PREFACE

This book is written as both a text and a reference book. It contains numerous images from the biological sciences and clinical practice, tables, graphs, and figures, as well as exercises that are worked out to aid the reader in understanding principles or solving problems. In some cases, derivations are placed in appendices so as not to break up the flow of the subject matter in the text.

The book is intended for a broad audience interested in molecular imaging with positron emission tomography (PET). It is expected that the readers will range from undergraduate, graduate, and medical students to residents, physicians, and scientists with backgrounds from various physical, biological, and medical specialty areas. Each chapter presents material in a straightforward manner that is well illustrated and explained. Because of the diverse audience for the book, certain chapters or sections of chapters will be of more interest than others to certain segments of the readership.

Chapter 1 introduces the fundamental physics upon which PET imaging systems is based and discusses in detail the technologies and methods used to produce PET images. The chapter starts out by reviewing the physics of positron emission and annihilation and explains how positron range and photon noncolinearity in coincidence detection place certain limits on spatial resolution.

Next, detector technologies suitable for detecting 511 keV annihilation photons are introduced and the geometries for typical PET scanner configurations discussed. The corrections needed to achieve quantitative images, namely detector normalization, detector dead-time correction, attenuation correction, and correction for scattered and accidental coincidences are explained. The various types of algorithms used to reconstruct the data recorded by the PET scanner into tomographic images are described.

Finally, methods for assessing the performance of PET imaging systems are presented. The PET systems described range from human PET and PET/CT scanners to those used for small animal imaging.

Chapter 2 presents molecular imaging assays as a central theme to using PET as a fundamental tool for dissecting molecular events that constitute biological processes. The assay developer must integrate information from all the other

chapters of the book in order to produce quantitative tracer kinetic models and biological assays. A knowledge of tracer kinetics also guides the development of new molecular imaging probes.

The fundamental requirements of quantitative PET data for tracer kinetic modeling are initially discussed followed by defining the central principles underlying tracer kinetic modeling including compartmental models, perfusion, volume of distribution, rate constants, rate coefficients, and flux. The "tracer thought experiment" is used to help the reader visualize the movement of a tracer throughout the body in order to build an understanding of how to develop a comprehensive tracer kinetic model and assay.

Specific examples of various PET tracer kinetic models including the ^{18}F-fluorodeoxyglucose three-compartment model, ^{13}N-ammonia and ^{15}O-water perfusion models, and receptor–ligand models are presented. The fundamental nature of the input function, tissue time–activity curve, and differential equations governing various models are described. In addition, the approach to structuring new models for imaging PET reporter gene expression are presented in detail to highlight the step-by-step process of building a model. Model validation and fitting of PET data to a given model are also detailed. The translation of PET assays from animal models to human subjects is examined.

Numerous work sets and systematic guidelines, reinforced with specific examples, provide the reader with an intuitive and fundamental understanding of PET assay development.

Chapter 3 describes the concept of the "electronic generator" for preparing PET molecular imaging probes. An electronic generator represents the integration of a small cyclotron with an automated molecular imaging probe synthesizer operating under the control of a personal computer. This technology, revolutionized by joint efforts between academia and industry, enables production of multiple doses of various PET molecular imaging probes by a technician for clinical and research applications.

Discussed in this chapter are the fundamental principles behind positive, and negative-ion cyclotrons and the advantages of the latter for the automated production of positron emitting isotopes for PET. A description of the relevant parameters that determine the course of nuclear reactions and a conceptual design of a cyclotron target body appropriate for the production of positron emitting isotopes are also provided. A number of numerical examples are included to accentuate and facilitate understanding of all these basic concepts and the mathematical relationships defining them.

Important ^{15}O-, ^{13}N-, ^{11}C- and ^{18}F-labeled precursors that are currently used in the synthesis of labeled molecular imaging probes for PET are summarized. Representative examples of low-energy small cyclotrons, target systems, and automated radiosynthesis modules are also discussed from the standpoint of the genesis and future of electronic generators.

Finally, the crucial role of the recent FDA legislative action, namely, FDAMA '97, on PET radiopharmacies and their impact on the emerging clinical PET are addressed.

Chapter 4 describes the fundamental principles of molecular imaging probe design as a biochemical tool to reveal the molecular basis of normal biological processes and those of disease. Emphasis is given to the ultimate objective of the

molecular imaging determination, namely, how properly designed molecular probes are used to select out and quantify the target process to be measured. Specific examples illustrate the main concepts and their extension to the development of other imaging probes.

Molecular imaging probes (diagnostics) and drugs (therapeutics) share common concepts in structural design and common biochemical targets of enzymes, receptors, neurotransmitter systems, RNA, DNA, and pathological depositions. Application of molecular imaging to aid in drug development (e.g., receptor occupancy determinations, pharmacokinetics, surrogate markers, the development of combinatorial radiolabeled drug libraries) is discussed. The concept of making molecular imaging probes available to physicians and researchers via distribution centers is also illustrated.

Chapter 5 focuses on the integration of PET imaging with ^{18}F-fluorodeoxyglucose (FDG) into the care of patients with cancer. PET has now been incorporated into diagnostic algorithms for many cancers, and the number of PET studies performed in the United States is approaching a million per year in 2003 and is increasing at a rate of about 50%/year. A similar magnitude and rate of growth is occurring for the rest of the world.

The chapter reviews the clinical role and accuracy of FDG-PET for diagnosing, staging, and detecting recurrent disease in various cancers in the context of other diagnostic imaging modalities. In addition, the role of PET for monitoring various cancer treatments is discussed. Further, the prognostic value, cost-effectiveness, and impact on patient management with FDG-PET are reviewed.

New concepts for molecular imaging of cancer with PET are introduced. These include the emergence of combined PET/CT imaging devices and the development of new tracers that target specific biological properties of cancer cells including ^{11}C-acetate and ^{18}F-fluoroethylcholine for lipid synthesis and ^{18}F-fluorothymidine (FLT) for assessing DNA replication and cell proliferation.

Chapter 6 examines the principles, methods, and applications of PET to the study and characterization of the cardiovascular system. The chapter proceeds from studies of normal cardiac function to its failure in disease. The impact of the heart's anatomical and functional properties on PET images of the cardiovascular system are examined. Approaches are presented for deriving qualitative and, more importantly, quantitative information on regional molecular imaging probe tissue concentrations. Since quantitative information is fundamental to the application tracer kinetic principles to the heart, it is reviewed in considerable detail together with a description of how this information can be employed for the determination of regional rates of blood flow, oxygen consumption, and substrate metabolism in the myocardium. PET-derived estimates of these processes for the normal human heart are summarized in several tables together with data established through invasive techniques.

The chapter then explores the value of PET for diagnosing and characterizing coronary artery disease by utilizing measurements of myocardial blood flow and its response to physiological and pharmacological stresses. The use of these types of studies for detecting pre-clinical coronary artery disease, as well as for monitoring responses to lifestyle and pharmacological risk factor modification, are also described.

Alterations of myocardial substrate metabolism as observed with PET in

non-coronary cardiac disease are then reviewed. This is followed by an extensive description of the utility of PET for the assessment of myocardial viability in cardiac disease. Underlying pathophysiological mechanisms are examined and related to alterations in blood flow and substrate metabolism as observed with PET.

Relevant to the clinician, the chapter then discusses clinical implications of viability assessments with PET, especially in the severely symptomatic patient with end-stage coronary artery disease. The chapter concludes by reviewing current and future clinical applications of PET in patients with cardiovascular disease.

Chapter 7 covers the ways in which imaging studies with PET have advanced our understanding of the brain through in vivo assessment of diverse aspects of neurobiology and biochemistry. In vivo measurements of cerebral glucose metabolism, blood flow, enzyme activities, neurotransmitter synthesis, and receptor binding are described, along with the ways in which such parameters are affected by normal development and by a host of neurological and psychiatric disorders.

The properties and actions of the molecular imaging probes used in studying the brain are integral to understanding the measurements of cerebral function made with PET. This knowledge of molecular imaging probes is discussed alongside the kinds of investigations in which the probes are employed.

Since the synthesis of over 95% of the adenosine triphosphate (ATP) molecules that are hydrolyzed to fuel cerebral function originates from metabolism of glucose, PET imaging of glucose metabolism with FDG provides an excellent way to evaluate the distributed function of the brain. Studies of various normal and disease states of the brain are presented to illustrate this approach to mapping cerebral function and providing an accurate disease diagnosis.

Studies are presented to show how the anatomical pattern of blood flow imaged with diffusible tracers such as ^{15}O-water closely parallels that of the cerebral metabolic rate for glucose throughout much of the normal brain. Examples are also shown where under certain pathologic circumstances the normal coupling between glucose metabolism and blood flow is disturbed.

PET provides a unique window through which to view neurotransmitter systems in the brain with a continuing goal in PET research to design molecular imaging probes and tracer kinetic models that provide detailed assessments of neurotransmitter system function in vivo. PET methods have been developed to assess occupancy of receptors by pharmacologic doses of drugs and the effects of drugs on neurotransmitter release. As studies on other neurotransmitter systems have largely mimicked approaches used for the dopamine system, a detailed presentation of dopaminergic PET probes and their applications are first presented, followed by probes used in studying serotonergic, cholinergic, GABAergic, and opioid neurotransmitter systems.

Phenomena that had previously been studied at only the psychological level, such as human mood states, pain perception, and substance abuse, are explored in terms of their underlying neuroanatomical and neurochemical substrates, in living human beings. Many diseases that show no gross structural abnormalities on CT and MRI have been revealed with molecular imaging studies with PET. Disorders in which PET is used to examine biological abnormalities in human brain that are detailed in the text include Alzheimer's, Parkinson's, and other

neurodegenerative diseases, epilepsy, cerebrovascular disease, pain syndromes, depression, obsessive–compulsive disorder, schizophrenia, and addiction. In addition, related work conducted with PET in non-human primates and rodents is highlighted.

Finally, this chapter looks at some of the future directions of PET in the study of the biological basis of both normal and abnormal states of the brain.

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