From Molecular Imaging To Molecular Medicine

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 29th in the series, was given June 7 in San Diego, CA.

Only a few years ago, I would arrive at the SNM meeting and prepare for this lecture with 4 carousels, each containing as many as 80 2 × 2-inch slides. Each time I added a new slide over the course of the meeting, I would have to manually move as many as 100 slides. Today, the entire highlights talk is now in a single presentation pen that can be inserted into any computer. I can rearrange the entire order in only seconds. This is impressive—and is also representative of the kinds of extraordinary changes that have come to nuclear medicine in only a short time, providing new opportunities for exploring disease and health on a molecular level and speeding novel discoveries from the laboratory to routine clinical use.

Trends

The numbers of presentations at the annual meetings, included in both oral and poster formats, continue to grow in an almost linear fashion, as they have for almost half a century (Fig. 1). This indicates continued growth, excitement, and progress within the society. This is unrelated to growth in the size of venues to accommodate presentations—a fact made obvious each year through the poster selection process. An unlimited number of posters can be presented, provided they pass the quality and educational standards of the reviewing committee. Each year more and more posters are included, evidence of the growing numbers of investigators performing significant work in nuclear medicine.

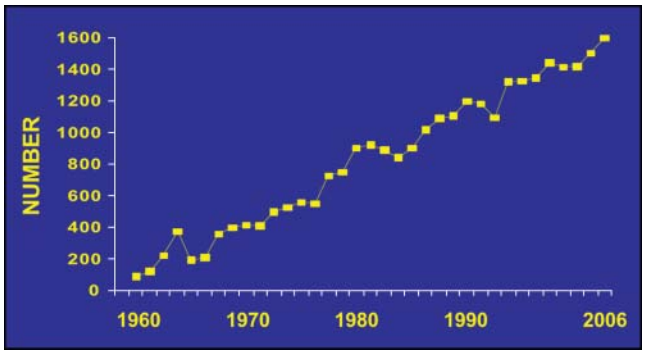

FIGURE 1. Total numbers of presentations at SNM annual meetings, 1960–2006.

Henry N. Wagner, Jr.

Distance is no longer a factor in communicating findings with colleagues in our specialty. At this meeting, persons from 42 countries presented oral papers or posters. As has been the case for the last 3 years, half the presentations came from outside the United States. However, as you can see in Table 1, this year also saw a significant increase in the number of presentations from the United States, from 702 to 822. You can see also the very large numbers of papers from Japan, Germany, and Korea. I'd like to ask for a round of applause to show our appreciation to those who travel

TABLE 1
SNM Meeting Abstracts 2004–2006

Country*	Number of presentations		
	2004	2005	2006
United States	732	702	822
Japan	153	132	165
Germany	148	147	133
Korea	109	110	113
China	33	59	60
Italy	30	56	55
France	64	58	52
United Kingdom	33	40	47
Canada	28	55	38
The Netherlands	30	36	31
Switzerland	26	32	27
Austria	4	9	24
Australia	17	15	24
Taiwan	26	31	23
Belgium	26	25	22
India	11	27	21
Israel	20	18	21
Spain	6	19	11
Denmark	9	6	10
Turkey	7	16	8

*Other countries represented in 2006 included Brazil, Sweden, Iran, Greece, Ireland, Russian Federation, Czech Republic, Poland, Saudi Arabia, Hungary, Argentina, Bangladesh, Cuba, Egypt, Finland, Jamaica, Kuwait, Mexico, Norway, Philippines, Singapore, Thailand, and Uruguay.

internationally to our meeting and have contributed so much this year and over so many years in the past.

I would also like to call attention to individuals such as Peter Conti, MD, who has served as SNM president over the past year, and Virginia Pappas, chief executive officer of SNM, and the SNM staff, all of whom have made substantial contributions to our success.

Oncology still represents the major topic at our annual meeting, with 742 (46%) papers concerned with cancer. Table 2 indicates that the neurosciences also contributed 280 (18%) papers and that cardiology contributed 163 (10%) papers. Several themes emerge in looking at the overall presentations. Among the most prominent are prognosis (78 presentations, 4.9%), treatment decision making (161 presentations, 10.1%), and assessment of response to treatment (216 presentations, 13.6%). These are remarkably high numbers.

Figure 2 shows the numbers and corresponding percentages of accepted abstracts for PET and SPECT, from 1990 to the present. A continuous growth for PET is apparent, and this growth was paralleled by SPECT up to the point in about 1997 when the rate of increase doubled for PET. As PET presentations increased, the numbers of SPECT papers remained relatively constant. As I will note later in this lecture, however, I think a major message of this meeting has been the growth of SPECT through SPECT/CT.

^{18}F remains the dominant radionuclide, with 710 presentations (Table 3). The use of other β-emitters, such as ^{11}C, with 188 presentations, is increasing. Of the γ-emitters, ^{99m}Tc was the focus of 301 papers, with the old reliable ^{131}I a distant second at 95 papers.

This year's meeting saw a major increase in the numbers of papers concerned with the imaging of animals with dedicated devices, reflecting the increasing role and influence of basic sciences in nuclear medicine. More than 100 presentations were based on the use of a dedicated PET imaging device, and about 40 were based on the use of a SPECT imaging device (Fig. 3). Notice, however, that 5 papers were focused on PET/CT for small animals, but 11 were focused on SPECT/CT. This reflects a growing interest in the research value of SPECT, particularly when combined with the anatomic information derived from fusion with CT imaging.

TABLE 2
Selected Topics of Oral and Poster Presentations at SNM 2006

Topic	2005	2006
Oncology	688 (46%)	742 (46%)
Neuroscience	254 (17%)	280 (18%)
Dementia	39 (2.6%)	49 (3.1%)
Movement disorders	29 (1.9%)	27 (1.7%)
Cardiology	200 (13%)	163 (10%)

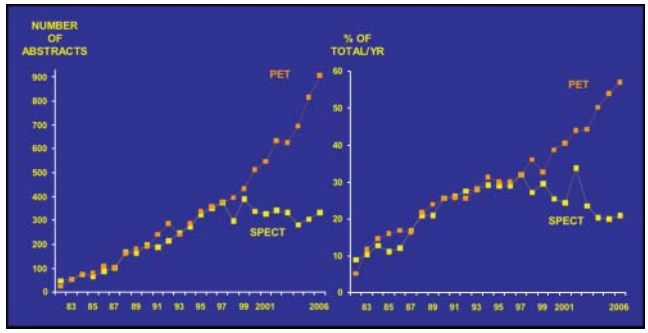

FIGURE 2. Left: Numbers of PET and SPECT presentations at SNM annual meetings, 1983–2006. Right: PET and SPECT topics as percentages of total presentations at each meeting, 1983–2006.

In Figure 2, we saw a plateau for the numbers of SPECT papers over the last decade, which leads to a not infrequently posited question: Will PET and its tracers come to be the dominant and almost exclusive approach in nuclear medicine? This meeting, in my opinion, shows that, to the contrary, single-photon tracers are alive and well. One example came from Schramm et al., representing a multinational consortium from Germany, the Netherlands, and the United States, who presented a nanoSPECT/CT system that included a high-sensitivity, multipinhole SPECT with submillimeter resolution. It is possible to achieve virtually limitless resolution with single-photon tracers, whereas with PET tracers the ultimate spatial resolution is more limited.

SPECT is now becoming preferred over autoradiography, particularly by pharmaceutical companies and academic pharmaceutical laboratories. Figure 4 shows an exquisite skeletal image obtained in a mouse that received 1 mCi ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP). The instrument consisted of 4 banks of 9 pinholes, with a spatial resolution of 1 mm. Figure 5, from Chin et al. at Duke University (Durham, NC) shows a left ventricular aneurysm

TABLE 3
Radiopharmaceutical Isotopes Represented in Presentations at SNM 2006

Isotope	No. of presentations	Isotope	No. of presentations
β-emitters		**γ-emitters**	
^{18}F	710 (545 ^{18}F-FDG)	^{99m}Tc	302
^{11}C	118	^{131}I	95
^{15}O	25	^{123}I	88
^{68}Ga	23	^{111}In	81
^{124}I	19	^{201}Tl	27
^{64}Cu	19	^{133}Xe	5
^{13}N	18	^{67}Ga	4
^{82}Rb	13	^{72}As	1
^{22}Na	8		
^{62}Cu	7		
^{76}Br	2		
^{86}Y	1		

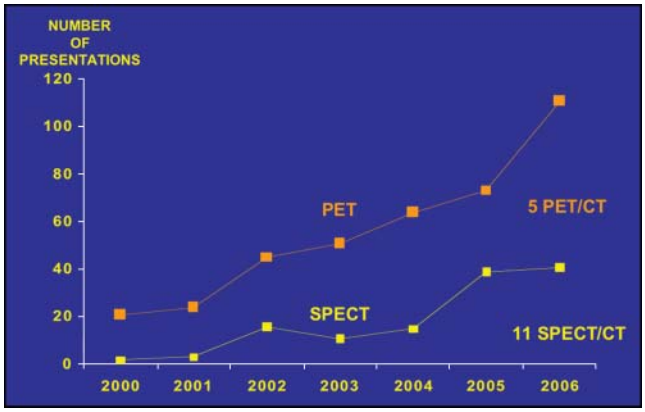

FIGURE 3. A major increase in the numbers of papers concerned with imaging of animals with dedicated devices reflects the increasing role and influence of basic sciences in nuclear medicine.

in a mouse, using high spatial and temporal resolution gated blood pool SPECT imaging with this apparatus.

A commercial exhibitor presented a device with the unique ability to perform both PET/CT and SPECT/CT in small animals. The industry has now incorporated all 3 modalities into a single instrument. Figure 6 shows a PET/CT fusion image of a myocardial blood flow study, again in a mouse.

Moving Toward Molecular Medicine

Each year I pick a theme for the Highlights Lecture. This year I've chosen, "From Molecular Imaging to Molecular Medicine," to reflect the movement of our technology out into ever-broadening circles of modern medical applications. We continue to work to promote a knowledge-based health care system. We must consider more than the costs of space, labor, and capital investment. We must now consider the economic value of knowledge, which is the most valuable asset we possess. I propose the following equation:

$$dV/dt = fK$$

where V = value, and K = knowledge of cellular and molecular manifestations that decrease the cost of diagnosis, prognosis, treatment, and treatment monitoring.

An example of the need in modern medicine for valuable knowledge can be seen in the fact that emergency rooms in the United States see more than 95 million individuals each year, 8 million of whom are complaining of chest pain (8.4% of total visits). Although 60% of these patients are admitted to a hospital or, in some institutions, to a chest pain unit, only 1.3% are eventually found to have experienced acute myocardial infarction (MI). Serum enzyme level (such as troponin) elevations may occur only after 24 hours. A successful effort to correctly identify patients who have experienced MI in a more timely manner

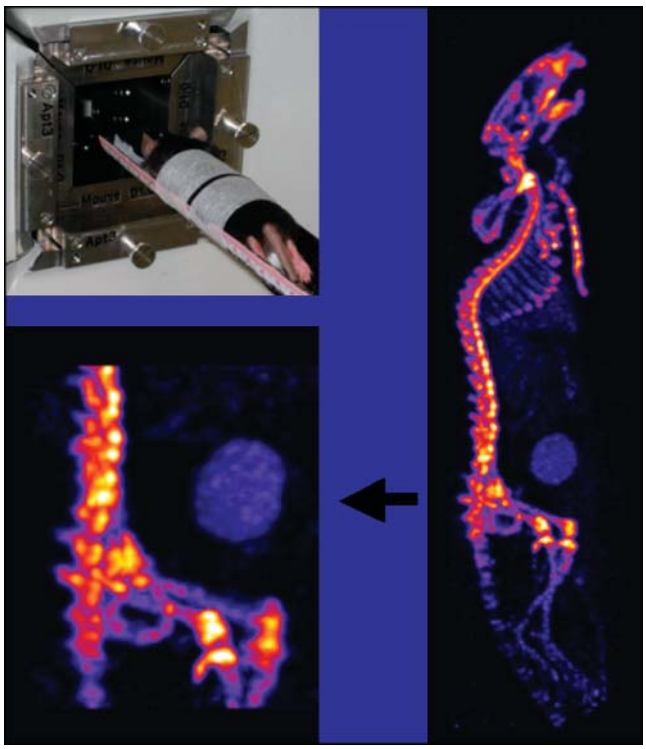

FIGURE 4. This dedicated scanner (top left) was used to obtain a ^{99m}Tc-MDP bone image (right) and detail (bottom left) in a mouse.

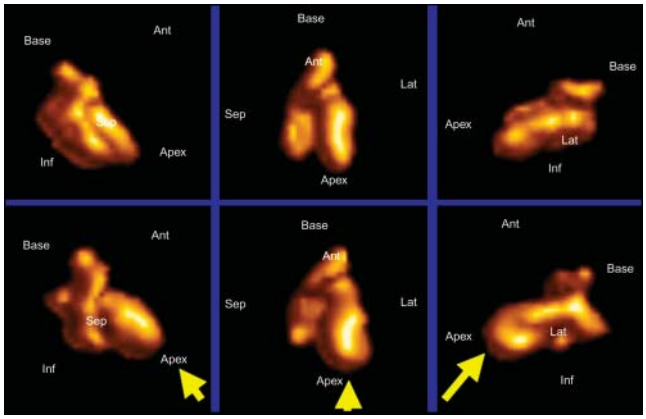

FIGURE 5. Left ventricular aneurysm studies in mice, using high spatial and temporal resolution gated blood pool SPECT. Top row: normal control; left ventricular ejection fraction (LVEF) = 72%. Bottom row: mouse after myocardial infarction; LVEF = 41%. Arrows indicate apical aneurysm.

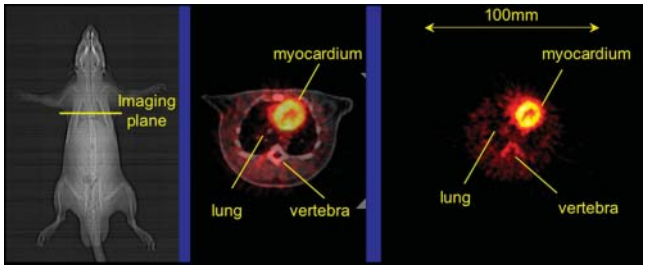

FIGURE 6. Incremental value of fusion imaging in small animal research illustrated by myocardial blood flow in a mouse model. Left: CT. Middle: PET/CT fused image. Right: PET image.

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would reduce unnecessary hospitalization, resulting in cost savings that could be used for the care of other patients, support research, and justify further development of technology. This type of application of new knowledge would have significant and immediate benefits in both patient care and in overall health care efficiency.

In molecular imaging and therapy, terms now increasingly used by the SNM, we define disease by relating the patient's genome, body structures, histopathology, and cellular chemistry to specific problems, whether apparent in the present or as potential future complications. We design therapeutic drugs by defining disease at the cellular and molecular levels. We treat disease by correcting abnormal cellular or molecular processes. We express disease manifestations in units of micromoles/minute/milliliter of disease tissue.

The image that I now have of our bodies is that molecules circulate around the body until they "bump" into recognition sites. If they fit in these recognition sites, they stick and then act. The recognition sites decrease the entropy of all these molecules in our body; that is, these recognition sites correct the disorder or randomness of these molecules within the body. The 3 molecular disciplines of molecular imaging, genetics, and pharmacology are now being woven together to create a new, knowledge-based health care system that focuses on these circulating molecules as a nexus for understanding disease, developing both preventive measures and effective therapies and monitoring treatment efforts.

The success of molecular imaging in improving health care results from its diversity of imaging technologies and expertise, integration of imaging modalities, and competition as well as cooperation among experts in different imaging modalities. For example, Kauppila et al. from Kuopio University (Finland) related genotype to phenotype in a study of brain dopamine and serotonin transporter receptors and cardiovascular activity in young, healthy homozygotic twins. They found a significant correlation in dopamine transporter binding in the striatum with heart rate and diastolic blood pressure in female twins but not in males (Fig. 7).

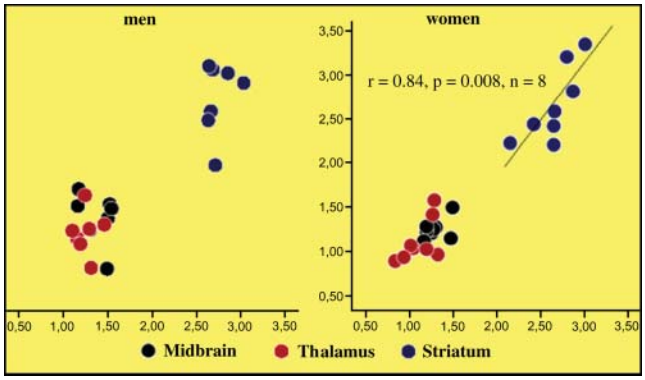

FIGURE 7. Results of study of brain dopamine and serotonin transporter receptors and cardiovascular activity in young, healthy homozygotic twins. Significant correlation in dopamine transporter binding in the striatum with heart rate and diastolic blood pressure was noted in female twins but not in males.

Isaias and colleagues from Italy and Germany examined striatal dopamine transporter binding in patients with the genetic mutation associated with Parkinson's disease (PD). The transporter was studied with ^{123}I-ioflupane in 10 patients with the gene and in 15 gene-negative patients with idiopathic PD (Fig. 8). They found no significant differences in the dopamine transporter uptake in the striatum between the patients with the gene abnormality and patients with idiopathic PD.

This brings up what I call the "pragmatic paradigm" of molecular imaging. We should be careful to avoid confining the patient to a diagnostic box, such as schizophrenia, depression, arthritis, etc. Instead, cellular and molecular dysfunction should be the basis for diagnosis and treatment. Pragmatism says, "Even if you don't know the cause of the disease, as is often the case, if you provide the right treatment, the problem can be addressed." Several examples illustrate this principle at work in molecular imaging today.

Santiago-Ribeiro et al. from the Service Hospitalier Frédéric Joliot (Orsay, France) and the Hôpital Necker–Enfantes Malades (Paris, France) presented a study showing an example of the effect of molecular imaging on decision making. Congenital hyperinsulinism is a genetic defect affecting potassium channels in β cells of the pancreas. Brain damage is the most severe complication, and a 95%–99% pancreatectomy is often required to treat these patients. However, focal lesions of the pancreas may be removed by less invasive surgery. The investigators assessed the value of ^{18}F-fluoro-L-DOPA PET to distinguish between focal and diffuse disease in 40 children with hyperinsulinism. (The use of this tracer, originally developed for the study of PD, also illustrates the movement of tracers from 1 organ specialty and application to another.) Fourteen children showed abnormal focal increases of tracer uptake, and the remaining 26 showed greater and more diffuse uptake of the tracer (Fig. 9). The researchers achieved an effective, noninvasive means of differentiating children who were operable from those who were not. A similar study on diagnostic imaging using ^{18}F-fluoro-L-DOPA PET to assist in treatment planning in children with hyperinsulinism was presented by Wintering

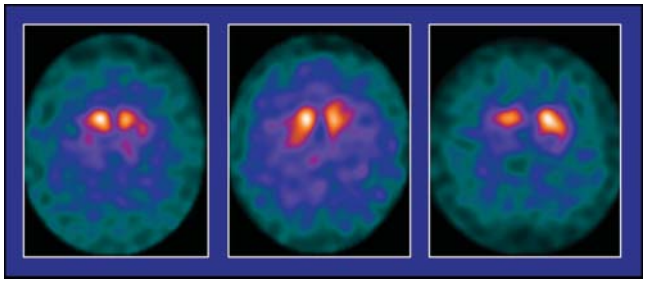

FIGURE 8. No significant differences in dopamine transporter uptake in the striatum were noted among patients with the gene abnormality for Parkinson's disease (PD), patients with idiopathic PD, and normal controls in these ^{123}I-ioflupane studies.

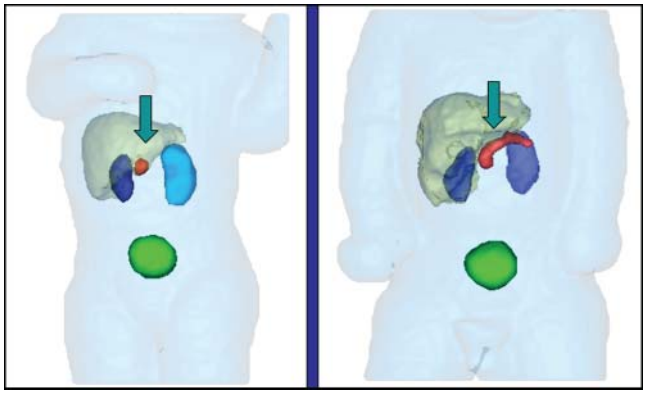

FIGURE 9. ^{18}F-fluoro-L-DOPA PET provided significant information in distinguishing between focal (operable, left) and diffuse (inoperable, right) disease in children with hyperinsulinism.

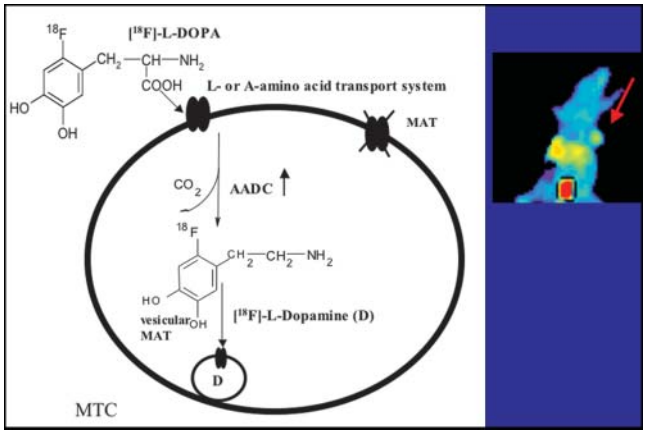

FIGURE 10. Mechanism of accumulation of the amino acid L-DOPA into intracellular dopamine in medullary thyroid carcinoma (left), with ^{18}F-DOPA PET/CT image in a mouse model (right).

et al. from the University of Pennsylvania (Philadelphia) and the Children's Hospital of Philadelphia. The study included 38 children with hyperinsulinism who underwent PET imaging under sedation. The study accurately differentiated 15 patients with focal disease from 22 patients with diffuse disease. The gold standard was histologic examination of excised tissue samples.

Another example of the effect of molecular imaging on decision making was a study by Beheshti et al. from the PET–CT Centre and St. Vincent's Hospital (Linz, Austria), who compared ^{18}F-DOPA PET/CT with ^{18}F-FDG PET/CT for preoperative assessment and follow-up in patients with medullary thyroid carcinoma (MTC). In a group of 15 patients, ^{18}F-DOPA PET/CT detected 28 lesions whereas ^{18}F-FDG PET/CT detected only 14. They concluded that ^{18}F-DOPA PET/CT provides more sensitive and superior results in preoperative determination and staging as well as in the early detection of recurrence and distant metastases in patients with MTC. Figure 10, from a presentation by Mottaghy et al. from University Ulm (Germany) on detection of recurrent MTC with ^{18}F-DOPA PET/CT, shows the mechanism of accumulation of the amino acid L-DOPA into intracellular dopamine.

Fanti et al. from the Azienda Ospedaliero-Universitaria di Bologna (Italy), the Policlinico S. Orsola-Malpighi (Bologna), and the University of Pennsylvania (Philadelphia) looked at the role of whole-body ^{18}F-DOPA PET/CT in 20 patients with neuroendocrine tumors. The studies were positive in 17 of the 20 patients with gastroenterologic cancer. ^{18}F-DOPA PET/CT was useful and contributed to optimal patient management in 4 patients and detected more lesions in 13 patients than did CT alone or ultrasound.

Helisch et al. from University Hospital Mainz (Germany) compared the efficacies of ^{18}F-DOPA PET and ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy in the pretherapeutic localization of multifocal pheochromocytomas and paragangliomas. Figure 11 shows the superiority of the ^{18}F-DOPA PET in a 22-year-old woman with hereditary paraganglioma syndrome. The ^{123}I-MIBG scintigraphy failed to reveal the 3 paragangliomas in the neck, which are seen quite clearly in the PET image.

Yoh et al. from the Kinki University School of Medicine (Osaka, Japan) compared adrenocortical scintigraphy, CT, and chemical-shift MR imaging for differential diagnosis of adrenal cortical functioning adenoma. They found that the old reliable tracer, ^{131}I-norcholesterol, first developed at the University of Michigan many decades ago, was more dependable in making the differential diagnosis of functioning adrenal adenoma than attenuation value in noncontrast CT or inhibition index on chemical-shift MR imaging.

Kumar et al. from the Emory University School of Medicine (Atlanta, GA) reported on ^{99m}Tc-folate SPECT/CT imaging of nonfunctioning pituitary ademonas. Figure 12 shows a 78-year-old man before surgery. The folate receptor to which the tracer binds is a cell surface protein that is an immunologic or pharmacologic target for selective cancer therapy.

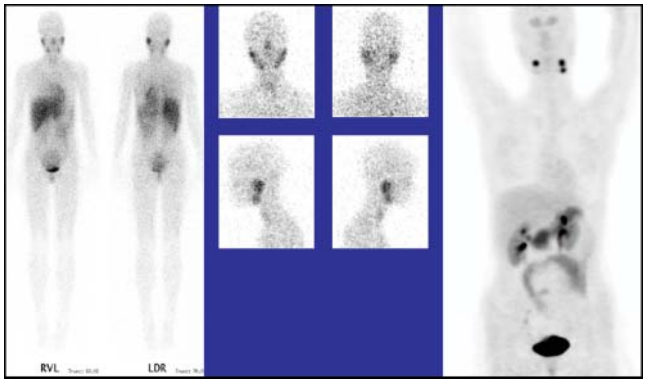

FIGURE 11. ^{18}F-DOPA PET at 1 hour after injection (right) was superior to ^{123}I-MIBG scintigraphy at either 24 (left) or 48 hours (middle images) after injection in the pretherapeutic localization of multifocal paragangliomas.

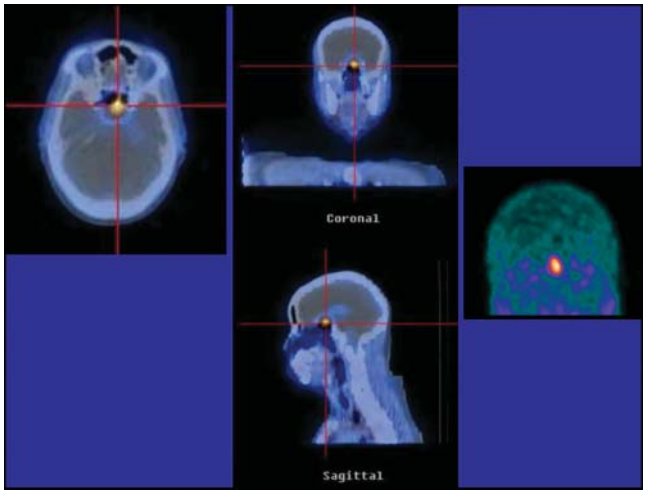

FIGURE 12. ^{99m}Tc-folate SPECT/CT imaging of nonfunctioning pituitary ademona in a 78-year-old man before surgery.

Another example of the impact of molecular imaging on health care was the presentation by Patel et al. from the All India Institute of Medical Sciences (India) and the International Atomic Energy Agency (Vienna, Austria) on the role of ^{99m}Tc-ethylcystenate dimer brain SPECT in the evaluation of patients with dementia and mild cognitive impairment (MCI). In the 74-year-old man with dementia shown in Figure 13, the MR image indicated only mild cortical atrophy, whereas the SPECT images showed severe hypoperfusion. In most cases in this research, SPECT was able to localize abnormalities to a specific area, whereas MR imaging revealed nonspecific generalized cortical atrophy. SPECT revealed abnormalities in 11 patients (8 with dementia and 3 with MCI) who had normal MR studies. Abnormalities on the SPECT and MR images were independent of initial cognition test scores or the presence of the ApoE4 allele.

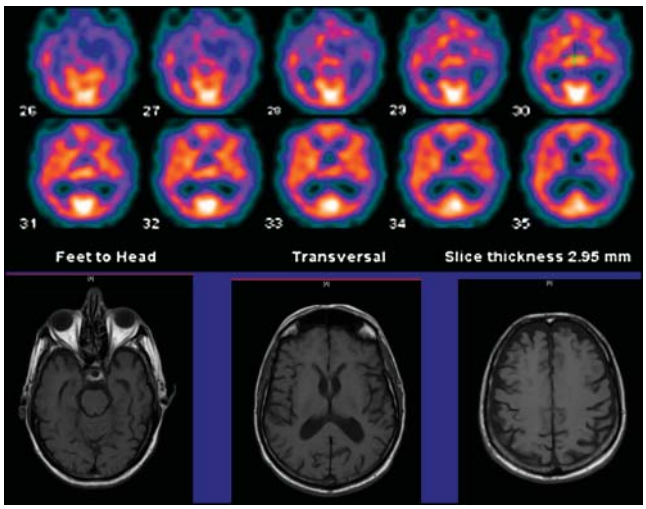

FIGURE 13. ^{99m}Tc-ethylcystenate dimer brain SPECT in the evaluation of dementia in a 74-year-old man. MR (bottom) indicated only mild cortical atrophy, whereas SPECT (top) showed severe hypoperfusion.

TABLE 4
Highlights in Early Brain Imaging

1945	Cerebral blood flow by N_2O (Kety and Schmidt)
1955	Regional cerebral blood flow (rCBF) by ^{85}Kr (Lassen)
1959	Radionuclide tomography (Kuhl)
1963	rCBF by ^{133}Xe (Lassen)
1969	SPECT scanner (Kuhl)
1975	PET scanner (Ter-Pogossian)
1977	Deoxyglucose (Sokoloff)
1979	^{18}F-FDG brain tomography (Reivich, Kuhl)
1979	Glucose metabolism by ^{18}F-FDG PET (Phelps)
1980	^{15}O steady-state method by PET (Frackowiak)
1980	rCBF by ^{123}I-IMP SPECT (Kuhl)
1983	Dopamine receptor imaging by PET (Wagner)

Nuvoli et al. from the University of Sassari (Italy) reported on the use of ^{123}I-*N*-omega-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (^{123}I-FP-CIT) SPECT in early-stage diagnosis of PD. Results were normal in 33 of 82 patients (40.2%) and abnormal in the remaining 49 patients (59.8%). The diagnosis of PD in the latter group was confirmed, and patients proceeded to early treatment with L-DOPA.

Of great significance in these and other studies presented this year are the increasing numbers of patients in studies. We are moving beyond showing the feasibility and validity of technologies and tracers into studies that explore applications in what may become routine practice.

Neuroimaging

In 1890, in his classic book *Principles of Psychology*, William James said, "We need to know a little better what are the molecular changes in the brain on which thought depends." What William James imagined, we can now image. Table 4 shows a brief "slice-of-time" in the development of functional neurologic imaging, going back to Kety and Schmidt at the University of Pennsylvania in 1945 up to 1983 and the first dopamine receptor imaging with PET. Table 5 indicates that out of 280 neuroimaging presentations this year, 74 focused on dopamine.

TABLE 5
Neuroscience Presentations at SNM 2006

Topic	No. of presentations	% of total meeting
Total brain studies	280 (68 ^{18}F-FDG)	17.5%
Neurotransmission	114	7.1%
Brain tumors	35	2.2%
Receptors		
Dopamine	74	4.64%
Nicotinic acetylcholine	13	0.81%
Serotonin	12	0.75%
Benzodiazepine	8	0.50%
Norepinephrine	4	0.25%

Dopamine is in vesicles in the presynaptic neuron, is secreted, crosses the synapse, and binds to the postsynaptic receptors. What is not bound is then taken back up by the dopamine transporters. The overall neuronal activity, in a nonspecific way, can be measured by tracers such as ^{18}F-FDG. Leroy et al. from the Service Hospitalier Frédéric Joliot (Orsay, France) presented the results of work with a high-spatial-resolution PET camera for imaging the neuronal dopamine transporter with ^{11}C-PE2I. This is an example of the fantastic improvements in instrumentation that were presented at this meeting and shown in the exhibits. In Figure 14 you can see the detail with the T1-weighted MR images, with the nuclear studies superimposed. Notice that you can see a clear separation in this study. The lower study has a volume resolution of 16 μL, with the various parts of the striatum, such as the caudate and the putamen, clearly visible. The earliest dopamine PET images, such as those from 1983 (Fig. 15), showed evidence of accumulation of tracers in the striatum but showed no separation of the caudate nucleus from the putamen.

Schizophrenia is associated with increased synaptic dopamine in associative rather than limbic regions of the striatum. Kegeles et al. from Columbia University (New York, NY) and the University of Rochester (NY) showed that the improved resolution of PET can separate the striatum into its various regions, including the limbic, associative, and sensory regions. In their study, 18 patients diagnosed with schizophrenia and 18 age-matched controls underwent ^{11}C-raclopride PET imaging. They found that schizophrenia was associated with increased synaptic dopamine in associative rather than limbic regions in the striatum, a finding with significant implications for the mechanisms and effectiveness of antipsychotic drugs (Fig. 16). These types of studies are important in determining the site of action of drugs within specific parts of the striatum that turn out to be associated with very different mental processes.

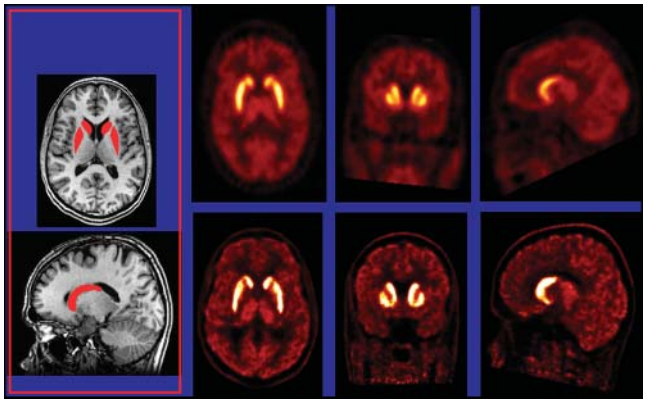

FIGURE 14. A high-spatial-resolution PET camera for imaging the neuronal dopamine transporter with ^{11}C-PE2I added important information when overlaid on corresponding MR images (left). The new PET camera produces a volume resolution of 16 μL (right, bottom) and, in contrast with PET images with volume resolution of 2.5 μL (right, top), shows a clear separation in the parts of the striatum.

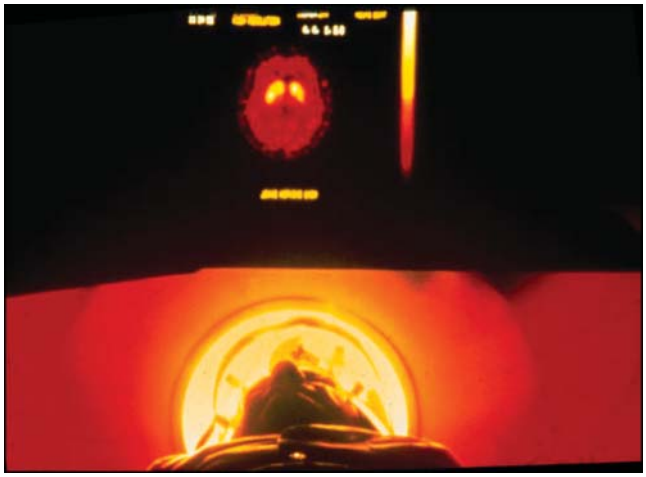

FIGURE 15. Very early dopamine PET images, such as this 1983 photograph of apparatus and resulting image, showed evidence of accumulation of tracers in the striatum but no separation of the caudate nucleus from the putamen.

Hesse et al. from the University Hospital/University Leipzig (Germany) and the Max Planck Institute of Cognitive Neuroscience (Leipzig) showed that striatal dopamine transporter availability is reduced in adults with attention deficit/hyperactivity disorder (ADHD). They studied 17 never-treated patients with ADHD using ^{123}I-FP-CIT SPECT to image striatal dopamine transporter and thalamus/midbrain monoamine transporter availability. They found significantly reduced binding ratios in the whole striatum, in all striatal subregions, and in the thalamus in individuals with ADHD (Fig. 17). Midbrain and brainstem binding ratios, however, did not differ in ADHD individuals and controls.

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

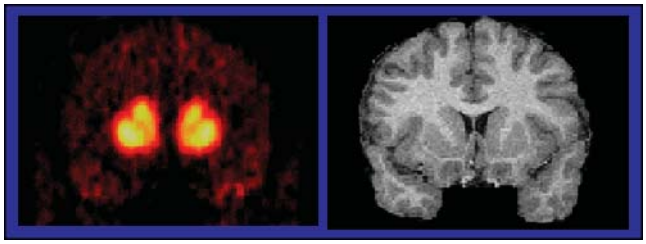

FIGURE 16. ^{11}C-raclopride PET imaging in schizophrenia indicated increased synaptic dopamine in associative rather than limbic regions in the striatum.

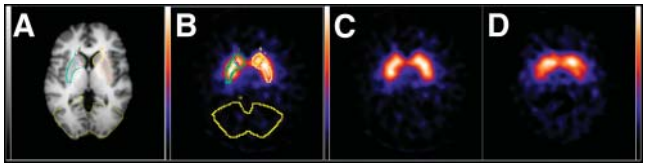

FIGURE 17. ^{123}I-FP-CIT SPECT analysis of striatal dopamine transporter availability in adults with attention deficit/hyperactivity disorder (ADHD) found significantly reduced binding ratios in the whole striatum, in all striatal subregions, and in the thalamus in individuals with ADHD (D) compared with normal controls (C). (A) and (B) represent MR-based region-of-interest analyses of imaging activity.

Nora Volkow, head of the National Institute on Drug Abuse (NIDA), and colleagues continue their work on imaging the effects of addiction in the brain. An ^{11}C-raclopride study showed that the release of dopamine in response to methamphetamine is mimicked by the stimulation of a normal person eating (Fig. 18).

In the early days of dopamine imaging, it was shown that dopamine receptors decrease strikingly with age. Another study from NIDA presented at the meeting showed that in normal controls, the dopamine receptor availability was higher on a case-by-case basis than in cocaine abusers. Even a month after stopping the administration of cocaine, the receptors were still unavailable or diminished, perhaps due to neuronal damage, and even 4 months after stopping the drug the abnormalities were still seen (Fig. 19).

A very interesting study from Wang et al. at the Brookhaven National Laboratory (Upton, NY), NIDA, and the State University of New York at Stony Brook reported on the relationship of mental activity and actions to brain activity in a study of brain satiety circuit activated by gastric stimulation. They studied the results of electrical stimulation of the stomach and its effects on the brain as revealed by ^{18}F-FDG PET. They found that the brain regions activated by gastric stimulation in obese individuals

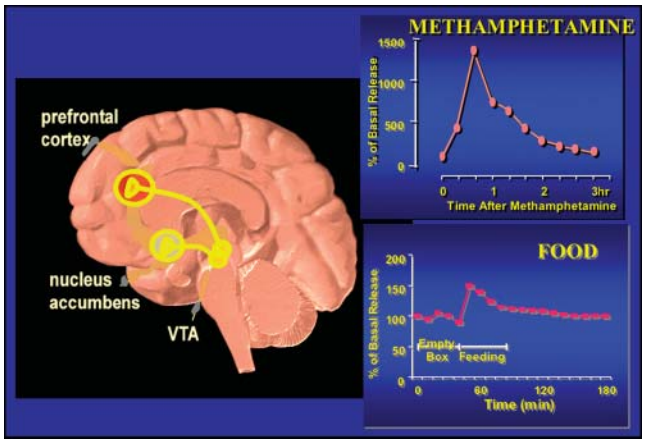

FIGURE 18. The release of dopamines in response to methamphetamine in an addict (right, top) was compared with similar releases associated with the ingestion of food (right, bottom) in an ^{11}C-raclopride PET study indicating that similar mechanisms are at work.

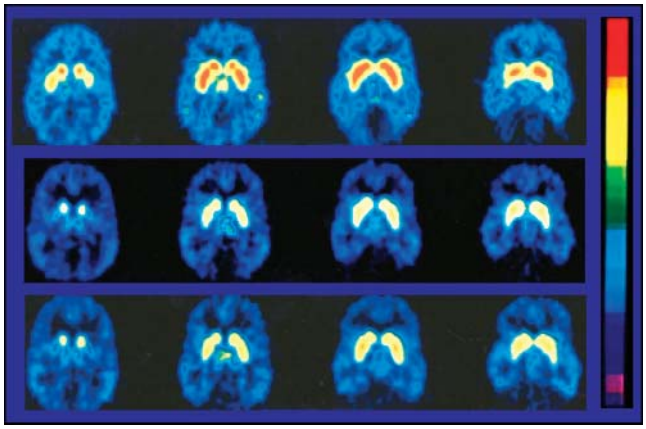

FIGURE 19. PET study of the effect of cocaine abuse on dopamine D_2 receptors. A month after stopping the administration of cocaine (middle row), receptors were still unavailable or diminished; a condition that persisted even 4 months after stopping the drug (bottom row), when compared with scans in healthy individuals (top row).

are similar to those activated during craving responses in addicted subjects, supporting the commonalities between compulsive food eating and compulsive drug intake.

Other dopamine receptors were discussed in scientific presentations and posters at the meeting. Mach et al. from Washington University School of Medicine (St. Louis, MO) reported on the development and evaluation of a tracer for imaging the D_3 dopamine receptor (Fig. 20). Again, the higher spatial resolution of the improved instrumentation

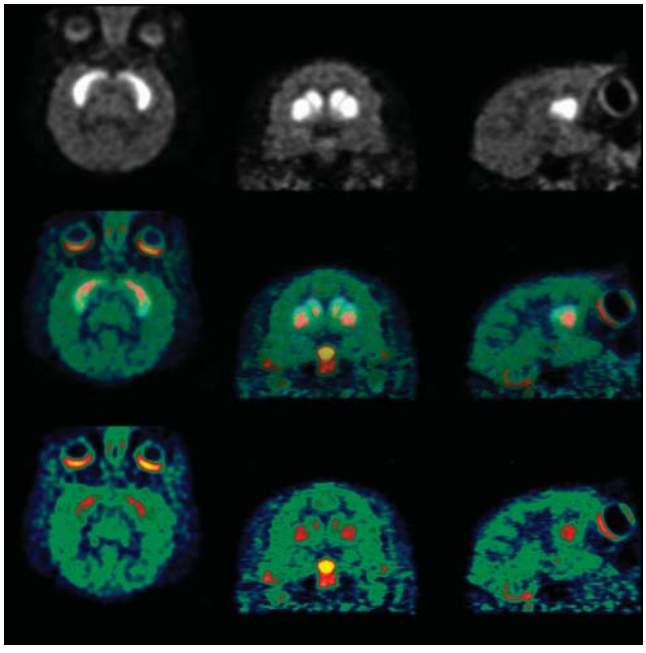

FIGURE 20. Coregistered (middle row) ^{11}C-raclopride (top) and ^{11}C-WC-10 (bottom) images indicate that the basal ganglia contain fewer D_3 than D_2 receptors.

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(Continued from page 21N)

showed that D_3 receptors are fewer than D_2 receptors in the basal ganglia. In the coregistered images, the pink areas representing D_3 receptor binding are of a smaller volume and number than the D_2 areas.

Horti et al. from Johns Hopkins Medicine (Baltimore, MD) reported on simian studies of a tracer developed for studying marijuana addiction in humans. ^{11}C-JHU75528 has a lower lipophilicity and higher binding affinity and is a potential tracer for quantitative PET imaging of the so-called cannabinoid (CB1) receptors.

Odano et al. from the Karolinska Institute (Stockholm, Sweden) and the Institute of Human Brain (Saint Petersburg, Russian Federation) showed the first central benzodiazepine receptor mapping study with ^{18}F-flumazenil PET in humans. The accurate values of the binding parameters, such as binding potential and distribution volume, were obtained by reference tissue models, in this case using the pons as a reference region. It eliminates the need for blood sampling. Figure 21 shows the wide distribution of these benzodiazepine receptors, seen best in the fusion images in the middle vertical row.

For decades I have been promoting simple devices where the imaging problem does not require high resolution in terms of location. At Hopkins, we used a very simple dual-detector probe device, for example, in a peer-reviewed study that resulted in approval of the drug nalmefene. We were able to show that nalmefene blocked opiate receptors with a half-time of 12 hours, whereas naloxone, the drug widely used in postoperative patients, blocked the receptors for only 2 hours. The problem with the naloxone is that patients undergoing surgery must be monitored closely to make sure that it is not wearing off before the narcotic anesthetic wears off. Nalmefene's long duration of action had to be demonstrated, and our PET study provided objective evidence that resulted in U.S. Food and Drug Administration (FDA) approval for the drug. That's why I often say that every psychiatrist needs a dual-detector probe system—something that may someday happen.

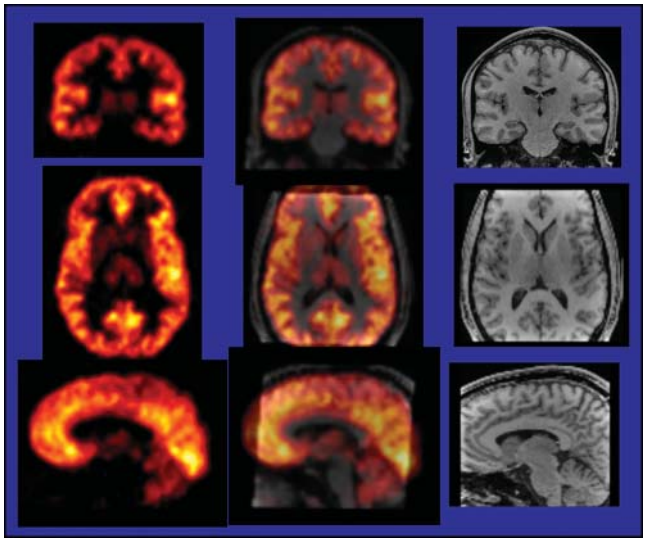

FIGURE 21. Central benzodiazepine receptor mapping study with ^{18}F-flumazenil PET (left) and fusion (middle) with MR images (right).

Hesse et al. from the University of Leipzig (Germany) reported on a study focusing on the effects of deep brain stimulation of the subthalamic nucleus on striatal dopaminergic transmission in patients with advanced PD. The patients had bilateral surgical stimulation of the nucleus subthalamicus (Fig. 22). The researchers used ^{123}I-FP-CIT and ^{123}I-iodobenzamide SPECT to image striatal dopamine transporter and striatal dopamine D_2 receptor activity, respectively. They were able to show that 1 year after deep brain surgical stimulation, dopamine D_2 receptor availability was significantly (18%) higher, whereas the dopamine transporter availability was unchanged. I should also note that the Kuwait Foundation for the Advancement of Sciences (KFAS) awarded the 2005 KFAS Prize to Dr. Osama Sabri, one of the authors of this paper, as "the best Arabic nuclear medicine researcher."

Matsunari et al., representing a consortium of Japanese universities and research institutions, presented a head-to-head comparison of ^{18}F-FDG PET and voxel-based morphometry (VBM) in MR imaging for the detection of Alzheimer's disease (AD). Figure 23 shows this comparison. They found that the PET study had a far more favorable receiver operating characteristic curve with better sensitivity and better specificity than the VBM study. Sensitivity, specificity, and accuracy with PET were 96%, 97%, and 96%, respectively, but only 61%, 94%, and 80%, respectively, with MR.

Another receptor of interest is the cerebral nicotinic acetylcholine receptor (nAChR), which was studied in the

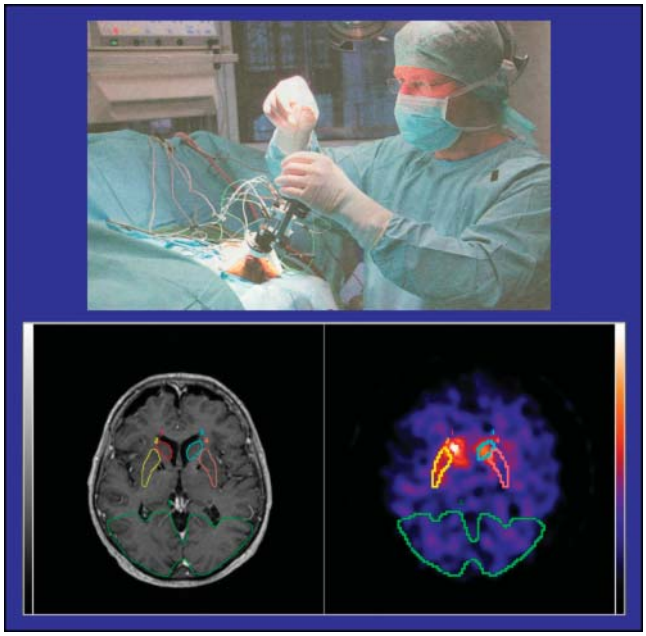

FIGURE 22. ^{123}I-FP-CIT and ^{123}I-iodobenzamide SPECT (superimposed with MR data, bottom) were used to assess the long-term effects of surgical deep brain stimulation of the subthalamic nucleus (top) on striatal dopaminergic transmission in patients with advanced Parkinson's disease.

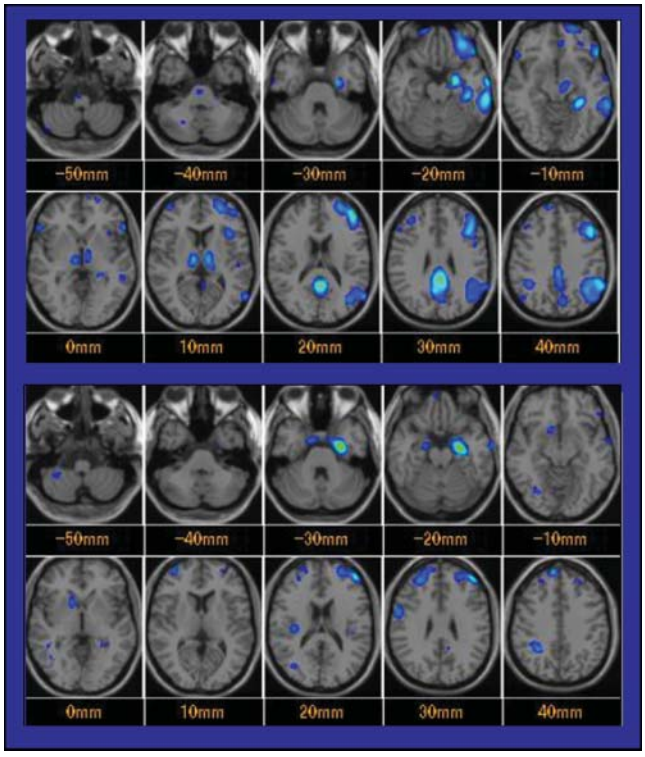

FIGURE 23. ^{18}F-FDG PET (top 2 rows) was compared with voxel-based morphometry in MR imaging (bottom 2 rows) for the detection of Alzheimer's disease.

periventricular white matter in patients with AD and in patients with vascular dementia by Kendziorra and the group from Leipzig University using 2-^{18}F-F-A85380 PET. These researchers found a deficit in nAChRs in different cortical regions in both AD and vascular dementia, indicating that both have abnormalities in cholinergic neurotransmission. The availability of these receptors in the periventricular white matter was reduced in vascular dementia but normal in AD. This may help in distinguishing patients with variants of dementia and in identifying those who may benefit from early treatment strategies.

Eggers et al. from the University of Cologne, the Max Planck Institute for Neurological Research (Cologne, Germany), and the University of Manchester (UK) reported on a study of acetylcholine-esterase imaging of brainstem nuclei in sleep disturbance associated with AD. Their findings suggested that sleep disturbances in AD may be associated with a cholinergic impairment in brainstem nuclei (Fig. 24).

A classmate of mine at Johns Hopkins was the late George Glenner, who was among the first to study the chemistry of amyloid deposits and amyloidosis. He reported for the first time in 1984 that the plaques seen in AD and first described by Alzheimer himself consist of amyloid. His work has resulted in a tremendous body of ongoing research throughout the world.

The amyloid precursor protein (APP) is encoded on chromosome 21 and is overexpressed in Down syndrome and AD. Researchers from the Flanders Interuniversity Institute

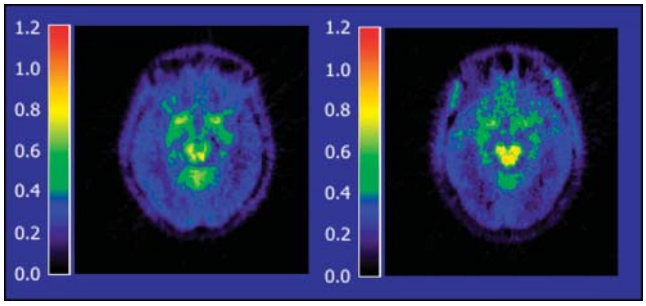

FIGURE 24. ^{11}C-labeled acetylcholine-esterase imaging in Alzheimer's disease patients with (left) and without (right) sleep disturbance indicated that such disturbances in AD may be associated with a cholinergic impairment in brainstem nuclei.

for Biotechnology at the University of Antwerp (Belgium) were the first to show that the quantity of amyloid protein in brain cells is a major risk factor for AD. Today, the hypothesis is that β-amyloid imaging facilitates earlier and more specific diagnosis of AD, allowing earlier intervention and specific therapy. What we need now are longitudinal studies of large populations beginning with people who are totally asymptomatic to define when the process of plaque formation begins in the development of dementia.

Will molecular imaging come to be a part of routine medical screening? Screening became increasingly popular in the late 1950s, on the assumption that the discovery of any abnormality was worthwhile. In his 1971 book, *Effectiveness and Efficiency* (London, UK: Burgess and Son), A.L. Cochrane said, "A test is suitable as a diagnostic screening test if there is hard evidence, preferably based on randomized clinical trials, that the application of the test to certain populations would alter the natural history of the disease in an appreciable portion of the persons screened at a reasonable cost." Certainly AD is a suitable candidate for which imaging screening procedures may prove to be appropriate.

Rowe et al. from Austin Hospital (Melbourne, Australia) and the University of Melbourne used ^{11}C-PIB PET imaging to illustrate brain abnormalities in patients with mild or moderate AD. Figure 25 shows the striking accumulation of

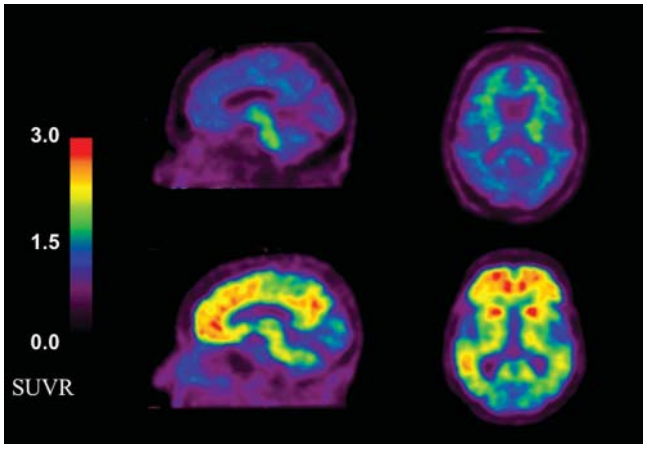

FIGURE 25. ^{11}C-PIB PET shows the accumulation of tracer in a healthy patient (top) and a patient with Alzheimer's disease (bottom).

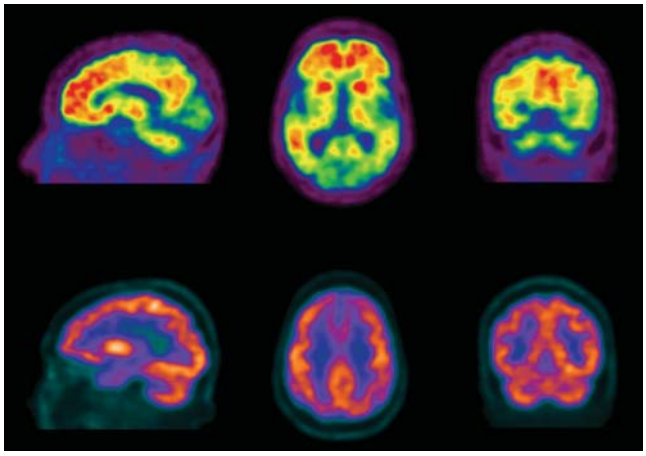

FIGURE 26. ^{11}C-PIB accumulation on PET in an elderly individual with mild Alzheimer's disease (top), clearly showing uptake in the visual cortex, with ^{18}F-FDG images (bottom) providing less information.

this tracer that binds to amyloid plaque in a patient with AD and a healthy patient. The authors stressed the fact that the cutoff between controls and patients with AD is good both from a simple visual standpoint as well as with quantitative ROC assessments. Figure 26 shows the same study's results in an elderly individual with mild AD, again clearly positive for amyloid plaques. The comparative ^{18}F-FDG PET study in the same patient showed only marked atrophy and was equivocal for the diagnosis of AD.

Villemagne and a group of the same Australian researchers, along with researchers from Monash University (Melbourne) and the University of Pittsburgh (PA), looked at the differential diagnosis of dementia using the ^{11}C-PIB tracer. Assessing the distribution volume ratio (DVR) of the neocortex relative to the cerebellum, they found good separation between healthy controls and patients with AD. The DVRs overlapped, however, in patients with MCI, dense Lewy body disease, and frontotemporal disease, all of whose images were indistinguishable from those of healthy controls. Figure 27, for example, shows another variant of dementia, posterior cortical atrophy. Uptake of tracer in the amyloid plaque is much greater in patients with posterior cortical atrophy than in those with AD.

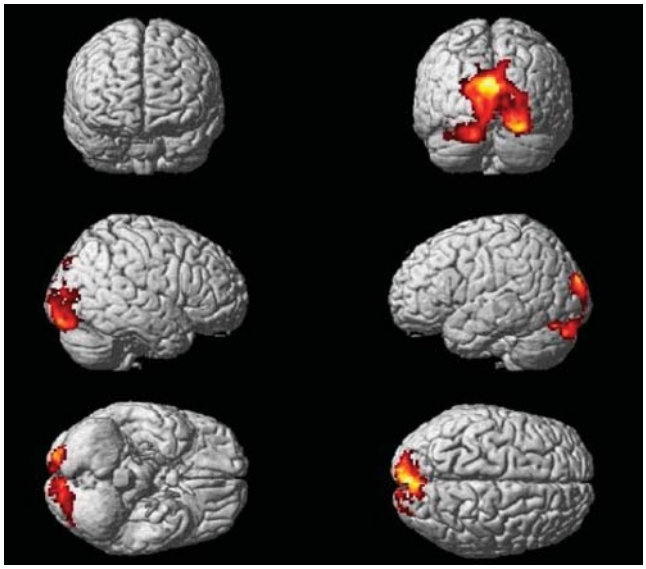

FIGURE 27. ^{11}C-PIB tracer imaging of amyloid plaque in a patient with posterior cortical atrophy, showing uptake higher than that seen in patients with Alzheimer's disease.

Drzezga et al. from Dr. Schwaiger's group at the Technische Universität München (Germany) compared amyloid plaque imaging in patients with AD and with so-called semantic dementia (SD). SD is another type of frontotemporal lobe degeneration, manifested by impaired semantic memory, word comprehension, and knowledge about persons and objects. Working memory and autobiographical (so-called episodic) memory are not affected. The group used ^{18}F-FDG PET to assess cerebral glucose metabolism and ^{11}C-6-OH-BTA-1 PET to assess cerebral amyloid plaques. ^{18}F-FDG PET studies indicated bilateral temporal hypometabolism in both SD and AD, but the ^{11}C-labeled tracer found no amyloid plaques in SD, differentiating the 2 patient populations (Fig. 28).

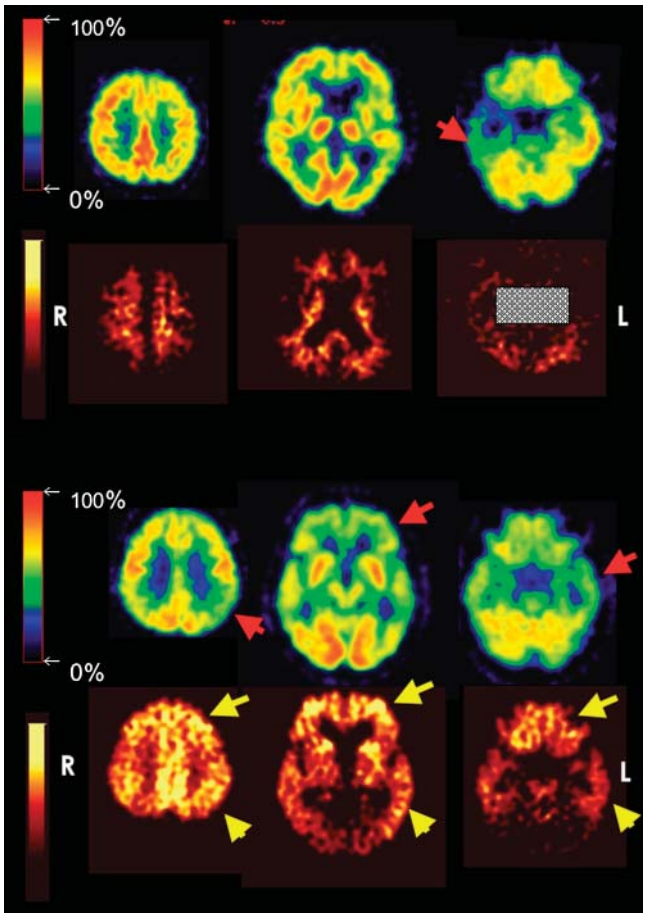

FIGURE 28. ^{18}F-FDG PET and ^{11}C-6-OH-BTA-1 PET were used to assess cerebral glucose and cerebral amyloid plaques, respectively, in patients with semantic dementia (top 2 rows) and Alzheimer's disease (bottom 2 rows).

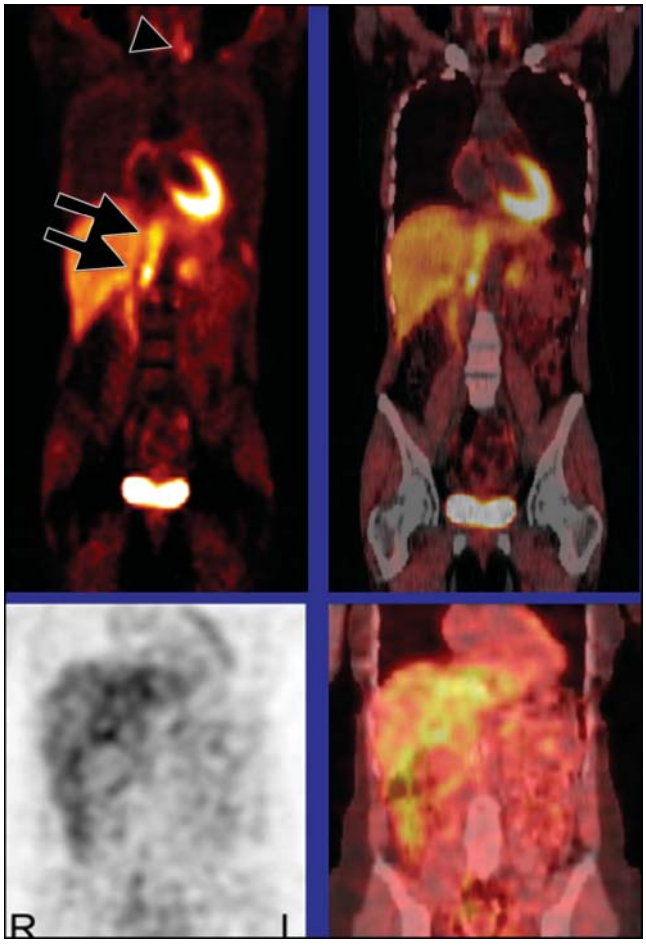

FIGURE 29. Tumors of the sympathetic nervous system were imaged with whole-body ^{11}C-HED PET/CT (top) and ^{123}I-MIBG SPECT/CT (bottom). PET was found to detect more lesions.

Neuroimaging is moving from the brain out into oncology and also into the autonomic nervous system. Franzius et al. from the University Hospital Münster (Germany) reported on imaging tumors of the sympathetic nervous system with whole-body ^{11}C-labeled metahydroxyephedrine (^{11}C-HED) PET/CT and compared the results with the more widely used tracer ^{123}I-MIBG SPECT/CT. More lesions were detected with the ^{11}C-HED PET/CT tracer than with ^{123}I-MIBG SPECT/CT (Fig. 29).

Cardiology

Slart et al. from University Medical Center (Groningen, The Netherlands), University Hospital (Ghent, Belgium), and University Medical Center (Leiden, The Netherlands) described a challenge test in which nitrate was administered before the performance of ^{12}N-ammonia PET studies in patients with left ventricular (LV) dysfunction. Most of the emphasis in the past decades has been on coronary artery disease (CAD), but cardiologists all over the world are also focusing on heart failure and LV dysfunction. Figure 30 is an example of this group's efforts to detect myocardial

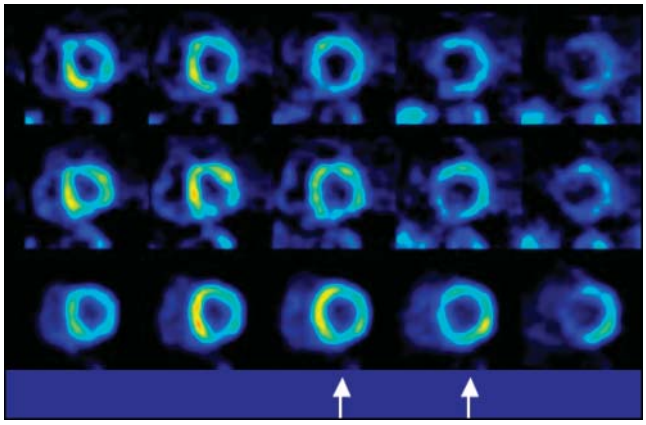

FIGURE 30. ^{13}N-ammonia myocardial perfusion was quantified at baseline (top) and in response to nitrate administration (middle) in patients with left ventricular dysfunction and regional irreversible perfusion defects on previous rest gated ^{99m}Tc-tetrofosmin SPECT, using ^{18}F-FDG PET as a reference method for viability (bottom).

viability in patients with heart failure. They quantified ^{13}N-ammonia myocardial perfusion changes in response to nitrate administration in patients with LV dysfunction and regional irreversible perfusion defects on previous rest gated ^{99m}Tc-tetrofosmin SPECT, using ^{18}F-FDG PET as a reference method for viability. They concluded that the use of nitrates enhances the detection of ischemic but viable myocardium and identified an optimal cutoff value for the challenge/baseline ratio on PET imaging.

Jang et al. from the Mount Sinai School of Medicine (New York, NY) compared the efficacy of ^{99m}Tc myocardial SPECT with that of ^{82}Rb PET in identifying CAD. The results showed that the sensitivity was far greater with the ^{82}Rb PET than with the ^{99m}Tc. The differences were relatively small in the positive predictive values of the 2 approaches but were more significant in the negative predictive values.

Image Fusion

Image fusion clearly is a major area of research today in nuclear medicine. If you look back over the last 6 years (Table 6), you can see this striking growth. It's very interesting to me to look at the growth of SPECT/CT fusion: from 2003 to 2005, the number of presentations

TABLE 6
2006 Presentations on Image Fusion*

Modalities	2000	2001	2002	2003	2005	2006
PET/CT	13	33	55	96	242	243
PET/MR	14	25	21	21	28	42
SPECT/CT	11	8	14	19	41	65
SPECT/MR	5	18	6	11	18	5

*Includes both hard- and software fused modalities.

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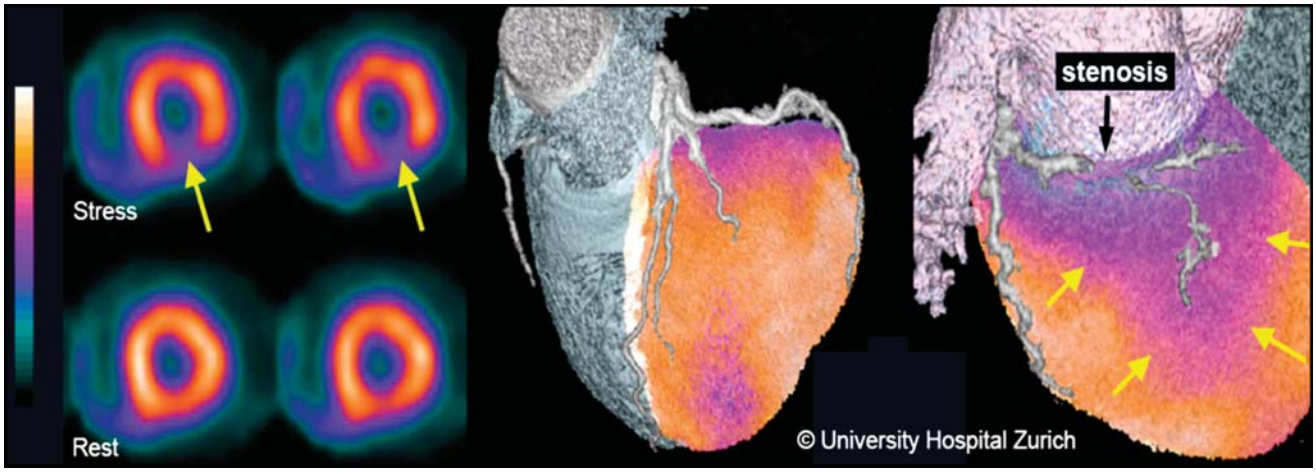

FIGURE 31. Co-Image of the Year. Left: Myocardial perfusion SPECT of ischemia at stress (top) and rest (bottom). Right: Software fused image of combined ^{99m}Tc-tetrofosmin SPECT and 64-slice CT angiography in the evaluation of functionally relevant coronary stenoses.

went from 19 to 41. I was eagerly waiting to see what the number would be this year—and it turned out to be 65, a great increase but still well below the numbers for PET/CT. This may seem odd, given the fact that the total numbers of SPECT studies in the United States and elsewhere are 10–20 times greater than the numbers of PET studies. The reason behind the takeoff of PET/CT is that when David Townsend and others came up with this great technique, it seized the attention of the radiologists, who, in turn, got the attention of the manufacturers. But judgment about SPECT/CT was deferred until now. However, the consensus is clear that from now on, SPECT/CT and PET/CT will develop side by side.

This year I've chosen as 1 of 2 Images of the Year an example of combined ^{99m}Tc-tetrofosmin SPECT and 64-slice CT angiography (CTA) in the evaluation of functionally relevant coronary stenoses, acquired by Gaemperli et al. from University Hospital Zurich (Switzerland) (Fig. 31). The purple areas in the image indicate decreased bloodflow resulting from stenosis of the circumflex artery. The image was created through software fusion; that is, the computerized blending of the 2 separately acquired images. The study included 62 patients with suspected or known CAD. Myocardial perfusion defects on SPECT were identified in 67% of patients who had >50% stenosis on CTA, but SPECT showed no perfusion defects in 33%. In those with >75% stenosis on CTA, 85% had perfusion defects on SPECT and 15% had no perfusion defects.

The second Image of the Year (Fig. 32) is quite similar to the first but was acquired with true hybrid imaging; that is, hardware fusion of SPECT and CTA on the same gantry. Keidar et al. from the Rambam HealthCare Campus and the Technion Institute of Technology (Haifa, Israel) assessed hemodynamically significant coronary artery lesions with an integrated SPECT/CT device (Fig. 33). Their investigations showed that CTA alone, now widely used in

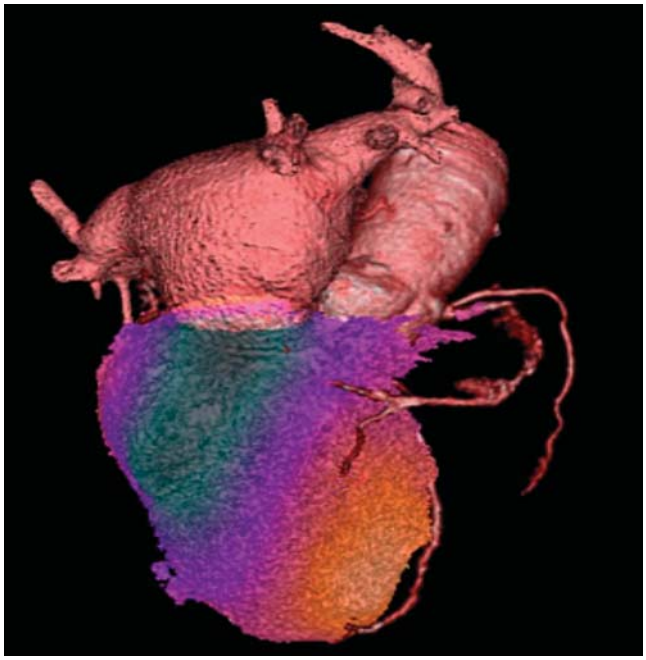

FIGURE 32. Co-Image of the Year. This hardware-fused imaged reveals the incremental value in fusing information from SPECT and CT angiography in the setting of coronary artery disease.

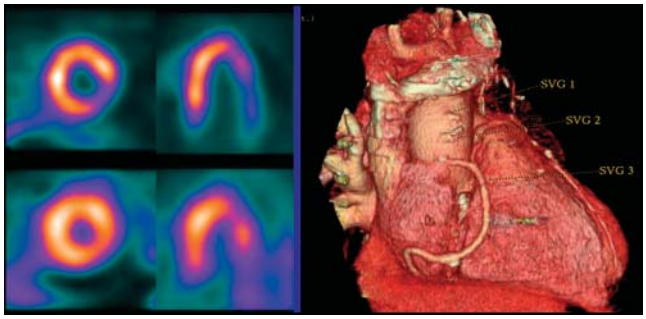

FIGURE 33. Left: Myocardial perfusion SPECT of lateral wall ischemia at stress (top) and rest (bottom). Right: CT angiography revealed multiple stenoses and occluded grafts.

screening patients for CAD, has a good negative predictive value—a normal study indicates a high probability that the patient does not have CAD. However, an abnormal finding on CTA translates into only a 31% possibility of an associated reduction in regional myocardial blood flow. The second Image of the Year, shows the incremental value in fusing information from SPECT and CTA in CAD.

Hacker et al. from the University of Münich (Germany) showed that 64-slice spiral CTA does not reveal the hemodynamic relevance of coronary artery stenoses in patients with stable angina. Figure 34 shows abnormalities in a patient's artery, with calcium deposits in the coronary arteries but normal perfusion. The 64-slice CTA failed to predict the functional relevance of coronary artery stenoses in many patients. In the patient whose results are seen in Figure 35, the significance of stenotic lesions seen in angiography was emphasized by perfusion defects seen in the nuclear study. The authors concluded that myocardial perfusion imaging remains mandatory for evaluating the functional relevance of coronary artery lesions.

Rapid advances in technologies can help to increase the availability of images and decrease cost. In the technical exhibits at the SNM 2006 Annual Meeting, Hermes Medical Solutions (Stockholm, Sweden) presented a Web-based image processing system that can provide analysis and display on regular desktop computers. The example seen in Figure 36 is from CTA, showing vessels in the lung and the coronary vessels on the surface of the left ventricle.

Let me pose a hypothetical but important question: If you or a loved one experienced severe chest pain and all of the following studies were available, which would you choose: (1) CTA; (2) ^{82}Rb PET/CTA; (3) ^{99m}Tc-sestamibi or ^{201}Tl SPECT/CTA; (4) ^{13}N-NH_3 PET/CTA; (5) troponin serum enzyme measurements; (6) exercise EKG; or (7) exercise SPECT? The correct answers, in my opinion, are 2 or 3.

Discussion continues about the degree of confidence needed to interpret the CT portion of PET/CT. I believe and have advocated the belief (that is not yet widely accepted but also not widely resisted) that every person in nuclear medicine should know as much about CT as a diagnostic radiologist. And I believe that every radiologist should know as much about PET and SPECT as a nuclear medicine physician. Just as the techniques are fused, I believe that the

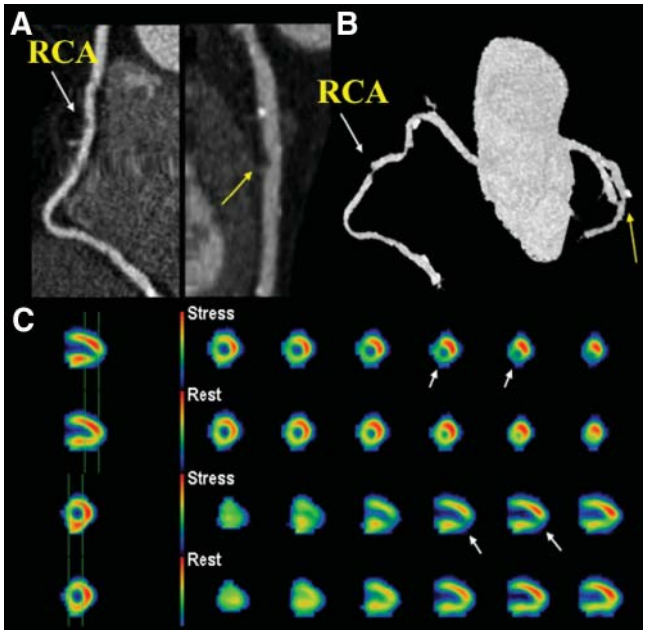

FIGURE 35. In the patient whose results are seen in Figure 34, the significance of stenotic lesions on angiography was emphasized and clarified by perfusion defects seen in the nuclear study.

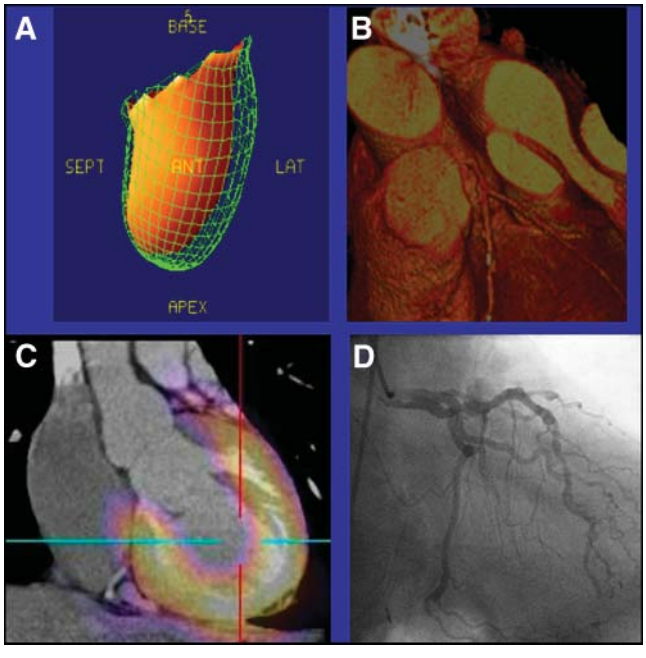

FIGURE 34. 64-slice coronary artery abnormalities (D) in a patient, with calcium deposits (B) but normal perfusion (C).

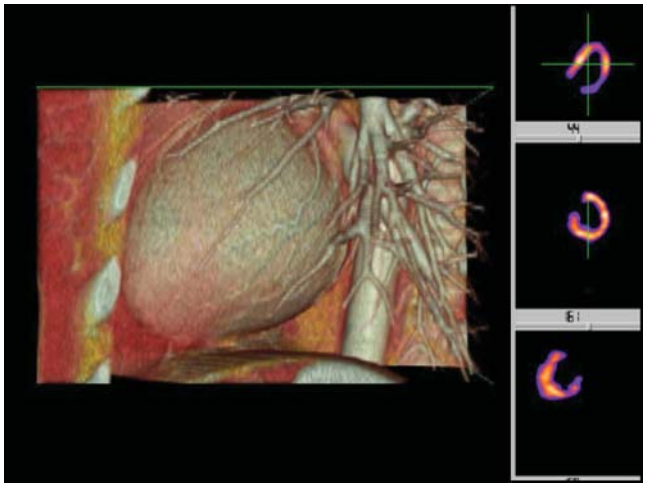

FIGURE 36. A Web-based image processing system provided this analysis and display of CT angiography, showing vessels in the lung and coronary vessels on the surface of the left ventricle.

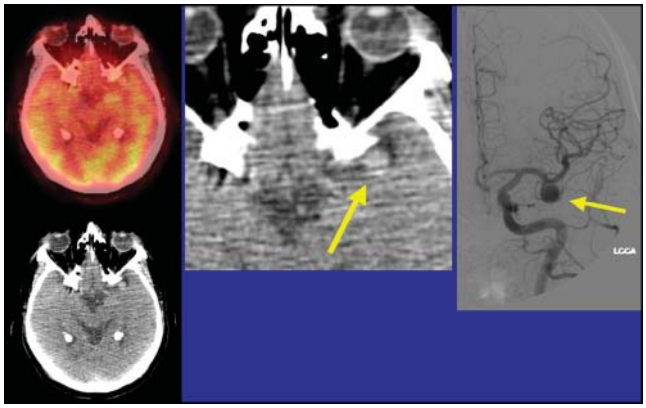

FIGURE 37. One example of life-threatening incidental findings identified on PET/CT studies were these images of an unsuspected 12-mm middle cerebral artery aneurysm.

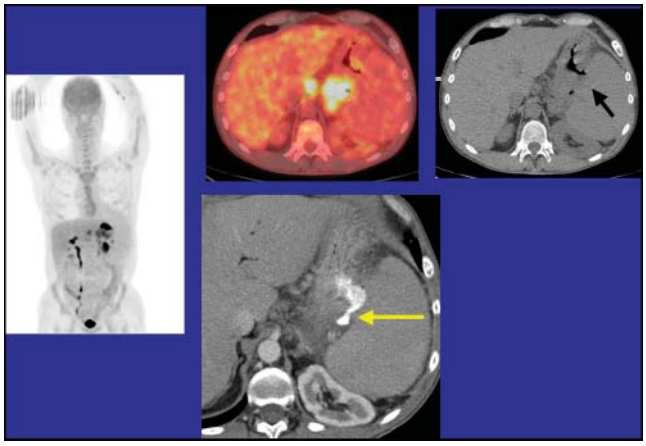

FIGURE 39. Images of incidental finding of a gastric perforation (arrows) with contrast material outside of the stomach.

expertise should also be fused in each practitioner, whether he or she is a nuclear medicine physician or radiologist.

This paper from Millstine and Britz-Cunningham at the Brigham and Women's Hospital (Boston, MA) looked at life-threatening incidental findings identified on PET/CT studies. Figure 37 contains images acquired in a patient with an unsuspected 12-mm middle cerebral artery aneurysm. Other incidental findings presented were hemopericardium in an ^{82}Rb/^{18}F-FDG PET/CT study (Fig. 38) and a gastric perforation with contrast material outside of the stomach (Fig. 39). If you miss one of these findings, you will almost certainly see the patient again in a wheelchair—being pushed by his or her lawyer.

Fusion imaging is being applied in many areas outside cardiology and oncology. Harris et al. from the Royal North Shore Hospital and the Woolcock Institute of Medical Research (Sydney, Australia) reported on fusion imaging of CT pulmonary angiography (CTPA) and SPECT ventilation/perfusion scintigraphy. Figure 40 shows a wedge-shaped defect in the blood flow to the right lung in a patient suspected of having a pulmonary embolism (PE). They achieved good registration of the images using commercial software. In 11 patients who were initially reported as having intermediate probable PE in the V/Q scans, the addition of CTPA allowed the researchers to confidently reclassify 3 as low probability for PE. This technique is particularly useful in the setting of inconclusive CTPA.

Dr. Shahid Mahmood from Singapore studied patients with lung perfusion SPECT/CT angiography, measuring perfusion with ^{99m}Tc-macroaggregated albumin lung SPECT. Figure 41 shows a 45-year-old patient 2 days after hip surgery who experienced sudden onset of severe shortness of breath. Blood flow is seen only in the right upper lobe. Thrombi in major arteries account for absence of blood flow to the entire left lung and right lower lobe. On the fused nuclear study (Fig. 42), peripheral perfusion defects are also visible. When shown as a cine displaying 64 coronal slices, the concave defects at the periphery of the study are quite clear. The conclusion was that CTPA reveals emboli only in large and medium size arteries and that SPECT perfusion reveals small defects out to what are called the fifth order; that, is the 5th branching of the coronary arteries. V/Q imaging, then, is still alive and well, preferably performed by SPECT/CTPA.

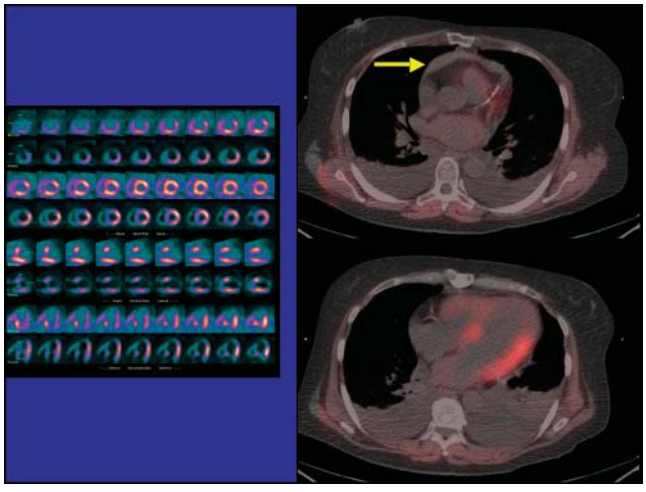

FIGURE 38. Other incidental findings presented included hemopericardium in a ^{82}Rb/^{18}F-FDG PET/CT study.

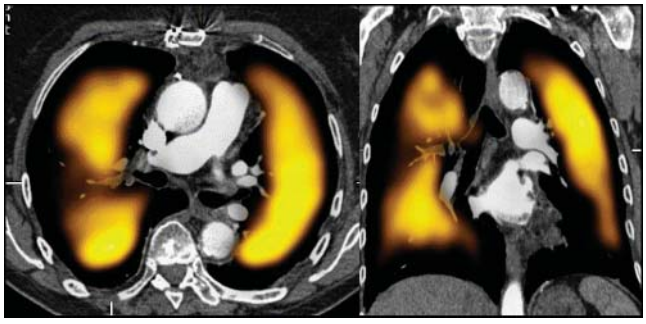

FIGURE 40. Postacquisition fusion of CT pulmonary angiography and SPECT ventilation/perfusion scintigraphy showing a wedge-shaped defect in the blood flow to the right lung in a patient suspected of having a pulmonary embolism.

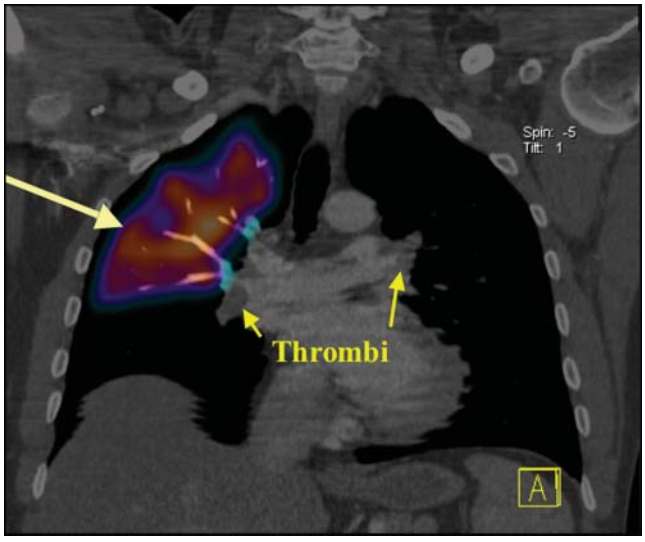

FIGURE 41. ^{99m}Tc SPECT/CT angiography in a 45-year-old patient 2 days after hip surgery, who experienced sudden onset of severe shortness of breath, showed absence of blood flow to the entire left lung and right lower lobe.

It is interesting to me that macroaggregated albumin and xenon ventilation studies are still widely used in perfusion imaging. In 1963, we carried out 42 studies in dogs, with experimental PE induced by intravenously inserting balloons filled with contrast media that would then go out to the pulmonary arteries. These studies clearly showed that perfusion imaging with iodine compounds could show visual defects. I then carried out the first pulmonary perfusion study on myself in 1963. We followed this with something that would be impossible today: we repeated the study in 18 medical students and then examined the first patient. Essentially the same procedure has persisted over all those years. What is new on the scene now is the combination of SPECT with CTPA.

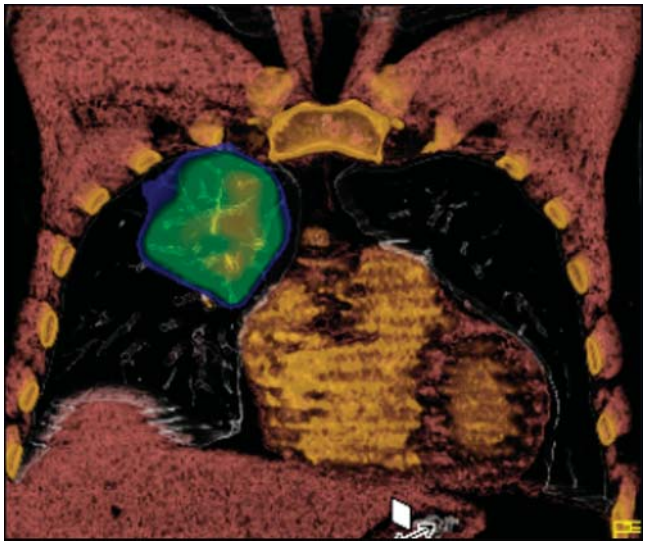

FIGURE 42. In the same patient seen in Figure 41, peripheral perfusion defects are again visible.

Kato et al. from Nagoya University (Japan) and the University Hospital Münster (Germany) compared ^{11}C-choline, which examines fatty acid metabolism, and ^{18}F-FDG PET/CT in the evaluation of calcifications in the aortic and common carotid arterial walls. Eighty-eight of 93 (95%) patients showed ^{11}C-choline uptake in the arterial wall, but only 5 showed ^{11}C-choline uptake in the areas of calcifications. With ^{18}F-FDG, 102 of 111 (92%) of patients had uptake in the arterial wall, and only 14 patients showed uptake in areas of calcifications. Neither ^{11}C-choline uptake nor ^{18}F-FDG uptake at PET/CT correlated with areas of calcifications of the arterial wall. This is an example of a new and very useful type of study in which biochemistry shows that some structural abnormalities do not actually result in biochemical or physiologic abnormality. I remember in the days when unilateral renal disease was being examined and renal stenosis was first associated with hypertension, it was striking to me that autopsy revealed large numbers of patients who had renal artery stenoses but were normotensive throughout their lives. Stenoses and calcifications have a high sensitivity but a low specificity.

Ogawa et al. from the Hamamatsu University School of Medicine (Japan), the National Center for Geriatrics and Gerontology (Obu, Japan), Kyoto University (Japan), Kyushu University (Fukuoka, Japan), and Kobe University School of Medicine (Japan) examined the therapeutic effect of anti-inflammatory drugs on stabilization of vulnerable atherosclerotic plaques. They found that 6 months after treatment with probucol there was a decrease in ^{18}F-FDG accumulation in the thoracic aortic lesion. They concluded that ^{18}F-FDG PET could image the course of plaque stabilization with anti-inflammatory treatment; that is, provide a way to monitor the decrease in macrophage infiltration.

Oncology

Oncology has continued to grow in importance as a focus of nuclear medicine at the SNM Annual Meeting. Figure 43 shows the numbers of presentations on oncology going back to the 1980s. What emerges as new in our approaches to cancer? In my opinion, one challenge is the need

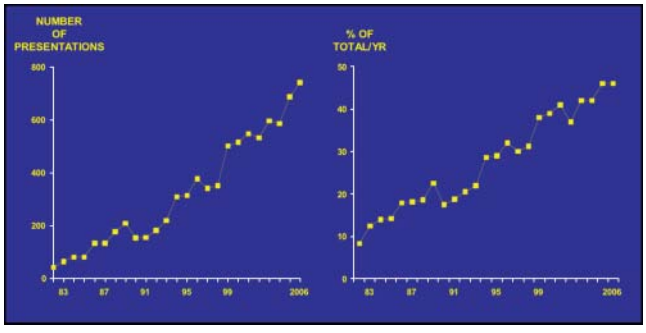

FIGURE 43. Left: numbers of presentations on oncology at SNM meetings, 1983–2006. Right: Oncology topics as percentages of total presentations at each meeting, 1983–2006.

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to tell the public about the value of PET/CT and SPECT/CT. The time really has come to diffuse knowledge of our technology further into the medical community and the public—and the SNM is taking active steps in this direction.

Strobel et al. from University Hospital Zurich presented an evaluation of the utility of integrated ^{18}F-FDG PET/CT in the detection of metastases in staging high-risk melanoma. Again the large numbers of patients now appearing in our studies was apparent. In this study, 53 of 124 patients (42.7%) had melanoma metastases, and 46 of these (86.8%) had PET-positive metastases. The authors concluded that dedicated CT analysis improves the sensitivity and accuracy of integrated PET/CT in staging patients with high-risk melanoma.

Another area of screening that is showing great promise is in whole-body PET/CT colonography, a new staging concept in patients with colorectal cancer. Veit et al. from University Hospital Essen (Germany) studied 52 patients who underwent visual colonoscopy 1 day before PET/CT colonoscopy. The evaluation of "all-in-one" staging comprised of optical colonoscopy and PET/CT colonography (rectal water filling, bowel relaxation) was compared with "conventional" staging with optical colonoscopy and CT staging. They found that PET/CT colonography was significantly more accurate in TNM staging than CT alone in 47 patients who proceeded to surgery. With PET/CT, the T staging was correct in 86% and N staging was correct in 88%. With CT alone, these figures were 68% and 80%, respectively. Overall for TNM staging, PET/CT was 76% correct and CT alone was 54% correct. "All in one" staging changed therapy decisions in 5 patients compared with "conventional" staging.

Prognosis was a major topic of interest in oncology studies at the meeting. Chen et al. from the University of California, Los Angeles, and the Southern California Permanente Medical Group (Los Angeles) predicted the response of malignant brain tumors to bevacizumab and ironotecan therapy with ^{18}F-fluorothymidine (^{18}F-FLT) and ^{18}F-FDOPA PET. Figure 44 shows changes that showed up on MR imaging after 3 months, whereas the same changes were found to be visible on ^{18}F-FLT PET after 1 week. In 1 week, the responders could be distinguished from the nonresponders.

Pauleit et al. from the Research Center Jülich (Germany) and the University of Düsseldorf (Germany) reported on a double-tracer study using ^{18}F-fluoroethyltyrosine (^{18}F-FET) and ^{18}F-FDG PET in patients with cerebral gliomas. The study included 28 patients who first underwent ^{18}F-FET PET, with the ^{18}F-FDG PET performed 30 minutes later. ^{18}F-FDG uptake was calculated by subtraction of the ^{18}F-FET scan from the combined tracer scan. Figure 45 shows an MR image of a patient with a cerebral glioma, along with the ^{18}F-FET PET study and the ^{18}F-FET/FDG accumulation. It's notable that the^{18}F-FET showed a far greater contrast with normal brain than did the ^{18}F-FDG study.

Bodet-Milin et al. from the Cancer Centre (Saint Herbalin-Nantes, France) compared ^{18}F-FDG PET and MR in monitoring chemotherapy response and recurrence in patients with glioma. They found PET to be more sensitive than MR imaging (80% and 70%, respectively) in detecting recurrent high-grade glioma, although both modalities had the same specificity (100%). The negative predictive value of ^{18}F-FDG PET was higher than that of MR (83.3% and 63.0%, respectively).

Lung cancer poses a particular challenge in the development of imaging, monitoring of treatment, and

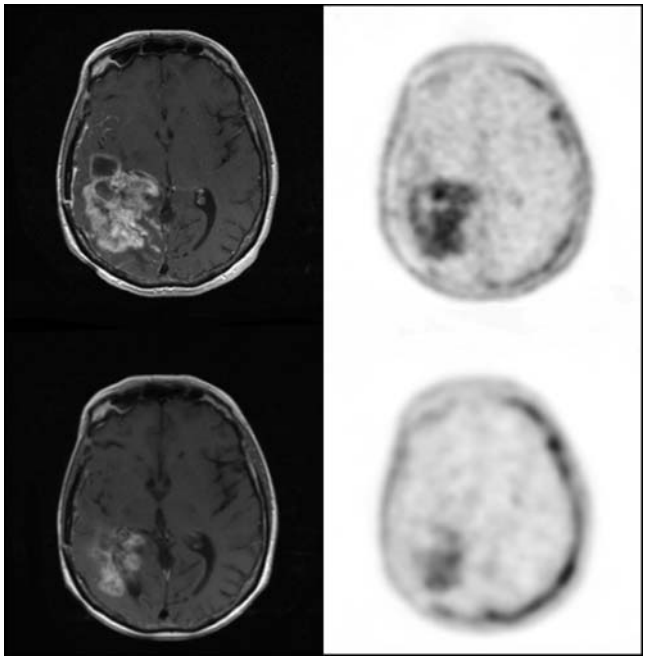

FIGURE 44. Status before (top) and response after (bottom) treatment with bevacizumab and ironotecan therapy for malignant brain tumor was assessed with MR imaging at 3 months (left) and with ^{18}F-FLT PET at only 1 week (right). ^{18}F-FLT PET was able to distinguish responders from nonresponders much earlier.

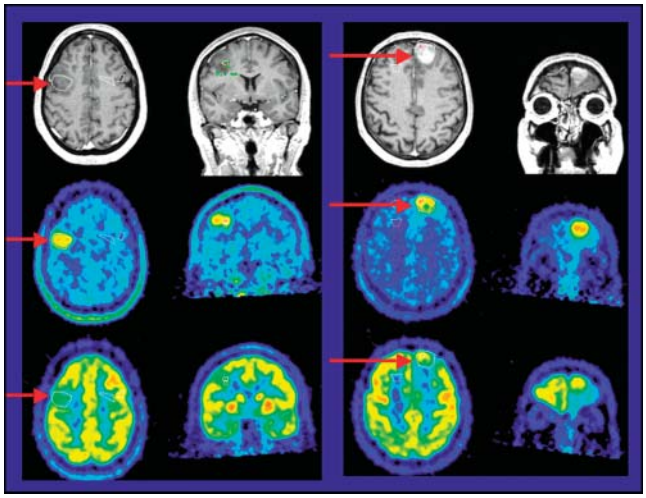

FIGURE 45. Images acquired in patients with low-grade (left) and high-grade (right) gliomas with MR (top row), ^{18}F-FET PET (middle), and double-tracer ^{18}F-FET/^{18}F-FDG PET (bottom).

prognostic capabilities that can improve treatment and management. Small cell lung cancer comprises 15% of total lung cancers diagnosed, with 70% of patients having metastases at the time of diagnosis and only a 5%–15% 5-year survival rate. The blood serum marker (carcinoembryonic antigen [CEA]) does not reflect tissue expression in the tumor, and CEA blood levels increase only with metastatic disease. The need for accurate pretherapy targeting is clear, and this is an area that I believe has enormous long-range potential for tracer development.

Goldenberg et al. from the Garden State Cancer Center (Belleville, NJ) reported on their approach in several papers and collaborations at the meeting, using bispecific peptides to create custom pretargeting in patients with lung cancer. Their results indicate very high and rapid tracer uptake, so that imaging can be performed <1 hour after injection. In addition to longer retention in lesions, the technique is comparable in sensitivity to ^{18}F-FDG PET and has greatly increased specificity. Figure 46 is a schematic diagram developed by Goldenberg to show the protein targets. This is a broad approach than can be expanded to a number of specific diseases. The diagnostic procedures can be combined with therapeutic procedures in the same new drug application (NDA). This may facilitate improvement in the approval of new tracers, currently a major challenge to the development of molecular imaging.

Infection and Inflammation

New tracers are also under development in the area of infection and inflammation imaging for use in PET and SPECT/CT. Mahmood et al. from the Nuclear Medicine and PET Centre (Singapore) presented a ^{99m}Tc-MDP SPECT/CT image clearly showing a Brodie's abscess (Fig. 47). This is another example of the extreme value obtained by doing high-quality hybrid fusion of SPECT/CT with tracer studies such as, in this case, ^{99m}Tc-MDP.

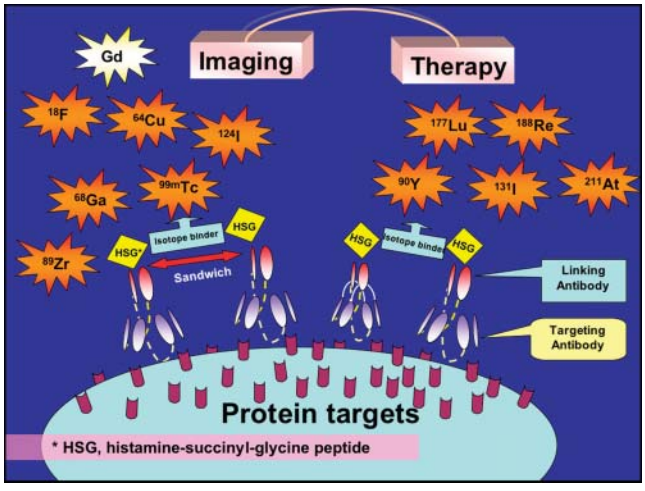

FIGURE 46. Schematic showing mechanism of protein targeting using bispecific peptides to create custom pretargeting.

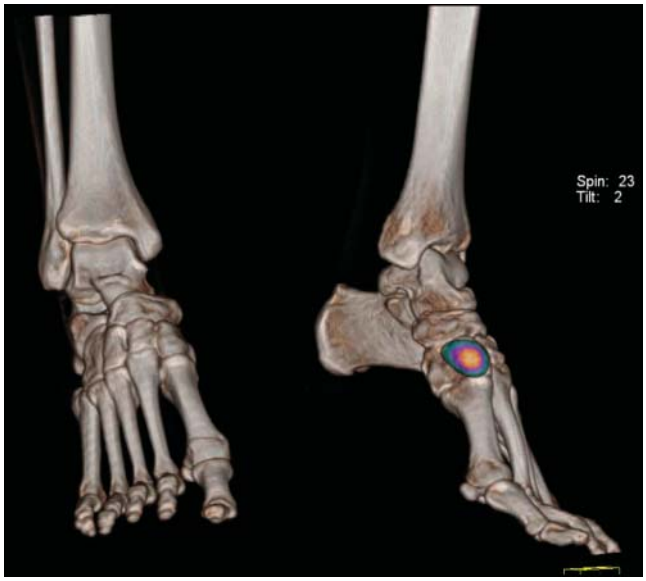

FIGURE 47. ^{99m}Tc-MDP SPECT/CT image (right) showing a Brodie's abscess. Left: 6-slice CT image.

Pharmaceuticals

It is important that we work to facilitate and expedite the approval of new pharmaceuticals. One approach we might consider is incorporating diagnostic and efficacy-monitoring tracers in primarily therapeutic clinical trials to encourage financial support from pharmaceutical companies and facilitate regulatory approval and reimbursement. We are limited by the fact that large pharmaceutical companies favor the development and marketing of therapeutic drugs administered over long periods of time. They hesitate to invest in developing diagnostic tracers that will be used only once or twice in a specific patient. If we could find effective ways of combining studies of therapy and diagnosis, the results might be safer, more effective, and less costly pharmaceuticals and radiopharmaceuticals. The suggestion is to include molecular imaging in treatment-oriented NDA applications to Internal Review Boards and the FDA and then expand off-label uses after the FDA has approved the treatment protocol that included the diagnostic information. The next step, of course, would be to educate the public, political leaders, and the Centers for Medicare & Medicaid Services on the results of the clinical trials. Perhaps this is a fruitful direction for securing approval for novel diagnostic tracers and making them available for routine use.

Instrumentation and Technology

The production and diffusion of technology depends on people, ideas, and inventions. One example of this principle is in the area of data processing. Nie et al. from the University of Chicago (IL) reported on a computerized method of distinguishing between benign and malignant pulmonary nodules seen on PET and CT using an artificial neural network. They found that when they used the

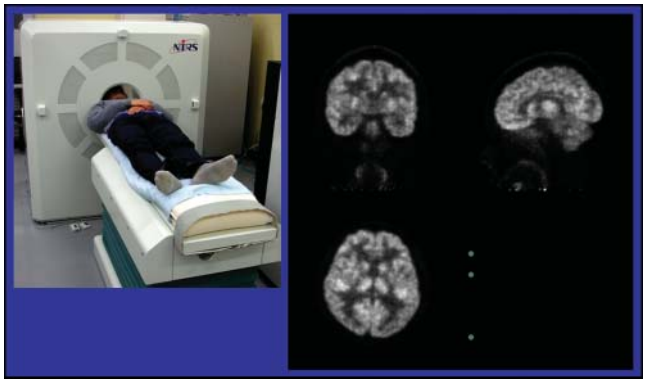

FIGURE 48. Human brain images (right) acquired with a novel 4-layer depth-of-interaction PET scanner (left).

computer to analyze the study with 3 different computer-assisted detection schemes for CT alone, PET alone, and PET plus CT, PET/CT was clearly superior—a difference that could be quantified and predicted. This represents an area in which enormous advances can be made.

Many technological advances were presented at the meeting. Chinn et al. from the Stanford University School of Medicine (CA) presented an example of an image reconstruction strategy for a 1-mm resolution, dual-panel breast-dedicated PET system.

Yamaya et al. from the National Institute of Radiological Sciences (Chiba, Japan), the Shimadzu Co. (Kyoto, Japan), and the Tokyo Institute of Technology (Yokohama, Japan) presented the first human brain images made with a novel 4-layer depth-of-interaction PET scanner, the jPET-DR (Fig. 48). The apparatus has 4 detectors in 4 planes, and through computer analysis a much better resolution and sensitivity can be achieved.

Another example of improved instrumentation in assessing dopamine transporters came from Syrota's group at the Service Hospitalier Frédéric Joliot (Orsay, France; Fig. 49). The image shows the improvement in volume and spatial resolution achieved by the systems as well as the clear separation of the caudate nucleus and putamen.

Berman et al. from a consortium of universities and institutions in the United States, Israel, and the United Kingdom reported the initial clinical results from a novel camera system for high-speed quantitative molecular imaging with double the conventional spatial resolution. The D-SPECT cardiac system has 10 independently rotating detector units, performs list mode acquisition, and uses proprietary algorithms to present the images. Figure 50 shows a clinical feasibility study with a 2-minute gated SPECT acquisition, producing serial 10-second images.

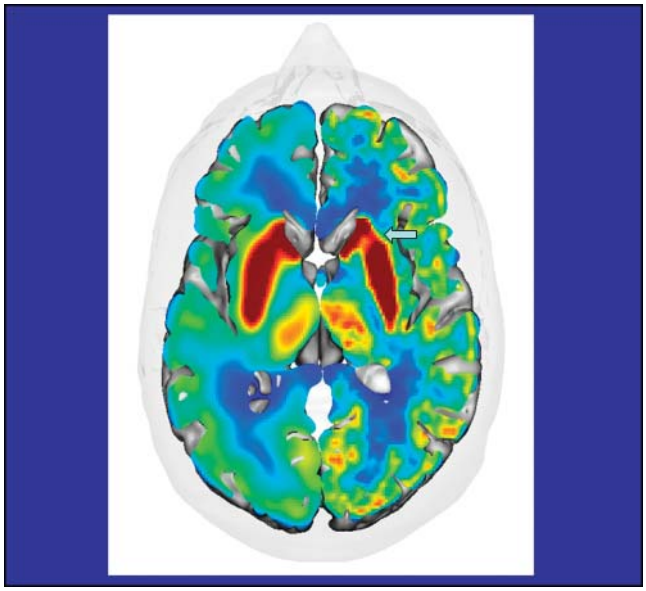

FIGURE 49. A clear separation between the caudate nucleus and putamen is seen in this dopamine transporter image from a high-resolution instrument shown at the 2006 SNM meeting.

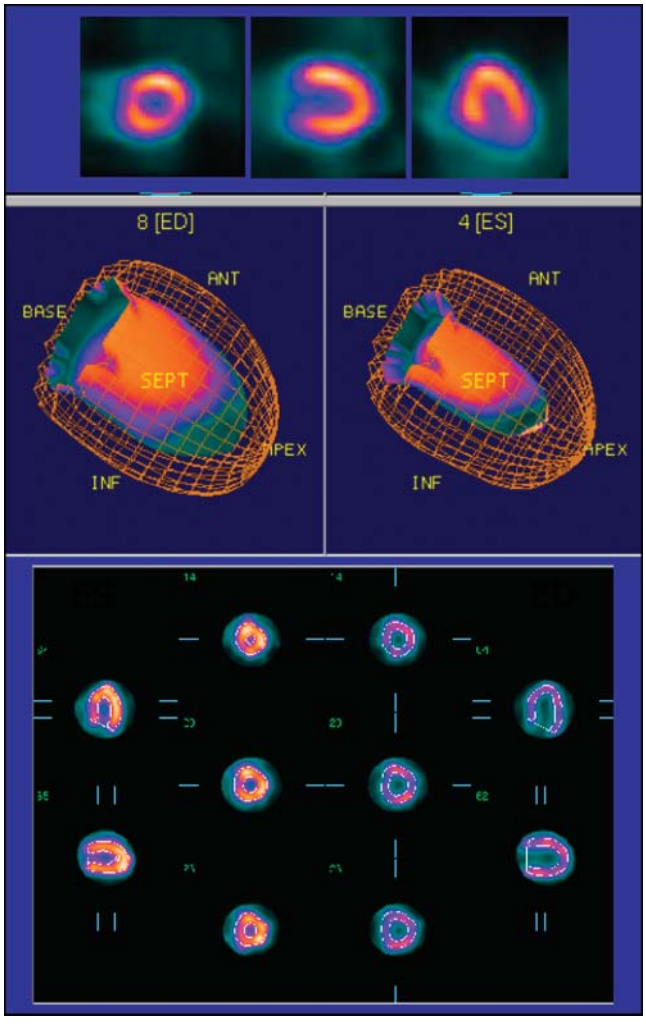

FIGURE 50. Clinical feasibility study acquired with the D-SPECT cardiac system, which provides a 10-fold increase in sensitivity and a 2-fold increase in resolution over most currently used systems.

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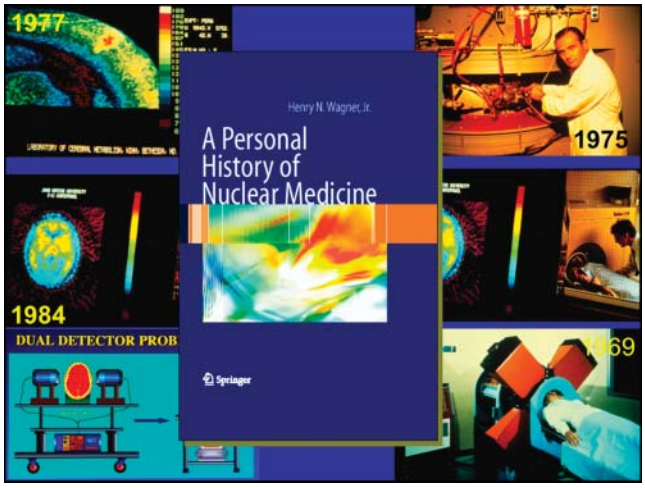

FIGURE 51. The author's recent memoir and historical retrospective, *A Personal History of Nuclear Medicine*.

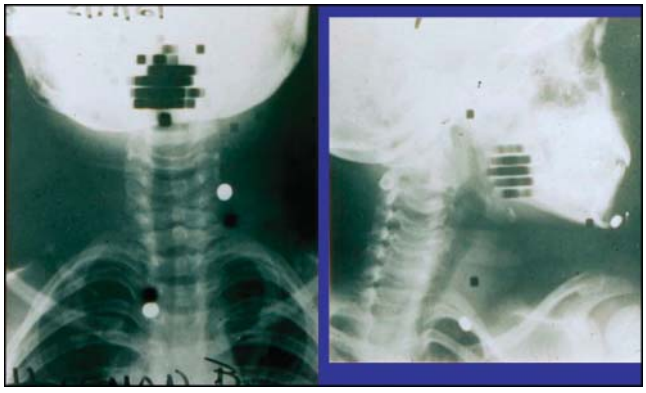

FIGURE 52. A 1961 rectilinear scan performed with ^{131}I and superimposed over a radiograph.

Looking Back and Thinking Forward

In the 29 years since I originated these Highlight talks, a number of accomplishments and trends lead to the formulation of several general observations about our progress as a discipline. These include:

- Positron-emitting tracers have become dominant, but single-photon tracers still thrive. SPECT/CT is gaining rapidly in use, and PET/CT continues to be accepted as a routine adjunct in clinical practice.
- Production of PET tracers, such as ^{11}C tracers, by cyclotron centers continues to increase. I still predict that every very large hospital and pharmaceutical company will have a cyclotron in 30 years.
- Structure, function, and biochemistry have fused to become complementary in research endeavors and in some areas of clinical practice.
- Imaging-focused companies have become active in radiopharmaceutical and drug development as well as instrument development.
- Dedicated animal scanners, first proposed in 1987, have been perfected and become widespread in industry and academia.
- Medicine has progressively increased its spatial resolution from the whole body to organs to tissues to cells to molecules.
- What we imagined, we have now achieved. Our imaging is truly "4-dimensional."
- The basic units of molecular medicine are micromoles/minutes/milliliter of tissue.
- The time dimension is a key parameter in molecular medicine. We study processes—not just states at specific points in time.

Looking back can be a rewarding endeavor. This week saw the publication of *A Personal History of Nuclear Medicine* (Fig. 51; New York, NY: Springer), which covers many of the trends I have addressed today. One example will show the value of retracing our steps from time to time. A patient came to our hospital in 1961 because of a mass at the back of the tongue. The question was: should the mass be removed? A rectilinear scan was performed with ^{131}I and superimposed over a radiograph (Fig. 52). (Since 1958 at Hopkins, we had superimposed scan images on radiographs—early "fused" images.) The mass accumulated iodine, which showed that it was thyroid, whereas no thyroid was seen in the normal position in the neck. Had the mass been removed simply because it was present, without referral for nuclear studies, the patient would have become hypothyroid. Here we see a chemical reaction measured with external measurements, the use of chemical tracers, the combining of anatomy and physiology, and the application of the resulting knowledge in decision making for the patient's benefit—all at a time when nuclear medicine was still in its infancy. We have often known very early on where we need to go, but the challenge is in finding effective, efficient, and beneficial ways to get there.

In my opinion, we should work proactively for the future of our discipline by:

- Presenting to the public our unique and new approach to the practice of medicine, including the value unit of knowledge;
- Educating the public about how we prevent, diagnose, and treat disease, and how we can then assess the effectiveness of the treatment;
- Interacting with other specialists more than ever before; and
- Developing and assessing our competence in all aspects of imaging of regional structure, chemistry, and function.

The final sentence in my book is, "Many pioneers of nuclear medicine are no longer with us, but those who remain can be very proud." I leave you with that thought today. ✳