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Preface

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In 1973, Hounsfield and Cormack introduced x-ray computed tomography, which truly revolutionized the field of radiology [1,2]. Later that year, the concept of 18-fluorodeoxyglucose (FDG)-PET was born when three investigators from the University of Pennsylvania (Penn)—Abass Alavi, Martin Reivich, and David Kuhl—discussed the feasibility of labeling deoxyglucose (DG) with gamma-emitting radionuclide for in vivo imaging of regional brain function in humans [3]. Up until that time, researchers at the National Institutes of Health (NIH) and Penn had tested the beta-emitting ^{14}C-DG in rats as a novel radiotracer to image regional cerebral glucose metabolism and, therefore, function in a variety of physiologic and pathologic states [4]. Because ^{14}C is a beta-emitter and the electrons emitted are stopped internally, a technique called *autoradiography* was used to map its distribution in the brain and elsewhere in the body. Using this technique, regional glucose metabolism can be visualized with exquisite detail. By the early 1970s, the potential of this preparation as a probe to map regional metabolism and function in humans had increasingly become evident to the scientific community, including the group at Penn.

Thereafter, the concept of labeling DG with radionuclides was discussed with Alfred Wolf at the Brookhaven National Laboratory (BNL) who suggested 18-fluorine (^{18}F) as the best option for exploring its potential applications in human beings by PET. By 1975, the synthesis schemes for ^{18}F had been perfected, and in August of 1976 the first brain and whole-body images of a human being were acquired at Penn. The first brain images were acquired using a SPECT instrument (Mark IV, designed and built at Penn) that was equipped with high-energy collimators for this purpose. Whole-body images were acquired by employing an Ohio Nuclear dual-head scanner that also was capable of imaging high-energy gamma rays. Simultaneous with these attempts to synthesize FDG, investigators at Washington University (Drs. Ter-Pogossian,

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Phelps, Hoffman, and Mullani) [5] and Searle Radiographics (Dr. Muehllehner) [6] had initiated and successfully built instruments that would allow for optimal in vivo imaging of positron-emitting radionuclides in humans. Because of these early successes, the NIH decided to establish several research centers to explore the potential applications of this powerful modality in mapping body metabolism and function as quantitative images.

The initial focus of the research in these centers was brain imaging by way of FDG and several neuroreceptor compounds (particularly dopaminergic ligands) to determine alterations that occur in the central nervous system (CNS) in a variety of neuropsychiatric disorders. In fact, during most of the 1980s, the majority of the work reported in the literature dealt with the applications of this methodology in assessing derangements in the CNS physiology and metabolism in a multitude of diseases [7–9].

However, based on the observation made by Warburg in the 1930s that malignant cells prefer glucose over other substrates as a source of energy, some attempts were made in the late 1970s and the early 1980s to use FDG in assessing disease activity in cancer. Pioneering work at the BNL by Som and colleagues in animals [10], Di Chiro and colleagues at the NIH [11], and the Penn group in human brain tumors [12] clearly demonstrated the importance of FDG-PET imaging in the evaluation of cancer. In the meantime, performance of whole-body imaging with PET was optimized late in the 1980s [13]. By the early 1990s, investigators from UCLA, and later from the Universities of Michigan, Duke, Nebraska, and Heidelberg, demonstrated the importance of FDG-PET imaging in the management of several common malignancies. These efforts were applicable to diagnosis, staging, and monitoring response following treatment and detecting recurrence of cancer. By the late 1990s, a large body of literature of FDG-PET imaging had clearly shown that FDG-PET imaging was essential for optimal assessment of patients with a number of malignancies, and its routine use was well justified [14]. Among these clinical applications, certain entities appeared most impressive, including differentiating benign from malignant lung nodules, staging lung cancer, detection of recurrent colon cancer, and assessing lymphomas at various stages of disease [15].

The use of FDG-PET as an effective method for determining myocardial viability is well established and is considered the gold standard for this purpose [16]. Increasingly, FDG-PET imaging is being employed for the detection of orthopedic infections, fever of unknown origins, and inflammatory disorders [17]. In addition, FDG-PET may prove to be an important method for detecting atherosclerosis, blood clots, and muscle dysfunction [18,19].

The introduction of dual-modality PET/CT systems in the late 1990s added a major dimension to the use of this powerful methodology, particularly in certain clinical settings [20]. The combination of structure and function in the same image to allow precise localization of the diseased sites will play an important role in optimal use of this technology. This is particularly true for preoperative and prebiopsy interventions in patients with cancer and possibly other disorders. An area in which PET/CT imaging will become the standard of care is in radiation oncology which, in our view, may prove to be the most important application of this powerful modality [21]. In head and neck pathologies, because of the complexity of the structures visualized by the radiologic and functional imaging techniques, precise coregistration of PET and CT images is essential for accurate interpretation [22]. In certain anatomic sites such as the brain, heart, and lower extremities, the impact of PET/CT may not be as dramatic as in other sites in the body. Combined PET/CT is now being challenged by the promise of simultaneous PET/NMR, which has many additional features compared to PET/CT [23]. The advantages of PET/MR imaging over PET/CT include the possibility of simultaneous imaging with both modalities (instead of sequential scanning with PET/CT), potential for administering MR contrast agents during imaging, superior soft tissue delineation, and the ability to provide some complimentary physiologic data for the tissues examined. The latter includes temporal correlation of blood flow data with the metabolic and receptor data provided by PET. Also, MR can provide images of diffusion, perfusion, and organ motion (particularly in the heart) in a single imaging session. In addition, MR imaging can be combined with MR spectroscopy to measure spatially matched regional biochemical content and to assess metabolic status or the presence of neoplasia and other diseases in specific tissue areas. Finally, MRI does not use any ionizing radiation and therefore can be used without restrictions in serial studies, for pediatric cases, and in many other situations where radiation exposure is a concern. This technology may replace PET/CT in certain anatomic sites such as head and neck, pelvis, and the extremities [24].

It is expected that over the next 5 to 10 years, the majority of nuclear medicine procedures will be generated employing PET. Therefore, it is essential that the imaging community makes every effort to define the necessary indications for which combined modalities (PET/CT or PET/MR) are required for optimal results [21,25]. This is a challenge that

should be addressed soon so that the cost and the space requirements will not interfere with the widespread use of PET in the day-to-day practice of medicine.

Several new tracers will be approved and routinely used in the coming years. Agents that measure regional hypoxia in malignant tumors (eg, FMISO, EF5, Cu-64 ATSM) and possibly in some benign disorders will be frequently employed [26]. Hypoxia is considered the main factor in lack of response following radiation or chemotherapy. Therefore, in patients with hypoxia radiation and/or chemotherapy may be postponed until optimal oxygen levels have been restored in the tumor. In certain cancers, ^{18}F-labeled fluorothymidine may prove to be of value in monitoring response to therapy instead of FDG [27]. This tracer, however, does not appear to be optimal for diagnostic purposes, because it is insensitive for detecting slow-growing tumors. ^{18}F-labeled DOPA is expected to be used for the diagnosis of Parkinson's disease and will be widely adopted for this purpose [28]. Also, this tracer along with ^{68}Ga-labeled DOTA octreotide and ^{124}I-labeled MIBG appear to have the promise of improving the management of patients with neuro-endocrine tumors [29]. Estrogen receptor (ER) targeting agents may be used to assess noninvasively, the ER section of tumors in vivo by ^{18}F-labeled estrogen analogues such as fluoestradiol [30]. Angiogenesis, the formation of new vessels is the target of a multitude of novel therapies and drugs. Therefore, direct visualization of this biologic response to tumor hypoxia and cell proliferation will be of great importance in developing these drugs. Peptides containing the amino acid sequence arginine-glycine-aspartate appear to have an affinity toward integrins that are present on activated endothelial cells in tumors with angiogenesis [31]. Apoptosis or programmed cell death can be imaged with radiolabeled Annex V to monitor response to therapy in cancer [32]. There are several amyloid imaging agents that may become the test of choice in the early diagnosis of Alzheimer's disease [33] although more recent studies combining autoradiography and histochemical techniques provided a molecular explanation for [^{11}C]-PIB's (Pittsburgh Compound B) limited specificity in diagnosing and monitoring disease progression in AD [34] suggesting that FDG will still play a pivotal role as a key imaging probe [35]. Obviously, the list of new tracers is very long, and many have the potential for routine use in the near future.

This is an exciting time for molecular imaging. During the last few years, the number of published papers on this topic has been increasing steadily, which motivated us to assemble this special issue on PET instrumentation and novel quantitative techniques as a snapshot of this dynamically changing field. The development of PET has been rapid and exciting, and there is every reason to believe the field will move forward more rapidly in the near future with the advent of novel technologies and methodologies and the unlimited imagination of researchers in the field. Despite the remarkable achievements summarized in this special issue and other peer-reviewed journals, there is still scope for further research. There is no shortage of challenges and opportunities for PET instrumentation and quantitative imaging techniques nowadays. We hope that in this limited space, we were able to give you a flavor of recent developments in the field and their potential applications in clinical and research settings. We found the compilation of this issue to be a rewarding and educational experience and hope that the reader is left with the same experience.

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