2004 SNM Highlights Lecture

Creating Lifetime Images of Health and Disease

The Highlights Lecture is presented annually at the meeting of the SNM by Henry N. Wagner, Jr., MD. This year's lecture, the 27th in the series, was given June 23 at the closing session of the meeting in Philadelphia, PA.

Once again, the annual Society of Nuclear Medicine (SNM) meeting has been a spectacular success. You can see that this has been a period of steady growth in nuclear medicine, as illustrated by the number of presentations and posters at meetings from 1960 to the present (Fig. 1). Points that are worthwhile mentioning over this time span are the formation of the American Board of Nuclear Medicine in 1971 and the recognition that PET was moving into the clinic in 1991. It's interesting to pause for a moment to think about the fact that for decades the SNM was the major and, in fact, only important source of nuclear medicine meetings. Today there are additional societies and many meetings concerned with growing areas of nuclear medicine interest. I think this should be an inspiration for us to explore new horizons.

Dag Hammerskjöld, the first secretary-general of the United Nations, once said, "only he who keeps his eye on the far horizon will find the right road." Through the context of results reported in a number of presentations from this year's meeting, I am going to suggest new roads that the Society and its members might consider following.

Trends

Once again, half of the papers and posters at this meeting came from overseas (Table 1). Thirty-nine different nations were represented at this meeting. I would like to call for a round of applause in appreciation for those people from outside the United States whose participation for decades now has made this a very important meeting. We hope you will all come back.

Henry N. Wagner, Jr., MD

Over the past half century, we have seen the continued growth of PET imaging (Fig. 2). In the past 7 years, SPECT has been relatively flat. It is interesting that the point at which the curves for the 2 modalities diverge corresponds to the point at which PET was reimbursed for the first time in 1999 and PET/CT became a reality. ^{18}F-FDG still leads as the major radionuclide used in PET. Approximately 70%–80% of PET and PET/CT studies at this meeting involved ^{18}F-FDG (Fig. 3). Oncology still plays a major role and continues to have spectacular growth with ^{18}F-FDG (Fig. 4).

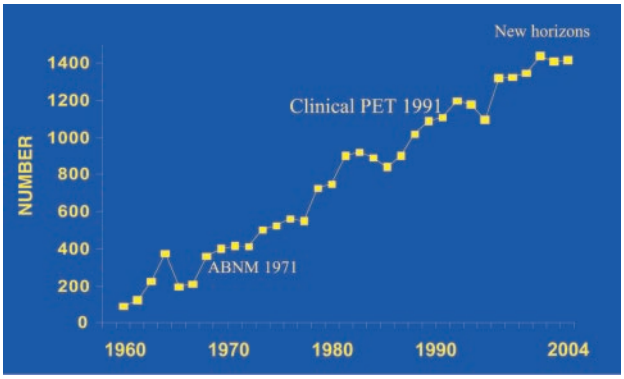

FIGURE 1. Total numbers of presentations at SNM annual meetings, 1960–2004.

TABLE 1
2004 SNM Abstracts

Country*	Number of presentations	Percentage of total
United States	732	51.6
Japan	153	10.8
Germany	148	10.4
Korea	109	7.7
France	64	4.5
China	33	2.3
United Kingdom	33	2.3
Netherlands	30	2.1
Italy	20	2.1
Canada	28	2.0
Belgium	26	1.8
Switzerland	26	1.8
Taiwan	26	1.8
Israel	20	1.4
Australia	17	1.2

*Other countries represented included India, Denmark, Spain, Austria, Hong Kong, Czech Republic, Uruguay, Brazil, Colombia, Greece, Islamic Republic of Iran, Kuwait, Hungary, Russia, Thailand, Argentina, Cuba, Finland, Norway, Armenia, Ireland, Saudi Arabia, and Bulgaria.

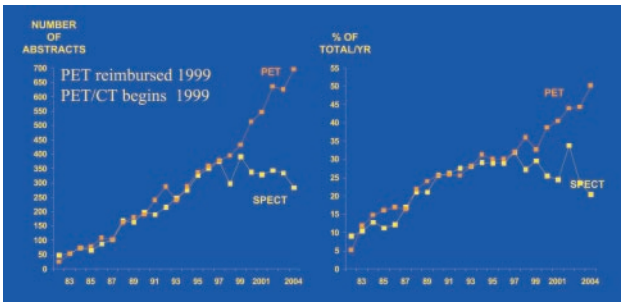

FIGURE 2. Left: Number of PET and SPECT presentations at SNM annual meetings, 1983–2004. Right: PET and SPECT presentations as percentages of total presentations at each meeting, 1983–2004.

Lifetime Images and Data Maintenance

Every year, I pick a theme that I believe illustrates a direction in which nuclear medicine is going. This year, I chose "Creating Lifetime Images of Health and Disease." In the future, everyone will have a periodically updated computer chip containing lifetime manifestations of his or her state of health. The individual's health information will be periodically entered into an international database of disease manifestations (and, by manifestations, I mean symptoms, physical signs, lab tests, imaging, etc.—all the aspects of health and disease). He or she will be alerted when abnormal manifestations are identified or predicted. The health chip will periodically search an international health manifestations database (IHMD) to answer the following questions: (1) Is anything wrong? (2) What is going to happen? (3) What can be done about it? And (4) Is the treatment helping?

Rather than simply giving a name to a person's disease, the health chip should reveal all aspects of that person's health and illness. The health manifestations on the computer chip will search the IHMD to characterize the disease, predict what is likely to happen, and suggest possible treatments.

A very good example of the way in which nuclear medicine may begin to prepare for this revolution in health care technology was presented at the meeting by Lin et al. from Chung-Yuan University and Taipei Veterans General Hospital (Taiwan), who looked at

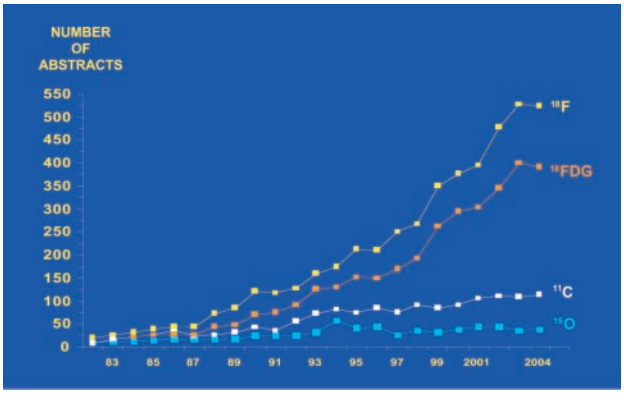

FIGURE 3. Numbers of presentations on 4 radionuclides at SNM annual meetings, 1983–2004.

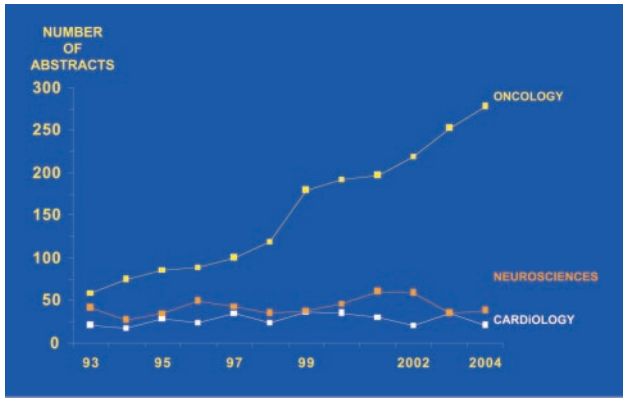

FIGURE 4. Subject areas in which presentations involving the use of ^{18}F-FDG have been made at SNM annual meetings, 1993–2004.

3-dimensional deformable image processing and integration. In the top row of Figure 5 are PET scans of the brain imaged with ^{18}F-FDG. Using statistical averaging, these images have been integrated to show, at the bottom, composite computer images of "normal" individuals.

Okada et al., in a joint effort by Hamamatsu Photonics (Japan), the University of Washington (Seattle), and the University of Michigan (Ann Arbor), studied an existing brain population-based cohort made up of 551 normal individuals and 31 patients with Alzheimer's disease (AD). They derived a composite, statistically analyzed distribution of ^{18}F-FDG in the brains of patients with AD (Fig. 6, middle row). The MRI images showing the volume of the brain are in the lower row. Because this image represents the direction in which the Society should (and I hope will) be going, I have selected it as the 2004 SNM image of the year. I should note that not only did this meeting have many excellent papers on research into AD, but it was during the meeting that the Centers for

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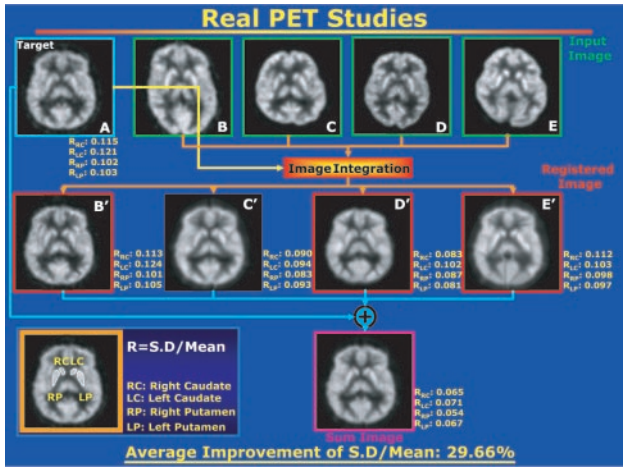

FIGURE 5. Three-dimensional deformable image processing and integration. In the top row are PET scans of the brain imaged with ^{18}F-FDG. Using statistical averaging, these images have been integrated to show, at the bottom, composite computer images of "normal" individuals.

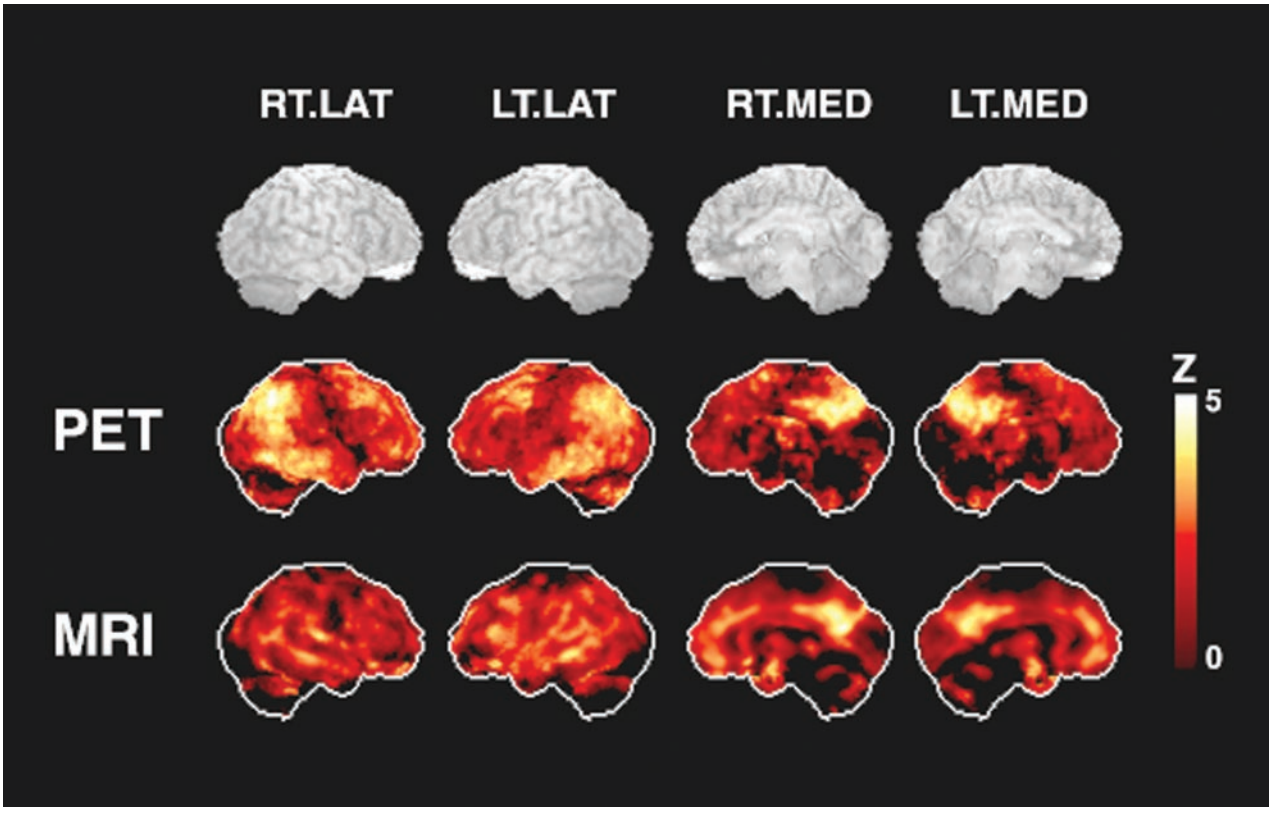

FIGURE 6. 2004 SNM Image of the Year. Distribution of ^{18}F-FDG in a large, existing brain population-based cohort was statistically analyzed to yield composite PET references images. In this series, composite results from 31 patients with Alzheimer's disease include brain anatomy in 3-dimensional stereotactic surface projections (top), PET images of brain function (middle), and MR images, showing regional gray matter loss (bottom).

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Medicare and Medicaid Services finally announced their decision to reimburse for expanded applications of PET in AD. At the same time, public attention was brought to AD by the death of President Reagan. It is, however, a coincidence that the image of the year, with its use of a large imaging database to provide useful reference images of standardized individuals, was also of AD.

Price et al. from the University of Pittsburgh (PA) presented studies carried out with a new product that binds to the β-amyloid plaques in patients with AD (Fig. 7). These images reveal the distribution of β-amyloid plaques, of importance in the pathogenesis of AD.

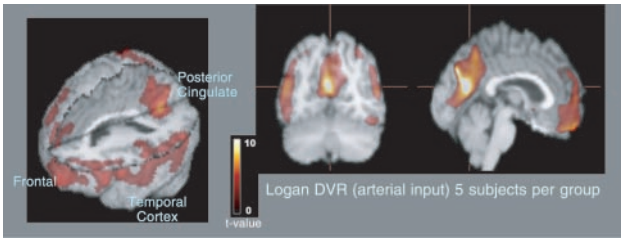

FIGURE 7. Pittsburgh compound-B (PIB), a new β-amyloid plaque imaging tracer, had significantly higher retention in the brains of patients with Alzheimer's disease than in the brains of control individuals. Future research with the compound will include voxel-based group comparisons in statistical parametric mapping.

To create the IHMD, we need to continue to create well-defined subsets of images of disease manifestations, such as the ones with AD. We need to then enter them into an Internet format. This process would be analogous to what many of you may be familiar with as the "open source" approach to computer programming, with resources that are available to all. Eventually, we will be able to compare the patient's anatomical, functional, and biochemical imaging studies with images in the IHMD through corregistration or precise overlay of the database image. Even today, if you have an ^{18}F-FDG PET scan of a patient, you can go online and compare it manually with, for example, the dataset of the 531 normal people from the image of the year study. This capability should be extended to all diseases.

Taking the Lead in New Directions

One might ask why the SNM should take the lead in creating the IHMD? Molecular imaging is the process of identifying, localizing, and quantifying normal and abnormal regional molecular processes and relating these processes to genotypes, histopathology, and the patient's clinical problems (that is, the phenotype). As such, molecular imaging will be a key component of the IHMD. So much information is generated by the tens of thousands of

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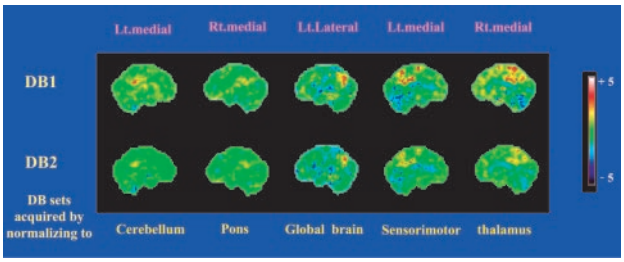

FIGURE 8. The selection process for normal individuals in an imaging study may affect the diagnostic performance of automatic imaging analysis. Patient selection for database 1 (DB1) excluded some individuals on the basis of risk factors, behaviors, family history, and direct examination. These factors were not applied in database 2 (DB2). The comparison between 2 Z maps derived from ^{18}F-FDG PET imaging of the 2 groups shows large areas of severe hypometabolism in the DB2 population.

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molecular processes going on in the body that we can no longer rely on what is in the physician's brain to interpret the image and integrate it with the rest of the information. Nuclear medicine will face the consequences of this challenge before any other area of clinical practice. So much information is available that we must turn to the Internet and the computerized approach to medical literature and databases to realize advances.

Is it beyond our wildest dreams to create such a database? The IHMD is achievable. Think, for a moment, about the fact that Google, a single Internet search engine, can scan 60 billion Web sites in 90 different languages for 138,000 people every minute. What we need to do is persuade Microsoft, Google, Yahoo, or another information technology company to collaborate with the SNM, seize this business opportunity, and provide financial support. This effort would be substantially different from the National Library of Medicine's PubMed, which includes primarily published articles. I am suggesting something that contains images and supporting data as well.

In creating such a database, we need to carefully select and define "normal" individuals. A presentation by Chen et al. from the Medical Pharmacological Research Foundation (Hakui, Japan), Kanazawa Graduate School of Medicine (Japan), and the University of Washington, showed that the selection process for normal individuals in an imaging study may affect the diagnostic performance of automatic imaging analysis. The group studied 2 populations, selected according to different criteria, who underwent ^{18}F-FDG PET imaging of the brain (Fig. 8). In the first group (DB1), patients were excluded on the basis of a range of vascular risk factors, smoking and drinking habits, family history of dementia, and results of neuropsychological examinations. In the second group (DB2), these exclusion factors were not applied. When the statistical maps derived from these 2 databases of "normal" individuals were compared, large areas of severe hypometabolism were noted in DB2.

Alleman et al. from the Oklahoma University Health Sciences Center (Oklahoma City) provided answers to the clinical question of whether accumulation of ^{18}F-FDG in a specific patient's thyroid is a normal variant or is abnormal. The group searched the literature for data on location and frequency of physiologic uptake of ^{18}F-FDG in head and neck imaging. They found, for example, that in normal individuals, the tracer accumulated in the base of the tongue in 63% of patients. They found that in 17% of normal individuals, ^{18}F-FDG accumulation was noted in the thyroid. Other accumulation sites identified were the parotid glands, the soft palate (Fig. 9), vocal chords, cricopharnygeus muscle, mylohyoid muscle, palate, submandibular gland, genioglossus/geniohyoid muscles, and other sites.

New Tracers and Techniques in Neuroimaging

We look forward to continued success in the imaging of β-amyloid plaques in AD. It is likely that the first use of these important advances will be in selecting patients and validating results of clinical trials of drugs. As noted previously, the group from the University of Pittsburgh discussed the in vivo quantification of amyloid binding in humans using the PIB compound. The study by Kepe et al. from the University of California at Los Angeles (UCLA) and the University of Ljubljana (Slovenia) focused on the accumulation of ^{18}F-FDDNP, another tracer that binds to amyloid plaques. Their results showed that global or overall accumulation of this tracer is greater in patients with AD than in patients with minimum cognitive impairment or in control groups (Fig. 10).

These new tracers will also be available to enhance research in drug development. The presentation by Toyama et al. from Fujita Health University (Aichi, Japan) and the National Institutes of Health (NIH; Bethesda, MD) used small animal PET to image β-amyloid with the tracer ^{11}C-6-OH-BTA-1 in a mouse model of AD. They found that the binding was minimal in mice that were 20 months old but was abnormal in mice that were 32 mos old.

The chemical connection between the brain and the mind was already a focus of attention more than a century ago. William James, in *Principles of Psychology* (1890),

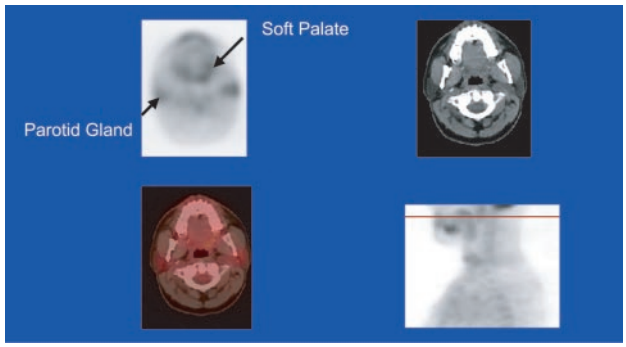

FIGURE 9. ^{18}F-FDG accumulation was noted in a number of sites in healthy individuals. Here normal accumulation is seen in the soft palate and parotid glands.

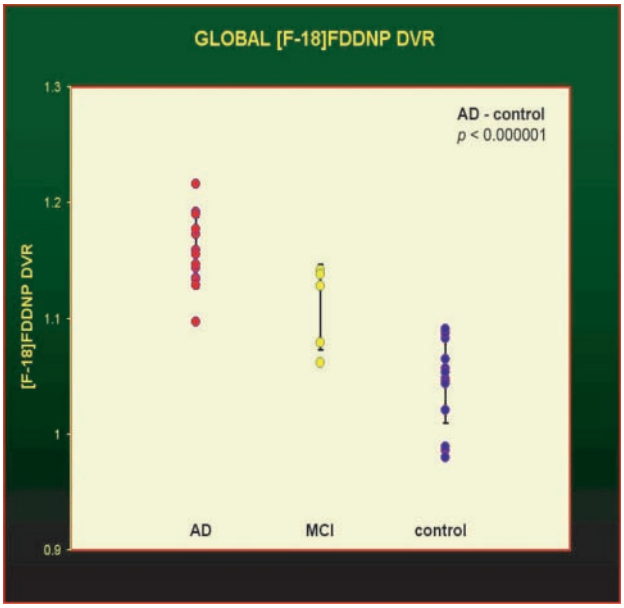

FIGURE 10. Global or overall accumulation of ^{18}F-FDDNP, which binds to amyloid plaques, is greater in patients with AD than in patients with minimum cognitive impairment or in control groups

wrote, "We need to know a little better what are the molecular changes in the brain on which thought depends." On February 8, 1979, I received a letter from Dr. Bob Heyssel, who was CEO of Johns Hopkins Hospital. Bob had been the head of nuclear medicine at Vanderbilt before coming to Hopkins. He wrote, "I happened to see the article in the [Baltimore] *Evening Sun* in which you are quoted extensively concerning expansion of your 'brain study program' for thought imaging. . . .We have enough problems as it is without our faculty and others helping to make us look like idiots or incompetents or worse." Four years after Bob's letter, on May 23, 1983, we reported in *Science* on the first PET imaging of a neuroreceptor (the dopamine receptor) in the living human brain. This illustrates my point that only one person in the world has the power to put you down—and you are that person.

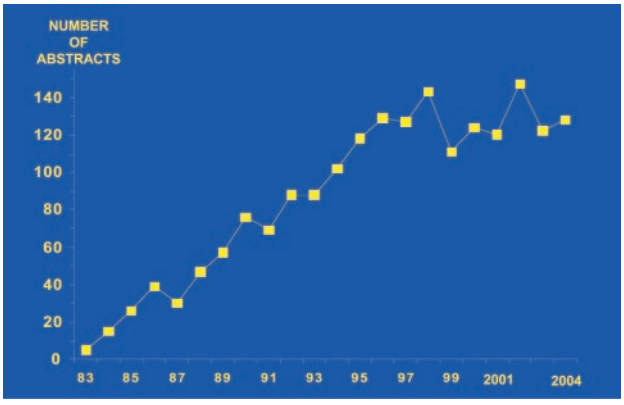

FIGURE 11. Number of presentations on neuroreceptors/transmission at the SNM annual meeting, 1983–2004.

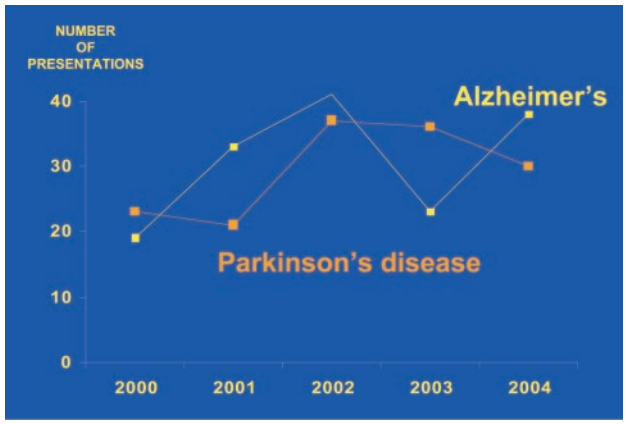

FIGURE 12. More than 200 presentations have been made on Parkinson's or Alzheimer's diseases at the SNM annual meeting over the last 5 years.

For a number of years now, more than 100 papers have been presented on neuroreceptors at each SNM meeting (Fig. 11). For example, more than 200 papers on aspects of Parkinson's disease (PD) and senile dementia/AD have been presented in the last 5 years (Fig. 12).

I referred earlier to manifestations of disease. Multiple tracers yield multiple manifestations. Park et al., from Seoul National University College of Medicine (Korea), showed that the relation of the presynaptic dopamine transporter and the D2 dopamine receptor in the postsynaptic neurons was a way to differentiate PD from dementia related to Lewy bodies. In Figure 13, the lower row shows that the ratio of ^{11}C-raclopride, which binds to the dopamine receptor, and ^{11}C-carbomethoxyfluorophenyl tropane (^{11}C-CFT), which binds to the dopamine transporter, varies significantly among normal individuals, those with PD, and those with dementia related to Lewy bodies. Here again, we see a biochemical differentiation that is very difficult to make with routine clinical methods.

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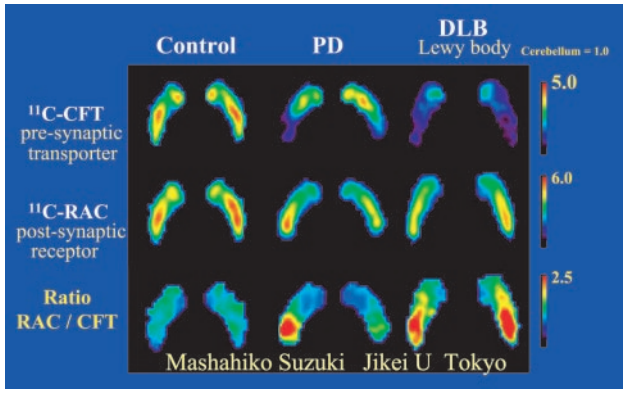

FIGURE 13. Multiple tracers yield multiple manifestations. The lower row shows that the ratio of ^{11}C-raclopride, which binds to the dopamine receptor, and ^{11}C-CFT, which binds to the dopamine transporter, varies significantly between normal individuals, those with Parkinson's disease (PD), and those with dementia related to Lewy bodies (DLB).

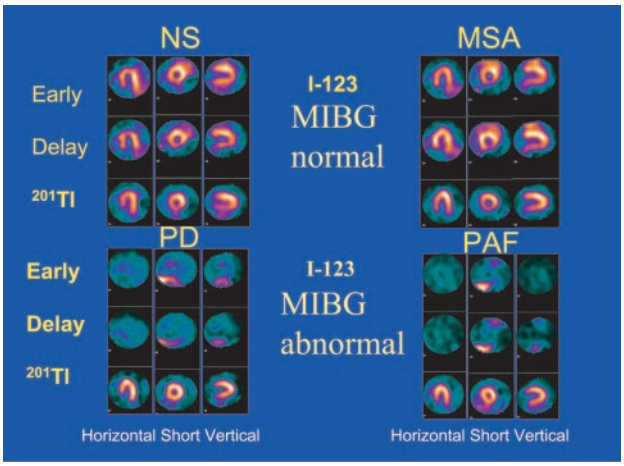

FIGURE 14. ^{123}I-MIBG imaging of the autonomic nerves of the heart differentiated among normal subjects (NS), Parkinson's disease (PD), multiple system atrophy (MSA), and pure autonomic failure (PAF).

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New Definitions of Disease and Revised Perspectives

We are moving from traditional definitions of disease to definitions based on regional, molecular processes. Zhang et al. from the Mount Sinai School of Medicine (New York, NY) were able to differentiate PD from multiple system atrophy (MSA) and pure autonomic failure. They used ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) to look at the autonomic nerves of the heart in these 3 clinical syndromes. In the upper left of Figure 14, where NS represents normal subjects, thallium images showed that the myocardial blood flow was normal and that there was no abnormality in the sympathetic innervation of the heart. No involvement of the heart was seen in MSA. In PD and pure autonomic failure, the accumulation of ^{123}I-MIBG was abnormal, revealing the involvement of the autonomic nervous system in both these groups.

Okulski et al. from the North Shore Long Island Jewish Research Institute (NY) mapped decreased striatal D2 receptor binding in individuals who carried the DYT1 gene, which characterizes dystonia, before they became

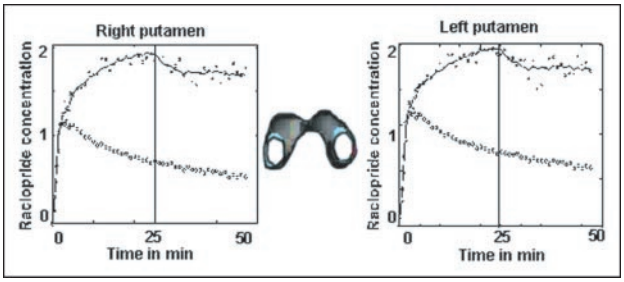

FIGURE 15. Molecular imaging with ^{11}C-raclopride was able to detect endogenously released neurotransmitters and localize sites of release during performance of an anticipatory cognitive task (thinking about where dots would appear on a screen).

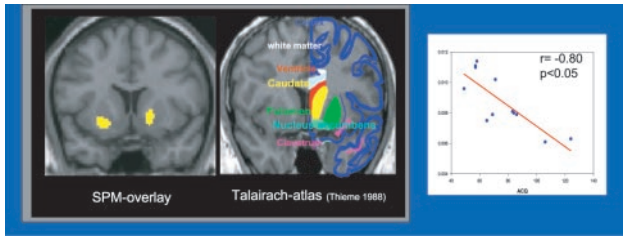

FIGURE 16. A negative correlation was seen between alcohol craving (ACQ) and dopamine decarboxylase activity (reflected in increased FDOPA uptake).

symptomatic. These researchers showed for the first time that striatal D2 receptor availability is reduced in nonmanifesting DYT1 carriers. Their results imply that there may be a threshold of D2 receptor loss related to the development of overt dystonia symptoms.

Another group showed we do, indeed, think before we act. Badgaiyan et al. from the Massachusetts General Hospital (MGH) and Harvard Medical School (Boston) showed that dopamine is released during an implicit memory task (Fig. 15). Molecular imaging with ^{11}C-raclopride, which binds to D2 dopamine receptors, was able to detect endogenously released neurotransmitters and localize sites of release when normal subjects thought about an activity that was about to occur (i.e., thinking about where 1 of 3 targets would appear on a screen). After anticipating where the target would appear, subjects responded much more rapidly and, in association with that rapid "intellectual" response, there was a release of dopamine in the putamen.

Many attendees at the SNM meeting heard the excellent plenary address by Nora Volkow, MD, head of NIH's National Institute on Drug Abuse. She discussed the great strides nuclear medicine has taken in identifying biochemical mechanisms associated with addictions of many types. Heinz et al. from the Charité University Medicine (Berlin, Germany) and the University of Mainz (Germany) showed that low 6-fluoro-L-dopa (FDOPA) uptake, which is a reflection of dopamine synthesis in the striatum of alcoholics, can be correlated with craving for alcohol. The graph on the lower right of Figure 16 shows that as craving increased there was a decrease in dopamine decarboxylase activity, which indicates a decrease in dopamine synthesis. These researchers also showed a correlation between alcohol craving and the availability of the D2 receptor (Fig. 17). High craving was associated

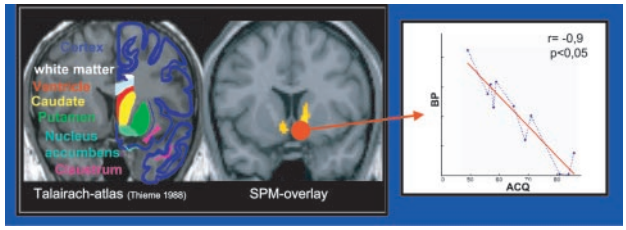

FIGURE 17. A high correlation was shown between alcohol craving and D2 receptor availability.

with low striatal dopamine decarboxylase activity, reflecting decreased dopamine synthesis and subsequent increased alcohol intake.

Clearly, nuclear medicine has had a major impact on drug design and development. Madras et al., from MGH and Harvard, showed that measurement of dopamine transporter occupancy was a good marker for drugs developed to treat patients with cocaine addiction. They pointed out that although drugs are available to treat heroin, tobacco, and alcohol addictions, no successful drug treatments are available for cocaine addiction. Cocaine agonists mimic the effects of cocaine and have side effects. The group's work with PET imaging of the dopamine transporter in monkeys predicts that new antagonists occupy a significant portion of the dopamine transporter, which offers considerable promise for effective drug development.

The fact that neuronal activity is associated with increased accumulation of ^{18}F-FDG underlies a number of current research efforts. Ogawa et al. from Hamamatsu University School of Medicine and the National Cardiovascular Center (Osaka, Japan) looked more closely at what the brain uses as its major substrate in regions that become activated. They carried out autoradiographic studies in tissue culture specimens using ^{18}F-FDG and various enzyme inhibitors (Fig. 18). They found that when a neuron becomes activated—in this case by adding a postassium chloride solution—an excess amount of lactate is produced, which becomes a principle source of energy. This suggests a topic that is being widely looked at today: that glial cells may be more important in mental activity than had previously been believed. These researchers showed that increased focal ^{18}F-FDG accumulation may reflect glial cell rather than neuronal activity. The link between the glial cell and neuronal activity is being studied further.

What is the energy substrate for different types of cancer? Liu et al. from the Taipei Veterans General Hospital and the National Yang-Ming University Medical School (Taipei, Taiwan) reported on ^{11}C-acetate PET in patients with meningioma. Figure 19 shows that the contrast was greater with ^{11}C-acetate than with ^{18}F-FDG PET. This is consistent with the fact that aerobic metabolism reflects tumors that are benign and anaerobic metabolism is a progressive development in tumors as they become more malignant. Meningiomas, both primary and recurrent, are benign; most prostate tumors are also benign. These are characterized by low uptake of ^{18}F-FDG and greater uptake of tracers associated with aerobic metabolism.

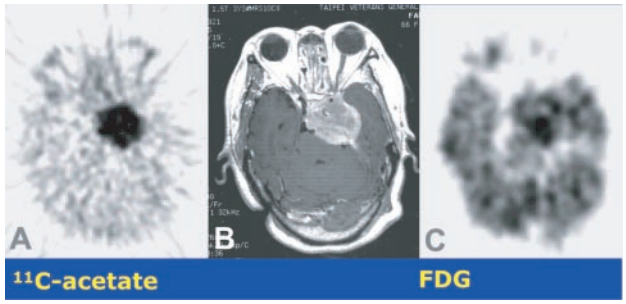

FIGURE 19. ^{11}C-acetate and ^{18}F-FDG PET imaging in a patient with a meningioma.

Although PET papers continued to dominate oncology, more studies are suggesting that interpretation processes and procedures require increasing levels of sophistication. Nishiyama et al. from the Kagawa University (Japan) showed that patients with cancer in the head or neck may have coexisting cancers—not metastatic cancer—elsewhere in the body. Figure 20 (left) shows a patient whose secondary primary was gastric cancer. On the right is a patient with a mesopharyngeal cancer whose secondary primary was in the rectum. It indicates that the entire body should be considered when caring for patients with thyroid cancer.

What is the significance of focal ^{18}F-FDG uptake in the abdomen? Nishizawa et al. from Hamamatsu, as part of the larger study that generated the image of the year,

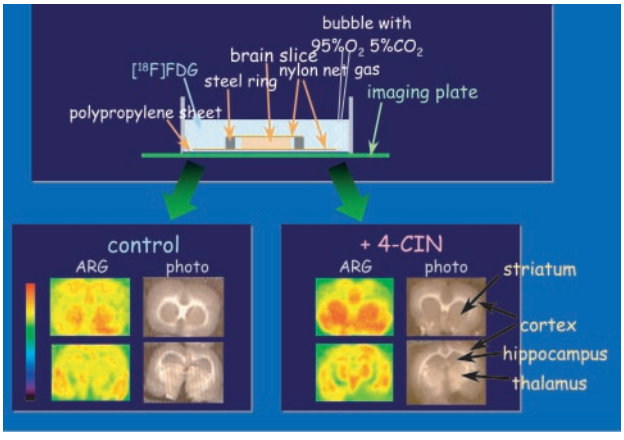

FIGURE 18. Dynamic positron autoradiography in tissue culture specimens using ^{18}F-FDG and various enzyme inhibitors suggested that increased focal ^{18}F-FDG accumulation may reflect glial cell rather than neuronal activity.

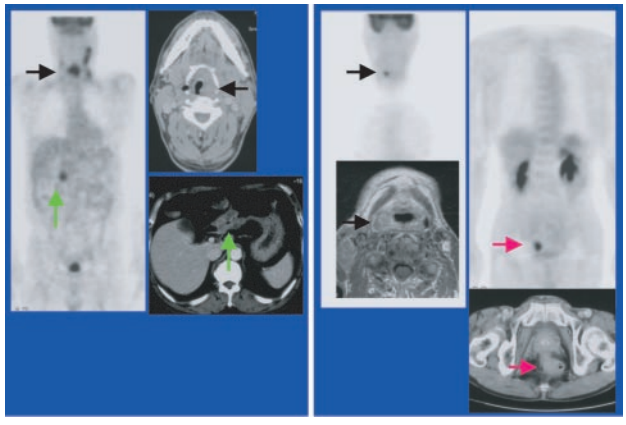

FIGURE 20. Left: A patient with glottic cancer who was found to have a secondary primary gastric cancer. Right: A patient with mesopharyngeal cancer who was found to have a secondary primary rectal cancer.

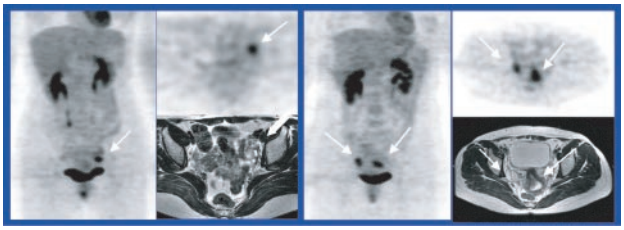

FIGURE 21. Left: Focal ^{18}F-FDG uptake was shown in the normal left ovary of a 37-year-old woman in ovulation phase. Right: Foci of intense ^{18}F-FDG uptake were observed in the normal ovary and uterine endometrium of a 42-year-old woman in the early luteal phase.

found that ^{18}F-FDG uptake in the normal ovary and uterus changes along with the menstrual cycle. The study of 78 pre- and 55 postmenopausal women showed that most premenopausal women had ovarian and endometrial ^{18}F-FDG uptake in the late follicular to early luteal phases of the menstrual cycle, whereas no physiologic uptake was noted in postmenopausal women. Figure 21 (left) shows a 37-year-old woman with uptake in the left normal ovary, as indicated by the white arrow. At the right is a 42-year-old woman who had 2 intense areas of uptake corresponding to the normal ovary and uterine endometrium. Figure 22 shows the correlation of uptake with the phases of the menstrual cycle. The authors recommend knowing the menstrual phase when interpreting pelvic ^{18}F-FDG PET images of women of reproductive age and performing such studies within a few days after or a week before menstruation to avoid misinterpretation. This is another example of important work derived from studying large numbers of asymptomatic people.

What is the significance of ^{18}F-FDG accumulation in the gastrointestinal (GI) tract in PET/CT imaging? This again is an area in which experience is needed in interpreting studies. Kamel et al. from University Hospital (Zurich, Switzerland) used PET/CT to image 69 patients in whom endoscopy was performed. They found unexpected ^{18}F-FDG accumulation in the GI tract in 3% of these studies.

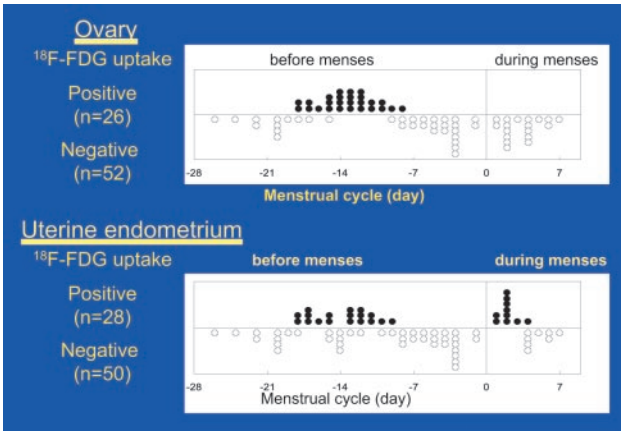

FIGURE 22. ^{18}F-FDG uptake in the normal ovary and uterus in relation to the menstrual cycle.

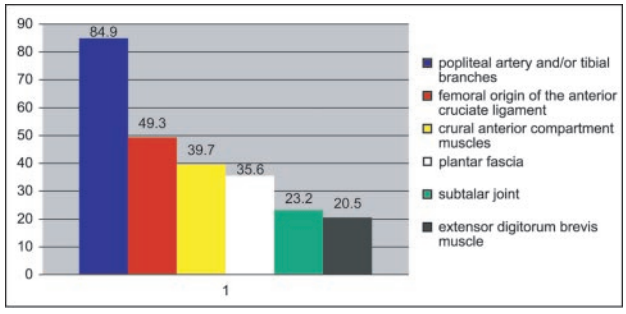

FIGURE 23. Prevalence and patterns of physiologic lower extremity uptake in true whole-body imaging of 70 patients. Percentages indicate most frequent patterns.

What do we mean by "whole-body" ^{18}F-FDG PET imaging? The study by Osman et al. from St. Louis University (MO) used true whole-body PET imaging to look at the prevalence and patterns of physiologic uptake in the lower extremities in 70 patients. What many of us currently consider whole-body imaging moves only from the chin to the thigh. True whole-body imaging, as this and other groups point out, should scan from the top of the head to the soles of the feet. Osman et al. found uptake in the lower extremities in the percentages shown in Figure 23, with examples shown in Figure 24. They also looked at bone metastases from non-small cell lung cancer (NSCLC) using true whole-body imaging. In a group of 84 patients with NSCLC, 16 (19%) had confirmed bone metastases. Of these, 16.6% had metastases in the lower extremities, 4.6% in the skull, and 4% in the upper extremities—sites often not included in routine whole-body PET imaging. A total of 25% of bone metastases in these patients were outside the typical whole-body field of view. Another finding from this study was that more bone metastases were seen by total whole-body PET than by technetium-labeled bone scan.

New Instrumentation and Techniques

New manifestations will continue to be found as new instruments are developed. For example, Yamamoto et al. from Kobe City College of Technology, Kyoto University

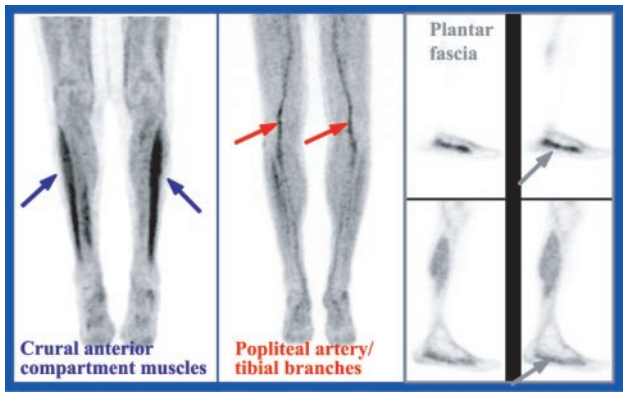

FIGURE 24. Examples of uptake in extremities in true whole-body imaging.

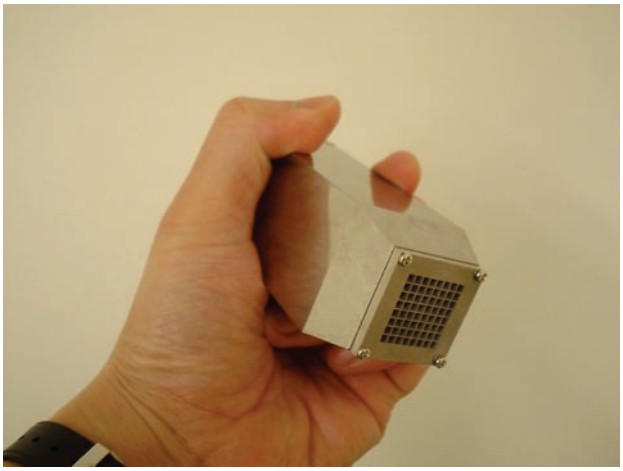

FIGURE 25. Hand-held positron imaging detector with background rejection capability for high-resolution, real-time imaging.

Hospital, and Kobe Institute of Biomedical Research and Innovation (Japan) presented what they called a "handy positron imaging detector with background rejection capability" with a 2-mm spatial resolution (Fig. 25). Members of the same research group also presented a new gadolinium orthosilicate (GSO) tweezer-type coincidence detector for use in intraoperative tumor location and identification. As seen in Figure 26, only the positrons between the GSOs can be detected. The apparatus needs no collimator and has high sensitivity and low background counts. Instrumentation like this is becoming more common and will be used increasingly in the operating room. Over the last 5 SNM meetings, more than 100 presentations have focused on intraoperative applications.

New scanners continue to be developed, and I'm sure

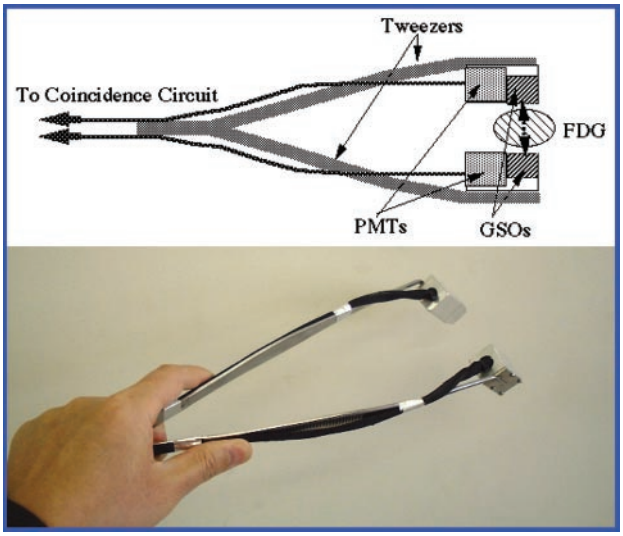

FIGURE 26. Only positrons between the 2 gadolinium orthosilicate (GSO) crystals can be detected in this tweezer-type coincidence detector for use in intraoperative tumor location and identification.

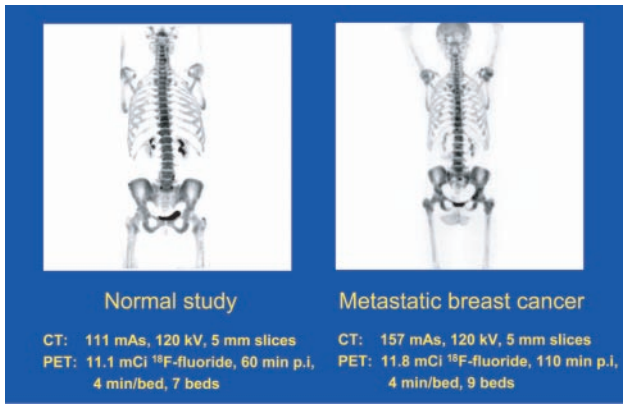

FIGURE 27. A high-resolution, 16-slice lutetium orthosilicate (LSO) PET/CT scanner produced these ^{18}F-fluoride bone scans in a healthy individual and in a patient with metastatic breast cancer.

you were impressed with the many demonstrations in the exhibit hall during this meeting. Townsend et al. from the University of Tennesee (Knoxville), CPS Innovations (Knoxville), and CTI Molecular Imaging (Knoxville) presented the results of research on the performace of a high-resolution, 16-slice lutetium orthosilicate (LSO) PET/CT scanner and showed high-quality ^{18}F-fluoride bone scans in a healthy individual and in a patient with metastatic breast cancer (Fig. 27).

It is clear that considerable improvement can be made with careful attention to the respiratory cycle when imaging with PET/CT. Townsend et al. from Knoxville, along with colleagues from Siemens Medical Solutions (Forchheim, Germany), reported on respiratory gating with the same 16-slice LSO PET/CT scanner (Fig. 28). The separation of the heart from the liver can be delineated to indicate partial respiration. The associated CT can be used to pick out particular areas of ^{18}F-FDG accumulation to eliminate problems associated with the effects of patient respiration.

Erdi et al. from the Memorial Sloan–Kettering Cancer

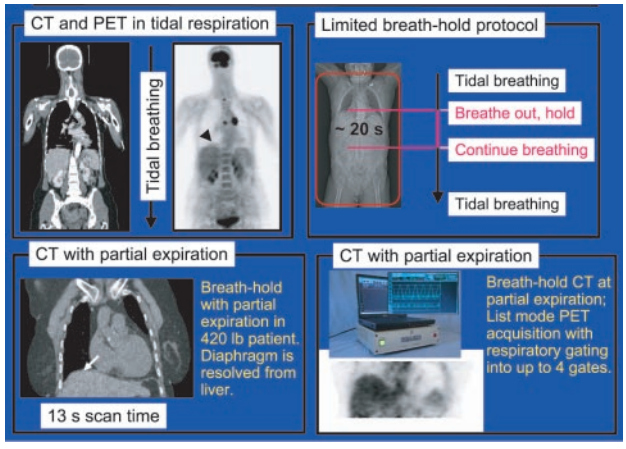

FIGURE 28. Respiratory gating with a 16-slice LSO PET/CT scanner. The separation of the heart from the liver can be delineated to indicate partial respiration (lower left).

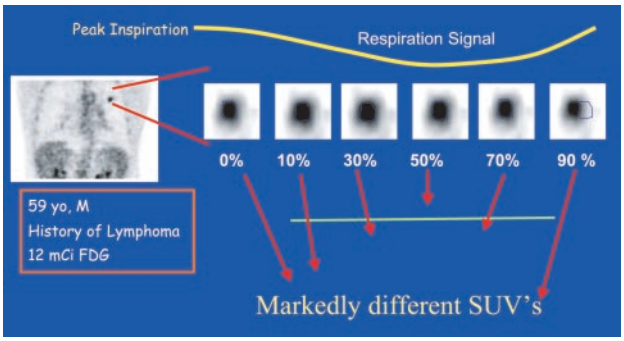

FIGURE 29. Measured standard uptake values (SUVs) with PET change considerably with the phase of the respiratory cycle.

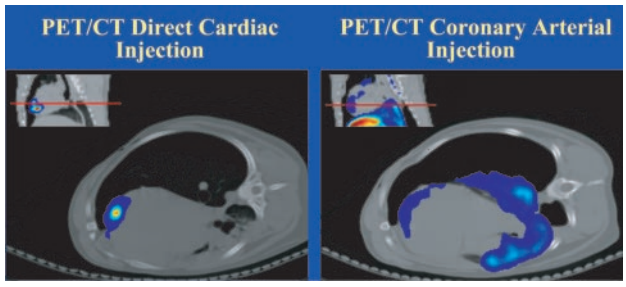

FIGURE 31. PET/CT and MRI were used to track stem cell distribution in mycocardial stem cell therapy, showing that distribution patterns differed with site of injection.

Center (New York, NY) and General Electric and Varian Medical Systems showed that measured standard uptake values (SUVs) with PET could change considerably with the phase of the respiratory cycle (Fig. 29). They measured SUVs for ^{18}F-FDG across the respiratory cycle and used CT images to pick out regions of interest. These showed markedly different SUVs, depending on the respiratory phase. The implications are clear for the performance of serial studies in the same patient, particularly when assessing the results of treatment. Care must be taken to ensure that breathing artifacts do not increase the statistical noise to the point that an effect is not measurable when it might have been had more attention been paid to the respiratory cycle. This challenge is being addressed by many institutions and industry efforts.

Nuclear Medicine and Genetics

For a number of years I've shown this triangle (Fig. 30), which depicts in vivo chemistry and physiology connecting genetics, pharmacology, and molecular nuclear medicine. A focus of many papers at this meeting was the use of nuclear medicine techniques in the assessment of gene therapy. One of the areas that seems to be advancing most rapidly in gene therapy is the use of myocardial stem cells in the treatment

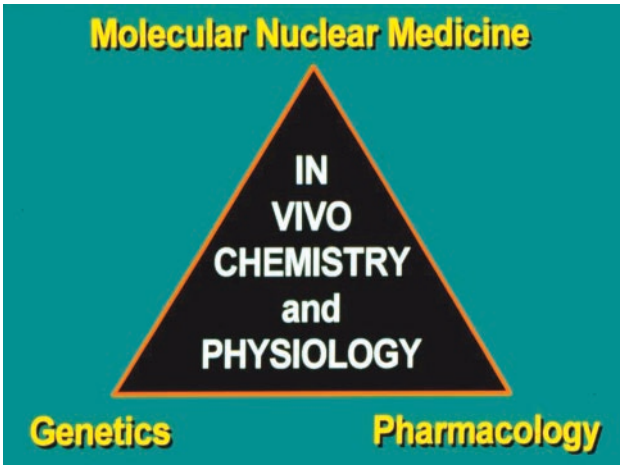

FIGURE 30. Molecular nuclear medicine continues to be tied to new developments in genetics and pharmacology through the basic sciences of in vivo chemistry and physiology.

of coronary artery disease (CAD). This is already being used widely in Europe, although it has yet to make great inroads in the United States. Kong et al. from the University of Western Ontario (London) reported on the use of PET/CT and MRI to track and evaluate myocardial stem cell therapy. They reported evidence of a clear difference of distribution of stem cells depending on whether the injection was directly into the heart muscle or into the coronary arteries (Fig. 31). Lang et al. from Charles University (Prague, Czech Republic) and the William Beaumont Hospitals (Royal Oak, MI), used ^{99m}Tc-hexamethylpropyleneamine oxime to evaluate early distribution of human adult bone marrow stem cells after intracoronary implantation in patients who had experienced myocardial infarction. The researchers showed that the stem cells were effective and stable in time and that commercially available kits could be used successfully for the labeling. They suggested that only early biodistribution can be investigated with this method.

More Oncology Innovations and Tracers

Data from 2002 indicate that many nuclear medicine procedures are experiencing rapid gains: cardiovascular procedures are growing at a rate of 12% annually, with non-hospital procedures growing at a rate 2.5 times faster than in-hospital procedures. More than 15.8 million nuclear medicine procedures were performed in the United States in 2002, again, growing at a rate of 8% annually. Oncology continues to be a primary focus of promising studies and breakthrough techniques reported at the SNM meeting (Fig. 32). Almost 40% of papers presented were concerned with cancer diagnosis, treatment, prognosis, or follow-up. This year 279 of the presentations focused on ^{18}F-FDG in oncology (Fig. 33). Nuclear oncology still has tremendous growth potential. I believe, along with many of my colleagues, that nuclear oncology will one day be equal to nuclear cardiology in terms of numbers of procedures and numbers of patients who are benefiting from these technologies.

PET/CT continues to advance. Bar-Sever et al. from Rambam Medical Center and Schneider Children's Medical Center (Israel) reported on a study indicating the incremental value of PET/CT over PET alone in the diagnosis of pediatric malignancies. PET/CT improved the diagnostic accuracy of stand-alone PET in 60% of

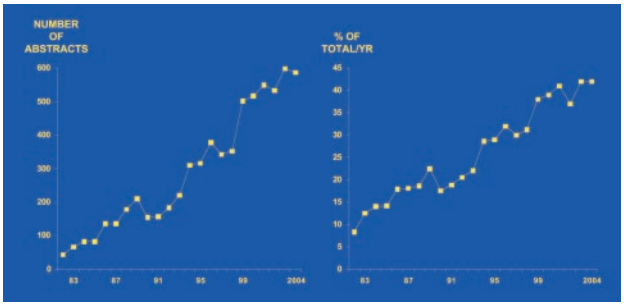

FIGURE 32. Left: Number of presentations on oncology at the SNM annual meeting, 1983–2004. Right: Percentage of total presentations focusing on oncology at the SNM annual meeting, 1983–2004.

pediatric oncology studies. It is clear from presentations at the meeting that we are moving more and more into the PET/CT and SPECT/CT domain.

Not only is the number of ^{18}F-FDG PET studies growing, but populations of interest seem to be expanding. Uno et al. from the Nishidai Clinic Diagnostic Imaging Center (Tokyo, Japan) reported on the use of PET in screening patients for colorectal cancer. They found that ^{18}F-FDG PET has a high sensitivity and specificity for early detection of colorectal cancer and provides useful information about asymptomatic patients with normal fecal occult blood tests. It is conventional to perform repeated fecal occult blood tests in patients who are at risk for colon cancer. The study by Uno et al. showed that ^{18}F-FDG PET provides higher sensitivity and specificity for detecting cancer at earlier stages.

Current good manufacturing processes for the production of ^{18}F-FDG demand that no more than 5% fluoride be present. I and others believe that ^{18}F should be included all the time or often in patients who have FDG studies, because it gives very important information, not only about localization but about bone metastases as well.

Kuang et al. from the University of Texas M.D. Anderson Cancer Center (Houston) presented results that indicated that ^{18}F-FDG PET was better than ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) bone scan for detecting bone metastases in patients with breast cancer. PET showed a sensitivity of 91.7%, specificity of 95.8%, and accuracy of 96.4%.

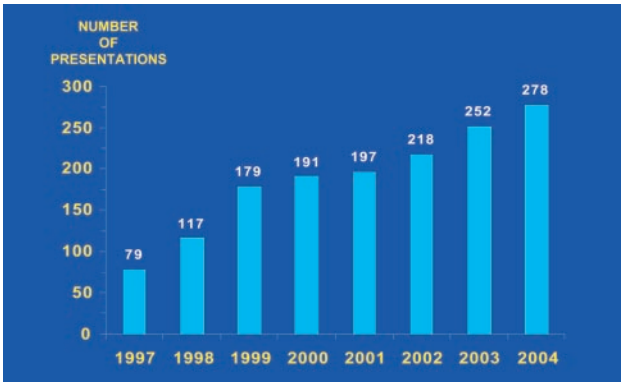

FIGURE 33. Numbers of oncology-focused presentations using ^{18}F-FDG at the SNM annual meeting, 1997–2004.

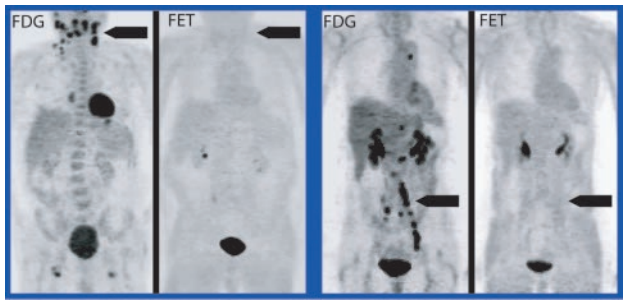

FIGURE 34. Comparison of ^{18}F-FDG and ^{18}F-FET imaging in patients with (left) non-Hodgkin's lymphoma and (right) ovarian cancer.

Corresponding figures for the technetium bone scan were 75.0%, 66.7%, and 69.4%, respectively.

Although ^{18}F-FDG retains its primary position, other tracers show great promise. Pauleit et al. from the Research Center of Jeulich (Germany) reported on a comparison of ^{18}F-FDG and ^{18}F-fluoroethyl tyrosine (^{18}F-FET) in 45 consecutive patients with suspected malignant tumors. Figure 34 (left) shows a patient with high-grade lymphoma in whom many lesions identified with ^{18}F-FDG were not seen with ^{18}F-FET. On the right are results in a patient with ovarian cancer. These researchers concluded that ^{18}F-FET is inferior to ^{18}F-FDG for general tumor diagnostics. However, these initial results also showed ^{18}F-FET uptake in all small cell cancers, and the tracer may facilitate more accurate differentiation between inflammation and tumor than does ^{18}F-FDG.

^{11}C-choline is a promising tracer, and a number of researchers are looking at whether its accumulation relates to degree of malignancy, that is, to the degree of cellular undifferentiation in the same way as ^{18}F-FDG. Yamaguchu et al. from the Yokohama University City School of Medicine (Japan) compared ^{11}C-choline PET with proton MR spectroscopy in patients with prostate cancer (Fig. 35). They found linear relationships between maximum SUVs on ^{11}C-choline PET and serum prostate specific antigen, and thus showed a clear relationship

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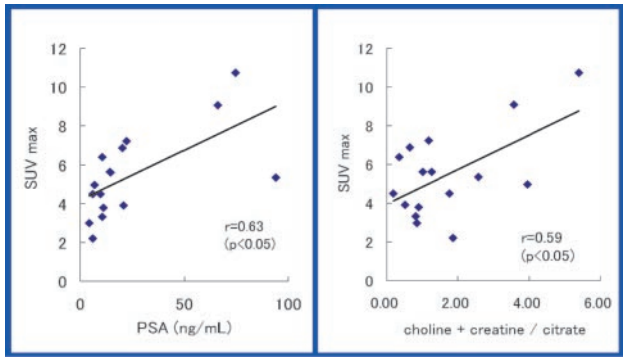

FIGURE 35. Linear relationships between maximum SUVs on ^{11}C-choline PET and serum prostate specific antigen showed a clear relationship between the degree of malignancy and the accumulation of choline.

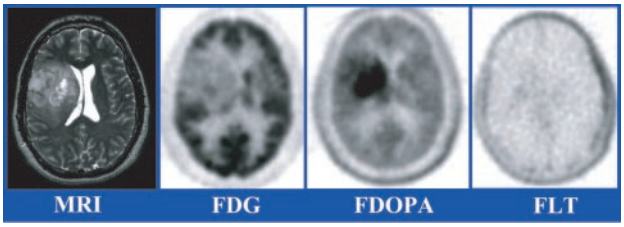

FIGURE 36. FDOPA is highly effective in visualizing low-grade brain tumor.

(Continued from page 32N)

between the degree of malignancy and the accumulation of choline.

It is interesting to see how the development of a nuclear medicine tracer for one purpose may find another use. Will FDOPA be helpful in oncology as well as in movement disorders? Chen et al. from UCLA looked at imaging gliomas with FDOPA and ^{18}F-fluorothymidine (^{18}F-FLT) PET and compared the results with those of ^{18}F-FDG PET. Figure 36 shows the high degree of accumulation of FDOPA in low-grade brain tumor. Figure 37 shows tracers in PET imaging of a patient who, 5.5 years after a resected grade II oligodendroglioma, re-presented with seizures. The FDOPA identified the focal abnormality better than the ^{18}F-FLT and ^{18}F-FDG. Thus, another tracer can be added to the armamentarium that can differentiate among different types of brain tumors. The authors concluded that FDOPA is sensitive and specific in patients with a history of gliomas and that the tracer is especially useful clinically to identify recurrent low-grade tumor. These tumors also showed an uptake pattern that differed from that of FDOPA in the striatum. FDOPA may define tumor borders better than T1 MRI in newly diagnosed tumors and may be better than MRI in distinguishing recurrent tumor from post-therapy changes.

Will ^{18}F-FLT become a widely used tracer? Its uptake correlates more directly with cell proliferation than does ^{18}F-FDG and may be better able to demonstrate the early effectiveness of response to chemotherapy. Pio et al. from UCLA reported on a patient being treated for breast cancer metastatic to the liver (Fig. 38). The accumulation of ^{18}F-FDG went up very early, whereas the accumulation of ^{18}F-FLT went down, both before any anatomical changes were detectable by CT. The authors concluded that a very early, 10-minute ^{18}F-FLT PET scan acquired 2 weeks after a first course of chemotherapy is useful for

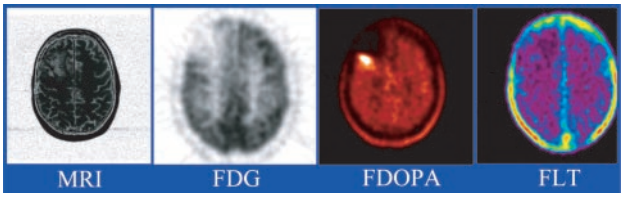

FIGURE 37. FDOPA PET provided effective imaging in a patient presenting with seizures 5.5 years after resection of a grade II oligodendroglioma.

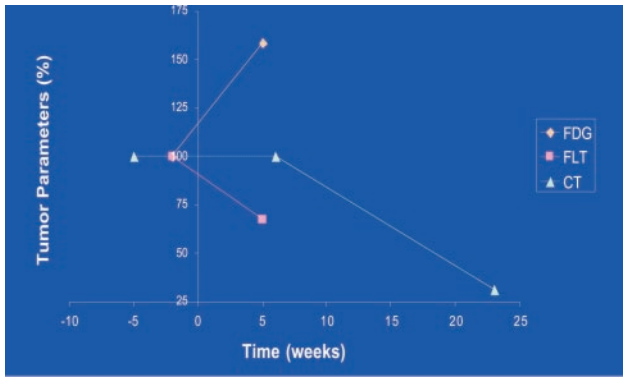

FIGURE 38. ^{18}F-FLT may be better able than ^{18}F-FDG to predict effectiveness of response to chemotherapy. Uptake of the 2 tracers is charted here for a 62-year-old woman with metastatic breast cancer (0 week = first week of treatment). The accumulation of ^{18}F-FDG went up very early, whereas the accumulation of ^{18}F-FLT went down, both before any anatomical changes were detectable by CT.

predicting longer-term efficacy of chemotherapy regimens in women with breast cancer. This may be an example of what is sometimes called a "flare" effect, where the ^{18}F-FDG uptake goes up as a result of changes such as inflammation, with the usual interpretation being that the patient's tumor is not responding. These results show that in this particular patient, and perhaps in large numbers of patients, ^{18}F-FLT may be a better indicator that cell division is being reduced, despite the fact that the signal is clearly 10 times stronger with ^{18}F-FDG than with ^{18}F-FLT.

A Proposal for Accelerating the Availability of New Tracers

What can we do to get these valuable tracers approved by regulatory and insurance bodies? The problem is the enormous cost of drug development and approval, particularly for diagnostic agents, which are used only once or twice in a given person. The potential market is often too small for drug companies to be willing to justify the great expense of developing and obtaining regulatory approval for radiopharmaceuticals. I learned, for example, that the process of getting Food and Drug Administration (FDA) approval for FDOPA has proven to be extremely expensive and that probably no more than 1,000 patients have been imaged with this tracer.

Radioactive drug research committees (RDRCs) could become an increasingly important approach to securing approval for new tracers. Suleiman et al. from the FDA (Rockville, MD) reported on human research without an FDA Investigational New Drug (IND) application, through the RDRC mechanism. RDRCs were established in 1975 and formally codified in Title 21 of the Code of Federal Regulations Part 361.1 This mechanism allows human research with radioactive drugs when (1) an RDRC approves, (2) there is no clinically detectable pharmacologic effect, and (3) radiation dose limits are

RDRC Radionuclides		
Imaging nuclides		Non-imaging nuclides
positron	gamma	beta
C-11 (32%)	Tc-99m (2%)	H-3 (15%)
O-15 (20%)	I-123 (1%)	C-14 (6%)
F-18 (18%)		
N-13 (2%)		
Other nuclides (4%): Cu-60, Fe-59, Ca-41, F-17, Fe-55, I-125, I-131, Ca-45, Ca-47, Cu-62, In-111, Tc-94m, Xe-133		

FIGURE 39. In 2002, 87 FDA-approved radioactive drug research committees conducted 28 studies with 2,872 human subjects.

met. In 2002, 87 FDA-approved RDRCs conducted 28 studies with 2,872 human subjects (Fig. 39).

I would like to propose a possible solution, somewhat analogous to the open-source model in information technology, that would make use of this already extant RDRC mechanism to expand the range and scope of tracer investigations and availability. RDRC biopharmacologic patient results could be entered into an Internet-based radiopharmaceutical development database. Physician-sponsored IND results would also be entered. Appropriate patient consent would be secured. The results in this database would be transparent to anyone able to log onto the data. A committee of experts would assess the results after hundreds of thousands of studies are accumulated. When sufficient data have been collected from multiple institutions, the regulatory agencies would be asked to consider approval for a new tracer. Approval of new tracers, then, would be based on validation by large numbers of RDRCs and independent experts of the ability of the radiopharmaceutical study to provide information that correctly answers the questions addressed by the

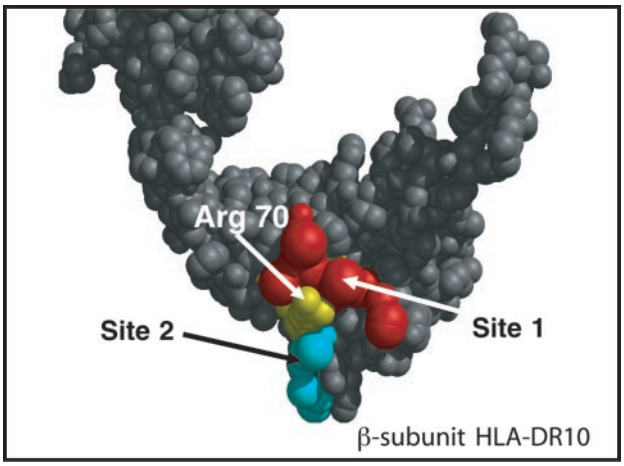

FIGURE 40. A novel selective high-affinity ligand "antibody mimic" for Lym-1 antibody binding in lymphoma/leukemia imaging and therapy.

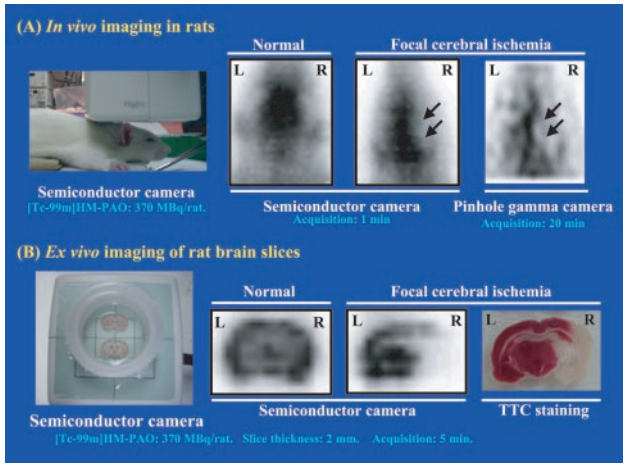

FIGURE 41. In vivo and ex vivo small animal imaging with a high-resolution small gamma camera based on a semiconductor detector.

study, that is, to satisfy the purpose of the study. The FDA would review the results and approve the radiopharmaceutical.

The number of potentially valuable tracers is enormous, so we must be innovative in securing approval for their use. DeNardo et al. from The University of California–Davis Medical Center (Sacramento) and the Lawrence Livermore National Laboratory (Livermore, CA), for example, reported on novel selective high-affinity ligand "antibody mimics" for lymphoma/leukemia imaging and therapy (Fig. 40).

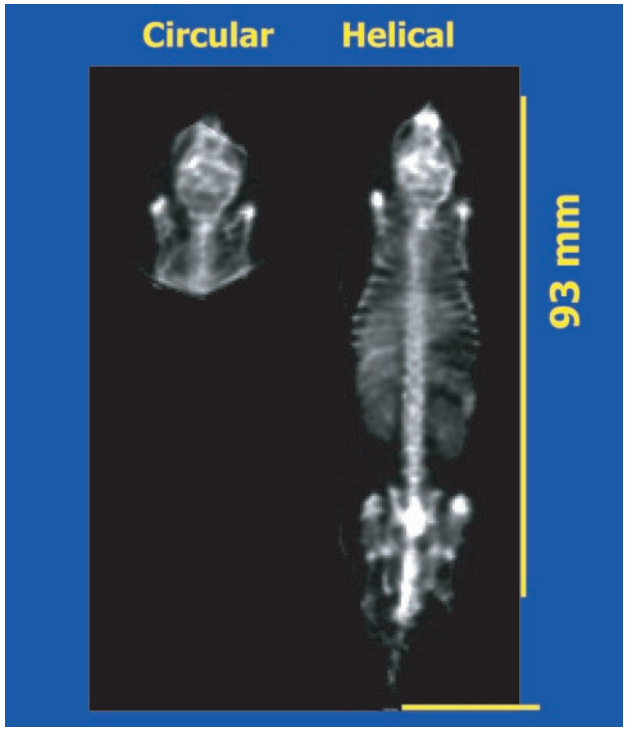

FIGURE 42. Animal co-image of the year. ^{99m}Tc-MDP whole-body mouse imaging with circular- and helical-orbit 2-headed pinhole SPECT.

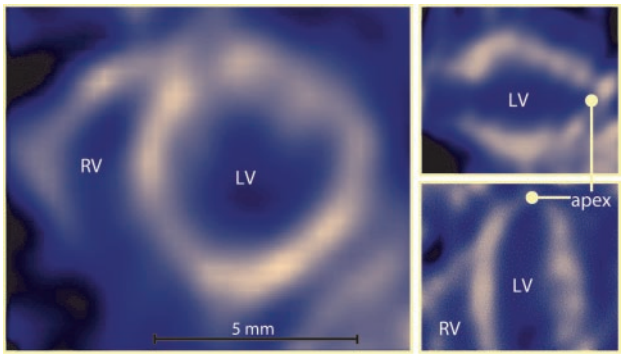

FIGURE 43. Animal co-image of the year. Image of a mouse heart with U-SPECT 1-submillimeter stationary small animal PET based on a triple-detector system.

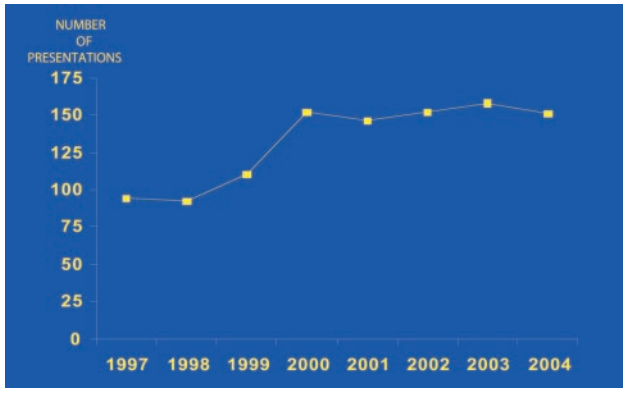

FIGURE 45. Number of presentations on radionuclide therapy at the SNM annual meeting, 1997–2004.

Small Animal Imaging

Imaging with dedicated small animal devices continues to increase with PET and SPECT, with more than 60 papers focused on small animal imaging at this year's meeting. Kuge et al. from Kyoto University (Japan) and Hamamatsu University School of Medicine reported on small animal imaging with a high-resolution small gamma camera based on a semiconductor detector (Fig. 41). Metzler et al. from Duke University (Durham, NC) reported on ^{99m}Tc-MDP whole-body mouse imaging with helical versus circular orbit pinhole SPECT and parallel-beam reprojection (Fig. 42). I have selected this as an animal co-image of the year, along with an image by Beekman et al. from University Medical Center (Utrecht, The Netherlands), who reported on U-SPECT 1 submillimeter stationary small animal PET based on a triple-detector system (Fig. 43). Moore et al. from the Harvard Medical School and the TRIONIX Research Laboratory, Inc. (Twinsburg, OH) reported on a triple-detector, multiple pinhole system for SPECT imaging of rodents. The system has 3 cameras with 2 pinholes per camera. A single rotation yields complete 3-dimensional SPECT volume of a whole mouse with submillimeter resolution (Fig. 44). This is our third animal co-image of the year. Heinrichs et al. from the Central Electronics Laboratory (Juelich) reported on ClearPET, a high-performance small animal PET system that is adjustable to allow whole-body studies of rodents and brain studies of primates.

Ben-Haim et al. from the Carmel and Rambam Medical Centers (Haifa, Israel) showed that the accumulation of ^{18}F-FDG in coronary arteries with PET/CT can change over consecutive studies. This is consistent with studies cited earlier in this lecture and indicates that some of the uptake is the result of transient inflammation that occurs

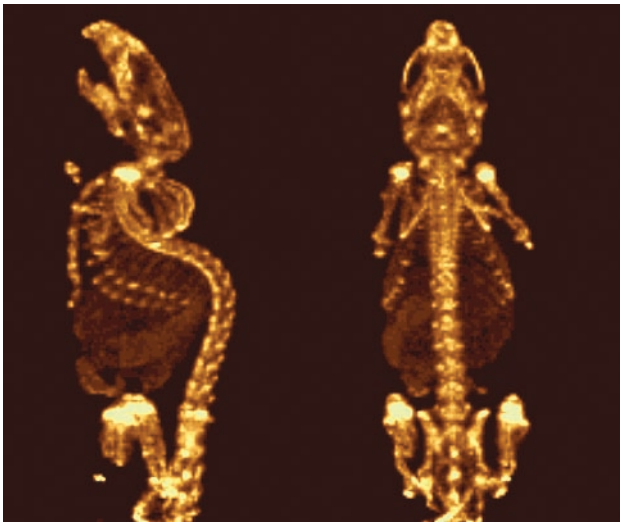

FIGURE 44. Animal co-image of the year. Three-dimensional, ^{99m}Tc-MDP bone image made with triple-detector, multiple pinhole system for single-rotation, high-resolution SPECT imaging of rodents. The system has 3 cameras with 2 pinholes per camera.

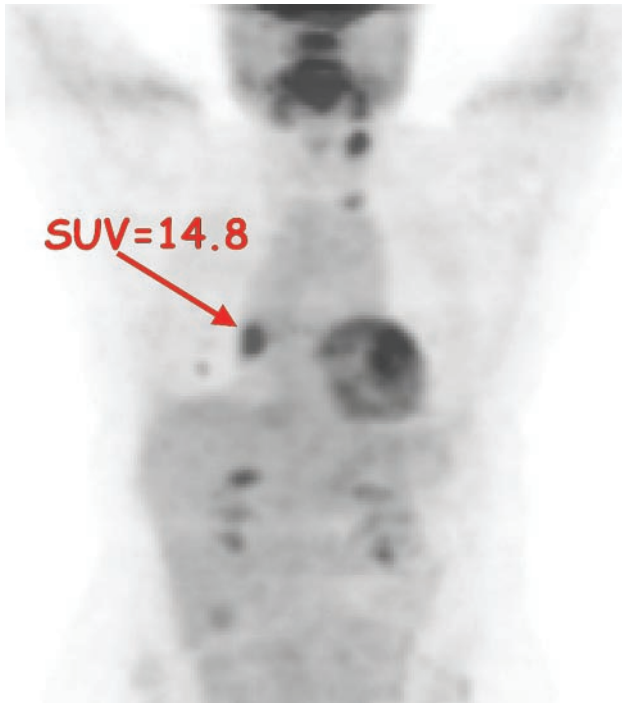

FIGURE 46. A patient dose of 7.5 Ci ^{18}F-FDG directed against metastatic lung cancer delivered 22 Gys of radiation to a tumor.

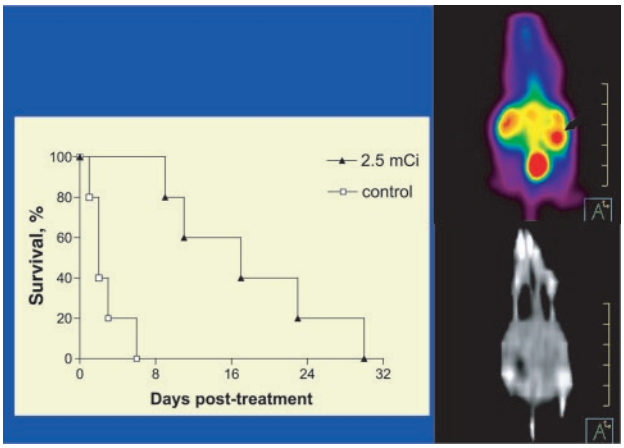

FIGURE 47. Large-dose ^{18}F-FDG therapy in experimental breast tumors in mice significantly prolonged survival.

in these plaques. This transient inflammation is sometimes a predisposing factor to myocardial infarction. The researchers performed a total of 121 serial studies in 28 patients. In half the patients, no change was found in accumulation of ^{18}F-FDG in plaque from initial study to repeat study. But in 38% of patients, previously positive sites of accumulation became negative. At the same time, 14 new sites of ^{18}F-FDG accumulation were identified. ^{18}F-FDG, then, can be used to look at the actual dynamics of change that occur in these plaques, which could have significance in patient management and outcomes.

Nuclear Medicine Therapy

Therapy remains the most attractive part of any medical field. Nuclear medicine therapy traces its origins to 1946, when radioactive iodine therapy was considered revolutionary. Radionuclide therapy now represents between 125 and 150 papers annually at the SNM meeting (Fig. 45). Moadel et al. from Montefiore Medical Center (New York, NY) presented striking results. They asked whether ^{18}F-FDG, with its well known ability to accumulate in cancerous lesions, might be used in large doses for treament. They found that, at least in theory, it would be possible to accumulate 22 Gys of radiation to a tumor (Fig. 46). In experimental breast tumors in mice, they found that ^{18}F-FDG could be used in large doses to improve survival (Fig. 47). Perhaps ^{18}F-FDG will expand to find an important place in radiotherapy.

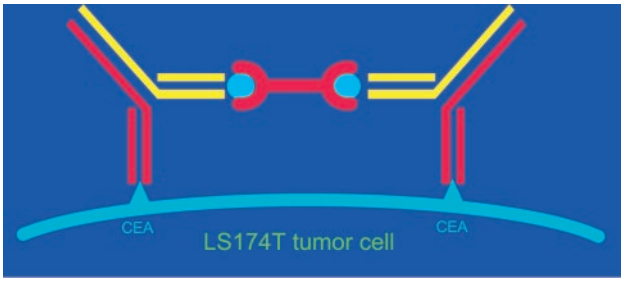

FIGURE 49. Pretargeting of CEA-expressing tumors with a biologically produced bispecific monoclonal antibody (MN14xDTIn-1) and a ^{111}In-labeled bivalent peptide.

New nuclides continue to be applied in therapy. Lantry et al. from Bracco in the United States and Italy reported on the biodistribution, dosimetry, and systemic radiotherapeutic efficacy of ^{177}Lu-AMBA, a bombesin-derived gastrin-releasing peptide-receptor agonist. In PC3 tumor-bearing mice, a single dose of 750 μCi ^{177}Lu-AMBA significantly prolonged survival (Fig. 48). The immunologist's gift to radionuclide therapy, given the fact that there are thousands of antigens on tumors, may be help in determining which can be used to develop stable and radiolabeled drugs. β-cell lymphomas, for example, express several antigens, the most widely studied of which at the present time is CD20. It is not expressed in bone marrow cells, so that the toxicity is tolerable. It is not expressed in stem cells or plasma cells but in more adult cells.

Some researchers are asking whether the excellent results of radioimmunotherapy (RIT) in patients with relapsed non-Hodgkins lymphoma (NHL) might indicate possible benefits in administering RIT as an initial treatment. Divgi et al. from Memorial Sloan–Kettering addressed this question by treating patients with mantle cell lymphoma initially with ^{131}I-tositumomab followed by

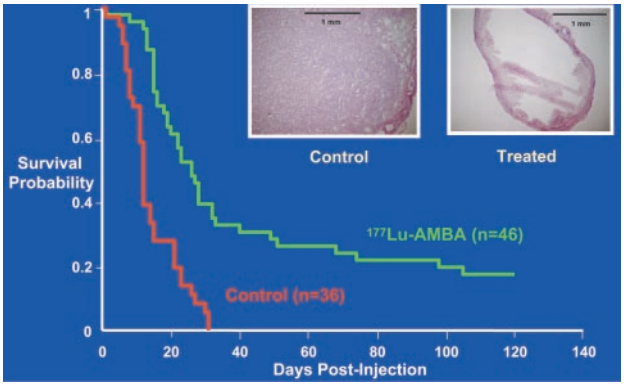

FIGURE 48. A single dose of 750 μCi ^{177}Lu-AMBA administered to PC3-tumor bearing mice significantly prolonged survival.

IMAGING	INFECTION		
2000	44	14	FDG
2001	54	16	"
2002	63	23	"
2003	59	23	"
2004	36	21	"

FIGURE 50. The middle column indicates the number of papers on imaging infection presented at SNM annual meetings from 2000 to 2004. The third column indicates the number of these papers that used ^{18}F-FDG as a tracer.

conventional cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy. They found that in patients with less than 25% marrow involvement, a protocol of RIT followed by CHOP was well tolerated. Results such as these indicate that RIT may become a first-line treatment for some groups of patients with NHL.

Pretargeting is an idea whose time has come. In this double tracer technique, one tracer binds to the antigen and the second is given as a chelate. Van Schaijk et al. from University Medical Center (Nijmegen, The Netherlands) reported on the pretargeting of carcinoembryonic antigen-expressing tumors with a biologically produced bispecific monoclonal antibody (Fig. 49).

If you ask what drugs have been approved recently in all of nuclear medicine, the answers are Zevalin and Bexxar, therapeutic agents. The reason they have been approved is that hundreds of millions of dollars were put into their development. It is clear that we must come up with a new system, such as the one I have proposed, that will help to get diagnostic agents through the difficult research and development stages to approval.

I promised a colleague to provide a comment on a question posed to me earlier at this meeting: Why have the approved RIT drugs, Zevalin and Bexxar, not been as widely used as they might be? I think there are 4 solutions to this problem: (1) Tell the medical oncologists that they will retain control over the care of the patient; (2) make sure the imaging procedures are performed in or immediately adjacent to the medical oncology department; (3) ensure that there is some financial benefit to pay for the medical oncologist's services when RIT is performed; and (4) find ways to let the public know about the effectiveness and benefits of these forms of RIT.

Infection

A number of papers over the past 5 years have been concerned with imaging infection (Fig. 50). At the 2004 meeting, 36 such papers were presented, 21 of which used ^{18}F-FDG as the tracer. Chen et al. from the Washington University School of Medicine (St. Louis, MO), for example, looked at the use of ^{18}F-FDG PET to evaluate pulmonary inflammation in patients with cystic fibrosis. Tracer uptake was correlated with cellular infiltration (Fig. 51).

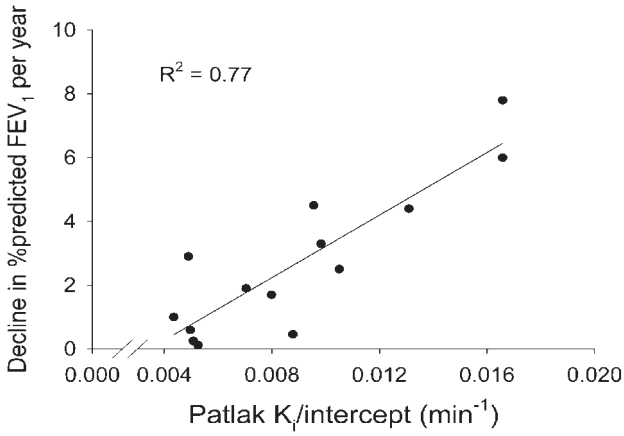

FIGURE 51. Pulmonary uptake of ^{18}F-FDG correlates with decline in lung function in patients with cystic fibrosis.

Conclusion

Many questions will face us when we meet in Toronto in 2005. Will collaboration among different scientific and clinical disciplines increase? We have seen evidence at this meeting that collaboration is greater than ever before, and we should work to see that it is continued and enriched. Will nuclear medicine continue to grow worldwide? This is a point for more study. Some evidence suggests that nuclear imaging may not be developing in some countries as quickly as we had hoped. Will there be new, widely used clinical PET and SPECT procedures using ^{18}F-FDG PET? Will radionuclide therapy continue to play an increasing role? Will we begin to construct an international database for molecular imaging?

We are faced with a number of challenges as we work in what is perhaps the most promising field in all of clinical medicine. Let's all do our part to identify and explore the new roads that will lead to those far but exciting horizons.