

Moonho Lee Memorial Lecture

## Nuclear Medicine for All the World – from Molecular Imaging to Molecular Medicine –

Henry N. Wagner, Jr. M.D.

Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

The specialty of nuclear medicine is living and well. The number of scientific presentations at the annual meeting of the Society of Nuclear Medicine (SNM) in the United States has increased linearly over the past half century. The excitement and progress resulting from the application of the tracer principle in living human beings continues.

Oncology is still the major topic in nuclear medicine, followed by neurosciences and cardiology. Among the major applications were those contributing prognosis, treatment decisions, and documenting the responses to treatment. There has been a continual growth in positron emission tomography (PET) applications, while the number of single photon emission computed tomography (SPECT) presentations has been relatively constant at a high level. One of the major trends in nuclear medicine today is the growth of SPECT/CT.

$^{18}\text{F}$  remains the dominant radionuclide, with 710 presentations at the SNM meeting: 545 being FDG (fluorodeoxyglucose); 118 presentations involved C-11. Technetium was the topic in 301 papers, with  $^{131}\text{I}$ , the old reliable, being there for 95 papers.

Another major trend is the increase of imaging of animals with a dedicated animal device. One hundred studies were based on a dedicated PET imaging device; about 40 were based on a SPECT imaging system. There were 5 PET/CT papers for small animals, but 11 presentations involved SPECT/CT.

There has been a plateau over the last 10 yr in the use of SPECT, which in the past has raised the possibility that nuclear medicine in the future will be based primarily on PET tracers. Today we can see that single photon tracers are alive and well. New instruments include high-sensitivity, multipinhole SPECT with submillimeter resolution. It is possible to get virtually limitless resolution with single photon tracers, whereas with a PET tracer being a plus tracer, there is a finite range of the positrons in tissue before annihilation occurs and 511 keV photons are emitted.

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Dr. MoonHo Lee (1922-2004) was the pioneer in the fields of endocrinology and nuclear medicine in Korea. During his term as the president of the Korean Academy of Medical Sciences (1972-1994), he launched the *Journal of Korean Medical Science* (JKMS), an English-language journal, and also served as the first publisher of JKMS.

SPECT is now becoming added to tissue sampling and autoradiography by pharmaceutical companies and academic pharmaceutical laboratories. A new instrument consists of 4 banks of 9 pinholes; the spatial resolution is 1 mm. A left ventricular aneurysm was seen in the beating heart of a mouse. Some new devices have the ability to perform both PET/CT and SPECT/CT in the same hybrid system for small animals. The industry has now incorporated all 3 modalities into a single instrument.

Molecular imaging is developing a knowledge-based health care system. We no longer consider only the costs of space, labor, and capital investment. We now consider the economic value of the knowledge that our studies provide.

An example of the need for valuable knowledge is the fact that in the United States there are 95 million visits to emergency rooms each year. Eight million of those visits are by patients who complain of chest pain (8.4% of total visits). Sixty percent of those patients are admitted to a main hospital or in some institutions to a chest pain unit, but only 1.3% turn out to have acute myocardial infarction—the primary reason patients are admitted to the hospital. The savings of the costs of unnecessary hospitalization of these patients could be used for the care of other patients, to support research, and to justify further development of expensive technology.

In molecular imaging and therapy, we define disease by relating the patient's genome, body structures, histopathology, and cellular chemistry to his or her problems, present or future. We design therapeutic drugs by defining disease at the cellular and molecular level. We treat the disease by correcting abnormal cellular or molecular processes. We express disease manifestations in units of micromoles/minute/milliliter of disease tissue.

Molecules circulate around our body until they bump into recognition sites. If they fit in spaces in these recognition sites, they stick and then produce a biological effect. The recognition sites decrease the entropy or randomness of all the circulating molecules in our body—the recognition sites decrease molecular randomness. Molecular imaging, genetics, and pharmacology are being woven together to create a new, knowledge-based health care system.

In what I call the “the pragmatic paradigm of molecular

imaging”, we do not confine the patient to a diagnostic box, such as schizophrenia, depression, arthritis, etc. We make cellular and molecular dysfunction the basis of diagnosis and treatment. Pragmatism says, “Even if you don’t know the cause of the disease, as is often the case, if you provide the right treatment, the problem can be addressed.”

An example of the impact of molecular imaging on health care is the role of  $^{99m}\text{Tc}$ -ECD (ethylcysteinate dimer)-brain SPECT in the evaluation of patients with dementia and mild cognitive impairment (MCI). In a prospective clinical trial, magnetic resonance (MR) imaging showed only mild cortical atrophy in some patients. SPECT was able to localize the abnormalities to a specific area, whereas MR imaging revealed nonspecific generalized cortical atrophy in most of the cases.

In 1890, in his classic book *Principles of Psychology*, William James said, “We need to know a little better what are the molecular changes in the brain on which thought depends.” What William James imagined, we can now image. In 1945, total brain whole blood flow was measured by Kety and Schmidt at the University of Pennsylvania. In 1983, the first dopamine receptor imaging was carried out by PET. Since that time, in the 2006 SNM program there were 74 presentations on dopamine (4.64% of the total).

Localization of function in the brain was first described in 1861 by Broca and in 1874 by Wernicke. fMRI blood oxygen level dependent (BOLD) technology measures the patterns of regional brain blood flow and helps select regions of interest for a further study—this is the nuclear medicine viewpoint of the BOLD study. Psychologists and others like to see the different patterns that occur in different behavioral states, but this is all just related to the structure. PET/CT and SPECT/CT look at the chemistry lying beneath the terrain of the brain—the terrain in many cases being selected by the technology, either the PET/CT or SPECT/CT, by itself or by associated fMRI BOLD images.

For decades I have been promoting simple devices where the problem does not require high resolution in terms of location. We used a simple, two-detector system in a peer-reviewed study that resulted in approval of the drug nalmefine. We were able to show that nalmefine blocked opiate receptors with a half-time of 12 hr, whereas naloxone, the drug widely used in postoperative patients after narcotic anesthesia, blocked the receptors for only 2 hr. The dual detector study provided objective evidence that resulted in the FDA approval of the drug. Every psychiatrist needs a dual detector nuclear probe system to plan and monitor the effects of drug therapy.

Another receptor is the cerebral nicotinic acetylcholine receptor (nAChR) that was shown in studies of the periventricular white matter in patients with Alzheimer disease (AD) compared with in those with another variant of dementia, vascular dementia (VaD). And it was found that there is a deficit in different cortical regions in nAChRs in both AD and VaD, indicating that both have abnormalities in cholinergic neurotransmission.

The availability of these receptors in the periventricular white matter is reduced in VaD but is normal in AD. This helps differentiate among VaD, AD, and other forms of dementia.

Again, going back to functional mental activities, there is a study of acetylcholine-esterase imaging of brainstem nuclei in sleep disturbance associated with AD. The researchers found that sleep disturbances in AD are associated with a cholinergic impairment in brainstem nuclei.

A classmate of mine at Johns Hopkins was the late George Glenner, who was the person who studied the chemistry of amyloid. He reported the discovery in 1984 that the plaques that we see in AD, first described by Alzheimer himself, consist of amyloid. This has resulted in a tremendous body of research.

Our hypothesis is that beta amyloid imaging would allow earlier and more specific diagnosis of AD, allowing earlier intervention and specific therapy. What we need now are longitudinal studies on large populations beginning with people who are totally asymptomatic to define when the process of plaque formation begins in the development of dementia. The question arises whether molecular imaging will be used in screening.

What’s new in cardiology? Image fusion clearly is a major area of research. From 2003 to 2005, the number of presentations at the SNM meeting rose from 19 to 41. I was eagerly waiting to see what the number of SPECT/CT presentations would be this year—it turned out to be 65. This year I chose as the Images of the Year: a  $^{99m}\text{Tc}$ -tetrofosmin blood flow study fused with a 64-slice CT angiography (CTA) study. This study is an example of “software” fusion. Many patients with visible stenotic lesions in their coronary arteries were found to have no abnormalities of myocardial perfusion.

Keidar et al. assessed hemodynamically significant coronary artery lesions with an integrated SPECT/CT device, called a “hybrid” system, with fusion of the SPECT and CTA with the patient in the same gantry. CTCA alone, which is currently being widely used in screening patients for coronary artery disease (CAD), has a good negative predictive value. If you have a normal finding, there is a very high probability that you do not have CAD. But if you have abnormal findings on CTCA, there is only a 31% possibility that you have an associated reduction in regional myocardial blood flow.

Ask yourself, if you or a loved one had severe chest pain, and all of the following studies were available, which would you choose? 1) CTA; 2)  $^{82}\text{Rb}$  PET/CTA; 3)  $^{99m}\text{Tc}$ -sestamibi or  $^{201}\text{Tl}$  SPECT/CTA; 4)  $^{13}\text{N}$ - $\text{NH}_3$  PET/CTA; 5) troponin serum enzyme measurements; 6) exercise electrocardiogram (ECG); and 7) exercise SPECT. If you’ve all voted, the correct answers in my opinion are 2 or 3. And I am sure there will be many disagreements.

There has been a lot of discussion about the degree of con-

fidence needed to interpret the CT in the PET. I believe and have advocated the principle that has not yet been widely accepted but not widely resisted that every person in nuclear medicine should know as much about CT as a diagnostic radiologist. I believe that every radiologist should know as much about PET and SPECT as a nuclear medicine physician. That is, the fusion of the expertise in one person—whether the nuclear medicine physician or the radiologist.

You can tell with the PET the separation between the responders and the nonresponders, whereas it took 3 months before the changes in the MRI.

Double-tracer studies can be done, as in the study by Paulleit et al. with fluorethyltyrosine (FET) and  $^{18}\text{F}$ -FDG PET in patients with cerebral gliomas. In this study, 28 patients had the first scan with FET, then the second scan was performed 30 min afterward, and the FDG uptake was calculated by subtraction of the FET scan from the FET/FDG scan. In the FET PET and FDG PET studies, the FET has a far better contrast with the normal brain than did the FDG study.

We need to facilitate and expedite the approval of new pharmaceuticals and procedures. Perhaps we should incorporate diagnostic and efficacy-monitoring tracers in primarily therapeutic clinical trials in order to attract financial support from pharmaceutical companies and to facilitate regulatory approval and reimbursement. We are limited by the

fact that big pharmaceuticals like therapeutic drugs that are administered over long periods of time. They hesitate to invest in developing diagnostic tracers that will be used only once or twice in a given patient. So if you can combine the two, it may result in safer, more effective, and cheaper pharmaceuticals and radiopharmaceuticals.

In summary, while positron-emitting tracers continue to produce striking results and valuable new knowledge, SPECT/CT is advancing rapidly. Structure/function/biochemistry have fused. Dedicated animal scanners, first proposed in 1987, have been perfected and become widespread in industry and academia. Medicine has progressively increased its spatial resolution from whole body to organs to tissues, and to cells to molecules. What we imagined, we have now achieved.

*Henry N. Wagner, Jr. is Professor of Environmental Health Sciences at the Johns Hopkins Bloomberg School of Public Health. He is the author of "A Personal History of Nuclear Medicine."*

This paper was presented in the Opening Ceremony of the 9th Congress of the World Federation of Nuclear Medicine and Biology, which was held from October 22nd to 27th 2006 in Seoul, Korea.