Guest Editorial: The Conception of FDG-PET Imaging

Abass Alavi and Martin Reivich

THE CONCEPT OF EMISSION and transmission tomography was introduced by David Kuhl and Roy Edwards in the late 1950s, which later led to the design and construction of several tomographic instruments at the University of Pennsylvania. These machines were able to successfully map regional distribution of radionuclides such as ^{99m}Tc as tomographic images. The instruments built at the University of Pennsylvania were designed to detect single gamma emitters and therefore their research and clinical applications were limited to the investigation of simple functions like breakdowns in the blood-brain barrier in disorders such as brain tumors and cerebral infarcts. The instruments manufactured in the late 1960s and the early 1970s were also designed to image only the brain and not other organs, which was dictated by the technical difficulties that were encountered at the time. Collaboration between investigators from Nuclear Medicine and the Cerebrovascular Center at the University of Pennsylvania (directed by Martin Reivich) resulted in great interest in quantitative measurement of regional cerebral function such as blood flow and blood volume. Although these attempts were successfully implemented, it became clear that synthesizing biologically important compounds with single gamma-emitting radionuclides, like technetium and iodine, was a major challenge at the time and therefore other avenues were to be explored to overcome these limitations.

By the early 1970s, Louis Sokoloff et al from the National Institutes of Health (NIH) and Martin Reivich from the University of Pennsylvania had clearly shown that the beta-emitting 14C-deoxyglucose (DG) could be successfully used to map regional brain metabolism, which was later proven to correlate well with local function. These investigators were able to show that DG crosses the blood-brain barrier and is phosphorylated by the hexokinse system to DG-6-phosphate similarly to glucose. However, in contrast to glucose-6-phosphate, which is further metabolized to CO_2 and H_20, DG-6-phosphate remains intact in the tissue for an extended period of time. This unique metabolic behavior makes radiolabeled deoxyglucose an excellent candidate for mapping regional function in the brain and other organs. Since ^{14}C is a beta-emitting radionuclide, optimal assessment of its distribution could be revealed by a technique called *autoradiography*. In animal experiments, 40 to 45 minutes after the intravenous administration of ^{14}C-DG, slices of the brain were exposed to radiographic films to reveal the beta particles emitted for a period of time. The film was then processed to capture the regional distribution of the compound with exquisite detail. After successfully showing ^{14}C-DG as a metabolic tracer, collaboration between investigators from the NIH and the University of Pennsylvania resulted in defining and measuring parameters that are essential for calculating regional metabolic rates for glucose in various structures in the brain.

By the early 1970s, this powerful technique had been adopted worldwide as an important research tool for the assessment of regional brain function in a variety of physiologic and pathologic states in different animal models.

It became increasingly clear that the use of DG as a noninvasive methodology for the investigation of brain function in healthy and diseased states in humans would substantially advance our knowledge of neuropsychiatric disorders.

In late 1973, the year that x-ray computed tomography (CT) was introduced by Hounsfield, Martin Reivich, Director of the Cerebrovascular Research Center, David Kuhl, Director of Nuclear Medicine at the time, and Abass Alavi, a junior staff member in nuclear medicine (all at the Hospital of the University of Pennsylvania), discussed the possibility of labeling DG with a gamma-emitting radionuclide for in vivo imaging by an appropriate instrument. It was clear to these investigators that only positron-emitting radionuclides would be suitable for this purpose. They consulted Alfred Wolf, an organic chemist at Brookhaven National Laboratory (BNL), who had developed a great interest in synthesizing positron-emitting compounds. At a joint meeting of investigators from BNL and the University of Pennsylvania in December 1973, Wolf suggested that ^{18}F rather than ^{11}C should be pursued as an appropriate option because of its relatively long half-life and its low positron energy. The long life of ^{18}F was also attractive for shipment of the compound from BNL to the University of Pennsylvania where the group had planned to conduct the first tomographic studies in humans. At the conclusion of the meeting, Wolf expressed his and his group's great desire to work on this project and made it clear that he wanted to be a close research collaborator with the University of Pennsylvania investigators after the synthesis had been accomplished.

During the ensuing 2 years NIH funding was secured, which resulted in establishing a positron emission tomography (PET) center at the University of Pennsylvania to initiate this project and, in the meantime, Tatsuo Ido had joined Wolf's laboratory as a visiting postdoctoral fellow from Japan and was assigned to this project. Dr. Ido became the author of the first paper describing the synthesis of this compound. By 1975, FDG was successfully synthesized at BNL and though the initial yield was low, it was sufficient to plan for human studies. The BNL group also was able to synthesize ^{14}C FDG, which was shown by Sokoloff et al to have a similar behavior to that of ^{14}C DG in in vivo experiments performed at the NIH. In addition, all the required steps were taken to make certain the product could be safely prepared for human studies. Soon thereafter, an Investigational New Drug application was filed with the Food and Drug Administration (FDA) in preparation for the administration of FDG to humans.

Investigators at the University of Pennsylvania, in anticipation of human experiments with a positron-emitting radionuclide, had assembled a set of high-energy collimators to equip the Mark IV scanner (designed and built at the University of Pennsylvania),

From the Division of Nuclear Medicine and the Cerebrovascular Research Center, Hospital of the University of Pennsylvania, Philadelphia, PA 19104.

Address reprint requests to Abass Alavi, MD, Hospital of the University of Pennsylvania, 3400 Spruce St, Philadelphia, PA 19104.

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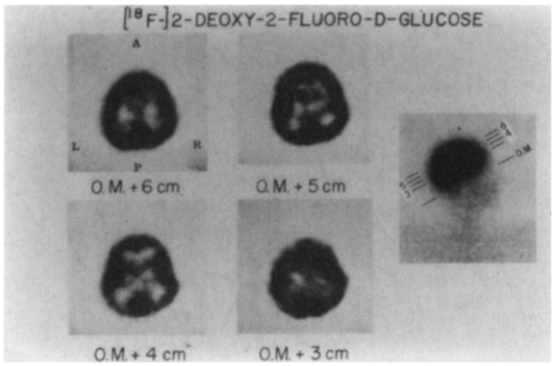

Fig 1. First whole-brain (planar) and tomographic FDG images of brain function of a normal volunteer reveal high concentration of the agent in cortical and subcortical gray matter. These images were acquired by using only 1 of the 2 ^{511}KeV γ rays emitted from the positron decay (instead of coincidence detection of the 2 γ rays with an appropriately designed PET instrument). The whole brain scan was generated by an Ohio Nuclear Rectilinear scanner whereas tomographic images were obtained with the Mark IV scanner, which was designed to examine CNS disorders with single α-emitting radionuclides. (Reprinted with permission from Reivich M, Circ Res 44:127-137, 1979.)

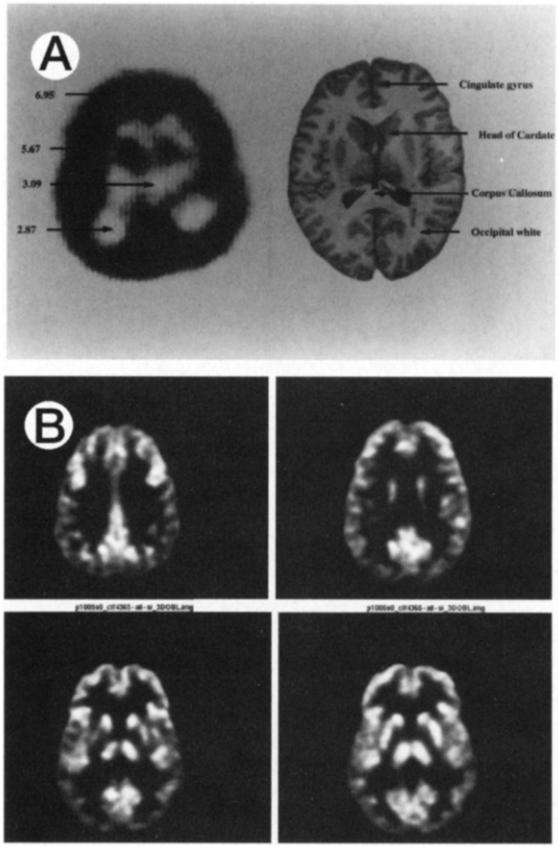

Fig 2. Comparable FDG images of the brain obtained (A) with Mark IV and (B) G-PET scanner, designed and built by investigators from the University of Pennsylvania and UGM Inc, Philadelphia, PA, clearly show substantial improvements in the capabilities of instruments introduced over the past 25 years.

which, until then, was only capable of imaging low-energy radionuclides such as ^{99m}T and ^{123}I, to be able to image the ^{511}Kev gamma rays emitted as a result of positron decay. By midsummer 1976, researchers from both institutions decided that the time had come to plan the first human studies at the University of Pennsylvania. In August 1976, 2 normal volunteers each received a dose of FDG, which was shown to concentrate in the brain by using only 1 of the 2 gamma rays emitted from the annihilation of positron particles (instead of detecting the 2 gamma rays as a coincident event) (Fig 1). This was a gratifying outcome for investigators from both laboratories who had worked so tirelessly over the proceeding years to achieve this goal, namely, to perform the first images of cerebral glucose metabolism in humans. The quality of the images generated was poor and is not comparable to that of modern scans acquired and reconstructed with modern instruments (Fig 2). A whole body image of the FDG distribution also was obtained in 1 subject by using a dual-head Ohio-Nuclear Scanner (Ohio Nuclear, Cleveland, OH) that was equipped with high-energy collimators for ^{85}Sr bone studies (Fig 3). Uptake of FDG in the heart and significant renal excretion of the compound was shown on this first human whole-body study. Obviously, the quality of whole-body images with FDG is substantially enhanced by using instruments that are optimally designed for this purpose (Fig 4).

Simultaneous with these developments at the University of Pennsylvania and BNL, investigators at Washington University, directed by Michel TerPogossian and in collaboration with Michael Phelps and Edward Hoffman, had developed the first successful PET machine for optimal imaging of positron-emitting radionuclides in humans. Soon thereafter, Gerd Muehelenner at Searle Radiographics (later purchased by Siemens) successfully showed the feasibility of using 2 opposing scintillation cameras as coincidence detectors to image position-emitting radionuclides. This approach was later perfected when he was a faculty member at the University of Pennsylvania. In mid-1976, David Kuhl was recruited by the University of California Los Angeles (UCLA) as the Director of Nuclear Medicine at that institution and by the fall of that year he had assembled on outstanding team of investigators to further explore the potential applications of PET in the central nervous system (CNS) and other organ disorders. At that time, UCLA was one of a few centers with a functioning cyclotron in a medical environment. Shortly, a PET scanner (designed and built based on principles established by the Washington University's PETT III scanner) was installed at UCLA that for the first time allowed investigators at that institution to image FDG uptake (the synthesis scheme was established with assistance from the BNL group) in the brain with an optimal instrument. This group, headed by David Kuhl, was able to demonstrate the ability of FDG-PET imaging in mapping cerebral function in a variety of physiologic and pathologic states. In the meantime, The PETT III scanner, which was designed and manufactured at Washington University, was transferred to BNL for conducting human studies at that institution. The next phase of collaboration between BNL and the University of Pennsylvania investigators was initiated when Wolf requested the research team from the latter institution to conduct FDG-based CNS projects at BNL. Every other week a research team, directed by Abass Alavi, traveled to BNL by car and by plane to perform several interesting and important research

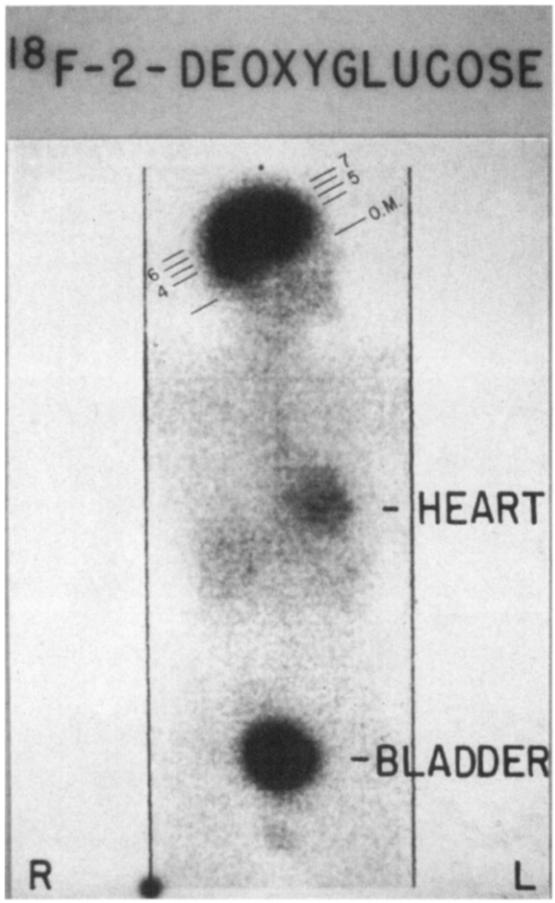

Fig 3. First total body images were obtained after the acquisition of tomographic studies of the brain by using a dualhead Ohio Nuclear Rectilinear scanner. This scanner was equipped with high-energy collimators for performing ^{85}Sr bone scans. These first whole-body FDG images revealed uptake of the compound in the heart (in addition to the brain) and significant excretion through the kidneys.

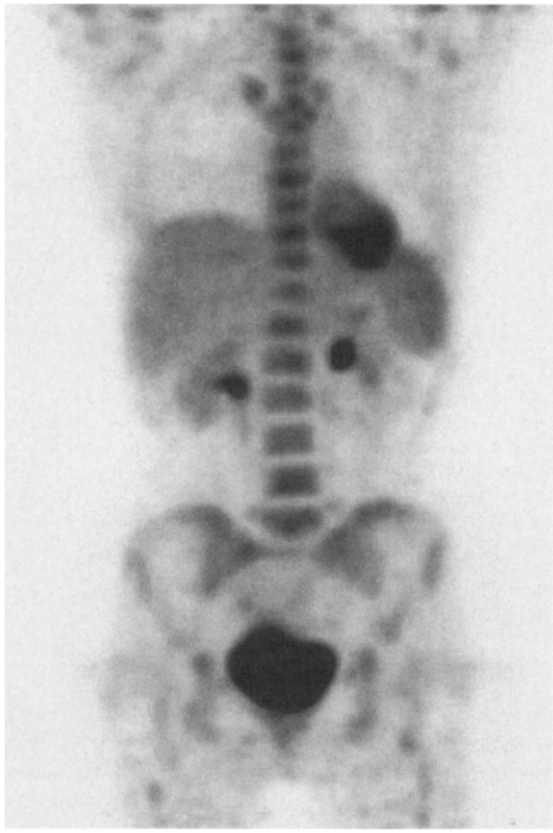

Fig 4. Whole-body FDG-PET projection images of a patient with a lymphoma reveal a great deal of detail about various structures included in the field of view. The high-quality of these images shows a substantial improvement in PET instrumentation for imaging irregular structures, which has further enhanced effective use of FDG in a multitude of malignant and nonmalignant disorders.

projects in normal volunteers and, later, in patients. By 1979, the group at the University of Pennsylvania, directed by Martin Reivich and Abass Alavi, had established a PET center independent of BNL, but collaboration between the 2 institutions continued for more than a decade.

The extraordinary power of functional imaging as evidenced by the FDG-PET technique generated a great deal of interest in the scientific community which later led the NIH to establish several centers that included the University of Michigan, Johns Hopkins, Washington University, and the NIH Campus at Bethesda (in addition to the University of Pennsylvania and UCLA), which expanded the domain of research beyond what had been achieved with FDG.

Based on an observation made by Warburg in the 1930s that malignant cells use glucose preferentially over other substrates, Som et al at BNL were able to show substantial concentration of FDG in tumor models in animals. Based on these principles and for the first time, FDG was used by Dr. Dichiro and colleagues at the NIH to investigate metabolic activities of brain tumors in humans at diagnosis and after treatment. They were able to show that the degree of FDG uptake correlated with the grade of the tumor and that it was a predictor of outcome at diagnosis. More importantly, it was noted that FDG-PET imaging was superior to contrast-enhanced CT and magnetic resonance imaging (MRI) in differentiating recurrent tumors from radiation necrosis. Investigators from the University of Pennsylvania (Jane and Abass Alavi) further confirmed these early observations and, since the mid-1980s, FDG-PET imaging has been widely used to examine patients with brain tumors specifically for the diagnosis of recurrent brain malignancies.

During most of the 1980s, performance of whole-body imaging with PET was validated, and, by the early 1990s, its application as an effective modality was realized for this purpose. Investigators from UCLA and later from the Universities of Duke, Michigan, Nebraska, and Heidelberg were among the pioneers in showing the efficacy of FDG-PET imaging in the management of patients with a variety of malignancies. These included diagnosis, staging, monitoring treatment, and detecting recurrence of a variety of tumors. The role of FDG-PET in differentiating benign from malignant nodules as a standard and as the study of choice is unchallenged at this time. This imaging technique has substantially simplified the management of patients with solitary pulmonary

nodules and staging patients with lung cancer with high accuracy. Detection of recurrent tumors by FDG-PET imaging after surgery for colon cancer as evidenced by elevated serum carcinoembryonic antigen (CEA) levels has been revolutionary because in the majority of these patients, CT and other anatomic imaging techniques fail to show the sites of disease. FDG-PET imaging is not only very cost effective in this setting, but is of great importance in providing an answer for a difficult clinical problem and has been well accepted by clinical oncologists.

FDG-PET imaging may completely replace other imaging techniques for the initial staging, restaging, and monitoring effects of treatment in patients with Hodgkin's and non-Hodgkin's lymphomas. The extraordinary sensitivity and specificity of FDG-PET imaging allows detection of disease activity in the lymph nodes and other organs with great precision. It is conceivable that in the near future, this modality will be used as the study of choice in the management of patients with lymphomas.

Similar statements can be made about the application of FDG-PET to other malignancies including head and neck tumors, breast cancer, melanoma, ovarian cancer, mesothelioma, and, possibly, thyroid cancer and genitourinary (GU) tumors.

Although FDG-PET imaging can play a role in the diagnosis of malignancies, its major contribution has been in the accurate staging of cancer, in the assessment of the effectiveness of therapy, and, above all, in detecting recurrence after medical, radiation, and surgical therapies. In the latter settings, changes caused by such treatments render structural techniques incapable of providing a definitive answer about the disease activity in many occasions.

FDG-PET imaging as an effective technique for the assessment of myocardial viability is well established and in fact is considered the gold standard for this purpose. However, because of successes of conventional imaging with single-emitting radiopharmaceuticals, PET is only requested in limited circumstances for determination of myocardial viability.

Increasingly, FDG-PET imaging is being used to detect suspected orthopedic infections, such as in failed prostheses, complicated fractures, and osteomyelitis. Detection of inflammatory processes including sarcoidosis, regional ileitis, and arthritis may allow applications of FDG-PET imaging for these challenging disorders and further enhance its clinical use.

Early data from our laboratory and Sloan Kettering Memorial Hospital show the feasibility of this technique in detecting atherosclerosis which, after validation, may become an added domain for this exciting modality.

What are the challenges ahead as we are witnessing the rapid expansion of FDG-PET to the day-to-day practice of medicine around the country and the world? The major difficulty that is being encountered by almost every group is the tremendous shortage of personnel who are properly trained in the discipline and are competent in performing various tasks that are associated with this technology. This applies to several categories of professionals whose contributions have been essential for the successful evolution of PET over the past 25 years. There is a great shortage of technical staff to manage cyclotron facilities, produce radionuclides, synthesize compounds, and perform required quality control for human studies. There is a great need for nuclear medicine technologists who are optimally trained to perform these studies.

Above all, experienced and competent physicians who can provide this service in a competent manner in the community are very few and in great demand. Training in diagnostic radiology and conventional nuclear medicine is inadequate for interpretation of these complex and artifact-prone studies. It may not be an exaggeration to consider FDG-PET images as some of the most difficult in the diagnostic discipline. It is not uncommon to spend 20 to 30 minutes of time to examine a case so that one can confidently render an accurate assessment of the findings portrayed on the scan. Knowledge of cross-sectional anatomy in understanding of such studies is helpful but not essential for optimal interpretation of FDG-PET images. There is a misconception that these studies must be interpreted by a radiologist rather than by a competent nuclear medicine physician who is not fully trained in cross-sectional anatomic imaging techniques. Currently, the majority of cases around the world are adequately and competently interpreted by nonradiologists and this trend will continue in the foreseeable future. In fact, most PET specialists have mastered skills in comparing FDG-PET images with other diagnostic techniques when such comparisons have been necessary.

It is becoming quite clear that acquiring optimal skills to interpret FDG-PET images will require at least 6 months of full-time training in this discipline. Fellowships for a period of 1 to 2 weeks as a certificate of competence are unjustified and in fact will be a disservice to the medical community if adopted by future practitioners. It would be unfortunate if such practices tarnish the image of the discipline as an effective modality.

Finally, it is also quite evident that this type of service should be provided by centers with active cancer programs. Such centers should be able to refer at least 2 to 3 patients to the PET facility on a daily and routine basis for financial viability of the operation of this complex technology. We are of the belief that fixed sites are preferable to mobile arrangements for this purpose. Fixed sites provide the continuity of operations on a routine basis, which translates into technically optimal operation. The future of mobile units for this modality may be questionable at this time. Surprisingly, FDG supply to the medical community has adequately kept up with the rapid expansion of this technique and does not appear to be a source of difficulty at this time. It is not clear whether future regulatory issues will limit its distribution within and across states.

In conclusion, FDG-PET imaging is increasingly playing a major role in the management of patients with a variety of disorders, especially those with cancer. This modality provides an exciting opportunity to the imaging specialists, which is also associated with serious challenges. The imaging community must make every effort to be certain that this modality is appropriately utilized and managed so that in the end, patients with difficult and challenging problems will benefit from its capabilities. It is important to note that FDG-PET imaging has made an everlasting impact on our field and, in fact, its routine use and acceptance by the medical community at large has rejuvenated the specialty into a powerful discipline as we entered into the 21st century. It may not be an exaggeration to project that, in the near future, the number of FDG scans performed in most active nuclear medicine services will exceed that of all other procedures performed in most laboratories. It is therefore quite fitting to applaud Dr. Henry Wagner for naming FDG as the "Molecule of the 20th Century" because of its unparalleled and unique impact on the evolution of the field of nuclear medicine.