

ANNUAL MEETING HIGHLIGHTS

## ONCOLOGY: A NEW ENGINE FOR PET/SPECT

The Society of Nuclear Medicine celebrated its 40th anniversary at the annual meeting in Toronto, Canada, in June. For the sixteenth 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.

**I**N REFLECTING ON OUR ANNIVERSARY, IT OCCURRED to me that this year also marks the 40th anniversary of Dwight D. Eisenhower's establishment of the Atoms for



Henry N. Wagner, Jr. MD

Peace program and Watson and Crick's elucidation of deoxyribose nucleic acid (DNA). Atoms for Peace led to the birth of the International Atomic Energy Agency (IAEA), which played a major role in the worldwide development of nuclear medicine. Watson and Crick established the molecular basis of genetics and laid the foundation for molecular biology.

Nuclear medicine makes it possible to measure in vivo chemistry.

Molecular nuclear medicine characterizes and examines interactions of molecular messengers in the living human body, beginning with DNA, the master messenger and template for production of molecules that translate genotype into phenotype. I am delighted that the Department of Energy used the term "Molecular Nuclear Medicine" in promoting and extending advances in molecular biology to patient care and the study of human disease.

This year, I have chosen *Oncology, a New Engine for PET and SPECT* to represent what for me was the most significant message of the meeting: PET and SPECT imaging of molecular messengers in patients with cancer are the most significant advances in clinical oncology in the past two decades. Large quantities of genetically engineered stimulatory molecular messengers, like growth hormone, and suppressor molecules, like somatostatin, are now available for labeling with radioactive tracers and examination in the living human body. Protein receptors of these messengers are already under intensive study because they participate in intercellular and intracellular communication.

In the face of the second law of thermodynamics, these structurally specific receptors establish that living organisms are not random. Recognition sites include enzymes, hormone receptors, neurotransmitter receptors and cytokines, which

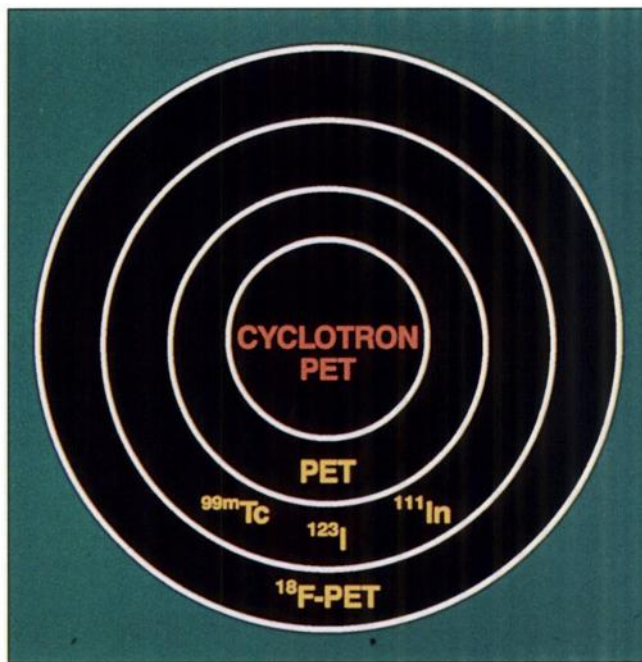
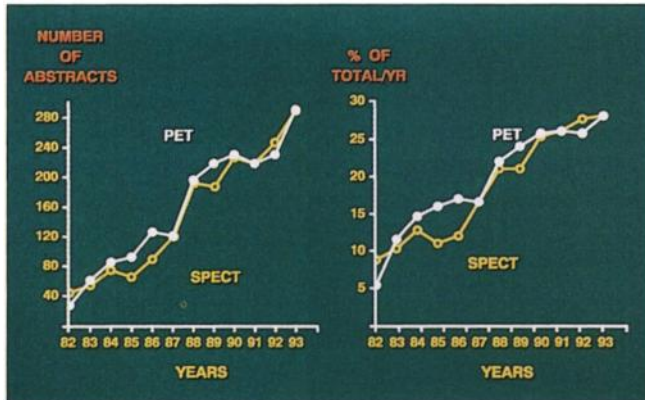


Figure 1. There was a dramatic increase in the number of  $^{18}\text{F}$  deoxyglucose (FDG) studies, especially in patients with cancer. The large number of  $^{111}\text{In}$  octreotide presentations resulted in  $^{111}\text{In}$ 's being added as a third workhorse, in the single-photon circle.

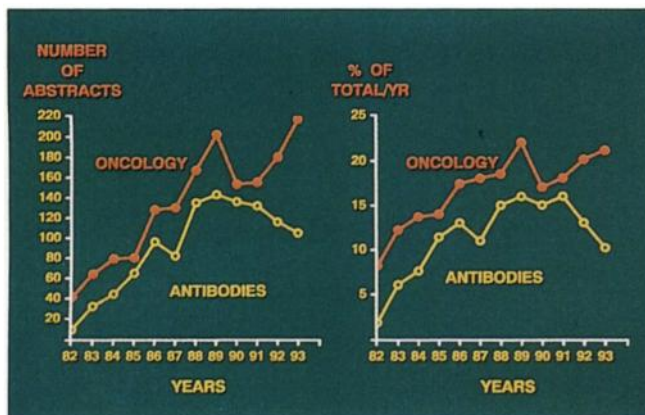
transfer information and facilitate co-valent chemical bonding. Molecules are extracted from their random state in the circulation to participate in chemical reactions. The mosaic that eventually will be the portrait of our lives results from interactions among trillions and trillions of these structurally specific molecules that maintain life by recognizing one another. Diseases like cancer are now viewed as dissonances of molecular messages—the result of excessive, deficient or wrong messages in intercellular and intracellular communication. In the past, I presented a model of nuclear medicine in which the cyclotron and PET are the central core from which new radiotracers pass in waves into medical practice via the workhorses  $^{99\text{m}}\text{Tc}$  and  $^{123}\text{I}$  radiotracers, with an intermediate ring consisting of hospitals with PET scanners of tracers that come from central radiopharmacies. This year I have added  $^{111}\text{In}$  as a third workhorse and placed  $^{18}\text{F}$ -deoxyglucose in the outermost clinical ring, because its widespread use in oncology has been a major force in its clinical use worldwide (Fig. 1).

### Clinical Pet

The numbers of both PET and SPECT presentations at the annual meeting have increased in tandem over the past 10



**Figure 2.** PET and SPECT presentations together continue to advance nuclear medicine.



**Figure 3.** FDG and octreotide have resulted in an increase in the number of oncology presentations.

years, documenting the complementary role that each plays in the growth of nuclear medicine (Fig. 2).

Fifty-eight presentations involved <sup>18</sup>F deoxyglucose in cancer. "Nonantibody" tracers in oncology accounted for growth over three years from 157 presentations to 217, with a doubling of PET and tripling of the SPECT presentations.

PET and SPECT are two hands that together identify clinical problems. Proponents of each should never diminish the value of the other—flourine-18 FDG might be held as a tool in one hand, with <sup>111</sup>In somatostatin analogs held in the other.

### Molecular Markers

Over the past decade enormous increases have occurred in the number of specific radiotracers developed in nuclear medicine. Searching for tumor markers is an old idea, while a newer one is to develop molecular markers of diseases. FDG—a tracer of the increase in glucose utilization that occurs in nearly every type of cancer—should not be thought of as a tracer of cancer only. FDG measurements also answer

\*Number in Parentheses refer to abstract numbers in Proceedings of the 40th Annual Meeting of the Society of Nuclear Medicine

questions about global or regional glucose utilization (Fig. 3). The somatostatin analogs octreotide and pentetreotide are not tumor markers, but somatostatin receptor markers. Similarly, MIBG is a marker of presynaptic neurons, not just neuroblastoma. Sestamibi and HMPAO are tracers of regional blood flow, although sestamibi is also a marker of cell membrane p-glycoproteins which increase in cancer cells resistant to chemotherapy (# 560).\* These cell-membrane glycoproteins are an important new target for tracer development. They wave about in the extracellular fluid, where their recognition sites bind circulating molecular messengers, a stage in the transfer of information across the cell membrane via the smaller end of the glycoprotein protein that projects inside cells.

An example of membrane glycoprotein is the amyloid precursor protein (APP). Caillat-Vigneron et al., Paris, examined the metabolism of radioiodinated serum amyloid P-component in patients on renal dialysis predisposed to amyloidosis (# 513). Peters and colleagues, Hammersmith Hospital, London, used <sup>123</sup>I-labeled serum amyloid P-component to show that liver transplantation mobilizes amyloid from pathological deposits, supporting the efficacy of the treatment (# 473).

Glycoprotein receptors on the surface of platelets result in aggregation. Knight et al., Temple University, extracted integrins from snake venom, which is bound by glycoprotein receptors on activated platelets and facilitates platelet aggregation. The <sup>123</sup>I tracer "bitistatin" is more avidly accumulated by thrombi than another agent previously examined (#258). If developed commercially, the agent will be among the first in a new class of glycoprotein receptor-binding ligands.

Seventeen presentations involved somatostatin receptors, which have been widely used in Europe. Somatostatin receptors are increased in pituitary and other neuroendocrine tumors (# 159, 456, 799), medullary thyroid carcinoma (# 555), paragangliomas (# 555) gastrointestinal tumors (# 388, 389), and lymphomas (# 472, 800). On May 27, the FDA's Medical Advisory Committee recommended that this tracer be approved for use in the United States, hopefully this year.

The somatostatin story has become a classic example of the elegance of nuclear medicine — first by illustrating how basic science discoveries are translated into better health, and second by illustrating how disease can be characterized at the molecular level, which then determines type of treatment and makes possible the monitoring of the molecular as well as the phenotypic effects of treatment (#1031). NanoDx tracers guide NanoRx treatment. Not only cancer, but also granulomatous diseases, Sjogrens syndrome and rheumatoid arthritis can be characterized by somatostatin receptors found on activated lymphocytes and macrophages (#472). In rheumatoid arthritis and sarcoidosis, accumulation of <sup>111</sup>In somatostatin analogs reflects the degree of joint inflammation and could be used to assess the effectiveness of corticosteroid treatment (#472).

Investigators from the Technical University, Aachen, Ger-



many, described somatostatin receptor and FDG-PET imaging in the same patients (# 391). Lesions in 14 of 114 patients with pancreatic cancer were classified as “false-negatives.” Actually, from my viewpoint, these need not be considered false-negatives; instead, they provide evidence that tumors did not contain somatostatin receptors, unless lesions had greater numbers of undetected somatostatin receptors.

The questions being asked are whether 1) a neuroendocrine tumor contains somatostatin receptors, 2) a breast tumor contains estrogen receptors, or 3) a prolactinoma of the pituitary contains dopamine receptors. To be sure, unsuspected lesions can often be detected by these molecular markers when clinical evidence or other imaging modalities fail to reveal them. However, the greatest value lies in the fact that molecular information can be used to select the most effective treatment. In the Aachen study, unsuspected lesions were found in 29 of 84 patients; in 17 patients, these new data determined the type of treatment. Finding metastatic lesions is necessary but is not sufficient. One needs to know chemical characteristics of lesions, what molecular messages cells are or are not receiving, or what wrong messages are being sent. In meningiomas, it has been shown that the increased number of somatostatin receptors reflects a deficiency in mRNA for the production of somatostatin. Cells are not getting the message to stop secreting, and consequently the receptors increase. In cancer, we have gone beyond ontology to physiology and chemistry.

### Image Of The Year

This year I have selected an image from a study by Krausz et al., Hadassah University Hospital, Israel (# 799) as Image of the Year (Fig. 4).

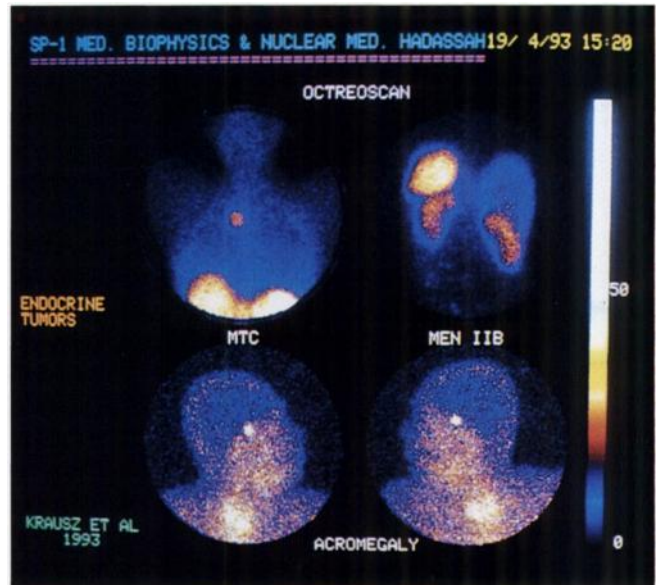
The patient had clinical and chemical evidence of a pheochromocytoma. Whole-body imaging with  $^{111}\text{In}$  pentetreotide revealed an adrenal tumor, unsuspected medullary carcinoma of the thyroid, and a tumor of the pituitary gland, when no prior clinical evidence of these last two neoplasms existed. Disease therefore was detected at an extremely early stage.

Illustrating how PET benefits from SPECT, and vice versa, Stocklin and colleagues, the Research Center, Julich, Germany, described preparation of  $^{18}\text{F}$  octreotide for quantitative somatostatin receptor imaging with PET (#315). Following the  $^{18}\text{F}$  estradiol work by Katzenellenbogen, Welch and colleagues, Rijks et al., Amsterdam, developed four  $^{125}\text{I}$  ligands for imaging estrogen receptors (#1056).

### Nuclear Medicine: The Integrated Specialty

Nuclear medicine does not focus on specific organs. Molecular nuclear medicine is characterized by extending the principles and technology of genetics, immunology, endocrinology, oncology, cardiology, radiology and the neurosciences to provide holistic patient care.

An example of the benefits of an integrated approach to disease is the study by Maffioli et al., the National Cancer Insti-



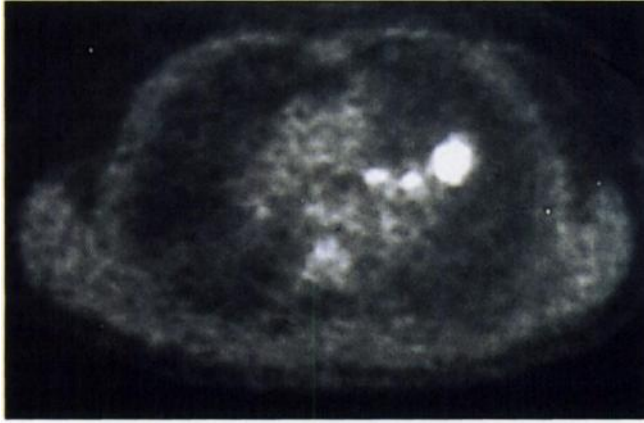
**Figure 4.** Image of the year from Hadassah University Hospital. The patient was found to have an adrenal tumor when imaged with  $^{111}\text{In}$  pentetreotide, and two other neoplasms were found, one in the pituitary and another in the thyroid, a condition known as multiple endocrine neoplasms (MEN).

tute of Milan (#1028). Kung et al. developed  $^{123}\text{I}$ -iodobenzamide (IBZM) to study dopamine receptors, whereas Maffioli et al. used the tracer to determine that dopamine receptors are increased in metastatic melanomas. While a neurologist would have been unlikely to make such a discovery, the nuclear medicine physician draws on the fact that melanin-producing cells develop from the same cell precursors as dopaminergic neurons. He or she knows that the site of injury in patients with Parkinson's disease is the substantia nigra, cells characterized by melanin pigment.

### Whole-Body Imaging

Both PET and SPECT whole-body imaging (WBI) are of great value, especially in oncology. For example, in rectosigmoid cancer, WBI helped in interpretation of studies, assessment of tumor extent and the detection of distant metastases (#1041). Brown, Blahd and colleagues presented a scientific exhibit which illustrated the value of whole body imaging with FDG in cancer of the thyroid (Computer 1212). In patients with ovarian cancer, FDG-imaging helped decide whether second-look surgery should be performed and was more accurate than other imaging modalities (#14, 16). Wahl et al., the University of Michigan, documented the use of FDG-imaging in monitoring response to chemotherapy of metastatic testicular neoplasms (#15). These presentations show that knowledge leads to better care at lower cost.

FDG studies included hepatocellular cancer (#12), liver metastases (#13), and metastatic bone cancer (#17). In pancreatic cancer, Bares et al. showed that FDG-imaging was



**Figure 5. FDG study in a patient with non-small cell carcinoma of the lung with ipsilateral lymph node involvement, but no nodes involved on the opposite side, indicating that thoracotomy could be helpful.**

superior to CT, ultrasonography and ERCP (# 392). In assessing solitary pulmonary nodules, Knopp et al., the German Cancer Research Center, found good separation of malignant and benign lesions (# 72). One fourth of patients had an increase in staging of the disease, while an equal number had decreased staging. This knowledge determined whether to treat with surgery or chemotherapy (#74). Morbidity and expense of fruitless attempts for surgical cures were avoided and patients were started immediately on chemotherapy.

The patient whose FDG study is shown in figure 5 had a non-small cell lung cancer. There was ipsilateral lymph node disease without involvement of the mediastinal lymph nodes on the other side. This knowledge led to the decision to operate. If nodes had been found on both sides, chemotherapy would have been initiated without surgery.

The finding that PET-imaging with FDG was more sensitive and specific than MRI or CT in cancer patients brought to mind an analogy based on ships and airplanes. It took time before there was enough confidence in motors to remove sails from ships, and in jets to remove propellers from planes. Someday, molecular imaging will not be limited to those patients in whom other imaging modalities have failed. Health plan managers and insurance companies will ask, "Why are you doing these other procedures first when nuclear medicine procedures are better?"

Two hands—PET and SPECT—are better than one. For example, in 10% of patients with pheochromocytomas, MIBG SPECT studies fail to localize lesions. But lesions can be detected with FDG/PET imaging (#41). If a patient has a high probability of pheochromocytoma, and MIBG fails to reveal location, an FDG-PET study can successfully detect the lesion.

Another PET tracer,  $^{11}\text{C}$  hydroxyephedrine, has advantages in being more specific than MIBG for neuronal presynaptic binding (#42). PET-imaging is better for localizing neuroblastoma lesions, except for abdominal lesions better visualized

by  $^{123}\text{I}$  MIBG/ SPECT (#1034). The Michigan group related their experience in FDG-imaging of children with cancer (#197). The same results were obtained as in adults—greater accuracy than other imaging methods and an important contribution to therapeutic decision-making.

### **Intraoperative In Vivo Biochemistry**

Intraoperative radiotracer monitoring is an idea whose time has come. Raylman and Wahl described a small fiber-optically-coupled plastic scintillator probe for use with positron-emitting tracers in surgery (#450). Detection of short-range positrons rather than coincident 511 keV photons eliminates interfering activity in the rest of the body. Intraoperative probes are also used in monoclonal antibody studies during colorectal and gynecological surgery (#325). Indium-111 octreotide detection with intraoperative probes is used to localize the tumor, to survey the surrounding tissue to insure that all the tumor has been removed, and to check for lymph node involvement. It is increasingly important to educate surgeons and nursing staff about the safe and effective use of radiotracers in operating and recovery rooms.

### **Improved Patient Throughput**

Now that FDG is used worldwide in the care of patients with cancer, it is necessary to improve efficiency of studies, lower costs, and increase patient throughput. Bailey et al. documented how 3D PET-imaging without lead septa between rings results in a sixfold decrease in scanning time without loss of image quality (# 880). In the past, lead septa were used in PET scanners to decrease scattered radiation. Continual advances in computer power make better scatter corrections possible in both PET (#545) and SPECT (#283, 909, 914, 926). Greater computer power has also improved the use of multiple tracers, made for better attenuation corrections, decreased scanning times, and given higher image resolution. Remarkably improved resolution was obtained by Tong, Hammersmith Hospital, using a finite-elements method (FEM) developed for calculating stresses and strains in complex physical objects (# 97).

Advances in computer power make it possible to efficiently conduct studies with both positron-emitting and single photon-emitting tracers in the same study by effective pulse-height analysis, used for example in combined FDG and neurotransmitter studies with an  $^{123}\text{I}$ - labeled tracer, such as dexametomidine.

As the demand for FDG/PET studies increases, the shortage of  $^{18}\text{O}$ , the precursor of  $^{18}\text{F}$ , becomes a problem. Firouzbahkt and colleagues, Brookhaven National Laboratory, developed a cryogenic solid target for cyclotron irradiations that makes possible recovery of 99% of frozen carbon dioxide target material after each production run (#269).

What about the role of other less specific tracers in patients with cancer? An example is  $^{99\text{m}}\text{Tc}$  sestamibi imaging in patients with breast lumps. Because of the increase in breast self-exam-



ination and mammography, the incidence of identification of breast lumps has increased. A study from Harbor General Hospital, Los Angeles, described use of  $^{99m}\text{Tc}$  sestamibi imaging in these patients (#559). One out of every five breast lesions biopsied is malignant. Technetium-99m sestamibi studies with the breast dependant on the side of the table found that one out of 17 patients with lesions that did not accumulate the tracer had cancer. The negative predictive value was 96%. Yet would we be willing to accept the 4% probability that a lesion is malignant and not biopsy it? Instead, I believe that one must strive for 99% certainty. In another study, combined use of thallium and gallium was able to differentiate Kaposi's sarcoma from malignant lymphoma and opportunistic infections in patients with AIDS (#834). In acute infections, thallium images are usually negative while gallium images are strongly positive. Use of multiple tracers can distinguish among these three frequently coexistent conditions.

### Antibodies

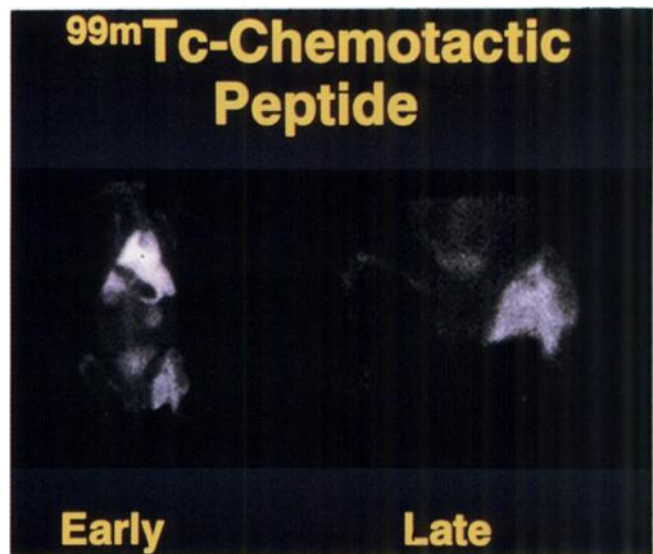
One hundred and five papers involved antibodies or antibody fragments. Since the last meeting, the FDA approved a monoclonal antibody for in vivo imaging of cancer. A multi-institutional study was carried out in patients with colorectal cancer (#1006). One FDA concern was whether HAMA immunological reaction to mouse protein causes problems in repeat studies. The group found that reducing the amount of injected monoclonal antibody from 27 to 1.9 ml/hr/kg resulted in only 2.7% adverse effects in repeat injections. Thirty of 38 recurrent tumors were detected, giving a sensitivity of 79%.

Zwas et al. conducted an IAEA-sponsored study of recurrent colorectal cancer (#324). The monoclonal antibody study helped in localizing occult disease and in surgical decision-making in patients with suspected recurrences.

### Increasing Tracer Specificity

In studies of infection and inflammation, a number of presentations were concerned with human immunoglobulin (IgG) (e.g., # 832, 839). One of the most difficult problems in medicine is fever of unknown origin (FUO), where no cause has been found after a three-week intensive search. Investigators from University Hospital Nijmegen, the Netherlands, found that  $^{111}\text{I}$  human polyclonal IgG imaging made important contributions to the diagnostic process in 70% of patients (#242).

A multicenter study of indium-labeled IgG had an overall accuracy of 96% in 100 patients who had focal infection (#831). Chemotactic peptides as imaging agents were an important focus of the meeting. These are secreted by microorganisms and leucocytes and bind to receptors on leucocytes, concentrating them at sites of infection and inflammation (#62, 415). In a study of infected rabbits, Babich et al., Massachusetts General Hospital, found that  $^{99m}\text{Tc}$ -labeled chemotactic peptides were more avidly accumulated at sites of infection than  $^{111}\text{In}$  WBC's (#833, 836).



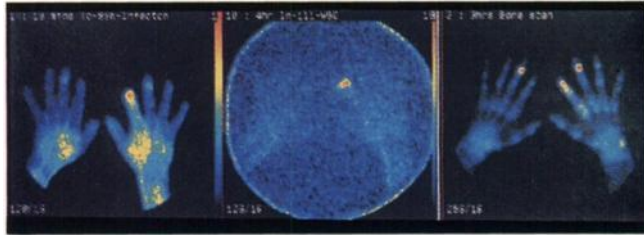
**Figure 6.** Accumulation of  $^{99m}\text{Tc}$  chemotactic peptide at the site of infection in a rabbit. Chemotactic peptides were a major focus of the meeting.

Vallabhajosula et al., Mount Sinai Hospital, New York, compared synthetic chemotactic peptide derived from platelets to  $^{111}\text{In}$  white cells in detecting focal infection (#414). Synthetic cyclic peptides derived from platelets have been labeled with  $^{99m}\text{Tc}$  and assessed as thrombus-imaging agents in peripheral thrombosis and pulmonary embolism (#60). Another thrombus-imaging agent is  $^{111}\text{In}$ -labeled fibronectin, an adhesive protein found in extracellular fluid (#475).

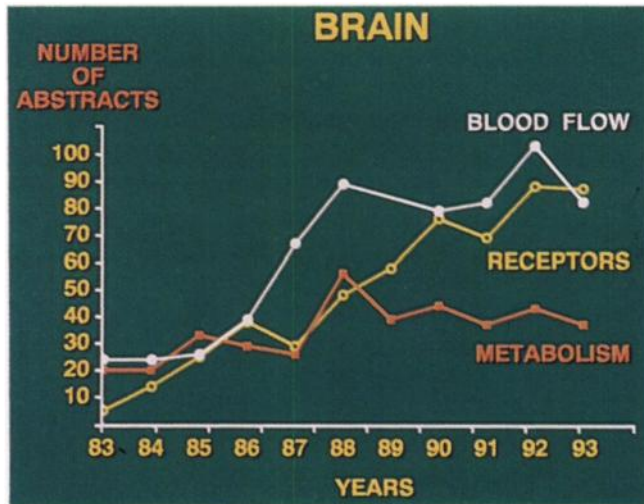
An example of progressively increasing specificity in the study of inflammation is the report by Solanki et al., St. Bartholomew's Hospital, London, which evaluates  $^{99m}\text{Tc}$  "infecton," a fluoroquinolone antibiotic that binds specifically to microorganisms, and compares the results with those obtained with less specific tracers (#474). In Figure 7, the right image shows multiple lesions detected with a  $^{99m}\text{Tc}$  phosphate tracer and reveals increased bone metabolic activity; the middle image with  $^{111}\text{In}$ -labeled white blood cells shows that one finger is inflamed; the left image shows that the lesion contains microorganisms, that is, is infected.

Monoclonal antibodies are used to image inflammation and vascular activation as well as neoplasms. Peters et al., Hammersmith Hospital, used an antibody directed against E-selectin, which is expressed by endothelial cells after activation by the cytokine, interleukin-1 (#243). Human interleukin-8 was found to be better than either  $^{67}\text{Ga}$  or  $^{111}\text{In}$ -labeled WBCs for imaging acute inflammatory lesions (#416).

Use of multiple tracers to solve a specific medical problem is illustrated in care of patients with peripheral vascular disease, as in diabetes. Distinguishing small-vessel from large-vessel disease is necessary, and, in advanced cases, a decision must be made at what level an amputation should be performed, and, then, whether an amputation site will heal or is infected. Smith et al., the University of Tennessee, used FDG-



**Figure 7.** The image on the right shows multiple bone lesions imaged with <sup>99m</sup>Tc phosphonate. The middle image with <sup>111</sup>In-labeled white blood cells shows that one finger is inflamed; the image on the far left shows that the lesion is an infection, by means of microorganisms which bind the tracer antibiotic "infecton". This series of images illustrates the progressive increase in the specificity of tracers.



**Figure 8.** Continued growth in the number of neuroreceptor studies.

imaging to determine viability of muscle flaps in patients with free-flap muscle transfers to amputation sites (#436). Those that could be shown to utilize glucose eventually healed. This extends the FDG viability test from heart to skeletal muscle, another example of integrated nuclear medicine. (Fig. 8)

### Brain Chemistry And Behavior

Although intercellular communication occurs all over the body, the greatest number of molecular messages are sent and received in the brain.

Glucose utilization reflects global neuronal activity and helps direct attention to specific regions of the brain involved in mental functions. Wang et al., Brookhaven National Laboratory, observed decreased left frontal glucose metabolism in young normal males between the ages of 20 and 40. In such studies, one would like to know whether the decrease is due to reduced neuronal mass or decreased neuronal activity per neuron. Meltzer et al. showed that in Alzheimer's disease atrophy contributed 39%, 29% and 7% of the apparent hypometabolism in the posterior temporal, parietal and frontal regions of the brain (#8).

### Movement Disorders

The dopaminergic system was again the most extensively studied neuronal system examined by PET and SPECT. Molecular nuclear medicine has made it possible to examine synthesis of dopamine with L-dopa, release of dopamine from the presynaptic vessels, binding of dopamine to the postsynaptic receptors, reuptake of dopamine from the synapse, and the relationship of the dopaminergic to the cholinergic system. In patients with Parkinson's disease, postsynaptic D1- and D2-dopamine receptors are normal, while there is a defect in dopamine synthesis.

A new single photon radioligand-<sup>123</sup>I IBF, developed by Buck, Kung et al., the University of Pennsylvania, has a higher affinity and other more desirable properties than IBZM, the widely used tracer of postsynaptic receptors (#934). As single photon tracers are added to the armamentarium of dopamine receptor imaging, PET develops tracers for the study of presynaptic reuptake sites. In patients with Parkinson's disease, even when mild, there are striking abnormalities in dopamine reuptake sites (#115).

Similar findings in Parkinson's disease were found with <sup>123</sup>I CIT (#116), also taken up by dopamine and serotonin transporters on presynaptic neurons. In a study of <sup>18</sup>F L-DOPA measurement of dopamine synthesis in presynaptic neurons, Dhawan et al., North Shore University Hospital, New York, demonstrated diminished dopamine synthesis in patients with Parkinson's disease, but did not find a decrease in normal persons between the ages of 20 and 80 (#989). Since there is evidence of a decrease in the number of dopaminergic neurons over that age range, it seems that despite reduction in the neuronal population, the dopamine synthesis remains normal. Findings suggest that a presynaptic reuptake marker may be a more sensitive indicator of presynaptic damage than measurements of dopamine synthesis in patients with movement disorders. (Fig. 9)

The radioiodinated reuptake marker is not specific for the dopamine transporter since it binds to the serotonin transporter as well. One can increase specificity of the measurement by blocking serotonin reuptake through the prior administration of clomipramine so that the studies reflect only the dopamine reuptake site (#952). A specific tracer to assess serotonin reuptake sites labeled with <sup>11</sup>C was also described, which makes this unnecessary (# 91, 1092).

New <sup>123</sup>I radiotracers for the study of brain chemistry include tracers for the study of sigma receptors (#353), benzodiazepine receptors (#352), and 5-HT 1A serotonin receptors (#354). New PET radioligands include <sup>11</sup>C naltrindole for the study of delta opioid receptors (#410).

### A New Approach To Disease

Molecular nuclear medicine does not simply develop new tests for old diseases but provides a whole new approach to disease. Alzheimer's disease is still defined by the abundance



of senile plaques and neurofibrillary tangles found at autopsy. The correlation between clinical manifestations of Alzheimer's disease and the histopathological diagnosis is relatively poor (#461). Specificity of the clinical diagnosis of Alzheimer's disease was 60%. SPECT studies of regional blood flow were far more specific.

Biochemical characterization of Alzheimer's disease by examining presynaptic cholinergic vesicular transport is now possible because of development of <sup>123</sup>I iodobenzovasisamol (#93). The tracer accumulates in synaptic vesicular transporter sites within muscarinic cholinergic neurons with high concentrations in the basal ganglia. The nicotinic cholinergic system can be assessed with tritiated cytosine (#946), or radioiodinated nicotine (#1093).

#### Advantages Of Continuous Infusion

The Yale group documented the advantages in simplification of kinetic analysis by maintaining a steady state with continuous infusion of the tracer, illustrated by their studies of benzodiazepine receptors with <sup>11</sup>C flumazenil (#432), and with <sup>123</sup>I iomazenil (#994). They were also able to demonstrate endogenous release of dopamine induced by D-amphetamine (Fig. 10). There was good correlation of results of complex kinetic modeling after single injections, compared to results obtained with the simpler modeling of equilibrium studies.

#### Stroke

Quantification of benzodiazepine receptors is helpful in delineating viable brain after stroke. One method consists of three injections—a tracer dose of <sup>11</sup>C flumazenil, a partial blocking dose of unlabeled fluaznil, and a low specific-activity tracer dose (#433). The model does not require blood sampling. Benzodiazepine receptor concentrations in damaged tissue provide a means of assessing viability (#935). When blood flow was reduced as indicated by <sup>99m</sup>Tc HMPAO, Matsuda et al. found a dissociation between blood flow and the regional concentration of benzodiazepine receptors imaged with <sup>125</sup>I iomazenil. Even when regional blood flow was greatly reduced, accumulation of the benzodiazepine receptor ligand revealed that many regions were still viable. Minoshima et al. were able to document that benzodiazepine receptor availability was normal, even when blood flow is functionally reduced, as in crossed cerebellar diaschisis in stroke (#977). Benzodiazepine receptor imaging may be an excellent indicator of recovery after stroke. Cells that have been severely damaged lose benzodiazepine receptors.

Hypoxic brain cells can be delineated with a <sup>99m</sup>Tc nitroimidazole derivative (#365). Use of this agent in stroke extends the use of hypoxia studies with PET tracers in cancer, brain and heart disease (#314), providing another example of the advantages of an integrated approach to patient problems. Immediately after a stroke, cerebral blood flow is reduced. But

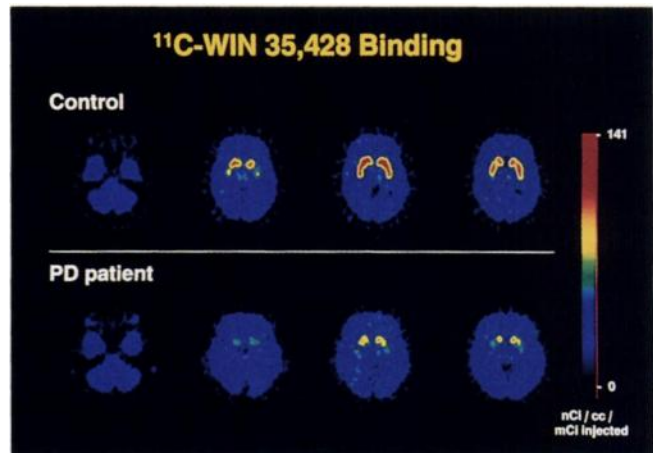


Figure 9. Decreased dopamine reuptake transporter concentrations in patients with Parkinson's disease (lower row).

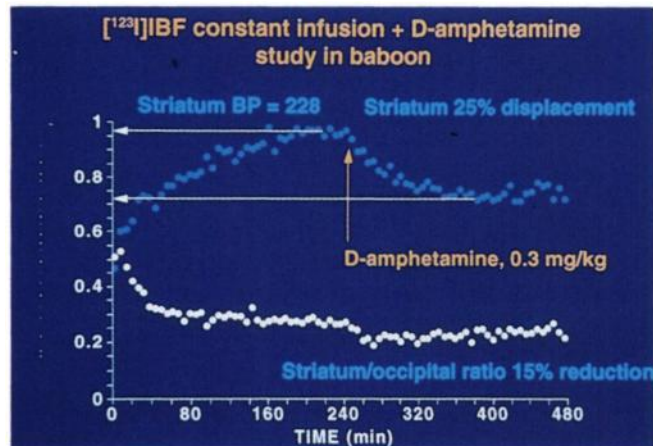


Figure 10. Effect of amphetamine in decreasing synaptic dopamine concentration, evidenced by a decrease in <sup>123</sup>I IBF binding to the basal ganglia.

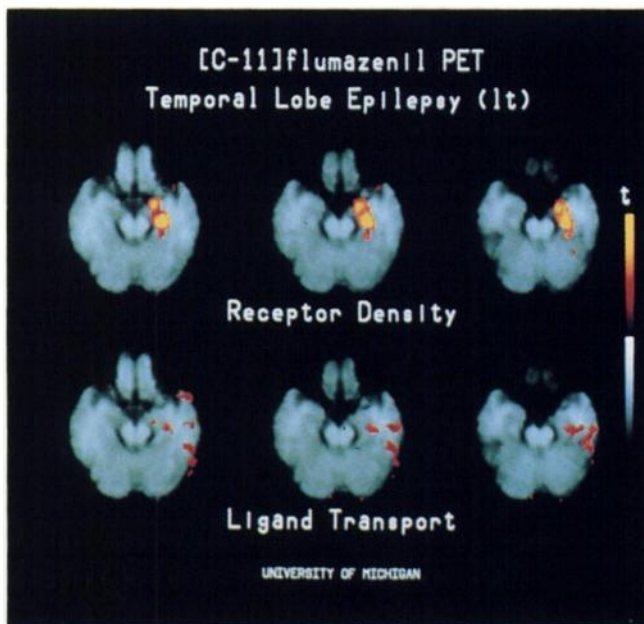
as time progresses, there is an accumulation of the nitroimidazole tracer delineating regional hypoxia.

#### Head Movement And Positioning

A study from Friedrich Alexander University, Germany, exemplifies studies of mood disorders (#181). Benzodiazepine receptors examined with <sup>123</sup>I iomazenil were found to be abnormal in hippocampal, inferotemporal and frontal regions. In patients with obsessive compulsive disorder, <sup>15</sup>O water revealed regional changes after provocation (#180). Greene et al., NIH, emphasized the difficulty in preventing head movement during perturbation studies (#276). They described a strategy to correct for inevitable head movement.

#### Regional Blood Flow And Chemistry

Standardized stereotactic atlas used in several institutions for PET regional blood flow studies during activation paradigms also should be used in SPECT studies (#277). Com-



**Figure 11. Decreased benzodiazepine receptor availability in an epileptic.**

bined registration of multimodality images was exemplified by Becker et al., Harvard University (#863).

The need for precise anatomical assignment of blood flow and chemical changes is demonstrated in the study of autistic children in whom there are multiple regions of decreased blood flow (#308). More information about the normal patterns in children is necessary to assign abnormalities to anatomical regions. To help solve this problem, Schiepers et al., Leuven, Belgium, defined patterns of regional cerebral blood flow measured with  $^{99m}\text{Tc}$  ECD in children of various ages (#990). The study population was a group of children with febrile convulsions in whom subsequent evidence made it clinically certain they were normal.

#### Attenuation Correction

Improvements in attenuation correction are being applied in clinical studies. Hoh and colleagues, UCLA, showed how attenuation correction improved detection of metastatic axillary lymph nodes in patients with breast cancer (#547). Similar improvements by attenuation correction also were documented for SPECT (#96, 908). Dual-energy windows can be used for scatter corrections (#909). In clinical cardiac studies, simultaneous transmission and emission imaging resulted in dramatic improvement in quantitative assessment, improving resolution and decreasing noise (#111, 112).

With improved performance in all aspects of SPECT cameras, one can now ask how effective  $^{133}\text{Xe}$  can be in measuring regional cerebral blood flow in activation studies. Because xenon is exhaled rapidly, repeated studies in the same experiment are possible. Encouraging initial results were described from Cleveland and Oklahoma City (#906).

#### Epilepsy

Benzodiazepine receptor availability imaged with  $^{123}\text{I}$  iomazinil is reduced at the site of the focus in temporal lobe epilepsy (#80).

Similar results were found with  $^{11}\text{C}$  flumazenil (#81). In the presentation by the Dutch group (#80), patients were selected for surgery, based on clinical examination, EEG and magnetic resonance imaging. Iodine-123 iomazinil SPECT imaging of benzodiazepine receptors was a routine procedure. In patients in whom certainty of the location of the focus was not sufficiently high,  $^{18}\text{F}$  FDG studies were performed. Clinical use of these SPECT/PET studies resulted in complete surgical cure of 53% of 100 patients (Fig. 11). Muscarinic acetylcholine receptors are also reduced at the epileptic focus (as reported during last year's meeting).

#### Tailoring Medications To A Specific Patient

Pharmacologist Louis Lasagna wrote, "Often we don't know how to tailor specific drugs to specific patients very well. We could do that better and make a quantum jump in efficacy without even coming up with any new drugs." A distinguished German physician said: "If two patients receive the same treatment, at least one of them will be treated wrongly." Molecular nuclear medicine makes it possible to characterize a patient's abnormality as a molecular abnormality and use that information to plan treatment and subsequently monitor the effect of treatment on the molecular target, whether the treatment is pharmacological, chemical or surgical. Nuclear imaging can help in drug design and development as well as in individualizing patient therapy.

The Pharmaceutical Manufacturers Association says that only one of 5,000 molecules developed as potential medications ends up with FDA approval. Four of five Phase III clinical trials fail, in many cases because a wrong dose was used in trials or indices of effects of the drug were too subjective. In the experience of 24 major drug companies in the United States, the cost of developing a successful, approved drug averages \$400,000,000—yes, four hundred million dollars.

An example of how tracer technology applied to human beings can be used in drug development is a comparison of the blocking effect of reversible and irreversible monoamine oxidase-B (MAO) inhibitors by investigators at the Brookhaven National Laboratory and New York University (#525). One day after stopping treatment with a reversibly bound drug,  $^{11}\text{C}$  deprenyl binding, an index of the degree of blockade of the enzyme returned to normal; when deprenyl itself was administered, the blocking effect lasted for weeks. A radioiodinated tracer for examining brain monoamine oxidase is iodopargyline, described by the group from Tours, France (#1098).

Another example of radiotracer studies in drug development is measurement of  $^{11}\text{C}$  raclopride binding to D2 dopamine receptor after administration of a new neuroleptic drug (#434). Researchers asked what dose of a new drug should be used in



a phase III clinical trial; the answer came from a dose/response curve in which blocking the receptor was the response.

Human granulocyte colony stimulating factor was assessed using colloidal imaging (#840). There was a quantifiable expansion in bone marrow in the leg of a dog following administration of growth stimulating factor.

A study from UCLA found that chronic estradiol therapy does not have a damaging effect on the heart when it stimulates myocardial function (#802).

A penile detector system was used to measure blood volume of the penis in studies of impotence (#1160). Overall sensitivity of the system is 10 times that obtained when measurements were made with a scintillation camera. It is my understanding that partial volume was not a problem. When venoconstriction was produced by papavarine, penile blood volume increased. Important in the study of impotence is the discovery that nitric oxide is probably a neurotransmitter that stimulates vasoconstriction. Nitric oxide production may be deficient in some patients with impotence. McCarthy and Welch synthesized an  $^{125}\text{I}$  tracer for assessing nitric oxide synthase (#355).

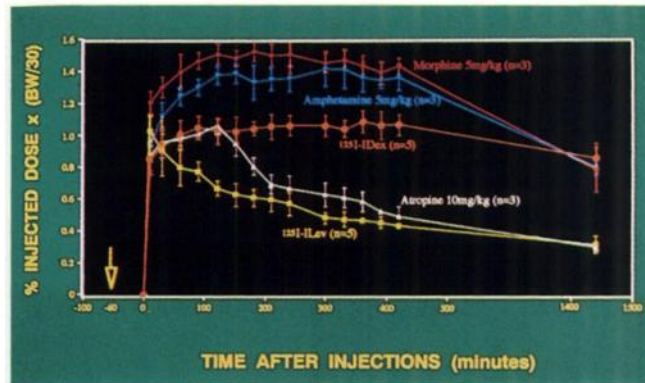
Another example of a probe study is the effect of morphine and amphetamine in decreasing accumulation of  $^{125}\text{I}$  dextetimide to muscarinic cholinergic receptors in living mice, indicating that acetyl choline has been inhibited—in the first case by direct inhibition of presynaptic neuronal secretion of acetyl choline, and in the case of amphetamine by dopamine's decreasing the inhibition of acetyl choline release (Fig. 12).

### Animal Scanners

Examples of the many presentations concerned with animal scanners include the following: a study from Duke in which a rotating SPECT camera with a pinhole collimator produced striking images (#29); a presentation from Lund University, Sweden (#27); a whole-body cylindrical imager using optical fibers developed at Southwestern Medical Center (#25); and a high-resolution slit aperture ring device (#26). Ljunggren and Strand described a beta camera for imaging tracer distributions within 30 minutes, a process that would take 24 hours by autoradiography (#449).

### Substance Abuse

In the United States, there are 100,000 emergency room visits by patients with cocaine toxicity, and 40,000 patients admitted to the hospital because of heroin overdoses. Overall substance abuse has decreased by 67%, but there has been no decrease in the number of heavy users. In cocaine abusers, there is decreased availability of D2 dopamine receptors in the basal ganglia. Volkow et al. administered methylphenidate to block reuptake of dopamine from dopaminergic synapses (#406). Increased synaptic dopamine concentrations compete with  $^{11}\text{C}$  raclopride uptake in normal persons. Cocaine abusers do not show this effect of methylphenidate on  $^{11}\text{C}$  raclopride



**Figure 12.** Effect of morphine and amphetamine in decreasing acetyl choline release, as evidenced by increased binding of iododextetimide by muscarinic cholinergic receptors.

accumulation in the basal ganglia, indicating that the postsynaptic neurons are impaired.

### Intracellular Communication

After acetylcholine is bound by muscarinic acetylcholine receptors, a series of biochemical reactions occur involving G-protein and phosphoinositide metabolism. Imahori et al., Kyoto, Japan, imaged phosphoinositide response in the primate brain by autoradiography and PET imaging (#94). Carbon-11 diacylglycerol (DAG) activity in the brain was increased by the agonist carbachol, which also increased regional glucose utilization. When the brain was stimulated with potassium, glucose utilization increased, but there was no phosphoinositide response, indicating that the phosphoinositide system was responsive to molecular agonists but not to ionic stimuli.

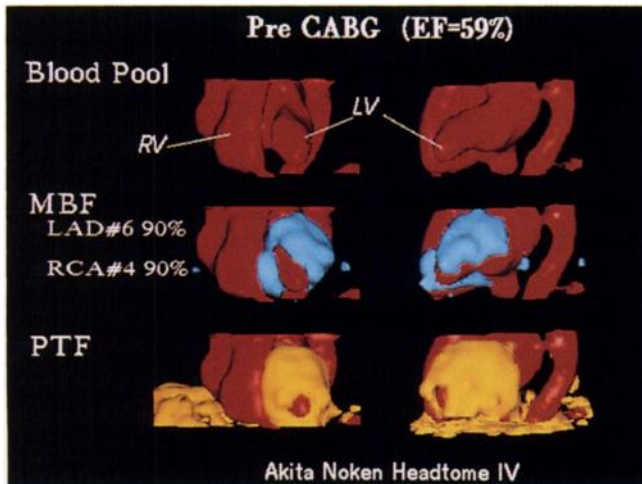
### Neurogastroenterology

A subtype of muscarinic cholinergic receptors—M2 receptors—are present in the heart and smooth muscle, while M3 receptors are in glands and smooth muscle. A piperidine methiodide (4-DAMP) for measuring M3 cholinergic receptors was described by van Waarde, University Hospital, Groningen (#1120). This tracer can be useful in neurogastroenterology.

In studies of the effect of misoprostol on postprandial intestinal transit and motility, Argenyi et al., the University of Iowa, found no effect on gastric emptying, but an increase in colonic filling which localized the effect of the drug on the small intestine (# 813). Vagotomy did not alter gastric emptying (#30). Urbain et al. showed how important it is to examine regional kinetics within the stomach. There may be normal gastric emptying with gross abnormalities in the movement of the tracer within the stomach (#31).

### Nuclear Cardiology

Advances in instrumentation, including attenuation and



**Figure 13.** Intracavitary blood volume (upper images), myocardial blood flow (middle row), and exchangeable water space (lower) in a patient with a myocardial infarction before and after bypass surgery.

scatter corrections, together with application of more useful filters, have brought about remarkable improvement in anatomical detail in the study of the heart. Faster processing has been an important factor in increasing patient throughput.

Iida et al., the Research Institute, Akita, Japan, showed surface volume imaging of the intracavitary blood pool; distribution of myocardial blood flow in the anterior view and in the left lateral view, showing defects in blood flow; and an image (PTF) that represents exchangeable water pool measured with <sup>15</sup>O water (#88). Exchangeable water space is an indicator that the myocardium is alive. After surgery, the area of the infarct did not change, but blood flow improved (Fig. 13).

Miller et al., Washington University, described gating of cardiac PET (#424). Why in fact would one want to gate cardiac PET? In his excellent Bloomgart lecture, Ernie Garcia noted that gating so improves cardiac studies it should be routine. Gating is used not only to get information about cardiac motion, but also to stop cardiac motion. In fact, cardiac gating was introduced initially to improve <sup>43</sup>K images of myocardial blood flow by stopping cardiac motion. In both PET and SPECT, gating can decrease the blurring effects of cardiac motion and decrease artefacts. Solid-state detectors are now being introduced to improve resolution (#403).

### Outcomes Research

Supino et al. reported a nine-year follow-up of a large number of patients after coronary artery bypass grafting (#126). In elderly patients, resting ejection fraction best predicted probability 1) of death within a few years post-bypass or 2) sustaining major cardiac events. It was necessary to quantify resting ejection fraction precisely, and even when the ejection fraction ranged between 30% and 45%, its value was a good prognostic indicator. One can concentrate preventive efforts on

patients with ejection fractions less than 45% because they are at the greatest risk. How many grafts could be implanted also affected survival. The more vessels that could be grafted, the better the survival.

Cardiac risk stratification by myocardial perfusion imaging prior to surgery had approximately the same accuracy as Holter monitoring (#293). Combined use of both methods provides a far better estimate of risk than that obtained by either method alone. Provided they are sufficiently independent (as are radiotracer and Holter monitoring studies), one can strive for 99% accuracy.

Myocardial metabolism studies included <sup>11</sup>C acetate studies, which have the important advantage of being based on measurement of rates of change in tracer activity. Partial volume effects, such as those associated with FDG studies, are less of a problem. In Graves disease, studies by Torizuka et al., Kyoto, Japan, showed that myocardial metabolism is greatly increased and is proportional to the pulse-pressure product (#428).

Choi et al., UCLA, presented a simpler model for measuring oxygen consumption using <sup>11</sup>C acetate (#878). The model was validated by independent measurements of myocardial oxygen consumption.

In another presentation from the Research Center, Julich, Germany, a new, much simpler method of modeling fatty acid metabolism was described (#425). Use of a Patlak-plot approach greatly decreased the time of acquisition of data, and simplified modeling. Diprydamole, which increases blood flow, did not affect the calculations, whereas exercise did. Thus, the simple Patlak model separated fatty acid metabolism from blood flow.

Regional hypoxia can be delineated in the ischemic myocardium (#722). Synthetic-labeled peptides are being developed to label atherosclerotic lesions in vivo (#259). The liver is a focus of study of LDL receptors in relationship to atherosclerosis. Patients at risk of coronary artery disease show high serum cholesterol due to LDL receptor deficiency in the liver. A <sup>99m</sup>Tc tracer is being developed for assessing LDL receptors (#261).

Another important tracer labels atrial natriuretic factor (#226), whose receptors are highly concentrated in the lungs and kidneys. This work opens up a vast horizon in the study of hypertension, congestive heart failure and sodium metabolism. Callahan and colleagues describe a polymer as a substitute for labeled red blood cells (#149).

For me, neurocardiology is the most exciting area of cardiology today; it can now approach the problem of sudden death due to arrhythmias. Cardiomyopathy is manifest by presynaptic neuronal degeneration revealed by a tracer such as <sup>123</sup>I-labeled MIBG. In myocardial infarction, the denervation zone of presynaptic neurons is characteristically larger than the defect in blood flow. An excellent study by Valette et al., Orsay, France, demonstrated up-regulation of myocardial beta



adrenergic receptors after chemical sympathetic denervation (# 175). When presynaptic neurons of the heart were damaged with the neurotoxin 6-hydroxydopamine, there was a low accumulation of  $^{123}\text{I}$  MIBG, but an increase in the binding of the tracer used to examine beta adrenergic receptors, indicating up-regulation. Receptor density doubled. When there is up-regulation, there may be hypersensitivity to epinephrine secreted by adrenals under stress, which could stimulate an excessive adrenergic response in the heart, and lead to arrhythmias. The most common presenting symptom of coronary disease is not chest pain, but sudden death, which, for some unknown reason, is about eight times more common in men than in women with the same-sized stenotic lesions.

### The Musculoskeletal System

Quantification of fluoride kinetics makes it possible to differentiate bone disorders on the basis of differences in fluoride influx rates in vertebral bodies (#437), an alternative to bone density measurements. Declerck et al., Belgium and the Netherlands, performed quantitative bone scintigraphy to evaluate leg growth in normal children (#1063). They used this baseline data to determine when surgery should be performed to lengthen the legs of children with unilateral congenital growth disorders (#1064). Knowledge of the growth characteristics of the bone in each child is necessary in selecting the optimum timing of surgery.

### Therapy

The cost effectiveness of  $^{32}\text{P}$  chromic phosphate synovectomy was illustrated by treatment of hemophilic patients at the University of Southern California (#715). Pain relief occurred without surgery, which is extremely complicated and expensive in hemophilic patients. Yttrium-90 was used in rheumatoid arthritis with great success by Picard et al., the University of Montreal (#718). Holmium-166 DOTMP was an effective new agent for bone marrow ablation (#125).

### Summary

PET and SPECT are marching in tandem and continue to make major advances, particularly in patients with cancer, heart and brain disease (Fig. 14).

Whatever the characteristics of health care reform in the United States, there will be change. We must be sure that the voice of molecular nuclear medicine is heard loud and clear. Cost-containment need not dull the sheen on the science and technology of nuclear medicine. We have heard at this meeting how radiotracer procedures, revealing regional physiology and biochemistry provide information that helps patients and decreases the cost of care by directing therapy that works. We can also contribute greatly to prevention by early diagnosis.

Marginally useful tests and treatments can be eliminated as we improve the care of individual patients and document the effects of radiotracer procedures in determining outcomes. The

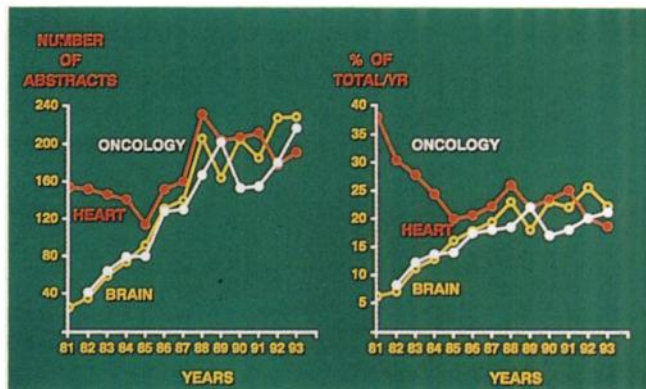


Figure 14. Oncology equals cardiology and neurosciences in the number of presentations.

quality of medical care can be improved by application of procedures presented at this meeting. Ignorance is the expense in the health care system—ignorance of the state of the patient and the best type of treatment. No specialty is better suited than nuclear medicine to contribute to health care reform in a climate of managed care. Better patient identification, treatment selection and better monitoring of therapy are needed.

In his excellent opening address, Bill Strauss noted that the Chinese character for crisis consists of combining two other characters—one meaning “danger,” the other “opportunity.”

In molecular nuclear medicine, we have the opportunity to determine what works and assess whether the patient has improved and by how much. Insurance companies and health care managers can be shown how cost-effective our contributions are. We can improve the practice of medicine at lower cost. Fruitless treatment is what is expensive. Health care purchasers tend to buy too much because they have no way to determine the specific effects of diagnostic tests and treatments on specific patients. We can provide that information and achieve financial benefit.

A journalist once said, “History repeats itself, because no one listens the first time.” In fact, in 1951, 42 years ago, a paper was published on the use of positron-emitting tracers in the localization of brain tumors. We have come full circle, but we still measure in vivo chemistry, and chemistry is what joins structure and function.

In this model, there will be a strong central pillar of autonomous nuclear medicine, through which we can continue to build strong bridges to pillars of cardiology, oncology, neuroscience and other specialties, including radiology. If we don't have a strong, autonomous profession (and I believe nuclear medicine cannot be strong unless it is autonomous)—if it remains a secondary branch of another specialty—we will have a circle around which nuclear cardiology, nuclear oncology and nuclear neurosciences will develop without the contributions of the central core.

If that happens our patients will suffer.