Unparalleled Contribution of ^{18}F-FDG PET to Medicine Over 3 Decades

Since the introduction of ^{18}F-FDG in 1976 (*1*) (Figs. 1–2), the last 3 decades have witnessed a revolution in medical imaging. The widespread use of ^{18}F-FDG PET as a molecular probe has made an immense impact on the investigation of cancer and many other serious disorders. The success of ^{18}F-FDG has led the way for the development of new PET tracers with great promise for future expansion of the role of PET (*2–5*). The potential for labeling positron-emitting radionuclides to numerous biologically important compounds has been a key factor and has allowed this modality to be employed for exploring complex biological processes. In addition, novel quantitative concepts and the refinement of existing techniques have made this modality the most accurate in vivo imaging technique for assessing regional and global function and metabolism (*6–9*). These developments have considerable implications for both clinical and research applications. In this communication, we discuss the impressive contribution and promising strides that this powerful approach has provided over the past 3 decades to the practice of medicine.

Role of ^{18}F-FDG PET in Neurology and Oncology

The impact of ^{18}F-FDG PET has been particularly impressive in patients with cancer, where it has become essential in disease staging, monitoring response to treatment, planning and choosing appropriate therapies, detecting recurrence, and providing accurate prognoses (*10–12*). ^{18}F-FDG PET plays a pivotal role in staging of a wide array of malignancies, including lung, head and neck, breast, cervical, esophageal, and colorectal cancers and melanoma and lymphoma, because of its sensitivity for detecting nodal and distant metastatic disease and its high specificity compared with structural imaging techniques alone (*10–12*). With the introduction of a modern generation of PET/CT scanners and well-established diagnostic criteria for interpretation of images, the role of ^{18}F-FDG PET in the evaluation of patients with cancer has been further enhanced. PET/CT, often regarded as the "one-stop shop" for many malignancies, provides coregistered structural and metabolic images, allowing for accurate localization of sites of disease. The degree of ^{18}F-FDG uptake in the lesions at baseline and during follow-up after therapeutic interventions provides important prognostic value (*13–17*). In conjunction with CT and MR imaging, this modality is increasingly being employed for defining the exact location of malignant sites for radiotherapy planning (*18–20*). The detailed structural and functional imaging information provided by PET/CT improves delineation of target volume at both the primary and metastatic lesions, thereby minimizing unnecessary irradiation of normal tissues and reducing the risk of local recurrence.

Although ^{18}F-FDG PET was introduced in 1976 (Fig. 3) as a research modality for assessing brain function in physiologic and pathologic states, today it is increasingly utilized in many clinical settings to improve diagnosis, monitor disease activity, and determine response to treatment (*11,21–25*). It is conceivable that the domain for molecular imaging with PET in central nervous system (CNS) diseases will be substantially larger than that of SPECT and will include a multitude of movement, seizure, and neuropsychiatric disorders. ^{18}F-FDG PET has been used extensively to examine patients with dementia for early specific diagnoses and differentiation among various types of this disorder. Recent success in developing a specific ligand for β-amyloid plaques may further enhance the role of PET for early diagnosis of Alzheimer's disease and may serve as a biomarker for disease progression (*25*).

Twenty percent to 30% of patients who are candidates for surgery because of focal temporal lobe epilepsy have normal MR images (*26*). The main indication for PET in

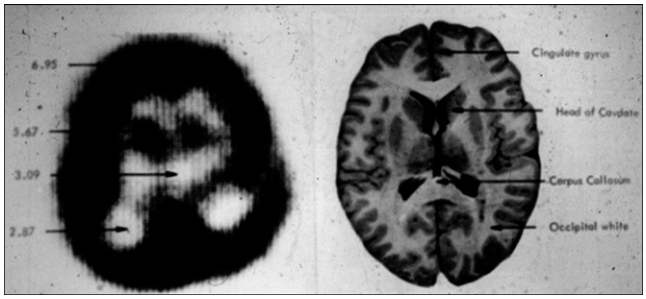

FIGURE 1. The first tomographic ^{18}F-FDG images of the brain were acquired in August of 1976 at the University of Pennsylvania (Philadelphia, PA) with a Mark IV scanner designed and built to examine central nervous system disorders with single-γ-emitting radiopharmaceuticals. These images were generated by using only 1 of the 2 511-Kev γ rays emitted from the positron decay, instead of coincidence detection as employed in today's dedicated PET instruments. The numbers on the ^{18}F-FDG (left) represent absolute regional glucose metabolic rates in mg/100gm/min. The image on the right shows a corresponding slice of the brain and its comparable structures. (Reproduced with permission from *Seminars in Nuclear Medicine*, 2002;32:2–5.)

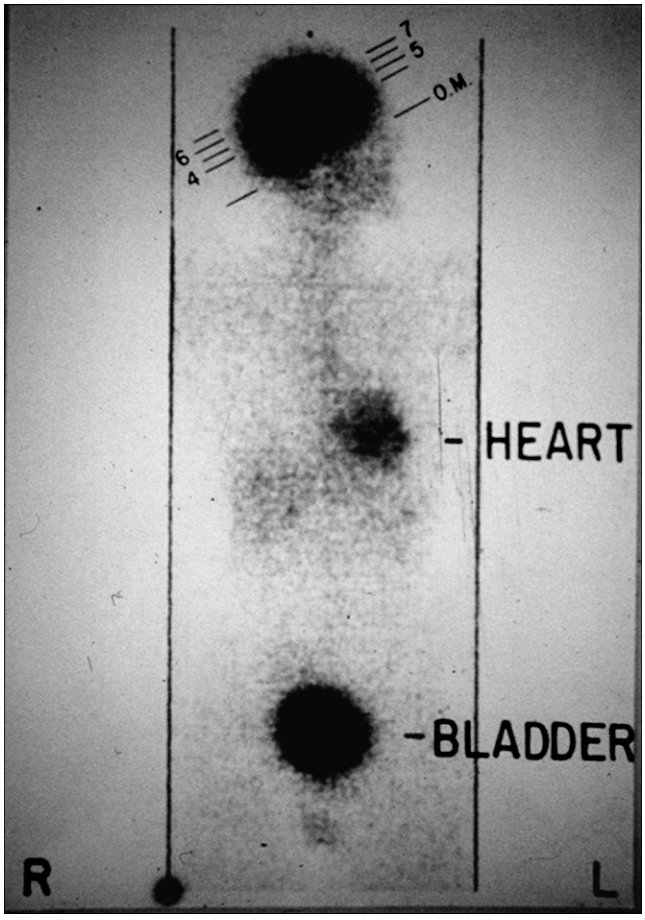

FIGURE 2. The first whole-body ^{18}F-FDG images were acquired using a dual-head Ohio Nuclear rectilinear scanner equipped with a set of high-energy collimators for performing ^{85}Sr (with an energy of 510 Kev) bone scans. These images were acquired soon after the completion of the brain studies with Mark IV. The whole-body images revealed a significant concentration of ^{18}F-FDG in the heart (in addition to the brain) and substantial excretion of this compound through the kidneys. (Reproduced with permission from *Seminars in Nuclear Medicine*, 2002;32:2–5.)

temporal lobe epilepsy is localization of the epileptogenic site for surgical excision and potential cure.

In the setting of stroke, the "penumbra" region surrounding the "core," as delineated by PET images, has relatively normal oxygen consumption and can be salvaged by reperfusion (*27*). A substantial degree of cortical penumbra is observed in up to 90% of patients studied within 6 h after onset of stroke and can be seen in about a third of patients even at 5–18 h after stroke onset (*28*). The variability of the degree of the penumbra suggests that the therapeutic window for reperfusion strategies may be different for a certain subset of patients, which may allow for individualized plans for thrombolysis treatment.

^{18}F-FDG PET provides important prognostic information in CNS malignancies. Significantly increased glucose metabolism in gliomas correlates well with higher histologic grades (III and IV) and poor survival (*29,30*). Response to chemotherapy and radiotherapy is associated with a substantial reduction in tumor glycolysis (*31,32*). Therefore, ^{18}F-FDG PET can be successfully employed to assess disease activity at different stages of disease and provide objective evidence for response to treatment in brain tumors. Similarly, increased uptake of ^{11}C-methionine, which reflects cellular amino acid uptake, is indicative of high-grade glioma and poor survival (*33*). Combined use of ^{11}C-methionine and ^{18}F-FDG PET enhances the accuracy of discrimination between recurrent tumors and postradiotherapy changes (*34*). The high glucose metabolism in cerebral lymphoma is of value in distinguishing it from cerebral infections (toxoplasmosis and tuberculoma) in patients with AIDS (*35*).

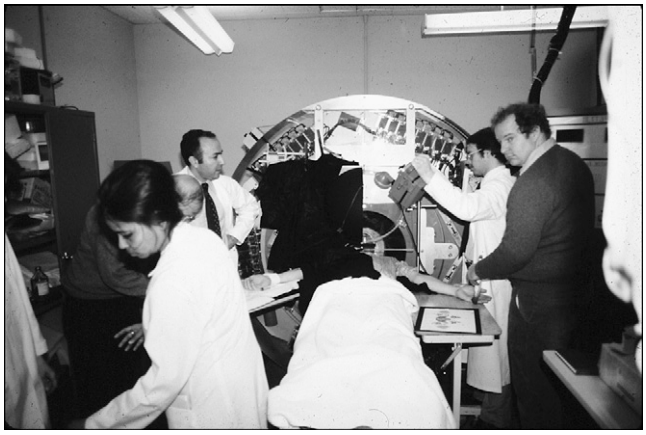

FIGURE 3. In this photograph taken in the late 1970s, Abass Alavi, MD (third from the left), and a team of investigators from the University of Pennsylvania and Brookhaven National Laboratory were conducting a visual stimulation (hemifield activation) research study. ^{18}F-FDG PET was the first tomographic imaging modality employed for elucidating brain function under various physiologic conditions. These groundbreaking experiments improved our understanding of this complex organ in health and in a multitude of pathologic states.

PET has also been investigated as a potential biological marker of disease severity and progression in Parkinson's disease (*36*). ^{18}F-DOPA is the most commonly used ligand for studying the dopaminergic system in movement disorders. Differentiating among various types of parkinsonian syndromes, especially in the early stages, is difficult with either clinical or conventional imaging (MR) assessment. ^{18}F-DOPA PET can differentiate Parkinson's disease from the striatonigral degeneration form of multisystem atrophy in 70% of cases and from progressive supranuclear palsy in 90% of cases (*37*) but is relatively less effective in discriminating among the atypical parkinsonian syndromes. Tracers that bind to the presynaptic dopamine transporters (such as ^{11}C-methylphenidate) and dopamine terminal vesicle monoamine transporters (such as ^{11}C-dihydrotetrabenazine) have also been investigated as markers of presynaptic dopaminergic function.

PET has also been widely tested to study hyperkinetic movement disorders such as Huntington's disease. Reduced striatal D_2 binding and glucose metabolism in some Huntington's carriers (*38,39*) are of importance in identifying those carriers, with implications for initiating treatment with neuroprotective agents at preclinical stages of the disease.

Cardiology

Assessment of myocardial viability with ^{18}F-FDG along with perfusion imaging is considered the standard of care for patients with coronary artery disease (CAD). Patients with viable ischemic myocardium diagnosed by a flow/metabolism mismatch (decreased flow with preserved glucose metabolism) represent a high-risk subgroup for serious coronary events in the near future, in the absence of myocardial revascularization (*40–43*). Interest is growing in the use of cardiac PET for the evaluation of patients with CAD because of its ability to detect changes in left ventricular function from rest to peak exercise and to quantify myocardial perfusion (in mL/min/g of tissue). The emergence of integrated PET/CT has ushered in an era of great promise for cardiac imaging, because it provides an opportunity to delineate the anatomic extent (CT coronary angiography) as well as the physiologic and metabolic severity of CAD (ischemic burden) in a single setting (*44*).

Promising Applications in Infection and Inflammation

Nonspecific ^{18}F-FDG accumulation observed at the sites of inflammation during PET imaging of patients with cancer has evolved into a promising imaging technique to examine, diagnose, and manage inflammatory disorders (*67–72*). ^{18}F-FDG PET has several advantages over conventional scintigraphic techniques, including high spatial resolution and the ability to secure results within a short period of time. Several studies have documented the role of ^{18}F-FDG PET in diagnosing patients with chronic osteomyelitis. Detecting infection and differentiating it from acute neuropathic osteoarthropathy in the setting of a complicated diabetic foot is another major potential application of ^{18}F-FDG PET. The nonspecificity of ^{18}F-FDG is an asset in evaluating patients with fever of unknown origin, because the tracer accumulates in infections, malignancies, and inflammatory diseases—the 3 principal causes of fever of unknown origin. ^{18}F-FDG PET can help in the correct assessment of disease activity in sarcoidosis, providing critical information in deciding on an optimal management plan (*68*). ^{18}F-FDG PET has a great potential for detecting infection in hip prostheses and, to a lesser extent, in knee prostheses (*69*). ^{18}F-FDG PET also holds great potential to assess atherosclerosis as an inflammatory process at the early stage of the disease, during its natural course, and after therapeutic intervention (*72*). ^{18}F-FDG PET has the potential to be added to the imaging armamentarium as a functional technique for several other disorders, such as environment-related lung diseases, vasculitis, back pain, transplantation, and blood clot. Therefore, it is predictable that PET will secure a major role in the management of patients with inflammatory, infectious, and other disorders.

Innovative Tracers and Novel Applications: Life Beyond ^{18}F-FDG

Although the impact of ^{18}F-FDG is unparalleled by any other tracer in nuclear medicine, several radiotracers have shown promising results in the management of various cancers and even more are likely to be investigated in the future (*2–5,45–47*). These radiotracers are more specific, with mechanisms of uptake based on distinct biochemical pathways. Although the positron-emitting radionuclides ^{11}C, ^{15}O, and ^{13}N have been used with some success, their short half-lives have prevented routine utilization of compounds labeled with these elements. Those with longer half-lives (e.g., ^{124}I, 4 d; ^{64}Cu, 12 h) or positron-emitters that can be eluted from generators (i.e., ^{68}Ga or ^{82}Rb) are being investigated increasingly at several centers across the world. A number of quantitative techniques are being explored for optimal assessment of disease activity at different stages (*6–9,48*). It is quite likely that in the era of fusion imaging, approaches for accurate quantitative analysis will change substantially, which will further enhance the role and reliability of these potential PET techniques.

PET scans can be used to track changes in patients who have received experimental gene therapy (*49*). An example is the use of radiolabeled 2L′-fluoro-2L′-deoxy-1-β-D-arabinofuranosyl-5-[^{124}I]iodouracil (^{124}I-FIAU) as a probe for investigating the herpes simplex virus (HSV) thymidine-kinase gene in the cells. ^{124}I-FIAU has allowed imaging of cells infected with HSV (*50*). Bennett and colleagues (*51*) showed that ^{124}I-FIAU PET could detect differences in viral infectivity at 0·5 log increments. ^{18}F-FIAU PET has also been used to investigate HSV1-*tk*-suicide gene treatment in patients with glioblastoma (*52*).

Angiogenesis, the therapeutic target in several malignancies (*53,54*), can be imaged successfully by ^{18}F-galacto-arginine-glycine-aspartate (RGD) PET, which targets $\alpha_v\beta_3$ integrins that are expressed on activated endothelial cells undergoing angiogenesis (*55*) and are linked with the metastatic potential of the tumor. ^{18}F-galacto-RGD PET also has potential applications in monitoring antiangiogenic treatment.

Somatostatin receptor–targeted PET tracers (e.g., ^{68}Ga-D-Phe1-Tyr^3-octreotide [^{68}Ga-DOTATOC] and Gluc-Lys [^{18}F-fluoropropionyl-TOCA]) have been developed and can be employed to image neuroendocrine tumors with higher accuracy than ^{111}In-pentetreotide SPECT imaging (*56–58*).

In vivo imaging of apoptosis offers an attractive noninvasive approach to monitor therapeutic response. Annexin V, which binds to phosphatidylserine that has moved to the outer surface of cell membranes during apoptosis, can be labeled with either ^{124}I or ^{18}F for imaging this important biologic phenomenon. These agents have potential applications in detecting early response after chemotherapy and radiotherapy (*59,60*).

Estrogen receptor (ER)–targeting tracers, such as 16α-^{18}F-fluoroestradiol-17β (^{18}F-FES), have the ability to assess the functional presence of these receptors in breast cancer and metastatic lesions for optimal treatment planning. The potential role of FES PET is to determine whether antiestrogen therapy will be effective and to demonstrate an early treatment response at 7–10 d after initiation of hormone therapy (*61*).

Assessment of tumor hypoxia, a critical factor in defining tumor biology and guiding intensity-modulated radiation therapy, can be achieved by compounds such as ^{18}F-fluoromisonidazole (^{18}F-MISO), ^{18}F-EF5, and ^{64}Cu(II)-

diacetyl-bis(*N*4-methylthiosemicarbazone) (^{64}Cu-ATSM) (*62–65*). The impact of such compounds in radiation therapy will be enormous.

Cell proliferation imaging with 3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT) can be employed for assessing therapy response, especially in the context of treatment with antiproliferative cytostatic agents (*66*). Similarly, the advantages of imaging amino acid metabolism with analogs of methionine, tyrosine (*45*), and L-dihydroxyphenylalanine (L-DOPA) are well documented in certain specific clinical contexts.

Impact of Fusion Imaging on Evaluation of ^{18}F-FDG PET Imaging

The introduction of PET/CT in the late 1990s added a major dimension to the utility of this powerful methodology, particularly in certain clinical settings. By combining structure and function in a single examination, precise localization of the diseased sites became possible for accurate diagnosis and regional intervention (surgery and radiation therapy). This further enhances the role of this technology in a wide array of malignant and benign disorders (*73*). One area in which PET/CT imaging is likely to become the standard of care is in radiation therapy planning. In the head and neck region, because of the complexity of the structures, precise coregistration of PET and CT images appears extremely valuable for accurate interpretation. Many techniques have been proposed for accurate quantitation using the fusion technology (*6*). The merits and potential applications of these techniques must be precisely defined in the future so that optimal applications in both research and daily practice can be implemented (*6–9,74*).

Drug Development

PET metabolic and receptor ligand studies have generated a wealth of knowledge in support of novel drug development, especially in the domains of oncology and neuropharmacology (*10*). PET allows precise determination of the pharmacodynamics and biodistribution of pharmaceutical agents. It has also aided in molecular target–based drug screening and definition of in vivo target specificity, thereby ensuring that the compounds precisely target organs of interest (*75*). The use of FLT PET to monitor preclinical testing of histone deacetylase inhibitors and the utility of ^{18}F-FDG PET as the surrogate marker for early response evaluation with imatinib mesylate are 2 examples of this promising application (*76–78*).

PET-Guided Personalized Medicine

Molecular imaging–based personalized medicine, an evolving concept in the 21st century, will rely much on the success of functional imaging with current and future novel PET tracers. The exquisite sensitivity of PET in assessing disease activity at its various stages will drive this success. Molecular imaging with PET will take a pivotal role as a surrogate marker to determine individualized treatment planning. The National Institutes of Health (NIH) Road Map Initiative has emphasized molecular imaging as a main focus for this major undertaking, which further demonstrates the importance of this approach in the scientific community. Metabolic imaging with PET tracers is likely to be the centerpiece of this initiative and will prove to be significantly superior to the existing techniques.

Future Directions

The unprecedented impact of ^{18}F-FDG PET imaging on the day-to-day practice of medicine has substantially improved health care throughout the world. This powerful imaging technique has minimized the suffering of a growing number of patients with serious diseases, including cancer, infection and inflammation, brain and cardiovascular disorders. These represent some of the most burdensome maladies that affect humans, and the potential for continued improvements using this technique is limitless. In addition, newer applications of ^{18}F-FDG PET imaging, such as the detection of atherosclerosis and clots and assessment of muscle function, will significantly enhance the role of PET in the academic and clinical arenas.

^{18}F-FDG PET methodology has clearly demonstrated the extraordinary power of PET in medicine. This has led to the development of many novel radiotracers designed to explore new diagnostic and therapeutic domains. We therefore expect that molecular imaging with PET will play an increasingly central role in research and in the optimal management of patients with many disorders. This will include diagnosing pathologic processes at the molecular level and individualizing treatment for these patients. Instead of administering drugs to patients blindly and without a clear idea of their effectiveness, the use of PET and appropriately labeled pharmaceuticals will allow the physician to select the most suitable and specific therapeutic drugs. PET imaging will allow accurate staging of cancer and other serious diseases and will be adopted as the most accurate technique for monitoring response to treatment and detecting recurrence. Likewise, PET will increasingly play a major role in drug development in animal models and humans by demonstrating the degree to which the intended pharmaceutical targets diseased tissues. PET will also demonstrate the rate of metabolism of the administered drugs by various tissues in the body. The role of CT and/or MR imaging as standalone, independent modalities in medicine will decrease as the efficacy of PET is realized by scientists and clinicians alike. In particular, the use of contrast agents such as iodinated compounds and gadolinium-based agents will be minimized as the impact of molecular diagnosis with PET is realized by the community at large. Similarly, imaging with single γ-emitters, either as planar or tomographic techniques, will be increasingly replaced with PET.

Without equivocation, then, PET, led by ^{18}F-FDG imaging, has truly brought about a revolution in medicine, with an impact that is extraordinary and far-reaching. As this technology plays an increasingly significant role in research and clinical applications, it will enhance the scientific basis of medical practice, provide sound and logical grounds for decision making, and continue to improve outcomes for patients around the world.

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tial, and cell-factor secretion of adipose-derived stem cells (ASCs) and whether SPIO-enhanced MR imaging detects viable stem cells. Rat ASCs were incubated in SPIO-containing cell culture medium for 2 d and then subjected to adipogenic, osteogenic, and myogenic transdifferentiation. The reverse transcription polymerase chain reaction was used to measure expression of vascular endothelial growth factor, hepatocyte growth factor, and insulin-like growth factor 1 by the SPIO-treated ASCs, and cell viability was assessed with trypan blue stain. In a separate set of in vivo experiments, SPIO-labeled ASCs were injected into 10 rat hearts that were monitored with MR imaging. The survival rate of ASCs cultured in the SPIO-containing medium was 97%−99%. These ASCs continued to express specific markers for the 3 types of transdifferentiation. Expression of cell factors was not affected by SPIO labeling. Signal voids on MR images in the living rats were associated with living SPIO-labeled ASCs in the hearts. The authors concluded that "SPIO does not affect viability, transdifferentiation potential, or cell-factor secretion of ASCs" and that MR imaging "mainly highlights living SPIO-labeled stem cells."

Magnetic Resonance Imaging

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