DISEASE AS DISSONANCE

The Society of Nuclear Medicine celebrated its 41st anniversary at the annual meeting in Orlando, Florida, in June. For the seventeenth consecutive year, Henry N. Wagner, Jr., MD, professor of medicine, radiology and environmental sciences at the The Johns Hopkins Medical Institutions, presented his view of the scientific highlights at the final session of the meeting.

Henry N. Wagner, Jr. MD

THE FIRST STEPS TOWARD modern medicine were taken in 1543 with the publication of the exquisite atlas of human anatomy, entitled *De Fabrica Humani Corporis*, by Andreas Vesalius of the University of Padua. Two centuries later, another great Italian physician, Giovanni Morgagni, developed the "anatomical concept of disease," in which he related the clinical manifestations of disease to specific organs of the body. In his book *De Sedibus*, Morgagni formulated the basic principles that are at the core of modern clinical medicine. In 1894, the German pathologist, Rudolf Virchow, took the next important step of relating diseases to histopathological abnormalities of the cells within organs.

The greatest physicians have been identified as those who were best at predicting the gross and histopathological findings at autopsy from the clinical and laboratory manifestations of a patient's clinical illness.

The New Nuclear Medicine

The modern physician must not only "make the diagnosis" but select the most effective therapy and monitor its effectiveness.

As John Maynard Keynes pointed out, "The difficulty lies not in new ideas, but in escaping the old ones." And although the practice of medicine is still based largely on attempts to attribute diseases to specific organs, modern medicine is increasingly moving beyond gross anatomy and histopathology into the domain of molecular medicine, and no specialty is better able to contribute to the transition.

Nuclear medicine can provide new images of disease, not just new tests for old diagnoses. Many patients with the same diagnosis, such as cancer, or even Parkinsonism, can be shown to differ in their regional biochemical and physiological manifestations of disease. Even cancers with similar histopathological characteristics, such as islet cell tumors of the pancreas, can be differentiated according to whether they do or do not express somatostatin receptors.

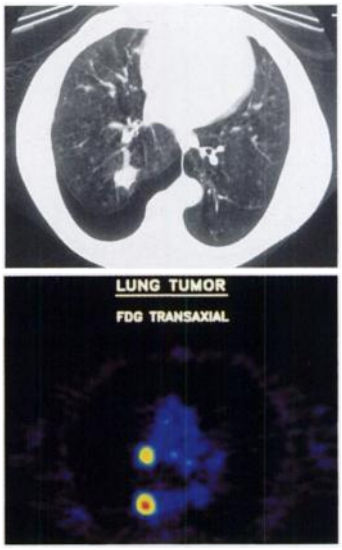

Figure 1. (A) A coin lesion in the right lung. (B) The high levels of glucose utilization indicate that the lesion is malignant, and that there is a metastatic lymph node on the same side (298).

Diseases such as cancer of the colon develop because of mutational inactivation of one growth suppressor gene after another, these genes expressing growth suppressor substances, such as somatostatin. These suppressor genes and their products have evolved as primitive cells became more differentiated. Their failure results first in adenomas and eventually in undifferentiated cancer. Throughout the lives of susceptible individuals, a series of somatic cell mutations result in dissonant messages being sent to colon cells, and the cells become cancerous. A person may be predisposed to somatic mutations because of a failure of the genes that control mutations. Periodic examination of such patients with whole body FDG scans might reveal when and where colon cancer develops, an example of the synergism of human genetics and nuclear medicine.

Cell membrane and intracellular receptors have become a major domain of nuclear medicine, involving neurotransmitters, hormones, growth factors, and cytokines controlling cellular behavior. Measuring these receptors in different parts of the body with radiotracers makes it possible to characterize diseases as failures in communication-"disease as dissonance."

Disease results when mutations change the molecular structure of molecular messengers. Cancer is not something that invades the body like a germ but is rather a failure of the molecular processes that keep us all from getting cancer. Mutations of suppressor genes cause the cells in certain parts of the body to return to a more primitive, undifferentiated, uncontrolled state that is cancer.

Orlando Meeting Underscores "Molecular Medicine"

Among the highlights of the 41st Annual Meeting were many examples of the safe and effective use of radioactive tracers in characterizing disease at the molecular level. For example, Gupta and colleagues from Creighton University reported a predictive accuracy of 92% in differentiating benign from malignant solitary pulmonary nodules and lymph nodes (298).* Figure 1A is an example of an anatomical study of a "coin" lesion within the lung. Figure 1B is a "glucose utilization" image, per-

*Numbers in parentheses indicate abstract number, Supplement, *J Nucl Med* (May) 1994.

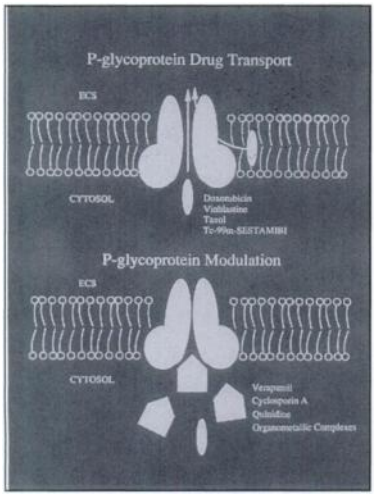

Figure 2. ^{99m}Tc sestamibi is transported by p-glycoprotein which pumps chemotherapeutic and other foreign drugs out of cancer cells and reduces their cidal effects. Sestamibi accumulation can be used to develop agents to modulate this transport process (66).

formed in the same patient with ^{18}F deoxyglucose (FDG). Not only did it indicate that the lesion is metabolically very active, and therefore probably malignant, but there was another metabolically active lesion in the hilar region on the same side of the thorax. Since the patient did not have any evidence of an involved metabolically active lymph node on the opposite side of the thorax, the decision was made to attempt cure by thoracotomy. If there had been bilateral hilar lymph node involvement, the patient would have been treated immediately by chemotherapy and thoracotomy avoided.

Last year there were 217 presentations in oncology; this year there were 308, a 42% increase (Figure 3). One quarter of the presentations, from both the United States and abroad, were in oncology; with nearly equal numbers in cardiology and neurosciences.

Seventeen presentations described the results of ^{18}F FDG imaging in patients with lung cancer. One was from investigators at the Northern California PET Imaging Center, whose cyclotron is operated by the radiopharmaceutical industry, which is another important trend in nuclear medicine (299). PET imaging with FDG was more accurate than CT in identifying patients who would not benefit from pulmonary resection (94% vs 79%). Mediastinal or hilar node involvement by cancer could be predicted with a positive predictive value of 90% and a negative predictive value of 97%. These high values exemplify how medicine is moving into a "new era of certainty," where decisions will be made and procedures performed only in those patients who can clearly benefit. Uncertainty is what makes medicine expensive today. Eighty percent accuracy does not permit cost-effective decision-making. Being wrong 20% of the time is not only medically, but economically, unacceptable. The goal is to eliminate surgery or other complex procedures that do not help the patient but are performed only to assure that the lesions are inoperable. If such surgery can be avoided, hospitalization and surgical complications can be avoided.

Pounds et al showed that FDG studies changed the staging in 33% of the patients with metastatic cancer of the lung (299). Glucose metabolic rate of the lesions was then used subsequently to determine the response to chemotherapy.

Outcomes Research

Just as diagnosis can be based on regional physiology and biochemistry, so can the effectiveness of treatment be measured by the same procedures. Such measurements of effectiveness are not only objective and quantitative but can be made immediately after treatment is started. In a Harvard study of patients with lung cancer, glucose utilization within the lesions fell from 0.44 to 0.06 micromol/min/gm in response to chemotherapy (141). Knopp et al from Heidelberg reported that PET FDG studies made it possible to predict the response of small cell lung cancer to chemotherapy with an accuracy of between 83% and 90% (297).

Multidrug Resistance in Cancer

The marriage of genetics and nuclear medicine is also illustrated by studies of multidrug resistance that develops in patients receiving cancer chemotherapy. Resistance to one cancer chemotherapeutic agent, such as adriamycin, often leads to cross resistance to other chemotherapeutic drugs due to the overexpression of a p-glycoprotein (pgp), called multidrug resistance factor (MDR) (891). This p-glycoprotein is involved in the excretion of foreign chemicals from cells. Piwnica-Worms and colleagues first reported this phenomenon in studies with ^{99m}Tc sestamibi and have subsequently developed a new ^{99m}Tc isonitrile useful not only for imaging the transport process but also in modulating it (66).

Figure 2 illustrates the mechanism of action of the transporter. The administration of chemotherapy agents results in the increased expression of the p-glycoprotein in the cancer cell membrane. This protein facilitates the pumping of the chemotherapeutic drug out of the cytosol of the cancer cell into the extracellular fluid, thereby preventing its cidal action on the cell. The p-glycoprotein-mediated cellular excretion process rids the cell of the foreign drugs, including adriamycin or ^{99m}Tc sestamibi. Measuring this excretory mechanism with ^{99m}Tc sestamibi provides a possible means of developing drugs that will modulate or decrease the transport process, and make chemotherapy more effective, a whole new approach to cancer chemotherapy. If one can block this excretion of chemotherapeutic agents from the cancer cells, resistance would not develop and the cancer cells would continue to be killed. Illustrating the synergism between SPECT and PET, Elsinga et al from Groningen developed ^{11}C daunorubicin as a positron-emitting radiotracer for study of multidrug resistance (328).

The human genome can be thought of as a reference dictionary of nucleotide words that bring about the production of peptides, proteins, and other molecules that make up the structure and control the biochemical processes of the body. Only a few of the messages carried by these genetic words are known. Nuclear medicine can play a major role in deciphering the meanings of these nucleotidic words, as they form the sentences and paragraphs that control life processes. Excellent examples include radiolabeled somatostatin (SS) and vasoactive intestinal peptide (VIP). Vasoactive intestinal peptide (VIP) has been successfully labeled with ^{123}I (384).

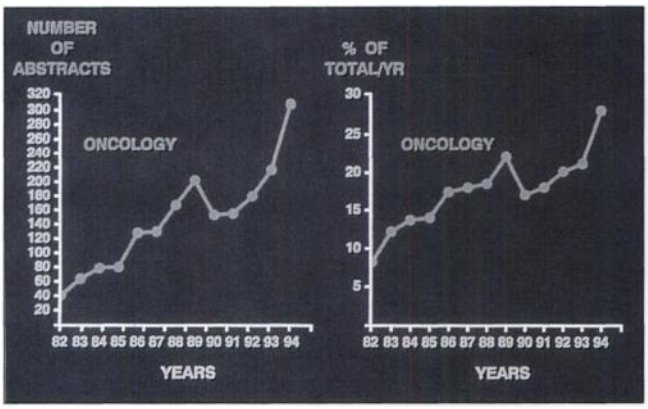

Figure 3. Presentations in nuclear oncology increased 42% from 1993 to 1994.

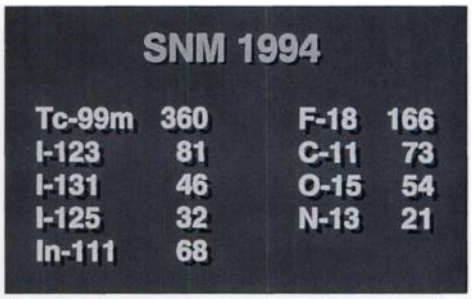

Figure 4. The presentations in 1994 reflect the importance of both PET and SPECT radiopharmaceuticals.

PET versus SPECT: Time to End the Competition

Some persist in viewing PET and SPECT as competitive. This is unfortunate and unwarranted. Because of ^{11}C, the chemical power of PET will always be great. On the other hand, if a patient or research problem can be solved with SPECT, the longer half-life of ^{123}I and ^{99m}Tc provide important advantages. PET will always be more sensitive than SPECT, and mathematical modeling in quantification will be more accurate.

The synergism of PET and SPECT is illustrated by the imaging of somatostatin receptors with a single photon-emitting radiotracer, indium-^{111}In, while glucose utilization and many other receptor-imaging radioligands have involved PET. The transfer of SPECT to PET is illustrated by the development of ^{11}C daunorubicin to permit study of multidrug resistance by means of PET (328).

Peptides

The development of the somatostatin analogue, ^{111}In octreoscan, recently approved by the FDA in the United States, illustrates how basic science advances are translated into health care benefits. The message carried by somatostatin to cells is to stop secreting, which in turn results in diminution of cell division. Vasoactive intestinal peptide (VIP) carries the message to the cells to start secreting. Certain tumor cells express somatostatin receptors, while others express vasoactive intestinal peptide (VIP) receptors. Investigators from the University of Vienna labeled vasoactive intestinal protein with ^{123}I, and showed that many tumors including adenocarcinoma of the pancreas express VIP receptors (384). The latter do not express somatostatin receptors, unlike functioning and non-functioning islet cell tumors of the pancreas.

The roles of both PET and SPECT are documented by the 166 presentations involving ^{18}F; 73 involving ^{11}C; 81 involving ^{123}I; and 32 involving ^{125}I (Figure 4). The increasing role of ^{111}In, both in the study of cancer and infectious diseases, adds another single photon-emitting agent to the nuclear medicine armamentarium.

Octreotide labeled with a positron-emitting tracer has been developed at Washington University (422). Such labeled molecules may be useful in the future for peptide therapy. A ^{99m}Tc labeled analogue of somatostatin (P587) is now undergoing clinical trials (1057).

Nuclear Medicine Reduces Costs

As medicine becomes more competitive, the time has come for nuclear medicine to demonstrate its cost-effectiveness in patient care, demonstrating economic benefits as well as the contributions to patient care. Results presented at this meeting showed how nuclear medicine procedures can decrease surgical costs. Both the costs of surgery and the necessary costs of hospitalization and occasional complications are high. Better selection of patients and more accurate pre-operative information can decrease costs.

Presentations at the meeting indicate that nuclear medicine studies can reduce costs in the following ways:

(1) Colon cancer: Detecting occult carcinoma of the colon in the early stages in patients who are shown by genetic studies to be at exceedingly high risks can reduce costs. In patients at later stages of colon cancer, fruitless surgical attempts at cure can be avoided.

Many patients with advanced colon cancer are operated upon with the hope that they can be helped. If what was found at surgery were known pre-operatively, operation could be avoided. FDG accumulation in recurrent rectal cancer is related to tumor size and cellularity (471). The increase in deoxyglucose utilization in cancer is due to increased expression of glucose transport proteins and hexokinase synthesis (894). A ^{64}Cu monoclonal antibody was more accurate than CT in detecting small colorectal cancers after radiation therapy (38).

(2) Brain tumors: ^{123}I methyl tyrosine (IMT) is as effective as ^{11}C methionine in characterizing brain tumors (23). Accumulation of the tracers indicates a poor prognosis, regardless of the histological diagnosis (24). Malignant meningiomas can be detected with ^{201}Tl SPECT imaging (27). In patients with gliomas, ^{201}Tl and ^{11}C methionine gave similar results (165). FDG accumulation was helpful in prognosis in pediatric primary brain tumors (169). In patients with brain lesions characterized by very low levels of deoxyglucose or methionine accumulation, surgery can be avoided, especially if the lesions are in difficult locations. In patients with operable brain tumors, exact localization of the lesion can decrease operative time and the complications of brain tumor surgery. Of particular value is the ability to distinguish between the lesion and surrounding edema, or from radiation necrosis. Radiation therapy does not decrease glucose utilization in normal irradiated brain, but does so in brain tumors (867).

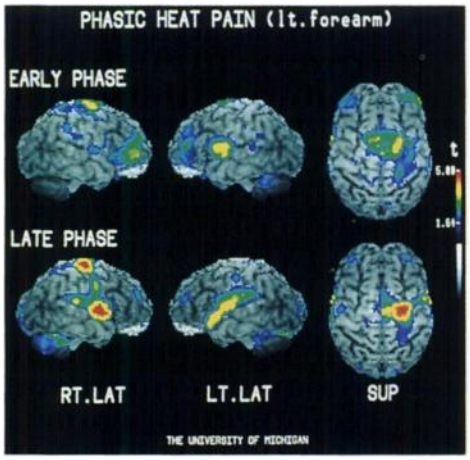

Figure 5. A study performed with ^{15}O H_2O indicates that the cortical areas of the brain which initially respond to a painful stimulus differ from those that show increase activity with prolonged pain (122).

(3) Lung cancer: Nuclear medicine procedures can help eliminate the 25,000 thoracotomies performed every year in the United States in patients subsequently proven to have benign solitary pulmonary nodules. Studies from Omaha (298) and Duke (932) described the high positive and negative predictive value of FDG studies in these patients.

Thirty thousand thoracotomies are performed in the United States every year in patients found at the time of surgery to be inoperable because of pleural or extensive mediastinal and hilar node involvement. This can be determined pre-operatively (301, 932).

(4) Prostate cancer: Prostatectomies are performed only when the lesion is confined to the prostate. In 50,000 prostatectomies performed every year in the United States, the lesions are found to extend beyond the prostate. This can be determined pre-operatively with ^{111}In CYT-356, a monoclonal antibody (878). The Washington University group continues their studies of ^{18}F labeled testosterone tracers in patients with carcinoma of the prostate (204). The FDA recently approved the use of ^{89}Sr for treatment of bone pain in patients with metastatic carcinoma of the prostate. Many at the meeting had the opportunity to hear a patient describe how he had been chair-ridden for one year because of pain, and had spent $12,000 for medications. After receiving ^{89}Sr therapy, he got up from his wheelchair and resumed his hobby of dancing, taking no medications for the following year. Another agent under evaluation for the relief of bone pain is ^{186}Re (965).

In studies of the regions of the brain activated by experimental production of pain, it was found that the cortical areas initially involved in response to pain were different from those involved later as the pain persisted (122) (Figure 5).

(5) Breast cancer: In the United States, 400,000 of the 600,000 breast lesions removed at surgery every year prove to be benign. The patients are operated upon because of the risk of malignancy. If one can determine with a 98% certainty that the lesions are benign, surgery could be avoided and the patient followed by periodic examinations. Most surgeons will not rely on needle biopsy because of the sampling problem; cancer may be present when most of the lesion is benign. ^{99m}Tc sestamibi diagnosed primary breast cancer in lesions less than 1 cm in size, as well as detected involved nodes (78, 79). The negative predictive value was 97% (80). ^{99m}Tc MDP was also effective (81). FDG-PET was more sensitive than ^{18}F fluoroestradiol (FES) for detecting malignant breast lesions (569). PET imaging with FDG was highly specific in evaluating axillary metastases (571). Negative estrogen receptors and low grade ^{201}Tl uptake in breast lesions was a sign of a poor prognosis, presumably related to the degree of undifferentiation of the lesions (929). SPECT imaging is more sensitive than planar scintigraphy in detecting non-palpable breast cancer (933, 934).

In the diagnosis of breast cancer, ^{18}F FDG had a 94% specificity (571). If there is some doubt about whether a lesion in the breast is or is not malignant— if it accumulates FDG above a certain quantitative threshold level— the lesion should be removed because it is almost certainly malignant. On the other hand, if the lesion has low levels of glucose utilization, it can be watched, possibly after performing a needle biopsy.

Ongoing, carefully designed, multi-institutional ^{99m}Tc sestamibi studies will better define the role of this tracer in breast cancer diagnosis (935). It is possible that a combination of tracers will be used to achieve both high sensitivity and specificity. As many as 75% of 52 breast tumors accumulated ^{111}In octreoscan (77). This tracer, used in combination with a ^{99m}Tc sestamibi or FDG study, might bring about absolute certainty in determining whether a lesion is benign. Combining tracer studies may be needed in some cases to achieve absolute certainty.

Other tracers used in breast cancer include ^{18}F fluorotamoxifen, an estrogen receptor antagonist, as well as radioiodinated tamoxifen (1051). High doses of ^{131}I tamoxifen may be useful in treating primary and metastatic estrogen-positive breast cancer.

(6) Lymphoma: Bares and colleagues from Aachen found that FDG studies assessed tissue viability in assessing patients for relapse after treatment (526). Somatostatin receptor imaging detected active lymphomatous disease in 30% of cases not revealed by conventional staging methods (529). In non-Hodgkin's lymphoma, radioimmunotherapy without bone marrow transplant cured many patients (402).

(7) Ovarian cancer: Every year in the United States 5,000 "second-look" abdominal operations are performed in patients with ovarian cancer to assure that the patient does not have persistent disease. With FDG, the question was whether one can be sufficiently certain that no disease persists without surgery. This question was addressed by Holdeman et al from the University of Nebraska, who found that although FDG studies were not sensitive enough to replace 2nd look laparotomy, the studies were helpful in patients with elevated CA-125 and negative CT (470).

(8) Pancreatic cancer: To identify the nature of lesions within the pancreas, ^{111}In octreoscan detected not only functioning tumors that produce hypoglycemia but also non-functioning islet cell tumors, thereby avoiding complex and expensive surgery in the belief that the patient is suffering from adenocarcinoma of the pancreas. Islet cell tumors are more benign than adenocarcinomas and can be treated without radical Whipple procedures.

In studies of pancreatic cancer with FDG, both sensitivity and

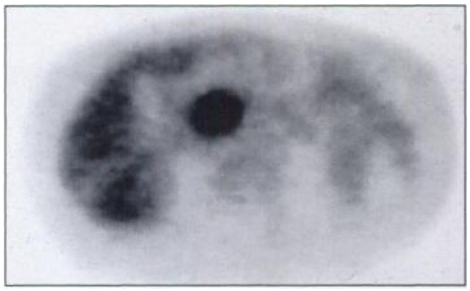

Figure 6. FDG-PET imaging of cancer of the pancreas (911).

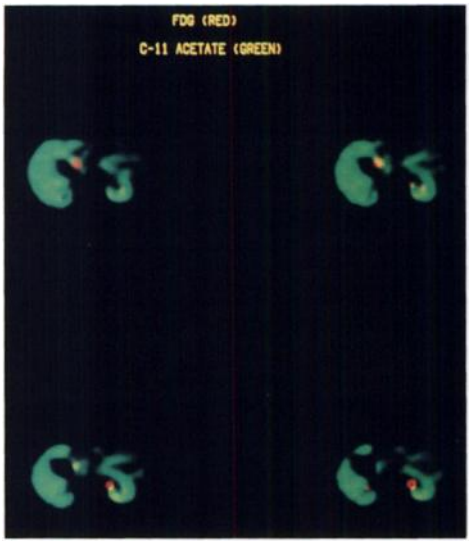

Figure 7. ^{11}C acetate failing to accumulate in carcinoma of the pancreas, unlike FDG which accumulates avidly in the lesions (430).

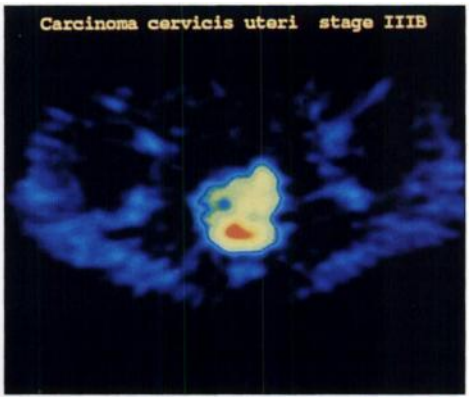

Figure 8. Uterine cancer is successfully imaged with ^{11}C methionine (469). The contrast is higher than with FDG.

specificity were more than 90% (904). In 45 patients with pancreatic cancer, 43 were positive. In chronic pancreatitis, only 4 out of 31 were positive (911). Figure 6 is an example of an FDG study in a patient with carcinoma of the pancreas.

A most interesting finding was that cancer of the pancreas has a high level of glucose utilization, but a low metabolism of ^{11}C acetate (430) (Figure 7). The cancerous lesions function anaerobically.

^{201}Tl was also investigated in the detection of pancreatic tumors (904). In comparisons of FDG PET with thallium SPECT, FDG PET had a sensitivity of 92%, while ^{201}Tl SPECT had a sensitivity of 67%.

(9) Melanoma: Investigators from the Netherlands used handheld probes at surgery to detect sentinel nodes with ^{99m}Tc colloid in patients with skin melanomas (914). This is but one example of the increasing use of probe detectors at surgery.

(10) Uterine cancer: ^{11}C methionine was found to be better than FDG in distinguishing cancerous lesions from surrounding structures (469) (Figure 8).

New Instrumentation

Townsend and colleagues described the results obtained with a rotating positron tomographic camera, which represents a lower-cost instrument than more widely used ring detector PET scanners (155). Another innovative nuclear imager was described by Barrett and colleagues (102, 367). This device is based on the use of multiple pinhole collimators, and takes advantage of the new high-resolution detectors that can be placed very close to the pinhole to simplify the design. The scanner has no moving parts, which facilitates temporal studies with high spatial resolution.

A word of caution must be stated with respect to imaging positron-emitting tracers such as FDG with SPECT instruments fitted with high-energy collimators. Investigators from the University of Michigan compared FDG SPECT and PET studies in the same patients (19). SPECT imaging of FDG had a low sensitivity (36%) in tumors less than 3 cm in size, which is unacceptably low. Sensitivity was 75% in the case of larger tumors. The investigators concluded that FDG SPECT is not a satisfactory alternative to PET in cancer imaging.

Cost-Effectiveness

Many presentations were directly concerned with cost effectiveness. In the staging of patients with malignant melanoma, the total cost of whole body PET imaging of all 33 patients was $62,700. Prior to the PET imaging, $132,000 had been spent in diagnostic imaging studies that did not solve the problem (20) (Figure 9). Chemical characterization of these lesions was much more accurate. One must also consider the high cost of unhelpful surgery when performed with uncertain knowledge of whether the lesions are operable.

Thirty percent of a thousand patients with hypertension were found to have renal artery stenosis (1091). If one depends on arteriography to make the diagnosis, one can rule out renal artery stenosis in 700 patients at a cost of $1.2 million. If you make the diagnosis with radiotracer renography with captopril, the diagnosis can be excluded in the same number of patients at a cost of $540,000.

Investigation into the pathogenesis of renovascular hypertension may be aided by the successful imaging of angiotensin II receptors (497) (Figure 10).

Nuclear Neurosciences

Studies of regional cerebral blood flow with single photon tracers increased dramatically since last year—from 59 to 71, compared to an increase from 23 to 39 in the case of PET. There were 54 presentations of ^{15}O, in some cases produced by a dedicated, relatively inexpensive tandem cascade accelerator (1021). Fazio and his colleagues from Milan compared the areas of the brain that were activated when a subject moves a hand to those regions activated when the subject imagined moving the hand (426). In patients with Wernicke's aphasia, Wernicke's

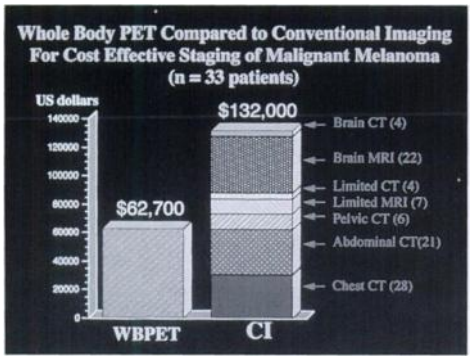

Figure 9. Staging of patients with malignant melanoma was more cost-effective with PET than with other imaging modalities (20).

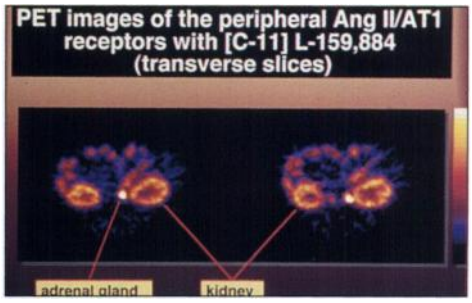

Figure 10. Angiotensin II/AT1 receptors imaged with a new ^{11}C compound in the kidneys and adrenal (497).

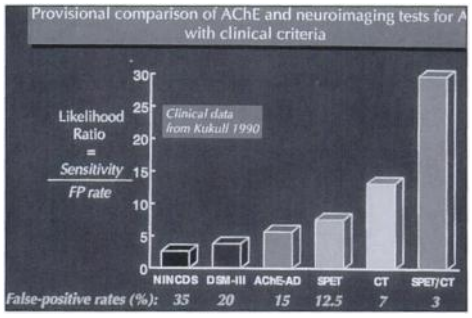

Figure 11. False positive rates with various diagnostic tests in Alzheimer's disease (72).

area was not activated when the patient generated a verb to match a noun that had been spoken to the patient (120, 123). There was activation of Broca's area.

It was possible to distinguish the areas of the brain activated in patients with simple phobias from those activated in patients with obsessive-compulsive behaviors (295).

Dementia

One of the best illustrations of the "new era of certainty" was the study from Oxford University in which HMPAO SPECT studies were combined with CT (72) (Figure 11). Thinning of the medial temporal lobe, when found together with SPECT regional cerebral blood flow abnormalities, were very specific in the diagnosis of Alzheimer's disease, confirmed at autopsy in a large series of patients. In the clinical examination of the patient by a neurologist or neuropsychologist, there were 35% false positives; 20% false positives when DSM III criteria were used; 13% false positives with SPECT alone; 7% false positives with CT alone; but only 3% when both CT and SPECT were used. This means that when a patient is classified as having Alzheimer's disease, the error rate will be only 3%. The importance of these findings in selecting patients for clinical trials of the drug treatment of Alzheimer's disease is clear. The Michigan group used statistical criteria in establishing ROC curves in the diagnosis of Alzheimer's disease with FDG (476).

The Michigan group also presented the results of their studies of pre-synaptic acetylcholine neurons, using ^{123}I iodobenzovesamicol (265) (Figure 12). In the cortex of normal persons, there were many more presynaptic acetylcholine neuronal vesicles than in patients with Alzheimer's disease.

PET FDG studies were more accurate than SPECT blood-flow studies in distinguishing Alzheimer's disease from vascular dementia (477). One can use ^{15}O water perfusion studies to obtain objective evidence of the beneficial effect of high-dose aspirin treatment of vascular dementia (835). Camargo and colleagues from Brazil used SPECT to illustrate the improvement of patients with an unusual form of aphasia when treated with steroids (856).

Many studies illustrated the importance of using radiotracer studies to homogenize the groups of patients examined in clinical trials of drug therapy. For example, in spinocerebellar degeneration (SCD), the degree of involvement of the cerebellum might be greater in cerebellar cortical degeneration (CCD) than in olivopontocerebellar atropy (OPCA), but the latter involves the striatum as well, as indicated by ^{18}F L-DOPA studies (854) (Figure 13 A and B).

Another important Japanese presentation pointed out the use of radiotracer studies in patients with transient blindness (amaurosis fugax) (823).

Misonidizole Analogues

Misonidizole analogues and technetium PNAO derivatives were described in studies of regional hypoxia, not only hypoxia of the brain but also hypoxic focal infections and myocardial infarction. Yeh and colleagues from Taiwan illustrated the ischemic penumbra in acute stroke demonstrated with ^{18}F misonidazole (830) (Figure 14). There were 8 PET and 8 SPECT papers involving misonidizole analogues.

Epilepsy

In focal epilepsy, Mountz et al from the University of Alabama illustrated the importance of fusion of anatomical and functional imaging (112). They emphasized ictal studies. In another study, there was excellent correlation between PET FDG studies and invasive EEG studies (113). The positive predictive value of postsurgical improvement was 94%. Benzodiazepine receptors in focal epilepsy were examined with ^{11}C flumazenil (839) (Figure 15). Iodomazenil is another tracer used in studies of patients with epilepsy (63).

Neurotransmission

There were 102 papers on neurotransmission, 52 of them involving the dopaminergic system. Others included a presentation of imaging cholecystokinin receptors (1016); another concerning substance P receptors (1042). Tasch et al examined patients with schizophrenia who were receiving typical neuroleptics, such as haloperidol, and those receiving atypical neuroleptics (291) (Figure 16). Those patients treated with atypi-

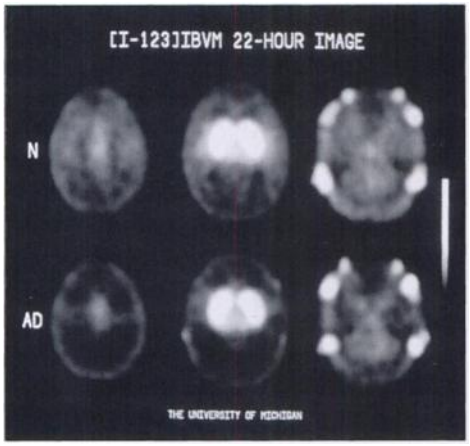

Figure 12. ^{123}I Iodobenzovesamicol imaging of the acetylcholine transporter on presynaptic vesicles in a normal person (top) and a patient with Alzheimer's disease (AD) (265).

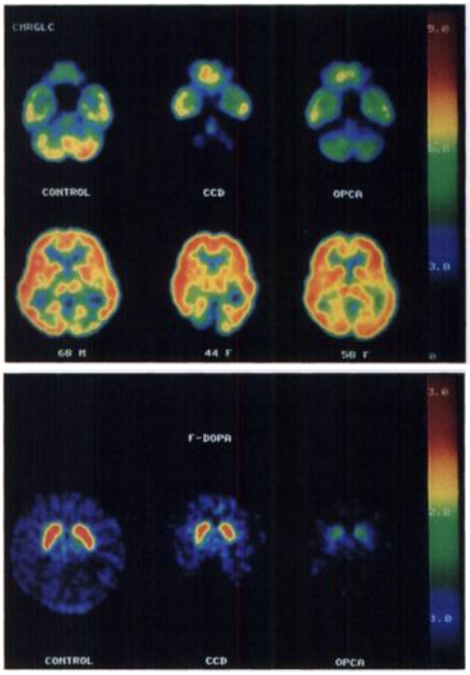

Figure 13. (A) In patients with cerebellar cortical degeneration, (CCD) the degree of involvement of the cerebellum is greater than in patients with olivopontocerebellar atropy (OPCA). (B) OPCA involves the striatum, as documented by ^{18}F L-DOPA (854).

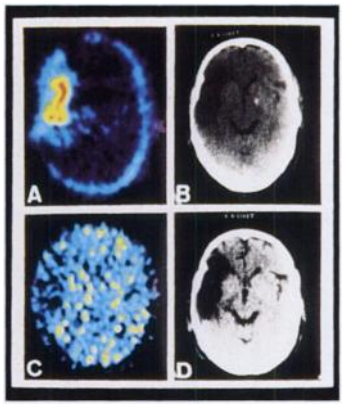

Figure 14. The ischemic penumbra in acute stroke is demonstrated with ^{18}F misonidazole, a hypoxia imaging agent (830).

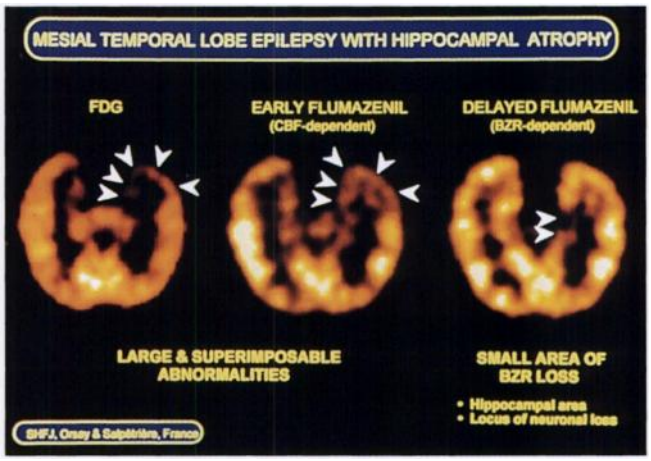

Figure 15. ^{11}C flumazenil imaging of benzodiazepine receptors in focal temporal lobe epilepsy. (839).

cal neuroleptics did not have a degree of receptor blockade that was different from the normal subjects. In those patients treated with typical neuroleptic drugs, such as haloperidol, there was a greater degree of blockade in those patients who developed tardive dyskinesia, or extrapyramidal complications, than in those who did not.

Endogenous Dopamine Release

^{123}I iodobenzofuran was used to measure endogenous dopamine release, stimulated by administration of amphetamine (332). Endogenous dopamine release competes with the binding of the tracer by D2 dopamine receptors. The investigators related the degree of endogenous dopamine release to the subjective sensations of alertness and cheerfulness produced by the amphetamine (Figure 17). To me, this was the most interesting presentation of the meeting.

Parkinson Disease

Postsynaptic dopaminergic receptors are normal in patients with classical Parkinson disease, but it is clear that presynaptic terminals are deficient, when examined with tracers that bind to dopamine transporters on presynaptic nerve terminals in the caudate nucleus and putamen. The UCLA group developed a ^{18}F tracer for studying dopamine reuptake sites on the presynaptic neurons (327). The Yale group synthesized several presynaptic transported tracers and selected ^{123}I beta CIT for imaging the dopamine transporter (516). They found a striking decrease in presynaptic neuronal transporter in aging persons, comparable to the known decrease in post-synaptic D2 dopamine receptors (33) (Figure 18). Since the rate of synthesis of dopamine does not fall with age, it is likely that the synthesis of dopamine increases per residual neuron. Beta CIT labeled with ^{123}I is a marker for early Parkinson disease, which will greatly facilitate clinical trials of potential therapeutic agents. The decrease in pre-synaptic transporters in patients with Parkinson disease is greater than that observed in normal aging (28; 30). Figure 19 indicates that the decrease in transporter binding is correlated with the severity of the disease, as estimated by the Hoehn-Yahr scale.

Serotonin Transporter

A major advance was the report of the imaging in human beings of the pre-synaptic serotonin transporter (337) (Figure 20). The tracer β-CIT is not specific for the dopamine transporter because it binds to both the dopamine and serotonin transporter. The tracer developed by Suehiro and colleagues is more spe-

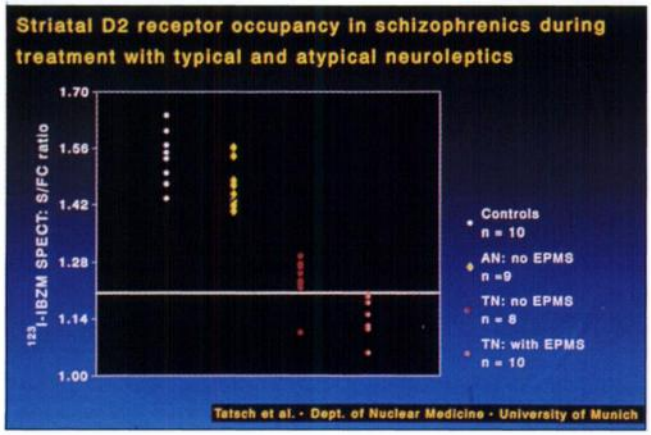

Figure 16. ^{123}I Iodobenzamide binding to D2 dopamine receptors was the same in normals and schizophrenic patients treated with atypical neuroleptics (AN). Schizophrenic patients treated with typical neuroleptics (TN), such as haloperidol, show a greater degree of blockade, which was even greater in patients who developed tardive dyskinesia or extrapyramidal symptoms (EPMS) (291).

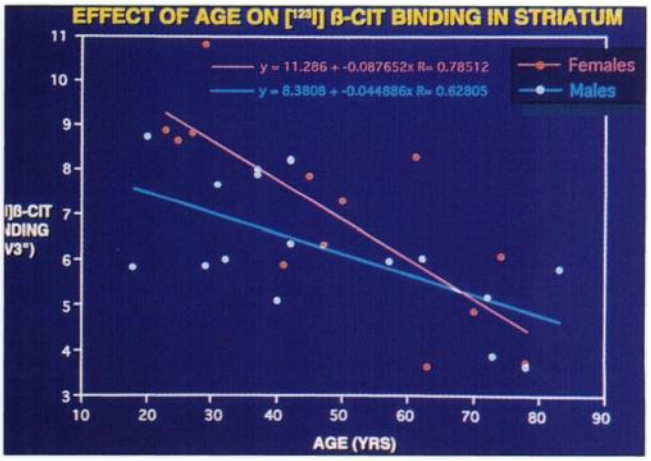

Figure 18. SPECT and ^{123}I 2β-carbomethoxy-3β-(4-iodophenyl)tropane, β-CIT, show the decline in binding to the presynaptic dopamine transporter in the human striatum as a function of age (33).

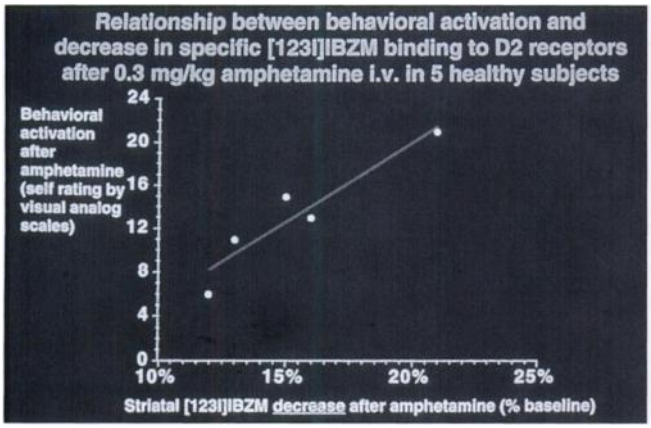

Figure 17. After establishing an equilibrium with ^{123}I Iodobenzofuran, d-amphetamine was injected to induce endogenous dopamine release. The degree of subjective sensations of alertness and cheerfulness was directly related to the degree of dopamine release (332).

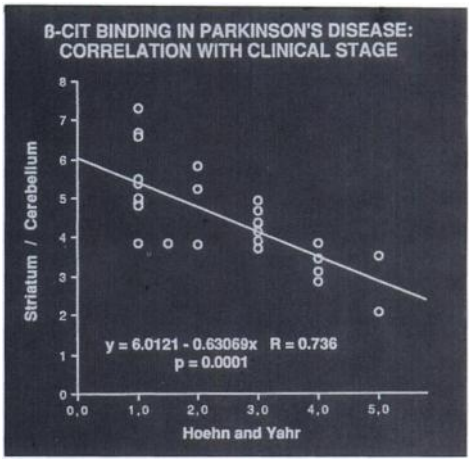

Figure 19. The decrease in presynaptic dopamine transporters correlated with the severity of clinical symptoms as graded on the Hoehn-Yahr scale (30).

cific (1040). There was a very good correlation between tracer binding and the number of nerve endings of the serotoninergic neurons (262).

Nuclear Cardiology

An ^{123}I fatty acid tracer has been approved for clinical use in Japan and is useful in risk stratification of patients with myocardial infarction (231). The relative size of the defects seen by fatty acid imaging and the size of the defect in regional blood flow imaged by ^{201}Tl was of prognostic significance.

^{11}C acetate, ^{18}F FDG and the fatty acid tracer were able to differentiate patients with hypertrophic cardiomyopathies into those with asymmetric septal hypertrophy and those with apical hypertrophic cardiomyopathy (439).

Left ventricular function studies were used to show that patients with acromegaly have intrinsic myocardial abnormalities, not just dysfunction secondary to hypertension (662). Ventriuclar filling was abnormal even in the normotensive acromegalic patients.

Outcome Studies

Ventricular function studies help predict persons susceptible to cardiac deaths (233) (Figure 21). In patients whose global left ventricular ejection fraction fell 7 - 8% after exercise, there was improved survival in patients treated by coronary artery bypass surgery (233).

In patients with ventricular aneurysm detected by simple observation of whether or not the walls of the left ventricle diverged from base to apex, survival was poor (505). SPECT myocardial perfusion studies that did not reveal ischemia in women with chest pain was a good prognostic sign (235). The chance of subsequent death from myocardial infarction was only 0.2% per year (Figure 22). Angiography need not be performed in such patients—a great economic saving.

Peripheral vascular disease is another area where radiotracer studies are cost-effective. Amputation has a very high mortality, as great as 18%, because of the severity of the underlying disease. ^{82}Rb is useful in measuring muscle blood flow (622). FDG can be used as an indicator of musculoskeletal inflam-

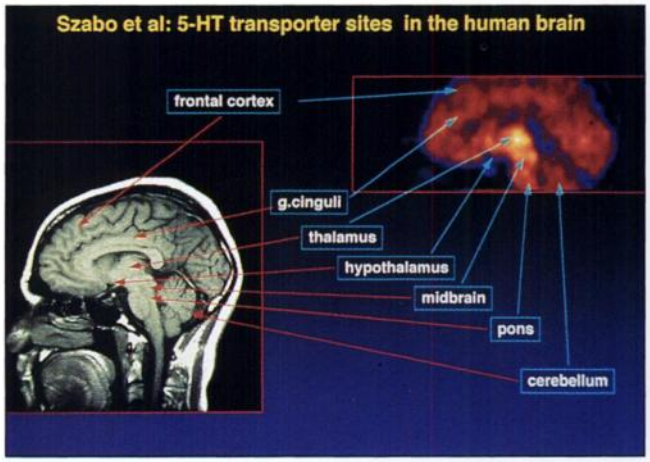

Figure 20. ^{11}C (+)McN5652 imaging of the serotonin transporter sites in the human brain (337).

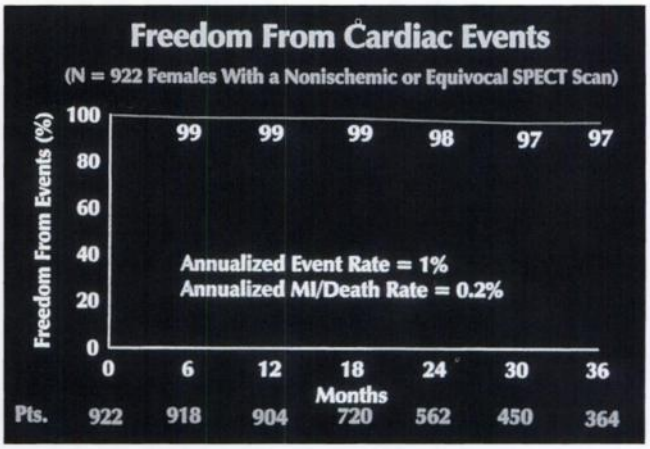

Figure 22. In a follow-up study of almost 800 women, it was found that if ^{201}Tl did not show evidence of ischemia, the chance of death was only 0.2% per year (235).

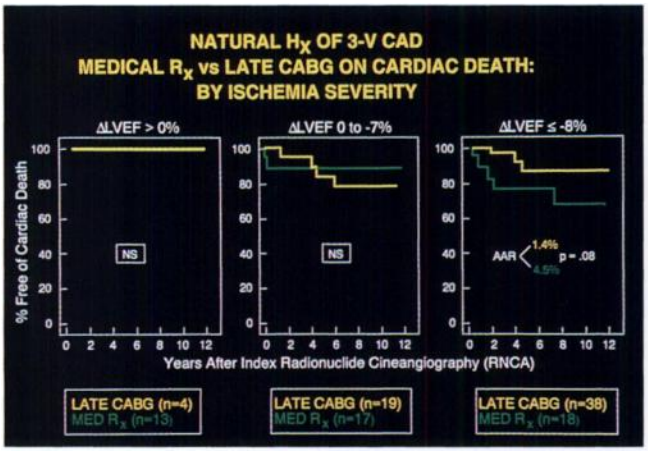

Figure 21. When a patient's ejection fraction decreased 7 -8% with exercise, surgical rather than medical therapy resulted in a longer survival (233).

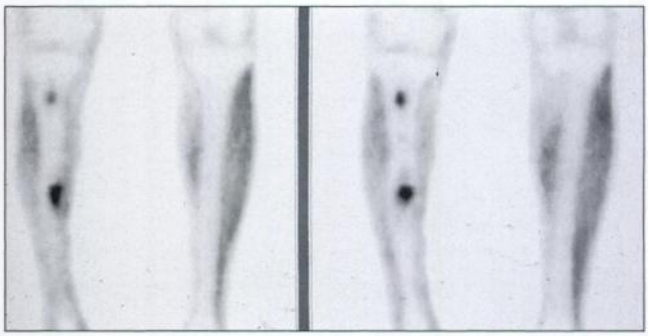

Figure 23. FDG PET was used to detect and localize active musculoskeletal inflammatory lesions in the legs and was found to be more sensitive and specific than ^{99m}TC antigranulocyte antibody imaging (451).

mation (451). Figure 23 shows foci of inflammation in the legs imaged with FDG PET.

Metaiodobenzylguanidine (MIBG)

Everyone at the meeting was delighted that Don Wieland from the University of Michigan received the Paul Aebersold award for his major accomplishments in the basic sciences of nuclear medicine. Included among them was the development of MIBG, involved in 18 presentations at the meeting. Everyone was also pleased that ^{131}I MIBG had been approved recently by the Food and Drug Administration. ^{123}I MIBG, which is more useful for imaging studies, is approved for use in Japan, and we hope this will soon be true in the United States as well, and that it will be available for study, not only for patients with neuroblastoma, but also for patients with coronary heart disease. Patients with diabetes often have autonomic neuropathy. ^{201}Tl myocardial perfusion imaging is normal in most of these patients, but MIBG myocardial uptake is reduced, as well as the rate of washout of the tracer (613). Measurements in non-insulin-dependent diabetic patients could be distinguished from those in normal persons, while the results in insulin-dependent diabetic patients were abnormal (612). In coronary heart disease, the defects in MIBG accumulation are far greater than the perfusion defects. In both groups of patients, it is important to identify such patients because they are at great risk of cardiac arrhythmias. A Japanese study related MIBG defects to increased electrical excitability of the myocardium (318) (Figure 24).

This tracer with a single photon-emitting label led to the development of ^{18}F labeled MIBG (1017). While most neuroblastomas can be detected using FDG, the use of MIBG is valuable in patients who fail to accumulate MIBG. FDG can also be used in monitoring treatment (542).

Conclusion

After several years of planning and painstaking execution, the Hubble telescope was still found to possess flaws in its delicately ground mirrors, dissonances in the way the instrument processed images. Thus, even the most finely tuned scientific instruments and techniques, like the body itself, can experience such dissonances.

So it is with medicine. In nuclear medicine today, it has never been more important to develop a strong, highly expert cadre of full-time nuclear medicine physicians and scientists, who can develop strong coordination with organ-oriented specialists,

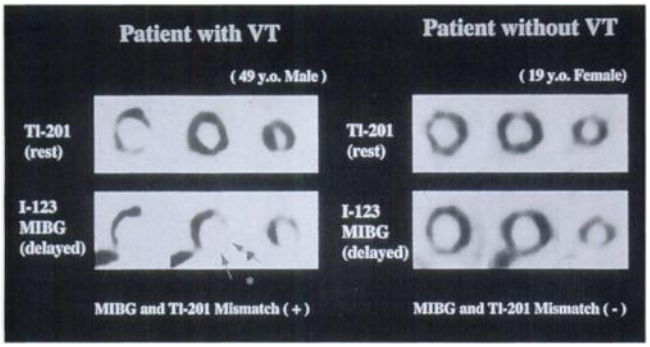

Figure 24. Patients with idiopathic dilated cardiomyopathy who have defects in the sympathetic innervation of the myocardium when imaged with ^{123}I MIBG are more likely to develop ventricular tachycardia and sudden death (318).

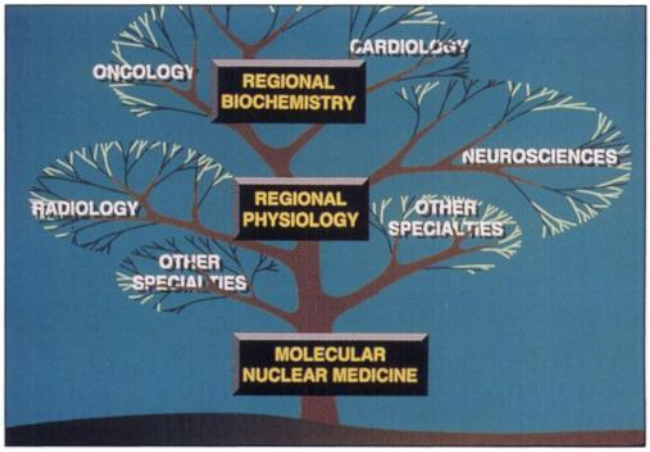

Figure 25. Molecular nuclear medicine, regional physiology, and regional biochemistry are the vine from which other medical specialties branch.

such as cardiologists and neuroscientists, and other holistic specialists, such as nuclear oncologists and infectious disease specialists. This consonance with other fields of medicine resembles the smooth growth of healthy branches from a common vine (Figure 25).

One mainstay of U.S. medicine—as crucial as recognizing the relation of clinical manifestations of disease to specific organs or to histopathological abnormalities of cells—has been peer review, a major quality-control mechanism, ensuring consonance in scientific findings. Now peer review must be extended to public view. Members of professional societies must work with persons in industry to perform and document cost-effectiveness studies and preach what we practice. The effectiveness of nuclear medicine procedures is among the best kept secrets in medicine. We must educate decision-makers, not just physicians, but also patients and third party payers.

Henry N. Wagner, Jr. M.D.

Part 3: The Physician Workforce

Visions and Revisions: Viewpoints of Nuclear Medicine and Health Care Reform

As reformers push for specialist rationing, a leveling-off of nuclear medicine workforce may mean decreases in training slots—or the specialty may define a new identity

A CENTRAL TENET IN THE MAJOR health care reform measures now emerging in Washington is that every citizen has the right to basic health care. An adjunct assumption holds that general practitioners offer the best route to such universal access. Not only are generalists supposedly less costly on average than specialists, reformers hold them up as symbols of the sort of back-to-basics approach that health care allegedly needs. Basing its numbers on Council of Graduate Medical Education (COGME) recommendations, proposed Congressional legislation has set a goal for the generalist/specialist ratio that varies from 50/50 to 55/45. Major reform measures, notably the Clinton plan, would achieve this goal through regulation—through COGME's limiting the number of annual residency positions in each medical field. The prospect of a government agency thus regulating nuclear medicine as just one of a set of specialties has practitioners in the field alarmed.

"A decrease of 51% in Nuclear Medicine residency positions would result in serious shortages of nuclear physicians by preventing the training of new practitioners that are needed to replenish the aging cadre in the field," wrote William H. McCartney, MD, ACNP president, and Richard C. Reba, MD, SNM president (at that time), in a March 29 letter to COGME. Though the number of physicians in the "other specialties" grew variously between 10% and 37.2% from 1985-1992,