Horizons Near and Far: Molecular Focus, Global Involvement

The Highlights Lecture is presented annually at the closing session of the SNM Annual Meeting by Henry N. Wagner, Jr., MD. This year's lecture, the 28th in the series, was given June 22 in Toronto, Canada.

Nobel laureate Dag Hammarskjöld said, "Only he who keeps his eye fixed on the far horizon will find the right road." No one could have foreseen the growth in the annual meeting of the SNM over the last 50 years, with an almost linear addition of about 33 presentations each year (Fig. 1). If you integrate this curve, the total number of scientific oral and poster presentations amount to more than 35,000. This number represents the contribution that these participants in the SNM have made to bring nuclear medicine to where it is today. If we were looking at this curve at an annual SNM "shareholders" meeting, we would declare a huge dividend and then reinvest the money.

Henry N. Wagner, Jr., MD

Trends

For the first time, the numbers of presentations from outside the United States in 2005 are greater than those from individuals living in the United States (Table 1). I'd like to ask for a round of applause to show our appreciation for those who travel internationally to our meeting and have contributed so much this year and over so many years in the past.

In 1975, I was privileged to go to Washington University (St. Louis, MO) and have a PET study performed after breathing ^{11}C-carbon monoxide as a blood pool agent. PET and single-photon tracers now have a long history, as illustrated in Figure 2, which shows the numbers of papers presented at the SNM meeting on positron-emitting tracers, beginning before the routine clinical use of PET, and of single-photon tracers, beginning before SPECT. The numbers show a steady increase in positron and single-photon papers, averaging about 37 additional presentations each year until 1999, when clinical PET/CT appeared. Since that time, the number of positron tracer papers has doubled. The number of SPECT presentations over the last 8 years has remained relatively stable but high at approximately 300. The decrease in the percentage of SPECT papers is a reflection of the growth of PET/CT, where, in the last 2 years alone, the

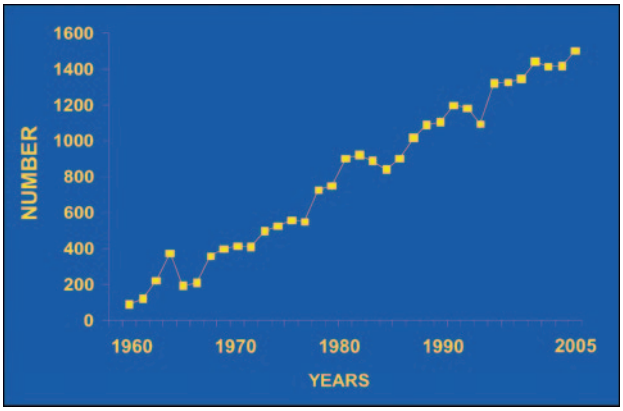

FIGURE 1. Total numbers of presentations at SNM annual meetings, 1960–2005.

TABLE 1
2004 and 2005 SNM Abstracts

Country*	2004 Number of presentations	2004 % of total	2005 Number of presentations	2005 % of total
United States	732	51.6	702	46.8
Japan	153	10.8	132	8.8
Germany	148	10.4	147	9.8
Korea	109	7.7	110	7.3
France	64	4.5	58	3.9
China	33	2.3	59	3.9
United Kingdom	33	2.3	40	2.7
The Netherlands	30	2.1	36	2.4
Italy	30	2.1	56	3.7
Canada	28	2.0	55	3.7
Belgium	26	1.8	25	1.7
Switzerland	26	1.8	32	2.1
Taiwan	26	1.8	31	2.1
Israel	20	1.4	18	1.2
Australia	17	1.2	15	1.0
India	11	0.8	27	1.8
Spain	6	0.4	19	1.3

*Other countries represented in 2005 included Turkey, Austria, Sweden, Denmark, Greece, Czech Republic, Hungary, Brazil, Argentina, Kuwait, Ireland, Slovenia, Indonesia, Thailand, Finland, Islamic Republic of Iran, South Africa, Portugal, Bangladesh, Russia, Croatia, and Mexico.

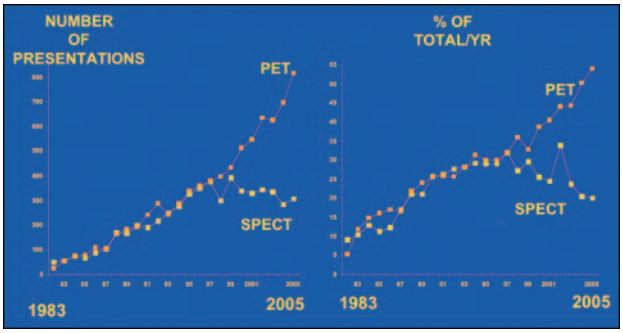

FIGURE 2. Left: Numbers of PET and SPECT presentations at SNM annual meetings, 1983–2005. Right: PET and SPECT topics as percentages of total presentations at each meeting, 1983–2005.

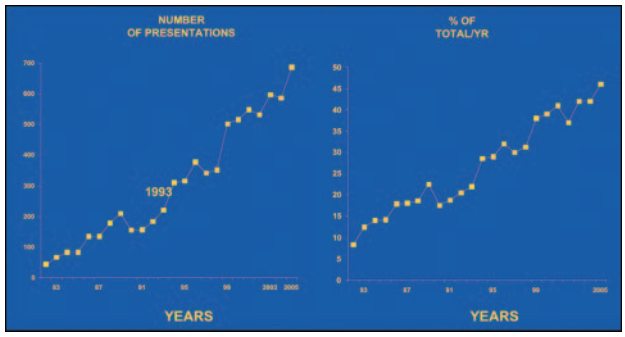

FIGURE 3. Left: Numbers of presentations on oncology topics at SNM annual meetings, 1983–2005. Right: Oncology topics as percentages of total presentations at each meeting, 1983–2005.

number of presentations has increased from 96 to 242 (Table 2). However, SPECT/CT is now experiencing similar growth, with presentations doubling since 2003. It is safe to say that we will see a great increase in SPECT/CT in the near future.

Oncology continues to dominate the meeting, with 688 presentations—and by presentations I mean both oral presentations and posters (Fig. 3). The reason that this reflects the field so well is that the number of accepted posters is essentially limitless. In the poster exhibit hall at the SNM meeting, many boards have not been filled. This indicates that the committee that selects the program picks papers above a certain level of acceptability, some for oral presentations and the rest for posters. The sum of the 2 types of presentations provides a reflection of the state of the art in nuclear medicine and offers insights on changing foci of attention in the field. Until about 1993, each year saw the addition of about 20 presentations in oncology. In 1993, with the advent of clinical PET and improved SPECT, it more than doubled, growing by about 48 additional presentations each year.

Neuroscience is number 2 on the topic list of presentations, with 254 (17%) presentations, and cardiology is third with 200 presentations (13%).

^{18}F continues to lead other positron tracers (Fig. 4). At this meeting, there were 638 oral and poster presentations that employed ^{18}F. Of these, 490 were on fluorodeoxyglucose (FDG). In addition to the tracers shown in Figure 4, more than 10 studies each with ^{13}N, ^{68}Ga, ^{124}I, ^{82}Rb, and ^{64}Cu were reported, indicating the continued exploration of imaging with different radionuclides. For example, 45 institutions in the United States are now using ^{82}Rb, principally in conjunction with CT angiography (CTA).

The number of papers on ^{99m}Tc and other common single-photon radionuclides has plateaued (Fig. 5). Keep in mind, however, that in the year 2004 more than 18 million SPECT scans were performed at more than 7,000 sites in the United States. Will new, specialized single-photon instruments be developed? One example of a presentation at the SNM meeting of such instrumentation was that by Liu et al. from Johns Hopkins University (Baltimore, MD), which described rotating multisegment slant-hole SPECT mammography using a special configuration of collimators on conventional cameras and a comparison of results with those from planar scintimammography for breast lesion detection. The advantages of this approach are that it is easy to implement (because it uses existing SPECT systems), the camera may be positioned very close to the breast, and very high spatial resolution can be achieved.

TABLE 2
2005 Presentations on Image Fusion*

Modalities	2000	2001	2002	2003	2005
PET/CT	13	33	55	96	242
PET/MRI	14	25	21	21	28
SPECT/CT	11	8	14	19	41
SPECT/MRI	5	18	6	11	18

*Includes both hardware- and software-fused modalities.

Moving Toward a Molecular Focus

Has the time come to change the name of the SNM to the Society of Molecular Medicine? This is a new name

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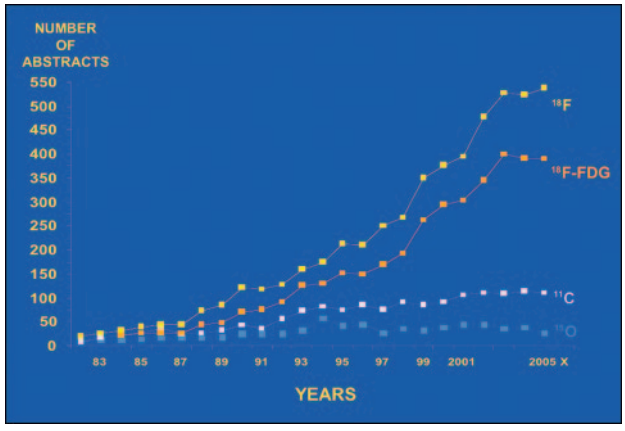

FIGURE 4. Numbers of presentations on studies using selected positron-emitting tracers at SNM annual meetings, 1983–2005.

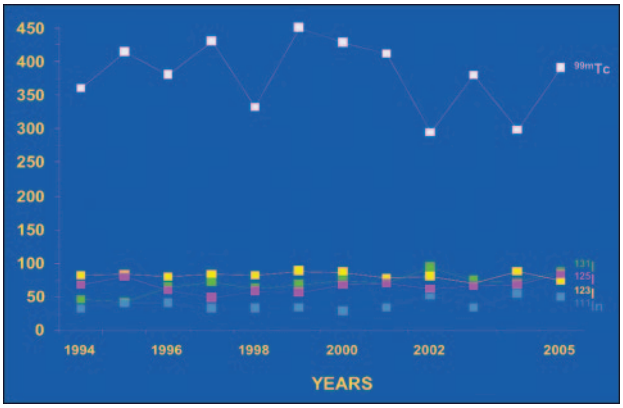

FIGURE 5. Numbers of presentations on studies using selected single-photon–emitting radionuclides at SNM annual meetings, 1994–2005.

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for an old idea. Nuclear medicine today is prepared to go beyond molecular imaging. It includes the use of single probes, in vitro studies, and, more and more, will provide important information about genotyping. The idea is old and goes back at least to 1943, when Georg de Hevesy won the Nobel Prize in chemistry and referred to radioactive tracers as "isotopic indicators." Medicine has increased its spatial resolution from the whole body to organs to tissues to cells and to molecules, the domain at which the field of nuclear medicine now rests. No other field has the basic unit of micromoles per minute per milliliter of tissue. The time dimension is a key parameter, because we examine processes as well as states. It is for this reason that we should consistently refer to PET/CT as a 4-dimensional (4D) imaging technique, particularly when studies are performed sequentially in the same patient.

The focus in nuclear medicine is shifting from cells to molecules, as the knowledge once provided by histology is complemented by biochemistry and molecular imaging. Histology will persist, obviously. It permits us to look at cells, but it suffers from the fact that it is not quantitative and looks only at selected sites. PET, SPECT, and optical tracer imaging permit us to go to a lower level of molecules and lead to the following new hypotheses that underlie practice and research in nuclear medicine:

(1) We define disease by relating structure (state), regional chemistry (process), and histopathology to the patient's problem (phenotype).

(2) We can design more effective drugs now that we have a way to define diseases at the molecular level.

(3) We treat disease on the basis of abnormal molecular processes expressed in units of micromoles per minute per milliliter of diseased tissue.

The questions we ask when practicing molecular medicine today include: What is the patient's problem? Where is the patient's problem? What is going to happen? Can anything be done about it? What is the best chance of treatment? Is the treatment helping? Is there still a problem at the end of treatment? Has the problem recurred? However, we do not focus solely on the causes of our patients' problems. Instead, we search for modifiable molecular manifestations of that problem in terms of location, structure, function, and biochemistry. Eventually, as applications in molecular medicine advance, the patient's diagnosis will be his or her name, characterized by the molecular manifestations in terms of regional molecular concentrations, processes, or change. Research will be directed to the continued identification of molecular regional processes by quantitative PET/CT, PET/CTA, SPECT/CT, SPECT/MRI, or optical imaging.

At this year's meeting, the following molecular states or processes were described in research reports: glycolysis, proliferation, hypoxia, angiogenesis, choline metabolism, receptor expression, transporter expression, antigen expression, apoptosis, gene delivery, and multidrug resistance.

For example, Even-Sapir et al. from the Tel Aviv Sourasky Medical Center (Israel), the Sapir Medical Center (Kfar Saba, Israel), and Tel-Aviv University (Israel) described malignant tumors and premalignant lesions found incidentally on PET/CT. In 2,360 patients, 156 suspicious lesions were identified, 44 of which were incidentally found primary tumors. Atypical locations for metastatic lesions were identified in 27 patients, and differences were often noted in ^{18}F-FDG avidity of the known primary tumor and other metastatic lesions.

Molecular Imaging and Genetics

The beginning of modern nuclear medicine corresponds almost exactly to the time in which James Watson and Francis Crick elucidated the molecular structure of DNA. Today, more than half a century later, a major characterization of health care is the uniting of molecular imaging, genetics, and pharmacology to provide new insights, treatments, and diagnostic methods. Molecular imaging, which includes in vitro as well as in vivo imaging, is an important participant in these efforts.

Strauss et al. from the German Cancer Research Center (Heidelberg), the Klinikum Ludwigschafen (Germany), and the University of Rostock (Germany) used gene chip data to look for new diagnostic targets in patients with colorectal cancer. They identified molecular targets for tracer development and identified patterns in large databases (Fig. 6). It is clear that much of what we have learned in image processing display and analysis with radionuclides and other types of imaging can be applied to work with these databases of genes.

Pan et al. from the German Cancer Research Center, Warsaw University of Technology (Poland), and the University of Zurich (Switzerland) used the same software platform for combined analysis of PET and gene chip data. With this technique, they applied powerful molecular imaging software to visualizing gene expression (Fig. 7). They then chose the site of the gene of interest for

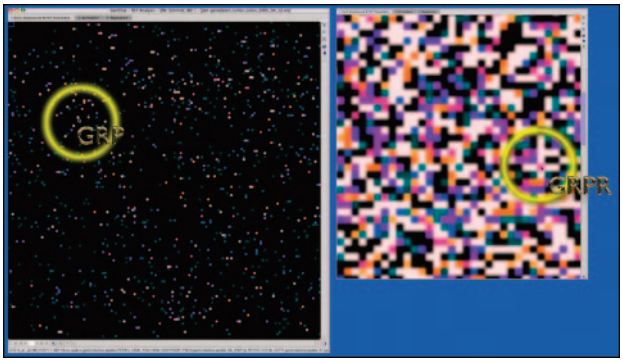

FIGURE 6. Gene chip analysis to identify molecular targets for tracer development. Left: Ratio of tumor to reference tissue. Right: Zoom view of circled area. GRP = gastrin-releasing peptide. Techniques such as these can aid in identifying patterns in large databases.

subsequent identification, again in a process that illustrates bringing together imaging of genetics and imaging of radionuclides and other tracers.

A good example of the movement from genotype to phenotype was a presentation by Fowler et al. from the Brookhaven National Laboratory (Upton, NY), Kings College (London, UK), State University of New York at Stony Brook, and the National Institute on Drug Abuse (Bethesda, MD). This group looked at the question of whether genotypes correlate with phenotypes. They used ^{11}C-clorgyline PET to relate brain monoamine oxidase (MAO) A to the genotype for MAO A. In 23 healthy nonsmoking males matched for age, education, and socioeconomic status, 14 were found to have a high MAO A genotype and 9 were found to have a low MAO A genotype. MAO activity, measured by nuclear techniques, was related to genotype in the occipital cortex, precuneus, prefrontal cortex, and brain stem.

Another example of moving from genotype to phenotype was seen in a presentation by Mueller et al. from the University Hospital Schleswig-Holstein (Kiel, Germany). This group used PET to look at glucose metabolism of ^{18}F-FDG in the skeletal muscle and liver of healthy subjects with genetic fatty acid protein binding polymorphism—that is, a different genotype. They studied 1,200 people, of whom 60% had the genotype GGAA and 40% had the genotype TTTT. They found in these normal persons that only the muscle ^{18}F-FDG uptake and the standard uptake value (SUV) for ^{18}F-FDG were significantly different between the 2 phenotypes. Those with genotype GGAA had lower glucose metabolism and SUVs and were predisposed to diabetes. Those with genotype TTTT had higher glucose metabolism as reflected in the muscle uptake and SUV, which the authors believed might protect these individuals from developing type 2 diabetes.

Toward 4D, Volumetric Fusion Imaging

We live in a 4D world. A presentation by Quon et al. from Stanford University (CA) was a perfect example of the bringing together of structure and function in 3D PET/CT fusion imaging in virtual mediastinoscopy, colonography, and bronchography for presurgical evaluation. I selected a bronchography image from this series as the 2005 SNM Image of the Year (Fig. 8; page 19N). The significant aspects of this image are that it is from a living patient, it uses 3D multislice spiral CT to provide exquisite anatomical detail in the lungs, and it uses ^{18}F-FDG to locate activity in a primary cancer and in an FDG-avid lymph node "hiding" behind the bronchus. The high degree of spatial resolution and high degree of precision in the fusion of the 2 images makes it possible to distinguish the fact that the lesion is not inside the bronchus but in a lymph node behind the bronchus.

Earlier technologies foreshadowed today's volumetric fusion efforts. In 1957, at Hammersmith Hospital (London, UK), I had the responsibility of using a Geiger-Muller (GM) tube placed at various points in a plastic grid after the administration of ^{132}I to the patient. We then drew isocount lines to provide images that would show whether a nodule in the neck avidly accumulated iodine, to assist in determining whether the nodule was malignant. The next year, a rectilinear scanner was constructed at Johns Hopkins, representing a combination of the concepts of Benedict Cassen and David Kuhl in doing photorecording of the distribution of radioactivity. This photorecording was an advance over the use of dots to record the amount of activity—and looking back at these early advances is a reminder of the great strides we continue to make.

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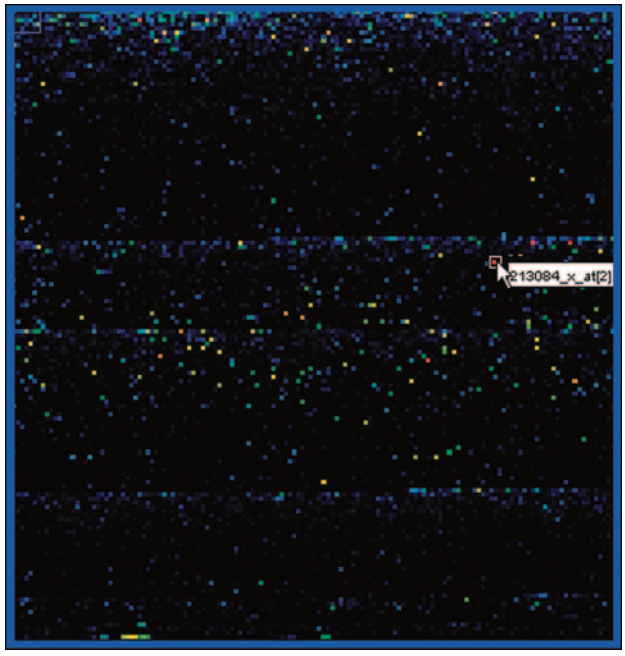

FIGURE 7. Powerful molecular imaging software can be used to visualize gene expression and genes of interest for subsequent identification, a process that illustrates the synergy in imaging of genetics and imaging with radionuclides and other tracers.

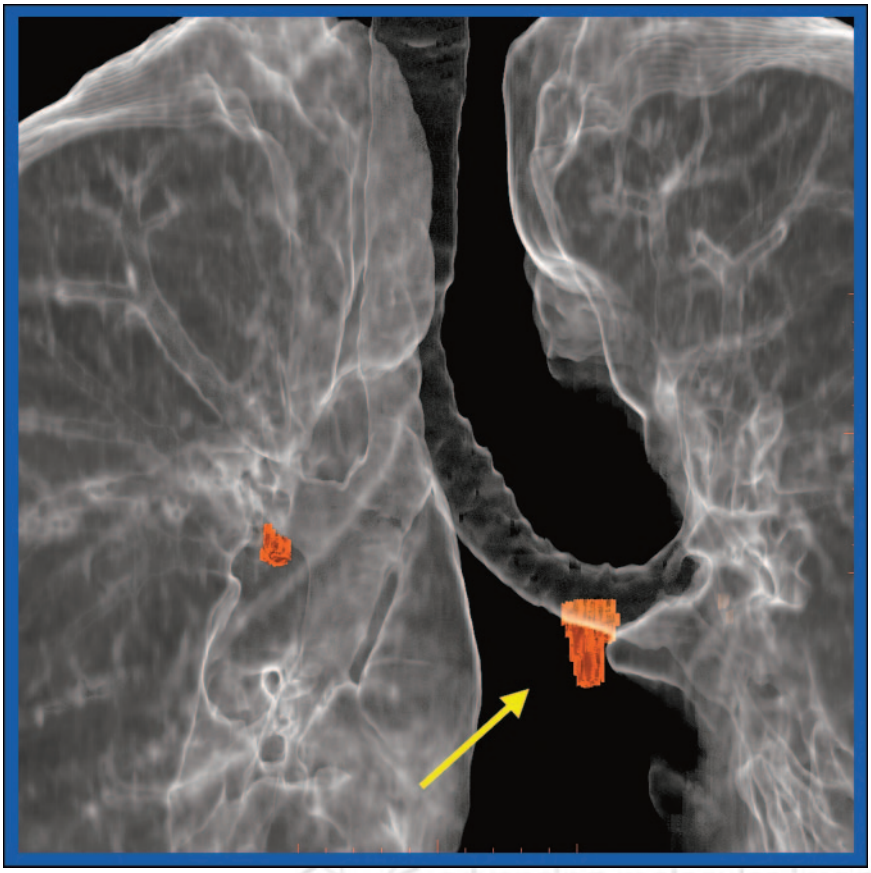

FIGURE 8. 2005 SNM Image of the Year. Three-dimensional PET/multislice CT fusion image of virtual bronchography for presurgical evaluation. Note the ^{18}F-FDG–avid lymph node "hiding" behind bronchus.

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A considerable amount of excitement has been shown in the new 4D volumetric world of nuclear medicine, including work with 3D PET/CT angiography, as reported at the meeting by Murakami et al. from the National Cancer Hospital East (Chiba, Japan) and GE Yokogawa Medical Systems (Tokyo, Japan). This group showed 4D volumetric images that facilitate image-guided therapy planning by localizing ^{18}F-FDG–avid foci and superimposing these on the detailed anatomy provided by CTA (Fig. 9). This type of technology requires very precise fusion of the techniques as it moves into the treatment domain, whether that treatment is by injection, lasers, or other effective noninvasive surgery.

Hacker et al. from the University of Munich (Germany) described multislice spiral CTA in the detection of functionally relevant coronary artery lesions and compared this technique with myocardial sestamibi (MIBI) SPECT (Fig. 10). They found that the multidetector CT identified areas of ischemia with a sensitivity of 45% and a positive predictive value of 29%. They concluded that although myocardial perfusion imaging remains mandatory for evaluating the functional relevance of coronary lesions, multidetector CT can reveal structural lesions in patients who show no myocardial perfusion image abnormalities. Thus the 2 techniques have now come together in the best approach to the patient.

As noted previously, fusion imaging is not a new concept. Years ago at Johns Hopkins, we routinely made radiographs in the x-ray department on which we superimposed the distribution of radionuclide activity, such as the rectilinear image of the distribution of radioactive iodine at the base of the patient's tongue seen in Figure 11. There was no accumulation of the tracer in the normal position of the thyroid in the neck. The accumulation of radioiodine proved that this was a sublingual thyroid, which meant that harmful surgery was avoided and the mass was not removed.

The 2005 SNM meeting included 327 oral and poster presentations on fusion imaging. Shammas et al. from the University of Pittsburgh School of Medicine (PA) presented a study on ^{18}F-FDG PET/CT in patients with suspected recurrent or metastatic well-differentiated thyroid cancer. Patient management was changed in 27 (44%) of 61 patients. A study of scintigraphic/visual fusion imaging for improved localization of thyroid abnormalities by Zuckier et al. from the New Jersey Medical School (Newark, NJ) emphasized the fact that although hybrid, single-gantry imaging has had and will continue to have a dramatic impact on medicine, we also need to continue to develop software fusion imaging so that multiple modalities can be effectively combined. Scintigraphic and visual imaging improved the localiza-

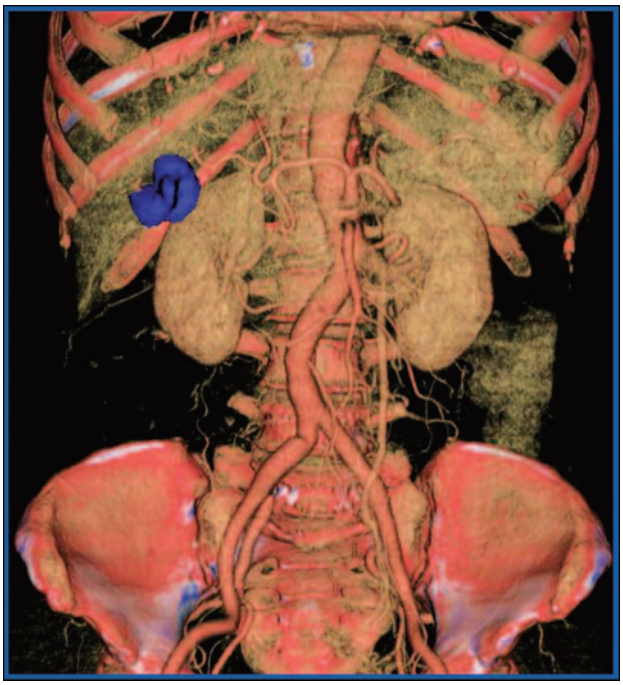

FIGURE 9. "Four-dimensional" volumetric imaging facilitates therapy planning by localizing ^{18}F-FDG–avid foci and superimposing these on the detailed anatomy provided by CT angiography. This technology requires precise fusion of the techniques as it moves into the treatment domain.

tion of thyroid abnormalities (Fig. 12). After performing the nuclear study, the authors took a photograph of the patient and superimposed (coregistered or fused) this optical image over the distribution of the radioactive iodine. This improved localization would be most helpful in planning approaches for thyroid surgery.

^{18}F-FDG and Other Tracers in Tumor Imaging

Like the Energizer bunny, ^{18}F-FDG PET just keeps going and going. In 2004, 1 million procedures were performed with ^{18}F-FDG at 2,000 different sites in the United States (Fig. 13). However, SPECT lives and will continue to prosper; as previously noted, 18 million SPECT scans were performed at more than 7,000 sites in the United States in 2004. Figure 14 shows that the growth in ^{18}F-FDG has been driven by the increase in oncology applications, with relatively flat accompanying curves for the neurosciences and cardiology. There were

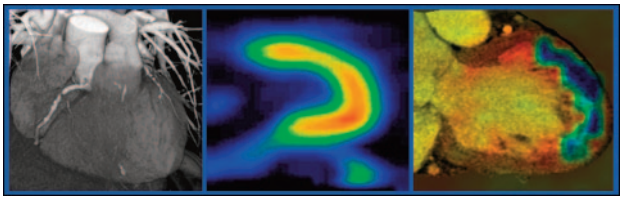

FIGURE 10. Multislice spiral CT angiography (left) revealed structural lesions when myocardial sestamibi SPECT (middle) showed no abnormalities. The 2 techniques can be combined (right) to yield additional information.

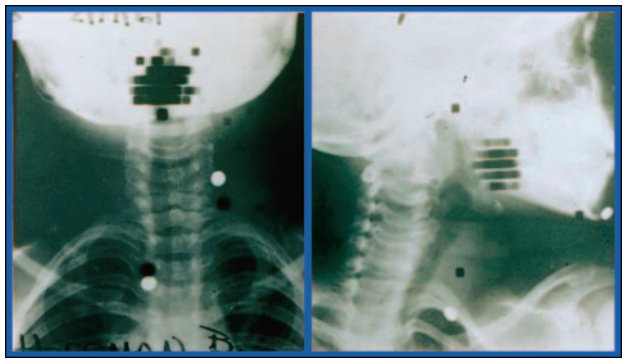

FIGURE 11. Fusion imaging is not a recent innovation. Half a century ago at the author's institution the distribution of radionuclide activity was routinely superimposed on standard radiographs. Here, the rectilinear image of the distribution of radioactive iodine at the base of the patient's tongue and lack of accumulation in the neck indicated the presence of a sublingual thyroid, information that facilitated avoidance of unnecessary surgery.

82 presentations on lung cancer at this year's SNM meeting, including a study by Bar-Shalom et al. from the Rambam Medical Center (Haifa, Israel) that looked at ^{18}F-FDG PET/CT for the evaluation of solitary pulmonary lesions in 63 patients. (One of the noteworthy characteristics of this meeting was the larger numbers of patients in individual studies.) In these patients, 31% did not accumulate ^{18}F-FDG and had benign lesions, and 32% had lesions that avidly accumulated the tracer and were found to have cancer (Fig. 15).

Quantification is necessary, as illustrated in this presentation by Obrzut et al. from the University of California, San Diego (La Jolla), who compared the use of SUVs with the method of assessing the cerebellum as a neutral reference area. They used ^{18}F-FDG PET to compare SUVs and lesion-to-cerebellum activity ratios in the evaluation of lung lesions in 60 patients with 129 known or

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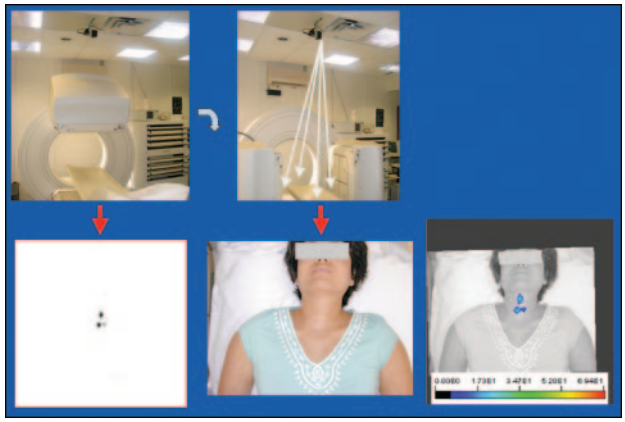

FIGURE 12. Scintigraphic and visual imaging improved the localization of thyroid abnormalities in this patient. The nuclear study showing the distribution of radioactive iodine was superimposed on an optical image to yield a functional/anatomical image of use to the surgeon preparing for thyroid surgery.

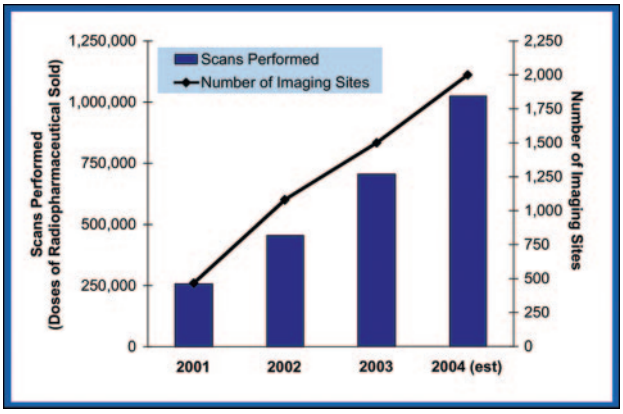

FIGURE 13. Numbers of scans performed (bars; as indicated by doses of radiopharmaceuticals sold) using ^{18}F-FDG in the United States, 2001–2004, and numbers of imaging sites at which these procedures were performed (line) during the same period. In 2004, more than 1 million procedures were performed at 2,000 different sites.

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suspected malignant primary or metastatic lung lesions. They found that with the cerebellum as a reference standard, the lesion-to-cerebellum activity ratio method yielded more favorable receiver operator characteristics (ROCs) than the lesion SUV in the assessment of pulmonary lesions.

Investigators are evaluating the relative imaging roles of ^{18}F-FDG, which can assess glycolysis, and ^{18}F-fluorothymidine (FLT), which can assess DNA synthesis. We have known for some time that only about 10% of malignant tumors are dividing at any one time, but all are constantly metabolizing glucose. The signal will always be stronger, therefore, with FDG than with FLT, but the question remains as to which tracer will be better able to reflect responses to therapy.

Yang et al. from the University of Ulsan College of Medicine (Seoul, Korea) looked at the prediction of gefitinib therapy response using ^{18}F-FLT in patients with non–small cell lung cancer (NSCLC). They found that within 1 week of initiating therapy, nonresponders had a marked rise in SUVs and responders had a marked fall. They concluded that ^{18}F-FLT PET could predict response to gefitinib therapy in patients with NSCLC and believed that the tumor SUV obtained by this method is a promising prognostic parameter.

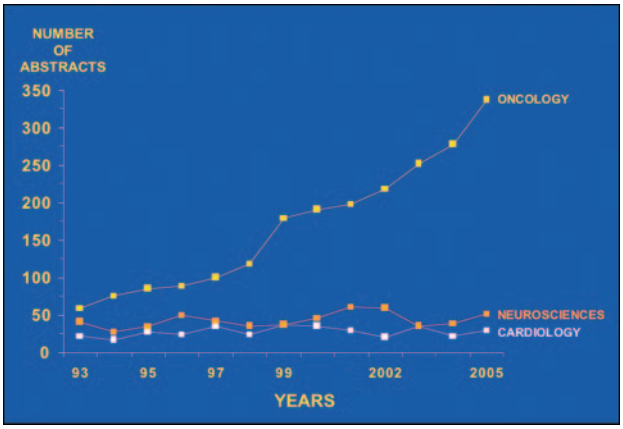

FIGURE 14. Numbers of presentations on studies using ^{18}F-FDG at the SNM annual meeting, 1993–2005. The growth has been driven by new applications in oncology, with the curve for the neurosciences and cardiology remaining relatively flat.

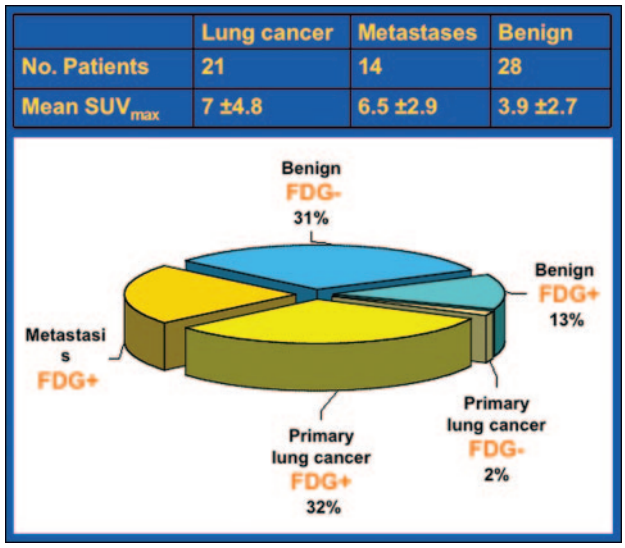

FIGURE 15. Results from a study in which ^{18}F-FDG PET/CT was used in the evaluation of solitary pulmonary lesions in 63 patients.

Labeled uracil can also be used to reflect DNA synthesis, as described by Robins et al. from Hammersmith Imanet, Ltd. (London, UK), who developed a novel, rapid, and high-yield method for preparing ^{18}F-5-FU using no-carrier-added ^{18}F. The results showed that ^{18}F labeling is more than 95% chemoselective for the uracil moiety of the precursor.

This year's SNM meeting included 33 presentations on neuroendocrine tumors, including one by Bao et al. from the University of California, San Francisco, on the performance characteristics of ^{99m}Tc-depreotide scintigraphy for the detection of pulmonary nodules. I want to note that one of the senior authors of this paper was Dr. Robert Lull, who died in May. Those of us who knew Bob Lull will certainly miss him and his wonderful personality and intelligence. These authors found that the performance characteristics of ^{99m}Tc-depreotide in the assessment of lung nodules were similar to published values for ^{18}F-FDG PET. The technetium-labeled tracer scans, however, were insensitive in the detection of deeply situated mediastinal nodes.

How are investigators comparing the relative merits of PET/CT and SPECT/CT when both hybrid modalities can do the same job? Oeksuez et al. from the Klinikum Stuttgart (Germany) and the University of Mainz (Germany) compared ^{68}Ga-DOTATOC PET/CT and ^{111}In-DTPAOC SPECT/CT in imaging somatostatin-expressing tumors. The

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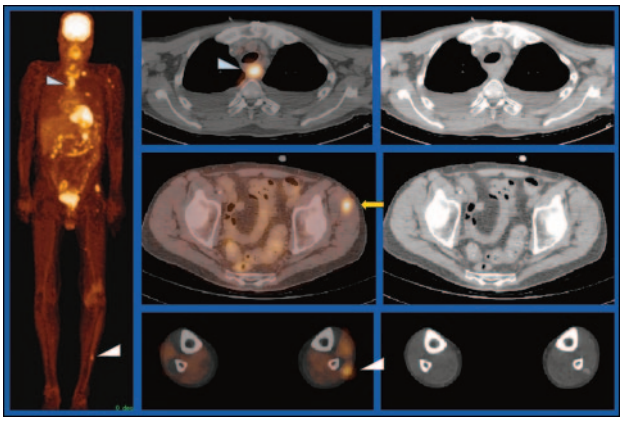

FIGURE 16. "True" whole-body PET/CT, scanning from the top of the patient's head to the soles of the feet, revealed soft tissue metastases outside the conventional field of view (base of the skull to the upper thigh) in 78% of patients in this study. This patient was found to have a metastatic lesion in the lower leg.

(Continued from page 22N)

^{68}Ga can be produced in-house from a long-lived ^{68}Ge/^{68}Ga generator, which makes it possible to carry out studies far away from a cyclotron. They found that imaging with the positron-emitting tracer ^{68}Ga-DOTATOC offered fast examination protocols, high sensitivity for even small lesions, and precise localization of lesions. They concluded that the ^{68}Ga-DOTATOC PET/CT was clearly superior to the ^{111}In-DTPAOC SPECT/CT in this application.

Head and neck cancer was the focus of 22 presentations at the meeting. Goshen et al. from the Chaim Sheba Medical Center (Tel Hashomer, Israel) and Tel Aviv University reported on PET/CT in the evaluation of patients with squamous cell cancer of the head and neck. In 25 patients who were found to have 45 PET/CT-positive lesions, the imaging results had an overall positive impact on subsequent management in 22 patients (88%). PET/CT provided important information for the initial staging of head and neck cancer, particularly in patients with distant metastases. It was especially helpful in patients with suspected recurrences, when anatomical imaging was inconclusive as a result of distortions caused by surgery or radiotherapy.

Lymphoma, which can be seen today in ever-expanding patient populations, was the topic of 59 presentations at the meeting, including the report by Kluge et al. from the University of Leipzig (Germany) comparing ^{18}F-FDG PET with conventional imaging, including CT and MR imaging and ultrasonography, in the initial staging of Hodgkin's disease in 179 children. Their results indicated that PET modified staging in 19% of patients compared with conventional imaging and that PET in children had an impact on staging of Hodgkin's disease similar to that shown in adults.

Six presentations focused on the use of ^{18}F-FDG PET to identify the site of a primary tumor after the diagnosis of distant metastases. Delgado-Bolton et al. from the Instituto PET Focuscan (Madrid, Spain) and the Hospital Clinico San Carlos (Madrid, Spain) reported on results in PET imaging of 82 patients in whom conventional imaging had yielded negative or inconclusive results in detecting primary sites. ^{18}F-FDG PET was found to have a sensitivity of 88%, specificity of 83%, and diagnostic accuracy of 85%. Information gathered from PET imaging had a high impact on the management of 59% of the patients.

What do we mean by whole-body imaging? Nguyen et al. from the University of St. Louis (MO) looked at the patterns and prevalence of soft tissue metastases as detected by whole-body ^{18}F-FDG PET. Many nuclear medicine practitioners perform "whole-body" PET/CT going from the base of the skull to the midthigh. Nguyen et al. believe that true whole-body studies should go from the top of the head to the soles of the feet, as seen in Figure 16 in a patient who was found to have a metastatic lesion in the lower leg. Soft tissue metastases occurred outside the "usual" field of view, that is the base of the skull to the upper thigh, in 25 of 32 lesions (78%) in the study. Moreover, the detection of soft tissue metastases provided more accessible biopsy sites and helped avoid invasive surgery procedures.

Will FDG replace some established ^{99m}Tc tracers? LeBlond et al. from the Centre Hospitalier de l'Université de Montréal (Canada) compared ^{18}F-FDG PET and ^{99m}Tc-methylene diphosphonate (MDP) in imaging bone metastases in patient with lung cancer. They found that PET was superior to the technetium bone scan in 38% of the patients. The relative positive predictive value was 44% for the technetium agent and 93% for PET (Fig. 17). Figure 18 shows a striking example of the comparison, with the negative ^{99m}Tc-MDP study on the left and the positive ^{18}F-FDG image on the right.

Beyond Oncology

Lim et al. from the Children's Hospital Boston (MA) and the Harvard Medical School (Boston, MA) presented an interesting study on ^{18}F-fluoride bone imaging in young athletes. Figure 19 shows imaging results in a

(Continued on page 26N)

	Tc99m MDP Bone scan	FDG-PET
Sensitivity	75%	81%
Specificity	82 %	99%
Accuracy	81%	96%
PPV	44%	93%
NPV	95%	97%
Equivocal lesions	16%	2%
# lesions/ patient	1.6	4.1

FIGURE 17. Results of assessment of relative efficacies of ^{99m}Tc-MDP bone scan and ^{18}F-FDG PET in imaging bone metastases in patients with lung cancer.

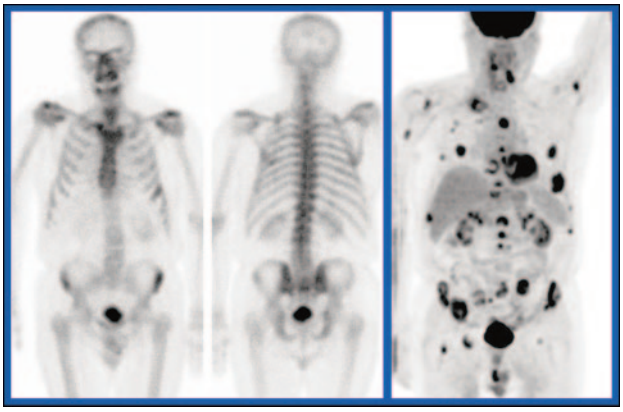

FIGURE 18. A striking example of the comparison of a negative ^{99m}Tc-MDP bone scan (left) and positive ^{18}F-FDG PET (right) in a patient with lung cancer.

(Continued from page 24N)

16-year-old boy with back pain. Tracer accumulated in the back, and the patient was found to have a pars interarticularis stress fracture and another in the transitional vertebra. In the 94 patients included in this study, the authors were able to localize the source of pain in 52 (55%), and 15 (16%) were found to have more than a single site of abnormal uptake (Fig. 20).

At the meeting, 29 presentations used ^{18}F-FDG to assess viability. This category of investigation is increasingly being called image-guided treatment planning. Stankewicz et al. from Emory University School of Medicine (Atlanta, GA) and Emory–Crawford Long School of Medicine (Atlanta, GA) reported on myocardial viability assessment with PET as part of decision making in coronary artery bypass graft (CABG) surgery. They found that in those patients where the infarcted areas did not accumulate the tracer, there was no viability. The patients did not proceed to CABG, and Figure 21 shows that the cumulative survival in this group was significantly lower than that in patients who proceeded to CABG on the basis of viable myocardial tissue in infarcted areas as shown by accumulation of ^{18}F-FDG.

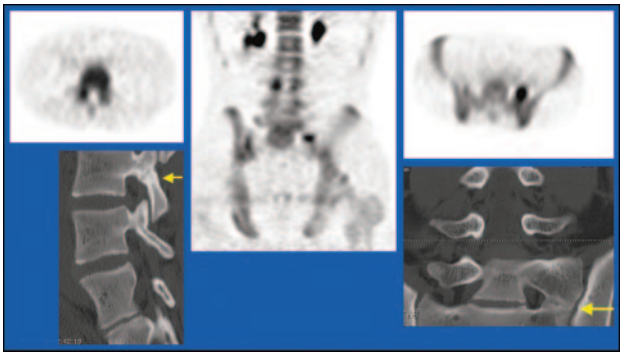

FIGURE 19. ^{18}F-fluoride bone imaging was used in this study of injuries in young athletes. Tracer accumulation in this 16-year-old boy with back pain led to the identification of a pars interarticularis stress fracture and another in the transitional vertebra.

Sites of High Uptake	N
Pars / Pedicle	32 (34%)
Vertebral-Sacral articulation	7 (7%)
Vertebral Body	13 (14%)
Spinous Process	15 (16%)
Sacroiliac Joint	3 (3%)

FIGURE 20. Results from the ^{18}F-fluoride study of injuries in 94 young athletes. The researchers were able to localize the source of the pain in 52 (55%) patients, and 15 (16%) were found to have 2 or more sites of abnormal uptake

Will one of the following tracers ever equal ^{18}F-FDG: ^{18}F-FLT, ^{18}F-fluoroacetate, ^{18}F-ethyltyrosine, ^{11}C-methionine, ^{11}C-choline, or ^{11}C-acetate? Hsueh et al. from the University of California at Los Angeles (UCLA) School of Medicine compared the merits of ^{18}F-FDG and ^{18}F-FLT as early predictors of response and survival after tumor therapy in mice. The results indicated that early postchemotherapy change in ^{18}F-FDG uptake was a better prognostic indicator of long-term survival than ^{18}F-FLT (Fig. 22).

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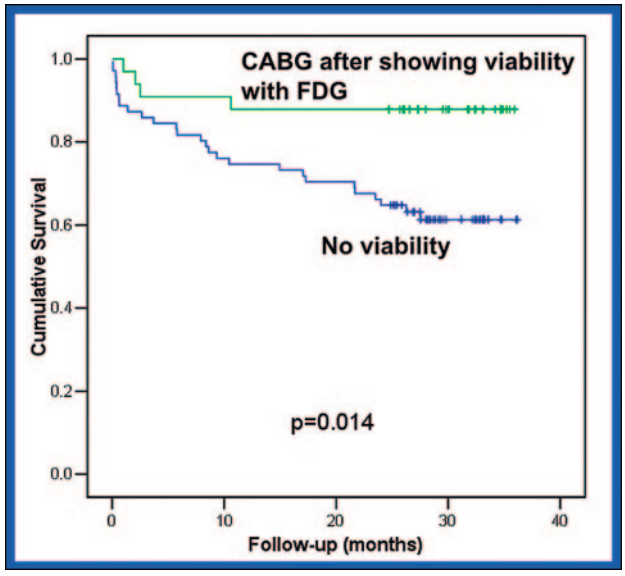

FIGURE 21. Follow-up results in patients in whom cardiac viability was assessed with ^{18}F-FDG. Patients with viability progressed to coronary artery bypass graft and showed improved survival (top line). Those whose imaging showed no viability did not progress to surgery (lower line).

Measure	Survivors	Non-Survivors
Δ FDG	- 15.3% ± 9.4%	+ 19.3% ± 14.8%
Δ FLT	+ 0.2% ± 5.6%	- 8.0% ± 5.8%
Δ Tumor Size	+ 7.6% ± 21%	+ 69.1% ± 49.2%

FIGURE 22. ^{18}F-FDG and ^{18}F-FLT were compared in mice as early predictors of tumor response and survival after chemotherapy. These results indicate that ^{18}F-FDG uptake was a better predictor of long-term survival.

(Continued from page 26N)

^{18}F-FDG imaging is going beyond oncology to imaging of infection and inflammation. Table 3 shows the steady growth of interest in this subject since 2000. Bleeker-Rovers et al. from Radboud University Nijmegen Medical Center (The Netherlands) reported on the promising role of ^{18}F-FDG PET in detecting secondary sites of infectious disease. They performed 44 scans in 39 patients, in whom an average of 4 previous diagnostic procedures had been performed to look for metastatic infection before referral for PET. Additional infectious lesions were diagnosed in 75% of the patients. ^{18}F-FDG PET diagnosed a clinically relevant new focus in 45%, a clinically irrelevant focus in 3%, and confirmed already diagnosed abnormalities in 30% of patients. The positive predictive value of PET in this series was 91%, and the negative predictive value was 100%.

Nishiyama et al. from Kagawa University (Japan) compared ^{18}F-FDG and ^{67}Ga scintigraphy in the evaluation of patients with sarcoidosis. PET was better than scintigraphy in terms of both sensitivity and specificity in identifying pulmonary and extrapulmonary lesion sites. Figure 23 shows the comparative imaging results in a 63-year-old woman with pulmonary and extrapulmonary sarcoidosis.

Richter et al. from the Charite–Universitätsmedizin Berlin (Germany) outlined indications for ^{18}F-FDG PET imaging in fever of unknown origin associated with autoimmune diseases. In autoimmune vasculitis (Fig. 24), increased glucose metabolism was noted in the vessels of the thoracic and abdominal aorta and the carotid, subclavian, and axillary arteries. In autoimmune myositis, diffusely increased glucose metabolism was noted in the skeletal musculature of the neck, shoulders, back, pelvis, and arms (Fig. 25).

TABLE 3
Imaging of Infection

Year	Number of presentations	Number using ^{18}F-FDG
2000	44	14
2001	54	16
2002	63	23
2003	59	23
2004	36	21
2005	52	27

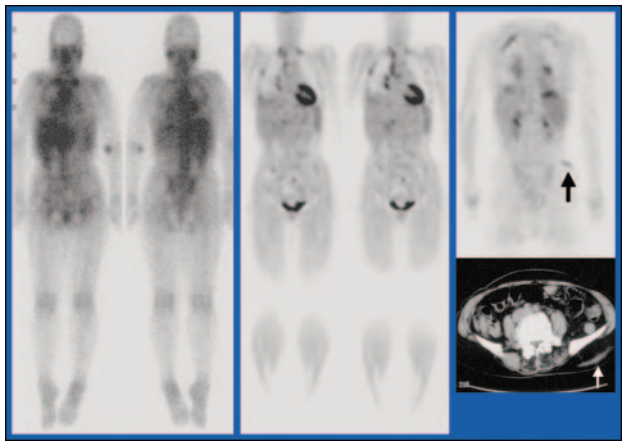

FIGURE 23. Comparison of ^{67}Ga scintigraphy (left) and ^{18}F-FDG PET (middle) in the evaluation of sarcoidosis in a 63-year-old woman. PET was better than scintigraphy in terms of both sensitivity and specificity in identifying pulmonary and extrapulmonary lesion sites.

Elucidating Relationships Between Brain Chemistry and Behavior

William James, in his classic book, *Principles of Psychology* (1890), wrote, "We need to know a little better what are the molecular changes in the brain on which thought depends." Nuclear medicine continues to enhance and expand the range of what medicine knows

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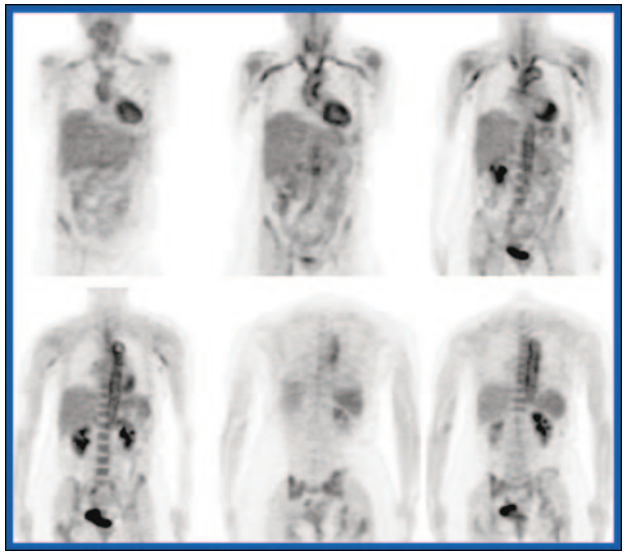

FIGURE 24. ^{18}F-FDG PET imaging was used to investigate fevers of unknown origin associated with autoimmune diseases. In autoimmune vasculitis, increased glucose metabolism was noted in the vessels of the thoracic and abdominal aorta and the carotid, subclavian, and axillary arteries.

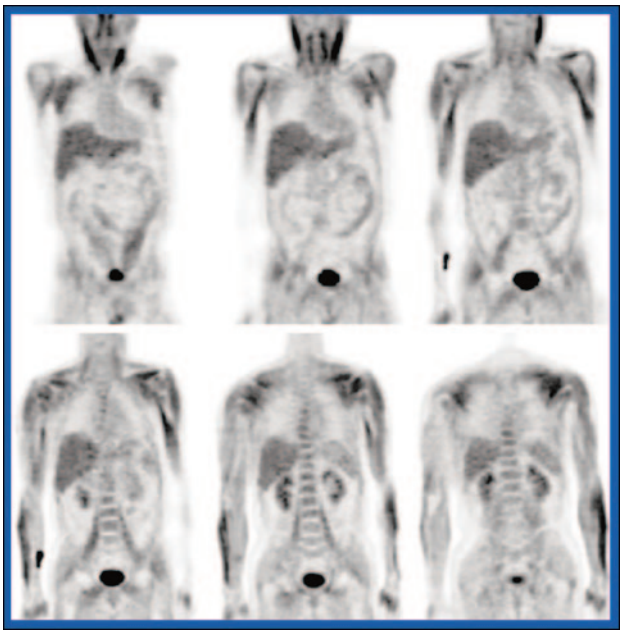

FIGURE 25. ^{18}F-FDG PET imaging was used to investigate fevers of unknown origin associated with autoimmune diseases. In autoimmune myositis, diffusely increased glucose metabolism was noted in the skeletal musculature of the neck, shoulders, back, pelvis, and arms.

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about the brain. Alhamrawy et al. from the Johns Hopkins University School of Medicine reported on the relationship of brain chemistry to behavior in a presentation on mu-opioid receptor binding of the tracer ^{11}C-carfentanil in patients with bulimia nervosa before and after cognitive behavioral therapy. The images in Figure 26 show that binging and vomiting, the urge to binge, the urge to vomit, and preoccupation with body image correlated with decreased mu-opioid receptors in the prefrontal, cingulate, and insular cortices in these patients.

Behl et al. from the University of Toronto (Canada) and the Sunnybrook and Women's Health Sciences Centre (Toronto, Canada) asked whether cholinergic therapy improves regional brain perfusion in moderate-stage Alzheimer's disease (AD). They found that with treatment regional blood flow improved in the dorsolateral prefrontal lobes, which are associated with mediating executive functions. Other regions of the brain, however, showed no improvement in blood flow after anticholinergic treatment.

As more and more studies are performed with patients experiencing severe dementing disorders, more attention is being paid to identifying precise relationships between behavioral changes and blood flow and other physiologic changes. Jeong et al. from the Dong-A University School of Medicine (Busan, Korea) used ^{99m}Tc SPECT to elucidate characteristic patterns of cerebral perfusion in patients with early-stage subcortical vascular dementia and compared these patterns with those observed in patients with AD. Previously, identifying the presence of patients with subcortical vascular dementia in clinical trials of treatment of AD has posed methodologic and interpretation challenges. Figure 27 shows statistical parametric maps generated from imaging data in the 2 groups in this study. It is safe to say that nuclear medicine is able to make a tremendous contribution to patient selection using these techniques in clinical trials.

Forty-eight presentations at the meeting used stastistical parametric mapping as a visual and quantitative tool.

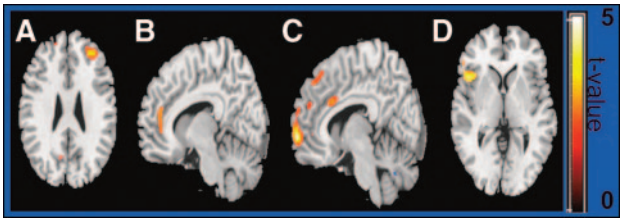

FIGURE 26. The relationship of brain chemistry to behavior was investigated with ^{11}C-carfentanil imaging of mu-opioid receptor binding in patients with bulimia nervosa before and after cognitive behavioral therapy. Binging and vomiting behavior (A), the urge to binge (B), the urge to vomit (C), and preoccupation with body image (D) correlated with decreased mu-opioid receptors in the prefrontal, cingulate, and insular cortices in these patients.

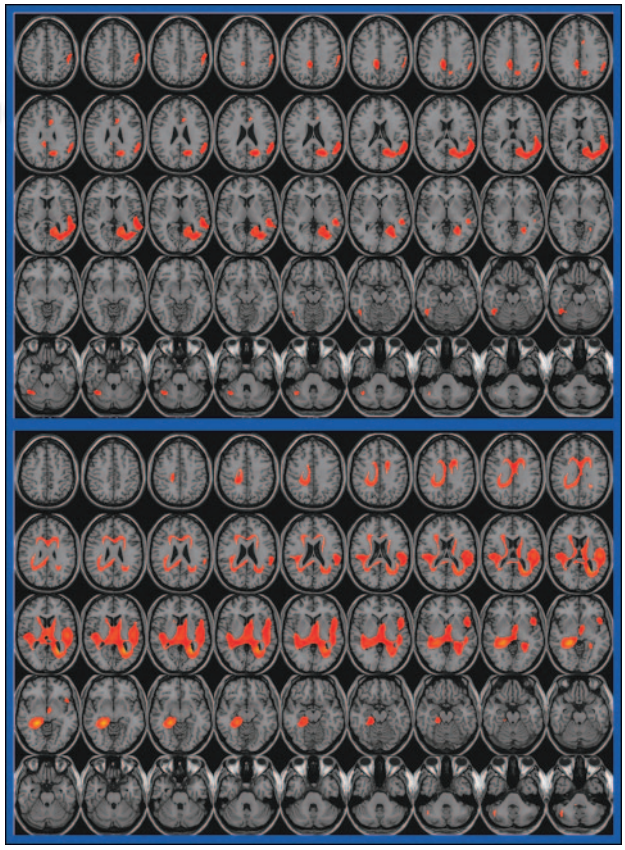

FIGURE 27. ^{99m}Tc-HMPAO SPECT elucidated characteristic patterns of cerebral perfusion in patients with Alzheimer's disease (top) and with early-stage subcortical vascular dementia (bottom) using statistical parametric maps. Such techniques promise to provide valuable information in directing patients with dementias to appropriate treatments.

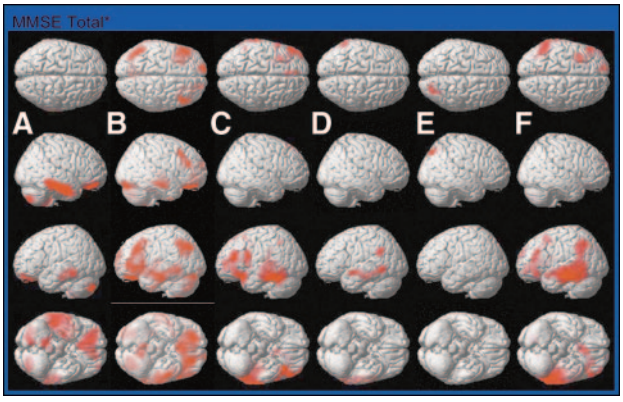

FIGURE 28. ^{18}F-FDG PET imaging revealed deficiencies in deoxyglucose in patients with Alzheimer's disease, varying by regions that correlated to symptomatic states associated with scores on the Mini-Mental State Examination, illustrating the connection between brain behavioral dysfunctions and regional glucose hypometabolism. Visible regional differences were associated with difficulties in orientation in time (A) or location (B) and with abnormalities in attention and calculation (C), writing (D), or in copying and drawing (E). Total uptake is depicted in (F).

Mishina et al. from the Nippon Medical School Chiba–Hokusoh Hospital (Japan), Tokyo Metropolitan Institute of Gerontology (Japan), the Nippon Medical School (Tokyo, Japan), and the Jikei University School of Medicine (Tokyo, Japan) reported on the correlation between brain behavioral dysfunctions and regional glucose hypometabolism in patients with AD. Patients underwent evaluation with the Mini-Mental State Examination to characterize their symptoms as associated with difficulties in orientation in time or location and with abormalities in attention and calculation, writing, or in copying and drawing. Figure 28 shows that the ^{18}F-FDG PET imaging revealed deficiencies in deoxyglucose in different regions of the brain for each of these symptomatic states, again illustrating one of the ways in which nuclear medicine is exploring more deeply the relationship between brain chemistry and behavior.

Henze et al. from the University of Heidelberg explored the neural correlates of cognitive defects in 43 AD patients by combining ^{18}F-FDG PET imaging with performance on a battery of neuropsychological tests. They found distinct and abnormal patterns of neural deactivation in those cortical areas associated with verbal fluency and naming in patients who showed verbal and naming difficulties on the tests (Fig. 29).

Mild cognitive impairment (MCI) was a topic of great interest at this meeting. It is defined as abnormal memory function with essentially preserved general cognition. Patients with MCI carry a high risk for developing AD, and coexisting neuropsychiatric symptoms are frequent. A number of researchers are asking whether MCI is related to the serotonin system and whether serotonergic deficiencies correspond to areas affected in early AD, including the mesial temporal lobe and the limbic/paralymbic structures. Drzezga et al. from the Technische Universitat (Munich, Germany) and Georgetown University Medical Center (Washington, DC) looked at the impairment of cerebral deactivation after activation in MCI and AD. Activation can be measured by increased accumulation of ^{18}F-FDG, and deactivation is a measurement of how long it takes for that increased metabolism to decrease. This study used ^{15}O-water PET, because the radionuclide's 2.5-minute half-life makes it much easier to perform repeat studies. Study participants were imaged while performing an active navigation task in a 3D virtual environment. Figure 30 shows the difference between the activation and deactivation regions, with significantly different patterns of cerebral deactivation in healthy volunteers and individuals with MCI and AD. A highly significant bilateral deactivation of task-irrelevant auditory regions was noted in healthy subjects. This effect was diminished in individuals with MCI and entirely absent in individuals with AD. In other words, even when performing an activity that did not require hearing, individuals with MCI and AD kept these auditory areas active.

Hasselbalch et al. from the Rigshospitalet (Copenhagen, Denmark) and the Hvidovre Hospital (Copenhagen,

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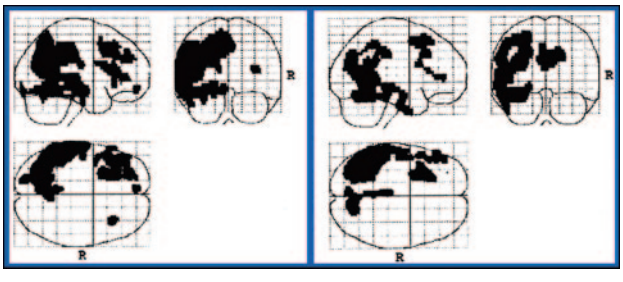

FIGURE 29. The neural correlates of cognitive defects in 43 Alzheimer's disease patients were explored by combining ^{18}F-FDG PET imaging with performance on a battery of neuropsychological tests. Distinct and abnormal patterns of neural deactivation were identified in those cortical areas associated with verbal fluency (left) and naming (right) in the same patients who showed verbal and naming difficulties on the tests.

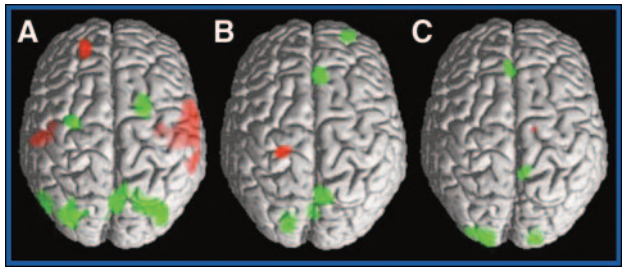

FIGURE 30. ^{15}O-water PET was used to assess impairment of cerebral deactivation after activation in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD). Study participants were imaged while performing an active navigation task with visual cues in a 3D virtual environment. These images show activation (green) and deactivation (red) regions, with significantly different patterns of cerebral deactivation in healthy volunteers (A) and individuals with MCI (B) and AD (C).

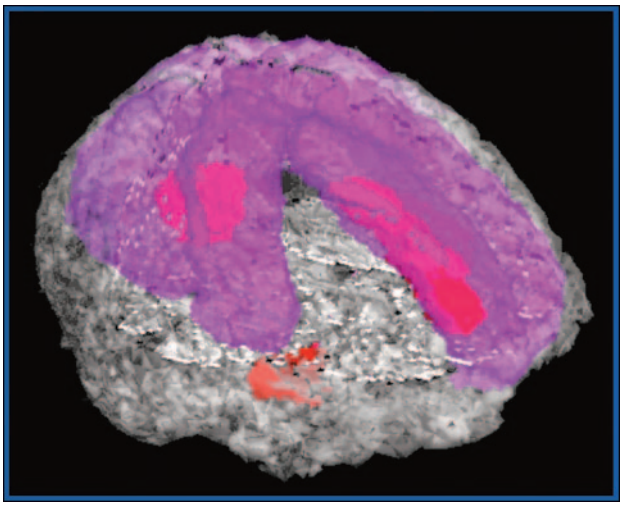

FIGURE 31. ^{18}F-altanserin PET was used to study serotonin receptor changes in individuals with mild cognitive impairment (MCI). When compared with healthy individuals, 5-HT2A binding potential was globally reduced by 20%–30% in the pink (right entorhinal, left insula, left anterior cingulate, and bilateral posterior cingulate) and blue (bilateral superior frontal and parietal, left superior temporal, and bilateral primary sensory-motor) areas in patients with MCI. This finding is consonant with previous studies that have shown more widespread reduction in 5-HT2A receptors in cortical areas in patients with Alzheimer's disease.

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Denmark) used ^{18}F-altanserin PET to study serotonin receptor changes in individuals with MCI and in controls. They found that 5-HT2A binding potential was globally reduced by 20%–30% in the pink and blue areas shown in Figure 31. This finding is in line with previous studies that have shown more widespread reduction in 5-HT2A receptor in cortical areas in patients with AD.

A very interesting behavioral study was outlined by Ichise et al. from the National Institutes of Health (NIH), who used ^{11}C-DASB PET in assessing the effects on brain serotonin transporters of early separation from the mother by comparing peer-and mother-reared rhesus monkeys. Peer-raised monkeys (those with no mother present from shortly after birth) showed lower cerebral spinal fluid 5-HIAA (a metabolite of serontonin) and were more aggressive, impaired in impulse control, withdrawn socially, and impaired in response to acute stress than the mother-reared monkeys. They concluded that decreased central serotonin transporter binding in the peer-raised group supports the hypothesis that maternal deprivation results in a dysfunction of the central serotonin system.

At this meeting, 55 presentations involved the thyroid. A presentation by Schreckenberger et al. from the Johannes Gutenberg University (Mainz, Germany) took a clever approach and used PET to study the relationship between brain metabolism and behavioral abnormalities in patients with hyperthyroidism, many of whom demonstrate neurologic or psychiatric symptoms. They found, for example, an increased level of glucose metabolism in the posterior cingulate of hyperthyroid patients suffering from anxiety and depression (Fig. 32).

Assessing Dementia and Amyloid Plaque

Dementia is a major focus today in the country, at NIH, and, increasingly, at the annual SNM meeting. The Alzheimer's Disease Neuroimaging Initiative is a $60 million 5-year public/private initiative to study serial MR imaging, physical examinations, biological markers, and clinical assessments in measuring the progress of patients with early cognitive disorders. The study includes PET imaging. One aspect that currently confounds many clinical trials in AD is that studies indicate that when the diagnosis is probable senile dementia Alzheimer's type and patients are followed until they die, plaques are found in only 81% at autopsy, with a 70% specificity. When the clinical diagnosis during life was possible AD, there is a 93% sensitivity and a 48% specificity.

Considerable interest and excitement has been expressed about using nuclear medicine techniques to detect Aβ plaques. Fifteen presentations focused on these techniques and their potential for permitting accurate diagnosis of early AD, clarifying whether plaques cause cognitive decline, monitoring the effectiveness of plaque prevention or therapy, and screening at-risk individuals before they develop permanent cognitive impairment. At the present time, 1,300,000 patients are being treated for memory loss in the United States each year. Sixty-five drugs for AD are in the clinical pipeline (23 in phase 1, 31 in phase 2, and 11 in phase 3), and 26 of these target amyloid plaques.

One of the agents being developed to image amyloid plaques is called Pittsburgh Compound B or PIB. Price et al. from the University of Pittsburgh (PA) reported on ^{11}C-PIB PET imaging in AD and MCI. They found increased retention of the novel tracer, with significantly higher binding in the AD group than in control subjects (Fig. 33). Values for the MCI group were intermediate

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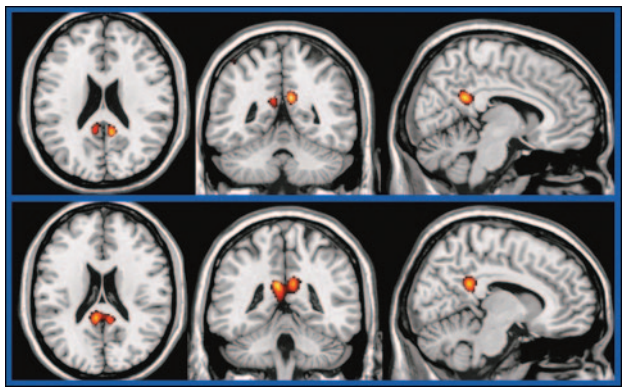

FIGURE 32. PET was used to study the relationship between brain metabolism and behavioral abnormalities in patients with hyperthyroidism. Images revealed increased levels of glucose metabolism in the posterior cingulate of hyperthyroid patients suffering from anxiety (top row) and depression (bottom row).

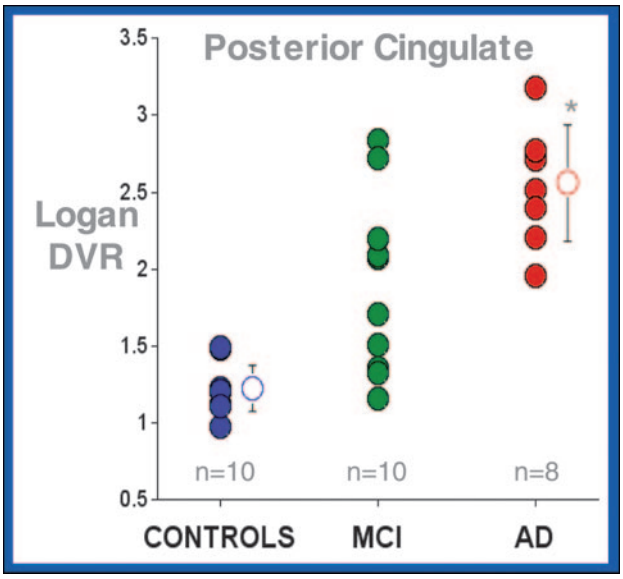

FIGURE 33. Plotted results from ^{11}C-PIB PET imaging in controls (left column), patients with mild cognitive impairment (MCI; middle column), and patients with Alzheimer's disease (AD; right column). Values for the MCI group were intermediate between those in controls and the AD group.

(Continued from page 34N)

between controls and the AD group. In another study from the University of Pittsburgh group, Ziolko et al. looked at the correlation between quantitative ^{18}F-FDG and ^{11}C-PIB studies in AD and MCI. They reported that the PIB studies were 100% specific and sensitive for AD. The technique was able to stratify MCI subjects by ROC curve analysis as AD-like, control-like, or intermediate.

Another study with ^{11}C-PIB PET was presented by Villemagne et al. from Austin Hospital (Melbourne, Australia), the University of Pittsburgh, and the University of Melbourne (Australia). They compared imaging results in aged controls, individuals with dementia with Lewy bodies, and individuals with AD. Figure 34 shows a striking

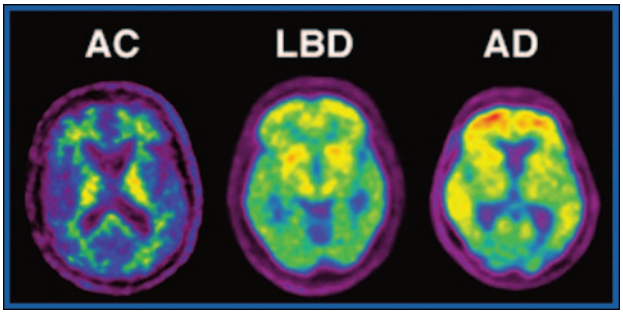

FIGURE 34. Results from ^{11}C-PIB PET imaging in aged controls (left), individuals with dementia with Lewy bodies (middle), and individuals with Alzheimer's disease (AD; right) were compared and showed striking differences in tracer accumulation. ^{11}C-PIB demonstrated an increase in cortical binding in dementias associated with Aβ deposition when compared with results in aged controls. The occipital cortex appeared to be relatively spared in AD but not in dementia with Lewy bodies.

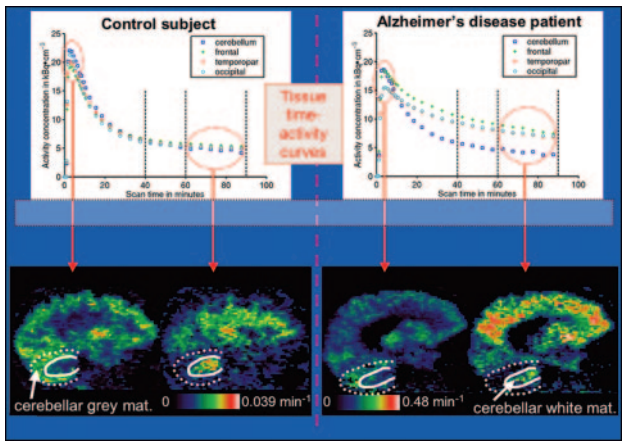

FIGURE 35. Plotted results and images from a novel method for analysis of ^{11}C-PIB imaging in patients with Alzheimer's disease (right) and healthy volunteers (left). The use of spectral analysis with arterial plasma input functions produced parametric images (bottom), in which the highlighted areas show the accumulation of tracer in plaques.

difference in the accumulation of tracer in plaques in the 3 groups. The authors concluded that the ^{11}C-PIB demonstrated an increase in cortical binding in dementias associated with cortical Aβ amyloid deposition compared with images in aged controls. The occipital cortex appeared to be relatively spared in AD but not in dementia with Lewy bodies. This is consistent with ^{18}F-FDG PET results and the clinical evidence of occipital dysfunction unique to diffuse Lewy bodies

Hinz et al. from Hammersmith Imanet, Ltd., Uppsala Imanet AB (Sweden), and MC Clinical Sciences Centre (London, UK) described a method for the analysis of ^{11}C-PIB images in patients with AD and in controls, emphasizing the importance for precise quantification. The use of spectral analysis with arterial plasma input functions produced parametric images, such as those in Figure 35, where the highlighted areas show the accumulation of the tracer in plaques.

Other groups are at work developing different agents for imaging and quantifying amyloid plaques. Oya et al. from the University of Pennsylvania (Philadelphia) studied ^{18}F-MAPO PET. Figure 36 shows a high accumulation in plaques with a very low background in initial

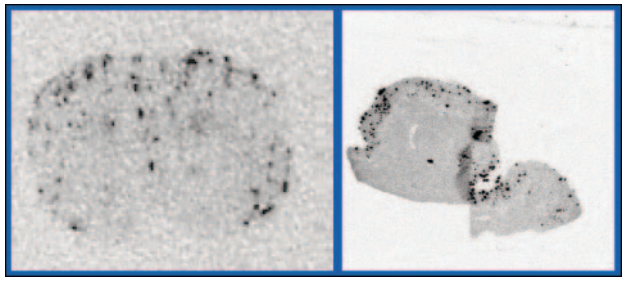

FIGURE 36. ^{18}F-MAPO PET shows a high accumulation in Aβ plaques with very low background in initial ex vivo (left) and in vitro (right) studies in mice.

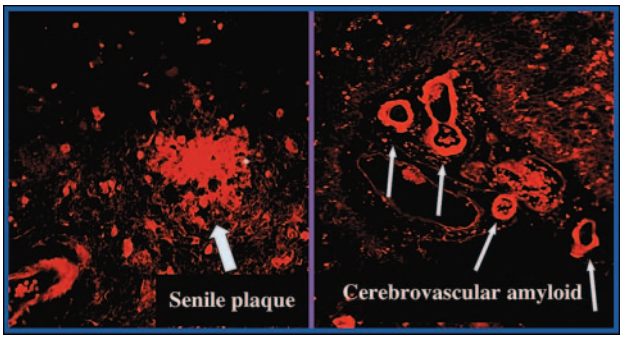

FIGURE 37. Novel flavones were evaluated as potential amyloid imaging agents. These images show fluorescent staining (left, ×40, G filter; right ×20, G filter) of a flavone compound in brain sections from individuals who had Alzheimer's disease.

studies in mice. Another tracer under investigation is radioiodinated quinilone, as reported by Kulkarni et al. from the University of Texas (Dallas, Texas). This group showed that radioiodinated clioquinol and oxine have favorable brain uptake and fast clearance from blood and normal brain tissue and bind selectively to amyloid deposits.

Ono et al. from Nagasaki University (Japan) and Osaka City University Medical School (Japan) evaluated novel flavones as potential amyloid imaging agents. These have the advantage of being fluorescent, which permits the extension to fluorescent imaging in small animals and in human AD tissue analysis (Fig. 37).

Imaging Neurotransmitters

Beginning in 1982, the SNM annual meeting saw an essentially linear growth in the number of presentations and posters on neurotransmission. This growth, however, leveled off in about 1996 (Fig. 38). In 2005, 30 presentations in this category looked at dopamine, 14 at serotonin, and 6 at norepinephrine. I believe this leveling off may be the result of the number of other disciplines that

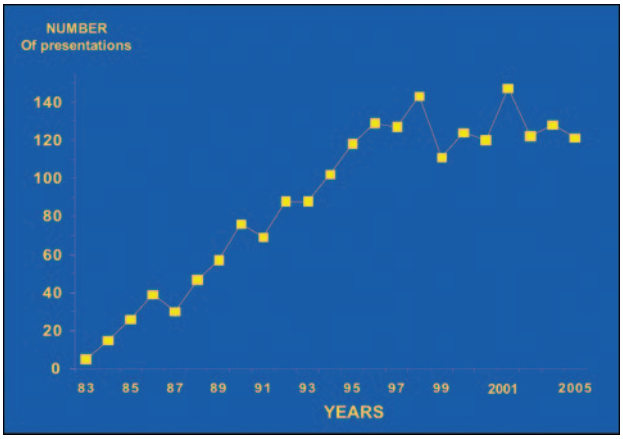

FIGURE 38. Number of presentations focusing on neurotransmission at the SNM annual meeting, 1983–2005. After strong growth, these numbers leveled off in about 1996.

Compound	Selectivity for DAT	Waiting time (hours)	BP2 (target/background)-1	Test – retest %variability
^{123}I-â-CIT	NS	24	4-5	12
^{123}I- FP-CIT (DaTSCAN)	NS	3-6	2.5	7
^{123}I-PE21	S	2	5.6	5*
^{99m}Tc-TRODAT	NS	3	2	10**

* manuscript in preparation
** PD

FIGURE 39. Characteristics of the 4 radiotracers now available for imagine of the dopamine transporter in Parkinson's disease.

have taken an interest in nuclear medicine techniques, and, as a result, some papers that might previously have been presented at the SNM now find their way to other venues, such as the Society for Neuroscience. Conversely, the leveling off in the numbers of presentations on neurotransmission may be related to the fact that research funding has not kept pace with innovations. It is important to look at these patterns, so that we can direct attention and effort to recruit individuals to maintain the high standards and good representation that the SNM introduced as a pioneering forum for these types of studies.

Four different tracers are available now for imaging the dopamine transporter in Parkinson's disease (PD) (Fig. 39). Thomsen et al. from the Copenhagen University Hospital (Denmark) described the use of ^{123}I-PE21 SPECT as a diagnostic tool in clinically uncertain parkinsonian syndromes. Figure 40 shows the striking results in patients found to have PD and in healthy individuals.

Santiago-Ribeiro et al. from the Service Hospitalier Frédéric Joliot (Orsay, France), the Hôpital de la Salpêtrière (Paris, France), and the Faculté de Médicine Paris (France) used ^{18}F-fluoro-L-DOPA and ^{11}C-PE21 imaging

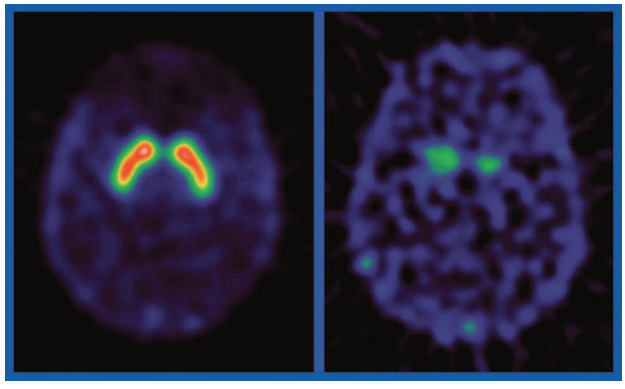

FIGURE 40. ^{123}I-PE21 SPECT has promise as a diagnostic tool in clinically uncertain parkinsonian syndromes. Striking results are seen when this technique is applied in healthy individuals (left) and those who have Parkinson's disease.

to look at striatal dopaminergic metabolism and dopamine transporter density in young-onset PD patients. They showed that both dopamine synthesis and dopamine transport were significantly decreased in these patients compared with control subjects. This indicates that the presynaptic neuron is deficient in the synthesis of dopamine and in its removal from the synapse.

Dual-Isotope Imaging

Will we see more dual-tracer PET investigations? Verhaeghe et al. from Ghent University (Belgium) reported on simultaneous dual-tracer ammonia and ^{18}F-FDG PET cardiac imaging. The question arises: Will we see more dual-tracers, not only in cardiology but in other parts of the body and in oncology? Figure 41, for example, is an image from Hamamatsu, with the differences between ^{18}F-FDG, ^{11}C-methionine, and ^{11}C-choline in a patient with brain tumors. The ^{18}F-FDG imaging resulted in a broad accumulation of tracer in normal brain as well as the lesion, whereas the accumulation of the methionine was more specific, as was the accumulation of choline.

Prostate Cancer

Mohsen et al. from the Policlinico S. Orsola–Malpighi (Bologna, Italy), reported on the role of ^{11}C-choline PET/CT imaging in early detection of clinically localized prostate cancer, where we know ^{18}F-FDG has not been particularly useful (most of the tumors of the prostate are not sufficiently malignant to accumulate FDG). Figure 42 shows the results of this study in 31 patients.

This year's SNM meeting had 39 presentations on prostate cancer. Husarik et al. from the University Hospital of Zurich (Switzerland), the Hospital of Uster (Switzerland), and the University Hospital of Geneva (Switzerland) looked at ^{18}F-fluorocholine PET/CT for staging and restaging prostate cancer. Figure 43 shows that technetium bone scans and SPECT/CT imaging in a patient after treatment for prostate cancer could not demonstrate the osseous metastases that were seen clearly with the ^{18}F-fluorocholine PET/CT.

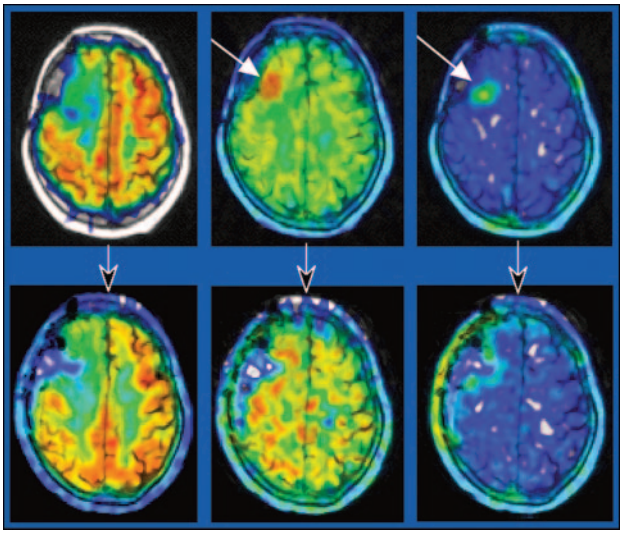

FIGURE 41. Image results differ with varying radiotracers (left, ^{18}F-FDG; middle, ^{11}C-methionine; right, ^{11}C-choline) in a patient with brain tumors before (top row) and after (bottom row) radiation therapy. The ^{18}F-FDG results in a broad accumulation of tracer in normal brain as well as the lesion, whereas the accumulations of methionine and choline are more specific.

	Sensitivity	Specificity	Accuracy	PPV	NPV
TBR>1.5 (tumor/ brain ratio	64%	82%	70%	87%	54%
SUVmax >3	65%	67%	66%	80%	50%

FIGURE 42. ^{11}C-choline PET/CT imaging was useful in early detection of clinically localized prostate cancer. These results indicate the accuracy of PET/CT as compared with histology findings after surgery. PPV = positive predictive value. NPV = negative predictive value.

Richter et al. from the University of Navarra (Pamplona, Spain) compared ^{18}F-FDG and ^{11}C-choline in PET in the early diagnosis of prostate cancer. ^{11}C-choline PET was found to have a sensitivity of 65.6%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 35% (Fig. 44).

Pretargeting Strategies

Goldenberg et al. from the Garden State Cancer Center and the Center for Molecular Medicine and Immunology (Belleville, NJ) and colleagues in the U.S. and abroad have been very active in using what is called pretargeting to enhance the sensitivity, specificity, and broad applicability of tracers in oncology. This technique separates the targeting agent from the subsequently administered tracers for PET or SPECT. The targeting agent is usually a bispecific antibody that targets the antigen/receptor binding site and subsequently binds the tracer. The result is higher tumor-to-nontumor ratios, enhanced uptake, and the facilitation of earlier imaging. The 2005 Paul C. Aebersold Award for outstanding achievement in basic science applied to nuclear medicine was presented to Goldenberg on June 19 at the SNM meeting. Among the presentations in which Goldenberg and his colleagues participated was one by van Schaijk et al. from the Radboud University Nijmegen Medical Center (The Netherlands), who described the pretargeting of carcinoembryonic antigen (CEA)-expressing tumors with biologically produced bispecific anti-CEA and anti-DTPA. The anti-CEA binds to the CEA antigen on the tumors and carries another antibody (the anti-DTPA), which binds the chelate and radionuclide. The subsequent administration of ^{111}In permits imaging with tracers containing this antigen.

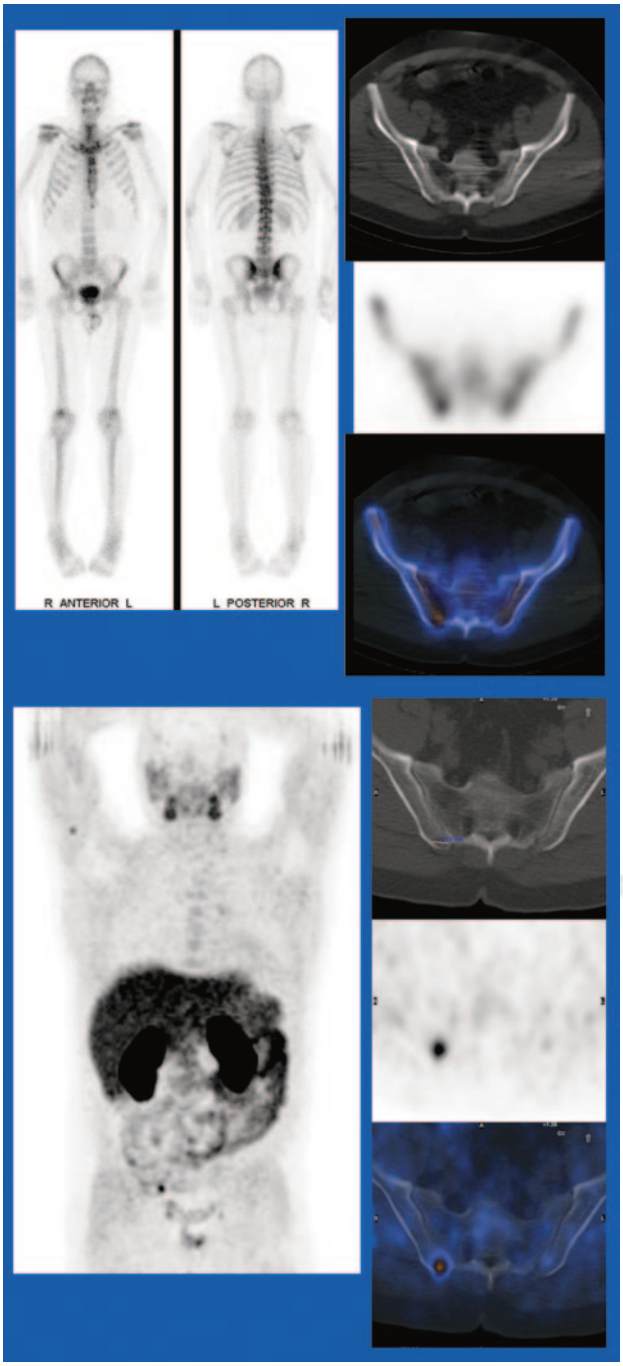

FIGURE 43. ^{18}F-fluorocholine PET/CT is promising in staging and restaging prostate cancer. Technetium bone scans and SPECT/CT imaging (above) in this patient after treatment for prostate cancer could not demonstrate the osseous metastases that were seen clearly with ^{18}F-fluorocholine PET/CT (below).

		Recurrence	No recurrence	
PET	Positive	21	-	21
	Negative	11	6	17
		32	6	

Se= 65.6 % Sp= 100 % PPV= 100 % NPV= 35.3 %

FIGURE 44. The efficacies of ^{18}F-FDG and ^{11}C-choline were compared as PET tracers in the early diagnosis of prostate cancer. The results for ^{11}C-choline PET (shown here) were superior to those from PET. Se = sensitivity; SP = specificity; PPV = positive predictive value; and NPV = negative predictive value.

Moving New Tracers from Research to Clinical Applications

The U.S. Food and Drug Administration (FDA) is now an important and very helpful partner in advancing nuclear medicine. The challenge is to help to select from the pipeline of potentially useful tracers and find ways to move these more quickly and effectively into clinical practice and research. Suleiman et al. from the FDA (Rockville, MD) presented an update on Radioactive Drug Research Committee (RDRC) activities. They reported that in the year 2003, 84 RDRCs throughout the United States carried out 284 studies in 2,797 human subjects with more than 120 different compounds, some of which are listed in Figure 45. The pipeline of new tracers is enormous, and the key is to get some of them approved by the FDA. Ten years ago, the only New Drug Approval (NDA) for ^{18}F-FDG was for a hospital in Peoria, IL, which did not subsequently produce it. Today, all of the work that you see in the United States involving ^{18}F-FDG operates under the Practice of Medicine and Pharmacy laws (that is, through prescription by a physician), and more than 100 sites in this country manufacture the radiopharmaceutical. We must continue to work closely with the FDA on these and other matters pertaining to the practice of nuclear medicine.

Vallabhajosula et al. from the New York–Weill Cornell Medical Center and New York–Presbyterian Hospital (NY) provided a very interesting presentation and timeline on the process by which they secured the second NDA approval for ^{18}F-FDG and the only one that has been put into production. In 1997, stimulated by the SNM, the FDA Modernization

Imaging nuclides		Non-imaging nuclides
Positron (77.1%)	Gamma (4.5%)	Beta (18.4%)
C-11 (36.6%)	Tc-99m (2.5%)	H-3 (12.4%)
F-18 (19.0%)	I-123 (1.3%)	C-14 (4.0%)
O-15 (17.5%)		Fe-59 (0.7%)
N-13 (2.6%)		Ca-45 (0.3%)
Cu-60 (0.7%)	I-131 (0.3%)	Fe-55 (0.3%)
F-17 (0.5%)	Xe-133 (0.3%)	I-125 (0.3%)
Tc-94m (0.2%)	In-111 (0.2%)	Ca-47 (0.2%)
"Gold" < 1.0 %	"White" > 1.0 %	Zn-65 (0.2%)

FIGURE 45. In 2003 84 Radioactive Drug Research Committees throughout the United States carried out 284 studies in 2,797 human subjects with more than 120 different compounds, a selection of which are included here.

Act directed the FDA to establish good manufacturing practice (GMP) requirements specifically for PET drugs. In 1999, FDA published a draft of these PET GMP regulations. In 2002, the FDA prepared GMP regulatory guidelines that mandated the minimum standards needed for PET radiopharmaceutical production in university and commercial PET centers. In November 2003, an abbreviated NDA application for ^{18}F-FDG was submitted by Weill Cornell Medical Center. In March 2004, the abbreviated NDA was resubmitted as a full NDA, and 5 months later the FDA approved an NDA for FDG prepared at Cornell. This is a model for what we need to do with different tracers in order to expedite their movement into practice.

The U.S. Pharmacopeia (USP) continues to play a role in PET tracer approval. The following PET tracers were approved by the USP in 2004: ^{11}C-carbon monoxide, ^{11}C-flumazenil, ^{11}C-mespiperone, ^{11}C-methionine, ^{11}C-raclopride, ^{11}C-sodium acetate, ^{15}O-water, and ^{18}F-fluorodopa. USP approval permits their use under the Practice of Medicine and Pharmacy; that is, under state laws. They can be used clinically but have not been approved by the FDA for reimbursement. Only 4 PET tracers are approved by the FDA for clinical use and reimbursement: ^{18}F-FDG, ^{18}F-sodium fluoride, ^{13}N-ammonia, and ^{82}Rb-chloride.

Waterhouse et al. from Columbia University (New York, NY) and Johns Hopkins University presented the first safety study and brain imaging evaluation of ^{18}F-FPS, a radioligand that binds to sigma receptors. This is an area that presents new challenges in testing and approval. With radiotracers that affect the process of neurotransmission, we are closer to a biological effect than with the much smaller doses with which we are accustomed in nuclear medicine. Receptor-binding radioligands are often not true tracers but have a small pharmacologic effect. An example would be the tracer ^{11}C-carfentanil, which is used to examine opiate receptors and with which I underwent PET imaging in 1984. I did not mind at all being in the scanner for 45 minutes, which was an indication of the pharmacologic effect of the blocking drug carfentanil. The ^{18}F-FPS developed by Waterhouse et al. did not elicit any clinically relevant effects when administered in 11 participants in tracer quantities, that is, the quantity that was going to be used in the diagnostic study. The next toxicity test depends on the specific activity, which will determine the multiplier for the clinical dose that can be used in testing for toxicity.

Molecular medicine is now being widely used in drug design and development. It took at least 30 years to get to this point. In 1983, soon after the first imaging of neuroreceptors with dopamine and opiates in human beings, we and others carried out collaborative studies with scientists in pharmaceutical companies via contracts. Today, several worldwide pharmaceutical companies have their own extensive molecular imaging activities, including Merck, GlaxoSmithKline, and Pfizer. Merck alone has 5 PET scanners—almost half the number in all of Canada and more than in several other developed countries.

Following are my own proposed rules and regulations to increase radiopharmaceutical approvals:

- Toxicity testing should be at 1 dose that is 10–100 times the diagnostic dose for both the RDRC and FDA submissions.
- RDRC regulations should be the controlling agent in the case of normal body constituent tracers before submission to the FDA.
- RDRC patient results should be published on the Internet as open source material for all.
- Radiopharmaceuticals that are not normal body constituents should go to the FDA directly for new phase zero and phase 2 regulatory approval with 1-dose toxicity testing. With stable drugs, 3 doses are routinely used for toxicity testing, and no more than 1/3 of that number is needed for radiotracer testing.
- Commercial development of all new radiopharmaceuticals needs NDAs under FDA phase 2 and 3 regulations.
- All institutional GMPs should be standardized.
- All results in phase 2 and 3 studies should be reported on the Internet.

Risk Assessment

Studies are being performed earlier and earlier for risk assessment and early diagnosis. Quite a few years ago I said, "A normal person is one who has been inadequately tested." And after thinking about it and seeing the increasing involvement in nuclear medicine in the detailed detection of risk factors, I've come to believe more than ever that this is a true statement. Here are a few examples from the wider medical literature. Boon et al. published an article relating silent ischemia to hypertension and diabetes (*J Hypertens.* 2000;18:1355–1364). The prevalence of silent ischemia in patients with essential hypertension varied from 15%–57% percent in studies without standardized techniques. Two studies used ^{99m}Tc-MIBI SPECT to assess the prevalence of silent ischemia in patients with type 2 diabetes. One study (De Lorenzo et al.; *Am J Cardiol.* 2002;90:827–832) found that 26% of these patients had silent ischemia when evaluated with ^{99m}Tc-MIBI exercise SPECT, whereas in an adenosine stress SPECT study (Wackers et al.; *Diabetes Care.* 2004;27:1954–1961) this figure was 22%. At the SNM meeting, Cote et al. from the Hôpital Saint-François d'Assise (Quebec, Canada) and the Centre Hospitalier de l'Université Laval (Quebec, Canada) looked at stress testing with ^{99m}Tc-MIBI in 595 patients with essential hypertension. They found silent coronary artery disease was frequent in hypertensive patients who did (42.7%) and did not (27%) have diabetes. The prevalence and severity of silent reversible ischemia was significantly greater in patients with diabetes, and proteinuria and dyspnea were significant predictors of silent ischemia in essential hypertension and diabetes.

In another presentation focusing on risk factors, Schindler et al. from the David Geffen School of Medi-

cine at UCLA showed that obesity is associated with impairment of the coronary circulation. Abnormally increased body weight was found to be associated with an abnormal circulatory response to the cold pressor test. This impairment progressed from endothelium-related coronary vasomotion to impairment of the total vasodilator capacity in frankly obese individuals.

Radionuclide Therapy

Figure 46 shows the numbers of presentations on radionuclide therapy going back to 1996. Again, I think the relative plateauing may represent the interest of other societies, such as the American Society of Clinical Oncology, in providing forums for the presentation of novel results from nuclear medicine. Again, it is historically interesting to realize that radioiodine therapy began more than half a century ago with radioiodine treatment of adenocarcinoma of the thyroid. Today, the CD20 antigen has been used for diagnosis and in treatments for NSCLC and other disease states. In a recent Congressional committee hearing, National Cancer Institute director Andrew von Eschenbach, MD, talked about the success of an anti-CD20 radioimmunotherapeutic agent in lymphoma patients whose cells expressed CD20 (Fig. 47). These patients, previously considered incurable, achieved a 75% complete response rate.

Baum et al. from the Zentralklinik Bad Berka (Germany) reported at the meeting on clinical results of 346 administrations of a ^{90}Y and ^{177}Lu-DOTA-Tyr^3-octreotate peptide receptor agent in patients with metastatic progressive neuroendocrine tumore. Zwas et al. from Tel Aviv University described the use of Zevalin in conditioning patients for stem cell transplantation. The inclusion of Zevalin in conditioning regimens prior to stem-cell therapy was safe and improved outcomes in patients with refractory non-Hodgkin's lymphoma. The projected 1-year response was 67%, far better than the less than 20% expected response rate with standard transplantation in this high-risk patient group.

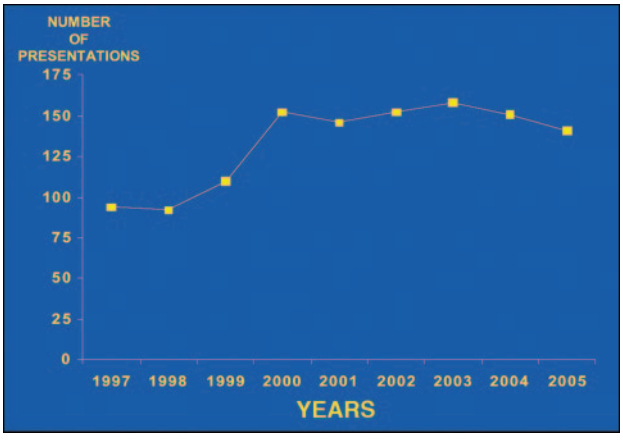

FIGURE 46. Numbers of presentations focusing on radionuclide therapy at the SNM annual meeting, 1997–2005.

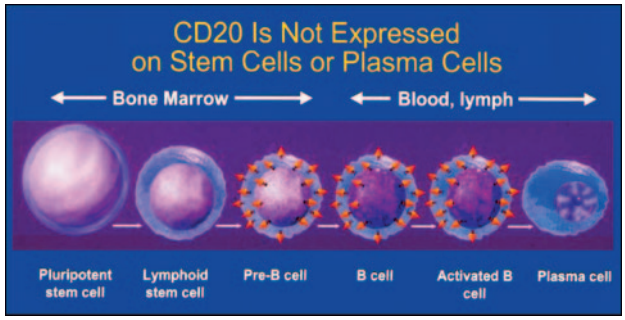

FIGURE 47. Anti-CD20 radioimmunotherapeutic agents are proving beneficial in lymphoma patients whose cells expressed CD20. Some patients previously considered incurable have achieved a 75% complete response rate. CD20 is not expressed on stem cells or plasma cells.

Improving Technology and Growing Competition

The demand for molecular medicine will continue to grow, and overseas competition will be a principal stimulus for growth. Korea, for example, has developed the 13-MeV proton KIRAMS-13 cyclotron, which is currently operating in Seoul and has been ordered by 6 other institutions in Korea. What is particularly interesting is that this unit costs $500,000 rather than the usual $2.5 million cost of cyclotrons. I am told by my Korean colleagues that the price will go up to $600,000, a result of the rising demand for this product. Competition fosters growth, a principle that Adam Smith described as "the invisible hand."

One stimulus for growth is that PET is moving rapidly into the broad international practice of medicine. For example, Zhang et al. from the PLA General Hospital (Beijing, China) and the Center Hospital of Jin Zhou (China) reported on a method for highly automated synthesis of ^{11}C-choline. The yield of ^{11}C-choline was 2,500 MBq at irradiation of 15 μA for 10 minutes and a total synthesis time of 8 minutes to go from ^{11}C-CH_3I to ^{11}C-choline.

Murakami et al. from the Medical and Pharmalogical Research Center (Ishikawa, Japan), Fujisawa Pharmaceutical Company, Ltd. (Ibaraki, Japan), and the University of Tokyo (Japan) presented additional evidence of the ways in which radiotracer production technology is improving. Their presentation focused on ultrarapid synthesis of ^{15}O-labeled deoxyglucose for repeated in vivo imaging. Figure 48 shows the timeline for this synthesis, which takes only a few minutes.

Sun et al. from the University of Fukui (Japan) described a method for the fully automated synthesis of sodium ^{18}F-fluoroacetate.

Endotoxin Testing

Endoxin testing continues to be improved through nuclear medicine investigations. Schwarz et al. from the Washington University School of Medicine and Wako

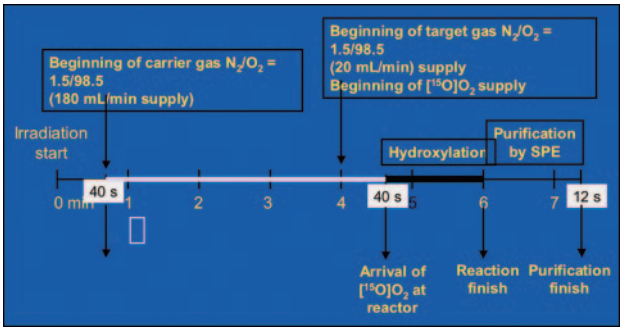

FIGURE 48. Timeline for ultrarapid synthesis of ^{15}O-labeled deoxyglucose for repeated in vivo imaging, a process that takes only a few minutes.

Chemicals USA, Inc. (St. Louis, MO) reported on the development and evaluation of a toximeter for bacterial endotoxin testing of PET radiopharmaceuticals. They described results with the Toxinometer ET-200, which can provide prerelease USP compliance for PET tracers, including ^{11}C-labeled radiopharmaceuticals (0.5 EU/mL), in approximately 10 minutes.

Another interesting presentation came from Jim Cooper (who in 1970 served as the first president of the SNMTS) et al. from the Massachusetts General Hospital (Boston, MA) and the University of Michigan (Ann Arbor). They described a new system for the rapid detection of endotoxin in PET radiopharmaceuticals. Their system, called PTS, is able to validate and release for patient use injectable PET drugs (^{11}C, ^{13}N, and ^{18}F) and ^{123}I-metaiodabenzylguanidine through a simple and robust 15-minute endotoxin quality control test. The validated test parameters were greater than 10 times more sensitive than the endotoxin limit.

Small Animal Imaging

Imaging small animals for innovative research is clearly an area of tremendous current interest, as shown in Figure 49, which indicates the growth in papers presented

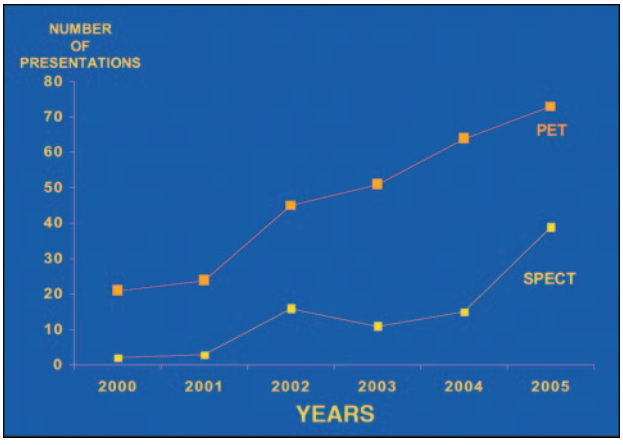

FIGURE 49. Numbers of presentations focusing on PET and SPECT small animal imaging at the SNM annual meeting, 2000–2005.

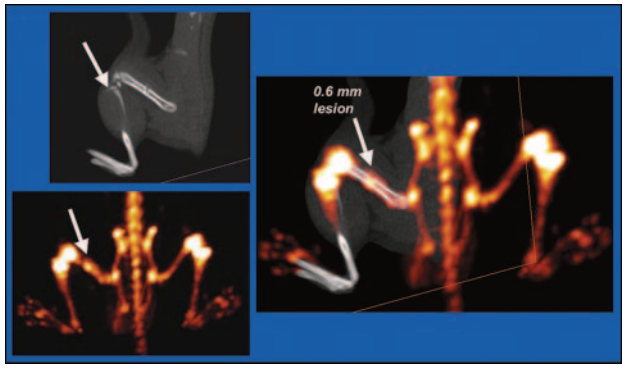

FIGURE 50. Images made with a compact, dedicated small animal microSPECT/CT system show the fused SPECT/CT image (right) of osteoblastic repair in a mouse model using ^{99m}Tc-HDP.

on this topic at the SNM meeting since 2000. Daibes Figueroa et al. from the University of Missouri-Coumbia and the U.S. Department of Veterans Affairs (Columbia, MO) reported on the performance of a compact, dedicated small animal microSPECT/CT system. Figure 50 shows the fused SPECT/CT image of osteoblastic repair in a mouse model using ^{99m}Tc-HDP. The 1-mm, pinhole, dual-head system provided exquisite resolution. Vastenhouw and Beekman from the University Medical Center Utrecht (The Netherlands) described another small animal SPECT system for submillimeter total-body imaging. Figure 51 shows the excellent resolution achieved by the U-SPECT-1 in the knees, ankles, and other joints in a mouse.

It seems easily predictable that the pharmaceutical industry will become increasingly interested in participating in research with SPECT in smaller animals and PET in larger animals and humans. Schramm et al. from the Research Center Juelich (Germany), Bioscan, Inc. (Washington, DC), and Scivis GmbH (Goettingen, Germany)

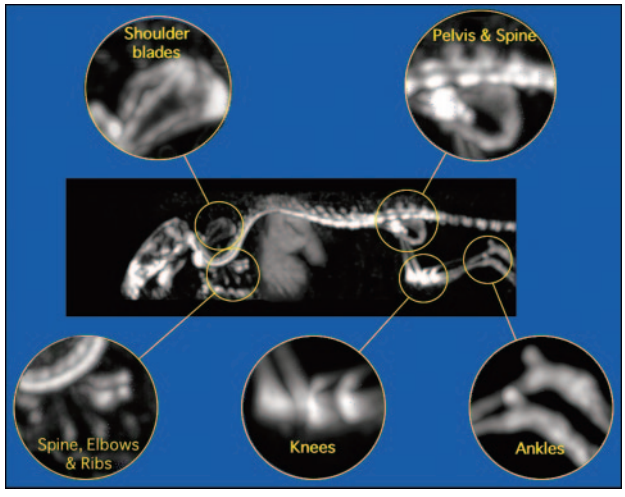

FIGURE 51. Submillimeter total-body imaging with this dedicated small animal SPECT system yielded excellent resolution in the knees, ankles, and other joints in a mouse model.

described a multipinhole SPECT imaging system for small animal research. Figure 52 shows the spatial resolution of a bone study, tumor study, and dual-isotope study in a mouse. Hoppin et al. from the Research Center Juelich and the University of Dusseldorf (Germany) used this high-sensitivity, high-resolution small animal scanner in clinical applications to look at small structures, such as the human hand. The images in Figure 53 were acquired with this apparatus in a 69-year-old male with osteoarthritis. Excellent spatial resolution was obtained when the hand was put in the 9-pinhole aperture of this instrument designed primarily for animal scanning.

Intraoperative Applications

Intraoperative nuclear medicine applications made up another area of interest at this meeting, with the numbers of presentations on this topic from 2000 to 2005 shown in Figure 54. I was interested that this curve did not really take off the way that some of the other curves have. We know from the literature that this is a promising area of research and practice, but do we need more education of surgeons? The technology is improving all the time and is highly accurate and useful. Eleven presentations focused on intraoperative procedures for thyroid tumors. Ugur et al. from Haceteppe University Medical Center (Ankara, Turkey) looked at in vivo characterization of parathyroid lesions using a gamma probe and compared this with ex vivo counts and frozen section results. Their results (Fig. 55) indicated that the success of gamma-probe guided parathyroidectomy depends on assessing optimal time between injecting the tracer and performing the surgical procedure.

Ishimori et al. from the Johns Hopkins University and West Virginia University (Morgantown, W. Va) looked at in vivo evaluation of a positron-sensitive beta probe for intraoperative use in a model of breast cancer. They found a good correlation between the results obtained by the probe and the results obtained when the tissue was removed and counted.

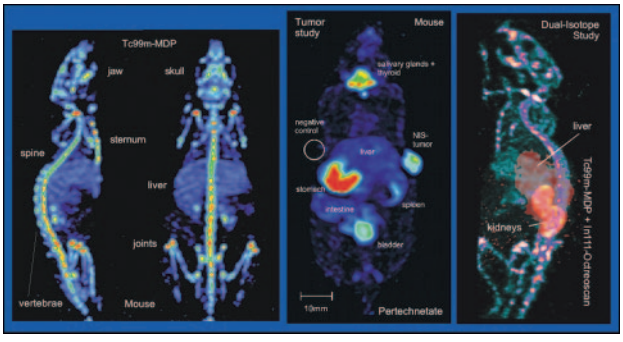

FIGURE 52. A multipinhole SPECT imaging system for small animal research yielded excellent spatial resolution in bone (left), tumor (middle), and dual-isotope (right) studies in a mouse.

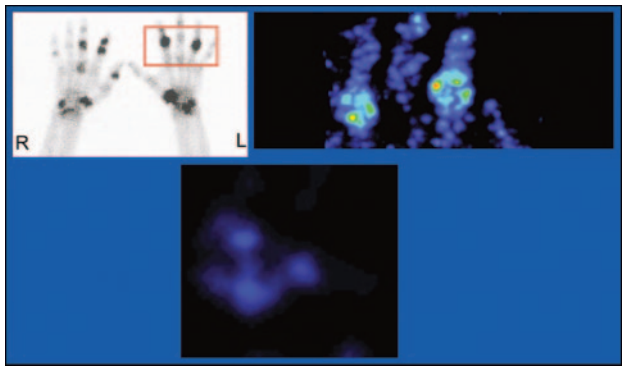

FIGURE 53. A high-sensitivity, high-resolution scanner developed for small animals was applied to clinical analysis of small structures, such as the human hand. These images were acquired in a 69-year-old male with osteoarthritis.

Looking Ahead

Positron-emitting tracers will continue to dominate, although SPECT tracers are playing an important and increasing role as well. Production of PET tracers, such as ^{11}C tracers, by hospital cyclotron centers will increase. This is debatable, because of the technical problems associated with the 20-minute half-life. But carbon defines organic chemistry and life, and these problems will be overcome. I believe that every large hospital will have its own cyclotron in 30 years.

Also in the future, hospitals will have integrated information systems including but not limited to imaging. Present imaging focus companies will continue to expand in order to offer full-service health systems. Vertical integration by these industries of the entire health care system will continue.

The economic value of nuclear medicine is being recognized and will continue to rise. As an example, in 2004, CTI Molecular Imaging reported sales of $402 million and a profit of $58 million. Siemens acquired the company for $1 billion in March of 2005. Also in 2004 GE acquired Amersham for $9.5 billion. Philips

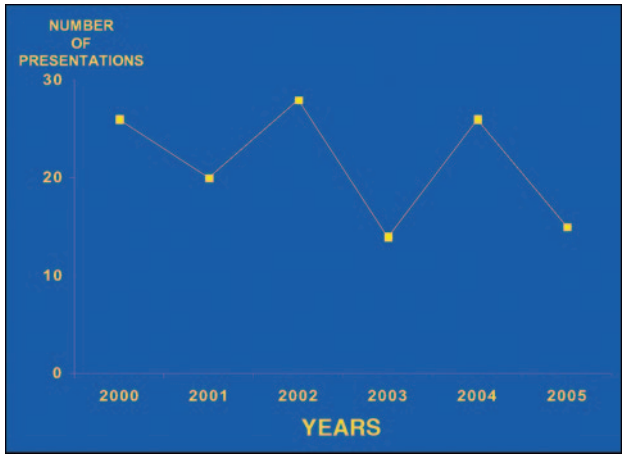

FIGURE 54. Numbers of presentations focusing on intraoperative nuclear medicine applications at the SNM annual meeting, 2000–2005.

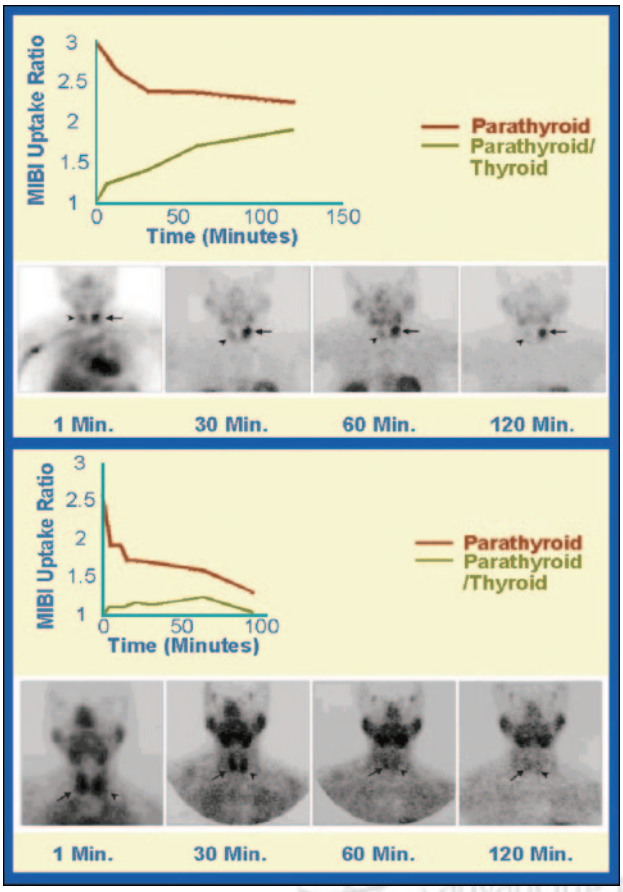

FIGURE 55. Results from a study assessing the efficacy of in vivo characterization of parathyroid lesions using a gamma probe. Results were compared with ex vivo counts and frozen section results and indicated that the success of gamma-probe guided parathyroidectomy depends on assessing optimal time between injecting the tracer and performing the surgical procedure.

Medical Systems' close working relationships with Berlax, Marconi Medical Systems, and ADAC continue. All are devoting resources to molecular medicine, including radiopharmaceutical development, approval, and bringing radiopharmaceuticals to market. One company that has been a major contributor to nuclear medicine has stated in an advertisement, "We've combined molecular technology and biomolecular manufacturing systems. Together we're creating revolutionary new ways to predict potential medical conditions before they even occur."

Many challenges remain. The cost of safety testing, approval, and regulation of new tracers must be lowered. The transit from bench to bedside must be shortened. We need to emphasize tracers of normal body constituents to simplify and expedite approval. Choline is one example that comes to mind immediately. We also need to simplify toxicity testing of tracer quantities of drugs. One example of such simplification would be 1-dose toxicity testing at 10–100 times the projected diagnostic dose.

I conclude by offering a few observational pearls to take home. SNM (which for a short while, until others join me, I alone will continue to call the Society of Molecular Medicine) continues to thrive and grow internationally, as evidenced by the fact that more than half of the papers presented here came from outside the United States. Image fusion across modalities, either with hybrid, single-gantry systems or software is key to our future. Multimodality imaging must be translated into better patient care. Nuclear medicine physicians must become experts in all aspects of PET/CT and SPECT/CT and report abnormalities on CT, even when these are not seen on PET or SPECT. Referring physicians still need more education. To succeed, molecular medicine must focus on coordination, interaction, communication, and integration with the entire health care system. Finally, we need to be conscious of territorial, self-interested colleagues while always remembering that the "invisible hand" described by Adam Smith indicates that competition is a good thing.