering the dopamine receptor agonist, bromocryptine.

There have been great improvements in the surgical

treatment of colon cancer, in which sphincters can be spared and the postoperative quality of life greatly improved. Persistence and recurrence of tumor remains a problem. Preoperative staging is of great importance. Careful follow-up can then reveal recurrences at an early stage when it is still worthwhile to remove recurrences by a second operation. Imaging is used in association with measurement of serum CEA levels. The resectability rate for recurrent disease is about 12%–15%, but the number of resections of liver metastases is increasing.

In ovarian cancer, metastases are often difficult to detect by x-ray computed tomography or other anatomical imaging methods. Thus, second or third operations are often carried out. Furthermore, pelvic masses detected by these imaging techniques may or may not represent metastases. For these reasons, and because the metabolic response to treatment can be assessed directly, biochemical imaging methods have been employed. Fibrotic deposits are seen after surgery and must be differentiated from viable tumor.

Max Planck once said: "A new scientific truth is not usually presented in a way that convinces its opponents...; rather the opponents gradually die off, and a rising generation becomes familiar with the truth from the start." Ready acceptance is the exception rather than the rule. Histopathology remains the cornerstone of cancer diagnosis and treatment, but in vivo chemistry is an idea whose time has come.