Molecular Medicine: From Science To Service

Henry N. Wagner, Jr., MD presents a view of the scientific highlights of the 38th Annual Meeting of The Society of Nuclear Medicine.

The 1991 Annual Meeting of The Society of Nuclear Medicine was held in Cincinnati, Ohio in June. The following article is derived from a presentation given by Dr. Wagner, professor of medicine, radiology, and environmental health sciences at The Johns Hopkins Medical Institutions, at the final session of the meeting—a tradition now in its 14th year.

Henry N. Wagner, Jr., MD

IN THE DAYS IMMEDIATELY AFTER WORLD WAR II, the use of radioactive materials in medicine was called atomic medicine. Most studies at that time involved radioactive carbon, tritium, iodine, iron and chromium. Atomic medicine became nuclear medicine. Today, the field could be called "molecular medicine," the name justified by the hundreds of radiolabeled molecules that could be used for diagnosis and treatment. More than any other medical specialty, nuclear medicine translates advances in molecular biology and biochemistry into ways of caring for sick human beings.

Diagnostic and therapeutic radiotracers can be thought of as "nanoDx" and "nanoRx" probes. The prefix nano indicates the nanomolar or picomolar sensitivity of the measurements, and the suffixes Dx and Rx indicate that these probes can be used to seek and treat abnormalities within the body. Labeled with therapeutic quantities of radioactivity, the probes can restore abnormal chemistry to normal in specific organs of the body. Injected intravenously, the hundreds of billions of molecular probes search throughout the body until they encounter recognition sites where the molecules' shape, water and fat solubility, and charge lead them to bind. The probes can then be detected and measured by their emitted photon radiation.

Figure 1 is a model of the nanoDx probe called dexetimide that has been used to map out the distribution and quantity of muscarinic acetylcholine receptors (#300). Because dexetimide can be labeled with fluorine-18 (^{18}F) or iodine-123 (^{123}I), muscarinic acetylcholine receptors can be imaged quantitatively by either PET or SPECT. The inactive enantiomer of dexetimide, called levetimide, has all of the properties of the dexetimide molecule except that it does not bind to acetylcholine receptors, and therefore can serve as a control in *in vivo* measurements of acetylcholine receptors (Figure 2).

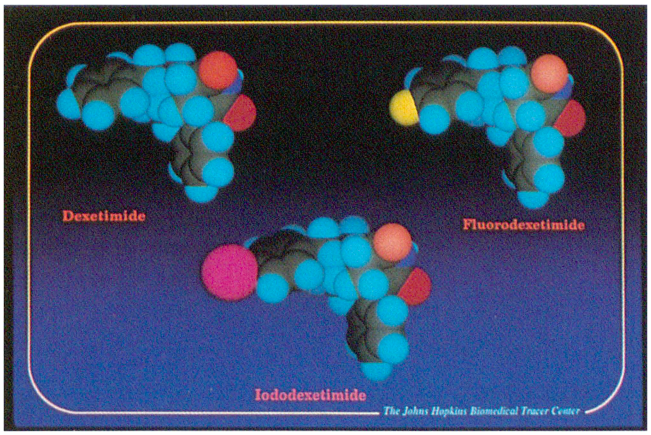

Figure 1.

Molecular medicine can characterize many illnesses by abnormalities in the information-transfer process involving substrate transport, enzymes, and neuron-to-neuron transmission of action potentials. In the process of neurotransmission, electrical depolarization stimulates the secretion of neurotransmitter molecules, such as dopamine, from vesicles at the end of pre-synaptic neurons. These molecular messengers cross the synapse and bind to specific receptor molecules on post-synaptic neurons that recognize them by their configuration and electrical charge. Parkinson's disease and Huntington's disease involve the dopaminergic system, the subject of many presentations at the meeting.

Thirty-six presentations involved dopamine. Some were among the 112 papers or posters that employed radioiodinated compounds. Of these iodine papers, 35 dealt with the development of *in vivo* markers for pre- and post-synaptic neurons. The approval by the Food and Drug Administration (FDA) of ^{123}I-labeled isopropyl amphetamine was an important factor in producing the 22 papers based on the use of this compound. FDA approval of three technetium-99m (^{99m}Tc) compounds brought about a burst of important research, much of it applicable to the development of practice parameters. Forty-eight papers involved HMPAO for the study of regional cerebral blood flow, 31 papers involved ^{99m}Tc-isonitriles for measur-

**The numbers in parentheses refer to abstracts listed in the Proceedings of the 38th Annual Meeting of The Society of Nuclear Medicine.*

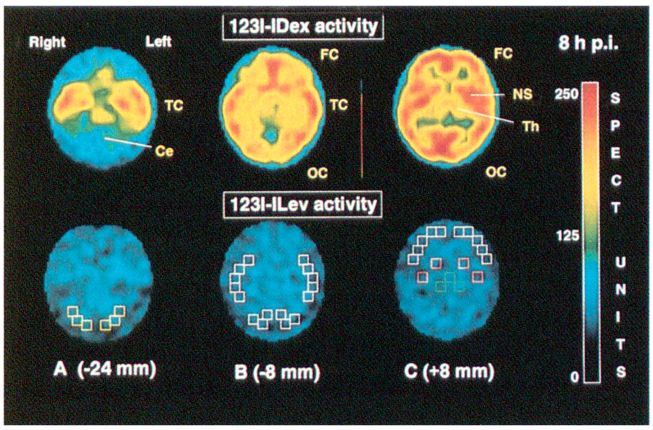

Figure 2.

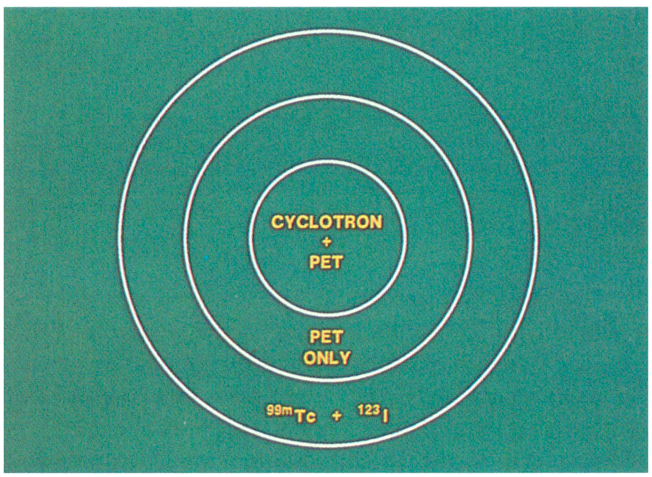

Figure 3.

ing regional myocardial perfusion, and 29 papers involved ^{99m}Tc-teboroxime. At this meeting, held 30 years after the introduction of ^{99m}Tc by Brookhaven National Laboratory (at a time when there was no thought of what it could be used for), 291 of the total number of 843 papers or posters (35%) dealt with ^{99m}Tc compounds.

The progress in the development of ^{123}I and ^{99m}Tc compounds was equaled by advances in the use of the positron-emitting radiotracers carbon-11 (^{11}C) and ^{18}F. Despite the large number of papers concerned with clinical PET, debate continued over whether PET will remain primarily a research tool. These discussions brought to mind the words of Max Planck, who said that "new scientific truth is not usually presented in a way that convinces its opponents. Rather, the opponents gradually die off, and a rising generation becomes familiar with the truth from the start."

Many years ago, a major topic at the annual SNM meeting was whether computers had a role in nuclear medicine. Respected scientists and practitioners debated the issue. Some held that computers were too complicated or too expensive for clinical use and would never be used widely except as research tools. The younger generation takes for granted the use of computers in nuclear medicine—the field that more than any other paved the way to widespread use of computers in medicine. The same thing will happen with cyclotrons and PET scanners. This meeting continued to support the concept illustrated in Figure 3, that PET and SPECT have a parent and child relationship—it is far easier to label molecules with ^{11}C than with ^{123}I or ^{99m}Tc. Nevertheless, PET successes are translated in SPECT applications on an ever-widening scale. The cyclotron and PET will continue as the core of nuclear medicine, with advances extending from the core to hospitals, which will soon be able to purchase positron-emitting radiotracers from regional radiopharmacies. Applications will extend still further through the development of radiotracers labeled with the workhorses of nuclear medicine, ^{99m}Tc and ^{123}I.

Of the 117 presentations involving positrons, ^{18}F was the most widely used radionuclide, and ^{18}F-deoxyglucose was the number one radiolabeled molecule with 75 presentations. Twenty-one ^{18}F presentations involved pre- or post-synaptic neuronal markers. Eighty-four papers involved neuroreceptors and 36 of these dealt with the dopaminergic neurotransmission system—remarkable since the first papers on imaging neuroreceptors were presented as recently as 1984. Twenty-eight papers using ^{11}C-labeled compounds involved the process of synaptic neurotransmission.

Among the highlights were the reports on the dopaminergic system. As shown in Figure 4, the amino acid L-dopa is converted to the neurotransmitter dopamine. When stimulated by appropriate numbers of pre-synaptic axonal action potentials, dopamine is released from vesicles, crosses the synapse, and binds to post-synaptic receptors. Any dopamine that is not bound by post-synaptic receptors is taken back into the pre-synaptic neuron via re-uptake sites where the dopamine molecules are either metabolized by enzymes or re-incorporated into vesicles. Parkinson's disease is characterized by deficiencies in the pre-synaptic dopaminergic neurons. Huntington's disease is characterized by abnormalities in the post-synaptic neurons. Brownell *et al* (#304) developed a model of Huntington's disease in monkeys by injection of quinoline, the glutamate-receptor agonist, into the caudate and putamen. The post-synaptic neurons were impaired, while the pre-synaptic neurons remained metabolically intact.

In another study (#680), the neurotoxin MPTP was used to produce a model of Parkinson's disease, which destroys pre-synaptic neurons. Figures 5 and 6 illustrate the images of pre-synaptic neuronal accumulation of a cocaine analogue that can be imaged by SPECT (Figure 5) and PET (Figure 6). In a baboon where the neurotoxin MPTP was injected into an internal carotid artery, the accumulation of cocaine analogue was eliminated, while the accumulation of ^{11}C-NMSP, a marker of post-synaptic neurons, remained intact. The baboon showed no signs of Parkinson's disease even though the basal ganglia on one side were severely impaired—supporting the concept

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that molecular diagnosis can often precede clinical diagnosis of disease. This important concept makes possible prevention of secondary effects by early molecular diagnosis. Only a limited amount of dopamine is needed to avoid the symptoms and signs of Parkinson's disease, and apparently it need not be distributed bilaterally.

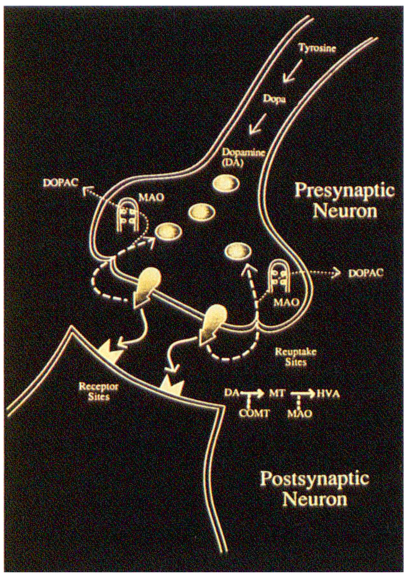

Figure 4.

Because of the 13-hour half-life of ^{123}I, measurements can be carried out for over 20 hours, to a time when essentially all of the tracer is bound to the neurons with very little non-specific binding. This makes it possible to use simple, inexpensive probes to detect the abnormalities of presynaptic neurons. A 24-hour uptake can be measured in a manner analogous to the use of non-imaging probes to diagnose hyper- or hypo-thyroidism. It is predictable that in patients with movement disorders, PET imaging, SPECT imaging, and simple probe systems will be used frequently to make molecular diagnoses at an early stage of disease.

PET and SPECT Advance Together

Despite the many advances in the development and use of ^{123}I tracers, the power of PET will continue, as illustrated in the study by Shiue *et al* from Creighton University in Omaha (#362). Taking advantage of cyclotron-produced ^{11}C, these investigators synthesized a whole series of amphetamine analogues in studies of substance abuse. Their work illustrates that it is not necessary to divide PET centers into research or clinical facilities. The Creighton PET Center was established primarily for clinical service, but the group has made important research contributions in the study of the molecular mechanisms of abused drugs. They showed, for example, that MDMA ("ecstasy") does not block post-synaptic dopaminergic receptors. The best thing that could happen for PET research is that the results be applicable to patient care. The public is vitally interested in studies that help people. If cyclotrons and PET continue their rapid growth, the public can benefit from a continual stream of important, new labeled molecules that will be translated into more widespread application by the use of ^{123}I and SPECT. If one looks back at the annual SNM meetings since 1986, PET studies were followed in steady progression by SPECT studies. Both now account for half of all the nearly 900 papers presented at the 1991 meeting. Stated briefly, if SPECT can do it, do it with SPECT. PET will always be able to do things that SPECT can't do. If SPECT can do tomorrow what PET is doing today, PET will go on to do other things.

Molecules of the Mind

Studies of the brain fall into three major categories: blood flow, metabolism, and neuronal markers. The rapid rise in studies of receptors (84 papers) has been possible because many drugs have been developed that act by binding to receptors. These drugs can usually be labeled with ^{11}C or ^{18}F. The number of studies of brain tumors with PET radiotracers began in 1988, and has increased since then. Over the next 5-10 years, both PET and SPECT are likely to increase in the study of patients with cancer, as in the studies of the heart and brain. Dementia, epilepsy, and stroke were extensively investigated, and drug abuse has become an area of increasing interest. A whole session was devoted to depression. Several studies reported reduced glucose metabolism or blood flow in the frontal cortex of depressed patients. Mayberg *et al* (#717) observed increased binding of ^{11}C carfentanil to opiate receptors in the anterior temporal and inferior frontal lobes of depressed patients. They observed a 31% increase in binding of carfentanil to opiate receptors, suggesting that, as in the case of temporal lobe epilepsy, there may be a relationship between the opiate system and neuronal activity reflected in glucose utilization.

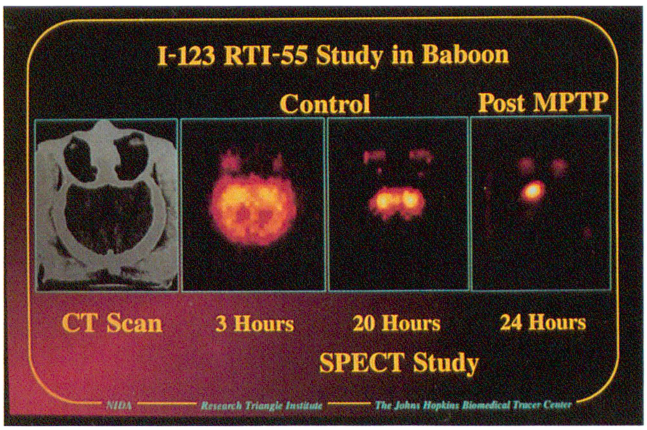

Figure 5.

In the study of regional cerebral blood flow, there were 41 papers using HMPAO, with 21 involving ^{123}I-isopropyl amphetamine. Progress was reported by Devous and his colleagues from the University of Texas Southwestern Medical Center (#266), describing the simultaneous measurement of ^{123}I and ^{99m}Tc radiotracers in studies of the effects of mental stimulation on regional cerebral blood flow. The patient was injected under controlled conditions with ^{123}I-IMP and then with ^{99m}Tc-HMPAO after sensory stimulation or administra-

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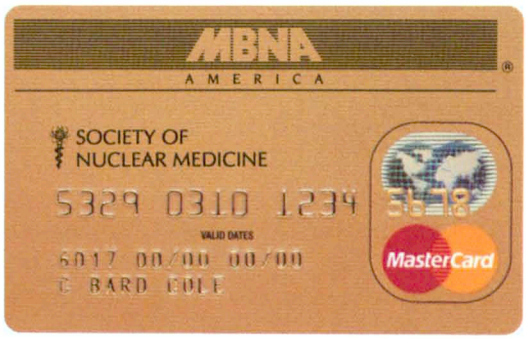

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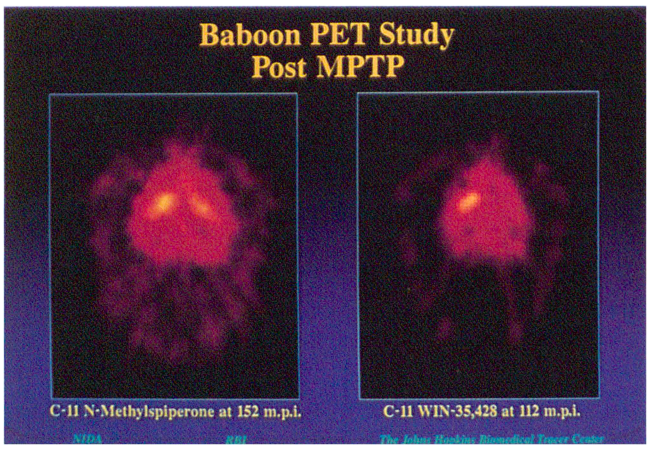

Figure 6.

tion of a drug such as Diamox. Both radionuclides are then imaged simultaneously, which not only halves the examining time, but also eliminates problems of positioning or movement. This dual-isotope method was also validated by Juni *et al* from William Beaumont Hospital in Royal Oak, Michigan (#202), who compared the number of vascular defects seen with IMP with those seen with HMPAO. In a few patients, more defects were seen with IMP.

Nakagawara *et al* from Sapporo, Japan (#697), compared ^{99m}Tc-ECD and ^{123}I-IMP in patients with cerebrovascular disease. Because the extraction efficiency of ECD is lower, this agent was less able to show reactive hyperemia, the so-called "luxury perfusion," in patients with stroke. Regions of increased regional cerebral blood flow were seen with IMP and HMPAO that were not seen with ECD. Podrecka *et al* (#348) showed that, with care, one can get very good reproducibility in serial measurements of HMPAO brain uptake. Several presentations described how stimulating cerebral blood flow with Diamox improves the detection and delineation of lesions (#695, 698, 700, 701).

Activation of the brain by performance tasks was carried out in studies with FDG, oxygen-15 (^{15}O) and, increasingly, with SPECT measurements of regional cerebral blood flow. For example, in a study by Fazio *et al* from Milan and Rome (#479), memory circuits of the brain were mapped out in patients with amnesia using FDG (Figure 7). In comparison with normal persons, the patients had a significant reduction of metabolism in interconnected cerebral regions, including the hippocampal gyri, thalamus, and cingulate cortex, and other cortical structures.

Momose *et al* from Tokyo University (#185) used ^{15}O-water to assess the response of normal and schizophrenic subjects to saccadic and anti-saccadic eye movements stimulated by watching parallel bar lights. The saccade inhibiting system of schizophrenic subjects was impaired, and PET objectively measured the degree of impairment (Figure 8). The same group also showed that activation of the visual cortex by visual stimulation persists for 15 minutes after the eyes have shut. This persistent cerebral activity was not seen in the case of hearing or somatosensory stimulation (#693).

Modeling of SPECT studies of regional cerebral blood flow was illustrated by Tanada and associates from Ehime, Japan (#10). Advantages not only in subjective interpretation, but also in quantification result from the use of high resolution or ultra-high resolution SPECT systems as illustrated in the report of Matsuda *et al* from Kanasawa University Hospital (#724, Figure 9). This paper exemplifies the increasing use of co-registration of anatomical information from MRI with molecular information from PET, and regional blood flow measurements with SPECT. With the ultra-high resolution system one can detect very small changes and by proper co-registration assign them to specific brain structures. Quantification is improved with better spatial resolution because "partial volume" effects are reduced.

An advance in instrumentation was presented by Barrett *et al* from the University of Arizona (#875). Their three-dimensional SPECT imaging system, with the spatial resolution of 5-6 mm, under advanced stages of development, is well suited to dynamic SPECT because the system has no moving parts. The designers have paid particular attention to correcting for attenuation and scatter. Barrett stated that "SPECT quantification has acquired a bad name." That, he says, no longer need be the case.

Cholinergic Neurotransmission

The molecular dissection of a mental disease was illustrated by the studies of the cholinergic system by the group at the University of Michigan under the leadership of David Kuhl, who this year presented an outstanding nuclear pioneer lecture. Lee *et al* (#143) presented parametric images of the brain indicating regional cerebral transport of the radioligand TRB that binds to muscarinic cholinergic post-synaptic receptors. Other images portrayed the distribution volume, which reflects the regional availability of acetylcholine receptors. In patients with Alzheimer's disease, the transport of the tracer to the receptors was reduced in the temporoparietal and other re-

Image of the Year

"So many exciting images have been presented over the past 14 years that it's very difficult to pick out one that represents a striking new development," Dr. Henry Wagner told the audience at his highlights talk in June. The image he chose was a painting, "The False Mirror" by the Belgian artist René Magritte. Over the artist's surreal sky of hovering eyes were superimposed schematic renderings of the molecules dopamine, serotonin, and acetylcholine. "The slide illustrates how molecules that compose external reality can now be imaged by PET and SPECT within the living human brain," says Dr. Wagner. Regrettably, permission to reprint the painting could not be obtained in time for this article.

gions, but the acetylcholine receptors were normal. The same group showed that increases in regional cerebral blood flow associated with visual stimulation in normal persons did not interfere with the measurement of the regional availability of benzodiazapine receptors, which were not affected (#301). These two papers illustrate the robustness of the mathematical modeling used in kinetic analysis of receptors. It was possible to clearly separate the delivery of the tracer to various regions from the receptor density within the regions, even in the presence of great increases or decreases in the delivery of the tracer to the receptors. Separate parametric images showed regional transfer rate constants or receptor availability. Extending the pioneering work of Reba and Eckelman, they found that the post-synaptic receptors are intact in Alzheimer's

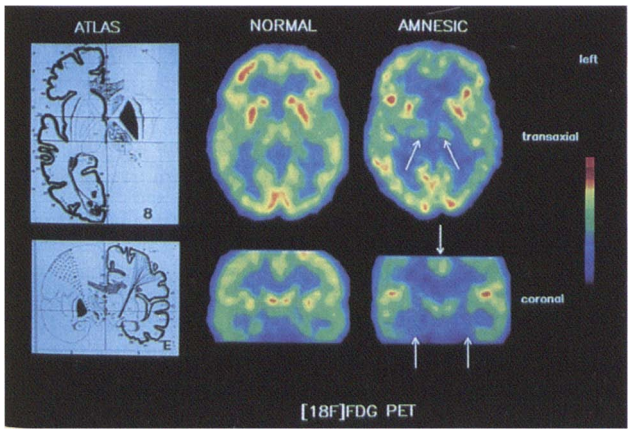

Figure 7.

disease. Perhaps the defects in Alzheimer's disease are in pre-synaptic neurons. This question is likely to be answered at next year's meeting now that pre-synaptic neuronal markers are available and their use validated.

Other Neuroreceptors

Advances in the development of better ligands for examining serotonin receptors were illustrated by Sadzot *et al* from Liege, Belgium, using ^{18}F-altanserine, which was more selective than previously described tracers. Miletich *et al* from the National Institutes of Health and Georgetown University used ^{18}F-fluorothienylcycloexylpiperidine (FTCP) to assess the excitatory amino acid neurotransmission process (#420). Delforge *et al* from Orsay, France presented a model for *in vivo* quantification of D2 dopamine receptors, the most widely studied receptor system to date. This group also found increased striatal dopaminergic D2 receptor density in Rett syndrome measured with ^{123}I-lisuride (#448). Whether D2 dopamine receptors are increased in some patients with schizophrenia remains unclear, but improved modeling and increasing numbers of studies over the next few years are likely soon to provide the answer.

In Parkinson's disease, Tatsch *et al* from the University of Munich (#445) were able to use ^{123}I-iodobenzamide to distinguish the density of dopamine receptors in patients with Parkinson's disease from those patients with variants of the illness, such as progressive supernuclear palsy. In the latter, receptors were impaired, but not in idiopathic Parkinson's disease. These findings are important for treatment. Patients with normal post-synaptic receptors are likely to benefit from treatment with receptor agonists such as bromocryptine, or the administration of the dopamine precursor L-dopa. Those patients with impaired receptors are not.

A study by Bartenstein *et al* from Hammersmith Hospital in Queen Square, London, (#215) represents the first example of being able to assess endogenous secretion of a neurotransmitter by competitive inhibition of the binding of a radiotracer. In patients with petit mal epilepsy, induced by hyperventilation, there seemed to be release of endogenous enkaphalin resulting in a more rapid washout of ^{11}C-diprenorphine from the brainstem and lateral parietal cortex. These studies need to be extended by mathematical modeling to be certain that increased blood flow is not a factor in the observations. Price *et al* (#648) used such modeling and ^{11}C-flumazenil to examine benzodiazepine receptors.

Focus on the Heart

Presentations concerned with the heart have increased steadily since 1985 as a result of the introduction of thallium, SPECT, and more recently, the new technetium blood flow agents. As in the case of studies of the brain, both PET and SPECT papers have increased in parallel, reflecting the synergistic relationship of the two modalities. There were 77 papers on thallium, 30 on isonitriles, 22 on teboroxime, and relatively few on ventricular function.

Nuclear cardiology illustrates how PET and SPECT can make important contributions to the development of practice guidelines, which are now under development as part of programs of "managed care" that are increasing in number in

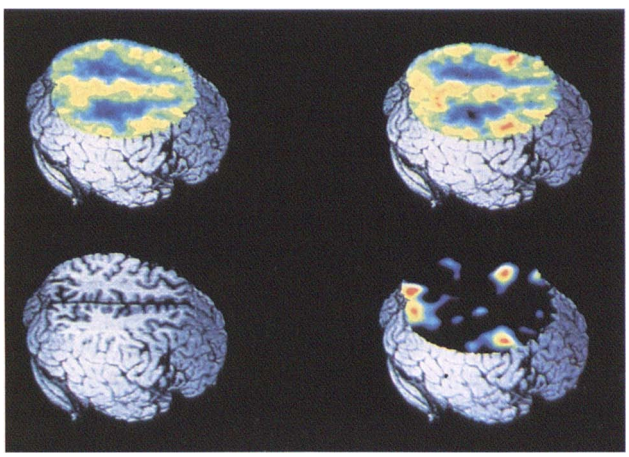

Figure 8.

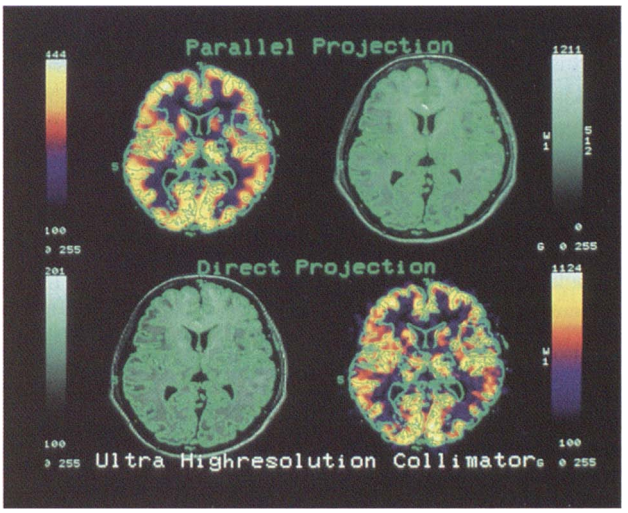

Figure 9.

the United States. Many reports indicated how nuclear cardiology can help predict and assess the effects of revascularization procedures, help avoid needless coronary angiography, and improve the diagnosis of coronary artery disease. With both thallium-201 (^{201}Tl) and ^{99m}Tc-teboroxime, Taillefer *et al* of Montreal (#46) were able to reveal normal regional myocardial blood flow despite the presence of angiographic evidence of coronary stenosis. Presumably, collateral vessels compensated for the stenotic lesions, or the lesions were subcritical. Such findings have the potential for greatly reducing needless revascularization procedures.

Differences among the various myocardial perfusion agents were illustrated by DiRocco *et al* of Bristol-Myers Squibb (#163), who showed that the agents differ in the so-called "roll-off" of tracer activity in regions of high blood flow, as in an exercise study. The extraction rolls off at high blood flow because the extraction efficiency falls. Teboroxime had the least roll off because of its higher extraction. The degree of liver accumulation of the tracer is another difference among myocardial perfusion tracers, as illustrated in the Montreal study (#46). Rapid development of new technetium-labeled myocardial perfusion tracers continues. An important advance in ^{99m}Tc chemistry was described by Duatti *et al* from Italy and France (#69), based on the use of a new class of compounds, the nitritodithiocarbamates. In their studies of different species, the pig was the only animal where this tracer was *not* extracted by the heart, a finding different from that of Deutsch and his colleagues, who found that the pig was the best model with other technetium compounds. Another interesting myocardial perfusion agent was described by Marmion *et al* (#70) from Italy and Cincinnati. The agent had a rapid clearance from the blood, prolonged retention in the heart, and little kidney uptake. Thus, while the presently available ^{99m}Tc tracers represent important advances, there still is room for thallium studies, with improved myocardial perfusion agents just around the corner.

Another advance in nuclear cardiology was simultaneous, double-isotope imaging with ^{201}Tl and ^{99m}Tc. Shimada *et al* from Jikei University, Tokyo, and Shimadzu Corp., Kyoto (#638) used multiple regression analysis to separate ^{201}Tl photon energy from that of ^{99m}Tc. They obtain a complete energy spectrum for each voxel, so that they can record activity voxel by voxel at 64 different photon energies, and then correct for the technetium scatter in the thallium window. They applied the method to the study of the thyroid.

A group from Siemens, working with investigators at Cedars-Sinai Medical Center in California (#388) applied the same principle to the heart. We may soon see studies where thallium is injected at rest and then the patient is exercised and injected with a technetium blood flow agent. Both radionuclides can then be imaged simultaneously. Comparisons with serial studies using only ^{99m}Tc tracers are needed.

Beanlands *et al* from the University of Michigan (#506) evaluated copper-62 (^{62}Cu) PTSM as a myocardial perfusion agent, before and after the administration of adenosine. The goal is to make PET studies possible without a cyclotron by using tracers obtained from a generator. Unfortunately, the

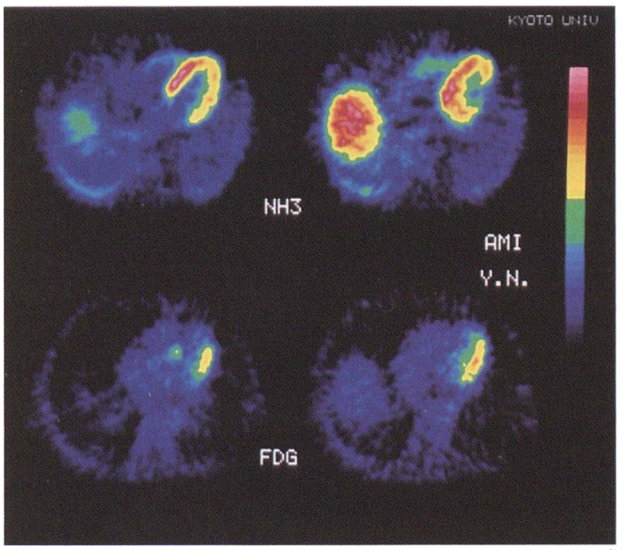

Figure 10.

^{62}Cu parent has a 9-hour half-life, and thus would require regional centers for efficient preparation and distribution. Gallium-68 tracers are also under development—the parent, germanium-68, has a long half-life, and would be a more feasible source for PET tracers.

Of the metabolic studies of the heart, there were 25 papers employing FDG, and 5 involving acetate metabolism. Myocardial viability was a major topic. It is quite possible that a segment of the myocardium may be viable, but not improvable by revascularization. Illustrating the importance of

radiotracer technology in prognosis as well as diagnosis, Tamaki *et al* from Kyoto (#549) looked at the prognostic significance of increased accumulation of FDG in a hypoperfused myocardial region (Figure 10). It has been suggested that glucose utilization indicates that revascularization may be needed. Yet, as seen in Figure 11, the percentage of the patients free from major untoward events, such as sudden death, myocardial infarction, or intractable angina, was far less in patients who had FDG accumulation in hypoperfused areas than in those who didn't, presumably because these patients had milder disease than the others.

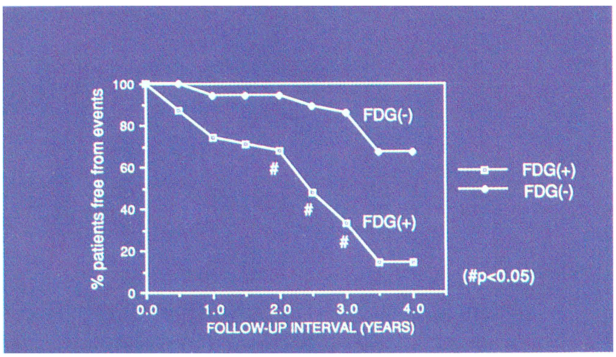

Figure 11. Difference in cardiac event free ratio on patients with and without FDG uptake in the infarcted areas.

Neurocardiology

There were 8 papers on adrenergic receptors. The Michigan group continues to lead in the development of tracers for the study of both the sympathetic and parasympathetic nervous systems of the heart (#556). The innervation of the ischemic heart shows a greater degree of impairment than does the reduction in blood flow, again supporting the concept that has been suggested in the past that the nerves to the heart may be the most sensitive indicator of ischemic damage. Wakasugi *et al* (#509) addressed the question of whether reduced uptake of MIBG by pre-synaptic neurons in cardiomyopathy was an indication that the neurons are damaged, or whether endogenous catechols occupying the receptor compete with the uptake of the radioligand. They examined the accumulation of ^{125}I-labeled MIBG by pre-synaptic neurons after administration of adriamycin for 7 weeks. They showed that there was a great reduction in the accumulation of the MIBG, which was the result of both neuronal damage and adrenal secretion of catechols. This study was an excellent example of dissection of the abnormalities of neurochemistry resulting from toxins.

In the area of preventive medicine, a study by Moerlein *et al* from Washington University (#71) examined the process by which LDL (low-density lipoproteins) or VLDL (very-low-density lipoproteins) are removed by receptors, many of which are in the liver. If the receptors are saturated, the LDL or VLDL continues to circulate and may end up in scavenger cells to form the basis of atheromata. The investigators labeled the very-low-density and low-density lipoproteins with ^{99m}Tc and found that when rabbits were fed with diets high in cholesterol, tracer accumulation in the liver was greatly reduced. The cholesterol impaired the accumulation of LDL by the liver, making it available for accumulation in atheromata. Although they used a scintillation camera, the study could be carried out with probes that could be more widely applied to populations at risk. The study indicates how it is possible to move back into the early stages of a disease when preventive measures can be applied.

Nuclear Oncology

Antibodies continue to dominate nuclear oncology, although many exciting papers involved PET studies of cancer. The use of monoclonal antibodies is becoming routine in studies of patients with colorectal cancer (#133). SPECT is what makes the difference. In a study by Chatal in France (#137) of carcinoma of the ovary, the negative predictive value of immunoscintigraphy was 92%, that is, the studies were 92% accurate in saying that these patients did not have metastatic cancer of the ovaries. Such patients require second-look operations, but if one can be 92% sure that a patient does not have metastatic carcinoma of the ovary, surgery would not be necessary.

With the large number of companies who have applied to the Food and Drug Administration to obtain approval of monoclonal antibodies or fragments, it is only a matter of time before one of these is approved. When that happens, it is likely that many more of these agents will abe available. Exemplifying the value of antibody studies, Berna *et al* from Barcelona (#491) observed striking bone marrow regeneration after hormonal therapy of carcinoma of the prostate using an anti-granulocyte antibody labeled with ^{99m}Tc. Munz *et al* (#608) studied patients with prosthetic or renal carcinoma. The detection of skeletal metastases with the monoclonal antibody directed against granulocytes was more effective than the use of phosphonates in patients with prostatic or renal cancer. Many more lesions were detected with the antibody.

The use phosphonates for monitoring treatment for carcinoma of the prostate hasn't worked well because of the difficulty in distinguishing residual tumor from the healing process. With the anti-granulocyte antibody, the lesions reveal themselves as "cold," while a favorable response to treatment of the lesion is "hot," representing a return of granulocyte precursors. Therefore, the antibodies were more effective in monitoring treatment.

Wahl *et al* (#306, 308) used PET to detect axillary metastases in cancer of the breast and evaluate the response of the patients to chemotherapy. They observed a decrease in metabolism before the tumor shrank. Many tumors have receptors such as steroid receptors in carcinoma of the breast and somastatin receptors in other cancers, including carconoid, glomus tumors, and medullary thyroid carcinoma. Kwekke-

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Thallium Tl 201 is cyclotron produced with no carrier added and contains no less than 98% Thallium Tl 201 as a percentage of total activity with contaminants less than 0.3% Thallium Tl 200, 1.2% Thallium Tl 202, and 0.2% Lead Pb 203 expressed as a percentage of Tl 201 activity at calibration.
It is recommended that Thallous Chloride Tl 201 be administered close to calibration time to minimize the effect of higher levels of radionuclide contaminant.

INDICATIONS AND USAGE: Thallous Chloride Tl 201 may be useful in myocardial perfusion imaging for the diagnosis and localization of myocardial infarction. It may also have prognostic value regarding survival, when used in the clinically stable patient following the onset of symptoms of an acute myocardial infarction, to assess the site and size of the perfusion defect.
Thallous Chloride Tl 201 may also be useful in conjunction with exercise stress testing as an adjunct in the diagnosis of ischemic heart disease (atherosclerotic coronary artery disease).
It is usually not possible to differentiate recent from old myocardial infarction, or to differentiate exactly between recent myocardial infarction and ischemia.
Thallous Chloride Tl 201 is indicated also for the localization of sites of parathyroid hyperactivity in patients with elevated serum calcium and parathyroid hormone levels. It may also be useful in pre-operative screening to localize extrathyroidal and mediastinal sites of parathyroid hyperactivity and for post-surgical reexamination. Thallous Chloride Tl 201 has not been adequately demonstrated to be effective for the localization of normal parathyroid glands.

CONTRAINDICATIONS: None known.

WARNINGS: In studying patients in whom myocardial infarction or ischemia is known or suspected, care should be taken to assure continuous clinical monitoring and treatment in accordance with safe, accepted procedure. Exercise stress testing should be performed only under the supervision of a qualified physician and in a laboratory equipped with appropriate resuscitation and support apparatus.

PRECAUTIONS: Data are not available concerning the effect of marked alterations in blood glucose, insulin, or pH (such as is found in diabetes mellitus) on the quality of Thallous Chloride Tl 201 scans. Attention is directed to the fact that thallium is a potassium analog, and since the transport of potassium is affected by these factors, the possibility exists that the thallium may likewise be affected.

GENERAL: Do not use after the expiration time and date (5 days maximum after calibration time) stated on the label.
Do not use if contents are turbid.
The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.
Thallous Chloride Tl 201, as all radioactive materials, must be handled with care and used with appropriate safety measures to minimize external radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to patients in a manner consistent with proper patient management.
Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to evaluate carcinogenic potential, mutagenic potential, or whether Thallous Chloride Tl 201 affects fertility in males or females.
Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.
Pregnancy Category C: Adequate reproductive studies have not been conducted in animals with Thallous Chloride Tl 201. It is also not known whether Thallous Chloride Tl 201 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Thallous Chloride Tl 201 should not be given to a pregnant woman except when benefits clearly outweigh the potential risks.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, nursing should not be undertaken when a patient is administered radioactive material.
Pediatric Use: Safety and effectiveness in children below the age of 18 have not been established.
Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

ADVERSE REACTIONS: A single adverse reaction to the administration of Thallous Chloride Tl 201 has been reported consisting of hypotension accompanied by pruritus and a diffuse rash which responded to antihistamines and steroids within one hour.

HOW SUPPLIED: Thallous Chloride Tl 201 for intravenous administration is supplied as a sterile, nonpyrogenic solution containing at calibration time 37MBq/ml (1mCi/ml) of Thallous Chloride Tl 201, 9mg/ml sodium chloride, and 9mg/ml of benzyl alcohol. The pH is adjusted with hydrochloric acid and/or sodium hydroxide solution. Vials are available in the following quantities of radioactivity: 81.4, 122.1, 162.8, 244.2, 325.6 and 366.3MBq (2.2, 3.3, 4.4, 6.6, 8.8 and 9.9mCi) of Thallous Chloride Tl 201.
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Prescribing Information ***For Intravenous Injection***

INDICATIONS AND USAGE IV Persantine® (dipyridamole USP) is indicated as an alternative to exercise in thallium myocardial perfusion imaging for the evaluation of coronary artery disease in patients who cannot exercise adequately.

CONTRAINDICATIONS Hypersensitivity to dipyridamole.

WARNINGS Serious adverse reactions associated with the administration of intravenous Persantine® (dipyridamole USP) have included fatal and non-fatal myocardial infarction, ventricular fibrillation, symptomatic ventricular tachycardia, transient cerebral ischemia, and bronchospasm.
In a study of 3911 patients given intravenous Persantine as an adjunct to thallium myocardial perfusion imaging, two types of serious adverse events were reported: 1) four cases of myocardial infarction (0.1%), two fatal (0.05%); and two non-fatal (0.05%); and 2) six cases of severe bronchospasm (0.2%). Although the incidence of these serious adverse events was small (0.3%,10 of 3911), the potential clinical information to be gained through use of intravenous Persantine thallium imaging (see Indications and Usage noting the rate of false positive and false negative results) must be weighed against the risk to the patient. Patients with a history of unstable angina may be at a greater risk for severe myocardial ischemia. Patients with a history of asthma may be at a greater risk for bronchospasm during IV Persantine use.
When thallium myocardial perfusion imaging is performed with intravenous Persantine, parenteral aminophylline should be readily available for relieving adverse events such as bronchospasm or chest pain. Vital signs should be monitored during, and for 10-15 minutes following, the intravenous infusion of Persantine and an electrocardiographic tracing should be obtained using at least one chest lead. Should severe chest pain or bronchospasm occur, parenteral aminophylline may be administered by slow intravenous injection (50-100 mg over 30-60 seconds) in doses ranging from 50 to 250 mg. In the case of severe hypotension, the patient should be placed in a supine position with the head tilted down if necessary, before administration of parenteral aminophylline. If 250 mg of aminophylline does not relieve chest pain symptoms within a few minutes, sublingual nitroglycerin may be administered. If chest pain continues despite use of aminophylline and nitroglycerin, the possibility of myocardial infarction should be considered. If the clinical condition of a patient with an adverse event permits a one minute delay in the administration of parenteral aminophylline, thallium-201 may be injected and allowed to circulate for one minute before the injection of aminophylline. This will allow initial thallium perfusion imaging to be performed before reversal of the pharmacologic effects of Persantine on the coronary circulation.

PRECAUTIONS See WARNINGS
Drug Interactions Oral maintenance theophylline may abolish the coronary vasodilatation induced by intravenous Persantine® (dipyridamole USP) administration. This could lead to a false negative thallium imaging result.
Carcinogenesis, Mutagenesis, Impairment of Fertility In studies in which dipyridamole was administered in the feed at doses of up to 75 mg/kg/day (9.4 times* the maximum recommended daily human oral dose) in mice (up to 128 weeks in males and up to 142 weeks in females) and rats (up to 111 weeks in males and females) there was no evidence of drug related carcinogenesis. Mutagenicity tests of dipyridamole with bacterial and mammalian cell systems were negative. There was no evidence of impaired fertility when dipyridamole was administered to male and female rats at oral doses up to 500 mg/kg/day (63 times* the maximum recommended daily human oral dose). A significant reduction in number of corpora lutea with consequent reduction in implantations and live fetuses was, however, observed at 1250 mg/kg/day.
*Calculation based on assumed body weight of 50 kg
Pregnancy Category B Reproduction studies performed in mice and rats at daily oral doses of up to 125 mg/kg (15.6 times* the maximum recommended daily human oral dose) and in rabbits at daily oral doses of up to 20 mg/kg (2.5 times* the maximum recommended daily human oral dose) have revealed no evidence of impaired embryonic development due to dipyridamole. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.
*Calculation based on assumed body weight of 50 kg
Nursing Mothers Dipyridamole is excreted in human milk.
Pediatric Use Safety and effectiveness in children have not been established.

ADVERSE REACTIONS Adverse reaction information concerning intravenous Persantine® (dipyridamole USP) is derived from a study of 3911 patients in which intravenous Persantine was used as an adjunct to thallium myocardial perfusion imaging and from spontaneous reports of adverse reactions and the published literature.
Serious adverse events (fatal and non-fatal myocardial infarction, severe ventricular arrhythmias, and serious CNS abnormalities) are described above (see WARNINGS).
In the study of 3911 patients, the most frequent adverse reactions were: chest pain/angina pectoris (19.7%), electrocardiographic changes (most commonly ST-T changes) (15.9%), headache (12.2%), and dizziness (11.8%).
Adverse reactions occurring in greater than 1% of the patients in the study are chest pain/angina pectoris (19.7%), headache (12.2%), dizziness (11.8%), electrocardiographic abnormalities/ST-T changes (7.5%), electrocardiographic abnormalities/extrasystoles (5.2%), hypotension (4.6%), nausea (4.6%), flushing (3.4%), electrocardiographic abnormalities/tachycardia (3.2%), dyspnea (2.6%), pain unspecified (2.6%), blood pressure lability (1.6%), hypertension (1.5%), paresthesia (1.3%), fatigue (1.2%).
Less common adverse reactions occurring in 1% or less of the patients within the study included:
Cardiovascular System: Electrocardiographic abnormalities unspecified (0.8%), arrhythmia unspecified (0.6%), palpitation (0.3%), ventricular tachycardia (0.2% see WARNINGS), bradycardia (0.2%), myocardial infarction (0.1% see WARNINGS), AV block (0.1%), syncope (0.1%), orthostatic hypotension (0.1%), atrial fibrillation (0.1%), supraventricular tachycardia (0.1%), ventricular arrhythmia unspecified (0.03% see WARNINGS), heart block unspecified (0.03%), cardiomyopathy (0.03%), edema (0.03%).
Central and Peripheral Nervous System: Hypothesia (0.5%), hypertonia (0.3%), nervousness/anxiety (0.2%), tremor (0.1%), abnormal coordination (0.03%), somnolence (0.03%), dysphonia (0.03%), migraine (0.03%), vertigo (0.03%).
Gastrointestinal System: Dyspepsia (1.0%), dry mouth (0.8%), abdominal pain (0.7%), flatulence (0.6%), vomiting (0.4%), eructation (0.1%), dysphagia (0.03%), tenesmus (0.03%), appetite increased (0.03%).
Respiratory System: Pharyngitis (0.3%), bronchospasm (0.2% see WARNINGS), hyperventilation (0.1%), rhinitis (0.1%), coughing (0.03%), pleural pain (0.03%).
Other: Myalgia (0.9%), back pain (0.6%), injection site reaction unspecified (0.4%), diaphoresis (0.4%), asthenia (0.3%), malaise (0.3%), arthralgia (0.3%), injection site pain (0.1%), rigor (0.1%), earache (0.1%), tinnitus (0.1%), vision abnormalities unspecified (0.1%), dysgeusia (0.1%), thirst (0.03%), depersonalization (0.03%), eye pain (0.03%), renal pain (0.03%), perineal pain (0.03%), breast pain (0.03%), intermittent claudication (0.03%), leg cramping (0.03%).
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boom *et al* (#305) from Rotterdam and Berne used indium-111 (^{111}I) octeotide, an analogue of somatostatin, to image tumors containing somatostatin receptors. They proposed that such agents have therapeutic as well as diagnostic potential.

The search continues for a ^{99m}Tc receptor-binding ligand for tumors. DiZio *et al* from Missouri (#68) used rhenium as an analog for technetium in the development of a labeled progesterone tracer for detecting carcinoma of the breast. Rhenium-188 (^{188}Re) reported by the Oak Ridge group (#155) can be used for both diagnosis and therapy. It emits a 155 KeV gamma 15% of the time, and can be obtained from a parent with a 69-day half-life, so it would be readily available both as an antibody label and as a therapeutic agent. Pappata *et al* (#716) from Orsay, France looked for peripheral benzodiazopine receptors on gliomas and found that the tracer PK 11195 labelled with ^{11}C accumulated in some but not all glial tumors. The tracer was displaceable, indicating that it was binding to the receptors when these were present.

Many studies showed how both PET and SPECT can help distinguish radiation necrosis from persistent or recurrent tumor (#38). Tonami *et al* from Kanasawa, Japan, (#222) showed that preoperative assessment of mediastinal involvement of the lung, using ^{201}Tl, was 84% accurate. Peter Bent of Brigham Hospital indicated that SPECT can distinguish radiation therapy effects from recurrent gliomas, based on the use of combined ^{201}Tl and HMPAO imaging (#101). The researchers found there was a good separation of patients with recurrent tumor from patients with radiation changes. Another study, however, by McKusick and colleagues concluded that thallium is *not* a reliable predictor of recurrent brain tumor (#194). In my opinion, no single type of study should be expected to be perfect. Glucose utilization by brain tumors is at times confounded by the fact that the normal brain consumes glucose. Thallium may not be taken up by some tumors. Both studies should be available and used in the light of the patient's specific problem.

Infections

Thirty-one papers concerned infection, illustrating an area where nuclear medicine is making strides. A study from the Mayo Clinic (#397) showed the value of indium-labeled leukocytes in detecting osteomyelitis in diabetic patients, a difficult problem. The investigators found that indium-labeled white blood cells were more accurate than technetium-labeled phosphonates. A large series of patients with infections studied with antigranulocyte antibody indicated the value of this approach (#393, 394, 395). One could get a more accurate picture of the extent of infection than with phosphonate bone scans. The sensitivity and specificity in the detection of suspected osteomyelitis was improved by kinetic analysis. In a series of patients with bacterial endocarditis, the combination of ECHO with antigranulocyte antibody-imaging was very effective. Another common disease effectively studied with monoclonal antigranulocyte antibodies was acute appendicitis (#595).

Practice Parameters and Managed Care

The costs of diagnostic and therapeutic medicine are undergoing close scrutiny, rather than the costs of one diagnostic test compared to another. In December, 1989, an act was passed by the U.S. Congress that created the Agency for Health Care Policy and Research. With a first-year budget of $160,000,000, the agency's goal is to enhance the quality and establish the effectiveness of health care services by considering diseases, such as myocardial infarction, or cataract, or diabetes, and assessing how patients should be cared for, and how decisions should be made. The agency will try to determine what works, how treatment should be planned and monitored, and how we can determine whether the patients have improved, by how much, and at what cost.

Naomi Alazraki, MD, has taken a step forward in establishing a group within The Society of Nuclear Medicine that will examine how nuclear medicine technology can increase the cost-effectiveness of medical practice parameters. This meeting demonstrates the important contributions that nuclear medicine can make. Cost effectiveness will be assessed in terms of whether we can exchange imaging costs with surgery costs, as well as by our ability to reduce operative complications through better selection of patients.

A study from the University of Pittsburg (#383) showed how complications after liver transplantation could be detected by mebrofenin hepatobiliary imaging. At this meeting 11% of all the papers presented had to do with monitoring treatment. No other field has the techniques that can monitor treatment the way that nuclear medicine can. Some 25 papers were concerned with the monitoring of cancer treatment, 19 with neuropsychiatry treatment. In a complicated and expensive operation such as a liver transplant, where the costs are in the hundreds of thousands of dollars per patient, simple measurements can detect complications at the earliest stages. A study from Guys Hospital (#18) in patients with a very common disease, chronic low back pain, indicated a lesion in 60% of the 70 patients. Such studies may help separate patients who have muscle spasms from patients to have lesions that should be further investigated. Another example of how nuclear medicine can improve medical practice was a study from Germany that took a quantitative look at patients with bone fractures (#21, 22). What better way to monitor the response of the patient to treatment than to study various physiological processes such as hyperemia, new bone growth, and disuse osteoporosis.

In summary, the meeting documented the spectacular growth in the science and clinical applications of nuclear medicine. It truly has become molecular medicine.

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