Henry N. Wagner, Jr., MD

The Society of Nuclear Medicine conducted its 42nd Annual Meeting in Minneapolis, MN in June. For the 18th consecutive year, Henry N. Wagner, Jr., MD, professor of medicine, radiology and environmental sciences at The Johns Hopkins Medical Institutions in Baltimore, presented his view of the scientific highlights at the final session of the meeting.

A New Era of Certainty

Anxiety and uncertainty pervade medicine and nuclear medicine today. Many nuclear medicine physicians and technologists have had their jobs disappear or be taken over by less well-trained people. As the winds of socio-economic change blow across the country, people are anxious about the future in the face of dramatic changes in the health care system, even without radical legislation at the national level. Thus, it may seem surprising that I have chosen *Molecular Nuclear Medicine in the New Era of Certainty* as the theme for this year's highlights of the research presented at the 42nd Annual Meeting.

At this meeting, we saw continuing evidence that the science and practice of nuclear medicine continued a pattern of growth that began 35 years ago **(Fig. 1)**. Since 1960, there has been a ten-fold increase in the number of papers presented in this field. No field of medicine is better able to respond to the new demands for certainty in the practice of medicine. Collaboration between academic institutions and industry are continuing to provide new and innovative tracers and instruments, making it possible to expand into new research domains, create more specific definitions of disease and treat our patients more effectively.

With the progression of managed care, nuclear medicine is poised to become a leader in this new age of certainty. More than ever, the public and gatekeeper physicians want to be assured about the technical quality of diagnostic studies. They want to know: Does this study perform according to its specifications? Does it measure what it's supposed to be measuring? For which medical problems is the study helpful in solving? All of these questions have been addressed at the meeting.

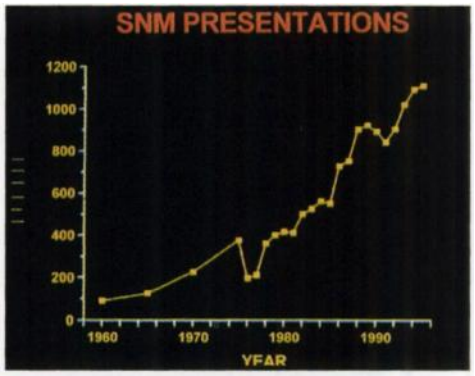


Figure 1. The number of scientific presentations at the SNM Annual Meetings increased exponentially over 30 years.

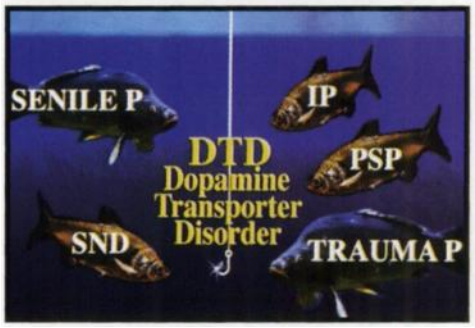


Figure 2. Distinguishing patients with dopamine transporter disease from those with other movement disorders is often akin to fishing from a sea of patients.

Dopamine Transporter Disease

As cerebral perfusion studies make their way into clinical use, neurotransmitter research has become a dominant area. It is telling that 115 presentations dealt with the process of neurotransmission, with 72 of those concerned with the dopaminergic system. Since the first imaging of dopamine receptors in 1983, there has been a steady increase of research in this field. In the papers presented at this year's meeting, 35 dealt with the presynaptic dopamine transporter, 33 involved D2 dopamine receptors and 4 addressed D1 receptors.

Today, we can examine all aspects of neurotransmission including: the synthesis of dopamine with ^{18}F L-dopa, the secretion of dopamine from the presynaptic neurons measured by its effect on postsynaptic receptors, the metabolism of dopamine by the monoamine oxidase enzyme system, the re-uptake of unbound dopamine by the presynaptic dopamine transporter with re-incorporation of dopamine into the vesicles of the presynaptic neuron.

Figure 2 illustrates the fishing for patients with dopamine transporter disease from the heterogeneous sea of patients with movement disorders such as senile Parkinson's disease, striatonigral degeneration, traumatic Parkinson's disease, progressive supranuclear palsy and idiopathic Parkinson's disease. This same molecular diagnosis can be applied to patients with other diseases, including cognitive as well as emotional disorders.

In patients with idiopathic Parkinson's disease, D1 and D2 dopamine receptors are normal. In striatonigral degeneration, there is degeneration of postsynaptic dopaminergic neurons. Early studies with the neurotoxin MPTP, injected into a carotid artery of baboons, found postsynaptic receptors were left intact, but presynaptic neurons were destroyed.

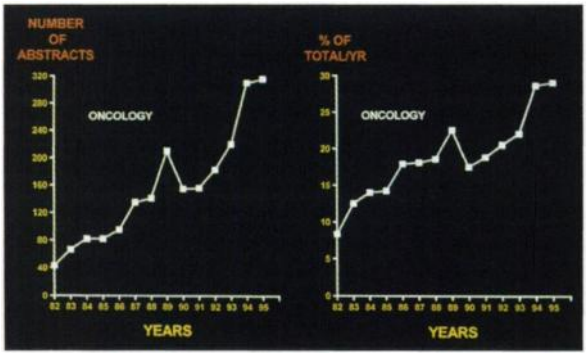


Figure 3. Oncology presentations have followed a continued pattern of growth since 1982.

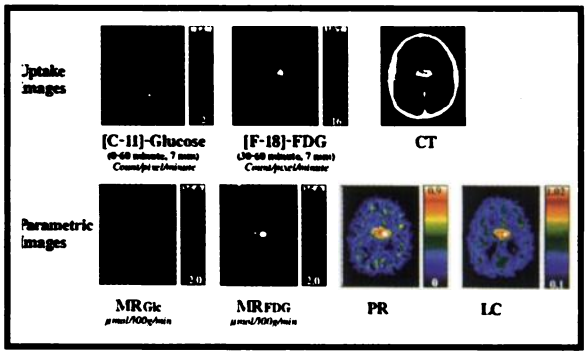


Figure 4. The images above show the relationship between FDG accumulation in glial tumors and the phosphorylation ratio rather than to the glucose utilization of the lesions.

One could chemically resolve abnormalities in structures that are only microns apart. Several reports at this meeting showed that in the earliest stage of Parkinson's disease, that is, when only half of the body is involved, there are major deficiencies in presynaptic neurons. These deficiencies were examined through the injection of radiotracers, which then accumulate by the presynaptic dopamine transporter. The tracer studies were shown to be more sensitive than clinical manifestations. Ilgin and colleagues at The Johns Hopkins Medical Insitutions in Baltimore used ^{11}C-WIN 35428, (Abstract #400) and found that patients with Stage I Parkinson's disease had striking reductions in tracer binding to the transporters in the anterior and particularly the posterior putamen when compared to healthy individuals.

Vermeulen and colleagues from Amsterdam (Abstract #401), using a single-photon emitting tracer ^{123}I-labeled ß-CIT, reported similar results; they showed that there were significant abnormalities in both sides of the brain in patients with hemi-Parkinson's disease. They also reported a very striking decline in the binding of ß-CIT by the caudate nucleus and putamen as a function of normal aging. The decline with age in normal persons was also reported by Volkow, Ding and colleagues from Brookhaven National Laboratory in Upton, NY who investigated using [^{11}C] d-threo-methylphenidate as a tracer (Abstract #122). Even in early Parkinson's disease, however, there was a clear distinction between the findings in patients with mild symptoms and the healthy controls.

These results and those of Mozley and colleagues at the University of Pennsylvania in Philadelphia (Abstract #123) showing a decline with age in dopaminergic presynaptic neurons, support the hypothesis that Parkinson's disease occurs when there is an environmental factor superimposed on the normal decline in presynaptic neurons with aging. The results with MPTP suggest the possibility of neurotoxin involvement.

Seibyl and colleagues from Yale University in New Haven, CT were able to relate the clinical manifestation of Parkinson's disease to the decline in ß-CIT binding by the basal ganglia (Abstracts #403, 404). In hemi-Parkinson's disease, they found severe deficiencies in the putamen on the side of the brain affecting the normal half of the body as well as on the abnormal side. They also found severe degeneration of the caudate and putamen on both sides of the brain in Stage IV disease. In the most severely involved side of the brain, there was a 70% reduction in the binding of ß-CIT to the putamen, with more than a 60% reduction in tracer binding to the putamen affecting the normal side of the body.

Prevention By Early Molecular Diagnosis

Since drugs such as monoamine oxidase inhibitors are effective if they are administered early in Parkinson's disease, the discovery that nuclear medicine can make a molecular diagnosis prior to the onset of Parkinson's disease symptoms represents one of the most important advances in neurology in the past two decades. The accumulation of radiotracers that bind to dopamine transporters—both positron and single-photon emitting radiotracers—can be used as a marker to examine the role of genetic and environmental factors in Parkinson's disease.

Disease as Dissonance

One can easily move from neuroscience to oncology because both can be viewed as communication disorders—disease as dissonance. The fact that so many neuroreceptors have been found on so many different types of neoplasms leads one to view the human nervous system as having evolved from unicellular organisms to facilitate intercellular molecular communication.

Cells become cancerous because they don't get the right messages, either because of a deficiency in the DNA transcription process or because of a failure in the execution of instructions. **Figure 3** shows the continuing growth in the number of presentations in oncology dating back to 1982. Over the past two years, the striking increase was due to the growth of both PET and SPECT studies in oncology. At this meeting, more than 320 presentations—one third of the entire program—addressed oncology. The number of [^{18}F] FDG presentations in oncology totalled 85. Cancer involving all organs of the body is now a prime focus of nuclear medicine. Fifty-eight papers focused on breast cancer, 38 on lung cancer, and 36 on colon cancer.

Although a smaller number of papers involved thyroid cancer, which historically has been the domain of nuclear medicine, an important finding was reported by Feine and colleagues from the University of Tubingen in Germany (Abstract # 899). In 185 patients with metastatic papillary or follicular carcinoma of the thyroid, 121 had no accumulation of ^{131}I in the metastatic lesions, while all of them had avid accumulation of FDG. This finding

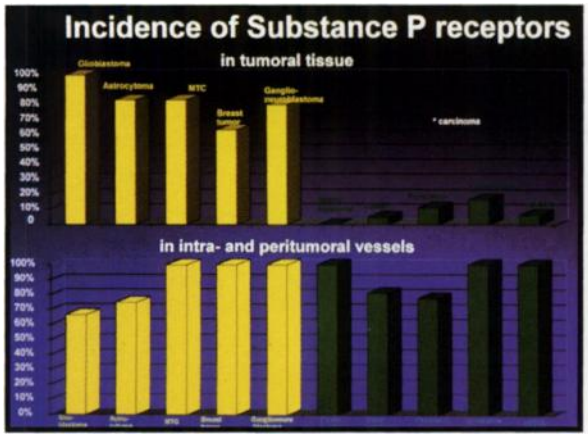


Figure 5. Substance P receptors can be used as a tracer to detect cancers containing neuroreceptors.

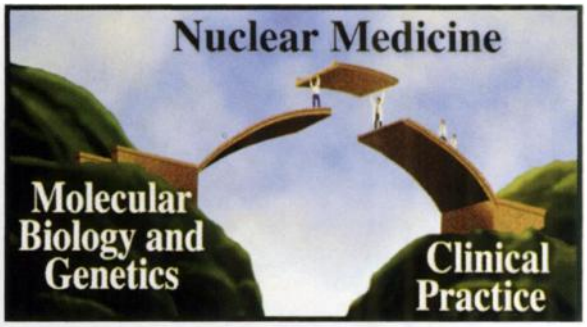


Figure 6. Nuclear medicine can provide the bridge between molecular biology and genetics and clinical practice.

provides an entirely new approach to the care of patients with metastatic thyroid carcinoma, some of whom may have an increase in serum thyroglobulin with no other indication of the metastases' location.

The value of radiotracer studies in the care of patients with cancer can be summarized as follows:

1. Detecting an unknown primary site of cancer in a patient found to have metastases, e.g. in lymph nodes.
2. Differentiating benign from malignant lesions.
3. Grading the degree of malignancy.
4. Staging the extent of disease.
5. Assessing the response to treatment.
6. Detecting recurrent disease.

Breast Cancer Imaging

Tiling and colleagues from the Ludwig-Maximilians University of Munich in Germany (Abstract #205) performed ^{99m}Tc-MIBI and dynamic MRI studies on 58 patients, 38 of whom had mammography suggestive of malignancies. They found a higher specificity when MIBI was added to the mammogram and MRI results. Combining MIBI with mammography results can be particularly helpful in women with dense breasts (Abstract # 208). There was one negative study of MIBI presented.

Ramsingh and colleagues from Christ Hospital in Cincinnati (Abstract #336) reported excellent results in FDG imaging of untreated cancer of the breast and observed that the accumulation of FDG was related to the S-phase of the cell cycle (i.e., the period of DNA replication).

Spence and colleagues from the University of Washington in Seattle (Abstract #245) were able to relate the avid accumulation of FDG in glial tumors to the phosphorylation ratio, in other words, the magnitude of the "lump constant" rather than to the glucose utilization of the lesions **(Fig. 4)**. Thus, one should refer to "increased FDG accumulation" rather than "increased glucose utilization" when referring to FDG uptake in tumors. The lump constant reflects the difference in the phosphorylation rate between deoxyglucose and glucose. An FDG parametric image, then, reflects the product of the lump constant and the metabolic rate for glucose. The increased lump constant reflects increased activity of hexokinase enzymes 2 and 3, which are associated with anaerobic glycolysis.

Substance P Receptors in Cancer

The list of potential agents to detect the numerous cancers that contain "neuroreceptors" now includes substance P receptor tracers. Reubi and colleagues from the University of Berne, Switzerland (Abstract #289) showed that substance P receptors were found in most astrocytomas, glioblastomas, medullary thyroid carcinomas, breast carcinomas and ganglioneuroblastomas **(Fig. 5)**. Substance P receptors were found not only in the tumors but also in peritumor vessels. The same investigators showed that many types of cancer express somatostatin receptors, at times with vasoactive intestinal peptide receptors, while others express only one or the other. Vasoactive intestinal peptide receptors are often found in ovarian, prostate, bladder and pancreatic cancers where there are usually no somatostatin receptors.

Multidrug Resistance

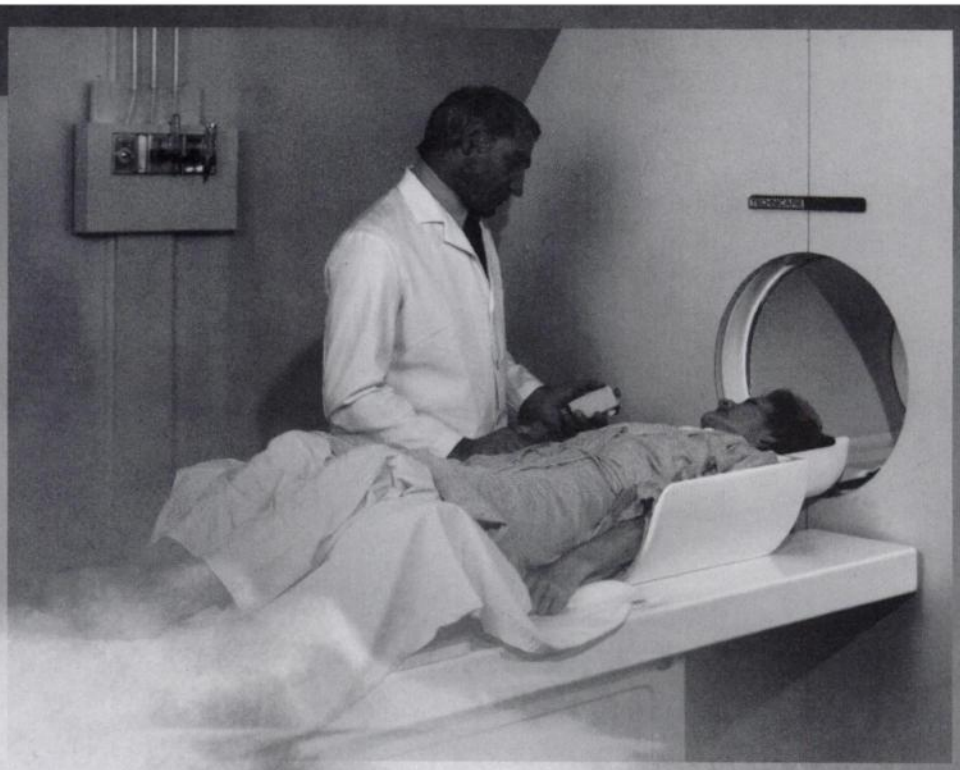
Figure 6 illustrates the concept that nuclear medicine can provide the bridge between molecular biology and genetics and clinical practice. There are relatively few diseases, such as alcaptonuria and color blindness, where it is possible to demonstrate the importance of genetic influences. It is much more difficult in diseases such as Parkinson's or Alzheimer's: that is until now when excellent markers of traits, such as presynaptic neuron markers, are more easily recognized. Multidrug resistance (MDR) is one clinical example that clearly illustrates how a radiotracer study can serve as a marker for genetic analysis of living human beings. The ability of radioactive tracers to measure in-situ biochemical processes and their responses to perturbations can provide the measurements that can be used as markers in genetic studies of processes such as MDR, a phenomenon that occurs when resistance develops to a single chemotherapeutic agent, and then results in cross resistance to other drugs.

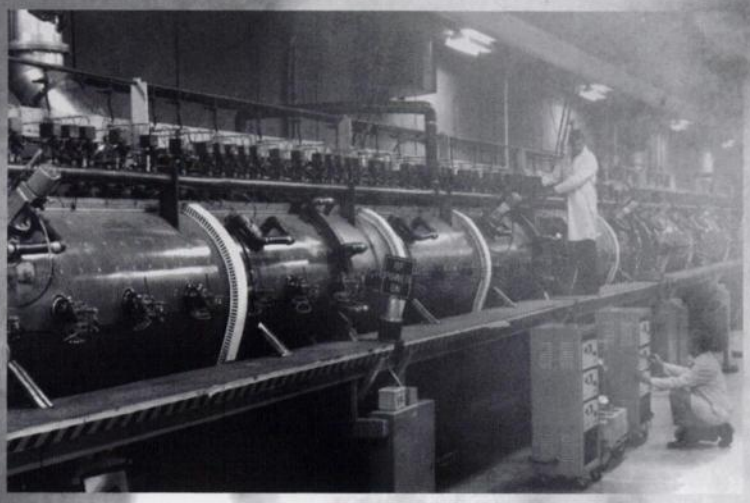
Twelve papers at this meeting addressed MDR, which is due to increased expression of a p-glycoprotein on the cell membrane. Ciarmiello and colleagues from Naples, Italy (Abstract #526) showed that the efflux of ^{99m}Tc-sestamibi was related to the degree of p-glycoprotein expression in breast cancers before treatment **(Fig. 7)**. The lesions with a low concentration of p-glycoprotein

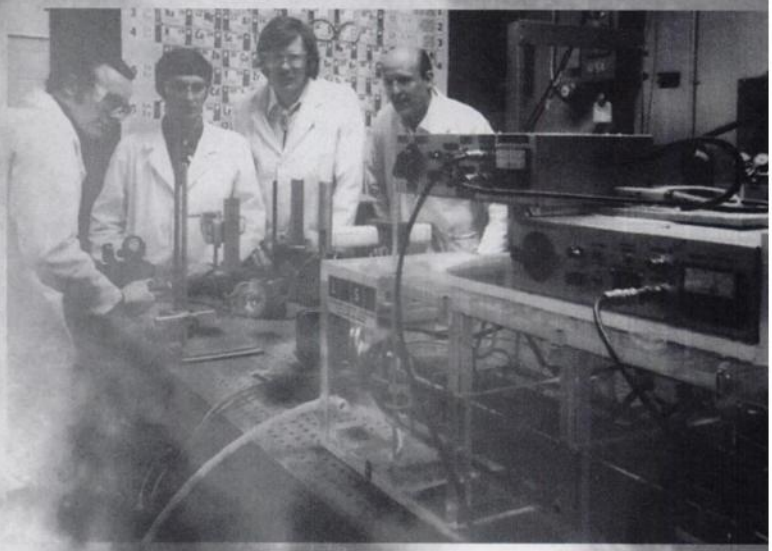
(Continued on page 24N)

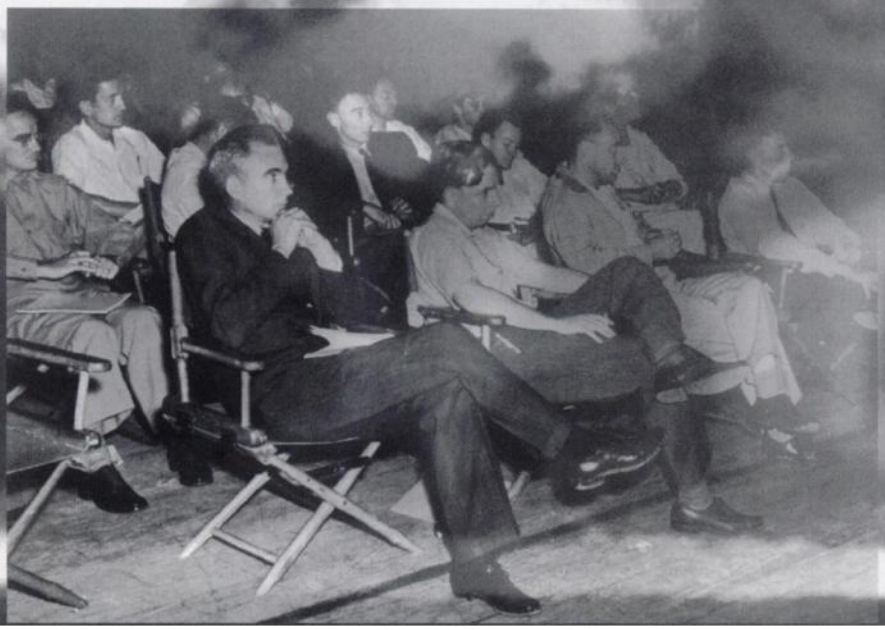
NEWSLINE

Nuclear medicine, as it is applied today, may not have been possible without the advances that stemmed from the development of the atom bomb. Photos clockwise from right: Patient receives a state-of the-art nuclear scan; scientists separating isotopes of three elements for the first time in 1975 in experiments that were part of a laser isotope separation program called JUMPer; mushroom cloud from the Trinity test bomb exploded on July 16, 1945; a weekly brainstorming session at Los Alamos during World War II with Enrico Fermi in the front row, third from left, and J. Robert Oppenheimer in the second row behind Fermi; the drift tube section of LAMPF, the half-mile-long linear accelerator built in 1972 at Los Alamos.









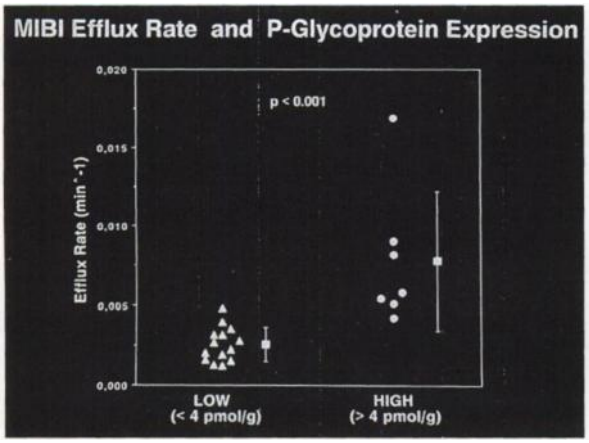


Figure 7. Researchers found the efflux of ^{99m}Tc-sestamibi was related to the degree of p-glycoprotein expression in breast cancers before treatment.

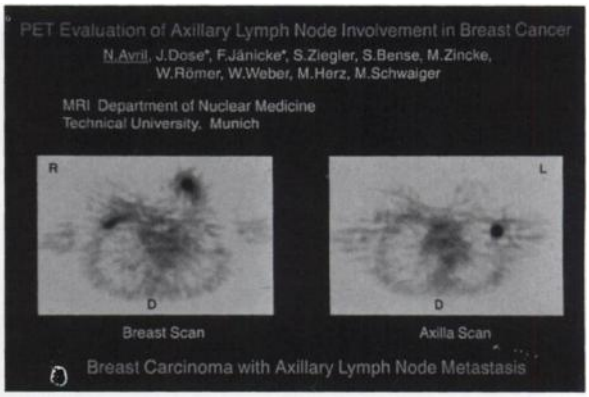


Figure 8. Researchers used ^{18}F FDG to search the axillary lymph nodes for metastases in patients with breast cancer.

Research Highlights

(Continued from page 15N)

in the tumors had a slow efflux rate, while the faster efflux rate characterized the lesions with high p-glycoprotein. The authors postulate that these measurements may help predict which patients will develop multidrug resistance. Groningen in the Netherlands reported results from a study in which ^{11}C verapamil was produced for in vivo studies of MDR.

Axillary Node Involvement

The question often arises about whether surgical exploration of the axilla should be carried out to search for involved lymph nodes in breast cancer patients. The important decision is whether the patient should have adjuvant chemotherapy or more intensive chemotherapy if nodes are known to be involved. Avril and colleagues from the Technical University of Munich in Germany (Abstract #335) searched for axillary lymph node involvement with FDG (**Fig. 8**). The researchers found that axillary exploration is not needed in patients who have macro-axillary metastases since they can be started on intensive chemotherapy. On the other hand, if patients do not have accumulation of FDG in their axillary nodes, axillary exploration is needed. The false-negative rate is too high to permit a negative FDG study to replace surgery for the detection of lymph node involvement.

Although the sensitivity was adequate with higher stage disease, it was not adequate in Stage T1. Taillefer and colleagues from Hotel-Dieu de Montreal, Canada (Abstract #209) used lymphoscintigraphy with ^{99m}Tc-sestamibi to detect macro-metastases in axillary lymph nodes. The results were promising, but not as good as those with FDG in studies by others. On the other hand, scintimammography with ^{99m}Tc-sestamibi studies can eliminate the need for axillary exploration if the patient is shown to have macro-metastases. The positive predictive value of lymphoscintigraphy with sestamibi was 98%, and the negative predictive value was 85% in detecting axillary node involvement.

Some Good News for Smokers

When Fowler and colleagues from Brookhaven National Laboratory used ^{11}C deprenyl, in which deuterium was used to facilitate kinetic analysis (Abstract #520), they observed that some volunteers had very low levels of binding of the ^{11}C deprenyl to the striatum. These volunteers happened to be smokers. Apparently there is something in tobacco smoke (or filters), not nicotine, that has a deprenyl-like effect on the MAO system in the basal ganglia. It is known that smokers have half the incidence of Parkinson's disease than nonsmokers.

Monitoring Treatment

In their study of neurological positron-emitting tracers, Brownell and investigators at MIT addressed the question: Is immunotherapy effective in treating MPTP-induced Parkinson's disease in monkeys who had fetal transplants (Abstract #352)? When no immunotherapy was given to the monkeys, there was very little accumulation of the tracer by the dopamine transporter in presynaptic neurons; when immunotherapy was administered, it brought about a persistent accumulation of the tracer for as long as 9 months after transplantation of fetal cells.

Behavior and Brain Chemistry

Fugita and colleagues from Nagoya, Japan (Abstract #353) found that measuring the accumulation of ß-CIT by the dopamine transporter can be used as an indication of the success of fetal transplantation in rats whose presynaptic neurons had been destroyed by 6-hydroxydopamine which was injected into the substantia nigra. One of the manifestations of Parkinson's disease in this model is that the animals run in circles; the degree of rotation is used as a behavioral indication of the severity of the disease. In this study, even before the ß-CIT accumulation had reached its maximum, the rotations disappeared.

Another positron-emitting tracer for the study of presynaptic dopamine transporters was described by Goodman and colleagues from Emory University in Atlanta (Abstract #150). This tracer had advantages in terms of specificity and affinity compared to ^{11}C WIN 35428 tracer or ß-CIT.

Measuring Endogenous Release of Dopamine

In studying the dopaminergic system, very high affinity tracers, such as ^{11}C N-methyl spiperone or ^{18}F-labeled benperidol, are useful for assessing the status of post-synaptic neurons because endogenous dopamine cannot compete with the high affinity trac-

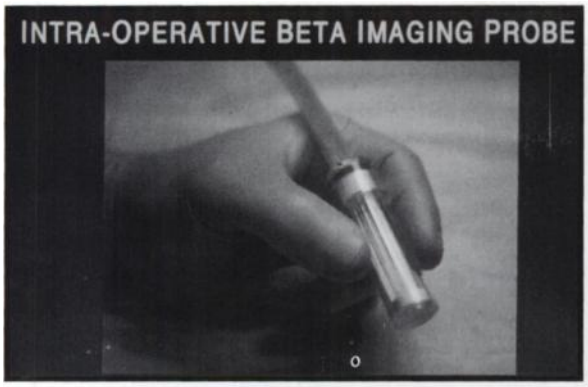


Figure 9. Unlike simpler nonimaging probes, the beta detecting imaging probe is not as dependent on the surgeon to direct it.

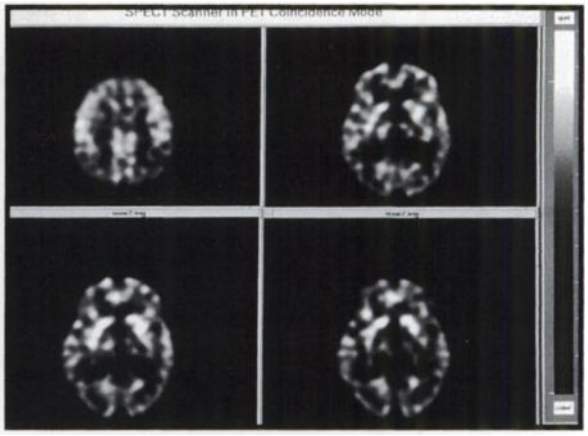


Figure 10. These high-resolution [^{18}F] FDG images of the brain were cited as the "Image of the Year." A "SPECT" scanner was used in a coincidence detection mode.

ers. These tracers, however, cannot be used to assess secretion of endogenous dopamine because of this competitive effect in binding to the dopamine receptors. Moerlein and colleagues from Washington University in St. Louis showed that endogenous release of dopamine, induced by administration of amphetamine, had no effect on ^{11}C benperidol binding (Abstract #34).

On the other hand, when researchers want to assess dopamine release, they must use a tracer with a lower affinity, so that the endogenous dopamine can compete with the tracer. Laruelle and colleagues (Abstract #31) at Yale found a decreased accumulation of ^{123}I iodobenzamide in patients with schizophrenia, which suggests higher dopamine levels in the basal ganglia of patients with schizophrenia compared to normal controls.

Deafferentation or Neuronal Damage?

Sasaki and colleagues at Kyushu University in Japan (Abstract #1070) provided an excellent example of the use of receptor imaging to differentiate deafferentation from neuronal damage. In a patient with thalamic infarction, they found a decrease in cerebral blood flow and FDG accumulation in the ipsilateral cerebral hemisphere. However, they found normal accumulation of ^{123}I iomazanil, a tracer that binds to benzodiazapine receptors, in both cerebral hemispheres, which indicates that the neurons were intact.

Tatsch and colleagues from the University of Munich (Abstract #393) examined the effect of cerebral hypoxia on post-synaptic dopaminergic neurons. In patients after cardiac arrest, they found a significant reduction in the striatum-to-frontal-cortex ratio of ^{123}I iodobenzamide (IBZ) binding when compared to the results in normal controls. They also documented an insignificant decrease in patients who had no or only very minor mental impairment after they had been resuscitated. Patients studied before and after coronary artery bypass grafts (CABG) had a significant reduction in the binding of IBZ to dopamine receptors. The authors attributed this to transient hypoxia associated with bypass.

A study by Singireddy, Mountz and colleagues from the University of Alabama (Abstract #440) used fused images to relate anatomy (MRI) to regional blood flow. In patients with microangiopathy, the white matter defects were clearly seen in the MRI studies, and the regional blood flow defects were visualized in the SPECT images of these patients with dementia.

Biochemistry of Mental Illness

One controversial area of research is the study of persons with criminal behavior in which researchers try to relate the behavior to brain chemical abnormalities. Kuikka and colleagues from Finland (Abstract #121) described both serotonin and dopamine transporter abnormalities in alcoholic patients, some of whom had habitual violent behavior. They reported a decreased uptake of ^{123}I ß-CIT in presynaptic serotonergic neurons in the medial prefrontal cortex in violent alcoholic subjects compared to nonviolent alcoholic subjects.

The importance of careful attention to modeling and quantification in such studies is illustrated by the paper of Petit-Taboue and colleagues from Caen, France (Abstract #523) who examined neocortical serotonin receptors using a single dose of a positron-emitting tracer, ^{18}F-setoperone. They expressed their results as "parametric images" of the K3:K4 kinetic rate constants.

Post-traumatic stress disorder (PTSD) is another behavior disorder in which biological manifestations are being discovered. Fig and colleagues from the University of Michigan (Abstract #345) exposed patients with PTSD to visual stimuli provoking fear, anxiety and other symptoms associated with the disorder. They found the patients had increased activation in certain brain regions including the parahippocampal gyri, left striatum and upper brain stem. Future studies can focus on these regions for detailed regional neurochemical analyses.

In studying cocaine addiction, Villemagne and colleagues from the National Institute of Drug Abuse (NIDA) showed that the neocortex is activated, as indicated by FDG accumulation, when cocaine addicts are presented with paraphernalia associated with taking the drugs, such as syringes, which stimulate their craving for cocaine. The psychological stimuli increased only cortical glucose utilization, whereas the actual administration of cocaine decreased cortical and subcortical activation (Abstract #171).

Mayberg and her colleagues from the University of Texas in San Antonio found significant differences in regional glucose utilization, particularly in the anterior cingulate, in depressed patients who responded to fluoxetine or other MAO inhibitors when compared to those who were nonresponders (Abstract #173).

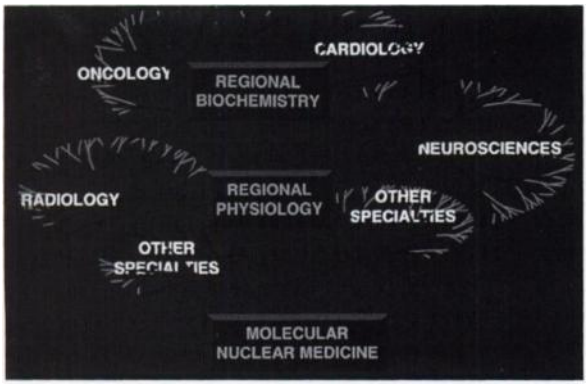


Figure 11. Nuclear medicine rests on an infrastructure of basic sciences, as seen in the tree's trunk, and branches out to other specialities.

Cancer: A Side Effect of Evolution

The process of communication exists even in unicellular organisms, and de-differentiation of the biochemical process within specialized cells can result in cancer. It is becoming increasingly clear that membrane receptors are often expressed in great numbers in cancer cells. Investigators from the Netherlands and Switzerland reported that somatostatin receptor imaging could differentiate between endo- and exocrine pancreatic tumors (Abstract #516). Some cancers express both somatostatin and VIP receptors while others express only VIP.

Many papers presented at the meeting discussed plasma membrane receptors. The next landmark will be the study of intracellular communication systems. The goal is to image mRNA in the cytoplasm and DNA in the nucleus. Fujibayashi and colleagues from Kyoto University in Japan (Abstract #276) produced an oligonucleotide labeled with ^{35}S that would bind to mRNA expressing peripheral benzodiazepine receptors. Using the technique of in situ hybridization, these investigators found that hypoxia-induced brain damage resulted in increased mRNA for these receptors which are known to be increased in glial cells in response to neuronal damage.

The next step is to extend these in vitro results to ex vivo studies in which the experimental animals are injected with this oligonucleotide. Developing single-photon or positron-emitting tracers of mRNA will not be easy because the numbers of binding sites are small and nonspecific binding may be high. Nevertheless, we continue along the pathway, with more and more studies of small peptide molecules (Abstracts #55, 57) and oligonucleotides.

Cost-Effectiveness

While there is clearly an over-capacity in much of the supply of medical care, there is an undercapacity and underutilization of nuclear medicine capacity, which is why the specialty has been called the "best kept secret in medicine." For example, one can substitute the cost of the nuclear medicine studies for surgery costs, which are far greater. One can reduce operative complications by increasing knowledge about the extent of cancer spread.

Nuclear medicine can provide the means to ensure that when patients do have surgery, they will not be found to have lesions that make the surgery fruitless. Over 30,000 thoracotomies are performed every year on patients who are subsequently diagnosed with inoperable lung cancer. About 25,000 thoracotomies are performed in the United States for solitary pulmonary nodules that prove to be benign. Valk and colleagues from Sacramento, CA (Abstract #386) used whole-body PET imaging to examine 237 patients with lung cancer. The scans indicated a change in stage in 26% (19/71) of the patients, with some patients going to a higher and some to a lower stage. Thoracotomy was avoided in 15% (16/104) of the patients with non-small-cell lung cancer.

Gupta and colleagues from the University of West Virginia in Morgantown (Abstract #384) found an accuracy of 92% in predicting whether a lesion was benign or malignant. Sensitivity was 94%, which was sufficiently high to avoid surgery when combined with other data such as the appearance of the lesion in the radiograph, and the clinical history and physical examination of the patient. Shreve and colleagues from the University of Michigan in Ann Arbor (Abstract #6) explored the role of FDG studies in detecting extrathoracic metastases in patients with lung cancer. In 15 of 52 patients, they found one or more foci of abnormal FDG accumulation beyond the lungs and mediastinal structures. In 3 of these 15 patients, the metastases were not detected on bone or CT scans. An important new approach was described by Sengupta and colleagues from UCLA (Abstract #226) in an analysis of the utility and cost effectiveness of FDG studies of patients with unknown primary cancer. Such an approach can now be applied to many other problem areas in oncology.

Tailor-Made Treatment

People are unique individuals and must be cared for as individuals, not according to statistical criteria. For example, at Johns Hopkins when patients are to have a partial hepatectomy for cancer metastatic to the liver, 25% are found at surgery to have inoperable masses. If the surgeon had this information prior to operating, surgery could have been avoided.

Pounds and colleagues from Sacramento, CA (Abstract #229) reported on the cost-effectiveness of FDG imaging in recurrent colorectal cancer. They found imaging studies resulted in major changes in the patient's care in 40% of the 38 patients: surgery was avoided in 20 patients; the type of surgery was changed in 2; partial hepatectomy was avoided in 12 patients; laparotomy in 6; and thoracotomy in 2. The cost of the PET studies was $68,000, and the savings in surgical costs was $350,000. One of the advantages of radiotracer studies in patients with cancer is that whole body imaging can be a routine procedure. For example, in 31 patients with elevated tumor markers, including CEA and CA-125, 53% of the lesions were detected by FDG studies.

About 5000 women are operated upon every year in the United States for a "second look" to see if they have residual ovarian cancer. Hubner and colleagues from the University of Tennessee in Knoxville (Abstract #431) examined such patients with ovarian cancer to find out whether they had metastatic disease. In 47 out of 50, lesions were located with FDG. Three false negatives occurred, which was far more predictive than CT or MRI results in the same patients.

Monoclonal Antibodies

Every year in the United States 50,000 radical prostatectomies are needlessly performed on tumors that are found to have spread beyond the prostate gland. If this had been known prior to surgery, the operation would have been avoided and patients would have received hormonal or chemotherapy instead. Maguire and colleagues from Princeton, New Jersey, (Abstract #29) studied 217 patients who were at high risk of having prostate cancer with ^{111}In labeled capromab pendetide. Of these, 40% had lymph node metastases. The positive predictive value in the MoAB study was 72%, the negative predictive value 76%. Philpott and colleagues from Washington University (Abstract #25) explored the use of ^{64}Cu-labeled monoclonal antibody fragments to detect tumors in patients with colorectal cancer. The results were encouraging and may pave the way for future radioimmunotherapy studies.

Imaging Devices with Limited Field of View

Specialized imaging systems for examining the breast include two being developed at the National Institutes of Health (Abstract #802). Another study proposed a system designed to study the breast and axilla using lutetium ortho-silicate detectors which have a high sensitivity (Abstract #280). **Figure 9** is a beta detecting imaging probe system developed by Tornai and colleagues from UCLA (Abstract #445). The system has an important advantage over simpler detector systems in that it is not as highly dependent on where the probe is directed by the surgeon.

Baum and colleagues from Frankfurt (Abstract #910) reported the use of a hand-held gamma probe to detect somatostatin-receptor-containing tumors at surgery after injection of ^{111}In pentetreotide. Several previously unidentified lesions were detected primarily in the lymph nodes.

Melanoma

Intraoperative detection of involved lymph nodes is a important new area. Kapteijn and colleagues from Amsterdam (Abstracts #997, 999) used a gamma detecting probe to detect the first draining lymph node in patients with localized melanomas. Similarly good results were reported by Essner and colleagues from Santa Monica, CA (Abstract #1000) and by Taylor and colleagues from Emory University in Atlanta, GA (Abstract #1001). The latter group also used lymphoscintigraphy with ^{99m}Tc-sulfur colloid to define the proper surgical approach in patients with clinical Stage I melanoma (Abstract #1002).

Macfarlane and colleagues from the University of Michigan (Abstract #472) used FDG studies to stage the degree of lymph node involvement in patients with cutaneous melanomas. Pounds and colleagues (Abstract #473) found that whole-body FDG imaging to detect metastatic melanoma was more accurate and cost-effective than CT. The FDG study detected 96% of the sites. CT identified only 55%. Brandau and colleagues from the University of Essen in Germany (Abstract #474) reported that ^{123}I IBZ imaging was very promising for detecting metastatic melanoma.

Somatostatin Receptor Imaging

Thirty-three presentations described the use of somatostatin analogs, seven of which involved radionuclide therapy with labeled somatostatin analogs. Bakker and colleagues from Rotterdam, The Netherlands (Abstract #964) reported that ^{90}Y-labeled analogs are preferable to ^{131}I-labeled somatostatin analogs. Webster and colleagues from Julich, Germany and Basel, Switzerland (Abstract #462) compared ^{68}Ga- and ^{86}Y-labeled somatostatin analogs using an ^{18}F-labeled analog as the standard.

Wagner-Manslau and colleagues from Munich (Abstract #165) assessed the somatostatin receptor density in glomus tumors to predict the response to pentetreotide radiotherapy. All tumors that responded showed avid accumulation of the tracer. Pauwels and colleagues from Brussels (Abstract #921) reported similar promising evidence for the use of imaging somatostatin receptor density in predicting the response of pituitary tumors to pentetreotide therapy. The use of ^{90}Y-labeled somatostatin receptor analogs in experimental tumors was described by Stolz et al. from Basel, Switzerland (Abstract #464). The development of a ^{99m}Tc-labeled somatostatin analog to image prostate cancer was described by Thakur and colleagues from Philadelphia and New Orleans (Abstract #374). Reynolds and colleagues from the NIH (Abstract #514) reported that imaging with ^{111}In pentetreotide, a somatostatin analog, was better than CT, MRI or angiography in detecting gastrinomas in patients with Zollinger-Ellison syndrome.

Bone Pain

An important new agent is ^{117m}Sn-DTPA, which was described as having better pharmacokinetics and less bone-marrow suppression than ^{89}Sr (Abstract #118). Resche et al. from Princeton, NJ (Abstract #119) found ^{153}Sm EDTMP helpful in the treatment of painful bone metastases. There was little hematological toxicity, and 70 to 80% of patients experienced pain relief when participating in a multicenter Phase II clinical trial.

Vascular Endothelial Tracers

Advances in the use of tracers that bind to plasma membrane receptors to detect and characterize tumors have been outstanding. This year, another class of receptors were the subject of nuclear oncology research. Kulkarni and colleagues from Dallas (Abstract #279) described the development of labeled analogs of heparin that can bind to vascular endothelial growth factor receptors. These so-called GLYCOS glycoproteins have the advantage of binding to nonsaturable receptors, and their targeting is rapid. Mulholland and colleagues from Indianapolis (Abstract #287) also described their results with a radioiodinated epidermal growth factor receptor ligand to detect epidermal growth factor present in many human cancers, including breast, lung, esophagus, bladder and the oral cavity. Ballinger and colleagues from Ontario (Abstract #288) reported the development of a ^{99m}Tc tracer for the detection of hypoxic regions in tumors.

Certainty in Cardiology

Cardiovasular nuclear medicine studies remain underused. At Johns Hopkins Hospital between January and April of this year, only 3% of the 249 patients who had CABG had prior nuclear medicine studies. The remainder fell into what I call the "anatomical shunt," that is, angiography followed by angioplasty or CABG, a therapeutic course described by some as,"Just say yes."

Weissman and colleagues from the University of Michigan (Abstract #359) studied the cost-effectiveness of performing myocardial perfusion SPECT imaging in patients who came to the emergency department with chest pain. About 80% of the patients were sent home because of negative SPECT studies. A few of them had recurrent chest pain for which they came back to the emergency room, but in most cases there were no further problems. The cost savings from the nuclear medicine studies was $88,000, far more than the cost of performing the studies.

The most interesting cardiology issues presented at the meeting involved the use of high-energy collimators on SPECT systems for FDG studies. A study by Chen and colleagues from the Cleveland Clinic (Abstract #3) compared the results of FDG PET imaging with the use of high-energy collimators. There was a match in the detection of regions of FDG accumulation in 228 patients and a mismatch in 18 patients. The studies with the high-energy collimator correctly identified 90% of the vascular segments that accumulated the tracer. Problems encountered included an attenuation artifact, low-contrast resolution and poor image quality due to a low count rate.

An imaginative study by Sandler and colleagues from Vanderbilt University (Abstract #138) used both ^{99m}Tc-MIBI and FDG with high-energy collimators and found 100% sensitivity and 80% positive predictive value in the detection of viable, in some cases,"hibernating" myocardial lesions. Other important presentations in cardiology included that of Yokoyama and colleagues from the University of Tokyo (Abstract #140) who showed that FDG studies were helpful in predicting the future course of patients with dilated cardiomyopathy. The more heterogeneous the distribution of myocardial glucose utilization, the worse the prognosis. Another study from the same institution (Abstract #144) showed that asymptomatic persons with hypercholesterolemia had reduced coronary flow as measured with [^{13}N] ammonia.

Venous thrombosis was detected with the use of a ^{99m}Tc synthetic peptide, P280, one of six peptides undergoing clinical trials by Pham and colleagues from Habor-UCLA Medical Center (Abstract #361). Dinkelborg and colleagues from Berlin (Abstract #415) reported their progress in developing enothelin derivatives for imaging atherosclerotic plaques. Jamar and colleagues from Hammersmith Hospital in London (Abstract #88) used an ^{111}In-labeled antibody fragment against E-selectin to image endothelial activation in inflammatory disorders.

Image of the Year

Advances continue to be made in both PET and SPECT instrumentation. Kaplan and others from the University of Washington (Abstract #243) exemplified the excellent research in scatter and attenuation corrections in SPECT. Huang and others from the University of Massachusetts (Abstract #156) reported on the use of asymmetrical fan geometry for attenuation corrections by transmission CT on SPECT systems. Kalki and others from the University of California (Abstract #62) built a combined x-ray, CT and SPECT imaging system for animal studies.

Gerd Muehllehner, one of the pioneers of nuclear instrumentation, and his colleagues at the UGM Laboratory, ADAC, and Wadsworth Veterans Administration Hospital in Los Angeles, (Abstract #284) took the collimators off a SPECT scanner and used coincidence detection instead of high-energy photon lead collimation to produce FDG images with doses of 3 mCi of FDG. The spectacular resolution they achieved led me to select their work as Image of the Year **(Fig. 10)**. The spatial resolution of the system that produced this high-resolution image of FDG in the brain is less than 5 mm. It represents an important advance over the use of high-energy collimators with SPECT systems. Most of the PET results seen at this meeting have been made with systems that have poorer spatial resolution.

High Resolution ET

I asked the assembled technologists at this meeting to try to stop using the terms PET and SPECT, replacing these terms with emission tomography (ET), referring to 511 keV ET, 140 keV ET, ^{99m}Tc ET, multienergy ET, as the case may be. Perhaps you will consider doing the same. Five years from now, we may not be referring to SPECT or PET scanners, only ET imagers.

In the domain of ET of both 140 and 500 kev photons using 3/8-inch thick crystals, the depth of interaction of the photon in the crystal becomes important. Pouliot and colleagues from the University of Montreal (Abstract #447) showed that the site of interaction for 511 keV photons is very important in comparison with 122 keV photons.

A whole new concept of high-resolution 140 keV ET is being explored by Eskin, Barrett and Woolfenden at the University of Arizona in Tucson (Abstract #508). The system uses solid-state detectors and multiple-pinhole collimators.

Predicting Response to Treatment

Ryan and colleagues from Guy's Hospital in London (Abstract #97) reported on their use of bone scanning to predict whether injection of steroids into a sacro-iliac facet would relieve pain in the lower back. When the scan was positive, the patients improved; if the scan did not reveal increased tracer accumulation, there was no improvement.

Conclusion

History repeats itself because no one listens the first time. **Figure 11** illustrates the tree of nuclear medicine resting on an infrastructure of basic sciences. The trunk is molecular nuclear medicine, regional physiology and regional biochemistry. Branches go out to specialties, such as cardiology, oncology, radiology and others. For the tree to bear fruit, the trunk must be strong and extend into healthy branches. The difficulty lies not in generating new ideas but in escaping the old ones.

In the past, we defined radioisotope scanning as the visualization of previously invisible organs by means of radioactive tracers—an anatomical orientation. Today, nuclear medicine can be defined as topographic physiological chemistry, resting on an infrastructure of physics, mathematics and communication sciences. This year there were 414 presentations about ^{99m}Tc, 83 about ^{123}I and an almost unbelievable 213 papers about ^{18}F. Nuclear medicine can truly say: "We have seen our atoms."

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