Henry N. Wagner, Jr., MD

THE SOCIETY OF NUCLEAR MEDICINE (SNM) CONDUCTED ITS 43ND ANNUAL MEETING IN DENVER, CO IN JUNE. FOR THE 19TH CONSECUTIVE YEAR, HENRY N. WAGNER, JR., MD, PROFESSOR OF MEDICINE, RADIOLOGY AND ENVIRONMENTAL SCIENCES AT THE JOHNS HOPKINS MEDICAL INSTITUTIONS IN BALTIMORE, MD PRESENTED HIS VIEW OF THE SCIENTIFC HIGHLIGHTS AT THE FINAL SESSION OF THE MEETING. AT THIS YEAR'S MEETING, THE SNM LEADERSHIP HONORED DR. WAGNER BY NAMING A PLENARY SESSION LECTURESHIP AFTER HIM.

1996 SNM Annual Meeting: Medical Problem Solving

The 1996 SNM Annual Meeting featured important new tracers and instruments—more than ever before at a single Society meeting. There was, however, an increasing number of presentations representing the "demand side" of nuclear medicine. For me, the theme of the meeting was a "Focus On Problem-Solving." Many presentations dealt with the six questions that characterize the practice of medicine:

1. What is wrong?
2. How did it happen?
3. What is going to happen?
4. What should be done about it?
5. Is the treatment effective?
6. Is the care of the patient cost-effective?

To illustrate my point: Of the more than 1200 presentations, 140 dealt with prognosis (48 in cardiology; 37 in neurosciences; 41 in oncology), 76 addressed treatment planning and 131 monitoring the effectiveness of treatment. Evidence was presented showing how nuclear medicine can reduce, not increase, the overall cost of medical care. This contradicts those who say that there has never been a worse time to introduce "high tech" procedures, such as PET and SPECT, into the practice of medicine. I have long believed that more widespread use of currently available screening and other diagnostic techniques would result in a significant reduction in health care expenditures.

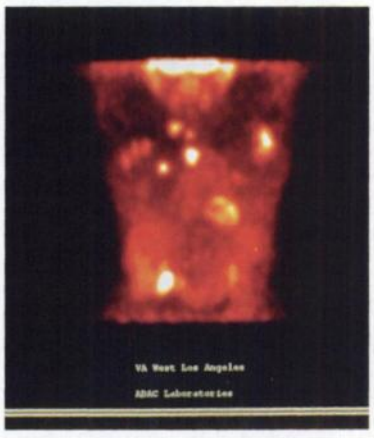


Figure 2. Convergent PET and SPECT. A dual detector (SPECT) FDG study of a patient with metastatic cancer.

Most health care economists reject this idea. Unfortunately, nearly all of them believe that the primary reason for the increase in health care costs is technological developments. Many of the presentations indicated otherwise. The new data provide evidence that can be used to educate referring doctors as well as health administrators about what nuclear medicine is and what it does. Ignorance is what is costly in the care of patients. **The information that nuclear medicine provides can lower overall costs of health care, both in prevention of disease and more cost-effective and better care.**

Surgeon Sherwin Nuland has written that often it is to main-

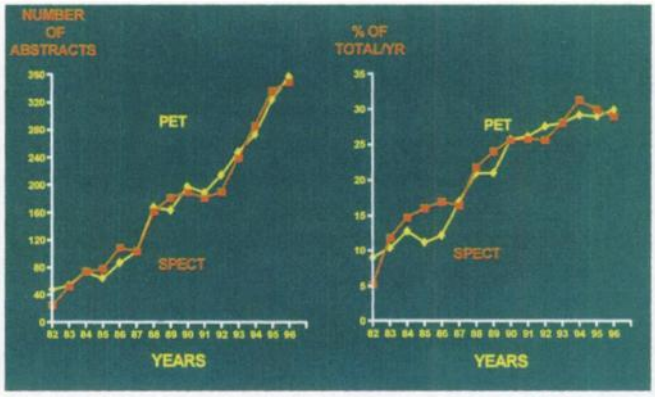


Figure 1. Comparison of presentations involving PET and SPECT.

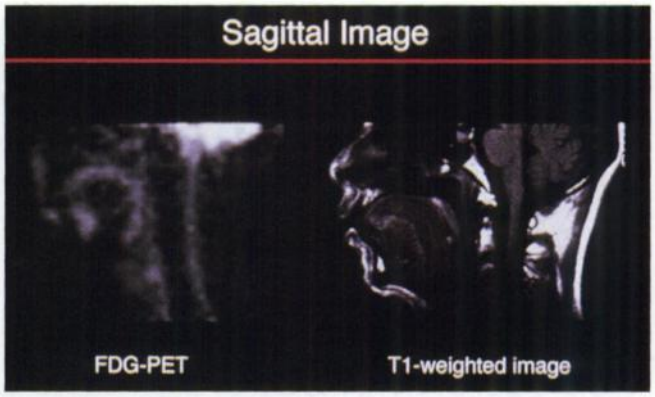


Figure 3. Use of FDG in locating recurrent head and neck cancer. No abnormalities were seen in this patient.

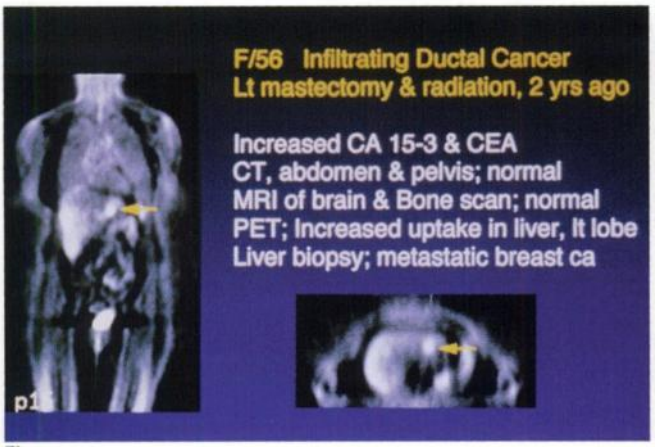


Figure 4.

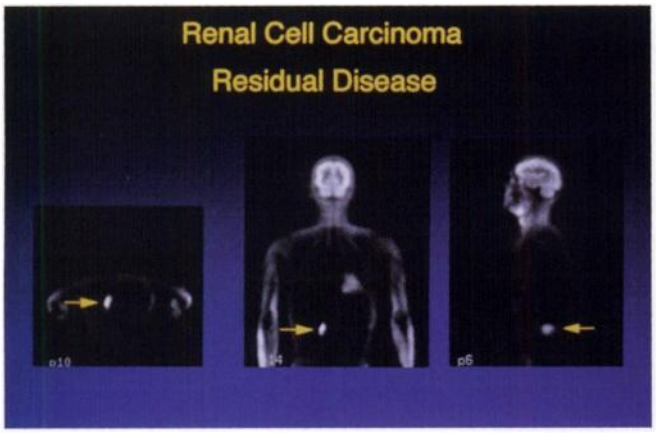


Figure 5.

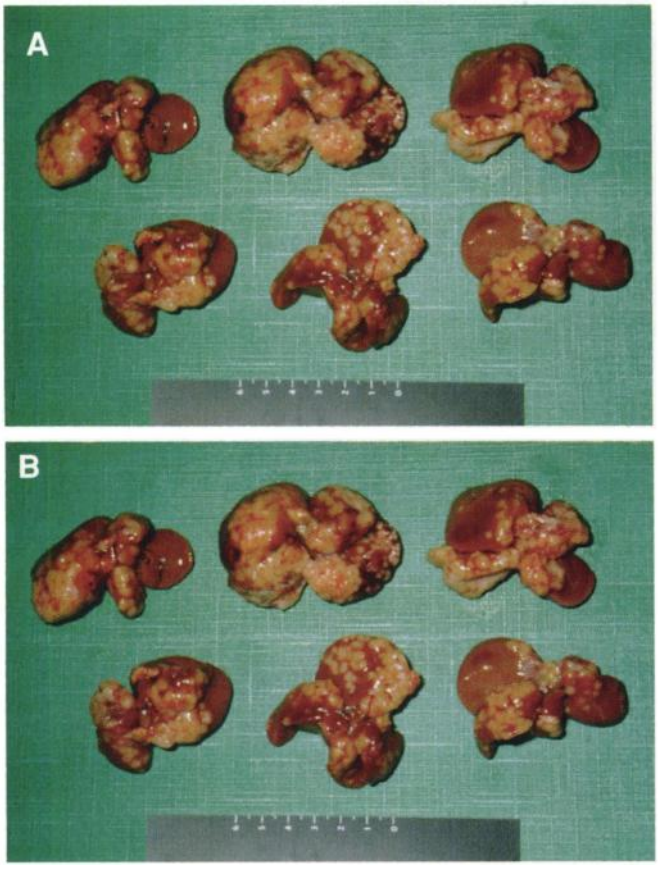


Figure 6.

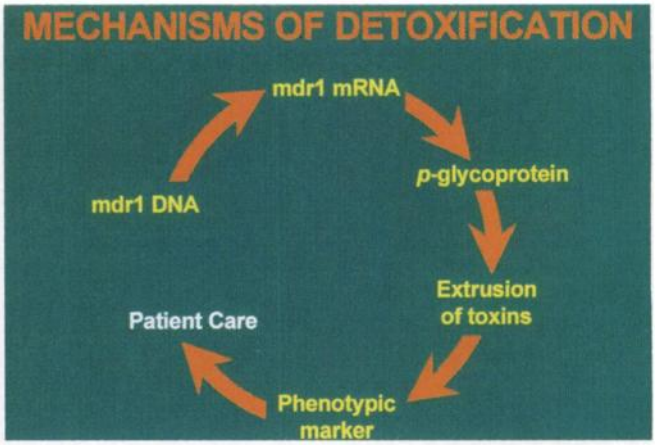


Figure 7.

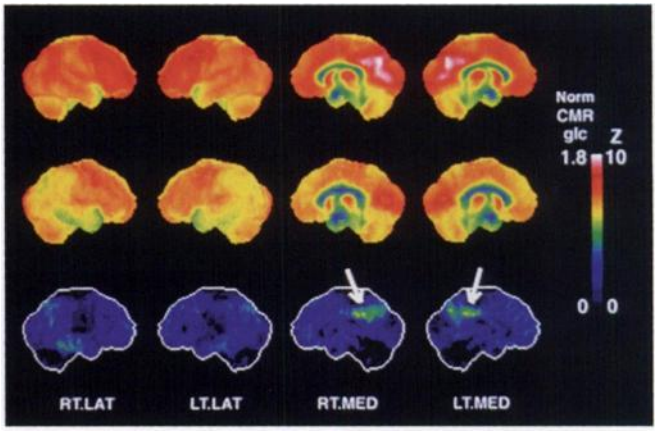


Figure 8.

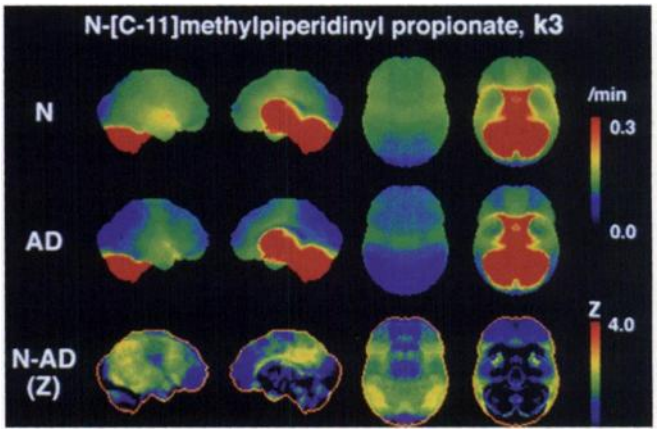


Figure 9.

Figure 4. Metastatic breast cancer in the liver revealed by whole body FDG-PET.

Figure 5. Recurrent renal cancer revealed by FDG-PET.

Figure 6A. Multiple neuroendocrine tumors in the liver of an experimental animal.

Figure 6B. No lesions were found in an animal treated with an ^{111}In somatostatin analogue in therapeutic doses.

Figure 7. Paradigm of transition from genotype to patient care.

Figure 8. Earliest regions of involvement in patients with Alzheimer's disease.

Figure 9. Abnormal regional acetylcholinesterase levels in patients with Alzheimer's disease.

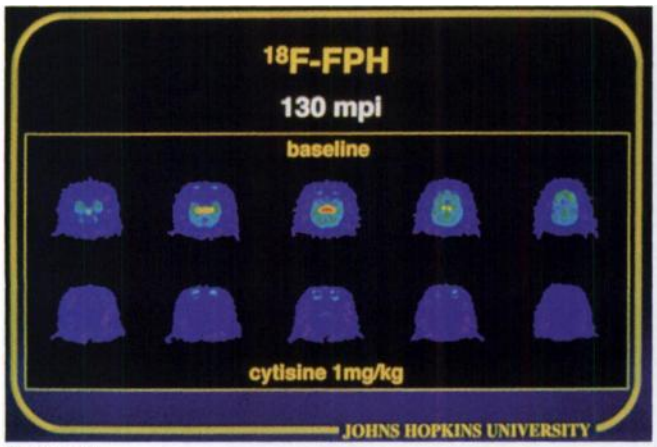


Figure 10.

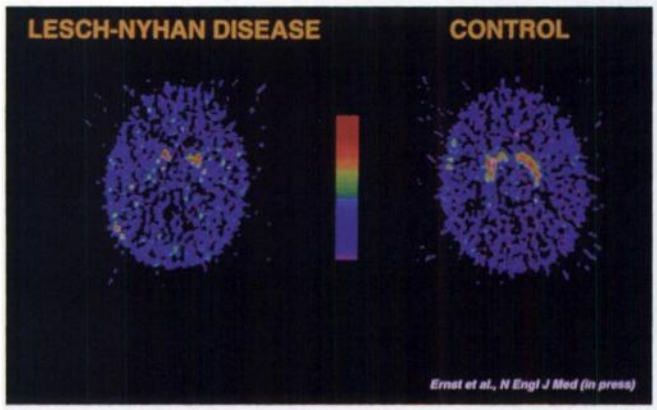


Figure 11.

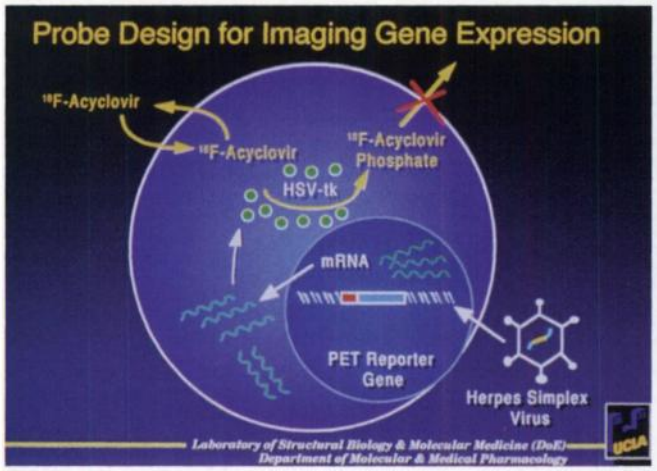


Figure 12.

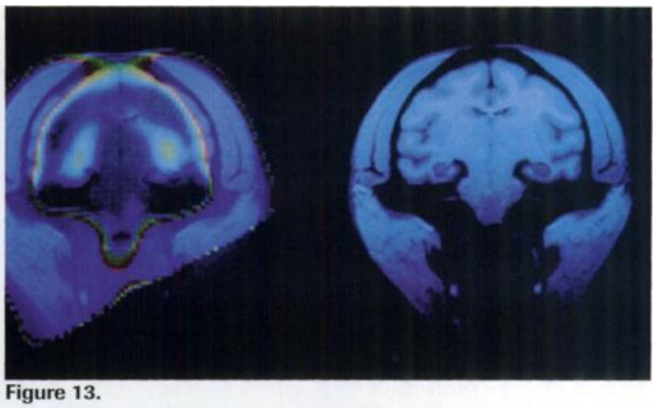


Figure 13.

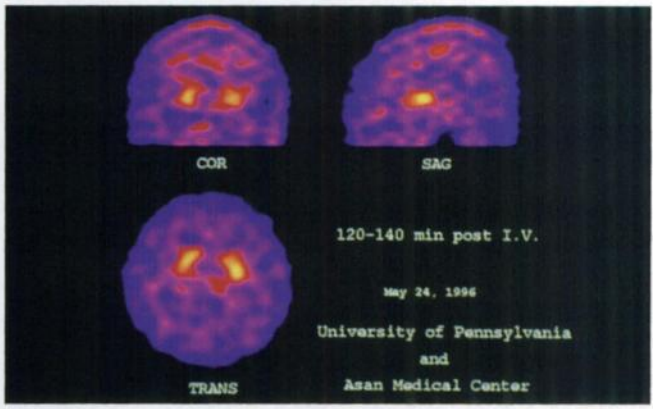


Figure 14.

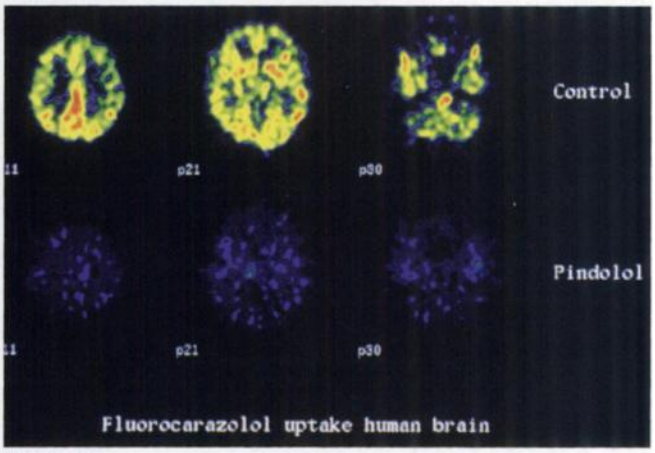


Figure 15.

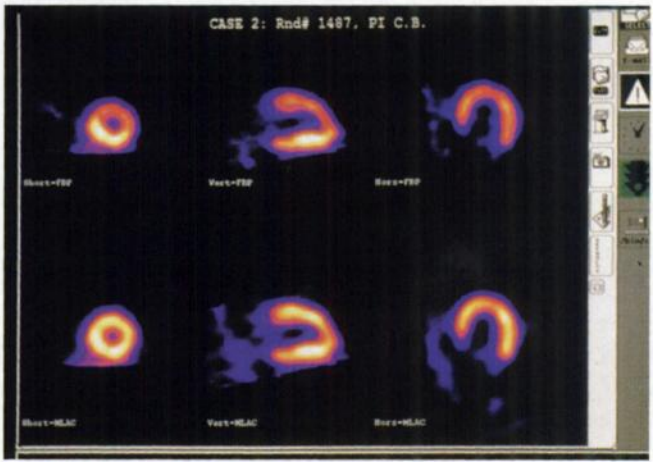


Figure 16.

Figure 10. Fluorine-18-epibatidine for imaging of nicotinic cholinergic receptors in the brain.

Figure 11. Reduced dopamine synthesis in Lesch-Nyhan disease.

Figure 12. Mechanism of ^{18}F-acyclovir accumulation in gene therapy.

Figure 13. First imaging of dopamine transporter with ^{99m}Tc-labeled tracer.

Figure 14. Image of the year. First imaging of dopamine transporter with a ^{99m}Tc-labeled tracer.

Figure 15. Imaging of norepinephrine receptors in the brain.

Figure 16. Attenuation artifacts in myocardial perfusion images caused by breast in women and diaphragm in men.

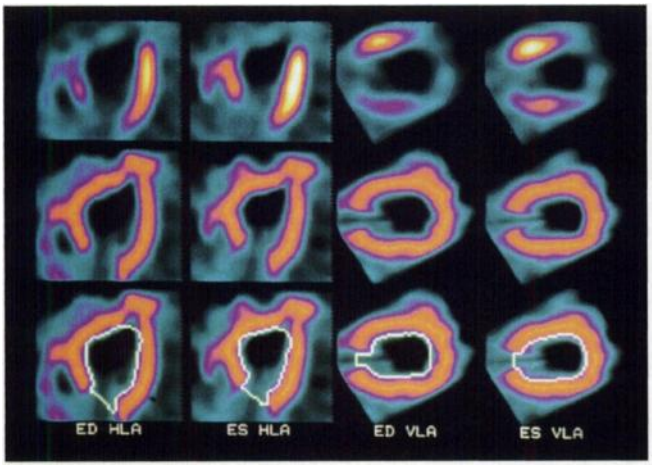


Figure 17. Left ventricular wall motion examined after myocardial blood flow measurement with ^{99m}Tc-sestamibi.

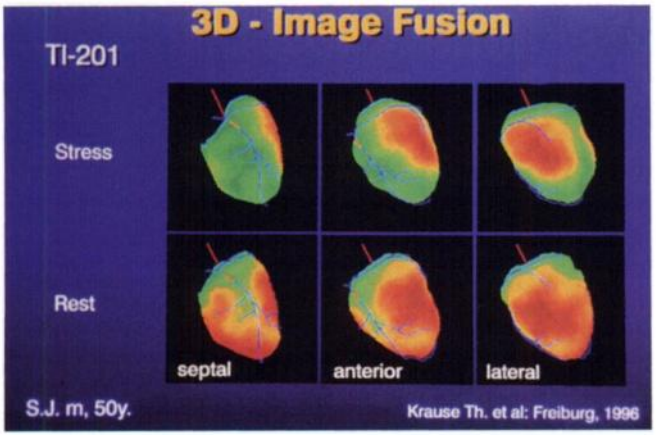


Figure 18. Co-registered images of coronary artery stenosis and the resultant diminution of regional myocardial blood flow.

tain their own hope that doctors delude themselves into taking courses of action whose chance of success are too small to justify the action. Many cancer patients undergo surgery only to be told their disease proved to be inoperable. We are moving medicine into a new age of certainty, when only those procedures with a high probability of being helpful will be performed.

PET and SPECT Presentations

As in past years, the number of presentations involving PET equaled those involving SPECT (Fig. 1). Many attendees perceived an increase in PET presentations at this meeting, but this was not the case. Rather, PET presentations received more attention this year than in the past, as nuclear medicine physicians and technologists recognize the growing clinical importance of PET. **They now realize that PET has joined SPECT in the mainstream of nuclear medicine.**

The striking clinical results obtained with dual-detector "SPECT" systems, used in a coincidence counting mode, support the concept that PET and SPECT are converging. Multienergy imaging systems, rather than dedicated PET or SPECT instruments, are likely to dominate the future of nuclear medicine (Fig. 2).

The importance of both single-photon and positron-emitting radiotracers is evidenced by the 380 presented abstracts that

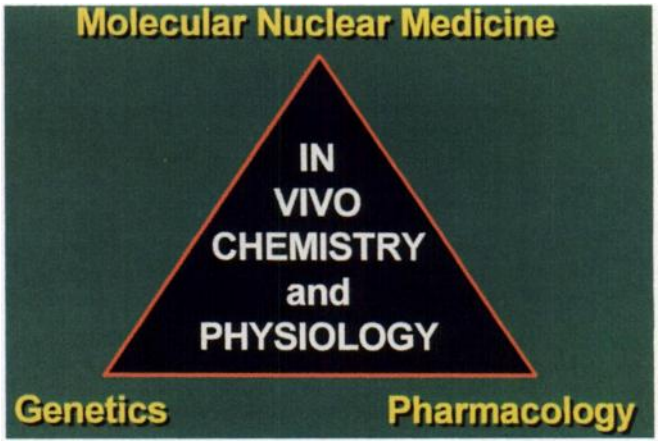


Figure 19. Nuclear medicine translates the advances in genetics and pharmacology into the care of patients.

involved ^{99m}Tc, 79 that involved ^{123}I and 60 that involved ^{111}In. Fluorine-18 was covered in 211 presentations, ^{11}C in 84, ^{15}O in 44 and ^{13}N in 12.

Oncology, neurosciences and cardiology presentations dominated the meeting, but the genetics category is gaining an important place. One hundred and fifty presentations involved ^{18}F-deoxyglucose (FDG). Of the FDG presentations, 88 were in oncology, 49 in neurosciences and 23 in cardiology. **I have nominated FDG as the "molecule of the century."** I solved the problem of what to dub deoxyribonucleic acid (DNA) by nominating it as the "molecule of the millennium."

One of the most important characteristics of nuclear medicine is that important developments and research results starting in one organ of the body are often extended into other organs. For example, dopamine receptors were first imaged in the brain and were then found to be present in pituitary tumors. Many other recognition sites in the brain are expressed in cancer cells. Examples include substance P, vasoactive intestinal peptide, sigma and bombesin receptors.

Recognition sites are as important in oncology as in neurosciences. Of the oncology papers dealing with intercellular and intracellular recognition sites, 23 involved somatostatin receptor-binding analogs, 5 involved estrogen receptors, 3 involved vasoactive intestinal peptide, 3 sigma receptors and 3 bombesin receptors, 2 involved epidermal growth factor and 2 involved melanocyte stimulating hormone receptors. There was one presentation on interleukin-2, one on androgen receptors and one on Mannan binding receptors.

Head and Neck Cancer

Presentations dealt with cancer of nearly every organ of the body. There was increasing interest in FDG-PET accumulation in the mucosal layers of the oral cavity and pharynx, and in the use of FDG-PET for detection and precise anatomical localization of recurrent cancer in the head and neck (Abstract 1125) (Fig. 3).

Distant metastases were found using FDG in 33% of patients who had in the past been operated on for head and neck cancer and were most often found in patients with recurrent squamous-cell cancer (44%) (Abstracts 602, 601). Anatomic imaging by

CT or MRI missed 30% of patients with confirmed distant metastases and 43% in patients with squamous-cell cancer. **PET findings of distant metastases avoided fruitless surgery in 33% (10/30) of the patients.** Clearance of ^{11}C-acetate was found to have advantages over FDG by Yeh and colleagues at the National PET/Cyclotron Center in Taipei, Taiwan in patients with nasopharyngeal cancer (Abstract 603). In preliminary studies, FDG imaging predicted the response to chemotherapy (Abstract 600).

Lung Cancer

Patients with lung cancer are often found to have nonresectable disease at the time of surgery. In 39 patients with non-small-cell lung cancer, 56% of the patients were found to have mediastinal involvement at surgery. FDG studies detected 86% of these, compared to 60% detected by CT (Abstract 1164).

In patients with small (less than 3 cm) solitary pulmonary nodules, investigators from the Technische Universitat in Munich reported that FDG-PET could differentiate 90% of the malignant lesions (Abstract 435). The negative predictive value of 87% was too low to replace invasive diagnostic tests. A feasible alternative would be to combine the lack of FDG accumulation with the clinical and other information and then observe the patient at three-month intervals rather than resorting immediately to fine-needle biopsy or thoracotomy, particularly in those persons at low risk of having cancer or with a high risk of surgical complications.

Several presentations involving patients with non-small-cell lung cancer found that when FDG studies were performed prior to bronchoscopy and mediastinoscopy, fewer invasive procedures were performed. This both improved the quality of care and decreased the overall costs (Abstracts 431-435, 475-478). For example, in a study by Baum and colleagues from University Medical Center, Frankfurt, Germany, FDG studies were decisive in surgical decisions in 11 of 26 patients (Abstract 473). FDG-PET correctly staged 26 of 32 patients (Abstract 474).

Worsley and colleagues from the Tri University Meson facility in Vancouver, Canada used a SPECT scanner equipped with a 511-keV collimator with FDG imaging to differentiate benign from malignant nodules (Abstract 134). The results were satisfactory in nodules greater than 2 cm.

In a review of the records of patients with suspicious pulmonary nodules, Gambhir and colleagues from University of California, Los Angeles developed a rigorous quantitative economic model based on decision tree sensitivity analysis. **When FDG studies were added to the diagnostic process, there was a projected cost savings of $5200 per patient without a loss of life expectancy.** When the data are applied to the entire U.S. population, the estimated savings totaled between $50 to $500 million/per year, depending on the assumptions (Abstract 432).

Further cost analysis studies conducted by Valk and colleagues from the Northern California PET Imaging Center in Sacramento found that the cost savings of procedures, such as thoracotomy or mediastinoscopy, that were avoided by the use of FDG-PET in 72 patients with non-small-cell cancer was $292,000, compared to the cost of $ 87,000 for the PET studies (Abstract 434).

Colorectal Cancer

When patients with colorectal cancer undergo surgery for treatment of hepatic metastases, between 25% and 50% are found to be inoperable. FDG studies can establish the extent of metastases without surgery. An entire session was devoted to FDG studies in colorectal cancer (Abstracts 515-520). FDG studies were comparable to CT in detecting liver metastases, but more accurate in detecting omental and lymph node metastases, and pelvic recurrences (Abstract 515). In a study of 52 patients from Vanderbilt University, **FDG studies altered surgical plans in 17 of 61 occurrences of unsuspected extrahepatic disease (Abstract 516).** Valk and colleagues at the Northern California PET Imaging Center in Sacramento found that FDG studies reduced the cost of the care of such patients by a factor of 3 (Abstract 518).

Breast Cancer

Sixty-three presentations focused on breast cancer. Seventeen involved ^{99m}Tc-sestamibi and nine involved FDG. The overall goal of many studies was to decrease the number of invasive procedures in differentiating benign from malignant breast lumps. Of the more than 600,000 lumps removed surgically each year in the U.S., 400,000 prove to be benign. With the most advanced ultrasound and mammographic procedures, the number of surgical biopsies might be reduced by half. At an average cost of surgical biopsy of $5000, this would amount to a savings of $1 billion/year.

A variety of tracers have been used to differentiate benign from malignant breast lumps. This year, 9 used FDG, 17 used ^{99m}Tc-MIBI and 2 used tetrofosmin (Fig. 4).

One can examine a solitary breast lesion to determine the probability of malignancy and search for axillary metastases. An example of many reports on this topic is that of Adler and colleagues from University Hospitals, Cleveland, OH, who performed FDG studies in 85 patients with newly discovered breast masses of at least 5 mm in diameter (Abstract 384). When there was a 99% sensitivity for the detection of malignancy, there was a 71% specificity. This means that patients with negative studies could be spared unnecessary biopsies. Similar results were reported from Technische Universitat in Munich (Abstract 385). These investigators recommended quantification of the FDG results combined with subjective visual interpretation of the images.

In their studies of patients with metastatic breast cancer, investigators at UCLA reported that whole-body FDG studies were effective in detecting recurrent metastatic breast cancer (Abstract 386). They found that ROC analysis was helpful in establishing decision thresholds. Washington University researchers used FDG and ^{18}F-estradiol to assess the response of tumors to tamoxifen therapy (Abstract 387).

The results of many presentations indicate that both FDG and ^{99m}Tc-sestamibi can contribute to the care of women who have suspicious breast masses. Two multicenter trials sponsored by DuPont Merck Pharmaceutical Company in North Billerica, MA, included 673 patients—286 of whom had palpable breast

(Continued on page 26N)

Annual Meeting (Continued from page 17N)

nodules and 387 had nonpalpable nodules detected by mammography (Abstract 287). When scintimammography was performed on these patients, it was found to have an 85% sensitivity in detecting malignancy, with a 19% false-positive rate, which is far less than mammography, for which the false-positive rate is 40% or more.

Interestingly, the results were similar for palpable and nonpalpable nodules, and, unlike the case with mammography, fatty or dense breasts did not present any special problems for the sestamibi studies (Abstract 288).

Axillary lymph node involvement in patients with breast cancer was detectable with ^{99m}Tc-sestamibi in 79% of the patients examined by Taillefer and colleagues (Abstract 289). Very little modification of the imaging procedure was needed to include the axilla in the initial study of the breast lesions.

Researchers from Cedars-Sinai Medical Center, Los Angeles, CA, reported that MIBI studies in conjunction with MRI were particularly helpful in detecting cancer in breast lesions greater than 10 mm (Abstract 290). Excellent results using scintimammography were also presented from the Nuclear Medicine Center in Naples (Abstract 682, 684), and the University of Naples (Abstract 683), as well as from the University of Munich (Abstract 685). Tiling and colleagues from the University of California San Francisco School of Medicine found that iterative reconstruction of the SPECT images was preferable to filtered backprojection (Abstract 687). They also found that scintimammography had far fewer false-positives than MRI in detecting breast cancer.

Newer myocardial perfusion agents, such as tetrofosmin, can also detect cancer. Three presentations reported the results of these agents in lung cancer (Abstracts 133, 1120, 456); two reported on breast cancer (Abstracts 683, 1143); and one on squamous-cell cancer (Abstract 1139).

The greatest value of scintimammography and FDG studies of the breast was in increasing the probability of cancer in lesions 3 mm or greater in size. Also, in patients with either fatty or dense breasts, anatomical imaging is particularly problematic, and the sestamibi results are as accurate in these two groups of women as in other women. The results of the nuclear medicine studies should not be interpreted as either positive or negative, but should be expressed in terms of probabilities, or at least the interpreter should use five categories for describing the results: definitely abnormal, probably abnormal, probably normal, definitely normal. Fibrocystic disease does not accumulate MIBI but may accumulate FDG. Carbon-11-tyrosine was a better tracer than FDG in breast cancer, because there was less accumulation in fibrocystic disease (Abstract 336). Other investigators used ^{11}C-methionine instead of FDG in evaluating the patient's early response to chemotherapy of advanced breast cancer (Abstract 1145).

Essentially, radiotracer studies are useful in the care of patients with suspected or proven breast cancer in the following ways: (a) decreasing the number of biopsies or removal of benign lesions, (b) detecting axillary metastases, (c) assessing the efficacy of chemotherapy, (d) detecting recurrences or metastatic disease and (e) evaluating therapy of lymphedema, when this unfortunate complication of surgery occurs (Abstract 1170).

If patients do have surgery, nuclear medicine procedures are being increasingly used in the operating room. New instruments for use in surgery included an ion-implanted silicon detector probe (Abstract 198), a cesium iodide detector with a tungsten collimator (Abstract 199), a surgical beta-ray camera (Abstract 303) and a probe used for sentinel node identification (Abstract 1160).

The effectiveness of such intraoperative studies was documented by Ricard and colleagues from the Institut Gustave-Roussy in Villejuif, France, who reported that in 18 of 27 patients with thyroid carcinoma, localization of lymph nodes or invasion of muscle was helpful during surgery (Abstract 199).

Ocular Melanoma

Everaert and colleagues from the Free University of Brussels in Belgium used [^{123}I]iodobenzamide to differentiate ocular melanomas from benign nevi (Abstract 1201). Ophthalmologists have to decide whether they are going to do radical surgery, such as removing the patient's eye in the case of a melanoma, or leave the lesion alone if it is benign. The researchers' true-positive rate was 83% in detecting malignancy. Because the false-negative rate was 14%, one cannot rely on the radionuclide study alone to make the decision regarding surgical removal of the eye. The results of the nuclear medicine study must be combined with other data, expressed as likelihood ratios for malignancy and then combined in a Bayesian analysis together with decision thresholds to determine the proper course of action. One should not practice "one-test" medicine, looking for the perfect test that by itself yields complete certainty. This is rarely the case.

Sentinel Nodes

In patients with malignant melanoma, researchers found that the initial lymph node draining of the primary site is an important indicator of whether the disease has metastasized. Herda and colleagues of Emory University in Atlanta, GA used an intraoperative probe with ^{99m}Tc-sulfur colloid to search for the sentinel node in 26 patients (Abstract 1427). Both early and delayed studies were needed for maximum effectiveness. Piipers and others from Academisch Ziekenhuis Vrige Universiteit in The Netherlands localized sentinel nodes in 93% of 28 patients with breast cancer (Abstract 1160). They found that an absence of sentinel node involvement makes regional lymph node dissection unnecessary.

Vera and others from the Universtiy of California, Davis, in Sacramento developed a receptor-binding radiotracer (^{99m}Tc-DTPA-mannosyl-PL), rather than ^{99m}Tc-sulfur colloid, to image sentinel nodes (Abstract 920). The so-called "Mannan-binding receptor" resides on the plasma membrane of reticuloendothelial cells.

Colorectal Cancer

Another situation where nuclear medicine can both benefit patients and save the health care system a lot of money is in the care of patients with colorectal cancer. Hustinx and colleagues at the University Hospital in Liege, Belgium, compared whole-

body FDG studies with CT in 62 patients (Abstract 1123). The sensitivity in detecting liver metastases was 97% with a 13% false-positive rate. FDG-PET correctly modified the CT results in 15 of 62 patients. Other tracers in gastrointestinal oncology included ^{111}In-pentreotide (Abstract 1121) and human monoclonal antibody ^{99m}Tc-88BV59 (Abstract 26).

An important stimulus to the growth of clinical PET, not only in colorectal cancer, but in lung, head and neck, melanoma, breast and other types of cancer, is the increasing number of regional radiopharmacies which include FDG in their product line. Other positron-emitting radiotracers in the pipeline are likely to be ^{18}F-l-DOPA, ^{64}Cu-PTSM and amino acids such as tyrosine or methionine. Zweit and colleagues from the Westminster Medical School, London, U.K. described their results using ^{64}Cu-PTSM to detect colorectal liver metastases (Abstract 208). Another interesting new positron-emitting radionuclide is ^{120}I, which was incorporated into MIBG by the Hammersmith group in collaboration with investigators from Duke University, Durham, NC (Abstract 874). Only one presentation reported the results of FDG studies in patients with renal cancer, but the results were encouraging. The positive predicted value was 95% (Abstract 621) (Fig. 5).

Avoiding Craniotomy

In one of a series of excellent presentations from the University of Kiel in Germany, Bohuslavizki and colleagues described how ^{111}In-somatostatin receptor imaging helped distinguish meningiomas from neurinomas. Because of the possibility that some of the meningiomas might be malignant, they are usually removed surgically, whereas neurinomas are only removed if they are causing local pressure effects on the brain (Abstract 1150).

New Recognition Sites in Cancer

The work of van Brocklin and colleagues at the Lawrence Laboratory, Berkeley, CA and Australian ANSTO is an example of the translation of discoveries in neurosciences into oncology. These authors described a new ^{123}I tracer, TPCNE, that binds to sigma-1 receptors in the brain (no abstract available). John and colleagues from George Washington University, Washington, D.C., and the National Institutes of Health, Bethesda, MD reported on their synthesis and validation of new sigma-1 and sigma-2 receptor ligands and reviewed the expression of sigma receptors in many types of cancer, including breast and lung cancer (Abstract 16). Mach and colleagues from Bowman Gray School of Medicine, Winston-Salem, NC, presented evidence that sigma-2 receptors can differentiate between proliferating and quiescent breast cancers, in which the receptors are expressed 10 times as frequently in the proliferating cancer cells as compared to the dormant cells (Abstract 337).

Technetium-99m and Rhenium-186/188: A Matched Pair

As the attempts continue to develop ^{99m}Tc radiotracers that can characterize recognition sites in different types of cancer, the similarities between the chemical properties of rhenium and technetium have stimulated the attempt to develop rhenium-labeled diaminodithiol complexed ligands for radiotherapy. Zamora, Knapp and colleagues from Oak Ridge National Laboratory, Oak Ridge, TN, the University of Bonn, Bonn, Germany, and RhoMed, Inc., Albuquerque, NM, reported the successful treatment of experimental tumors with ^{188}Re-RC-160, a somatostatin analog (Abstract 1064).

Radionuclide Therapy

Seventy-six presentations focused on treatment planning and 131 reported on monitoring therapeutic effectiveness. Radionuclide therapy has been given a boost by the excellent results in lymphoma and leukemia, as well as by the development of therapeutic recognition site ligands. DeNardo and colleagues reported strikingly increased survival in patients with advanced B-lymphocytic malignancies treated with Lym-1 (Abstract 742).

Anderson and colleagues from Washington University, St. Louis, MO, found that ^{62}Cu-TETA-octreotide therapy, in which the radionuclide was produced in a hospital cyclotron, delayed the growth of experimental pancreatic tumors in rats (Abstract 505).

The paradigm for radiotherapy with recognition-site ligands is: First, identify the recognition site on the tumor. Second, try treatment with the appropriate nonradioactive agonist or antagonist, depending on which has the desired effect for the specific recognition site. Third, treat the patient with a radiolabeled ligand in large doses.

Krenning and colleagues at the University Hospital Dijkzigr in Rotterdam, The Netherlands, described results in rats with neuroendocrine tumors expressing somatostatin receptors, who received large doses of ^{111}In-somatostatin analog. The tumors were not present when the animals were killed, although the livers of animals treated with nonradioactive somatostatin analog were full of tumor (Fig. 6A and B).

From Genotype to Patient Care

Assessing a person's genetic risk of developing a specific disease will be a major component of medicine in the 21st century. All or nearly all of the human genome will have been sequenced early in the next millennium. Susceptibility genes for cancer include BRCA1, BRCA2 and AT for breast cancer and p53 for nearly half of all cancers. The detection of gene mutations will tell us the probability that a patient will develop an illness sometime in the future.

More and more clinics now provide DNA-based susceptibility testing for mutations in several such genes to help identify those women at exceptional risk for developing breast or ovarian cancer. The new nuclear medicine tests described at this meeting can provide a course of action with respect to subsequent monitoring of persons who have an increased risk of developing cancer, and thus may influence patients' decisions about whether to undergo genetic testing.

No field of medicine is better able to translate the revolutionary advances in molecular biology and genetics into the care of patients. The human genome project has been a stimulus to the development of what might be called "genetic sciences"—molecular genetics, human genetics, molecular nuclear medicine and pharmacology.

Molecular nuclear medicine is based on 10 principles:

1. The tracer principle is fundamental in biomedical science.
2. Genetics is a whole new way to look at all diseases, not just mendelian diseases.
3. Nuclear medicine provides a whole new way to look at genetics.
4. All diseases involve genes.
5. A single mutated gene can result in multiple phenotypes.
6. Genetic linkage research requires exact characterization of a disease.
7. Homeostatic processes can be influenced by genes.
8. A biochemical homeostatic response to a perturbation can be viewed as a trait.
9. Disease can often be characterized by regional biochemical abnormalities.
10. Disease is often the result of a failure of homeostatic mechanisms.

Nuclear medicine can also help determine the relative importance of genetic and environmental factors in diseases, such as mental illness, hypertension, diabetes and other common diseases. For example, with ^{99m}Tc-sestamibi, we can now assess a person's ability to detoxify carcinogenic or other disease-causing agents. With other radiotracers, we can detect the earliest regional biochemical signs of disease in susceptible persons long before they develop symptoms. In some cases, detection of the first signs of disease will permit prevention of more severe consequences by treatment at a preclinical stage. More and more, physicians will deal with asymptomatic persons and not just the clinically sick.

Molecular medicine will make diagnosis more specific. Instead of treating the patient on the basis of statistical responses, each patient will have his or her specific regional molecular diagnoses.

An excellent example of the interplay of genetics and nuclear medicine is the question of why so many types of cancer manifest an increased accumulation of ^{18}F-deoxyglucose. Last year we learned that high FDG uptake is often the result of increased expression of Type II hexokinase, associated with anaerobic metabolism of glucose. This year, Schoenberger and colleagues from the University of Regensburg in Germany, suggested that overexpression of Glut-1, the glucose transporter in the cancer cell membrane, might be a sign of a greater degree of malignancy (Abstract 1113). Aloj, Neumann and colleagues from the National Institutes of Health, Bethesda, MD, reported that there was a poor correlation between Glut-1 mRNA expression and the amount deoxyglucose accumulation in studies of mice with tumor xenografts (Abstract 1140).

P-Glycoprotein Expression

Potentially, one of the most important contributions of nuclear medicine to genetics research, as well as clinical practice, was the demonstration that ^{99m}Tc-sestamibi can be used as a chemical phenotypic marker of the expression of the human multidrug resistance (MDR) gene MDR1. This gene leads to the overexpression of p-glycoprotein, an enzyme responsible for detoxification of foreign chemicals in the body (Fig. 7).

In 92 patients with osteosarcoma, the response to chemotherapy depended on the degree of expression of p-glycoprotein (*N Engl J Med* 1995;333:1839). At the SNM Annual Meeting, Born and colleagues from the Chonnam University Medical School in Kwangju, Korea, related the failure of patients with small-cell lung cancer to respond to chemotherapy to the 1-hour levels of ^{99m}Tc-sestamibi (Abstract 258). When the levels were low, the response was poor, presumably because of the rapid excretion (detoxification) of the chemotherapeutic agent.

In a effort to improve the effectiveness of chemotherapy by modulating p-glycoprotein effects, Franssen and colleagues, Groningen University Hospital, The Netherlands, administered PSC 833, a cyclosporine analog, and found a reduction of ^{99m}Tc-MIBI efflux from the liver and tumors of patients (Abstract 257). Piwnica-Worms and colleagues, Washington University Medical School, St. Louis, MO, have developed a ^{67}Ga-labeled phenolate complex that will enable characterizing p-glycoprotein activity with the positron-emitting tracer, ^{68}Ga (Abstract 197).

In patients with lymphoma, the accumulation of ^{201}Tl combined with poor retention of ^{99m}Tc-MIBI indicated that there would be a poor response to chemotherapy (Abstract 615). Piwnica-Worms has also found that other myocardial perfusion tracers are acted on by p-glycoprotein. The common denominator, he found, is that all are lipophilic and positively-charged.

Dementia Susceptibility Genes

Three diseases illustrate the relationship between genotype and molecular phenotype: Alzheimer's dementia (SDAT), Lesch-Nyhan and Rett's diseases. When genetic risk assessment (apolipoprotein E-4 allele APOE-4 mutation) was combined with FDG-PET in relatives at risk for familial Alzheimer's disease, those family members with APOE-4 had the same abnormal patterns of reduced temporo-parietal FDG accumulation that is characteristic of patients with SDAT. They had these patterns even though they were asymptomatic and several years younger than the average age of onset of SDAT (Abstract 307). This finding is important in the selection of patients for early trials of putative SDAT-prevention drugs and in providing persons at risk with a means of early diagnosis by periodic testing.

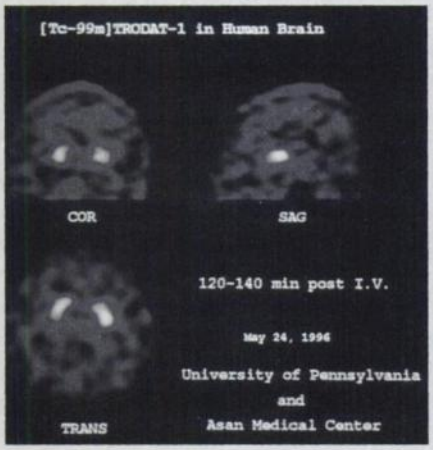
Minoshima, Kuhl and colleagues, University of Michigan, Ann Arbor, MI found that the posterior cinglulate cortex was the earliest site of decreased FDG accumulation in patients with SDAT (Abstract 713) (Fig. 8).

These same investigators have also constructed a functional brain image database for [^{18}F]FDG characterization of patients suspected of having SDAT. Their intent was to facilitate the determination of the probability that the abnormal patterns are characteristic of SDAT (Abstract 717).

Nine presentations reported on imaging of benzodiazapine receptor ligands to characterize neuronal degeneration. In patients with SDAT, investigators from Naples and Denmark observed that the binding of [^{123}I]iomazenil was reduced and correlated with mental deterioration (Abstract 716).

Sixteen presentations discussed cholinergic neurotransmission, considered to be one of the earliest systems affected in SDAT. Kuhl and colleagues used ^{11}C-methylpiperidinyl propionate to

Image of the Year



This year, I have selected the image of the dopamine transporter, accomplished with a ^{99m}Tc-labeled tracer to be the "Image of the Year." The dopaminergic system continues to be one of the most active areas of research in nuclear medicine. All aspects of dopamine neurotransmission can now be examined: The synthesis of dopamine from tyrosine in presynaptic dopaminergic neurons. The incorporation of L-DOPA into dopamine; the storage of dopamine in pre-synaptic vesicles. Release of dopamine into the synapse. Its metabolism by monamine oxidase enzymes (MAO). Its binding to postsynaptic receptors. Its re-uptake into the presynaptic neuron by the DA transporter. Fifty-seven papers reproted on the dopaminergic system: 30 focused on the dopamine transporter, whereas 6 addressed dopamine synthesis.

Last year, researchers found that even in presymptomatic Parkinson's disease, there is a deficiency of dopamine transporter on presynaptic neurons. This year witnessed a "tropane war:" academic medical centers and several companies are developing ^{123}I, ^{18}F and ^{11}C radiotracers to image the dopamine transporter. For example, fluoropropyl CIT FP labeled with ^{123}I binds more rapidly to the transporter than CIT (Abstract 522). Moreover, imaging can be performed sooner after injection of the radiotracer.

Fluorine-18-l-DOPA could differentiate patients with Parkinson's disease from healthy persons (Abstract 521). Researchers have determined that ^{18}F-fluro CIT has advantages over the ^{123}I tracer for quantification and provides better images (Abstract 521).

Two groups of scientists presented results of their successful development of a ^{99m}Tc-labeled tropane that crosses the human blood-brain barrier and binds to the dopamine presynaptic transporter (Abstract 56, 57). Until now, the commercially available ^{99m}Tc tracers could measure only cerebral blood flow or trace hepatic or renal clearance (i.e., excretory processes). No one had developed a tracer that could image a recognition site within the brain. Alan Jones and colleagues, Harvard University, Cambridge, MA, combined a diamo/dithiol complex with a binding site that recognized the dopamine transporter in the brain (Abstract 57) (Fig. 13).

Hank Kung and colleagues, University of Pennsylvania, Philadelphia, developed a different diamine/dithiol based ligand and produced beautiful images of the dopamine transporter in a baboon (Abstract 56).

Kung performed the first imaging of a ^{99m}Tc tracer bound to a recognition site within his own brain (Fig. 14, in color) on May 24, 1996, in collaboration with investigators from the Asan Medical School in Korea.

map the distribution of the enzyme actylcholinesterase in the human brain, which is believed to be deficient in patients with SDAT (Abstract 73). In patients with SDAT, the mean cortical ACHE activity was reduced by 23% compared to control subjects (Fig. 9).

An analog of epibatidine had been labeled with ^{123}I (Abstract 12) or ^{18}F (Abstract 33) for the study of nicotinic acetylcholine receptors. In patients with SDAT, nicotinic ACh receptors are about half normal, while muscarinic ACh receptors are normal (Fig. 10).

These new radiotracers will also be useful in assessing the pharmacology of nicotine. The physiological effects of smoking one cigarette is equivalent to injecting about l mg of nicotine intravenously. Sixty milligrams are a lethal dose. Now it will be possible to study the effects of nicotine on the brain of experimental animals and human subjects.

Lesch-Nyhan Disease

Lesch-Nyhan Disease (LND) is a devastating type of inherited mental retardation characterized by a virtual absence of the enzyme hypoxanthine guanine phosphoribosyl transferase (HPRT). Choreoathetosis is part of the syndrome. Ernst and colleagues, National Institute of Mental Health, Bethesda, MD, found that presynaptic incorporation of ^{18}F-L-DOPA was lower by 69% in patients compared to control subjects (Abstract 173) (Fig. 11).

Inherited Metabolic Disorders

A drastic decrease in regional brain oxygen metabolism where regional cerebral blood flow was preserved was found in patients with a mitochondrial gene defect that limits the human brain to anaerobic glucose utilization (Abstract 481). In patients with the same disease but with lactic acidosis, cerebral glucose utilization was normal.

Phenotypic characterization of genetic abnormalities is not limited to the brain. Huang and colleagues, National Disease Medical Center in Taipei, Taiwan, measured the time-activity curves over the liver to distinguish two causes of hyperbilirubinemia, Dubin-Johnson syndrome, in which the genetic defect is in transport of bile into the collecting system, and Rotor syndrome, in which the defect is in transport of bilirubin from plasma to hepatocytes (Abstract 1107).

Monitoring Gene Therapy

Herpes simplex virus (HSV), which has been genetically altered to express thymidine kinase, can enter cancer cells and increase the expression of the enzyme thymidine kinase (Fig. 12).

Radiolabeled antiviral antibiotics are phosphorylated by thymidine kinase and the product remains trapped in the cancer cells. Investigators from the University of California, Los Angeles, synthesized ^{18}F-acyclovir to assay the thymidine kinase induced by HSV as a measure of the effectiveness of entry of HSV into the cancer cells (Abstract 420).

Goldman and colleagues, Cliniques Universitaires de Bruxelles, Belgium, showed that ^{18}F-FHPG, an analog of gancyclovir, entered tumor cells and was a promising radiotracer for the evaluation of gene therapy involving viral thymidine-kinase genes (Abstract 205). Haberkorn and colleagues, German Cancer

Research Center, Heidelberg, Germany, found that the thymidine kinase expressing hepatoma cells accumulated deoxyglucose, which the researchers attributed to a "stress" reaction of the tumor cells (Abstract 1056).

Nuclear Neuroscience

The number of studies, 120 this year, in the neurotransmission category continue to increase. They now account for 10% of the entire program! Of the cerebral blood flow studies, 55 presentations were based on ^{99m}Tc tracers; 28 on ^{15}O. A total of 152 brain studies involved PET.

An example of an activation study with ^{15}O-water was the study of the neuronal patterns of activation induced by experimental visceral pain (Abstract 482). In healthy subjects, the anterior cingulate cortex had the greatest response, which was not seen in patients with chronic intestinal pain. Stimulation of cochlear implants produced different degrees and regions of activation in deaf persons, depending on whether they had been deaf since birth or became deaf after learning language (Abstract 484).

Serotonin Receptors

Twenty-one presentations reported on serotonin neurotransmission—some on serotonin synthesis, some on postsynaptic receptors and some on the serotonin transporter. The 5HT1a serotonin receptor was imaged by Karolinska Institute, Stockholm, Sweden (Abstract 424). The 5HT2a serotonin receptor is the target of new antipsychotic drugs and was successfully imaged by Farde and colleagues at Karolinska (Abstract 437) and Wong and colleagues at Johns Hopkins Medical Insitutions, Baltimore, MD (Abstract 439).

Monitoring the effect of beta blockade treatment of congestive heart failure in dilating cardiomyopathy helps document the usefulness of such drugs (Abstract 841). Researchers from Groningen University Hospital, Groningen, The Netherlands, used a ^{18}F-labeled tracer to develope the first imaging of norepinephine receptors in the brain (Abstract 35) (Fig. 15).

Szabo and colleagues, , developed a radiotracer to study angiotension 2AT1 receptors and showed that the receptor binding was affected by dietary salt intake (Abstract 179).

Neurocardiology

Sudden death from coronary artery disease remains a major unsolved problem for cardiologists. A step towards a solution is the study of norepinephrine neurotransmission. The most widely used radiotracer in neurocardiology is radioiodinated MIBG. Turkish investigators imaged regions of the myocardium that had normal blood flow but decreased MIBG accumulation, which they called a "mismatch." Diabetic patients with mismatch had a much higher incidence of ventricular tachycardia after coronary artery surgery (Abstract 660).

Attenuation Artifacts

The large number of false-positive ^{201}Tl studies of regional myocardial perfusion can at times lead to contrast angiography and unnecesary interventional procedures. The patients may have anatomical stenoses but adequate collateral perfusion of the myocardium. Attenuation artifacts appearing in ^{201}Tl myocardial perfusion images may result from breast tissue interference in women and the diaphragm muscle in men (Fig. 16).

Stone and colleagues at the University of Wisconsin—Madison reported that 60% of over 1000 studies contained such artifacts. Automated expert system analysis does not help decrease the number of false-positives (Abstract 365).

New Cardiology Imaging Agents

An exciting new hypoxia imaging agent labeled with ^{99m}Tc was presented by researchers from Osaka University Medical School, Osaka, Japan (Abstract 366) and from Guy's and St. Thomas's Hospital, London, U.K. (Abstract 340). New tracers also included a ^{99m}Tc-agent for detecting amyloid deposits in the myocardium (Abstract 849). Imaging of regional wall motion is having a renaissance, with the number of presentations on this topic increasing from 13 last year to 25 this year (Fig. 17). In patients with ventricular dysfunction who were particularly challenging to examine, investigators from Columbia University, New York, NY, showed that the use of carefully automated algorithms gave excellent results with good reproducibility (Abstract 411).

New Instruments

The value of co-registration was beautifully demonstrated in a study from the University of Freiberg in Germany, which showed the stenotic coronary artery and its effect on myocardial perfusion (Abstract 986) (Fig. 18).

A combination PET and MR imaging system is under development, although it might be easier to adapt PET scanners to permit simultaneous high-resolution x-ray CT. Moses and colleagues, University of California, Berkeley, CA, are developing lutetium silicate (LSO) imaging systems to facilitate multi-energy imaging (Abstract 329). Researchers could examine the presynaptic and postsynaptic dopamine receptors at the same time, using ^{123}I and a positron-emitting tracer simultaneously in patients with movement disorders.

A microPET imaging system with less than a 2-mm spatial resolution is an example of several animal scanners that are under development (Abstract 334). Another experimental PET system is the Sherbrooke avalanche photodiode system, which produces high-resolution images in animals (Abstract 744).

Conclusion

As our nation's health care system is being examined and changed, people still come from all over the world to learn about the advanced science and technology that characterizes American medicine. This meeting documents the important developments in nuclear medicine not only in the United States but also from overseas.

Nuclear medicine remains the best kept secret in medicine, but the knowledge of the importance of the field is spreading (Fig. 19). No medical specialty is better able to benefit from close public scrutiny of the overall cost-effectiveness of medical imaging.

The abstracts cited in this commentary can be found in *The Journal of Nuclear Medicine Abstract Supplement* (May, 1996).