Henry N. Wagner, Jr., MD

SNM 1998

Nuclear Medicine: The Road to Smart Medicine and Surgery

"It is a well-established historical generalization that the last thing to be discovered in any science is what the science is really about" (A.N. Whitehead). Forty years ago, when I entered the field, nuclear medicine was often called "radioisotope scanning," and it had an anatomical orientation, being defined as "the visualization of previously invisible organs by means of radioactive tracers." Many of the basic principles have remained; others have evolved. Figure 1A is an example of a "fused image" from that earlier period. An ^{131}I human serum albumin rectilinear scan of the cardiac blood pool was superimposed on a chest radiograph of a patient suspected of having a pericardial effusion. The separation of the blood pool from the liver indicated the presence of a pericardial effusion.

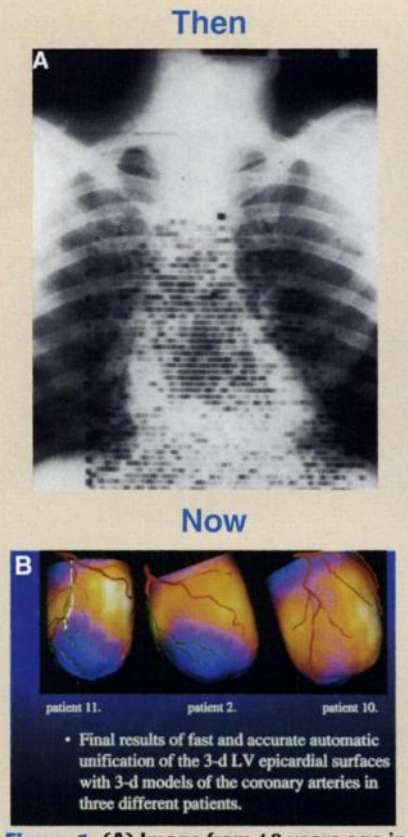


Figure 1. (A) Image from 40 years ago in which a chest radiograph was fused with an ^{131}I human serum albumin rectilinear scan of the cardiac blood pool in a patient with a pericardial effusion. (B) Fused images from automated contrast angiogram and ^{201}Tl images of myocardial perfusion in patients with coronary perfusion defects correlated with angiographic evidence of coronary artery stenosis (Abstract no. 574).

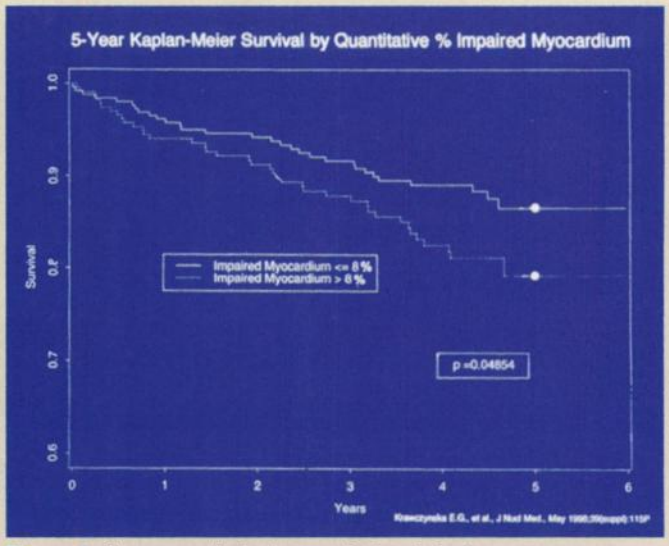


Figure 2. Poorer survival when perfusion defects involved more than 8% of myocardium (Abstract no. 574).

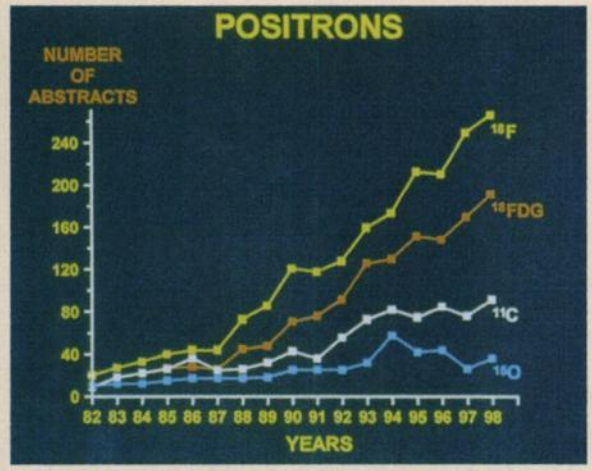


Figure 3. Continuing high rate of increase in ^{18}F and ^{18}F-FDG presentations at SNM Annual Meeting.

Today, nuclear medicine is more concerned with how disease acts, not just how it looks. We define nuclear medicine as the medical specialty concerned with global and regional in vivo chemistry and physiology, in vivo whole-body imaging or molecular nuclear medicine, closely aligned with pharmacology and, increasingly, with genetics. Nuclear medicine views disease as abnormalities in one or more of the four major domains of living organisms: (1) structure, (2) function, (3) viability (including bioenergetics) and (4) communication.

Faber, Garcia and colleagues from Emory University and the Georgia Institute of Technology (GIT; Atlanta, GA) fused automated images of the distribution of ^{201}Tl, revealing myocardial blood flow, with automated angiographic visualization of the coronary arterial tree (Fig. 1B; Abstract no. 574). Obstructions of the coronary arteries resulted in defects in perfusion that could be clearly identified and quantified as to the degree of cardiac involvement. The Emory/GIT group quantified the percentage of impairment of myocardial blood flow. The 6-year

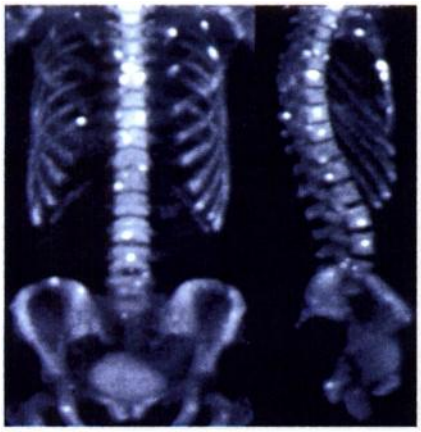
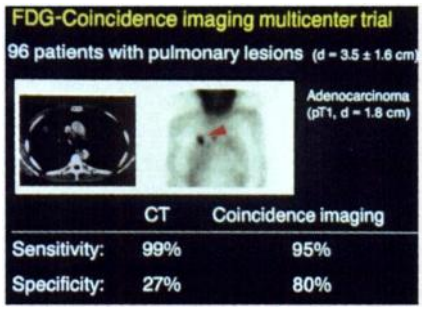


Figure 4.



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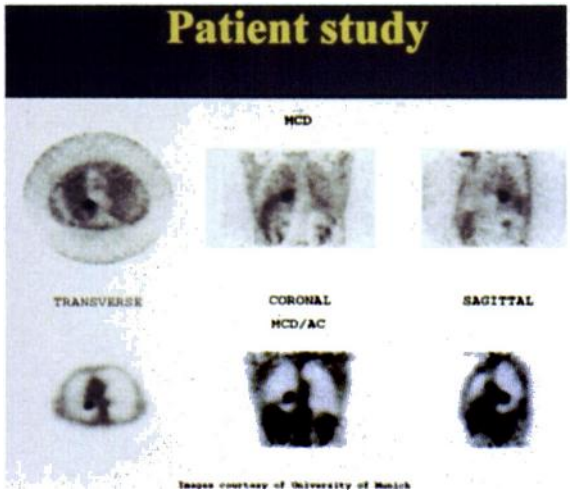

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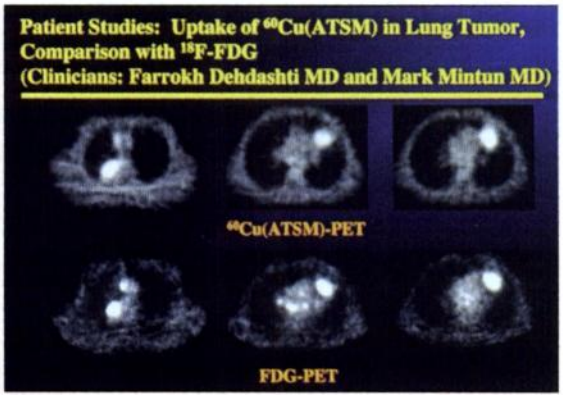

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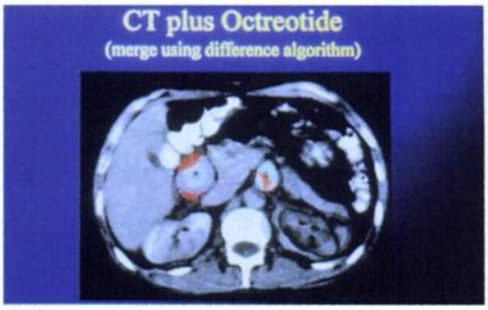

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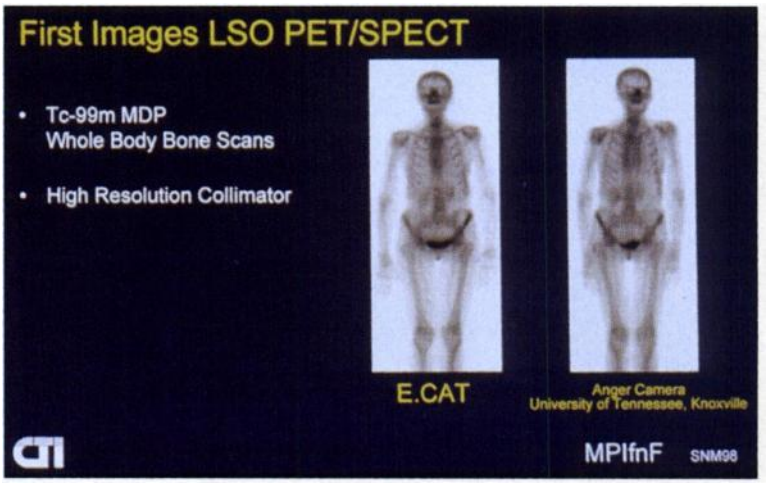

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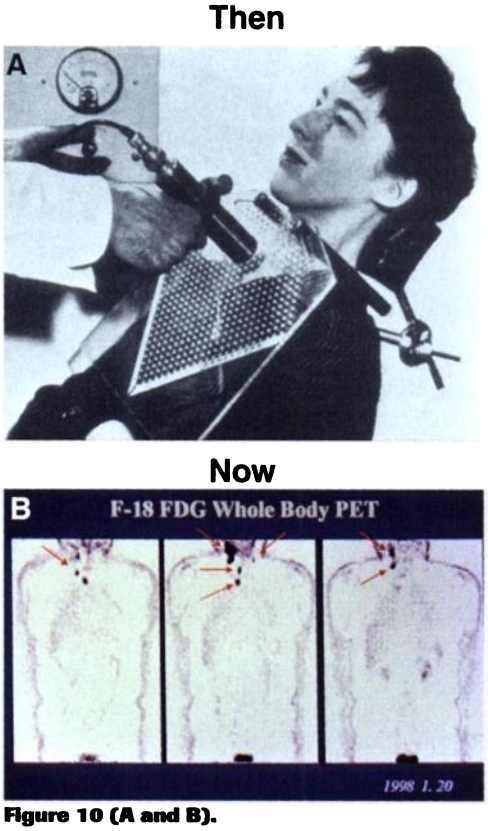

Figure 10 (A and B).

Figure 4. Fluorine-18-fluoride imaging of metastatic skeletal cancer (Abstract no. 444).

Figure 5. Results of multicenter trial of ^{18}F-FDG studies in patients suspected of lung cancer (Abstract no. 423).

Figure 6. Improvement of image quality with attenuation correction (lower row) in patient with lung cancer imaged after ^{18}F-FDG administration (Abstract no. 138).

Figure 7. Assessment of degree of hypoxia (upper row) and FDG accumulation (lower row) in patient with lung cancer (Abstract no. 352).

Figure 8. Fused CT and octreotide image showing exact location of neoplasm expressing somatostatin receptors (Abstract no. 1194).

Figure 9. Image of the Year. A ^{99m}Tc-MDP image of the skeleton produced by imaging device with NaI/LSO detectors. This represents the first single-photon image produced by a detector (LSO) modified to detect single photons as well as 511-keV photons of PET (Abstract no. 196).

Figure 10. (A) Forty-year-old image of Geiger-Müller detector being used to determine whether a thyroid nodule accumulated radioiodine, indicating it probably was not malignant. (B) Metastatic thyroid cancer revealed by FDG imaging in patient whose lesions did not accumulate radioiodine (Abstract no. 1133).

Figure 11. (A) Fifty-year-old imaging of radiotracers in the brain to detect tumors at surgery. (B) Imaging of brain tumors with ^{201}Tl, ^{11}C-Met and ^{18}F-FDG.

Figure 12. Growth of neurotransmission presentations at SNM Annual Meeting.

Figure 13. Multicenter trial of an ^{123}I tracer for assessing presynaptic dopamine transporter in patients with different types of movement disorders (Abstract no. 47).

Figure 14. Prediction of clinical course of patients with senile dementia of the Alzheimer type initially assessed with ^{18}F-FDG (Abstract no. 373).

Figure 15. Decrease in binding of ^{11}C-carfentanil by mu opiate receptors, reflecting secretion of endogenous opioids in response to painful stimulation of the hand by chili pepper (Abstract no. 923).

Figure 16. Electron beam CT images of calcified coronary arteries with ^{201}Tl images of associated defects in coronary artery blood flow (Abstract no. 720).

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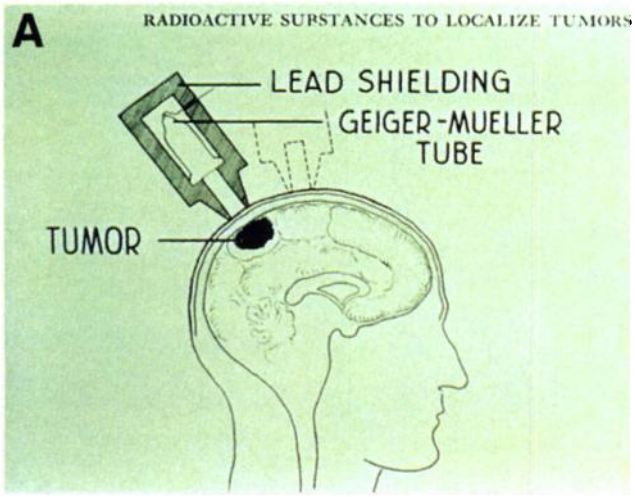

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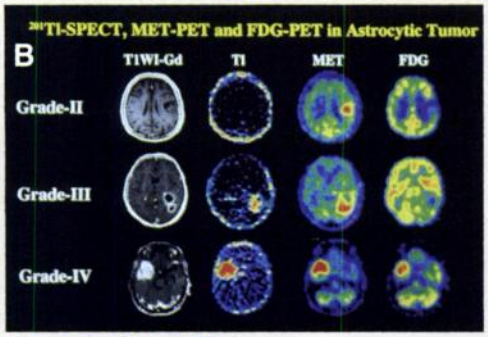
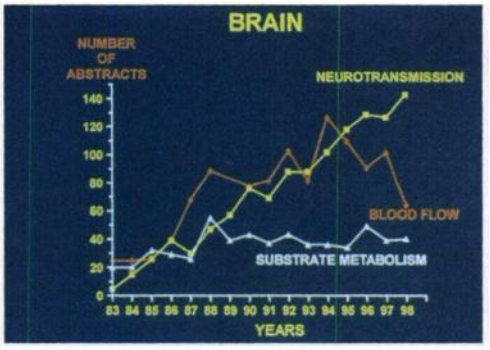


Figure 11. (A and B)



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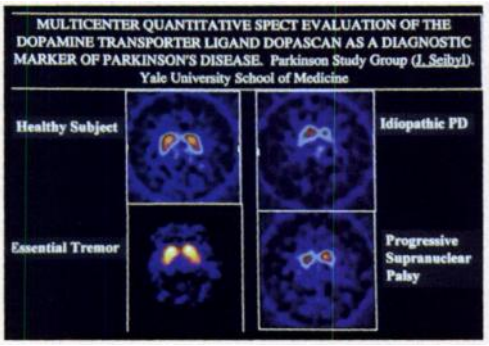

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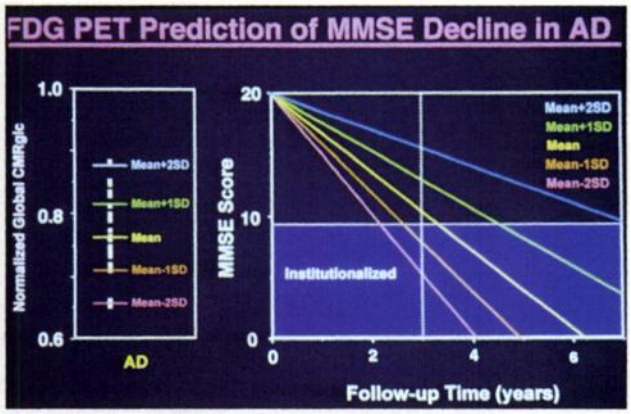

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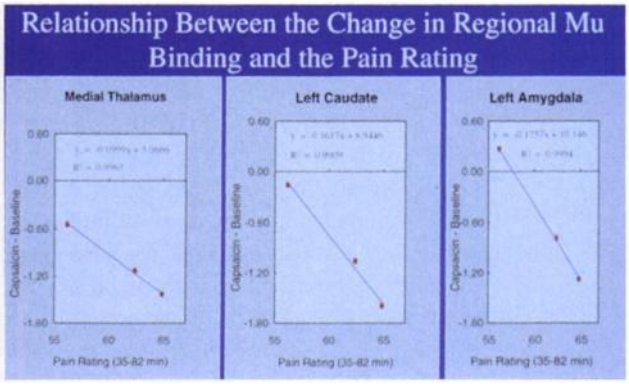

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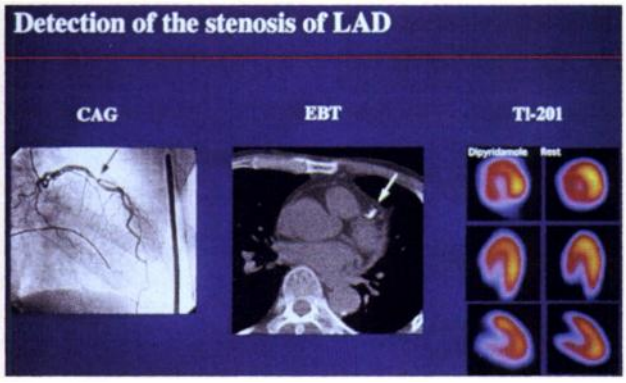

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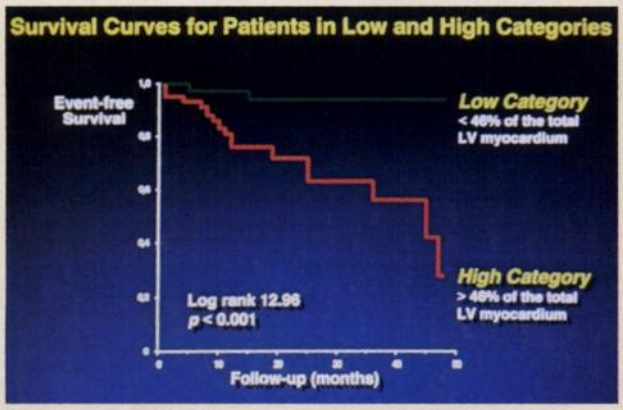

Figure 17. Prognostic use of radiotracer quantification of coronary artery disease (Abstract no. 394).

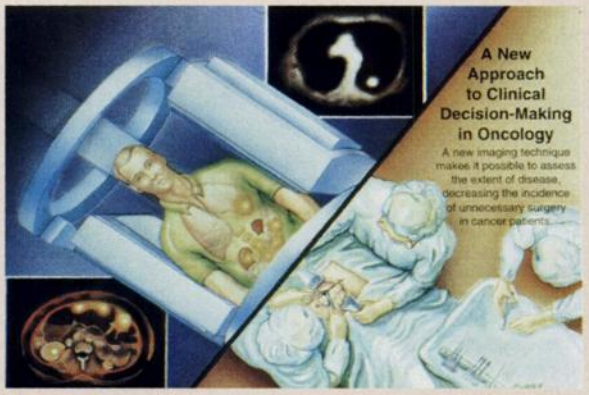

Figure 19. A new approach to surgical decision making.

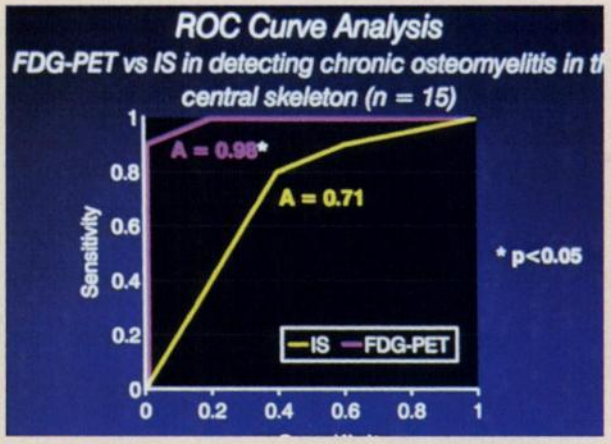

Figure 18. Better performance of ^{18}F-FDG compared to antibody detection of osteomyelitis (Abstract no. 122).

Figure 20. Nuclear medicine is the tail that is beginning to wag the health care dog.

survival of patients with coronary heart disease was much better in those patients whose initial perfusion defects involved less than 8% of the myocardium (Fig. 2).

When stressed, adaptive responses depend on extensive neuronal and hormonal communication within the body. Campisi et al. from the University of California, Los Angeles (UCLA), who won the cardiovascular Young Investigator award, described how immersion of the hand in ice water (cold pressor testing) increases the work of the heart and, in normal persons, results in an increase in coronary blood flow due to the action of nitric oxide, an endogenous vasodilator (Abstract no. 1). When both smokers and nonsmokers underwent cold pressor testing, the increase in myocardial blood flow, measured with ^{13}N-ammonia, was observed in the nonsmokers but not the smokers. In smokers, the coronary vessels were not stimulated to vasodilate. Administration of l-arginine, which increases nitric oxide levels, restored the increase in coronary blood flow in nonsmokers to normal.

To represent the direction in which the field of nuclear medicine seems to be heading, this year I have chosen the theme: Nuclear Medicine: The Road to Smart Medicine and Surgery. Nuclear medicine is the knowledge specialty, characterizing disease at the molecular, as well as the cellular, level. What patients want is certainty. What physicians provide is information. Informed patients are insisting more and more on smarter medicine and surgery.

The scope of applications of nuclear medicine is documented by the number of oral and poster presentations at the 1998 Society of Nuclear Medicine (SNM) Annual Meeting: 270 involving diagnosis; 105, prognosis; 92, radionuclide therapy; 220, pharmacokinetics; and 128, pathophysiology. Therapy planning was the subject of 124 presentations, whereas 112 focused on monitoring therapy.

The use of PET with ^{18}F-fluorodeoxyglucose (FDG) in surgical decision making was described by Schröeder et al. from the University of Frankfurt/Main, Germany, who used whole-body FDG PET to detect extrahepatic metastases before liver surgery in patients with recurrent colorectal cancer (Abstract no. 529). FDG studies can identify the 33% of patients with recurrent colorectal cancer who at surgery are found to have disease that has already spread to the opposite lobe of the liver, the diaphragm or abdominal lymph nodes.

In addition to using FDG PET studies in surgical decision making, Dohmen et al. of Eberhard-Karls-University, Tuebingen, Germany, used FDG PET studies to assess the response of an initial dose of chemotherapy to predict the response to subsequent high-dose chemotherapy (Abstract no. 256). A decrease in FDG accumulation in the initial trial dose predicted the ben-

eficial effects of the subsequent high doses. This knowledge not only improved care but also decreased the cost of care.

Fluorine-18-Fluorodeoxyglucose: Molecule of the Century

In 1996 I claimed that ^{18}F-FDG was the "molecule of the century." This meeting provided additional evidence that the title was deserved. The continued increase in the number of ^{18}F-FDG presentations documents its continuing increasing role (Fig. 3).

The number of presentations involving ^{99m}Tc has been relatively flat over the past 6 years and decreased from 430 last year to 332 this year. Schirrmeister et al. from Ulm, Germany, showed that ^{18}F-FDG was 97% accurate in detecting metastatic bone lesions, compared to an 81% detection rate with ^{99m}Tc-phosphonate in the same patients (Abstract no. 444). Figure 4 is an example of the high quality of ^{18}F-fluoride bone images.

In many nuclear medicine departments, the demand for SPECT studies exceeds their availability. Perhaps some of the bone imaging for metastatic disease should be performed with PET. Fluorine-18-fluoride PET imaging might increase the number of daily studies to the point where PET imaging could be introduced into the department.

As always occurs, good nuclear medicine clinicians provide us with clinical "pearls." Goldfarb et al., Beth Israel Medical Center, New York, taught us that abnormalities in bone scans found outside of the thorax should be interpreted as unlikely to represent breast carcinoma unless there are also thoracic or pulmonary lesions (Abstract no. 446). Isolated extremity lesions are likely to be traumatic or degenerative.

Oncology continues to represent one-third of all presentations at the Annual Meeting. FDG accounted for 117 oncology presentations, including 21 involving lung cancer. Other cancers studied by FDG PET included colon, 13; head and neck, 10; thyroid, 6; brain, 8; breast, 11; melanoma, 7; plus 41 others.

Lung Cancer

New methods should always be viewed in the context of the problems that they address. A common problem in patients found to have lung lesions (solitary pulmonary nodules) is differentiating benign from malignant lesions. That the problem is difficult is documented by the fact that 25,000 thoracotomies are performed each year in patients whose lesions prove to be benign. Another problem is that 30,000 thoracotomies are performed each year in the U.S. in patients with lung cancer in whom the disease has already spread to the point at which the patients should not be treated with thoracotomy but should be started immediately on radiation therapy or chemotherapy. Of the 30,000 patients, 15% have bilateral lymph node involvement and 40% have distant metastases at the time of surgery.

In an eagerly awaited report, Weber et al. described the results of a prospective, multi-institution study in which patients were to have thoracotomies because of solitary lung lesions (Fig. 5). Dual-detector coincidence imaging with ^{18}F-FDG was performed immediately before surgery, and the results were interpreted by three experts who were not provided any other patient data (Abstract no. 423). In these patients, no lesion was smaller than 1 cm. The average was 3.5 cm.

The sensitivity for detection of malignancy was 90%. The specificity was 80%, because of the accumulation of FDG in 2 patients with granulomatous lesions and 1 with a nonspecific inflammatory lesion. CT was used to determine lesion size. Attenuation correction was not used (Abstract no. 423).

When dual-detector coincidence imaging was compared to dedicated PET, Weber et al. reported that all 23 patients with lung cancer were correctly diagnosed by both modalities, whereas 2 of 8 patients with lymph node metastases were missed by the dual-detector coincidence system but detected by dedicated PET. The accumulation of FDG in the tumors compared to surrounding lung was higher for dedicated PET than for the dual-detector coincidence system (Abstract no. 1129). In the dual-detector coincidence imaging study, no correction was made for attenuation. The value of attenuation correction was clear.

Steinert et al. from Zurich, Switzerland, reported that surgery was canceled in 10 of 100 patients with non-small cell lung cancer because FDG PET detected extensive lymph node involvement or distant metastases (Abstract no. 309). The consensus of the many reports in which dual-detector coincidence imaging was compared with dedicated PET in assessing lung lesions was that lesions less than 1.0–1.3 cm could not be visualized, but that larger lesions could be seen to accumulate FDG. Decision making with respect to surgical treatment was correctly influenced in many patients. For smaller lesions (i.e., those less than 1 cm), the sensitivity of dedicated PET was greater than dual-detector coincidence imaging. Many of the 55% of patients to undergo thoracotomy, as described in the Comprehensive Cancer Research Network report, who are inoperable at the time of thoracotomy can be identified by both dual-detector coincidence and dedicated PET imaging.

In comparing PET with CT, Gupta et al. of West Virginia University, Morgantown, reported that an estimation of the likelihood of lymph node involvement detected by dedicated PET was 13.7:1 compared to 1.6:1 for CT (Abstract no. 310).

Attenuation correction with PET was extensively debated. When filtered backprojection was used for image reconstruction, attenuation correction often seemed of little value, but when iterative reconstruction, such as ordered subsegment expectation maximization, was used, attenuation correction was clearly of value (Abstract no. 308).

Shao et al. reported the importance of single-transmission attenuation correction for dual-detector coincidence imaging in reducing artifacts, in improving sensitivity and localization and in quantification in FDG studies of lung cancer (Fig. 6; Abstract no. 138).

Head and Neck Cancer

Complete surgical removal of head and neck cancer is possible in only two-thirds of patients. The other one-third have residual or recurrent disease. Kao from Taichung Veterans General Hospital in Taiwan, reported sensitivity of 100%, specificity of

96% and accuracy of 97% for FDG PET in patients with nasopharyngeal cancer (Abstract no. 1125). Fluorine-18-FDG accumulates in normal structures in the neck, such as the tonsils. Kawabe et al. from Osaka, Japan, reported symmetrical FDG accumulation in 61 of 132 patients (46%) (Abstract no. 1126). Of 79 patients with malignant head and neck tumors, 24 (30%) had asymmetrical uptake.

Lamonica et al. from Roswell Park Cancer Institute reported that 42 of 58 (72%) of cancerous lesions detected by dedicated PET were detected by dual-detector coincidence SPECT; lesions were greater than 2 cm in size (Abstract no. 1132). In 3 patients with head and neck cancer, the lesions were not identified as malignant by dual-detector coincidence imaging.

Cancer of Unknown Primary Origin

At times, patients are found to have metastatic cancer from an unknown primary site. Scheidhauer et al. from the University of Cologne, Germany, reported that 7 of 16 (44%) primary sites were correctly identified, findings that were important in prognosis and subsequent patient care (Abstract no. 1128).

Gastric Cancer

In patients with gastric cancer, detection of metastatic lymph nodes or peritoneal involvement is difficult. Yeung et al. from Memorial Sloan-Kettering Cancer Center, New York, reported that FDG PET is highly sensitive in detecting the primary malignant lesion in the stomach but is often falsely negative in patients with involved abdominal lymph nodes (7 of 9 were missed) (Abstract no. 532).

Colorectal Cancer

CT is thought to be the current "gold standard" for detecting recurrent colon cancer, and it is the first-choice imaging modality for follow-up of patients. It has been estimated that there are approximately 20,000 patients per year in the U.S. in whom recurrent colon cancer is a problem. Recurrence is common, and it is often suggested by a rising serum carcinoembryonic antigen antibody test. The comparative efficacy of FDG PET and immunoscintigraphy with ^{99m}Tc-labeled antibody fragments was examined by Willkomm et al. from the University of Bonn, Germany (Abstract no. 595). PET was better in detecting liver and lung metastases and lymph node involvement. FDG PET helped in detecting multiple metastases in patients in whom follow-up CT revealed a single suspicious lesion.

Akhurst et al. from Memorial Sloan-Kettering Cancer Center reported the results of FDG studies in 83 patients (Abstract no. 526). Lesions that accumulated FDG were almost always due to tumor, and surgeons could be confident they were not operating on patients with benign lesions. Lesions smaller than 0.6 cm were not detected. Equivocal lesions were biopsied. In a study from Leuven, Belgium, by Flamen et al. (Abstract no. 527), PET was found to be more accurate than other imaging modalities in staging patients: 64 were staged as operable and 22 were determined to have extensive disease. Valk et al. from the Northern California PET Imaging Center, Sacramento, found FDG PET to be significantly more sensitive than CT in detecting recurrent colon cancer lesions in all sites except the lungs and liver (Abstract no. 528).

Mechanism of Fluorodeoxyglucose Accumulation in Cancer

Kato et al. from Fukui Medical University, Fukui, Japan, reported that 2-deoxyglucose uptake reflected increased glucose transport into the cell in 16 cancer cell lines (Abstract no. 1103). Aloj et al. from the National Institutes of Health, Bethesda, MD, reported that the expression of neither glucose transporters nor hexokinase genes necessarily correlates with increased accumulation of FDG in cancer cells (Abstract no. 1105). Eary et al. from the University of Washington, Seattle, have carried out extensive studies of human gliomas with both ^{11}C-glucose and ^{18}F-FDG. Multiple factors related to the primitive nature of cancer contribute to the accumulation of FDG (Abstract no. 201). Investigators at the Institute for Genomic Research (TIGR) have sequenced all the nucleotides in the ancient anaerobic bacterium, archeoglobus fulgidus, and have related genes to specific carbohydrate, amino acid, ionic and toxic substance transporters. The accumulation of FDG and amino acids in cancer cells supports the concept that they have dedifferentiated to more primitive evolutionary forms.

Vogelstein et al. have postulated that colon cancer results from failure to repair accumulated mutations of the series of genes that have evolved in the evolutionary transition from undifferentiated cells through partially differentiated cells to highly differentiated normal colon mucosal cells. Thus, normal cells become adenomas and then undifferentiated carcinomas. Yasuda et al. from Yamanashi, Japan, reported high uptake of FDG in colonic adenomas (i.e., benign colon lesions) when they were greater than 1.3 cm in size (Abstract no. 1110).

Hypoxia is one stimulus for the expression of the enzyme hexokinase II, which is present even in ancient bacteria that have existed deep in the earth unexposed to oxygen. Murata et al. from Fukui Medical University examined FDG accumulation by autoradiography of living brain slices and found that increasing degrees of hypoxia produced in a variety of ways resulted in proportional changes in FDG accumulation (Abstract no. 913). Lewis et al. from Washington University, St. Louis, MO, used ^{64}Cu-diacetyl-bis(N'-methyliosemicarbazone), which emits both positrons and electrons, to image hypoxia in human tumors (Fig. 7; Abstract no. 352). Grierson and Shields from the University of Washington and Wayne State University, Detroit, MI, have extended their studies with ^{18}F-fluorothymidine in experimental animals to examine DNA synthesis in humans (Abstract no. 76).

Thus, multiple radiotracers are now available for characterization of malignant lesions. In addition to examining the expression of enzymes involved in energy supply, such as hexokinase, we can also characterize membrane and nuclear receptors expressed by different types of cancer to provide "fingerprints" of these cancerous lesions. Such molecular characterization can help in diagnosis, prognosis and the planning and monitoring of treatment. Future meetings will define how this will be done.

(Continued on page 23N)

Annual Meeting Highlights

(Continued from page 19N)

Today, we know that the finding of somatostatin receptors on carcinoid lesions or dopamine receptors on pituitary tumors can help in planning successful treatment.

The New Challenge

The difficulty lies not in new ideas, but in escaping old ones (John Maynard Keynes). PET should no longer be considered an elitist tool limited to academic medical centers but instead a revolutionary advance in the care of patients with cancer as well as heart and brain disease. Nuclear medicine departments need to have both PET and SPECT capabilities. At this Annual Meeting, 395 presentations involved PET; 298, SPECT; and 36, hybrid, dual-detector coincidence PET.

Today, the performance of dedicated PET is better than that of the hybrid systems in terms of sensitivity and image quality, but many presentations showed that large numbers of patients can be helped with the dual-detector coincidence positron detection systems available today. The perfect should not be allowed to interfere with the good.

In many institutions, "hybrid" PET/SPECT systems are being purchased when the primary goal is to increase the number of SPECT studies. Hybrid systems make it possible to do this and to begin providing FDG studies to help care for patients with cancer. Many of these departments will move on to dedicated PET when the demand requires more PET capabilities. Improvements have been made in the performance of hybrid systems by the addition of attenuation correction. Multienergy systems are needed because molecular nuclear medicine is expanding in the SPECT as well as the PET domain, and several tracer studies may be needed to solve many patient problems, including, for example, the search for molecular recognition sites, such as somatostatin receptors, which can be of importance in planning treatment. Continuing advances in physics and instrumentation of hybrid systems were documented in 17 papers.

Molecular Recognition Sites

Restriction enzymes, called ribonucleases, can dissect out short segments of DNA or RNA that "recognize" specific oligonucleotides. Other molecular recognition sites include enzymes, neuroreceptors, receptors on cancer cells and transport enzymes. One of the most important uses of receptor imaging in oncology is the identification of somatostatin receptors on neuroendocrine tumors, meningiomas, thymomas, lymphomas and breast cancer.

Lang and Bihl from Stuttgart, Germany, reported that FDG PET had sensitivity of 83% for neuroendocrine pancreatic tumors and 39% for carcinoid tumors. Overall, sensitivity of FDG PET was 58% for gastroenteropancreatic neuroendocrine tumors, compared to 93% for somatostatin-receptor imaging (Abstract no. 492). Adams et al. reported on a multi-institution study in which somatostatin-receptor imaging located lesions that were surgically removed later in 7 patients with gastrinomas (Fig. 8; Abstract no. 1194). The use of fused images greatly aided surgeons in locating lesions (Abstract no. 777). Intraoperative probes and imaging devices are also being used for this purpose (Abstract nos. 79, 358, 777).

Nano-Dx and Nano-Rx

Many cancerous lesions express receptors on their plasma surface membranes. These can be of diagnostic and therapeutic significance. Identification of these molecular recognition sites deep within the body can only be made with photon-emitting radiotracers because they are present only in nanomolar quantities. Molecular nuclear medicine is unique in providing sufficient sensitivity. Identification of receptors on tumors can lead to "smart" treatment, for example, with somatostatin analogs that can alleviate symptoms and slow growth of malignant carcinoids. Often, however, after treatment with nonradioactive receptor agonists, the cancer remains, and "smart" radiotherapy is needed. Hartshorne et al. from the University of New Mexico Cancer Research and Treatment Center, Albuquerque, reported the eagerly awaited first results of treating patients with ^{90}Y-SMT 487, a radioactive somatostatin-receptor ligand (Abstract no. 142). There was evidence of renal toxicity, so more research is needed to determine the effective, safe radiation doses. Nevertheless, this represents an important step along the road to increasing use of radionuclide therapy. Lewis et al. from Washington University and Mallinckrodt Medical, Inc., St. Louis, MO, described their use of a different radionuclide, ^{64}Cu-TETA-Tyr^3-octreotate, in treating somatostatin-receptor-bearing tumors in rats (Abstract no. 407).

The search for ^{99m}Tc-labeled receptor ligands continues. The growth-stimulating hormone bombesin/gastrin-releasing peptide was successfully labeled by Baidoo et al. from the Johns Hopkins Medical Institutions, Baltimore, MD (Abstract no. 16). The ligands had an adequately high affinity for human prostate cancer cells (Abstract no. 16).

Physics and Instrumentation

No one could fail to be impressed with the presentations and commercial exhibits that reflected the enormous advances in instrumentation. Nuclear medicine has now reached a size where industry is investing heavily in its future. One hundred seventeen instrumentation presentations dealt with SPECT and 108 with dedicated PET. Karp et al. from the University of Pennsylvania, Philadelphia, described the performance of their dedicated PET system using curved-plate sodium iodide (NaI) detectors designed to cover the entire body automatically within 1 hour to provide an image covering 100 cm of axial length (Abstract no. 190). Attenuation correction was performed with a ^{137}Cs single-photon source. This group proposed that National Electrical Manufacturers Association standards for assessing image quality in PET scanners be updated to facilitate comparison of different new imaging systems with the old (Abstract no. 525). The number of special-purpose imaging devices continues to increase, from small intraoperative cameras (Abstract no. 777) to a dedicated PET scanner for breast imaging using two curved-plate NaI detectors (Abstract no. 778).

Many clinical problems require the use of two or more radiotracers administered and imaged simultaneously. Therefore,

multienergy imaging is likely to continue to evolve. Zubal et al. from Yale University, New Haven, CT; Picker International, Highland Heights, OH; and Tel Aviv Medical Center, Israel, described phantom studies in which ^{99m}Tc was imaged in the presence of FDG and FDG was imaged in the presence of ^{99m}Tc with a dual-detector coincidence system (Abstract no. 519). This multienergy capability is an important advantage of dual-detector coincidence systems and is being developed by those previously concerned only with dedicated PET instrumentation.

A dedicated PET scanner was presented that has a variable aperture and can be used for whole-body or brain or breast imaging (Abstract no. 364). A multiwire gamma camera was described for first-pass imaging of left ventricular function using ^{178}Ta (Abstract nos. 291, 292). This same nuclide and multiwire imaging was able to obtain high-resolution cardiac images in mice, a procedure that is being used in the increasing number of experimental studies of mice, the mammal whose entire genome has now been sequenced (Abstract no. 182). The mouse will play a major role in "functional genomics," that is, determination of the phenotypic expression of genes identified by the fully sequenced mouse genome.

Image of the Year

The Young Investigator prize in the area of instrumentation and data analysis was won by Schmand, Dahlbom and colleagues from CTI, Inc., Nashville, TN; Max-Planck-Institute, Cologne, Germany; UCLA; and Karolinska Institute, Stockholm, Sweden (Abstract no. 24). This group presented a ^{99m}Tc bone scan that had been performed with an imaging device based on NaI/lutetium orthosilicate (LSO) bilayer detectors in a ring around the patient. In this system, the 140-keV photons from ^{99m}Tc are detected by the NaI layer and the positrons (e.g., from ^{18}F-FDG) by both the NaI and LSO layers. The group also described a YSO/LSO bilayer detector, the advantage of YSO over NaI being that the YSO is not hygroscopic.

Three years ago I chose as Image of the Year a brain image performed with ^{18}F-FDG and a dual-detector coincidence system designed originally as a SPECT scanner. The scanner had been modified to permit detection of the 511-keV photons from positron-emitting radiotracers, namely, ^{18}F-FDG. This year what had been primarily a "dedicated" PET scanner was modified by the use of bilayer NaI/LSO detectors and was able to detect the lower energy photons of ^{99m}Tc (Abstract no. 196). This further convergence of PET and SPECT to provide the ^{99m}Tc bone scan shown in Figure 9 led me to select this image as the Image of the Year for 1998.

Thyroid Imaging: Then and Now

Forty years ago, at Hammersmith Hospital in London, one of my responsibilities was to place a Geiger-Müller (GM) detector over each of the points in a grid placed over the neck of patients with thyroid nodules to map out manually the pattern of ^{131}I uptake (Fig. 10A). If the nodules in the thyroid accumulated radioiodine, they were less likely to be malignant. Thus, as long as 40 years ago, nuclear medicine played an important role in surgical decision making. It took a long time to achieve its current potential.

Compare that study with the ^{18}F-FDG images obtained by So et al. from Seoul National University, Korea, in patients with thyroid cancer whose metastatic lesions did not accumulate radioiodine (Fig. 10B; Abstract no. 1133). In patients with elevated serum thyroglobulin (TGB) levels (and even in some patients whose TGB levels were not increased), whole-body radioiodine imaging revealed metastases, many of which could be removed surgically. In other patients, high doses of ^{131}I were indicated by the ^{18}F-FDG study.

In another multi-institution study of 88 patients with thyroid cancer and negative whole-body ^{131}I scans, 86% of the cancerous lesions were detected by whole-body PET with FDG (Abstract no. 483). Reimer, Adler and Bloom of University Hospitals of Cleveland, OH, reported that FDG PET was helpful in distinguishing benign and malignant thyroid nodules (Abstract no. 482). The studies were cost-effective because surgery was avoided in 16 of 24 patients (saving $12,000 per thyroidectomy compared to $1,700 for each PET scan). This is but one of the many studies showing the cost-effectiveness of nuclear medicine procedures (Abstract nos. 80, 266, 367, 1094). Last year, my theme was that nuclear medicine was the best-kept secret in medicine. The secret now seems to be leaking out.

Brain Imaging: Then and Now

Fifty years ago, Moore et al. at the University of Minnesota first used radioactive diiodo-fluorescein with a GM detector to help locate deep-seated brain tumors at surgery (Fig. 11A). Today, multiple tracers are used to image brain tumors (Fig. 11B).

In brain tumor imaging, ^{11}C-methionine (^{11}C-Met) has the advantage over ^{18}F-FDG that it does not accumulate to the same degree in the normal brain. Many prefer ^{11}C-Met for this reason. What about other types of cancer? In lung cancer, the accumulation of ^{11}C-Met was half that of ^{18}F-FDG (Abstract no. 311). Carbon-11-methionine was also found to accumulate in inflammatory lesions of the lung and, therefore, did not improve specificity compared to ^{18}F-FDG.

In staging lymphomas, ^{18}F-FDG and ^{11}C-Met performed equally well, although the latter was preferred in patients with high serum glucose levels (Abstract no. 1117). In patients with thymic tumors, FDG accumulation was significantly higher than ^{11}C-Met in 10 of 12 thymic cancers (Abstract no. 1134).

Cremerius et al. from Aachen, Germany, used ^{18}F-FDG PET to differentiate between complete and partial remission after chemotherapy of malignant lymphoma (Abstract no. 1114).

Epilepsy

In a collaborative study from the Universities of Michigan and Munich, Germany, fully automated detection of epileptogenic foci resulted in improved performance of ^{18}F-FDG studies, especially in detecting extratemporal lobe foci from which the seizures originated (Abstract no. 96). Meltzer et al. from the University of Pittsburgh, PA, described their results in studies of patients with ^{18}F-FDG injected within 30 minutes of seizures (Abstract

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no. 942). Global glucose utilization is significantly less than normal in adult epileptic patients, although during the childhood development of the brain, levels of global brain glucose utilization are higher than those observed in normal adults (Abstract no. 216).

Neurotransmission

Discoveries concerning the chemical basis of brain function are as exciting as those in atomic physics at the turn of the century or genetics in the 1950s. As shown in Figure 12, the number of presentations concerned with the neurotransmission process continues its phenomenal rise.

A multicenter trial of beta-CIT in assessing dopamine and serotonin transporters on presynaptic neurons showed that imaging of the decreased tracer accumulation in the basal ganglia can distinguish patients with idiopathic Parkinson's disease (PD) from persons with benign familial tremor. It could not distinguish between PD and a variant movement disorder, progressive supranuclear palsy (PSP), in which presynaptic transporter availability is similarly reduced (Fig. 13; Abstract no. 47). Postsynaptic dopamine receptors are abnormal in PSP, but not in PD.

Presynaptic dopaminergic neurons have reduced transporter availability in patients with untreated PD disease when examined with ^{123}I-beta-CIT, but postsynaptic D_2 dopamine receptor binding is increased (up-regulation) (Abstract no. 45). Simultaneous measurement of presynaptic transporter binding with ^{99m}Tc-TRODAT-1 and postsynaptic dopamine receptors with ^{123}I-IBF/IBZM should be able to differentiate idiopathic PD from variants such as PSP (Abstract no. 17). Kerner, Tatsch et al. from the Universities of Munich and Ulm, Germany, and the University of Pennsylvania, Philadelphia, measured presynaptic transporter availability and postsynaptic dopamine receptor availability to differentiate idiopathic and nonidiopathic PD (Abstract no. 46).

The dopamine transporter, which removes unbound dopamine from the synaptic cleft after secretion from the presynaptic neurons, was the subject of 25 presentations. Iodine-123-altropane is more selective for the dopamine transporter than beta-CIT (Abstract no. 1055). TRODAT-1 and analogs have the advantage of being labeled with ^{99m}Tc, but to date their affinity for the transporter has been less than for the ^{123}I ligands (Abstract no. 978).

Ichise et al. used the expression "functional morphometry" to describe the use of SPECT images of the striatum carried out with ^{123}I-beta-CIT to measure the length and thickness of the striatum, as well as the bound activity. With these structural measurements, they were able to differentiate patients with PD from normal persons, just as they were with measurement of the binding of the radiotracer (Abstract no. 934). In some cases, nuclear medicine imaging can reveal structural information that is obscured in classic anatomic imaging in which the target and nontarget regions of interest have the same attenuation or magnetic characteristics.

Most studies of postsynaptic dopamine receptors have focused on the corpus striatum. A substituted benzamide, ^{11}C-FLB457, was used to quantify extrastriatal D_2 receptor availability, which is less than 3% of striatal levels and of great interest in neuropsychiatric disorders (Abstract no. 276).

In identifying D_2 dopamine receptors on pituitary tumors, which is of importance in planning therapy, Kwekkeboom et al. from University Hospital, Rotterdam, found that ^{123}I-epidepride was better than ^{123}I-IBZM (Abstract no. 65). Nakamura et al. imaged the dopamine transporter with ^{18}F-FPCIT and were able to show a decline in binding with normal aging and an accelerated decrease in binding in patients with PD (Abstract no. 933).

The clinical use of SPECT tracers to study neurotransmission will require the same attention to detail in data acquisition, display and analysis of the images that has been used in PET. Almeida et al. from Paris applied corrections for attenuation, scatter and collimator blurring in SPECT studies of the brain with ^{123}I-epidepride to image striatal and extrastriatal D_2 dopamine receptors and obtained results identical to the data in the same studies using ^{11}C-epidepride (Abstract no. 764). As SPECT moves into the domain of PET and is more widely used in community hospitals, quality control must be of greatest concern.

Serotonin Neurotransmission

Nearly 100 presentations dealt with the dopaminergic system. Interest in serotonergic transmission was documented by 27 presentations, 15 on receptors, 8 on the transporters and 4 on serotonin synthesis.

Drawing on the example of the excellent attention to detail of PET users, Ito et al. from Akita Research Institute, Akita, Japan, used the anatomic standardization techniques of PET to form a statistical image database for localizing and quantifying 5-HT1A serotonergic receptors in normal humans (Abstract no. 534). The technique can be used for comparisons of groups of patients on a pixel-by-pixel basis. This paper sets a standard for both PET and SPECT quantitative imaging of neurochemistry.

There were striking differences in serotonin synthesis rates measured with ^{11}C-methyl tryptophan between normal male and female subjects and patients with obsessive compulsive disorder and borderline personality disorder (Abstract no. 322). Abnormalities of the serotonergic system were also described by Messa et al. from Milan, Italy, who assessed dopamine and serotonin receptors with ^{18}F-fluoro-ethyl spiperone (Abstract no. 150). Midbrain serotonin transporter binding was reduced in patients with major depression (Abstract no. 151).

Alzheimer's Disease

Forty-five presentations involved neurodegenerative disorders, and 47 dealt with neuropsychiatric disease. Stereotactic surface projection images and statistical image databases continue to improve the diagnostic classification of persons with memory disorders. In persons with impairment of memory examined with ^{18}F-FDG long before the clinical diagnosis of senile dementia of the Alzheimer type (SDAT) could be made on neuropsycho-

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logical grounds, Minoshima et al. from the University of Michigan, Ann Arbor, were able to predict the development of Alzheimer's disease (AD) 5 or more years later (Fig. 14; Abstract no. 373). Early characterization of patients who are likely to develop AD provides an objective means to assess drug treatment to eliminate or delay the appearance of the disease. After the diagnosis of SDAT was made, measurement of global glucose utilization with ^{18}F-FDG was able to predict the rate at which the disease would progress to the point where institutionalization was needed (Abstract no. 374).

Acetylcholinesterase activity measured with ^{11}C-N-methyl-4-piperidyl acetate was reduced in patients with AD, supporting the cholinergic hypothesis of dementia in SDAT (Abstract no. 372). Many patients with advanced PD also showed profound cholinergic deficiencies.

Schizophrenia

Amphetamine-induced release of dopamine is increased in patients with schizophrenia. D_2 dopamine receptors were occupied by dopamine to a greater degree in schizophrenic patients than in normal subjects (Abstract no. 316). The enzyme dopadecarboxylase, measured with ^{18}F-fluorodopa, was increased in patients with schizophrenia, a finding that seems to be a trait marker independent of antipsychotic treatment and the state of the patient at the time of the study (Abstract no. 321).

Narcotics, Marijuana and Nicotine

Previous studies of the opioid system have been with ^{11}C-labeled ligands, whose short (20-minute) half-life limits availability of the tracers for wider use and the time over which measurements can be made in a patient. Wester et al. from Munich have synthesized ^{18}F-diprenorphine (DPN), validated its use in animals and carried out the first human studies. The results were similar to those obtained with ^{11}C-DPN (Abstract no. 280). Studies are in progress to use the longer-lived tracer to measure the rate of release of endogenous opioids.

Painful stimulation of the hand by chili pepper resulted in diminished binding of ^{11}C-carfentanil to mu opioid receptors, presumably due to competition from release of endogenous opioids (Fig. 15; Abstract no. 923). The GR89696 molecule was labeled with ^{11}C and its use validated for measuring kappa opioid receptors (Abstract no. 465). The same group synthesized ^{18}F-SR144385, a selective radioligand for PET studies of cannabinoid receptors (Abstract no. 1012).

Until now, studies of nicotinic cholinergic receptors have been limited by the toxicity of the labeled ligands. Musachio et al. from the Johns Hopkins University Medical Institutions and Georgetown University, Washington, DC, have now labeled a radioiodinated analog of A-85380, a potent acetylcholine receptor agonist, that will facilitate studies of nicotine dependence (Abstract no. 183).

The Heart

Once again, we see anatomic studies being presented as a competitor rather than a complement to functional and biochemical imaging. Clearly, electron beam CT (EBCT) is a sensitive method for revealing calcium in coronary arteries, an important development. EBCT was more sensitive (71%) than ^{201}Tl imaging (45%) in detecting coronary artery disease as reflected in calcified arteries, whereas ^{201}Tl was more specific in detecting reduction in myocardial blood flow (79% versus 65% specificity) (Fig. 16; Abstract no. 720). Both studies should be performed for maximum patient benefit, EBCT providing anatomic information, and ^{201}Tl or ^{99m}Tc tracers providing functional information.

The prognostic value of nuclear medicine studies and their effect in determining treatment and outcome are becoming increasingly documented. The many presentations in cardiology included the study of Cuocolo et al. from Naples, Italy, in which combined assessment of left ventricular function and regional myocardial ^{201}Tl activity was able to predict subsequent cardiac events over a period of 25 months in patients who had had previous myocardial infarction (Fig. 17; Abstract no. 394). Cardiac fatty acid metabolism measured with ^{123}I-BMIPP was better than conventional clinical parameters in identifying those patients at high risk of subsequent cardiac events after acute myocardial infarction (Abstract no. 498). The prognostic value of dobutamine stress SPECT studies with ^{99m}Tc-sestamibi in 310 patients was the same as that obtained in patients who were able to exercise or be stressed with vasodilator agents (Abstract no. 450). In 128 patients studied after percutaneous transluminal coronary angioplasty, even though the results of electroencephalogram stress testing were equivocal, rest/stress SPECT studies were of great prognostic value for subsequent cardiac events (Abstract no. 449).

PET myocardial perfusion imaging with ^{82}Rb was more cost-effective in eliminating unnecessary invasive diagnostic and therapeutic procedures than SPECT imaging (Abstract no. 350). With ^{82}Rb there was a 50% reduction in contrast angiography and coronary artery bypass grafting. Another PET tracer for measuring regional myocardial perfusion is ^{62}Cu-PTSM, a myocardial perfusion tracer (Abstract no. 561). Obtained from a ^{62}Zn generator with a 9-hour half-life, ^{62}Cu can be attached to PTSM and provides PET images comparable to ^{15}N-ammonia. Its cost is less than ^{82}Rb. The Washington University group has continued development and used ^{64}Cu extensively to label octreotide and antibodies (Abstract no. 1032).

Rhenium-188 was the radionuclide used in 11 presentations. Restenosis after angioplasty was prevented by radiation of the coronary endothelium with ^{188}Re contained in balloons positioned in the previously stenosed coronary artery to prevent infiltration of fibroblasts (Abstract no. 181).

Although it was not possible to document improvement in regional myocardial perfusion by transmyocardial laser revascularization in patients with end-stage coronary artery disease (Abstract no. 116), the use of nuclear imaging is now of major importance in assessing the exciting new methods to induce coronary artery revascularization, including intramyocardial injections of vascular endothelial growth factors.

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to do so. SNM has been a member of the Practice Expense Coalition for over 2 years. The Coalition was successful in delaying implementation for 1 year, ensuring the development of a new methodology and the 4-year transition period. The Coalition will lobby for improvements in the new methodology proposed by HCFA. SNM staff will continue to participate in meetings related to this issue and will further analyze HCFA's data before developing formal comments on the NPRM.

You may download the June 5 NPRM by accessing the *Federal Register* on HCFA's home page at http://www.access.gpo.gov/su_docs/aces/aces140.html. From there, do a search on Federal Register, date 6/5/98, keyword "Medicare." If you would like to provide comments to SNM on these issues, submit your comments to Wendy Smith no later than August 21, 1998. For more information, contact Wendy Smith at (703) 708-9000, ext. 242, or by e-mail at wsmith@snm.org.

HCFA CONTINUES DELAY OF PHYSICIAN SUPERVISION RULE

On October 31, 1997, HCFA adopted a final rule clarifying the appropriate level of physician supervision for diagnostic tests payable under the Medicare physician fee schedule. The physician supervision rule was scheduled for implementation on January 1, 1998. Issues were raised about the level of supervision required for some diagnostic services. HCFA is working with physicians and others to resolve these issues, and a revised ruling was expected by July 1, 1998. However, at a meeting in June, HCFA announced that it would not implement the rule at this time. Medicare carriers have been advised to continue to following existing policies (prior to January 1, 1998) on physician supervision of diagnostic tests until HCFA provides further instruction. The CHCPP will keep you updated on this important issue.

—Wendy J.M. Smith, MPH, is the SNM director of health care policy.

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Infection and Inflammation

The widespread use of nuclear medicine in the care of patients with infectious diseases is an idea whose time is about to come. Thirty-nine presentations in this area included 6 involving labeled leukocytes; 11, antibodies; 7, chemotactic peptides; 3, ^{67}Ga; 7 liposomes; 6, FDG; and 13, others. For example, ^{18}F-FDG PET was more sensitive and specific than ^{99m}Tc-labeled monoclonal granulocyte antibodies in the diagnosis of chronic vertebral osteomyelitis, another example of the encroachment of FDG PET on SPECT (Fig. 18; Abstract no. 122).

Ten Critical Questions

Some of these have been answered. Some remain to be answered.

1. Will nuclear medicine assume an increasing role in health care?
2. Will there be increasing use of nuclear medicine technology in pharmacology, toxicology, infectious diseases, aging, mental illness and nutritional disorders?
3. Will nuclear medicine imaging become the leader of biomedical imaging?
4. Will nuclear medicine play a major role in "functionalizing" the genome, that is, in defining the messages contained in the genes?
5. Will multienergy imaging devices become as common as dedicated PET and SPECT devices?
6. Will the use of positron-emitting tracers equal that of single-photon agents?
7. Will there be a role for specialized devices dedicated to breast, brain and extremity imaging and small, handheld devices for intraoperative applications?
8. Will referring physicians think of nuclear medicine first, rather than last?
9. Will we be able to convince everyone that nuclear medicine decreases, not increases, the overall cost of health care?
10. Will we be able to ensure the availability of nuclear medicine technologists, physicians and scientists?

We are entering the Age of Certainty in medicine. The popular medical writer, surgeon Sherwin Nuland, has written that most people believe that doctors always know exactly what they are doing, that uncertainty is alien to the specialists who treat the most seriously ill people. They are convinced that the more high-tech the doctor, the more he or she always has very sound scientific reasons for recommending a course of action. People are beginning to realize that much of medical practice is based on intuitive experience. Nuclear medicine can help define the road to smart medicine and surgery. Today, surgical decision making is aided by preoperative ^{18}F-FDG studies, with both dedicated PET and dual-detector coincidence imaging (Fig. 19). Identifying somatostatin receptors is important in planning chemotherapy. We are beginning to decrease the "excessive intervention into the human body" that Princeton economist Uwe Reinhardt said was common in medicine today. Nuclear medicine physicians provide knowledge. What patients want is certainty. Nuclear medicine is entering its golden age, but we cannot depend on the kindness of strangers. We must carry our message to referring physicians, patients, the public and our political leaders.

Among the many success stories at this meeting were the presentations involving ^{99m}Tc, FDG, dopamine and somatostatin. These must be shared with the public. We must begin to use the World Wide Web to record our own medical experience and combine it with the experience of our colleagues. Databases must be at our fingertips as we care for our patients. Using the Internet, we must send our images out to referring physicians in their offices on a daily basis, with systems such as the JAVA-based remote viewing described by Slomka et al. from London, Ontario, Canada (Abstract no. 767).

Nuclear medicine has the ability to wag the health care dog (Fig. 20).