SNM 1997

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Molecular Nuclear Medicine: The Best Kept Secret in Medicine

To judge by the scientific and clinical presentations at this meeting (Fig. 1), no other field of medicine is as exciting as nuclear medicine. Great advances were announced, not only from academic medical centers and community hospitals, but also from industry. The last thing to be known about a science is what that science is all about. In vivo measurement of regional biochemistry and physiology is now the essence of nuclear medicine.

We are again indebted to the individuals from thirty-two countries who enriched our scientific program, including participants from two brand new countries. Sixty-nine presentations were authored by persons from 45 different companies. The commercial exhibits were more impressive than ever, and the mood was optimistic. For some physicians, the inescapable uncertainty of the future has made them anxious as well as hopeful.

Every year I choose a theme that I believe grasps the spirit of the meeting. This year, I have chosen: Molecular Nuclear Medicine: The Best Kept Secret in Medicine. Few physicians and hardly any of the public have any idea what nuclear medicine can do. Fortunately, information technology has now advanced to a point where we can present to the public the vision, values and results obtained by efficient, enthusiastic and competent nuclear medicine physicians and scientists as they care for patients and serve the public. The bee that gets the honey does not stay close to the hive.

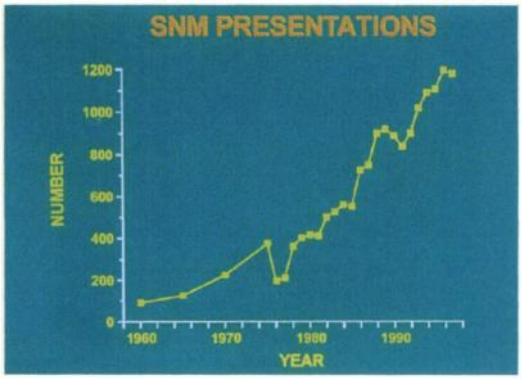


Figure 1. Number of oral presentations and posters at the SNM meeting over the past three decades.

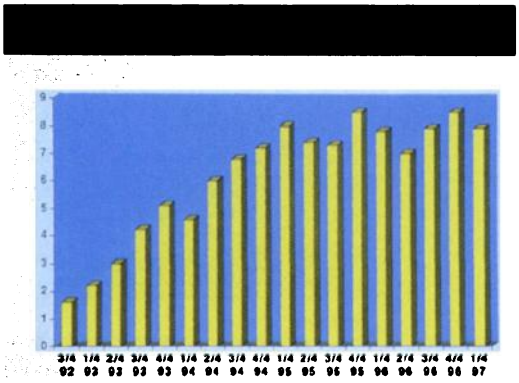


Figure 2. The number of ^{18}F-FDG PET studies has averaged eight studies per day for the past 10 quarters at the Royal Prince Alfred Hospital in Sydney, Australia (Abstract no. 1028).

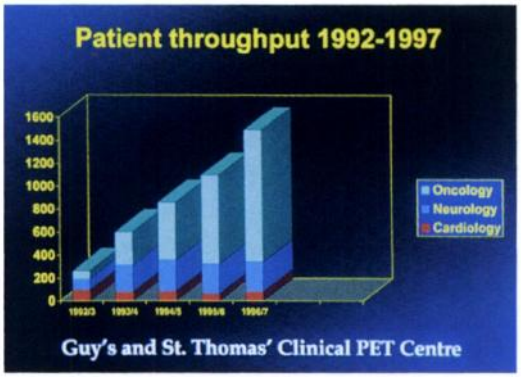


Figure 3. The growth in PET studies at Guys' and St. Thomas's Hospitals in London.

What Can Be Done?

Figure 2 portrays the growth in the number of PET ^{18}F-FDG studies per day at the Royal Prince Alfred Hospital in Sydney, Australia (Abstract no. 1028). Brian McCaughan, MD, a thoracic surgeon at the Royal Prince Alfred Hospital, Sydney, Australia, who has personally performed 5000 thoracotomies in patients with lung cancer said, "If I or anyone dear to me were scheduled for major cancer surgery, I would insist on a whole-body FDG study first."

At Guy's and St. Thomas's Clinical PET Center in London, there was a similar increase in patient throughput from 1992 to 1997, the greatest growth being in PET oncology studies (Fig. 3). All patients in these London hospitals have an FDG-PET study before thoracotomy.

These data show what can be accomplished by dedicated physicians who interact with referring physicians and provide up-to-date, high quality studies. Public concern about the increasing cost of health care provides a whole new educational ("marketing") opportunity for nuclear medicine. What is costly in medical decision-making is ignorance; what is cost-effective is knowledge. More than ever before, data presented at this meeting document how nuclear medicine procedures can bring about better patient care and still be cost-effective for society (Abstract no. 331-336). Never before has there been greater urgency to monitor and document the effectiveness of the health care that nuclear medicine provides.

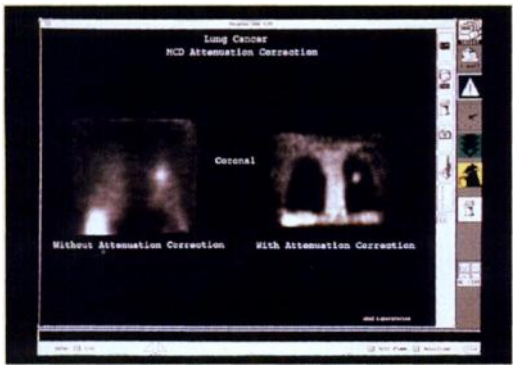


Figure 4.

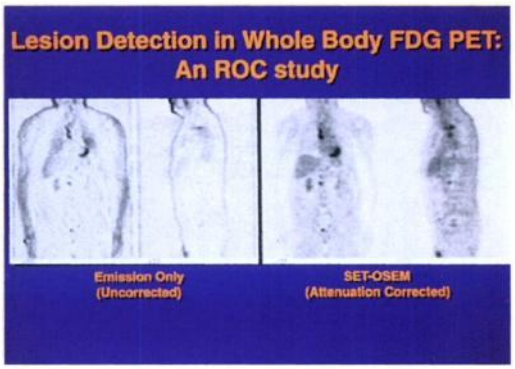


Figure 5.

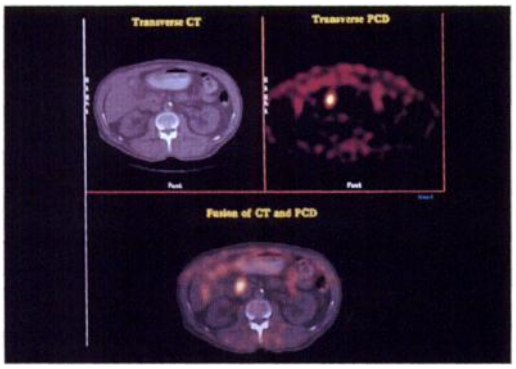


Figure 6.

ESTIMATED NEW CANCER CASES AND DEATHS U.S. 1995

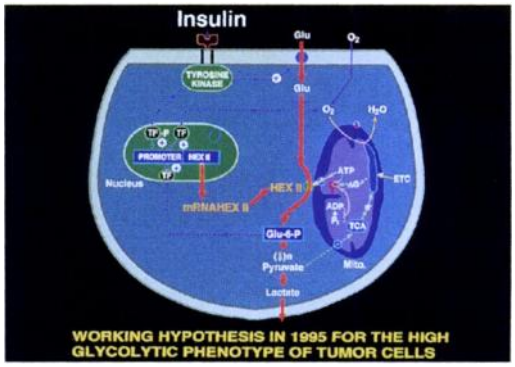
Cancer	New Cases	Deaths
BREAST (female)	182,000	46,000
CERVICAL	15,800	4,800
COLO-RECTAL	138,200	55,300
LUNG	169,900	157,400
SKIN (nonmelanoma)[b]	800,000	2,100
MELANOMA	34,100	7,200
OVARIAN	26,600	14,500
PROSTATE	244,000	40,400
UTERINE	32,800	5,900
VAGINAL and OTHER	5,700	1,200
TOTALS	1,252,000	547,000

Figure 7.

FDG ONCOLOGY

	Patients	Presentations
Lung	650	6
Pancreas	639	8
Breast	314	11
Melanoma	279	3
Head and Neck	249	4
Colon	207	6
Liver	190	3
Brain	188	9
Lymphoma	141	4
Other GI	95	3
Thyroid	75	4
Bone	36	2
Prostate	25	2
Kidney	25	1
Adrenal	20	1
Misc.	2773	12
Total	5906	89

Figure 8.



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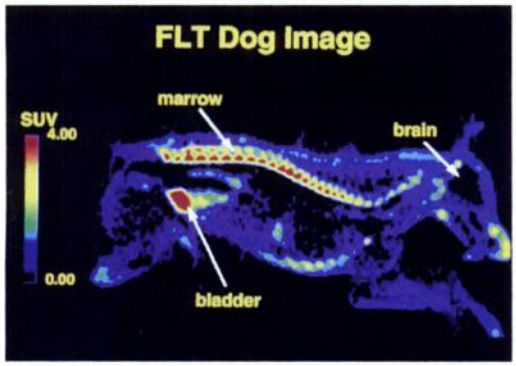


Figure 10.

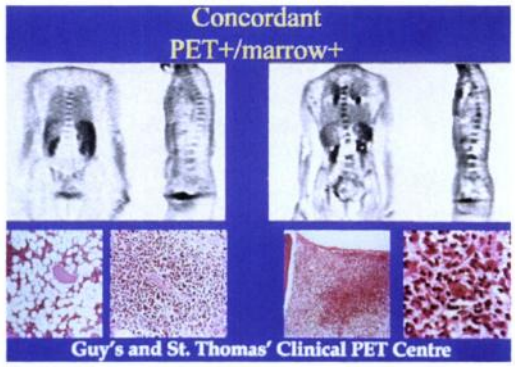


Figure 11.

Figure 4. Fluorine-18-FDG images of a lung tumor obtained with a dual-head coincidence system uncorrected (left) and corrected (right) for attenuation.

Figure 5. Study from the Royal Prince Alfred Hospital showing excellent image quality (Abstract no. 287).

Figure 6. Fusion of CT and ^{18}F-FDG studies in a patient with cancer (Abstract no. 283).

Figure 7. The incidence and death rate from various types of cancer in the United States. As shown in Figure 8, presentations at the SNM meeting covered all of these diseases.

Figure 8. Eighty-nine presentations described the results of ^{18}F-FDG in patients with cancer, representing studies of 5906 patients.

Figure 9. Mechanism of FDG accumulation in cancer. (Courtesy of Peter L. Pedersen, Johns Hopkins School of Medicine)

Figure 10. Image of the year. Fluorine-18-FLT in rapidly proliferating bone marrow cells and in a lymph node in the neck. The increased nasal activity probably represents mucous gland proliferation (Abstract no. 1055).

Figure 11. Bone marrow involvement with lymphoma shown by ^{18}F-FDG accumulation (Abstract no. 479).

Clinical PET

In 1991, the cover of *The Journal of Nuclear Medicine* proclaimed: "Clinical PET: Its Time Has Come." An accompanying editorial pointed out that the persons offering PET studies had to document technical capacity, diagnostic accuracy, diagnostic and therapeutic effects and patient outcome.

Focus on Quality

Tremendous emphasis is now being placed on the quality of nuclear medicine imaging, evidenced by the increase in PET instrumentation studies from 109 last year to 132 this year and for SPECT instrumentation from 105 to 143. Attenuation correction is possible in dual-head coincidence PET imaging

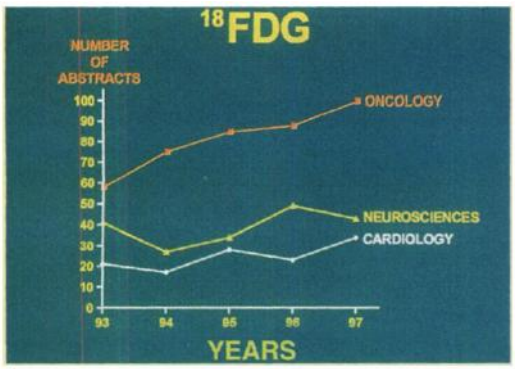
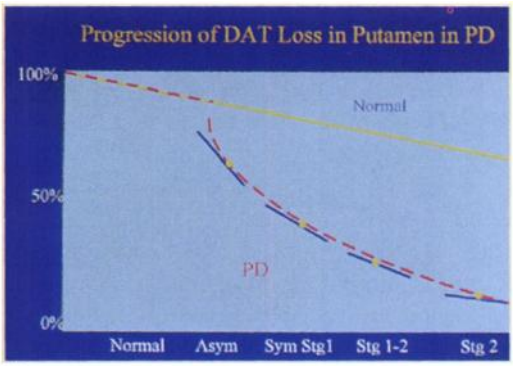


Figure 12.



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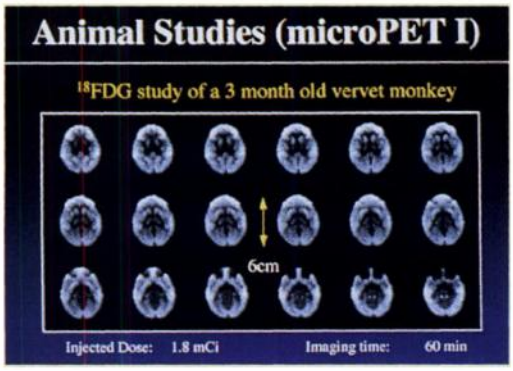

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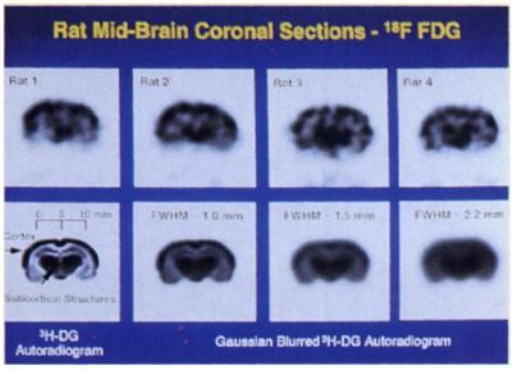

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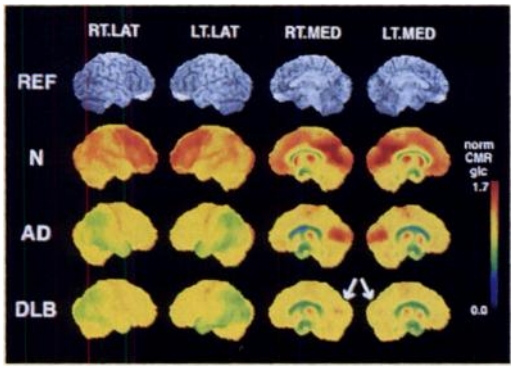

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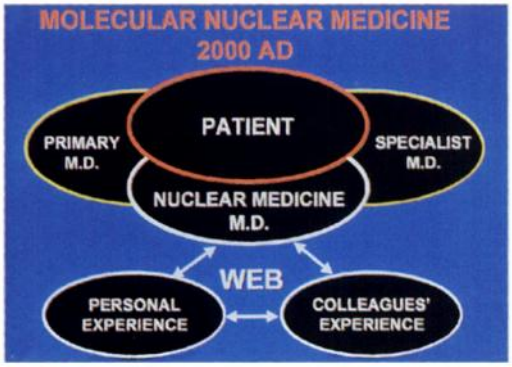

Figure 17.

Figure 12. Relative growth of FDG-PET presentations since 1983.

Figure 13. Decline in availability of dopamine transporter in the basal ganglia of patients with increasing stages of Parkinson's disease compared to the effect of normal aging (Abstract no. 522).

Figure 14. High degree of spatial resolution of an ^{18}F-FDG study in a monkey performed by Chatziioannou (Abstract no. 19).

Figure 15. Results obtained with an NIH animal brain scanner in a rodent (Abstract no. 157).

Figure 16. Surface projection images of ^{18}F-FDG studies in normal subjects, patients with classical Alzheimer's disease and patients with Lewy body dementia, in whom the visual cortex, as well as the temporo-parietal cortex are impaired (Abstract no. 257).

Figure 17. A model for nuclear medicine practitioners to follow to insure their success and the success of the specialty. It is not only necessary to interact with patients and many physicians, but to supplement one's own experience with that of others by utilizing WEB technology to access the vast database of knowledge it offers.

(referred to by some as "hybrid" PET/SPECT as compared to "dedicated" PET). Images produced by dual-head coincidence systems with attenuation correction were of high quality (Fig. 4).

An example of the value of simultaneous attenuation correction (SET) in dedicated PET together with iterative reconstruction with ordered subset expectation maximization (OSEM) reconstruction is illustrated in Figure 5, which was presented by the Royal Prince Alfred group, in Sydney (Abstract nos. 287, 1028). With the maximum likelihood iterative reconstruction methods, attenuation correction results in greatly improved image quality.

Investigators from the University of Pittsburgh, Louvain and Brussels also presented their accelerated reconstruction methods for both dedicated PET and dual-head coincidence imaging (Abstract no. 377). With previous use of reconstruction by filtered backprojection, the improvement by attenuation correction was less clear-cut because of decreased sensitivity. The OSEM method provides higher useful count rates for image reconstruction.

The dual-head coincidence systems can image tracers emitting the 140-keV photons of ^{99m}Tc as well as the 511-keV photons of ^{18}F. The fusion of PET and CT images is shown in Figure 6 (Abstract no. 283).

In patients with cancer, the combined use of CT and PET provided the best information for surgical decision-making, such as whether a solitary pulmonary nodule should be removed surgically. Important advantages of PET in cancer patients are the ability to examine the entire body and then focus on selected regions. PET frequently detects unsuspected metastatic disease, often in patients thought to have solitary pulmonary nodules.

FDG: Still Number One

The FDG story dates back to the brain study by Ido, Wolf, Kuhl,

(Continued on page 36N)

Annual Meeting Highlights *(Continued from page 17N)*

Reivitch and colleagues and illustrates how the creativity, curiosity, instruments, discoveries and knowledge applied to one organ system can apply to all organs of the body. The strength of nuclear medicine is that it is a "whole-body specialty." A tracer developed initially to study the brain turned out to be revolutionary in the study of cancer, especially when combined with advances in instrumentation by Phelps, Hoffman and colleagues at UCLA.

Twenty years ago, no one would have dreamed that 258 presentations (25% of the total abstracts) at the SNM meeting would focus on ^{18}F, with 70% of those reporting the results with ^{18}F-FDG! Figures 7 and 8 show how the FDG presentations cover nearly every type of cancer.

Figure 9 illustrates the mechanism of ^{18}F-FDG accumulation in cancer cells. The initial transport of FDG into the cancer cell is determined by the enzymatic action of the glucose transporters, such as Glut-1. Insulin, plasma glucose concentrations and hypoxia stimulate the expression of the promoter gene that activates the hexokinase II gene to express the hexokinase II mRNA. This results in increased production of hexokinase II, an enzyme that catalyzes the anerobic production of lactate at the mitochondrial membrane, and causes an increased accumulation of ^{18}F-FDG.

In breast cancer, the intensity of FDG accumulation was not found to correlate with Glut-1 (glucose transporter) levels as determined by immunohistochemistry in 60 lesions from 49 patients (Abstract no. 250).

Korean investigators reported a better correlation of FDG uptake with Glut-1 than with hexokinase in transplanted colon cancer in nude mice, but they did not separate the different types of hexokinase, especially hexokinase II (Abstract no. 1045). FDG accumulation was weakly associated with tumor cell proliferation in breast cancer cells (Abstract no. 1046). By binding to hexokinase II, FDG may serve as a sensitive tracer to detect cancer. FDG accumulation reflects glycolysis and mRNA synthesis of hexokinase II.

Image of the Year

While most cancer cells preferentially obtain energy by anerobic glycolysis of glucose to lactate, only about 10% of the cancer cells are dividing at any time. This leads to the hypothesis that monitoring thymidine incorporation into DNA may provide a marker of cell proliferation. The short half-life and rapid metabolism of ^{11}C-thymidine has led to the search for an ^{18}F-labeled analog of thymidine with more desirable properties. Shields, from Wayne State University and Grierson from the University of Washington have developed ^{18}F-fluorodeoxythymidine, which is retained by rapidly proliferating cells in bone marrow (Abstract no. 1055). Although further validation is needed to show that it indeed reflects cell proliferation in neoplasms, their results lead me to select their work as the "Image of the Year" (Fig. 10).

FDG-PET has been used to assess the response of tumors to chemotherapy, even though it does not reflect DNA synthesis, which is the target of many chemotherapeutic agents (Abstract no. 1054).

A Challenge to Technetium-99m Chemists

Today only positron-emitting tracers can reflect anerobic glycolysis. The small size of the glucose molecule has made it difficult to label with ^{99m}Tc or any other single-photon emitting nuclide because the binding to hexokinase II no longer occurs. Knowledge of the role of hexokinase II in neoplasms suggests an experimental approach to developing a ^{99m}Tc tracer that accumulates in neoplasms, that is, to develop a ^{99m}Tc-oligonucleotide that binds to hexokinase II mRNA. Hjelstuen and colleagues from Oslo and Leuven showed the feasibility of this approach by successfully linking ^{99m}Tc via MAG3 to a 20-base antisense oligonucleotide that bound to the breast cancer oncogene CAPL in vitro (Abstract no. 322). Of course, problems remain in getting an anti-sense tracer into tumor cells without excessive nonspecific binding that would reduce the signal-to-noise ratio. The key that ^{18}F-FDG has put in the nuclear oncology lock will be turned all the way if chemists can develop a ^{99m}Tc tracer equivalent to ^{18}F-FDG.

Safety as well as Effectiveness

Silberstein, University of Cincinnati Medical Center, reported his survey of the safety of PET radiopharmaceuticals in 22 PET centers throughout the United States (Abstract no. 415). In over 75,000 administrations, 90% of which were ^{18}F-FDG, there were no adverse pharmacological reactions. There were, however, some infiltrations of the dose at the injection site, some vaso-vagal fainting and some misadministrations. Overall, this study documents the extraordinary safety of PET.

Focus on Lung Cancer

In March 1996, the National Comprehensive Cancer Network (NCCN) reported that there were 177,000 new patients with lung cancer per year in the United States. The best chance for surgical cure was in Stage I and II disease. Stage I means the lesion is less than 3 cm in size, surrounded by lung or visceral pleura with no invasion more proximal than a lobar bronchus. Stage II means the lesion is greater than 3 cm or invades the main bronchus or visceral pleural or has associated atelectasis or pneumonia and only ipsilateral involvement of lymph nodes.

Computed tomography (CT) is essential but not completely satisfactory in distinguishing benign from malignant solitary pulmonary nodules or in staging the patient for surgical or other therapy. CT is reported to have 30% false-positives and 10% false-negatives in assessing lymph node involvement. The NCCN survey reported that at the time of thoracotomy, 15% of the patients had bilateral lymph node involvement and 40% had distant metastases, totaling 55% with unresectable lesions at the time of thoracotomy. McCaughan stated that "there is no such thing as a palliative thoracotomy. It is an oxymoron." What surgeons and other oncologists want to know is who they should operate on and who they should refer for chemotherapy without delay!

Yeung and colleagues from Memorial Sloan Kettering Cancer Center, New York, NY reported that FDG-PET was very sensitive and more specific in preoperative staging of patients with

lung cancer for therapy compared to CT (Abstract no. 292). Stroobants and colleagues from Leuven, Belgium reported that PET was significantly more accurate than CT in the detection of mediastinal node involvement by lung cancer, but that correlation with CT improved the interpretation of the PET studies, particularly in determining the location of the involved nodes (Abstract no. 291). Steinert and colleagues from Zurich, Switzerland reported that in nearly 100 patients with non-small-cell lung cancer, whole-body FDG-PET examinations revealed distant metastases in 20 locations, including bone, adrenal, liver, supraclavicular nodes, and the brain in one patient (Abstract no. 294). They pointed out that one must use care in distinguishing supraclavicular node involvement from sternocleidomastoid muscle uptake of FDG in tense patients. Bénard and colleagues described the use of ^{18}F-FDG PET in distinguishing benign pleural abnormalities from mesothelioma and assessing the extent of disease (Abstract no. 1033). The FDG studies were also helpful in selecting biopsy sites.

Benign Versus Malignant Solitary Pulmonary Nodules

One of the important advantages in assessing whether lesions, such as benign versus malignant pulmonary nodules (SPN), is availability of anatomical imaging such as CT to direct the imaging device and select the regions of interest. In staging, patients are known to have cancer or to have a high preoperative probability of having cancer.

Gupta and colleagues from Wheeling, WV, reported a sensitivity of 94% in detecting primary non-small-cell lung cancers in 56 patients and a specificity of 100% for lesions larger than 3 cm and 88% in smaller lesions (Abstract no. 289). PET accurately detected lymph node involvement in 12/13 lesions missed by CT. Higashi and colleagues reported that bronchioalveolar carcinoma was less likely to accumulate FDG than moderately or well-differentiated adenocarcinoma of the lung (Abstract no. 290).

When factors such as the age of the patient are taken into consideration, a strategy including FDG-PET was believed to be more cost-effective than CT or chest radiography alone in the follow-up of the patients and did not compromise patient survival (Abstract no. 1037). Gambhir and colleagues presented a theoretical decision analysis model for determining the cost-effectiveness of dual-head coincidence imaging in the presurgical staging of non-small-cell lung cancer (Abstract no. 1038).

Colorectal Cancer

FDG-PET was superior to CT in staging 37 patients with colorectal cancer (sensitivity 78% versus 37% with the same specificity of 90%) (Abstract no. 511). There was a limited sensitivity (29%) in detecting lymph node involvement. In patients with recurrent colorectal cancer, FDG-PET provided additional information after CT in 15/37 patients (Abstract no. 513). In detecting liver neoplasms, Delbeke and colleagues from Vanderbilt University, Nashville, TN, reported that in 107 patients with lesions in the liver greater than 1 cm, FDG-PET was able to distinguish metastatic colorectal cancer from benign lesions (Abstract no. 514).

Adrenal Cancer

Maurea and colleagues from Naples were able to distinguish 10 benign masses from 13 malignant adrenal lesions (Abstract no. 1024). Of the 13 patients with malignant tumors of the adrenal glands, 8 were shown to have extra-adrenal metastases.

Head and Neck Cancer

Bender and colleagues reported excellent results in the primary diagnosis, staging and follow-up of 157 patients with head and neck cancer (Abstract no. 622).

Breast Cancer

Hubner and colleagues at the University of Tennessee in Knoxville reported that FDG-PET was not sensitive enough to eliminate the possibility of axillary node involvement in breast cancer, but was able to detect distant metastatic disease in 16 of 36 patients, including five patients with axillary node involvement (Abstract no. 251). Yutani and colleagues from Osaka reported that FDG-PET (79% sensitivity) and ^{99m}Tc-sestamibi (77% sensitivity) have equal diagnostic accuracy but the contrast between lesions and normal tissue was greater with FDG. Neither could detect cancer in 5/36 patients (Abstract no. 248). Ductal carcinomas had a higher accumulation of ^{99m}Tc-sestamibi than other lesions (Abstract no. 991).

In a comparison of FDG with ^{99m}Tc-tetrofosmin, FDG studies with a dual-head coincidence detection system had a higher sensitivity than the ^{99m}Tc studies, but FDG planar imaging was unsatisfactory (Abstract no. 249).

When aggressive treatment with high-dose chemotherapy and bone marrow transplantation is being considered, whole-body FDG-PET can play an important role in optimum selection of patients (Abstract no. 252). In patients with bone metastases from breast cancer, FDG is more sensitive than ^{99m}Tc bone scintigraphy in detecting purely osteolytic lesions but not osteoblastic lesions (Abstract no. 477). Moreover, high avidity for FDG in lesions is a poor prognostic sign.

Goldenberg and his colleagues worldwide have improved the use of monoclonal antibody fragments labeled with ^{99m}Tc. In 59 consecutive patients with nonpalpable lesions and indeterminate mammograms, cancer could be identified in 60% of the patients with a negative predictive value of 86%, obviating the need for surgical biopsies in many patients (Abstract no. 25).

A prospective European multicenter trial of ^{99m}Tc-sestamibi in 246 patients revealed a sensitivity of 86% in the detection of palpable breast lesions, but only 63% for nonpalpable lesions (Abstract no. 67). In 60% of the false-negative mammograms, ^{99m}Tc-sestamibi could diagnose the presence of malignancies.

A new ^{123}I tracer, Z-MIVE, can reveal the estrogen receptor status of breast tumors and can improve the selection of patients for hormonal therapy (Abstract no. 68).

Sentinel Nodes

Nuclear medicine has been likened to a tree with branches extending to other medical specialties. A branch, which is

increasing in girth is surgery, where staging prior to surgery is being greatly aided by radioactive tracer studies. A recent development increasing with use is the identification of the spread of cancer to the first lymph node that drains the tumor site, the "sentinel node," so-called because its involvement helps determine the degree to which the tumor cells have spread to the entire lymphatic drainage.

Paganelli and colleagues from Milan found the sentinel node in 160 patients with breast cancer using an intraoperative probe after injection of ^{99m}Tc-albumin microcolloids in the region surrounding the primary breast lesion (Abstract nos. 116, 996). The use of a gamma probe for detection of sentinel nodes successfully revealed 97.5% of the nodes. Pathological examination revealed cancer in the nodes in 69/115 specimens.

Krag and colleagues had excellent results in 27 consecutive patients examined with ^{99m}Tc unfiltered sulfur colloid rather than nanocolloid (Abstract no. 119).

Breast Imagers

Several groups are developing dedicated imaging devices for breast examinations. Wang and colleagues at Emory University, in Atlanta used a vertical axis-of-rotation with half-cone beam collimation around the breast with the patient lying prone to obtain impressive images with ^{99m}Tc tracers compared to conventional whole torso SPECT imaging (Abstract no. 936). Patt and colleagues from UCLA and Lawrence Berkeley National Laboratory described their progress in developing a single-photon dedicated breast imaging system based on a cesium/iodide (Tl) scintillator with a spectral resolution of 8% and spatial resolution of less than 1.5 mm (Abstract no. 535). Freifelder and Karp of the University of Pennsylvania compared the characteristics of a dedicated versus a whole-body PET scanner for breast studies (Abstract no. 285). The Penn group also described a curved sodium iodide (Tl) detector for PET and SPECT that would seem to be advantageous for breast studies (Abstract no. 540).

Lymphoma

Gallium-67 imaging remains the mainstay for imaging lymphomas. Researchers from Milan reported on 332 patients with Hodgkin's and 83 with non-Hodgkin's lymphoma involving the mediastinum who underwent follow-up during radiation and chemotherapy. The ^{67}Ga studies were more accurate than CT and MRI (Abstract no. 428). Similar results were reported from Israel by Front and colleagues (Abstract no. 430). The cost-effectiveness was demonstrated because ineffective treatment could be identified early.

Fluorine-18-FDG PET could predict bone marrow involvement in patients with lymphoma and thus avoid bone marrow biopsy could be avoided (Abstract no. 479). The excellent quality of the images is shown in Figure 11.

Somatostatin receptor imaging is also helpful in staging patients with Hodgkin's lymphomas (Abstract no. 379). In a prospective study of 126 patients, sensitivity was 99%. The best results were obtained in detecting lesions above the diaphragm, and in many patients new unsuspected lesions were found.

Melanoma

Surgical oncologists need to identify the 20% of patients with melanoma in whom the disease has spread to lymph nodes so that lymph node dissection can be performed. The key is to avoid unnecessary surgery in the 80% of patients in whom the disease remains localized in the primary lesion.

Planar scintigraphy was performed soon after injection of ^{99m}Tc nanocolloid at four points around the primary skin lesion. The first lymph node in which the tracer accumulated was marked on the skin and identified by an intraoperative "probe" scintillation detector. Thirty percent of the sentinel nodes were found to contain metastases (Abstract no. 995). A degree of caution was presented by investigators from Humboldt University in Berlin (Abstract no. 998), who found disease in distant nodes in two patients where the sentinel node was not involved.

Brenner and colleagues described a new prognostic immunoradiometric serum assay to diagnose metastatic malignant melanoma (Abstract no. 600). Follow-up studies over a period of 5 years revealed good correlation with survival in 412 patients.

Valk and colleagues, Sacramento, CA, reported their results in 64 patients with melanoma, in whom the cost impact of PET in staging patients resulted in savings of $1800 per patient. The finding of distant metastatic disease by whole-body FDG-PET imaging resulted in the cancellation of six lung resections, four lymph node dissections, two liver resections, one laparotomy and one pelvic exenteration (Abstract no. 333).

Pancreatic Cancer

Virgolini and colleagues, from the University of Vienna found that iodine-123-labeled vasoactive intestinal peptide (VIP) had a sensitivity of 90 % (19/21 patients) in disease confined to the pancreas and 32% (8/25) when the disease also involved the liver (Abstract no. 383). Ninety percent (29/32) of liver metastases were detected.

Carbon-11-Methionine

Nuclear medicine goes beyond the detection of disease because it can characterize disease as specific molecular abnormalities. Specific questions are addressed by specific molecular tracers in patients with cancer. Fluorodeoxythymidine can characterize the degree of malignancy of a neoplasm. FTY can characterize its rate of cell proliferation. Carbon-11-methionine characterizes amino-acid transport, especially when tryptophane is used to block methionine trapping and increase specificity of the measurement. Carbon-11-methionine can at times detect brain tumors that cannot be detected with FDG, because the latter accumulates in normal brain tissue and the lesions may not be expressing hexokinase II (Abstract no. 1057). Kubota and colleagues from Tohoku University, Japan, clarified the relative roles of ^{11}C-methionine, ^{18}F-FDG, and ^{18}F-fluoromisonidazole (FMISO), the latter reflecting hypoxia (Abstract no. 1051). When accumulation of FMISO was high, methionine uptake was low.

Carbon-11-Choline

Choline accumulation reflects the biosynthesis of phosphatidylcholine, a major constituent of phopholipids in cell membranes. In studies of patients with brain tumors with magnetic resonance specroscopy, a higher level of phospholipids was found in high-grade gliomas. Hara and colleagues reported the results of ^{11}C-choline accumulation for the detection of bladder cancer (4 patients), prostate (19 patients) and colon (7 patients), in which urinary excretion of FDG can sometimes present a problem in differentiating urinary activity from lesions (Abstract no. 1058).

Multi-Drug Resistance

Cancer in many patients is resistant to treatment with chemotherapeutic agents initially or after a period of treatment. Resistance to one agent often extends to others, a phenomenon called "multi-drug resistance" (MDR). The use of ^{99m}Tc-MIBI tracers is an excellent example of how nuclear medicine can contribute to closing the circle between phenotype and genotype. The MDR1 gene product, P-glycoprotein (PgP) pumps drugs and other toxic substances out of tumor cells, as well as normal cells, especially in the liver and kidneys. Breast cancer, lymphomas, neuroblastoma, ovarian cancer and osteogenic sarcoma express varying amounts of P-glycoprotein, which can determine how the patient will respond to chemotherapy. As a result of the pioneering work of Piwnica-Worms, we now know that lipophilic monovalent cations, including sestamibi, tetrofosmin and the Q tracers, are excreted from cells in proportion to the amount of P-glycoprotein expressed.

Mice in which the MDR1 gene is "knocked out" confirm the role of this gene in determining the rate of efflux of ^{99m}Tc-sestamibi which is prolonged when P-glycoprotein is not expressed (Abstract no. 371). A positron-emitting radiotracer, ^{64}Cu-diphosphine complex, makes it possible to monitor P-glycoprotein activity with PET (Abstract nos. 499, 531). In patients with sarcomas, rapid ^{99m}Tc-sestamibi clearance was successfully overcome by high doses of the chemotherapeutic agent (Abstract no. 1021).

The measurement of tracer efflux in patients receiving neoadjuvant chemotherapy a few weeks before removal of primary breast cancer lesions predicted which tumors had persistent mitoses in the surgical specimens (Abstract no. 1020).

One approach to overcoming MDR to chemotherapeutic agents is to administer drugs that block the P-glycoprotein pump, which would result in prolonged retention of the cancer chemotherapeutic drugs. Such agents to increase chemotherapeutic effectiveness are under development using ^{99m}Tc-sestamibi or tetrofosmin as a phenotypic marker. Nakamura and colleagues from Tokyo University used ^{99m}Tc-sestamibi and tetrofosmin in the in vitro development of such drugs (Abstract no. 776). Piwnica-Worms and colleagues, who originally described the use of ^{99m}Tc tracers for this purpose, reported their excellent progress with a P-glycoprotein inhibitor, PSC 833 (Abstract no. 1022).

Thallium Imaging in Oncology

Thallium accumulation reflects the progressive clinical behavior of neoplasms (Abstract no. 52). Patients whose differentiated thyroid carcinomas had a high degree of ^{201}Tl accumulation had high incidences of recurrence (Abstract no. 1119). Early imaging of ^{201}Tl accumulation in thyroid nodules was a better discriminator between benign and malignant nodules than cytodiagnosis (Abstract no. 1117). Thallium-201 avidity is also a predictor of outcome of treatment in children with brain tumors (Abstract no. 432). High thallium-201 accumulation in brain lesions is indicative of a malignant tumor or pituitary adenoma (Abstract no. 431).

Radionuclide Therapy

Seventy-five presentations on radionuclide therapy included seven concerned with alleviation of bone pain. Atkins and colleagues from Brookhaven National Laboratory, Upton, NY, reported the results of ^{117m}Tn DTPA treatment of bone pain due to metastatic cancer (Abstract no. 166). Relief was obtained in 75% of the patients, and there was less hematologic toxicity than with other bone pain palliation agents.

Vose and colleagues reported treating 17 patients with relapsed or refractory non-Hodgkin's lymphoma with ^{131}I-labeled LL2 anti-CD22 (Abstract no. 211). There was minimal extrahematopoietic toxicity and complete remission in three patients.

Yttrium-90-DOTA-Tyr3-octreotide is under study as a way to treat patients with cancer which expresses somatostatin receptors. Investigators in Germany and Switzerland assessed its pharmacokinetics using the ^{86}Y tracer and PET imaging in baboons (Abstract no. 215). Initial results in a normal human were presented by Krenning.

Direct injection of ^{131}I and ^{90}Y antisense monoclonal antibodies into cerebral glioblastomas prolonged survival (23 versus 12 months) and disease-free periods compared to other treatment (Abstract no. 216).

Cellular Communication and Control

Inter- and intracellular communication, not only in the nervous system, but throughout the body, is now a major focus of medicine, genetics and pharmacology and nuclear medicine as well. Advances made by nuclear medicine in the neurosciences are being directly applied to the care of patients with cancer (Fig. 12). For example, amine and peptide receptors are expressed by many types of cells and lesions (Abstract nos. 55, 1122).

Nuclear medicine is concerned with the entire body, not just one or another organ system. Cancer can be viewed as a disease of impaired communication and control of cell growth and function, involving intracellular signaling pathways, glucose metabolism, messenger RNA transcription, ion channels and neurotransmitter receptors.

The Dopaminergic System

This neurotransmission system remains the most extensively studied in nuclear medicine, with great emphasis on Parkinson's disease and substance abuse. Assessing the presynaptic dopamine transporter with a ^{11}C-labeled tracer, WIN 35,246, Frost and colleagues, at Johns Hopkins documented the decline in dopamine transporter availability during progression of Parkinson's disease (PD) as compared to the slower decline in normal aging (Abstract no. 522) (Fig. 13).

SPECT imaging with [^{123}I]-CIT distinguished diminished dopamine transporter binding in some relatives of patients with PD, but it could not depict as severe a decline as occurs in the PD patients themselves (Abstract no. 519).

Progressive decline in dopamine transporter availability was observed in patients with PD studied over a six-month interval (Abstract no. 517). The decline in transporter binding of tracers corresponded to the increase in the patients' symptoms, indicating possible use as a marker of disease progression or response to treatment.

Until now, dual-head coincidence systems have been most widely used for FDG studies. They can, however, also be used to study neurotransmission. Goodman and colleagues from Emory University described their results in imaging striatal accumulation of a ^{18}F-labeled tropane analog by the dopamine transporter in presynaptic neurons (Abstract no. 619).

Ichise and colleagues from Toronto reported that there was an increase in dopamine transporter binding as measured with ^{123}I-βCIT in patients with Alzheimer's disease, perhaps secondary to abnormalities that occur in the cholinergic system, which is impaired in Alzheimer's disease (Abstract no. 253).

Mutations in apolipoprotein E subtype 4 are thought to increase the risk of Alzheimer's disease. Van Dyck and colleagues from Yale University, New Haven, CT, reported greater asymmetry in ^{18}F-FDG accumulation in the parietal regions of the brain in patients with this genetic abnormality (Abstract no. 254).

Animal Scanners

Studies of the dopaminergic system are affecting drug design and development. Such research is facilitated by the development of animal scanners. The use of live animals, especially rodents, decreases the cost of research by an order of magnitude. The UCLA group, working with Majewski and colleagues from the Thomas Jefferson National Accelerator Facility, reported their striking results of FDG studies in animals (Abstract nos. 19, 159) (Fig. 14).

Green and colleagues at the National Institutes of Health, Rockville, MD, described a specially designed dual-head coincidence system with 5×5 centimeter detectors and a spatial resolution between 1 and 1.5 millimeters (Abstract no. 157) (Fig. 15).

Other animal scanners were described by investigators from Massachusetts General Hospital (Abstract no. 158) and the Max Planck Institute in Munich (Abstract no. 160).

Substance Abuse

The important contributions of nuclear medicine to the design and development of helpful drugs extend to the study of abused substances. For example, the cocaine-induced high as determined by neuropsychological testing correlates with the substance's binding to the dopamine transporter (Abstract no. 125). Pharmaceutical companies all over the world are trying to develop drugs for the treatment of cocaine abuse, focusing on the dopamine transporter system. Among the screening criteria are the ability of the drug to block or stimulate to some degree the dopamine transporter system (Abstract no. 123). The loss of dopamine transporter activity in normally aging persons was not found in cocaine abusers (Abstract no. 124). Another abused drug, methamphetamine, produced a lasting loss of dopaminergic neurons (Abstract no. 349).

In abstinent, alcohol-dependent persons, there was a decrease in dopamine and/or serotonin transporter availability in the raphe system of the brain (Abstract no. 174). The same investigators observed a decrease in dopamine transporter availability in the basal ganglia of smokers compared to non-smokers.

The Beck score is used to assess the degree of a person's state of depression and to monitor the effects of pharmacological treatment. Increased binding of the radiotracer, ^{11}C-carfentanil, to opioid receptors in the putamen and the temporal cortex was found in women treated for depression but not in depressed men (Abstract no. 400). Perhaps depression is a different disease in men than in women, possibly related to hormonal differences.

Mu opioid receptor binding of ^{11}C-carfentanil was increased in various regions of the brain of alcoholic patients withdrawn from alcohol and could be related to the degree of craving (Abstract no. 121).

Gene Therapy

An example of the value of the holistic approach of nuclear medicine is that a radiotracer developed to examine dopamine receptors is now used in gene therapy to mark successful transfer of a gene to a therapeutic site (Abstract no. 760).

Cardiology

When I was a medical intern, patients suffering from a heart attack were treated by bed rest; the mortality rate was 30 %. In the 1960s and 1970s, coronary care units, antiarrhythmic drugs and defibrillators were introduced, and mortality rates declined. Cardiologist Eugene Braunwald designated the decades between 1970 and 1990 as "the high-tech phase" during which time nuclear ventricular cardiology and myocardial perfusion imaging were developed. We are now in an evidence-based coronary care phase and are being asked to document the value of nuclear cardiology.

Today, only those patients with myocardial infarction who are in shock go directly to invasive revascularization procedures. The decision of whether to perform thrombolysis depends a combination of clinical, ultrasonographic or nuclear medicine assessment. Only patients shown to be at high-risk undergo cardiac catheterization.

Nuclear medicine procedures are increasingly available in the emergency room to assess patients with chest pain (Abstract no. 47). Today, as many as 40% of patients admitted to coronary care units are found not to have had a myocardial infarction. If they had been sent home, there was always the possibility that they might have had serious heart disease, with both medical and medico-legal consequences. Nuclear cardiology in the emergency room not only improves care but can save hundreds of millions of dollars in unnecessary hospitalization costs. The number of cardiovascular events was essentially zero in those patients who were sent home based on a normal myocardial SPECT study (Abstract no. 47).

In a study from Massachusetts General Hospital, exercise, dipyridamole and exercise, adenosine and adenosine and exercise were equally effective in the diagnosis of coronary artery disease (Abstract no. 270).

There is an increasing interest in ventricular function studies, that is, gated SPECT and PET, because they provide information about ventricular function, wall motion, myocardial thickening, as well as regional myocardial blood flow (Abstract nos. 641, 639, 642).

Estimation of the amount of viable, but injured myocardium remains one of the principal factors in the decision to attempt surgical revascularization in patients with severely impaired left ventricular function (Abstract nos. 357, 706, 732).

Investigators from Columbia University found that 35% of the patients with ischemic cardiomyopathy who were initially denied revascularization on the basis of thallium scans were found to have viable myocardium when subsequently studied with ^{18}F-FDG. They underwent coronary bypass procedures with excellent outcomes (Abstract no. 195).

Prevention by Early Diagnosis

Hattori and colleagues from Hokkaido University reported their finding of reduced global coronary flow reserve, measured with ^{13}N-ammonia, in severely hypertensive patients who had normal myocardial perfusion imaging (Abstract no. 743). This could account for ichemic attacks during stress in these patients.

Investigators from Munich found that global coronary flow reserve measured with ^{13}N-ammonia before and after adenosine administration was reduced in asymptomatic hyperlipidemic men but not women (Abstract no. 742).

Treatment of patients with hypercholesterolemia resulted in improvement in reduced global coronary flow (^{13}N-ammonia) in patients who had angiographically normal coronary arteries (Abstract no. 313).

In patients with dilated cardiomyopathy, increased spatial heterogeneity in the distribution of regional myocardial perfusion, measured with ^{13}N-ammonia, was found to be correlated with a much shorter survival, 38% being alive after 3 years compared to 90% of those with more homogeneous distribution of flow (Abstract no. 739). This illustrates an important principle: in many organs, including the heart and liver, heterogeneity of function is a manifestation of disease.

Detection of Atherosclerosis

Dinkelborg and colleagues from Berlin have developed a ^{99m}Tc-endothelin derivative that accumulated in neointimal smooth muscle cells in experimental animals (Abstract no. 748). The goal is to detect atherosclerosis before there is impairment of blood flow.

Radioactive Stents

Complications of balloon angioplasty include subsequent recoil of the artery back to its original narrowing, acute occlusion following the angioplasty, or gradual restenosis through the formation of scar tissue. World-wide sales of tiny coil-like "stents" to prevent these complications were $ 1.1 billion dollars in 1996, but the results have not been completely satisfactory.

Nickles and colleagues at the University of Wisconsin, Madison, have developed radioactive stents to help solve these problems (Abstract no. 17). Phosphorus-32, ^{90}Y, and ^{48}V have been used for this purpose, the latter being introduced by Li et al. from UCLA.

Gene Therapy in Cardiology

Zanzonico and colleagues from The New York Hospital-Cornell Medical Center used ^{99m}Tc-sestamibi to document improvement in myocardial perfusion in experimental animals in whom the gene-expressing vascular endothelial growth factor was injected directly into the territory of stenosed coronary arteries, resulting in blood vessel proliferation (Abstract no. 148).

Technetium-99m-Peptides

Line et al. who described their results with ^{99m}Tc-MH1- Fab' antifibrin in detection of pulmonary embolism in patients (Abstract no. 462). This work should be an important accompaniment to visualization of in situ clots by MRI.

A technetium-labeled peptide specific for CD-15 neutrophil receptors was effective in the diagnosis of atypical appendicitis (Abstract no. 86). Equally good results were reported by an anti-NCA-90 granulocyte antibody (Abstract no. 85). In acute non-classic appendicitis in children, the sensitivity of planar imaging with this antibody was not as good as with SPECT (Abstract no. 79).

Information Technology

Using a database describing the distribution of ^{18}F-FDG accumulation in the brains of 30 normal people, Minoshima and colleagues from the University of Michigan could distinguish patients with dementia with cortical Lewy bodies from patients with Alzheimer's disease because of the involvement of the visual cortex in Lewy body dementia (Abstract no. 257) (Fig. 16).

Minoshima et al. also showed that the level of education has an effect on language performance in patients with Alzheimer's disease (Abstract no. 352). Flourine-18-FDG studies presented as three-dimensional sterotactic surface projections improved the classification of patients with dementia and facilitated interpretation of the results by less experienced physicians (Abstract no. 1146). Their image databases can be shared among different institutions by the use of the World Wide Web and Internet and spatial filtering to standardize the results (Abstract no. 1166). The Washington University group used JAVA programming language to develop an Internet-based, interactive nuclear medicine image and display system (Abstract no. 897).

An example of the use of the Internet was the description of a recent course at Johns Hopkins in nuclear oncology. The announcement on a Hopkins web site stated: "Imaging technique can prevent most fruitless cancer surgery." We were swamped by responses, not from physicians, but from patients. Patients are becoming increasingly involved in their care. As long ago as 1981, the AMA Council on Ethics said: "The patient's right of self-decision can be effectively exercised only if the patient possesses enough infor-

mation to enable an intelligent choice. The patient should make his own determination on treatment." In addition one must have the best possible relationship and lines of communication with primary physicians and specialist physicians (Fig.17).

With a personal computer, the nuclear physician can store his or her records of all patients, as well as take advantage of one's colleagues' experiences via databases on the Internet. Molecular nuclear medicine is the knowledge specialty. Informed patients and physicians can bring about not only "smart surgery," but also "smart radiotherapy," and "smart chemotherapy." Nuclear medicine can benefit greatly from the increasing attention being paid to the quality and value of all facets of the health care system.

Many presentations from the U.S. and overseas showed what can be accomplished by experienced, well-trained nuclear medicine physicians who can fathom the complex problems of patients and provide in vivo physiological and biochemical knowledge to help solve the patient's problems.

What do physicians provide, particularly nuclear medicine physicians? They provide knowledge. What do patients want? They want certainty. It is time we stopped fiddling on the roof and move down into the house where the physicians and sick patients live.

—Henry N. Wagner, Jr., MD

Radionuclide Availability *(Continued from page 28N)*

emitters, university cyclotrons may provide adequate quantities of the others.

Astatine-211 ($t_{1/2}$ =7.2 hours) is a promising alpha-particle emitter for certain oncologic applications, such as the treatment of patients with ovarian cancer or brain tumors. Research centers in Finland, Germany, Italy and Switzerland have discussed the possibility of collaborating to produce the European supply of ^{211}At for clinical research (*11*). A similar approach in the U.S. could meet the North American demand for ^{211}At.

Bombarding natural ^{209}Bi targets with 28-MeV alpha-particles can produce ^{211}At via the ^{209}Bi(α,2n)^{211}At reaction. Larson et al. (*12*) recently described an internal target system that provides ^{211}At production yields of 1.1 mCi/μA/hour (40.7 MBq/μA/hour) (*13*). An 8-hour run at 90 μA would yield 527 mCi (19.5 GBq) of ^{211}At. Assuming a 65% distillation efficiency and 8-hour decay in transport, about 160 mCi (5.9 MBq) of ^{211}At could be delivered from that 8-hour run. Zalutsky estimated the production cost at US$21/mCi (US$0.57/MBq); he proposed that a reasonable 100% mark-up to US$42/mCi (US$1.14/MBq) would still make this material available at an acceptable cost.

Iodine-124 ($t_{1/2}$ = 4.2 days), a positron emitter, could be used in PET imaging to provide dosimetry estimates for radiotherapeutic compounds labeled with ^{131}I. Most methods for producing ^{124}I involve irradiation of enriched tellurium targets with deuterons or protons (*13-16*). Yields from thick targets range from 0.5 to 1.8 mCi/μA/hour (18.5 to 66.6 MBq/μA/hour). Certain reactions with ^{124}Te and ^{125}Te—e.g.,the ^{124}Te(p,n) and ^{125}Te(p,2n) reactions yield—sufficient quantities for patient doses at proton energies of <18 MeV.

To date, the largest batches of ^{124}I have been produced using the ^{124}Te(d,2n) reaction; a 6.25-hour irradiation with an 80-μA deuteron beam yielded 270 mCi (9.9 GBq) of ^{124}I (*13*). Therefore, an estimated 300 mCi (11.1 GBq) of ^{124}I could be delivered offsite from one production run with an 8-hour irradiation, 90% recovery of ^{124}I, and 8-hour decay during transport. Based on the US$425/hour cost of running the CS-30 cyclotron at Duke University, the estimated cost of producing ^{124}I would be US$11/mCi (US$0.30/MBq); a reasonable marked-up price would be $22/mCi (US$0.60/MBq).

Bromine-77 ($t_{1/2}$ = 57 hours), which emits Auger electrons, might serve as a useful alternative to ^{125}I for therapeutic radiopharmaceuticals designed to target sites close to cellular DNA. Irradiating natural ^{75}As with 28-MeV alpha-particles can produce ^{77}Br via the ^{75}As(α,2n)^{77}Br reaction. The chemical form of the arsenic target determines the potential yield of ^{77}Br. An arsenic trioxide target, for example, can handle beam currents up to 65 μA; a 1-hour run has yielded 18.9 mCi of ^{77}Br, very close to the theoretical yield of 293 μCi/μA/hour (10.8 mBq/μA/hour) (*17*).

CONCLUSION

The future of nuclear medicine depends on the long-term, uninterrupted availability of research radionuclides on a routine basis at reasonable costs. The radiopharmaceuticals of tomorrow depend on the investigational radiotracers and therapeutic nuclides of today. The vast potential of molecular nuclear medicine may not be realized with current limitations in the supply of research radionuclides.

Ideally, a National Biomedical Tracer Facility (NBTF) in the United States would provide a reliable supply of accelerator-produced radionuclides for biomedical research. A facility dedicated to biomedical radionuclide production would resolve the untenable dependence on unrelated research programs of U.S. national laboratories.

Until an NBTF becomes reality, however, a coordinated effort among national laboratories, universities and industry to pool accelerator resources may provide an interim solution. Although production of some radionuclides, such as ^{67}Cu, may be most efficient with the high-energy accelerators of the national laboratories, many others can be readily produced with low- or medium-energy cyclotrons. Several PET centers, for example, have low-energy (≤15 MeV) cyclotrons that could produce ^{18}F and ^{64}Cu—and many of the other radionuclides listed in Table 2—for investigators outside those institutions. It may also be possible to make use of medium-energy (30 to 40 MeV) cyclotrons at commercial facilities (e.g., Mallinckrodt, DuPont, Amersham/MediPhysics), if radiopharmaceutical manufacturers agreed to participate in this effort.

Several reactors are currently available for complementary production of reactor-based research radionuclides. It is essential that their efforts also be coordinated to ensure a constant, uninterrupted and affordable supply of neutron-rich radionuclides to the biomedical research community.