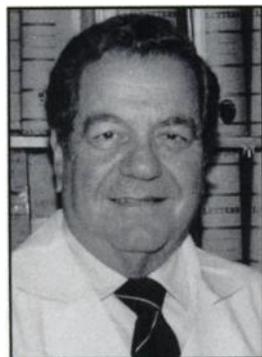


ANNUAL MEETING HIGHLIGHTS: MOLECULES WITH MESSAGES

The Society of Nuclear Medicine held its 39th Annual Meeting in Los Angeles, California in June. For the fifteenth consecutive year, Henry N. Wagner, Jr., MD, professor of medicine, radiology, and environmental health sciences at The Johns Hopkins Medical Institutions, presented his view of the scientific highlights at the final session of the meeting.

ECONOMIST JOHN MAYNARD KEYNES SAID "the difficulty lies not in new ideas but in escaping the old ones." One of the oldest ideas in medicine is



Henry N. Wagner, Jr. MD

that medical specialties should be based on individual organs, an emphasis on anatomy that originated with Vesalius centuries ago. An organ-based specialization in medicine leaves the problem of what to do not only with nuclear medicine, but also with genetics, molecular biology, oncology, metabolic diseases, and infectious diseases. Nuclear medicine goes far beyond anatomy into the domains of physiology and biochemistry.

An example of the new molecular nuclear medicine is the patient of Fulham who complained of headaches and impotence that persisted after radiation therapy (#38)*. A lesion in his brain revealed by MRI was found to be hypometabolic when examined by PET studies with fluorine-18 deoxyglucose. His pituitary gland was hypermetabolic, indicating the presence of a tumor. The binding of carbon-11 methyl spiperone by such a pituitary tumor indicates that the tumor contains dopamine receptors and can be treated with bromocriptine, a drug that stimulates dopamine receptors. Activation of the dopaminergic system by bromocriptine inhibits the growth of the prolactin-secreting cells of the pituitary tumor. The beneficial effect of the bromocriptine therapy can be demonstrated on the first day of treatment by documenting that the drug inhibits the accumulation of radiolabeled glucose, amino acids, or thymidine by the tumor. Molecular messages can characterize a lesion, aid in the planning of treatment, and determine whether or not the treatment has been effective. This approach goes far beyond relying solely on clinical manifestations or anatomical changes which may take weeks

**The numbers in parentheses refer to abstracts listed in the Proceedings of the 39th Annual Meeting of The Society of Nuclear Medicine.*

or months before they occur.

The primary molecular message controlling each cell of the body is contained in messenger RNA (mRNA), which can be examined in vitro by in situ hybridization. The hundred thousand genes of the body contain 3 billion units of the four base nucleotides that encode the messages which direct the synthesis of polypeptides and proteins. Dewanjee and colleagues from the University of Miami developed an indium-111 chelate to label mRNA (#656). They labeled an "anti-sense" oligonucleotide that blocks the synthesis of the protein histone. The anti-sense oligonucleotide was produced by genetic engineering. This pioneering approach to labeling mRNA can eventually be applied to the cells of various organs and blood components in the living body. Such radiotracers would in theory be extremely specific in characterizing molecular disease. When Dewanjee and colleagues injected the radio-labeled oligonucleotide, they observed that it bound to circulating leukocytes.

Peptide Messengers

The fifty peptide messengers that have been identified over the past several decades are an important new frontier for nuclear medicine. Somatostatin is a peptide isolated in the mid-1970s that binds to specific receptors and suppresses cell division. Because of advances in genetic engineering, such peptides can be made in large quantities and their detailed structure can be characterized by x-ray crystallography. The Sandoz Research Institute and scientists at the University of Rotterdam labeled a somatostatin analogue called octreotide with a chelate incorporating ¹¹¹In or iodine-123 (#294, 333, 378, 379, 639, 548). The labeled molecule has the right shape, wetness and charge to "bump, fit and stick" to somatostatin receptors. When this process occurs, a chain of chemical reactions signals the cells containing the receptors to stop dividing.

Drug Design and Development

Three approaches to drug development are pharmacological, biochemical and genetic. The genetic approach is to determine the detailed structure, charge, and hydrophobic/hydrophilic properties that effect the "fitting and sticking" of the messenger molecules to recognition sites. Krenning and colleagues described hundreds of patients with neuroendocrine and other types of cancer, including cancer of the breast, characterized by presence of somatostatin receptors in measurable quantities (#333, 378). Activated T-lymphocytes also have been found to possess somatostatin receptors. In neoplasms containing somatostatin receptors, naturally-occurring somatostatin may be deficient and the increase in receptors

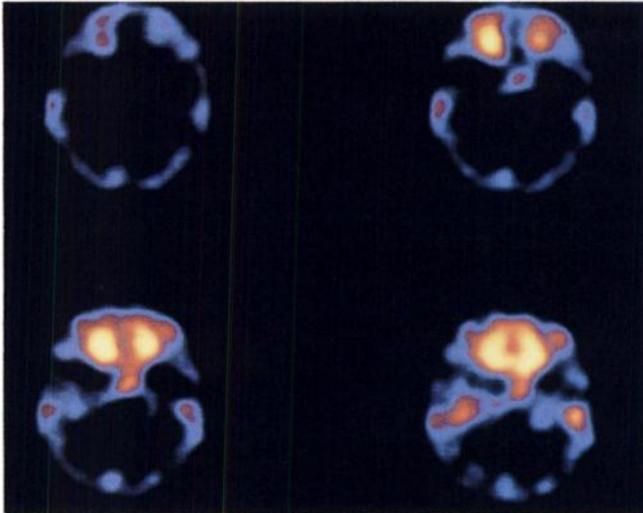


Figure 1. Accumulation of indium-111 octreotide by the lymphocytes behind the orbits in a patient with Graves' exophthalmopathy.

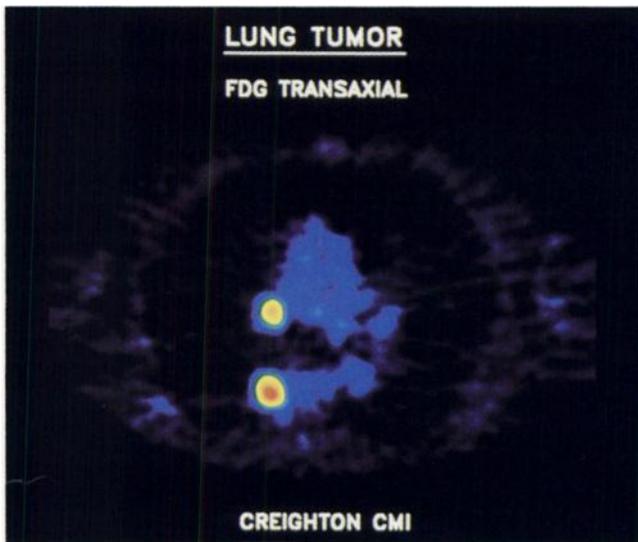


Figure 2.

a manifestation of a compensatory "up-regulation" of the receptors. Krenning pointed out that in carcinoid, a gastrointestinal neuroendocrine tumor, most of the tumors contain somatostatin receptors (#378). Patients with lymphoma, both non-Hodgkin's and Hodgkin's disease, were found to have lesions detectable by their accumulation of the ^{111}In octreotide (#333). T-lymphocytes themselves could be labeled with a technetium complex, which can be used as a universal label for cell-tracking (#404).

Image of the Year

In the autoimmune diseases, hyperthyroidism and Grave's ophthalmopathy, Krenning and colleagues described their finding of a very avid accumulation of ^{111}In labeled octreotide in the tissue surrounding the eyes (#294). The degree of

accumulation of the tracer was related to the symptoms and degree of exophthalmopathy. The more active the disease clinically, the greater the accumulation of the tracer, presumably because of the increased infiltration of T-lymphocytes. If the disease is active, it can be treated successfully with immunosuppressive therapy, while if the exophthalmopathy is caused by retro-orbital fibrosis, surgery may be necessary. Octreotide, a SPECT radiotracer, joins carfentanyl, the PET radiotracer used to examine opiate receptors, for the study of peptide receptors.

Because octreotide exemplifies how characterization of disease on the basis of in vivo biochemistry can provide the basis for planning and monitoring treatment, I have selected the octreotide imaging of the retro-orbital in patients with hyperthyroidism as the image of the year (Figure 1).

Focus on Oncology

While the most impressive radiotracer of the meeting was ^{111}In octreotide, oncology was the most impressive field. PET imaging of deoxyglucose can be used in the differential diagnosis of solitary pulmonary nodules (#47). With CT one cannot detect nodules that are smaller than 1 cm, or that are buried in the mediastinum. Figure 2 is an example of a peripheral and a mediastinal metastatic lesion in a patient with cancer of the lung. In the differential diagnosis of solitary pulmonary nodules, there was good separation of benign from malignant nodules, in both well differentiated or poorly differentiated lesions.

In the study by Knopp and others (#13), the staging of the patients with mediastinal lymph node disease was changed as a result of the ^{18}F deoxyglucose study in nearly forty percent of the patients. Patients who were thought to be operable on the basis of anatomical imaging with CT were found to be inoperable with PET. Thus, they were spared the morbidity of surgery, as well as the great expense of what would have been fruitless efforts to cure them by surgery. The patients could be treated immediately with chemotherapy, and the response to treatment assessed immediately by its biochemical effect on the lesions.

Anatomical localization by PET of the most metabolically active foci within cancerous lesions improved the accuracy of stereotactic biopsy, which was important in determining the operability of lesions (#12). At UCLA, whole-body FDG imaging of cancer patients is quantified using the graphic or Patlak method of analysis (#14). Quantification methods for PET are now simple enough for clinical use. The same care and attention to acquisition and quantification must now be given to SPECT. Investigators from North Shore Hospital described a fully quantitative method to measure the input of a tracer into the brain from the circulating blood without arterial sampling (#41). The results obtained by their method correlated well with those obtained using continuous arterial blood sampling. Simplification of the imaging procedures plus the addition of positron-emitting tracers to the product line

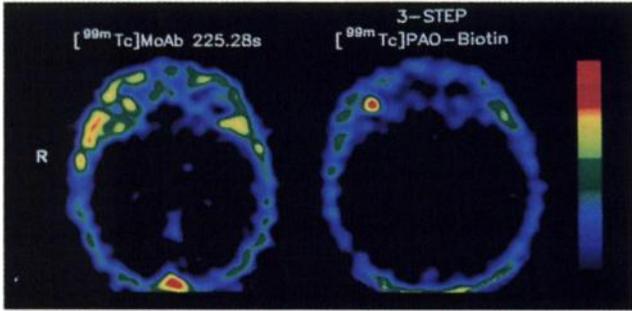


Figure 3. An ocular melanoma visualized by biotin/avidin monoclonal antibody pretargeting, compared to the use of a single antibody.

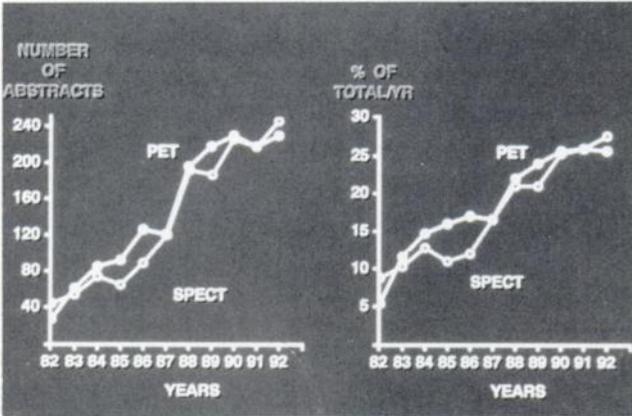


Figure 4. The parallel advance of PET and SPECT over the past decade, as indicated by the numbers of presentations at the annual SNM meeting.

is providing great impetus to the growth of clinical PET.

The New Nuclear Medicine

Nuclear medicine does not just provide new tests for old diseases, but new ways of defining disease. Nuclear medicine characterizes patient's problems in regional biochemical terms. It answers questions such as whether a lesion is metabolically active, or whether it contains certain recognition sites as markers of disease. In a patient with a breast tumor, the question is whether the lesion contains somatostatin or estrogen receptors, and, if so, how the tumor will respond to the administration of a growth suppressor substance, somatostatin, or to the estrogen receptor antagonist, tamoxifen. The planning of treatment and assessment of the response to treatment is based on regional biochemistry.

Goldman and colleagues from Brussels presented their results using FDG to make possible more accurate stereotaxic biopsy of brain tumors (#183). Using fiducial markers for exact alignment of CT and PET, stereotaxic biopsy was directed to the most hypermetabolic region of a tumor. Particularly in the case of grade 3 astrocytomas, the histopathological findings are heterogeneous, and a single biopsy directed only

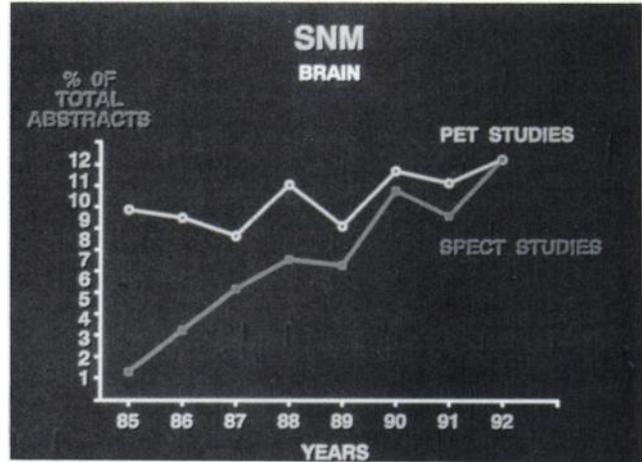


Figure 5. The increase in the number of SPECT presentations at the SNM meeting have followed PET studies of the brain.

CARBON-11 COMPOUNDS		
	1991	1992
PRE OR POSTSYNAPTIC NEURONAL MARKERS	28	40
DOPAMINERGIC	9	18
ADRENERGIC	5	3
CHOLINERGIC	4	4
BENZODIAZEPINE	4	7
OPIATE	3	1
HISTAMINERGIC	2	2
SIGMA	1	0
SEROTONERGIC		3
MONOAMINERGIC		2
DEOXYGLUCOSE		2
AMINO ACID		1
CARBON MONOXIDE		1
DNA SYNTHESIS		1
C-11 ACETATE	5	5
FATTY ACID	1	0
CEREBRAL BLOOD FLOW	1	0
SECOND MESSENGER	1	1
TOTAL	36	61

FLUORINE COMPOUNDS		
	1991	1992
FLUORODEOXYGLUCOSE	76	90
PRE OR POSTSYNAPTIC NEURONAL MARKERS	21	28
DOPAMINERGIC	17	21
BENZODIAZEPINE	1	3
SEROTONERGIC	1	1
CHOLINERGIC	1	2
GLUTAMATE	1	0
SIGMA RECEPTOR		1
STEROIDS	4	1
MISONIDAZOLE ANALOGUES	3	2
ANTIBODIES	3	0
BIOTIN		1
FATTY ACIDS	2	0
FLUOROMETHANE	1	0
ANTIFUNGAL AGENT	1	2
ANESTHETICS	1	0
DNA SYNTHESIS		1
TOTAL	111	125

Figure 6.

by means of CT or MRI may not reveal the true degree of malignancy. Regional chemical assessment makes it possible to sample the most malignant site. Far greater accuracy in staging disease and planning treatment is possible by proper

A5Q = CP + PT + MT
= characterizing patient +
planning treatment +
monitoring treatment

Figure 7.

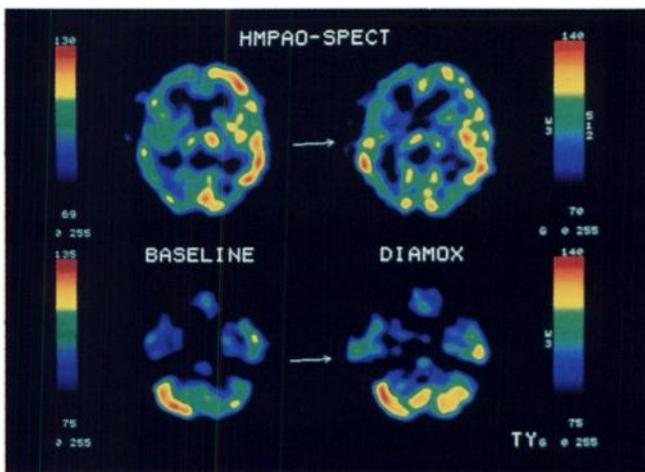


Figure 8. Decreased blood flow to the thalamus and contralateral cerebellum increased by the administration of diamox. There was no associated increase in glucose utilization.

selection of the biopsy site.

Oncology has joined epilepsy and heart disease as a focus of clinical PET. To meet the demand for the increasing number of FDG studies, Hughey and colleagues from Massachusetts have developed a new type of windowless target that produces ^{18}F from very small amounts of enriched oxygen-18 water, which at the present time is in short supply (#453).

Of the 180 oncology papers, a large number involved thallium-201. There was good differentiation of recurrence of brain tumor from radiation necrosis (#83). Imaging with ^{201}Tl also correlated with whether a tumor was a meningioma, transitional, fibroblastic, or malignant brain tumor (#616). In the detection of parathyroid adenomas, the overall accuracy of CT in the detection of parathyroid adenomas was 70%, ultrasound 65%, thallium 83%, and MIBI 96% (#297). The detection and localization of parathyroid adenomas decreases the morbidity and cost of surgical removal of these lesions. Linkage of nuclear medicine procedures to surgical decision making illustrates the value of advanced technology in providing information that optimizes patient care and reduces expenses.

Another example is the diagnosis of thymoma in patients

with myasthenia gravis. Tonami and colleagues from Kanazawa University detected false-positive x-ray CT diagnoses of thymoma by using ^{201}Tl imaging. Operation was avoided when ^{201}Tl imaging failed to reveal a tumor.

In patients with aldosteronism, Ishimura and colleagues from Hyogo College of Medicine used SPECT after administration of ^{131}I NP59 to differentiate patients with essential hypertension from those with primary aldosteronism and to localize the lesions (#37).

Monoclonal Antibodies

Eleven papers involved the use of a combination of biotin and avidin in monoclonal antibody studies. One of the problems in the use of monoclonal antibodies is a binding site barrier (#288), that is, the antibodies bind to blood vessels entering the tumor—a problem accentuated when low doses of antibody are administered. According to Juweid and colleagues from the NIH, the binding site barrier can be overcome if high doses of monoclonal antibody doses are given. Paganelli and colleagues from Basel and Milan administered biotin complexed to antibody in non-radioactive form (#565). They then allowed 24 hours for the binding of the antibody to the tumor to occur and the blood level to fall to low values. Then they administered avidin which bound selectively to the biotin attached to the antibody. The third step was to administer radiolabeled biotin-antibody complex which then binds to the avidin. This approach helps overcome the problem of the vascular barrier, and other problems of non-specific binding. In a patient with an ocular melanoma, the non-specific binding was greatly reduced by the three-step procedure (Figure 3).

PET Versus SPECT

If one examines the number of PET and SPECT papers over the past decade, one can see that the two modalities have been advancing together. In 1991 and 1992, PET and SPECT studies accounted for half of all the papers presented at the meeting. The concept that PET advances are extended by SPECT continues to be valid (Figures 4 and 5).

Advances in cyclotron chemistry are based on ^{11}C and ^{18}F , and are then extended via ^{123}I and technetium-99m into the domain of SPECT. Some important advances originate with SPECT tracers, as was the case of ^{111}In octreotide. The extensive list of ^{11}C compounds presented at the 1992 meeting is shown in Figure 6.

Since last year, the number of papers concerned with pre-synaptic neuronal tracers has gone from 28 to 40; those concerned with the dopaminergic system accounted for the greatest number. The ^{18}F compounds increased and this year were involved in 125 papers. The number of ^{18}F fluorodeoxyglucose papers increased from 75 to 90. Thirty-five SPECT papers dealt with post-synaptic neuronal markers. SPECT studies of the dopaminergic system increased from 10 to 25. Seventeen papers involved ^{123}I iodobenzamides, which illustrates what happens when a useful radiotracer becomes generally avail-

SNM								
	1985	1986	1987	1988	1989	1990	1991	1992
NEURORECEPTORS	25	39	27	50	73	76	84	118
DOPAMINE	11	24	13	21	37	46	36	64
ADRENERGIC							16	18
CHOLINERGIC	5	4	1	7	5	13	11	9
BENZODIAZEPINE	4	1	3	5	2	5	8	11
SEROTONIN	3	4	4	4	3	2	5	7
SIGMA								4
OPIATE	2	5	4	8	6	5	3	1
GLUTAMATE							1	0
HISTAMINE							2	2
OTHER							2	3

Figure 9. The number of presentations concerned with neuroreceptors over the past decade.



Figure 10. Normal dopamine receptors in a patient with Parkinson's disease, and deficient in a patient with a movement disorder resulting from multiple system atrophy, imaged by SPECT.

able. None of these papers using iodobenzamides were from the United States, emphasizing how great the need to overcome the delay in getting regulatory approval in the United States in order to translate scientific advances into the care of patients. Of the nearly 900 papers presented, 35% involved ^{99m}Tc .

The Practice of Nuclear Medicine

Nuclear medicine addresses all the questions that comprise the practice of medicine. Symbolically, four dimensional imaging (three dimensions in space, one dimension in time) yields A5Q (Figure 7), that is, the answers to five questions: What's wrong with the patient? How did it happen? What is going to happen? What can be done about it? Is the problem being solved? Nuclear medicine is not organ-oriented, but problem-oriented, and defines patients' problems in terms of regional physiology or biochemistry and then uses the measurements to help solve the problems. Biochemical character-

ization also provides the basis of treatment, whether it be surgery, radiation therapy or drug therapy.

Many studies demonstrated how the cognitive, high-technology procedures of nuclear medicine can actually reduce the costs of health care. Decision-making under conditions of uncertainty is what makes health care expensive. Increased certainty results in better patient care and lower costs.

Nuclear medicine extends advances in molecular biology, genetics, and other basic sciences involved in the study of intracellular communication to the care of patients. With these labeled messengers, we can examine every organ of the body, including the brain, the main site of intercellular communication. Nuclear medicine is beginning to close the circle between brain chemistry and behavior, to put chemotype between genotype and phenotype.

Regional Cerebral Blood Flow

Mountz and colleagues from the University of Alabama found that the variation in regional cerebral blood flow measured with ^{99m}Tc HMPAO was 3% within the same person, and 10% between different persons (#7). As the number of SPECT studies of regional cerebral blood flow has increased, the number of PET studies of cerebral blood flow has decreased—illustrating the concept that if SPECT can solve a problem effectively, it should do so, because the half-life of SPECT nuclides simplifies the studies. This use of SPECT then frees PET to solve other problems. Tracers of ^{11}C and ^{18}F will always be able to do things that SPECT can't do.

SPECT can be used clinically in planning interventional treatment of vascular aneurysms and tumors (#6). Investigators used ^{99m}Tc HMPAO to predict the effect of ligation of the internal carotid or other cerebral artery. Of the 30 patients studied, interventional treatment was altered as a result of the SPECT study. For example, the decision was made not to ligate the internal carotid artery in treatment of vascular lesions, thereby preventing untoward complications, decreasing morbidity and cost. Few fields of medicine will benefit more than nuclear medicine by the new emphasis on outcome studies.

Research continues to show the high sensitivity of SPECT in patients with cerebrovascular disease. In patients with acute aphasia, Janicek and colleagues found that 26% of the patients had normal CT studies, while clear-cut abnormalities were found with SPECT (#615). The sensitivity of SPECT cerebral blood flow studies in detecting the effects of drugs on the cerebral circulation was seen in the study by Kuwabara and others from Kyushu University (#221). In some cases, the administration of diamox increased blood flow to the involved thalamic region. When diamox was administered, regional blood flow increased in both normal and deafferented areas, even though there was no increased glucose utilization. Diamox did not increase neuronal activity, but increased regional blood flow, illustrating that an increase in regional blood flow does not necessarily indicate an increase in neuronal activity.

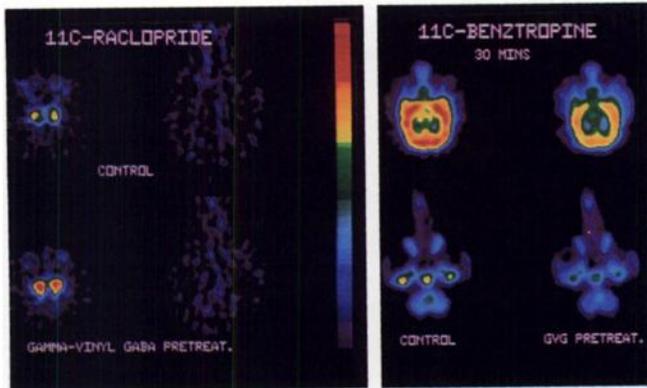


Figure 11. The left image shows the increased binding of raclopride resulting from increased concentrations of dopamine stimulated by increased synaptic GABA concentrations. The right image shows the inhibition of benztropine binding to acetylcholine receptors resulting from the decreased inhibiting effect of dopaminergic neurons on acetylcholine secreting neurons.

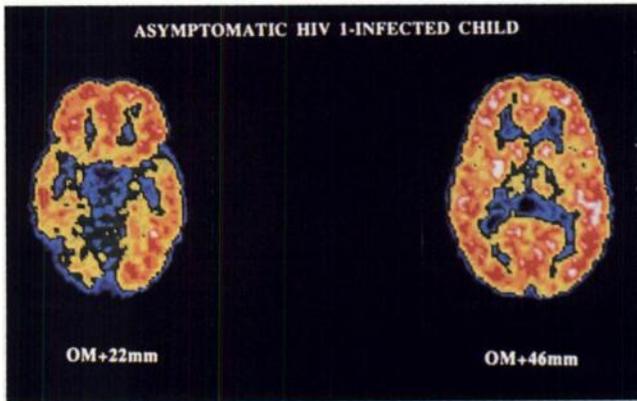


Figure 12. Decreased glucose utilization in the right temporal lobe of an asymptomatic three and a half year old child born to an HIV-infected mother.

As seen in Figure 8, the left thalamus initially had a much higher blood flow than the right. When diamox was given, blood flow increased in both the left thalamus and the cerebellum. The very high technical quality of the images documents the great advances that industry has made in SPECT imaging devices.

Both ^{15}O water and ^{18}F deoxyglucose are used in cerebral activation studies with PET. In SPECT studies, $^{99\text{m}}\text{Tc}$ HMPAO is used. In all cases, neuronal activity is inferred. With ^{15}O water, one measures changes in regional blood flow. Many other factors are involved in determining regional cerebral blood flow (#10). Neuronal activity increases both blood flow and glucose utilization, but many other factors affect global and regional glucose metabolism, including the metabolic state of the patient. In Cushing's disease, for example, there was significantly lower glucose utilization in all regions except the centrum semi-ovale and brain stem (#38).

A novel way to assess the reactivity of the cerebral circulation was described by Inoue and colleagues of Saitama Medical Center (#610), who used continuous SPECT imaging of the regional concentrations of radiolabeled human serum albumin to detect the increase in regional cerebral blood flow induced by the intravenous administration of diamox. In patients with transient ischemic attacks, the involved regions did not have the same increased rate of inflow of labeled albumen as did the normal areas of the brain.

Monitoring Drug Effects

Nuclear medicine can be used to assess the effects of drugs, as shown by Baird et al from Melbourne, Australia (#223) who assessed the value of thrombolytic therapy in the treatment of stroke. Other papers dealt with the effects of drugs on recognition sites. Most drugs involve stimulation or inhibition of these recognition sites. The number of papers concerned with neuroreceptors numbered 118—a steady increase from the 25 presented in 1985 (Figure 9).

Sixty-four presentations involved the dopaminergic system. Six different dopamine receptor subtypes have been cloned, and are now available for detailed study in pure form. The dopaminergic system operates through second messengers, which in turn activate mRNA, which bring about the synthesis of amines, peptides, or proteins, including receptors. The dopaminergic system has been well characterized in living persons by PET, in terms of the synthesis of dopamine, the binding of dopamine to post-synaptic receptors, and the reuptake into vesicles via pre-synaptic transporter sites. The studies of the dopaminergic system are being applied clinically in the differential diagnosis of movement disorders, while other systems, such as the serotonergic system, are moving into the foreground of basic science studies.

In studies of dopamine receptors, Wong et al (#95) added further information concerning the results obtained in Sweden with raclopride and at Johns Hopkins with N-methyl spiperone in the study of patients with schizophrenia. The Hopkins group has now carried out studies with both raclopride and n-methylspiperone in the same patients. Receptor availability (B-max) was 1.8 times higher for both raclopride and N-methyl spiperone, and there were no differences between normal persons and patients with schizophrenia. Although the number of patients was small in both groups, and the schizophrenic patients were older than the controls, no significant difference were found, although there was a very striking decrease with age with both raclopride and n-methylspiperone.

Moerlein et al from Washington University (#98) showed that some benperidol derivatives are more specific for D2 dopamine receptors than spiperone. The benperidol analogues do not have a very high affinity for serotonin receptors, but they have a higher affinity for dopamine receptors than does raclopride. Baldwin et al (#97) compared the 3 radioiodinated D2 dopamine receptor ligands, and found all of them suitable for SPECT imaging of the dopaminergic system.

Shinotoh and colleagues from Chiba University set the standard for studies of patients with movement disorders in their excellent images of D1 and D2 dopamine receptors (#392). They were able to easily separate patients with Parkinson's disease from another type of movement disorder, striato-nigral degeneration. There were striking differences in that patients with idiopathic Parkinson's disease had normal available receptors on the post-synaptic neurons, and can therefore be successfully treated, at least for a while, with L-dopa, while the patients with striatal nigral degeneration have abnormal post-synaptic D1 and D2 dopamine receptors in the putamen. This finding means that the patient will not respond to the administration of L-DOPA or dopamine receptor agonists, such as bromocryptine, both of which have potent side effects and should not be used unless there is a reasonable chance that they will help the patient. If the receptors are not available, the patients will not respond.

Seventeen papers involved iodobenzamide, which available in Europe in the form of a kit. Tatsch et al (#393) and Yonekura et al (#305) used SPECT to differentiate idiopathic Parkinson's from other Parkinson's syndromes in patients with movement disorders (Figure 10). There was a very striking difference in the involvement of the post-synaptic receptors in multiple system atrophy of the brain, compared to idiopathic Parkinson's disease. Because of the availability of the SPECT tracers, 60 patients with idiopathic Parkinson's disease could be compared with 17 control patients, plus a large number of patients with variants of Parkinson's disease. With SPECT, the results were expressed as the basal ganglia to frontal cortex ratio, the most elementary form of quantification. One danger is that SPECT quantification may not be sufficiently rigorous, especially if insufficient care is given to accurate positioning, partial volume, and other effects that increase the variance and decrease the usefulness of the study of an individual patient.

Tatsch et al also studied Wilson's disease, which also involves the basal ganglia (#308). The severity was related to the decrease in iodobenzamide binding. In patients with severe disease, there was greatly reduced binding of ^{123}I iodobenzamide to post-synaptic dopamine receptors. The availability of ^{125}I and ^{131}I , as well as ^{123}I , is an important advantage of single photon agents for in vitro as well as in vivo studies. The ^{125}I and ^{131}I agents will be of special value in basic neurosciences and neuropharmacology. For PET, the most suitable agents are ^{18}F compounds. Radioiodinated agents simplify and extend PET successes to SPECT.

Advances in the investigation of presynaptic neurons include the study of the dopamine transporter with ^{11}C WIN-35 (#586) and the use of radioiodinated cocaine analogue, designated CIT (or RTI-55), which can be used to examine both dopamine and serotonin transporters (#510). There is a deficiency in the accumulation of these tracers in the striatum of baboons and monkeys whose presynaptic dopaminergic neurons have been damaged by the neurotoxin MPTP. The chemical changes are more sensitive in the detection of disease than the clinical

signs. It is likely that next year we will hear of the study of presynaptic transporters as well as postsynaptic receptors in patients with Parkinson's and other movement disorders.

The serotonin transporter system in presynaptic neurons was examined with a specific tracer by Suehiro and others (#148). The difference between the distribution of the positive isomer compared to the inactive negative isomer was used to assess the availability of the serotonin transported. High concentrations were found in the hypothalamus, substantia nigra, dorsal raphe, and superior colliculus, reflecting the high concentrations of serotonergic neurons in these regions.

An approach to the treatment of Parkinson's and other diseases of the basal ganglia is direct infusion of drugs into the corpus striatum via an indwelling catheter. Compensatory increases in postsynaptic dopaminergic neurons were observed in unilaterally damaged MPTP-treated rats, and this increase could be prevented by the infusion of dopamine. Amines and peptides could be administered directly into involved regions of the brain in persons afflicted with Parkinson's disease, focal epilepsy, or intractable drug abuse.

Doudet and colleagues at the NIH (#591) employed a head holder to permit studies with accurate positioning over a period of up to two years in the same monkeys, treated bilaterally or unilaterally with the neurotoxin MPTP. There was a clear-cut diminution in the accumulation of ^{18}F L-dopa into presynaptic neurons on the side damaged by MPTP. There was an associated reduction in deoxyglucose utilization in the corpus striatum, although the reduction in glucose utilization was far less than the reduction in fluoro-dopa accumulation.

A pioneering study by Dewey et al (#94) documented the interactions among three neurotransmitter systems, the GABA neurons in the corpus striatum that secrete the inhibiting neurotransmitter, GABA, which in turn has an inhibitory effect on the dopamine neurons in the substantia nigra. When the secretion of dopamine was inhibited by the increased concentrations of GABA produced by the administration of a drug (GVG) that blocks the metabolism of GABA, there was an increased binding to the dopamine receptors of the post-synaptic receptor tracer, ^{11}C raclopride. The decrease in activity of the dopaminergic neurons resulted in increased secretion of acetylcholine by acetylcholine-secreting neurons. This resulted in decreased binding to the acetylcholine receptor of the acetylcholine receptor binding tracer, ^{11}C benztropine. This study shows that the multiple interactions of neuronal systems can be examined by PET and the endogenous secretion of neurotransmitters can be measured by their competing effect on the binding of radiotracers that bind to the receptors (Figure 11).

New Tracer Development

Ding and colleagues at Brookhaven National Laboratory described their results in developing a tracer for sigma receptors, which may be involved in diseases such as schizophrenia (#23). Another receptor ligand under development is ^{11}C pyrilamine, which binds to H1 histamine receptors in the brain

(#254). An important general concept was illustrated in this presentation. Using traditional compartmental analysis, it was not possible for Szabo and colleagues to show clearly the blocking effect of the antihistamine drug, benadryl. Factor analysis, a statistical technique that maximizes different factors affecting the observed data was better than compartmental analysis in revealing the blocking effect of benadryl on the specific binding of ^{11}C pyrilamine. Non-specific binding was not affected. The advantage of factor analysis is that it is model-free, without the need to make assumptions as in compartmental analysis. The variance in the data is much less with factor analysis than with compartmental analysis.

Other radioligands described by Moerlein and colleagues of Washington University included analogues of flumazenil, designed for the study of the benzodiazepine system (#98). Sasaki and colleagues of Tokyo Gerontological Hospital presented a radiotracer, ^{11}C forskolin (#851) for study of AMP related second messenger system, which lies between certain membrane receptors and messenger RNA in controlling peptide and protein synthesis.

The current definition of Alzheimer's disease is based on the finding of plaques and neuronal tangles in histopathological specimens of the brain, common in Alzheimer's disease, but not completely specific. Opinions differ about what should be the basis of medical diagnosis. Some diseases are defined by etiology, e.g. mercury poisoning, while others are based on clinical manifestations, such as depression. Whatever the classification on which a diagnosis is based, the ultimate criterion of its usefulness is its role in prognosis and the care of the patient. Grouping patients into homogeneous categories also helps elucidate the causes of disease, such as the finding of specific organisms in neurosyphilis, which at one time was classified as a mental disease.

Histopathology adds chemistry to the anatomical definition of disease, because it is based on chemical stains, but the images are "slices of death." The tissue being examined is dead. Images in nuclear medicine are "slices of life" portraying regional blood flow, metabolism, or various aspects of the chemistry of intercellular communication.

Hanyu and his colleagues from Tokyo Medical College presented results using SPECT and PET to define the patterns of involvement of the brain in patients with Alzheimer's disease (#825). The pattern of predominantly temporoparietal involvement was 80% sensitive and 91% specific. The absence of this pattern in patients with memory loss suggests that there may be some other cause of dementia, such as depression or drug toxicity. Grouping of patients with the characteristic pattern of brain involvement also aids in developing new forms of drug treatment for memory loss, better than would be possible on the basis of subjective symptoms or mental performance tests.

Minoshima and colleagues from the University of Michigan described a method for calibration of absolute regional glucose metabolism in a given patient (#139). The patient is compared to fifteen normal persons, in whom the patterns of glu-

cose utilization are co-registered into a standard anatomical pattern. The mean absolute glucose metabolism was then averaged for different regions of the brain and presented in a composite image. One can then express the absolute regional glucose utilization in a given patient in relation to the normal values.

Prohovnik and colleagues from Columbia University found that patients with the same degree of dementia but with pronounced visual spatial abnormalities had larger areas of reduced temporoparietal blood flow than did other Alzheimer's patients (#488). They also found that the more highly educated patients with Alzheimer's disease with the same degree of dementia had more involvement of the temporoparietal lobes.

Muller-Gartner and colleagues described how important it is in making measurements to correct for the varying amounts of cerebrospinal fluid, white and gray matter within the regions of interest under investigation. By doing so, they were able to define quantitatively the effects of age and dementia on opiate receptors in the amygdala and neocortex (#407). Opiate receptors in the amygdala declined with age in normal persons, and to a greater degree in patients with Alzheimer's disease than in age and sex-matched control. In the neocortex there was an increase in opiate receptor availability with age, with no difference between the normal persons and patients with Alzheimer's disease. There was a 68% greater availability of opiate receptors in an 80 year old compared to a 20 year old. One hypothesis to explain the finding is that it may represent chronically reduced amounts of endogenous opioids with compensatory "up-regulation" of the receptors. In the Alzheimer's patients, the increase in lateral temporal lobe opiate receptor availability was greatest in the patients with the greatest degree of dementia as indicated by the mini-mental test.

Genetic Models of Mental Disease

Magata and others of Kyoto University described their results with a strain of mice that have accelerated senescence (#843). The decline in performance of a cognitive task involving an avoidance response system was found to be associated with a marked and parallel decline in nicotine receptor availability, manifest by a decreased binding of tritiated nicotine. Normal mice were used as controls in both the performance test and the brain chemical measurements. Another useful model was that of Saji and associates of Kyoto University, who described a strain of mice susceptible to spontaneous epilepsy (#847). With tritiated deoxyglucose, they found an interictal decrease in glucose utilization in the hippocampus.

Epilepsy

In a large group of patients studied by Newton and others at the Austin Hospital in Melbourne, Australia, SPECT measurement of regional cerebral blood flow was 97% correct in lateralizing the focus in partial complex epilepsy when the injection was made during the seizure. Interictal SPECT was accurate in only 50% (#440). This represents a great advan-

tage over PET studies which are very difficult to perform during seizures because of their unpredictability unless they are unusually frequent. Muscarinic acetylcholine receptors were found to be reduced in the anterior hippocampus in temporal lobe epilepsy (#438). This finding raises the possibility that there may be a greater concentration of the neurotransmitter acetylcholine in these regions, which competes for binding by the radioligand. Alternatively, there may be a deficiency of cholinergic neurons in the hippocampus. The latter explanation is consistent with the finding of decreased glucose metabolism in the hippocampus between seizures.

Infectious Diseases and AIDS

At least ten different radiotracers have been used in infectious diseases, including ^{99m}Tc labeled anti-granulocyte antibodies, and ^{111}In labeled white blood cells and immune globulin. Hoffman and others from Duke University addressed the question of the differentiation of lymphoma from infection in patients with AIDS (#57). Although few patients were studied, levels of glucose utilization clearly differed between those patients with lymphoma and those with toxoplasmosis.

Syrotta and colleagues from Service Hospitalier F. Joliot in Orsay, France, found that five of eight babies born by HIV-positive mothers had striking brain ^{18}F deoxyglucose abnormalities (#641). Before any neurological signs had occurred, there was objective evidence of brain involvement (Figure 12). Such findings are important because of the value of early treatment of HIV infections.

Another study of AIDS with ^{111}In labeled human immunoglobulin by Buscombe and others from Middlesex Hospital in London and University Hospital, Nijmegen, Netherlands, found a very high degree of accuracy in detection of both chest and extra-thoracic lesions (#332).

Anti-granulocyte antibodies are another important advance in the area of infectious diseases. Munz and others from Göttingen, Germany, reported good sensitivity and specificity in the detection of brain abscess (#557). A disadvantage of the anti-granulocyte method is that it's difficult to see infections in the abdomen, but otherwise the results have been outstanding. Anti-granulocyte antibody studies were effective in the differentiation of bone infections from other lesions in which ^{99m}Tc phosphonate agents are abnormal, reported Schembri and colleagues from the Mayo Clinic (#65). In patients with hip endoprostheses, Sciuk and others from the University of Munster reported excellent results (#64). With the less specific agent, one can't distinguish between infection and non-specifically increased metabolic activity.

Merrick and colleagues from Edinburgh, described a follow-up of 3600 patients with urinary tract infection (#202). The results indicated that nuclear imaging is essential in children under 2 years of age who are suspected of a urinary tract infection, in persistent or recurrent infection at all ages, and when there is an organism other than *E. coli* causing the urinary tract infection. Following these guidelines not only helps the

patients, but results in less cost in caring for the patients.

The Heart

A general conclusion about the optimum heart protocol cannot be given, because different institutions optimize different things. Many are concerned with streamlining the process of performing rest/stress studies in the detection of coronary artery disease and identifying the "jeopardized" myocardium. Berman and his associates advocated the combined use of ^{201}Tl for a rest study, followed by a ^{99m}Tc stress study (#218). The entire study can be completed within 2 hours, but the low doses of ^{201}Tl at rest do not achieve the quality that is possible with the higher photon yields of ^{99m}Tc when it is used for both rest and stress studies. With the double tracer study, one can quite easily separate the energy of thallium from the energy of technetium. In the Berman study, there was an 81% sensitivity and 91% specificity in the detection of regions perfused by arteries with greater than 70% stenosis.

The higher photon yield of ^{99m}Tc agents makes it possible to combine the study of ventricular function with the study of myocardial blood flow, as reported by Stowers and others from Jacksonville, Florida (#93). The combination of regional wall motion studies with measurement of regional myocardial blood flow improved specificity. The ability to examine multiple radionuclides is a major advantage of SPECT that was exploited in the design of a new scintillation camera in which each photomultiplier tube has an analogue-to-digital converter (ISIS exhibit). This increased digitalization improves field uniformity, corrects for scatter more effectively, and has a spatial resolution of 2.1 mm.

Taillefer and others from Hotel-Dieu of Montreal achieved results with an 8-minute acquisition time as good as with a 21-minute acquisition, which increases the number of studies that can be performed per day (#128).

Diphosphine (Tetrofosmin), a new ^{99m}Tc labeled myocardial blood flow tracer, was the subject of 8 papers (#211, 212). This agent is a four phosphorous chelate with the advantage of a longer retention time in the myocardium than teboroxime, so that one does not have to be as exact in timing the imaging after injection of the tracer. The hepatic uptake is also less. The percentage of the injected dose accumulated in the heart is significantly less than that of ^{201}Tl .

Adenosine and dobutamine have advantages over dipyridamole because of their short duration action. Although side effects have been reported, they are of very short duration and not serious. Dobutamine is useful in patients who have chronic obstructive lung disease, but should not be used in patients who have hypertension (#534). Adenosine should not be used in patients who have chronic obstructive lung disease but is the best choice in patients who have hypertension.

In validation studies, Delbecke and others from Vanderbilt University examined the hearts from patients having heart transplants (#5). The correlation coefficient between ammonia estimates of left ventricular mass and the actual left ventricular

mass in nitrogen-13 ammonia studies was 0.82. There was a 0.93 correlation coefficient in the estimation of infarct size. Estimating infarct size is helpful in drug assessment studies. Improvements in SPECT quantification in such assessments are important. Gullber and others from the University of Utah and Picker International reported their results in the use of simultaneous transmission and emission studies to correct for attenuation (#322). Subjective interpretations of the images improved and quantitative accuracy increased.

The major tracer used for studying myocardial metabolism continues to be ^{18}F deoxyglucose. In an outcome study of 208 patients with coronary artery disease from the University of Tennessee, patients with perfusion defects in which there was evidence of glucose utilization ("mismatch"), 80% of the patients improved after surgery while 8% of the patients died. In the patients with matched defects, only 23% improved compared to 80% in the mismatched group and 23% died—strong evidence of the clinical usefulness of PET studies of the heart.

Interest in the use of fatty acids in the study of coronary artery disease continues. A study by Fagret and others from Lyon, France, found that, using FDG as a standard, the positive predictive value of the fatty acid study was 93%, and the negative predictive value was 71% (#540).

Prognosis

Ventricular dilation during an exercise dipyridamole test is of prognostic significance, as reported by Lette and others from Montreal (#531). If the left ventricle dilates during a thallium study after the administration of dipyridamole, only 24% of the patients were event-free at follow-up, that is, they had not had a myocardial infarction, died, or had persistent angina. Of the patients that had ventricular dilation with exercise, 62% were event free.

Molecular messengers control the dilation and constriction of coronary arteries. Some such as adenosine or histamine act directly on smooth muscle; others such as serotonin act on the endothelial cells. Ventricular tachycardia is perhaps the major problem in patients with myocardial infarction because sudden death is still the number one presentation of patients with coronary artery disease. Using nuclear medicine techniques, we can now examine the biochemistry of vasoconstriction and vasodilatation. One of the first agents used for this purpose was metaiodobenxyguanidine (MIBG). Among the earliest findings was decreased sympathetic innervation of the heart in patients with cardiomyopathy or after cardiac transplantation. We learned from Merlet and others (#301) that it is a very bad prognostic sign if MIBG doesn't accumulate in the heart. The survival rate in patients who had low accumulation of MIBG in the heart was terrible, even worse than that associated with a left ventricular ejection fraction less than 20%.

The probability of congestive heart failure developing in patients with cancer treated with Adriamycin was studied in this experimental model by Wakasugi and others from the

Massachusetts General Hospital (#470). A decrease in ^{125}I labeled MIBG in the myocardium was a better predictor of heart failure than was a fall in left ventricular ejection fraction—support for the concept that chemical measurements are more sensitive than assessments of structural or physiological abnormalities in the detection of disease.

Advances in genetic engineering are being used in nuclear medicine research. Glowniak from the University of Oregon investigated the mechanism of uptake of MIBG by the myocardium (#469). MIBG is an indicator of the status of the presynaptic neuron, but Glowniak questioned whether the accumulation of MIBG was related to the transporters of norepinephrine, dopamine or serotonin. Studying receptors produced by genetic engineering, he found that MIBG uptake was not related to the dopamine transporter, but involves the norepinephrine transporter. He also found significant non-specific binding to non-neuronal structures. A more specific tracer of the beta-adrenergic system was described by investigators from the University Hospitals of Cleveland, who employed ^{11}C carazolol. Other tracers of the innervation of the heart included the study of Van Waarde and others of Groningen, who employed CGP-12177 and CGP-26505 to characterize beta-adrenergic receptors (#193).

The interrelation of organs was illustrated in a study by Leitha and colleagues from the University of Vienna of low density lipoproteins (LDL) in the liver, which play a role in the development of coronary atherosclerosis (#865). Failure of LDL receptors in the liver to remove lipoproteins leaves them available to be deposited in the coronary arteries. The authors recommend examination of the LDL receptors in the liver, and, if deficient, increasing their number by the administration of estrogens. Both $^{99\text{m}}\text{Tc}$ and ^{125}I labeled LDL were examined in the rat. Estradiol increased LDL receptors. This is a good example of the value of a holistic approach to problems of a specific organ.

Nuclear Gastroenterology

Hepatobiliary scintigraphy has proved helpful in the differential diagnosis of congenital biliary atresia and neonatal jaundice, another example of how surgery can be avoided and cost decreased if the diagnosis of neonatal jaundice can be diagnosed with certainty (#314). Based on a detailed analysis of the hepatobiliary data, Yeung and others from Hong Kong reported that the sensitivity was 92% and the specificity 87%. The overall accuracy was 90%.

In a study of diabetics, Vekemans and others from Belgium tracked the movement of food through the stomach and gastrointestinal tract (#32). The use of quantitative criteria improved the detection of gastrointestinal abnormalities in the patients with diabetic neuropathies. The results were of value in the assessment of medications.

Pancreatic imaging may be revisited based on the development of a new tracer by Scott and others from the Edmonton Radiopharmaceutical Center in Alberta, Canada (#69). This

agent is a modification of HIPDM, which was reported some years ago as accumulating in the pancreas. We will await its commercial development.

Another report that illustrates the value of nuclear medicine procedures in containing costs is that of Parker and others from Boston who found that administering the very expensive drug urokinase for a period of 2 hours was just as effective as giving it over a 24 hour period (#105). Treatment with 3 million units of urokinase over 2 hours was as effective as the FDA approved treatment with much higher doses. This study also shows that nuclear medicine procedures could play a major role in drug design, development and assessment.

Medical problems should be solved with the least expensive and least complex methods available. Simple devices are under development to take advantage of the many new positron and single photon-emitting radiotracers. Makino and others from Tokyo described a small detector that consists of a miniature photodiode only 0.5 cm across (#759). Ricard and others from Villejuif, France, described an interoperative probe using ^{125}I MIBG to take advantage of the short range of the radionuclide in searching for lesions at the operating

table (#827). Among the animal scanners designed to facilitate studies in neurosciences, pharmacology, and nuclear medicine was a device described by Green and colleagues at the NIH, which is a camera based on the use of position-sensitive photomultiplier tubes with rotation of the animal in front of the crystal detector (#117). The device costs about \$30,000 and provides high spatial resolution images of the guinea pig brain. One could see the bones of the head of a guinea pig imaged with high spatial resolution. Although the instruments of nuclear medicine are great, the real utility is in the tracers. Many different types of instruments can be used to study them.

For the 15th consecutive year of having the honor of presenting the highlights of the Annual Meeting of The Society of Nuclear Medicine, I am excited by the mounting evidence that nuclear medicine has added in situ biochemistry to regional physiology in its domain. The field continues to move science into service in a manner that not only helps the patient and the public, but also the economy.

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SNM Trustees Favor Central Office Move to Nation's Capital

The Board of Trustees of The Society of Nuclear Medicine in June approved plans to move the Society's central office to the suburban Washington, D.C. area by July 31, 1995, when the lease expires on the current office space in New York City.

Although several cities had been considered for potential cost-savings over New York, Washington emerged as the winner because of the widely held belief that an expanded presence in the Capital will be needed to gain funding for nuclear medicine research, and to represent nuclear medicine before the government officials who make regulatory, reimbursement, and technology assessment decisions.

"We as a discipline now have an opportunity to increase our strength and effectiveness with strong collaboration with the American College of Nuclear Physicians," said Leon S. Malmud, MD, then president of SNM, who presided over the trustees meeting. "We'll see opportunities available to us now which have not been available for the last decade."

The board of trustees met on June 8, 1992 at the SNM Annual Meeting in Los Angeles, California. A digest of some of the other actions of the board follows:

SPECT PROJECT

The trustees approved SNM participation

in an industry-sponsored program, provisionally referred to as the "SPECT Project," that will promote the diagnostic and prognostic use of single photon emission computed tomography. The project will be funded by the radiopharmaceutical and instrument manufacturers and managed by the Joint Government Relations Office of the ACNP and SNM. According to its mission statement, the project will encourage clinical and research utilization of SPECT, advocate "equitable" reimbursement for clinical SPECT, and facilitate the education and training of physicians and technologists in clinical SPECT imaging. A steering committee comprising three representatives from ACNP, three from SNM, and three from industry will select projects to support from an anticipated first-year budget of \$300,000.

STRATEGIC PLANNING

The board approved a strategic plan for the Society, with further refinements to be made as the strategic planning process continues. Directed by a "vision statement" (To improve the health of mankind through the use of nuclear techniques), the strategic plan lists a series of objectives for the advancement of nuclear medicine education, research, and clinical practice. The plan calls for SNM staff, committee chairpersons, and ultimately the executive committee and board of trustees

to annually assess progress and reexamine goals and objectives. The Society will also sponsor a meeting each year with ACNP and industry to assess strategic planning for the entire discipline of nuclear medicine.

OFFICE OF HEALTH CARE POLICY

The Society's new Office of Health Care Policy (OHCP) proposed a mission statement, which the board unanimously approved. The mission of OHCP is "to establish a forum through which nuclear medicine physicians, scientists, and technologists may contribute to the national effort to improve health care." OHCP will coordinate the establishment of quality standards for nuclear medicine and represent nuclear medicine in the inter-specialty development of practice policies. The office also intends to make recommendations for increasing the cost-effectiveness of medical care.

ACNP MEMBERSHIP

The American College of Nuclear Physicians has launched a membership drive and is encouraging SNM members who are not also ACNP members to consider the benefits of dual membership. The SNM board of trustees unanimously endorsed the concept that membership in both the Society and the College is a desirable goal for all nuclear medicine physicians and scientists.