Positron Emission Tomography: A Review and Prospectus

Symposium

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Commentary by Drs. Blaufox, Chervu, and Goodwin

When it was suggested that we take part in a symposium on positron emission tomography (PET) the question asked was: Why at Einstein?. Clearly any multimillion dollar investment at the medical school must be carefully considered and fully justified, having broad impact extending beyond any single department. PET scanning is of potential value in virtually all of the clinical departments and many basic sciences. No other tool currently exists with the ability to quantitate the basic organic units of carbon, oxygen and nitrogen and their compounds in the intact living organism. Its relevance to patient care and potential use in research have already been demonstrated at many centers throughout the country. It has enticing teaching possibilities, permitting students to be shown biochemical and physiological processes as they occur in humans. During the past several years the use of this technique has expanded rapidly because of simultaneous development in two areas:

1) rapid synthetic processes have become available for a wide variety of organic compounds (radiopharmaceuticals) incorporating short-lived positron emitters which are physiologically identical to the metabolic substrates within the body, and

2) computerized axial tomographic techniques have been integrated into scintillation detector systems for detecting positrons through their annihilation photons.

A cyclotron PET facility can be visualized by the flow chart shown in Figure 1. The unit is composed of many essential parts which will be described briefly here.

Cyclotron Facility

A cyclotron is one of a class of particle accelerators which can be used for radionuclide production by increasing the energy of a given type of atomic particle. Several other types of accelerators are available, such as the Van de Graaf and the linear accelerator (linac); however, the cyclotron is the preferred machine for the production of radionuclides for biomedical/clinical applications. Particularly attractive is that it can be designed in a relatively compact form. The word "cyclotron" derives from the fact that the charged particles are accelerated in circular orbits of ever increasing radii under the influence of magnetic and electric fields in order to propel them to higher and higher energies. The particles most commonly employed in cyclotron accelerators are protons, deuterons, alpha particles (^{4}He), and Helium-3 particles. Cyclotrons are rated in terms of the maximum energy (E_{max}), to which protons are accelerated; the E_{max} of other charged particles are proportional to $Z^{2/A}$, where Z = atomic number, and A = atomic mass. Thus a 16 MeV (million electron volts) proton unit yields 8 MeV deuterons and 16 MeV alpha particles. Individual cyclotrons vary in design features, simplicity of operation, reliability, compactness of structure, and the target system that is associated with the unit for production of the specific radionuclide in question.

Currently, accelerator produced radionuclides are widely used in routine nuclear medicine. These routine isotopes are not positron emitters and are produced with machines which are capable of providing high particle energies and beam currents for a wide variety of particles. Iodine-123, Gallium-67 and Indium-111 are examples of the nuclides which are made by medium energy cyclotrons (16 MeV – 40 MeV).

In order to fully utilize a PET facility it is essential that a small medical cyclotron system be located on site since most of the major positron emitters which are produced have half-lives which are measured only in minutes and cannot be transported at great distances. It is imperative that they are produced on site and synthesized promptly into radiopharmaceuticals for clinical and research applications. Cyclotron manufacturers have made special efforts in recent years to provide units that are relatively inexpensive, more compact and perhaps more amenable to routine use by fewer technologists than older models. The features of some of the cyclotrons designed for medical centers are listed in Table I.

Cyclotron Targetry and Radiopharmaceutical Preparation

The cyclotron provides the accelerated particles which subsequently induce nuclear reactions depending on the particle energy and the reaction cross-section. Either gas target materials, which are convenient to transport, purify and chemically manipulate, or liquid and solid targets which usually require dissolution of the target after bombardment, are used conveniently for production of most of the positron emitters of clinical interest. Therefore, various systems are designed to produce radioactive pre-

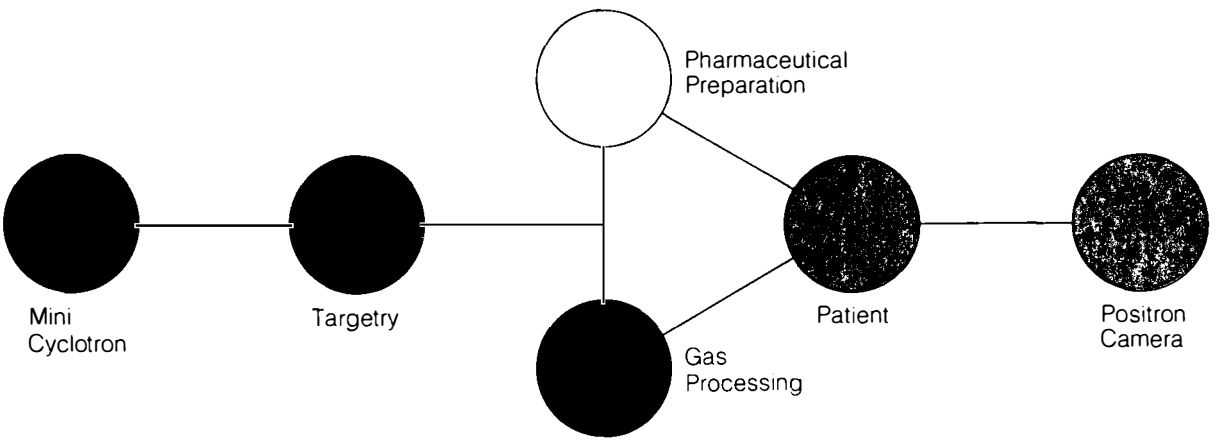

Figure 1. PET Facility Lay Out.

cursors in very high yield with high specific activity and least operator interaction. These include: ^{15}OO, $C^{15}O$, $C^{15}OO$, ^{11}CO, $^{11}CO_2$, $H^{11}CN$, ^{13}NN, $H^{18}F$, ^{18}FF.

These radioactive substances are available at the end of bombardment or shortly thereafter with remotely operated devices in lead shield containers ("hot cells") and are produced in very large quantities. For the routine delivery of several of these precursors, fully automated production under microprocessor control enables handling of curie levels of activities with minimal radiation exposure.

Positron Labeled Radiopharmaceuticals

Having produced the desired radioactive element, the next step is to formulate a compound incorporating it into a usable form. A positron itself is a charged particle emitted by an atom's nucleus. It has a charge equivalent to that of the electron or beta minus particle. Positrons have a wide spectrum of energies with an end-point positron energy which is characteristic of each positron emitter. The positrons travel only a few millimeters through the surrounding tissue before encountering electrons and annihilating into two gamma rays, each of 0.511 MeV energy and emitted characteristically in a direction 180° to each other. Positron emitters do not occur in nature. They are all produced artificially with the help of the accelerators or cyclotrons.

Table I. Clinical Cyclotron Models

Commercial model	Accelerated particles	Proton energy MeV
LOW ENERGY:		
Cyclotron Corp. CS15	p*,d, ^4He, ^3He	15
Cyclotron Corp. CP-16	p d (optional)	16
Scanditronix RNP-16	p,d	16
AECL/JSW	p,d	16
AECL/JSW	p,d	10
MEDIUM ENERGY:		
Cyclotron Corp. CS 22 PD	p,d ^4He, ^3He (optional)	20
Cyclotron Corp. CS-30	p,d	26
Cyclotron Corp. CP 32	p d (optional)	8–32 variable

*p represents proton, d represents deuteron.

Positron emitting radiopharmaceuticals which have been especially useful in in vivo investigation include Carbon-11, Nitrogen-13, and Oxygen-15. They have the unique advantage of incorporation into naturally occurring molecules and they do not alter the metabolic fate of these compounds in ordinary living systems. The positron emitter, Flourine-18 though not in the category of C,N, and O permits labeling in non-interactive sites in the molecule in place of hydrogen, often without causing significant changes in the response of the biological system to the change in the molecular structure. Fluorine is useful in that it has a 110 minute half-life, and is one of the few positron emitters which may be transported some distance before use.

Since most positron emission tomography work is carried out with radiopharmaceuticals incorporating C-11 and F-18, a cyclotron providing particles of energies up to 16 MeV is necessary to provide sufficient capability for production of these radionuclides. The physical properties of the positron emitters that are produced with these small cyclotrons are given in Table II.

Short-lived radionuclides can be used safely in larger activities because the radiation dose in the patient is proportionate to both the amount of activity administered and the rate at which it decays. Administration of higher levels of activity makes possible the acquisition of higher count rates, statistically more reliable data, and better spatial resolution in the final image.

Table II. Physical Properties of Commonly Utilized Positron Emitters

Radionuclide	Half-life (min).*	Typical production† reactions	Precursors and simple compounds
Carbon-11	20.4	^{10}B (d,n)^{11}C	^{11}CO, $^{11}CO_2$, ^{11}CN $^{11}CH_3I$, $H^{11}C$ HO
		^{11}B (p,n)^{11}C	
		^{14}N (p,α)^{11}C	
Nitrogen-13	10.0	^{12}C(d,n) ^{13}N	$^{13}N_2$, $^{13}NH_3$
		^{16}O(p,α) ^{13}N	
Oxygen-15	2.07	^{14}N(d,n) ^{15}O	^{15}O-O_2, $H_2{}^{15}O$, $C^{15}O$, ^{15}O-CO_2
Fluorine-18	110.0	^{20}Ne (d,α)^{18}F	^{18}F-F_2, $H^{18}F$, $^{18}F^-$
		^{16}O (^{3}He,p)^{18}F	
		^{16}O (^{4}He,p,n)^{18}F	

*The half life is the time required for ½ of the radioactivity to decay.
†In the production reaction, the first element is the target or material bombarded with the particles. The last element is the resultant products. The particles involved in the reaction are shown. n represents neutron

Several of the labeled precursors and simple labeled compounds like CO, CO_2, O_2, N_2, NH_3, H_2O, are readily available and they do not need further processing for patient use. Incorporation of C-11 or F-18 into various biochemical analogs is more elaborate and requires a remote synthetic procedure within a very short interval of time, usually less than 2 hours. The incorporation of these radionuclides into the molecule of interest is accomplished via biochemical, enzymatic or other synthetic means. Major effort has been directed in recent years to the preparation of various saccharides including C-11 glucose and ^{18}F-2 fluoro-2-deoxy-D-glucose (^{18}F-FDG), neuroleptics (^{11}C-dopamine and ^{11}C or ^{18}F-dopa), amino acids, polyamines, purines, pyrimidines, nucleotides and nucleosides, and fatty acid chains. With the availability of these advanced facilities at several centers, more sophisticated and novel synthetic procedures are bound to be made available and almost any compound conceivably could be prepared. The routine delivery of such compounds as C-11 palmitate and ^{18}F-FDG is a reality today at centers with moderate support facilities.

Positron Emission Tomographic Scanner

Radionuclides which decay by positron emission can be detected and their distribution imaged by special devices which take advantage of the fact that positron emission is followed by the emission of two gamma photons in exactly opposite directions. Devices which detect this coincident radiation are usually referred to as positron emission tomographs, PET scanners. Although they have been available in various forms for some years, it is only with the recent development of small inexpensive computers with sufficient speed and storage capacity that PET scanners have become practical for extensive use.

Positron cameras operate on a principle different from that used in the gamma cameras, now commonly encountered in nuclear medicine services. The gamma camera normally uses a parallel-hole collimator to localize the origin of the emissions resulting in a low efficiency of detection of photons: less than 0.01 per cent of the radiation emitted from the patient is actually detected and used for imaging. The PET scanner, on the other hand, requires no collimators, thus providing greater sensitivity in terms of useful counts per millicurie of radionuclide administered. Resolution and sensitivity are both more or less independent of the depth of the source in the object, contrary to single photon cameras. However, display electronics of a PET scanner are much more complex than those of a gamma camera; data are stored in a large computer memory and cross-sectional images are then reconstructed and displayed in a manner similar to an X-ray CT scanner.

Positron cameras have taken a number of forms over the years, but most units which are now commercially available use a ring of detectors, or several rings, which surround the patient. The principle of detection is as follows. The simultaneous detection of two photons in two opposite crystals defines a path along which the decay occurred. Subsequent decays produce other lines of coincidence. This information is stored and then processed by the computer to produce images of the distribution of radioactivity in a cross-sectional slice of the subject. If more than one ring of detectors is used, several slices can be imaged simultaneously. Three rings can produce five slices by utilizing coincidences between adjacent rings. Most of the newer PET scanners use crystals made of bismuth germanate (BGO) which has a density almost equal to that of lead, and thus offers a higher stopping power for the 511 KeV gamma photons as compared with the sodium iodide (NaI) detectors used in conventional gamma cameras. PET systems are capable of high count rates for dynamic studies, multiple slices, good resolution, rapid image reconstruction and absolute regional quantitation of radioactivity.

Clinical Applications of PET Scanning Procedures

The most dramatic impact of PET scanning so far has been in neurophysiology research. In clinical practice the

potential exists for sophisticated diagnosis of psychiatric disorders, stroke and epilepsy. The technique may also prove useful in Huntington's chorea, tardive dyskinesia, growth rates in brain tumors, and senile dementia, to name a few.

Areas of abnormal activity have been shown in schizophrenics with restoration to normal patterns after drug therapy. The portion of the visual cortex used for observing an object can be clearly shown on the PET scan (Figure 2). In epileptics the utilization of glucose during an induced seizure can be used to identify the focus of the disorder. Neurosurgeons at the University of California are presently using PET to distinguish between areas of primary epileptic foci of the severe type and healthy brain as an aid to direction in surgery. Infarcts can be quantitated in scans of the heart and clear visualization of the pancreas can be obtained using metabolic substrates.

Regional permeability characteristics and blood flow in various tissues including brain and lung using ^{15}O labeled water and ^{11}C labeled alcohols is another area of investigation attempted with this facility. The labeled amino acids might prove useful in imaging pancreas and other tissues of rapid amino acid turnover. The fact that malignant tumors consume glucose at a higher rate than the surrounding tissue may be utilized for measuring the efficacy of chemotherapy through the drug's ability to alter labeled glucose metabolism using PET scan procedures. Thus blood volume, oxygen and glucose metabolism, amino

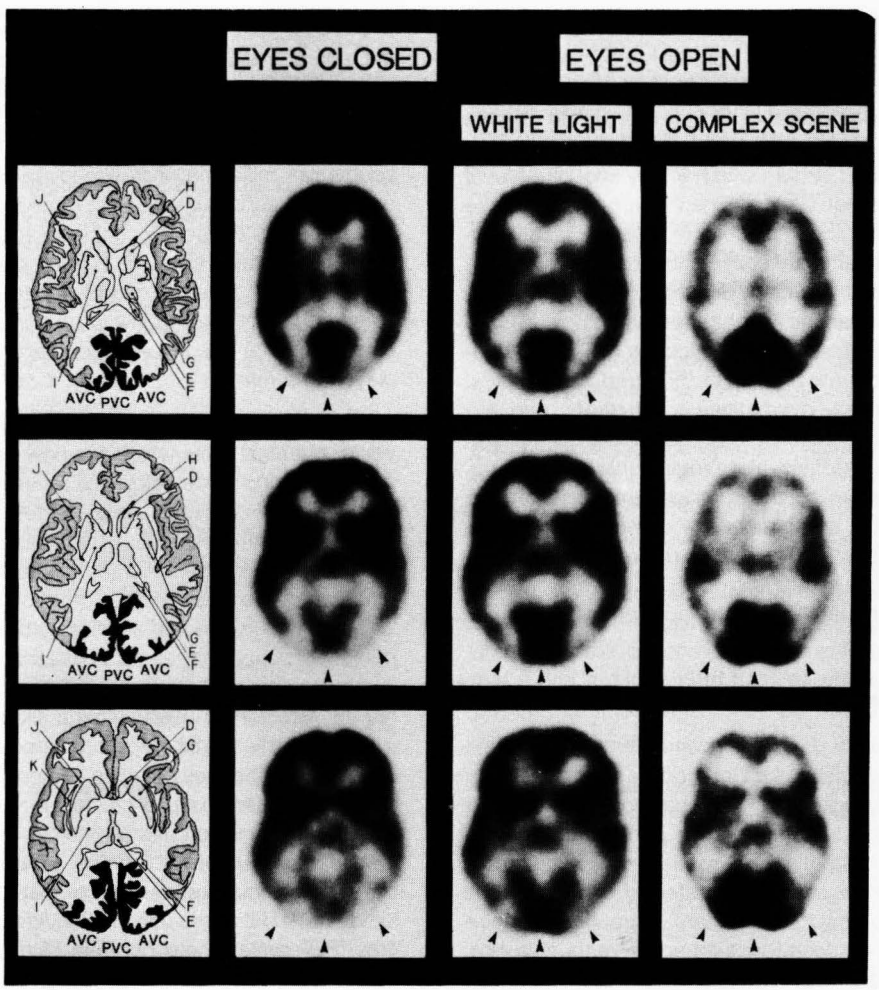

Figure 2. Study with ^{18}F-deoxyglucose showing response of the primary (PVC) and associative (AVC) visual cortex from eyes-closed control to white light stimulation to complex visual scene of a park. The control and the white light stimulation are the same subject, while the complex stimulation was a different subject, the tomographic levels of whom do not exactly correspond to the first subject's and the line drawings. Note the increasing metabolic activity of the visual cortex from the eyes-closed state to the increasing complexity of visual stimulation. Also note in the eyes-closed study the delineation of the posterior-parietal cortex from Brodman area 19 of the associative visual cortex. (Legend: D, caudate nucleus; E, thalamic nuclei; F, atrium of lateral ventricle; G, putamen and globus pallidus; H, anterior horn of lateral ventricle; I, internal capsule; J, external capsule. Adapted from Phelps, M. E. by permission from *Seminars in Nuclear Medicine 11:* 32–49.)

acid transport, protein synthesis, blood flow, receptor measurements, labeled antibodies for tumor localization, efficacy of chemotherapy drugs, trace metal metabolism, body nitrogen and electrolyte measurement are among the many diverse clinical applications envisaged using the unique spatial resolution in dynamic mode attainable with the use of the PET facility.

Layout and Cost of the PET Facility

The PET facility requires a large group of skilled specialists for optimal utilization. An estimate of initial costs is in the range of three million dollars, depending upon the choice of cyclotron, the remote processing equipment and hot laboratory, PET camera and the building facility.

Allocation of resources has become a major problem for hospital and medical school administration. We can no longer have everything. However, we cannot afford to make priorities solely on the basis of immediate needs. The responsibility of the medical school is to education. This process includes not only a presentation of the past and current state of the art, but also projection into the future. Medical graduates must be prepared to understand and utilize future development. The faculty must be forward-looking in order to carry out this task. A faculty functioning at the forefront of modern medicine clearly can help create a new physician who will offer future patients the greatest benefit. Medical faculties have broad and proved excellence in teaching and research. The acquisition of a PET facility will help them to achieve this potential and to maintain the position of the medical school as a leader in medical education and research, a position which is essential in continuing to attract first-rate students and faculty.

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Commentary by Dr. Leslie Wolfson

In human disease states, major insights have already been obtained through PET. With the labeled glucose analogs a depressed metabolic rate has been reported interictally in abnormal brain tissue, which is acting as an epileptic focus. Diminished cortical metabolism (especially in the frontal lobes) has been noted in patients with Alzheimer's disease, a disease which involves cortex, while diminished subcortical metabolism has been noted in patients with Huntington's disease, which involves subcortical structures. The pattern of metabolism in patients with stroke also is being actively investigated as well as in many other neurologic diseases.

The localized nature of these diseases in conjunction with the functional specialization of brain, makes the three dimensional resolving power of PET a powerful tool in understanding pathophysiology. This ability to localize brain regions with abnormal function and perhaps subtle structural abnormalities is the contribution of PET. The presence of a large number of productive research groups in the Departments of Neuroscience, Neuropathology, Neurosurgery and Neurology allow us to approach PET from a position of scientific strength. The likelihood that major understanding of diseases of the central nervous system will result from the unique capabilities of PET scanning dictate that we develop this area so that we may be in a position to lead in these discoveries.

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Commentary by Dr. Wagner H. Bridger

Structural and metabolic brain abnormalities have been hypothesized to be involved in many psychiatric disorders. This has been inferred from the aberrant findings in respect to neurotransmitters, endocrinological measurements, and the EEG. These are all peripheral measurements and post-mortem studies have not revealed major structural pathology. The assumption that functional brain disturbances are involved can only be confirmed through a technology such as PET. Future breakthroughs in psychiatric diagnosis and treatment will come about primarily through such a new technology.

Commentary by Dr. James Scheuer

Positron emission tomographic units for cardiovascular studies are now in place in several large institutions in this country. The capability of this approach in clinical research and in diagnosis has only just begun to be tapped. Because of the high resolution for localizing changes in isotope content and distribution, non-invasive studies can be performed in intact humans which provide precise information about small areas of myocardium in the beating heart. For instance, rates of coronary flow can be measured in a $1cm^3$ volume of myocardium and changes monitored. Using radioactively tagged substrates of various types, cellular metabolism of the heart can be measured in the same small segments using amino acids, fatty acids and carbohydrates. Using other tagged substances, the myocardium can be labeled and the geometry of the ventricular wall and the mechanical performance of small segments of myocardium can be followed. Thus, for instance, a segment of myocardium that may be subjected to ischemia in a patient with coronary artery disease could have blood flow through that area, metabolism, and mechanical performances all measured during the ischemic event and as the heart responds to the treatment of the ischemic event. This technique can be applied to patients with myocardial infarction, myocardial hypertrophy, myocardiopathies, some forms of congenital heart disease and even a current clinical enigma, acute myocarditis. It is difficult to forecast the ultimate role of this tool in clinical cardiology, but clearly it will make major contributions to diagnosis of disease and to monitoring treatment of patients with various forms of heart disease.

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The Editor's Commentary

With inflation and public service cutbacks, our first reaction to enthusiastically presented but expensive new medical technologies is to smile and check the whereabouts of our wallets. But even in these times, if there is a vision that promises revolutionary, or even utopian changes in the way we view patients and their diseases we must not fear a commitment now at tomorrow's expense. Rather we must rely on both the present facts and on our intuitions about the future in order to evaluate a costly investment such as one as Positron Emission Tomography. In their article, Dr. Blaufox and colleagues have presented the essence of the technique and its promise. We shall review selected aspects of the topic in order to strain from a growing body of scientific experience a sense of why PET has generated both enthusiasm and frustration in those who have come to know it intimately.

The great promise of PET is the quantitation of in vivo biochemical processes. But it should be kept in mind that the ability to supply a number is not a guarantee of usable or useful information. The Computerized Axial Tomagraphic (CAT) scanner supplies quantitated densities, but it is now forgotten that once it was hoped to correlate radiographic density with tumor histology. A critical evaluation of PET therefore must center around the prospects for an accurate and reproducible analysis of data which has scientific and clinical utility. To this end, three questions are posed: first, can consistent measurements be made; second, what precisely is being measured; finally, what is the significance of that which is measured.

A serious drawback to the applicability of PET scanning in the clinical situation lies in the strict constraints placed on the timing of studies due to the rapid decay of positron emitters. While semi-automated cyclotrons and radiopharmaceutical synthesizing equipment greatly increase the speed (and safety) of the preliminary steps of a PET study, it is not so easy to coordinate all the clinical and technological personnel necessary and to prepare the patient for the study. Nuclear bombardment, chemical synthesis, radiopharmaceutical and patient transport, intravenous injection, multiple simultaneous venous sampling for measuring blood levels, and scanning must all work smoothly and routinely. These are not insurmountable problems to the determined investigator, but an unpredictable, though probable, event such as last minute scheduling mix-ups, or lack of patient cooperation, (current scans require 5–6 minutes of absolute stillness) or equipment malfunction can frustrate an entire chain of command. It is for this reason that Fluorine-18 labeled radiopharmaceuticals with half-lives of 110 minutes, allowing a certain amount of flexibility, are replacing the Carbon-11 tags ($T_{1/2}$ = 20 minutes) for clinical studies.

A more profound difficulty is in the synthesis of the key element in the PET technology, the radiopharmaceutical. For any new radiochemical—and the great selling point of PET is its potential applicability to a study of virtually any compound of interest—a whole new methodology of chemical synthesis must be developed. For the synthesis of a positron-emitting target to be practical three criteria must be satisfied: it must be fast, efficient in yield quantities, and high in specific activity.

The maximum period of time for synthesis again depends upon the emitter. Both biosynthetic routes (e.g., ^{14}C-glucose from plants and algae) and radio-labeling of pre-existing reagents have been used with success. Yield is the amount of specific radiopharmaceutical produced relative to the amount of labeled target. The need for uniformity of radiopharmaceutical varies with the type of study. For example, in a localizing scan for tumor-associated glucose metabolism, the precise carbon atom on the glucose molecule to be labeled is not critical. On the other hand, in a quantitative study of dopamine receptors, the specific location of the F-18 on the labeled haloperidol determines its binding properties. A random mixture of forms of F-18 haloperidol, each with its own interaction with dopamine receptors, spells experimental confusion, if not disaster. Finally, the importance of specific activity—the ratio of positron-emitting compound to unlabeled compound, or "carrier" — also is determined by the experimental design. If the compound being studied is ubiquitous in the body, such as glucose, a high specific activity during synthesis is not useful. In this case, the dilution of the radiopharmaceutical must be determined by measuring the blood levels of labeled glucose. However, in a receptor study a high specific activity of ligand is the sine qua non. The amount of specific binding of radiolabeled ligand to receptor is so small that extremely minute quantities of the labeled agent must be administered to avoid a saturation of the specific binding and an overflow onto the non-specific binding sites. Therefore, every ligand molecule should ideally be labeled in order to avoid a high binding background and uninterpretable results.

The second question is: What precisely is being measured? Because biological compounds are being used, they will undergo compartmentalization and metabolism consistent with normal physiological processes. But if the radiolabeled agent is not strictly identical to its endogenous counterpart, or if the subject has disease which changes the pertinent physiology, complexities will arise. Studies with labeled glucose are extremely limited because metabolism through glycolysis is well underway within five minutes. Indeed, phosphorylation must occur in order to assure a proper study, for it is the phosphorylated metabolites of glucose which are impermeant to the cell membrane and thus become the measured "pool" of label inside the cell. Unfortunately, in the case of glucose, metabolism subsequently produces labeled substances, e.g., CO_2, which then diffuse out of the cell. Therefore, studies must be done quickly with full knowledge of the kinetics involved. Analogues of substances such as 2 deoxy-D-glucose, which remain trapped in the cells, avoid the time constraint but introduce other factors which were only fully described after years of basic research by Sokoloff, Revich, and colleagues (Sokoloff et al., 1977). How the range of human pathophysiologies will affect the basic assumptions about the biological activity of each radiopharmaceutical is unclear.

Similarly, studies of dopamine metabolism in the brain with the fluorinated precursor 5-[^{18}F] fluorodopa are hampered by the fluorine substitution itself, which makes the adjacent hydroxyl more acidic—and ten times more susceptible to methylation than unfluorinated dopa. The methylated precursor acts quite differently in the brain from dopa, making conclusions from such studies tentative at best. The upshot is that behind any human study *in vivo* must be a firm understanding of the basic biochemistry involved from *in vitro* and animal studies.

Finally the most difficult question, and perhaps the most controversial is: What is the ultimate usefulness of the information provided by PET? Clearly, considering only the nature of the data itself there are theoretical limitations. Positrons travel up to 6 mm before annihilation; of the biologically useful emitters Fluorine-18 produces positrons which travel the shortest distance and thus provides the greatest resolving power. Scanners presently are capable of assessing minimal volume units of around 1–2 ml; however, volume units of 0.05–0.1 ml will be distinguishable in the near future. This is not the resolving power of an *in vitro* autoradiograph — only the larger elements of the nervous system could be investigated. Most tracts and individual nuclei will be inaccessible to conventional PET, which unfortunately, is the level at which a true revolution in neurological understanding must occur.

Data from PET about disease states must always be viewed with respect for the subtleties of each clinical situation. Interpreting one variable, regional glucose metabolism in a series of patients with stroke, for example, each with a different serum glucose level, different baseline metabolic requirements, past medical histories, and present clinical courses, will be a difficult task for any clinician - investigator. Given the difficulties with which new synthetic routes for new radiopharmaceuticals are developed one can easily picture a scenario in which a few tantalizing discoveries are made quickly with the present agents, followed by years of slow laborious work in order to make sense out of the myriad clinical situations.

Given the technology's prospects for slow progress, we must address the most fundamental question: what profound new understanding of the brain can we expect to learn from PET? Its major achievement so far, that is, seeing pictures of living brain "light up" with metabolic activity, will not burn in the imagination of neuroscientists, neurologists, and psychiatrists (a jaded lot) for long. Even today's most exciting findings besides the precise functional mapping of cortex, that is, the changes in brain metabolism seen in patients with schizophrenia, Huntington's, and Alzheimer's Disease, can, on critical analysis, be viewed as epiphenomenal. The local changes in glu-

cose metabolism may be only secondary or tertiary changes, far removed from the causative molecular events in these diseases. Perhaps it is too early to say, but it seems unlikely that a parameter such as brain metabolism will point to the fundamental substrates of neurological and psychiatric disorders, which lie in the genome, in the specificity of neuronal cell-types, their interactions, with each other and their environment within and beyond the brain.

This scenario, however, is only an extrapolation based upon the progress in PET so far. The path described is not the only one to follow. For example, an alternative to the slow development of each radiopharmaceutical independently would be a single technology easily adaptable to many agents. Production of positron-emitting monoclonal antibodies by a standard technology of incubating a monoclonal antibody-producing hybridoma culture or cell-free protein synthesizing system with radiolabeled amino acids would answer such a need. Thus *in vivo* localization with positron-emitting antibodies to neurotransmitters, receptors, neural-surface and tumor antigens all could be achieved with essentially the same synthetic route. During the synthesis, time might be a limiting factor, but yield would be good, purification relatively easy, and specific activity excellent with multiple positron-emitting residues per antibody molecule.

The great difficulty of course with using a macromolecule such as an antibody for a radiolabeled probe in the brain is the problem of penetration across the blood-brain barrier. While a certain minimal amount of antibody does cross the blood-brain barrier by diffusion to bind specifically with its antigen, techniques to temporarily open up the blood-brain barrier to larger molecules are presently being investigated. Injections of hyperosmotic solutions such as 2M urea or 5 per cent NaCl have been shown to reversibly open the blood-brain barrier in animal models (Rapoport et al., 1972). High pCO_2 and other compounds such as dilute mercuric chloride have similar effects (Mayer et al., 1959).

A high specific activity of positron-emitting antibody would open up the possibility for a higher resolutional tomographic scan. While a positron does travel a radius of a few millimeters from the nucleus of its emission to the point of its annihilation with an electron, this should not establish an absolute minimal limit on scanning resolution. If the decay characteristics of the emitter are precisely known, one can construct a sphere of probability of annihilation emanating from the central point of emission. Given small enough volume units, a Fourier transform of the photon emission data points should describe the theoretical central points of positron emission. While radiation levels and the scatter produced by photon trajectories not precisely at 180° to each other may ultimately be limiting, this secondary analysis of data points might bring the resolution of the PET scan down to the level of neurological tracts and nuclei, which would begin to satisfy the needs of neurologists and neuroscientists.

Combining these methodologies, a Monoclonal Open-endothelial Ultraresolutional Scintillation Emitter scan would be called a MOUSE scan to continue and perhaps complete the trend in nuclear medicine and radiology to name technologies after household animals and plants. After initial embarrassment, the MOUSE scan would prove to be a revolutionary and flexible tool for the diagnosis and study of neurological and oncological disease. Such a technology would be the long-needed bridge between basic research on the expression and change of biological molecules and the clinical state. Thus in conclusion of this symposium, let us say that any decision on the future of the PET scan framed by the constraints of the moment must yet be with an eye towards syntheses of technologies seen still only in the imagination.

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Acknowledgments

The author gratefully acknowledges the inspiration gained from conversations with Dr. Marcus E. Raichle, whose work on PET is preeminant. Dr. Raichle is of the Edward Mallinckrodt Institute of Radiology and Department of Neurology and Neurological Surgery, Washington University School of Medicine, St. Louis, Missouri. For theoretical considerations of new mathematical models for scintillation scanning the author thanks Dr. Van Wedeen of the Department of Internal Medicine, The Roosevelt Hospital, New York, N.Y. and AECOM, Class of 1981.

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