JNM
COMMENTS AND PERSPECTIVES

CT, MRI, and PET were developed within a 2-y period. CT moved into clinical use and a decade later MRI did as well, whereas PET went through an evolution of technology, probes, and applications along a discovery pathway on the biologic basis of normal and disease states. Although clinical use of CT and MRI far surpass PET to date, grants and discoveries with PET far surpass CT and MRI.

As a 30-y historical note, when Carol Marcus asked me to give the 1974 SNM plenary lecture on CT, I said I would rather talk about PETT,* to which Carol responded, "What is PETT?" After I explained, Carol said, "Well then give the talk on PETT!" The program chair, Jerry DeNardo, agreed, and this was the first presentation on PET.

The research years built a scientific foundation for the entry of PET into clinical practice. In 1989 the Institute for Clinical PET (ICP)† was formed to provide a forum for academics and industry to educate physicians and technologists about PET and to gain Food and Drug Administration (FDA) approval and reimbursement. To date, this has resulted in Medicare and Medicaid national coverage for lung, colorectal, breast, esophageal, head and neck, and thyroid cancers and for melanoma, lymphoma, cardiovascular disease, and epilepsy, with the recent announcement of coverage for Alzheimer's effective September 15, 2004.

This year, about a million PET procedures will be performed in the United States, with a 4-y growth rate of 30%–50% per year and 2004 industry revenue of about $1 billion. There are also PET radiopharmacies within 100 miles of 95% of the hospital beds in America, along with growth in the rest of the world, to support clinical service. In the span of 3 y, PET/CT has gone from 0% to 85% of PET scanner sales, posing opportunities and a dilemma in the clinical practice of PET.

The expanding use of PET in the drug discovery process broadens its value and produces a larger resource for developing new PET biomarkers of disease. Most pharmaceutical companies now require a biomarker of disease before they will enter a drug into FDA trials—for

example, in blood to identify profiles of proteins ("protein finger printing") or in vivo with molecular imaging. Most drug companies now have internal programs or academic partnerships in PET, along with MRI, SPECT, and optical imaging, to broaden exploratory pathways from cells to patients.

The critical determination of how well a drug works in patients is made by testing it in patients, with a movement to biologic measures to directly assess the impact of the drug on disease. PET is allowing pharmaceutical companies to use labeled drugs in animals and patients safely (e.g., no pharmacologic effects due to a sensitivity on the order of fmol/g tissue or less) for pharmacokinetics, target occupancy of a drug, or imaging of biologic processes (metabolism, synthesis, DNA replication, receptor function, etc.) as measures of the side effects of the drug and its impact on disease. In turn, pharmaceutical companies are contributing to the development of PET biomarkers linked to therapeutics.

Genomics and proteomics are elucidating the mechanisms by which the genome writes instructions (messenger RNA) that are translated into proteins to self-assemble cell circuits and intercellular networks to form the structures and functions of organ systems and the whole organism. Within this systems-biology framework, disease is considered to be a reprogramming of cell circuits to gain or lose functions (e.g., in cancer to shut off programmed cell death and terminate intercellular communication allowing self-sufficient replication, growth of blood vessels, initiation of migration [metastasis]). Recognizing that disease is a developmental process, typically occurring over years as a continuum of cells in various stages of changing cell circuits, requires that a disease be partitioned into a series of "therapeutic windows" and that pharmaceutical companies produce more diverse arrays of drugs, matched to the critical targets in each window, with smaller populations of patients per drug but higher therapeutic effectiveness.

Molecular diagnostics must be developed that can identify critical cell circuit features and protein nodes to segregate patients by critical drug targets. For example, in the treatments of non–small cell lung cancer with gefitinib (Iressa; AstraZeneca), the pathologic tissue diagnosis is not informative of the therapeutic responses: 10% of patients have robust responses, whereas 90% are exposed to risk with no benefit. Although percentages vary, this is a common drug outcome. Molecular phenotyping has now shown that gefitinib inhibits protein nodes of cell circuits critical for cell survival that exist only in responders. Therapeutic windows must be defined along with drugs for the remainder of patients.

New technologies (e.g., nanotechnologies and microfluidics) being developed for systems biology, in vitro diagnostics, and drug discovery are the very same technologies that will be used to develop PET biomarkers of disease based on systems biology. Having biomarkers developed together with molecular therapeutics will keep molecular imaging diagnostics and molecular therapies focused on common goals from discovery to patient care with a higher probability of achieving common goals.

Molecular diagnostics (in vitro and imaging) and therapeutics are coming together to assist each other's development and applications in medicine. Everything, however, begins with molecular diagnostics to guide drug discovery, selection of therapy, and assessment of treatment responses based on systems biology. These changes require diagnostic medicine to be intimately involved in the evolving knowledge of the systems biology of disease and therapeutics directed at it. Molecular imaging continues to expand its capability to reach across physical, biologic, and pharmaceutical sciences in building its foundation. Basic and clinical sciences of molecular imaging must continue to engage their practitioners, and the industries that support them, to simplify the scientific complexities of new approaches to meet practical needs of patient care while maintaining the principles of molecular imaging of the biology of disease. Continued progress requires everyone to be good students and teachers of each other in making these transitions to become the masters of molecular imaging.

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*Initially I gave the name *positron emission transaxial tomography* (PETT) to this new technology, later dropping *transaxial*.

†ICP was transformed into the Academy of Molecular Imaging (AMI) in 1998 to address the broader issue of molecular imaging. ICP became 1 of the 4 Institutes in the AMI: ICP, the Institute for Molecular Imaging (IMI), the Society of Nuclear Imaging in Drug Discovery (SNIDD), and the Institute for Molecular Technologies (IMT).