The Society of Nuclear Medicine 36th Annual Meeting

SNM Highlights—1989: "Why Not?"

"Imaging in vivo chemistry remains the most fundamental principle of nuclear medicine."

The 36th Annual Meeting of The Society of Nuclear Medicine was held last June in St. Louis, Missouri. In the meeting's final session, Henry N. Wagner, Jr., MD, professor of medicine, radiology, and environmental health sciences at The Johns Hopkins Medical Institutions, a past president of the Society, presented his views of the meeting's scientific highlights, relating today's developments in nuclear medicine to past work and future directions.

Because 1989 is the two hundredth anniversary of the French Revolution, I've taken as the theme of the meeting the motto of the Marquis de Lafayette: "Why not?". As evidenced by the presentations, nuclear medicine can stake a claim as the most exciting field of medicine today. Why not? The *new* nuclear medicine is now able to address the most important scientific question of all time: why are we the way we are?

Some may say that the future of medicine lies in the *new* genetics, but genes don't cause disease, chemicals cause disease, those chemicals made by our bodies, and those that we inhale, inject, or ingest. Genes map our character, but chemicals express that character. Nuclear medicine has created the discipline of *in vivo* chemistry in living human beings, and can provide a chemical bridge between genotype and behavioral phenotype. Just as after World War II, carbon-14 and tritium revolutionized biochemistry, nuclear imaging can revolutionize *in vivo* chemistry in the coming decade.

PET and SPECT Advance Together

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) radiopharmaceuticals are being invented at a fast pace. This year, there were 78 papers on new PET agents, including not only fluorine-18 and carbon-11, but also other radionuclides, such as rubidium-82, with 11 presentations compared to four last year. A major highlight of the meeting was the development of SPECT radiopharmaceuticals chiefly involving iodine-123, with 23 presentations. Together, both PET and SPECT are moving nuclear medicine steadily ahead. Why not?

Focus on Neuroreceptors

Neuroreceptor imaging has had a dramatic growth since its introduction in 1983 and now involves SPECT as well as PET.

Over the last five years there has been a tripling in the number of papers on neuroreceptors, which were the subject of 73 presentations at this year's meeting.

Dopamine receptors are still the principal subject of PET research, with 37 presentations, but the list of new neuroreceptor radioligands grows every year. In the brain, SPECT dominated cerebral blood flow papers, while PET dominated metabolic studies. SPECT dominated the clinical studies of the brain with 187 presentations.

Henry N. Wagner, Jr., MD

The translation of PET advances into clinical practice continues primarily via SPECT. A major impediment to the translation of PET into clinical practice is the lack of coverage by third party payers. This inhibits the diffusion and availability of not only PET and SPECT, but most emerging technological advances and new procedures in American medicine. Medicare's prospective pricing policies, diagnosis related groups (DRG's), are

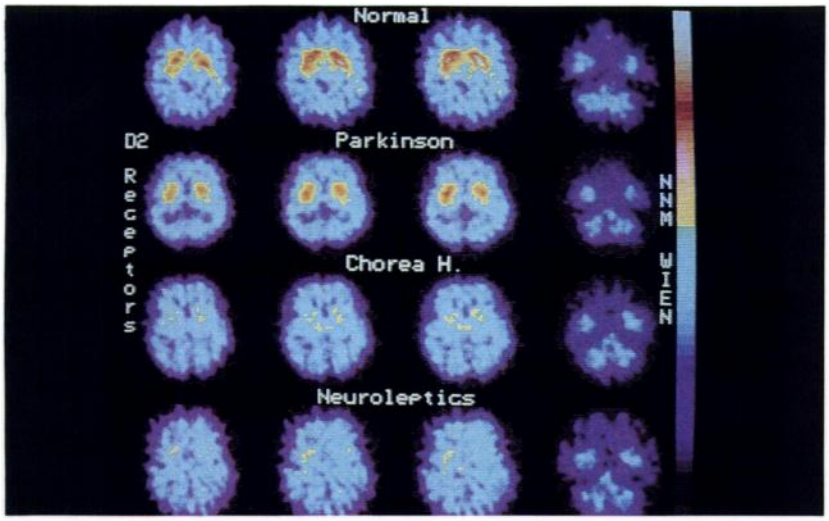

Figure 1.

also inhibitory factors because they are not sufficiently responsive to technological advances. Under prospective payments, it may be economically beneficial for a hospital *not* to have high technology available to its patients. Basic technological advances made in the US are applied clinically first in Europe and Japan rather than in the US because of regulatory obstacles and third party payer policies. This was made evident at this meeting.

A good example is ^{123}I iodobenzamide (IBZM), developed by Kung and his colleagues at the University of Pennsylvania. At this meeting, Brucke and his colleagues from the Neurological University Clinic in Vienna presented excellent quantitative imaging studies (Figure 1) that showed blockade of the uptake of IBZM by D2 dopamine receptors with neuroleptic drugs and a reduced binding in the caudate nucleus and putamen of patients with Huntington's disease (No. 11).*

SPECT has joined PET as a major research tool in its own right. In patients with Parkinson's Disease, binding of IBZM was normal, providing further evidence that in this disease D2 dopamine receptors are usually intact. Because the receptors are still present, L-dopa treatment is effective. It remains to be seen whether L-dopa-unresponsive patients have impairment of D2 dopamine receptors as well as degeneration of presynaptic neurons. These investigators found a difference between L-dopa treated and untreated patients. In treated patients, binding of the ^{123}I IBZM in the caudate/putamen was reduced, suggesting that the D2 dopamine receptor concentrations were reduced ("down-regulated") to compensate for the increased synaptic concentration of dopamine brought about by L-dopa treatment.

The exponential growth in the commercial distribution of ^{123}I compounds in Japan has been well-documented. The Japanese have been able to achieve effective teamwork among government, universities, industry, and the health care systems in radiopharmaceutical development, low-level radioactive waste disposal, and other fields.

Image of the Year

Each year an image is selected that exemplifies the most important advances presented at the SNM Annual Meeting. This year's image of the year (Figure 2) was produced by Weinberger and his colleagues from the National Institute of Mental Health at St. Elizabeth's Hospital in Washington in collaboration with Reba's group at George Washington University and the National Institutes of Health (No. 706). They examined muscarinic cholinergic receptors and glucose metabolism in patients with Alzheimer's and Pick's dementias.

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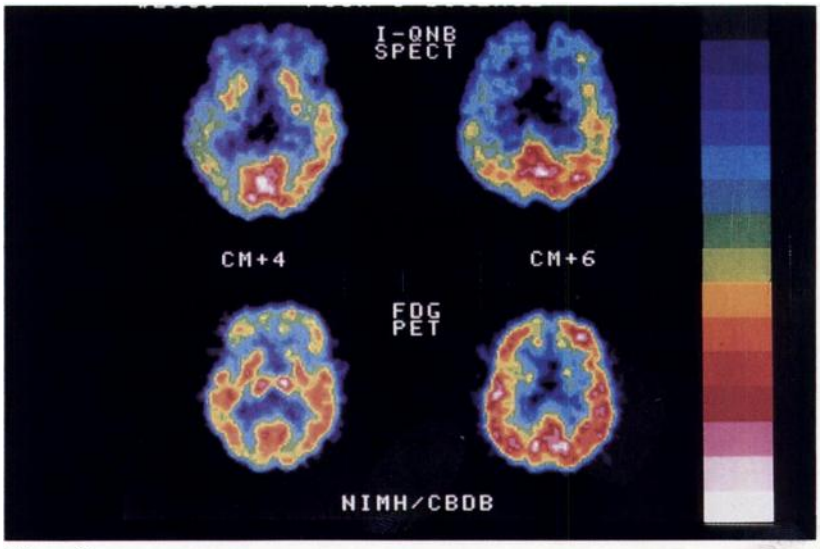

Figure 2.

**Subsequent nos. refer to abstract nos. in the Proceedings of the 36th Annual Meeting of The Society of Nuclear Medicine.*

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In Figure 2, the two upper images are of the distribution of ^{123}I QNB, which binds to muscarinic cholinergic receptors; the lower images are ^{18}F fluorodeoxyglucose (FDG) images of glucose metabolism in the same slices of the same patients. The radioligand—^{123}I-labeled QNB—was developed by the George Washington group in 1984. Not only do the Pick's disease images reflect the increasing technical quality of SPECT images, but their observations may represent a discovery of an important biological marker in Pick's disease, that is, decreased QNB binding to muscarinic acetyl choline receptors in the frontal cortex even when FDG metabolism in these regions of the brain is normal. Further studies will be needed to ensure that reduced blood flow to the involved regions and possible cerebral atrophy have been adequately taken into account. Other receptor studies will also be needed before one can conclude that the neurons in the frontal lobes have a specific abnormality of muscarinic cholinergic neurotransmission.

PET and SPECT radiopharmaceuticals often develop side by side. An example is the approach of Maziere, Syrota, and their colleagues from Orsay, France, who developed bromine-76 lisuride for PET and ^{123}I lisuride for SPECT imaging of D2 dopamine receptors (No. 12). These investigators found that unilateral chemically-induced brain lesions reduced binding of the tracer in the caudate/putamen before there was any observable motor dysfunction in the animals, although these could be induced by administration of apomorphine.

Major pharmaceutical companies are developing single photon radioligands for the study of receptors. In the past, drug companies worked primarily with carbon-14 and tritium for *in vitro* and animal studies. Leading pharmaceutical companies throughout the world now accept the potential role of PET/SPECT in drug design and development as well as in the assessment and translation of promising new drugs into clinical practice. Why not?

An example of the *new* pharmacology is the work of Mertens and his colleagues from Janssen Pharmaceutica in Belgium. These investigators developed the radioligand ^{123}I iodoketanserin for the study of S2 serotonin receptors and carried out the first human studies (No. 51). Several other new ^{123}I ligands were described, including radioiodinated diazepam, developed by Saji, Yokoyama, and colleagues from Kyoto University (No. 311) and improved D1 dopamine receptor ligands described by Chumpradit, Kung, and colleagues (No. 310).

Continuing progress in the development of positron-emitting radioligands for the study of neuroreceptors was evident in the presentation of Villemagne and colleagues who synthesized ^{11}C pyrilamine to study H1 histamine receptors in the primate brain (No. 53). The histaminergic neurotransmission process may be involved in diseases such as obesity, anorexia nervosa, and sleep disorders.

Wong and colleagues presented experimental data supporting the validity of their model for the quantification of D2 dopamine receptors by means of irreversible bound ligands, such as ^{11}C N-methyl spiperone (NMSP) (No. 8). The group also presented more data on D2 dopamine receptor availability in normal subjects and patients with schizophrenia, psychotic and non-psychotic bipolar manic depressive illness, and Tourette's syndrome (No. 9).

Dewey, Brodie, and colleagues developed ^{11}C benztropine to examine muscarinic cholinergic receptors in the caudate/putamen of schizophrenic patients (No. 52). Cholinergic neurons in this region inhibit excitatory neurons and are themselves inhibited by dopamine. Thus, the overall effect of dopamine is excitatory.

The next stage in the neurotransmission process after binding of neurotransmitters to neuronal membrane receptors is activation of second messengers that propagate the specific receptor-identified messages by more general neuronal activation processes. One such mechanism is the opening and closing of sodium, potassium, and calcium ion channels. Within the ion channels are other receptors, including the MK 801 receptor, named for a drug that closes calcium channels. Burns and colleagues from Merck, Sharpe, and Dohme developed an ^{123}I analogue of MK 801 that binds to a high degree to MK 801 channel receptors in the hippocampus, cerebellum, and corpus striatum (No 826). Another radioligand newly developed by Merck is the cholecystokinin antagonist MK 329 (No. 858).

Among the "second messengers" in the neurotransmission process is the enzyme *protein kinase.* The group of Imahori, Ido, and colleagues at Tohoku University have developed ^{11}C phorbal esters in order to image *protein kinase* C (No. 227). Thus, although these studies are just the first steps, nuclear medicine makes it possible to move further along the chain of chemical reactions involved in neurotransmission in living human beings.

Major Breakthroughs in Cocaine Addiction

Few fields of medicine translate basic science advances into practical solutions of health care problems as well as nuclear medicine. At this meeting, fundamental questions were asked, and then important health problems were addressed by the new technology. Some of the most exciting findings presented dealt with cocaine addiction. Last year, in an article in the Baltimore Sun, Gwinn Owens wrote: "The spreading effect of il-

legal drugs on the social order in America, especially in its large cities, is clearly so staggering, so pervasive and so destructive as to be the principal domestic menace to the survival of a civilized society." There is now convincing evidence linking cocaine addiction to the dopaminergic system. Kuhar and his colleagues at the Addiction Research Center of the National Institute of Drug Abuse in Baltimore described during the past year that addiction to cocaine could be correlated with its effect on the "transporter" process responsible for removal of synaptic dopamine from the synapse, that is, the process that takes dopamine "back up" into presynaptic neurons from which the neurotransmitter was originally secreted. Work from Brookhaven National Laboratory and the State University of New York (SUNY) at Stonybrook presented during the meeting suggested that the subjective "rush" that cocaine addicts feel may be due to the blocking of the dopamine transporter by cocaine (No. 133). This blockade results in a sudden increase in synaptic dopamine concentrations. In autoradiographic studies of rodents with ^{14}C cocaine, Som and colleagues from Brookhaven National Laboratory described how cocaine binds to uptake sites in the heart, kidneys, and adrenals, as well as the brain. Their new findings raise an important hypothesis about the mechanism of sudden death in some persons after taking cocaine. The sympathetic nerves of the heart seem exquisitely sensitive to ischemic injury, which may be a factor in ventricular arrhythmias.

Returning to the question of cocaine effects on the brain, Fowler and colleagues at Brookhaven synthesized ^{11}C cocaine, examined its pharmacokinetics, and showed that it was released rapidly from its binding to the caudate/putamen, coincident with the time course of subjective symptoms (No. 133). This ability to relate human behavior to brain chemistry is one of the most remarkable accomplishments of nuclear medicine. A further example of this relationship was the relating of psychotic symptoms in patients with manic depressive bipolar illness to the availability of D2 dopamine receptor binding sites (No. 9). Receptor availability was high when psychotic symptoms were most pronounced. D2 dopamine receptor availability is not the whole story because patients with Tourette's syndrome, who are not psychotic (that is, they don't have delusions, hallucinations, or thought disorder), also have elevated D2 dopamine receptor availability.

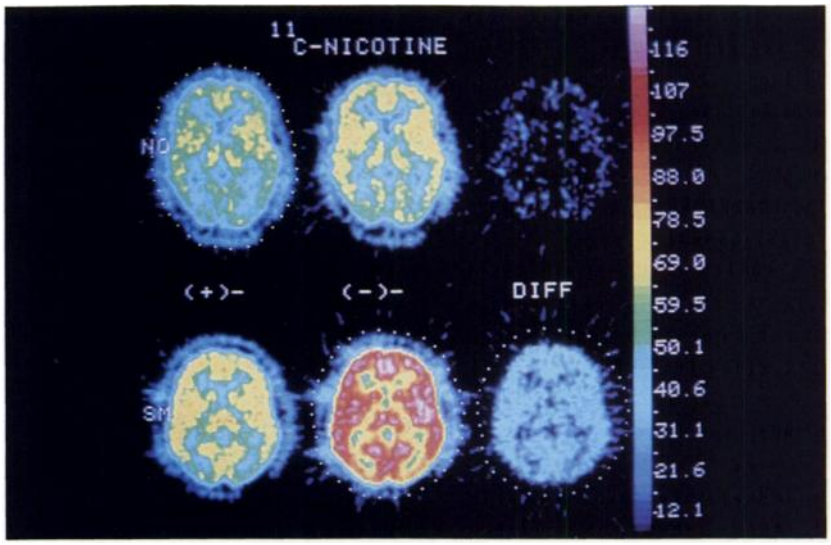

Figure 3.

Volkow and colleagues at Brookhaven found that D2 dopamine receptor binding of ^{18}F NMSP in the caudate/putamen was reduced in cocaine abusers compared to normal subjects (No. 7). Apparently, the increasing synaptic dopamine concentrations known to be produced by cocaine resulted in a compensatory "down-regulation" in available dopamine binding sites. The decreased availability of receptors may account for the increasing tolerance to the drug that cocaine addicts develop. Higher doses are required to get the same subjective pharmacological effect.

Smoking and Alcohol—Effects on Brain Chemistry

Nicotine is the most commonly abused drug affecting brain chemistry. The Karolinska group in Stockholm reported that ^{11}C nicotine binds to cholinergic receptors in the brain to a greater degree in smokers than in non-smokers (No. 54). Smoking only a few cigarettes raised nicotine levels in the plasma to the degree that the binding of ^{11}C nicotine decreased dramatically.

In Figure 3, the upper row are images of ^{11}C binding in the brain of a non-smoker; the lower row are of a smoker. The images on the far left are control studies; those in the middle show the binding of the specifically and non-specifically bound isomer. The images on the far right show that the specific binding to nicotine receptors is greater in the smoker (lower row) than in the non-smoker (upper row).

Carbon monoxide was found to have a dramatic effect on brain glucose metabolism. Tahara and colleagues presented quantitative data revealing the striking effect of severe carbon monoxide poisoning follow-

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ing mining accidents (No. 305). Anatomical studies with computed tomography (CT) and magnetic resonance imaging (MRI) indicated that the patients' abnormalities were chiefly in the white matter and globus pallidus, but FDG studies indicated that the abnormalities were much more extensive and severe. It will be interesting to see if smoking cigarettes has a measurable effect on global or regional cerebral glucose metabolism, especially since we could combine such studies with studies of nicotine receptors.

Volkow et al. showed that when normal people consume alcohol, there is a reduction in cortical cerebral glucose metabolism with lesser effect on subcortical structures (No. 302), an effect similar to that observed by London et al. after cocaine or narcotic administration. Persons suffering from chronic alcohol abuse had the most striking reductions in glucose metabolism after ingesting alcohol, involving both cortical and subcortical structures, even when they did not seem to be intoxicated, presumably because they had become tolerant to the subjective effects of alcohol. The relationship of neuropsychological performance and regional glucose metabolism is under investigation by this group.

Dopamine Synthesis

^{18}F L-Dopa was first used in 1983 to examine dopamine synthesis in the brain. Barrio and colleagues at University of California, Los Angeles (UCLA) have now synthesized ^{18}F fluoro-tyrosine, a precurser of L-dopa, which makes it possible to examine an earlier step in the metabolic pathway (No. 97). Whether this step in the chain of reactions will eventually be of greatest value in detecting increased or decreased activity of presynaptic metabolic pathways remains to be seen.

Patterns of Neuronal Activation

Most of the time, each of us is using only a small fraction of his or her brain power. With nuclear technology, we can now examine the temporal and spatial activation patterns during mental stimulation. A highlight of the meeting was the paper of Ackermann and Lear from UCLA and the University of Colorado (No. 457). They were able to measure cerebral oxidative and glycolytic glucose metabolism simultaneously (Figure 4).

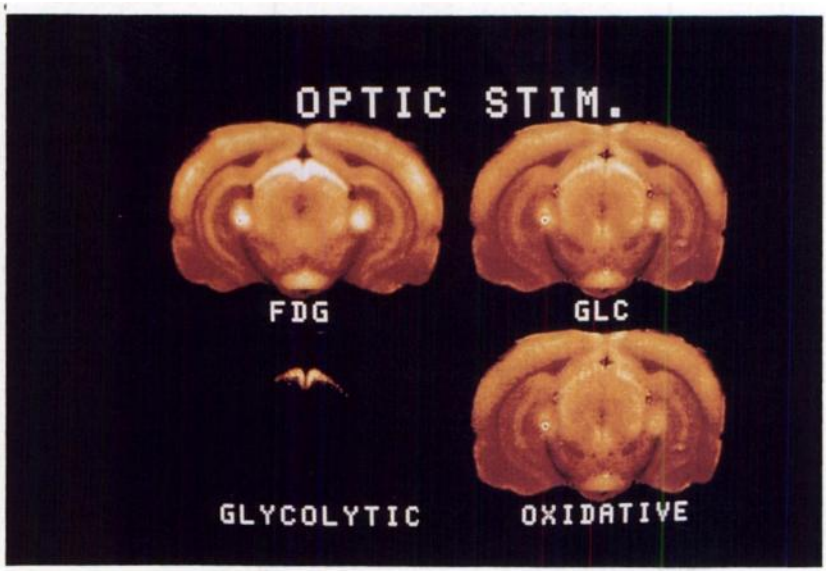

Figure 4.

In the brain, glucose is metabolized via oxidative aerobic pathways or the glycolytic anaerobic pathway, which results in the formation of lactate. In normal, unstimulated animals, glucose metabolism is almost entirely oxidative, with little being glycolytic. However, during seizures induced by kainic acid, there was a huge increase in glycolytic, anaerobic metabolism, with very little increase in oxidative metabolism. What is perhaps even more remarkable is that when the animals were stimulated with a strobe light, only anaerobic glucose metabolism increased along the visual pathways. That such an increase in anerobic metabolism can occur rapidly was illustrated in conditioned animals in which seizures were "kindled" within seconds of stimulation.

The image at the lower right shows that visual stimulation did not change oxidative metabolism compared to the control (upper right). The increase was in glycolytic glucose metabolism (lower left). ^{18}FDG tracks total glucose metabolism, both oxidative and glycolytic. The anaerobic conversion of glucose to lactate accounted for most of the increase in accumulation of deoxyglucose during mental stimulation. Thus, in the brain, as in muscle, "work" causes an immediate increase in anaerobic metabolism. Only in the "resting" state is glucose metabolism entirely oxidative.

The deoxyglucose method has become the standard for cerebral activation studies, preferred over ^{11}C glucose or oxygen-15 measurements of oxygen metabolism because deoxyglucose accumulation reflects the induced glycolysis.

The unique ability of nuclear medicine to relate chemical activity patterns in the brain to human behavior was illustrated again by the study by Nenov et al. from West Los Angeles VA and University of California, Irvine (No. 699). These investigators showed that when a subject looks at

a word and tries to decide whether the word is recognized, the angular gyrus as well as several other areas of the brain are involved in the process.

A study by Martinot et al. from Orsay, France, examined patients with obsessive-compulsive disorder. In these patients, there were changes in cerebral glucose metabolism observed during a so-called "stroop" test, in which the subject was asked to identify the color in which the letters of a word are written. For example, the word "red" is written in green. People with obsessive-compulsive disorder take a longer time to make the proper response than do normal subjects. The frontal lobes are believed to be involved in the process of inhibiting inappropriate responses to apparently conflicting stimuli. What was most impressive was that the response time was directly related to the reduction in glucose metabolisms in the inferior lateral frontal lobes.

Effect of Stress on Cerebral Glucose Metabolism

Last year Metz, Cooper, and colleagues from the University of Chicago studied the effect of alcohol on regional glucose metabolism of the brain and found differences in temporal and parietal lobes related to whether the subjects felt good (friendly) or bad (angry and aggressive) after drinking alcohol. They've continued these studies, but pointed out this year the importance of anxiety on deoxyglucose measurements (No. 718). They found that during the subjects first experimental session, global cerebral glucose metabolism was higher than in the subsequent three sessions. The increase in brain glucose metabolism could be correlated with measurements of anxiety.

Causes of Variability in FDG Studies

Variability in global cerebral glucose metabolism among normal subjects, and in the same subject at different times, is attributable to both technical and biological factors. Kumar and colleagues from the National Institute of Aging used a new PET scanner with improved spatial resolution in their continuing studies of patients with Alzheimer's dementia (No. 177). Even in patients with mild Alzheimer's disease, in whom FDG abnormalties had not been detectable with their previous scanner with poor spatial resolution, they found reduced glucose metabolism in certain regions, such as the parietal lobes, with the new scanner. The coefficient of variation (1 S.D.) with the new scanner was between 10% and 15%, compared to 20% to 25% with the older instrument. The improved precision could account for the improved detectability of the glucose abnormality in the patients with mild disease. For certain purposes, it may be desirable to "normalize" regional glucose metabolism by dividing by global glucose metabolism to get around the problem of variability in global glucose metabolism, but, if one can separate out technical factors, the causes of the biological variability in glucose metabolism among persons, or in the same persons at different times, should be of great interest.

The effect of spatial resolution on the accuracy of cerebral glucose measurements was illustrated by the study of Valk et al. from the Donner Laboratory and the University of California, Berkeley (No. 151). Not only were the images from their 600 crystal PET scanner of high technical quality, but they were also able to show that the higher spatial resolution resulted in an approximately 50% increase in the absolute values of glucose metabolism, an illustration of the "partial volume" effect.

The practical consequence of improved resolution was illustrated by a study from Kuwert and Feinendegen's group at the University of Dusseldorf (No. 175). In studies of cortical and sub-cortical glucose metabolism in patients with Huntington's disease (HD) and dementia, they found that the only significant relationship to the degree of dementia was reduction in cortical glucose metabolism, even though HD characteristically results in atrophy of the caudate nucleus and putamen. The cortical abnormality has not been described in HD in the past and possibly may be related to the high coefficient of variation with their previous scanners. With a variance of 20%, only differences on the order of 50% can be measured.

Better Instruments for PET and SPECT

Improvements continue to be made in both PET and SPECT scanners. To cite examples, a new PET scanner was presented by Nohara et al. that has been designed for use in a combined University/Pharmacology research program at Hamamatsu City, Japan (No. 689). Another advanced instrument is the ASPECT, a SPECT scanner developed by Smith and Genna that has now reached the point of clinical studies (No. 281). It represents a new design based on the use of a large annular crystal.

SPECT Moves Ahead in Clinical Research

Largely as a result of better radiopharmaceuticals, improved scanners, and quantification of the results, SPECT is now playing an important role in clinical investigations. Odano and his colleagues from Niigata University quantified regional cerebral blood flow in patients with Parkinson's disease using ^{123}I iodoamphetamine (No. 421). Using the microsphere model based on the time course of the tracer in arterial blood after injection, they observed a relationship between the reduction in blood flow to the basal ganglia and the abnormalities of gait and freezing

(continued on page 1289)

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behavior of the patients with Parkinson's disease. They were not able to correlate the severity of dementia with reduction of regional blood flow in the frontal or parietal cortices. The only parameter that correlated with cerebral atrophy was global cerebral blood flow.

Epilepsy

Epilepsy was a major topic this year. The encouraging results from several institutions in partial complex epilepsy indicate that a collaborative, multi-institutional study should now be planned. In the mid-1960's the introduction of thrombolytic therapy (urokinase) in the treatment of pulmonary embolism relied heavily on the development of lung scanning in order to assess the effectiveness of treatment. PET and SPECT could play a similar role in bringing about a more extensive application of surgical treatment of partial complex epilepsy. Why not?

Today, very few operations are performed in patients with temporal lobe epilepsy, despite the fact that 50,000 patients in the US are poorly responsive to medical treatment and might be cured by removal of the offending focus—if such foci could be identified. Many of these patients, even without anatomical lesions detectable by MRI or CT, have been found to have reduced glucose metabolism at the site of the seizure focus, usually in the temporal lobes, even when the patients are examined between seizures. Other chemical abnormalities were detected by Frost et al. from The Johns Hopkins Medical Institutions, who reported that ^{11}C carfentanil binding to mu-type opiate receptors was increased in 82% of 28 patients with temporal lobe epilepsy who had no CT or MRI abnormalities. Sixty-eight percent had reduced glucose metabolism on the affected side. Either reduced glucose metabolism or increased carfentanil binding was found in 93% of the patients (No. 91). The endpoint of the studies should be to determine whether the patients become seizure-free after removal of the offending focus, not simply whether the chemical results agree with the electrical. As is often the case in medicine, the best test is usually assumed to be perfect—until a better test comes along.

If PET clearly plays a role in epilepsy, what about SPECT? Park and colleagues from Indiana University measured regional cerebral blood flow with ^{123}I HIPDM (No. 95). They concluded that both interictal and ictal SPECT scanning are useful. In their experience, SPECT helped avoid invasive depth electrodes in 90% of the patients, with 80% of the identified lesions being in the temporal lobe. When the tracer was injected between seizures, the sensitivity was 74%. When the SPECT blood flow results were abnormal, the region was correctly identified 96% of the time. With injection during the seizure, the positive predictive value was also 96%.

In an excellent study by Rowe and colleagues from Melbourne, the results of regional blood flow studies in *interictal* studies were not able to meet the diagnostic challenge (No. 94). They preferred "post-ictal" injections of the tracer. In order to do the post-ictal studies, it was necessary to carry out continuous monitoring, often for days, to facilitate an injection after the seizure began but before the seizure activity spread throughout the brain. The Melbourne group was able to inject the patients within 5 to 10 minutes of the end of the seizures. This requires good communication, dedication, and speed. In these post-ictal studies, with blind visual inspection of the data and comparison with the results of depth electrodes, there was agreement in 69% of the cases, with 31% inconclusive. Quantification had about the same accuracy.

Good results with SPECT were also described by Devous, Bonte, and colleagues from The University of Texas Southwestern Medical Center, (No. 92), as well as by Feistel, Stefan, et al. from Erlangen, Federal Republic of Germany (FRG) (No. 93). The latter group also emphasized the value of injections during the seizures. A practical policy would seem to be to perform an interictal study, and then, if possible, to do an ictal study, although the latter may be difficult in some patients and impossible in others. The current improvements being made in the stability of technetium cerebral blood flow agents after labeling will simplify injecting the patients during seizures.

PET Focuses on the Heart

Over the past five years, there has been a twelve-fold increase in PET studies and a tripling in SPECT studies of the heart.

Several presentations pointed out problems with ^{201}Tl studies. Kalus, Schwaiger, and colleagues from the University of Michigan observed that ^{82}Ru had greater than 80% specificity compared to thallium studies where the specificity was approximately 50% in detection of coronary artery

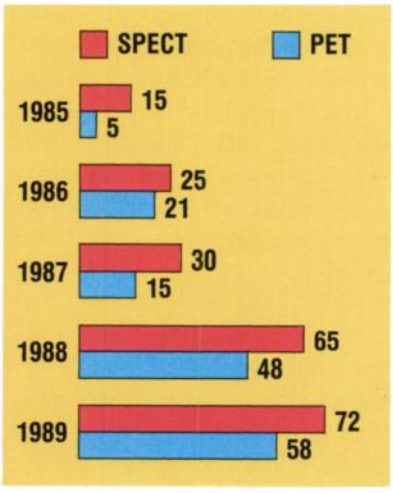

Figure 5. SNM Heart Studies

disease (No. 419). Both were very sensitive. Gould, a prominent advocate of the use of ^{82}Ru in coronary artery disease from the University of Texas, stated that PET can change cardiology practice from its traditional "symptoms and salvage" approach to an economical "screen and clean" approach with major health benefits. He believes that unexpected death or myocardial infarction need no longer be necessary outcomes of coronary artery disease. PET detection of ^{82}Ru defects correlated well with angiographic assessment of the degree of coronary blood flow restriction. Gould showed that if one can diagnose coronary artery disease soon enough, lowering the average concentration of serum low density lipoproteins by diet and other means resulted in a regression of stenotic lesions (No. 486). They also observed progression of the stenotic lesions in those persons with persistently high low density lipoprotein serum levels over the period of a year of follow up. Perhaps the documentation of coronary artery disease in an asymptomatic person can perhaps persuade him to change his life style and stick to a low fat diet. Such motivation usually follows an acute myocardial infarction, but then the diagnosis comes too late.

The question of whether ^{82}Ru PET studies of the heart can be successfully translated into clinical practice was addressed by Williams et al. from the Atlanta Cardiology Group and St. Joseph's Hospital (No. 485). These investigations carried out extensive comparisons of ^{82}Ru PET with coronary angiography, and found a sensitivity of 95% and a specificity of 92%.

The development of a three dimensional display of cardiac metabolism measured with ^{15}O by Miller et al. from Washington University illustrates the continually improving data display systems that can aid in subjective interpretation of cardiac images as well as help us move closer to automated interpretation of myocardial images (No. 329). The NIH group of Bacharach et al. described a way to measure myocardial blood flow with $H_2^{15}O$ without an accompanying blood pool scan, which is an important simplification (No. 326).

Shelton, Welch, et al. from Washington University and Purdue University proposed the use of a generator system to produce copper-62 PTSM, a semicarbazone, for measurement of regional blood flow in the heart and brain because of its high extraction even at high coronary flow rates (No. 325).

Oda and colleagues from Kyoto, Japan described the use of nuclear medicine technology in basic cardiology research (No. 578). In the past, the effects of nitrate were believed to be primarily on the peripheral circulation, not directly on the heart. This study with ^{15}O showed that in normal areas of the heart, there was a reduction in blood flow after nitrate administration, but in abnormal areas, there was an increase. For basic science studies, the use of ^{11}C acetate washout is a useful index of myocardial oxygen consumption and was shown by Henes et al. from Washington University to be related to myocardial work as indicated by the heart rate—pressure product (No. 452).

Just as in the brain it is often useful to combine electrical with biochemical measurements, so also it is true for the heart. Takahashi et al. of Akita Medical Center examined the relationship between electrocardiographic Q waves and glucose metabolism of the myocardium during induced ischemia (No. 420). In the normal fasting state, the heart metabolizes little glucose, but uses fatty acid as its principle energy source. When coronary blood flow is reduced, glucose metabolism increases proportionately, to a point where necrosis occurs when glucose metabolism falls dramatically. During a mild reduction of coronary blood flow, there are no Q waves, but as the heart becomes increasingly ischemic, glucose metabolism falls and Q waves appear. Another demonstration of the value of glucose metabolism as a reflection of live but impaired myocardium was the study of reperfusion by Bianco et al. from the University of Wisconsin (No. 285). In reperfusion autoradiographic images after release of coronary artery ligation, the distribution of ^{201}Tl may indicate nearly normal flow while glycogen stores in the reperfused region are depleted and glucose metabolism is greatly increased. Thus, it is increasingly clear that there may be detectable biochemical abnormalities in damaged but living myocardium even when blood flow has been restored. Reperfusion therapy is common in cardiology practice today, and nuclear medicine can play a major role in planning and monitoring the effectiveness of treatment.

Kotler, Berman, et al. at Cedars Sinai and UCLA compared ^{201}Tl rest-redistribution studies in detecting viable myocardial segments after thrombolysis. They found that fixed ^{201}Tl defects, even after 24 hours, were often found in regions where deoxyglucose metabolism persisted (No. 1). ^{201}Tl redistribution has only a 58% sensitivity in picking up reperfused, viable myocardial segments. Ohtani, Tamaki, et al. from Kyoto University (No. 561) reported that 18 out of 43 patients with persistent (fixed) ^{201}Tl defects in redistribution studies had either normal or only reduced glucose metabolism, indicating damaged but living tissue. Thus, the detection of transient ^{201}Tl defects—even in 24 hour delayed studies—may not be sufficiently sensitive for the detection of viable myocardical regions after myocardial infarction or after reperfusion techniques, such as thrombolysis.

An important question is whether technetium-99m myocardial blood

flow agents, such as the isonitriles, will eventually replace ^{201}Tl. In a direct comparison, Normand et al. from Clermont-Ferrand, France, reported that perfusion defects are usually larger in ^{201}Tl images than in those performed with isonitriles (No. 571). In *in vitro* studies of beating, cultured myocardial cells damaged by cyanide, Maublant et al. observed that both ^{201}Tl and ^{99m}Tc isontriles had greatly decreased accumulation, even before the cells were irreversibly damaged. (No. 551).

A major advantage of the ^{99m}Tc-isonitrile myocardial blood flow agents over ^{201}Tl is that the distribution within the myocardium remains fixed. As described by Faraggi et al. from Hospital Beaujon, Clichy, France, one can inject the patient immediately upon arrival in an emergency room, treat the patient with tissue plasminogen activator (TPA) or some other thrombolytic agent, and after a few hours carry out the imaging that will assess the original problem (No. 379). This distribution of the tracer is then a baseline for later assessment of the value of a particular treatment such as thrombolysis (No. 379). Another example of the use of myocardial perfusion agents to monitor treatment is that of Gregoire et al. of the Montreal Heart Institute who carried out serial isonitrile myocardial perfusion studies to assess reperfusion after myocardial infarction (No. 295). Nuclear medicine studies played a major role in the initial clinical trials leading to the Food and Drug Administration's decision to approve the use of TPA. This accelerated the application of thrombolytic therapy, which has greatly reduced the mortality from myocardial infarction in the US and other countries.

The Big News: Neurocardiology

The metabolism of norepinephrine in presynaptic and postsynaptic neurons has been explored in detail as a result of the pioneering work of Axelrod and his colleagues at the NIH. The amino acid tyrosine is converted to dopa, which in turn is converted into dopamine, which is converted to norepinephrine, which is then stored in vesicles until it is secreted into synapses. These vesicles also incorporate the guanethedine analogue, metaiodobenzylguanidine (MIBG), the first agent to be used to assess sympathetic nerves in the heart. The most recent agent for this purpose—from Wieland et al. from the University of Michigan—is ^{11}C hydroxyephedrine (No. 161), which can also be used to assess the status of presynaptic beta adrenergic neuronal activity by PET. In patients with heart transplants, which are denervated, there is an almost complete absence of accumulation of the ^{11}C hydroxyephedrine. Such agents complement the use of ligands, such as iodocyanopindolol, described by Sisson and his colleagues from the University of Michigan, to assess postsynaptic adrenergic receptors (No. 158). These radioligands can be used to assess the sympathetic innervation of the heart and may even prove to be more sensitive in the detection of coronary artery disease than myocardial blood flow agents.

Several papers reported that the MIBG defects are often larger than the perfusion defects in coronary heart disease. This phenomenon was first described by Wellman at Indiana University and has been confirmed by others.

Nishimura and colleagues from the National Cardiovascular Center in Osaka, Japan examined the canine myocardium after acute myocardial infarction. After release of occlusion, the greatly reduced epinephrine levels returned to normal except in the necrotic regions (No. 160). Even areas remote from the hypoperfused area had reduced epinephrine concentrations, as did the "jeopardized" areas surrounding the necrotic region. It is from such areas that subsequent arrhythmias occur. These and other studies support the important concept that the myocardial sympathetic nerves are very sensitive to damage. When synaptic epinephrine falls, it is possible that adrenergic receptors are increased ("up-regulated") and thus may become hyperresponsive to a sudden increase in plasma catechols from the adrenal gland after administration of cocaine (Som's work cited previously). The depletion of epinephrine in the damaged myocardium may be a factor in the predispostion to arrhythmias. McGhie et al. from Southwestern Medical Center related defects in sympathetic innervation to ventricular ectopy (No. 300). They found that when there was a large defect in innervation of the myocardium, there was a significantly greater likelihood of ventricular ectopy, that is, ventricular premature contractions, paired beats, etc. In other words, their work supports the concept that sympathetic denervation may predispose the patient to ventricular arrhythmias. This provides an important new approach that could result in a decrease in sudden death. Why not?

Merlet, Bourgignon, and their colleagues from Orsay, France, showed the value of examining the sympathetic innervation of the heart to predict whether patients with cardiomyopathy are likely to go into heart failure (No. 337). Such patients are known to have depleted epinephrine stores in the heart, and at times are treated by beta adrenergic stimulants (agonists). Bourgignon found that if there was evidence of sympathetic denervation, the patients were likely to go into heart failure. To increase the sensitivity of the MIBG test, Rabinovitch et al. of Montreal General Hospital proposed the administration of clonidine, a drug that blocks the alpha adrenergic system. The response to clonidine was increased accumulation or

delayed clearance of MIBG.

Another tracer of interest recently developed for the study of the heart, was serum amyloid protein (SAP), developed by Hawkins and colleagues of Hammersmith Hospital in London for the diagnosis of amyloidosis (No. 492). Using ^{123}I SAP, they were able to localize amyloid deposits in various parts of the body.

Several papers addressed the question of normal arteriograms in patients with unexplained chest pain. Results with labeled fatty acids suggest that coronary arteriography is another sacred cow that's going to join the herd of angiographic techniques assumed to have been 100% accurate until some thing better came along. Abnormalities in fatty acid metabolism were demonstrated by Kahn et al. from Southwestern Medical Center in patients with chest pain and normal coronary angiography (No. 415). In their study, 35% of the patients with normal coronary arteriograms and chest pain had either reduced up take of the iodophenylpentadecanoic acid (IPPA) or had both reduced uptake and washout of the tracer. Similar results were reported by Szabo et al. from Dusseldorf (No. 418).

To summarize, it is remarkable that 55 of the cardiology presentations were concerned with the jeopardized myocardium. Prognosis continues to be as important as diagnosis, with almost an equal number of papers addressing both aspects of heart disease.

Pulmonary Disease

Tulchinsky, Zeller, and Reba from George Washington University described the use of urinary fibrinopeptide as an adjunct to lung scanning in the diagnosis of pulmonary embolism (No. 19). Hatazawa et al. from Tohoku University in Japan reported the use of PET to improve the quantification of pulmonary mucociliary transport of inhaled particles (No. 798).

To explain the mechanism of the so-called "reverse mismatch" in pulmonary V/Q imaging (No. 24), Seo and others from Brooklyn, NY pointed out that the finding of greatly diminished ventilation with relatively normal perfusion is an emergency situation, which indicates acute, severe bronchial obstruction that should be treated by aspiration.

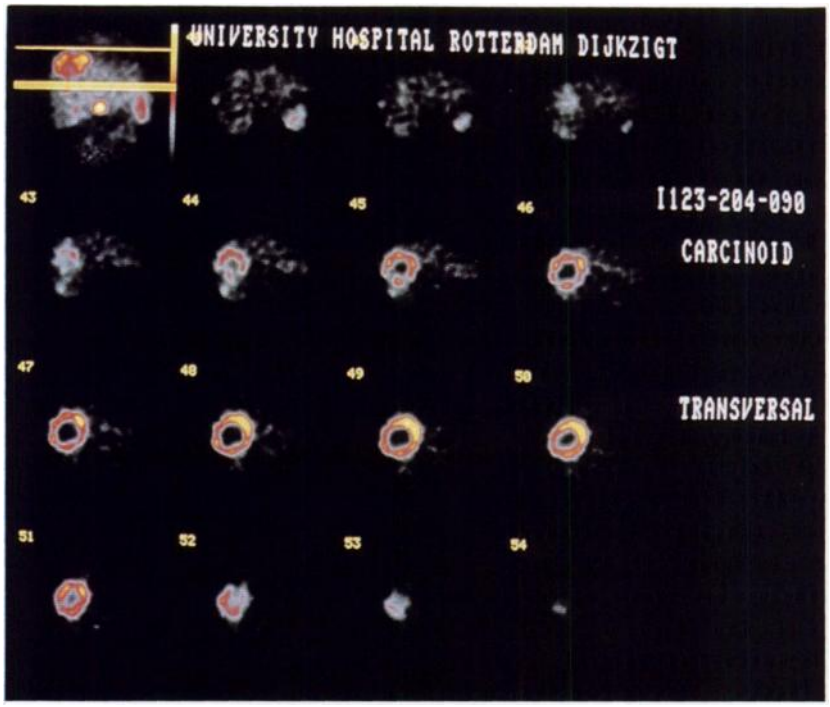

Figure 6.

PET Grows in Oncology

PET imaging is now achieving its deserved role in the study of cancer with 35 presentations at this meeting. SPECT is also advancing in this area. An important SPECT paper was that of Langen et al. from the University of Dusseldorf, who described the first clinical results of ^{123}I iodo methyl tyrosine in patients with brain tumors (No. 701). An example of a PET oncology presentation was that of Kubota et al. from Tohoku University who observed an accuracy of 79% for ^{11}C methionine in detecting metastatic cancer, compared to 86% for FDG in the same tumors. Strauss and colleagues from the German Cancer Research Center in Heidelberg have used positron-emitting tracers, particularly deoxyglucose and oxygen for measuring blood flow in both the detection of colonic metastases and in monitoring the metabolic response of tumors to chemotherapeutic agents (No. 249). Their results were particularly valuable in lesions near the bladder, where the use of monoclonal antibodies in the same patients presented problems.

Imaging estrogen receptors is now being used by McGuire et al. of Washington University and the University of Illinois to monitor therapy of breast tumors (No. 247). They also use PET imaging of estrogen receptors to assess whether metastases have estrogen receptors even when the primary breast tumor does not.

Another specific tracer in oncology described at this meeting was ^{123}I somatostatin, introduced by Bakker and colleagues from Rotterdam, in collaboration with the Sandoz Research Institute in Switzerland (No. 163). Striking results (Figure 6) were presented in patients with hepatic car-

(continued on page 1293)

(continued from page 1292)
cinoid tumors.

Monoclonal Antibodies

Twenty papers describing the use of monoclonal antibodies in human cancer were presented, the most effective uses being in colorectal and ovarian cancer, melanoma, and small cell cancer of the lung. A multicenter trial of monoclonal antibody fragments in imaging colorectal cancer was described by Serafini (No. 82). Accuracy in the detection of lesions greater than 1 cm in diameter in 60 patients in the six different institutions ranged from 69% to 82%. There were no untoward side effects of the drug. The value of this technique is to help identify the 25% or 35% of the patients with colorectal cancer who have metastatic disease within a year of the original diagnosis.

In ovarian cancer, Bockisch et al. from Bonn University described an overall accuracy of 80% in the study of 28 patients (No. 121). Is this accurate enough to eliminate the need for the "second look" operation, which is often performed routinely after about one year of the primary operation? In another study of 31 patients with ovarian cancer by Claessens et al. from Nijmegen, The Netherlands, 94% (17/18) of the patients with metastatic lesions identified at surgery were detected by preoperative imaging (No. 122). In small cell carcinoma of the lung, Abdel-Nabi et al. from SUNY at Buffalo and NeoRx Corporation reported a sensitivity of 72% (No. 373). The goal of these studies is to determine whether metastatic lesions can be found and removed surgically or need to be treated with chemotherapy. Another study of small cell carcinoma of the lung by Lamki et al. from MD Anderson Cancer Center in Houston, Texas, and NeoRx reported a sensitivity for detecting primary cancer of 100% and for metastatic cancer, 88% (No. 374). These presentations are examples of the 20 clinical papers concerning monoclonal antibodies, a doubling of the number presented last year.

> "Perhaps the greatest role that nuclear medicine can play in cancer is helping elucidate the body's normal mechanisms for keeping us all from getting cancer."

A question asked by Sumerdon et al. from Abbott Laboratories was whether combinations of diagnostic monoclonal antibodies would interfere with each other. Apparently they do not (No. 877). Perhaps diagnostic monoclonal antibody "cocktails" can be developed in the future in a manner analogous to broad-spectrum antibiotics.

There is a place for radiopharmaceuticals other than monoclonal antibodies, positron-emitting substrate tracers, and PET and SPECT receptor ligands in the study of cancer. These include ^{99m}Tc isonitriles and ^{201}Tl, used by Muller et al. from Essen, FRG, to detect tumors such as bronchial cancer (No. 483). For example, in the case of coin lesions detected in chest radiographs, the demonstration of high blood flow to the lesions is a sign that the lesion is probably cancer, and should be biopsied or removed.

Treatment of Bone Pain

The study of Lamki et al. from MD Anderson Cancer Center indicates that there is still a role for palliative radionuclide treatment of bone pain (No. 448). HR Maxon et al. used rhenium-186 HEDP to treat men with painful carcinoma of the prostate after hormonal or external radiation therapy had not proved satisfactory (No. 450). In their 20 patients, five became pain free, 11 experienced improvement.

Perhaps the greatest role that nuclear medicine can play in cancer is helping elucidate the body's normal mechanisms for keeping us all from getting cancer. The approach pioneered by Rosenberg et al. at the National Cancer Institute is based on the stimulation of natural defense mechanisms. One of these is the use of granulocyte and macrophage stimulating factors. A group from MD Anderson used ^{99m}Tc sulphur colloid bone marrow imaging to monitor the improvement in macrophage function resulting from this treatment (No. 38).

Novel Approaches

The use of simplified "probes" in nuclear medicine is finally becoming more commonplace. The VEST is a portable device that can be worn to continuously monitor ventricular function described by Kayden et al. from Yale University. (No. 171). A new surgical probe has been developed by Hartsough et al. from the University of Arizona (No. 683). The Arizona prototype is moved around by the surgeon and the data are gathered from as many as 42 positions, from which a computer generates images of the tracer distribution. In the future, perhaps a small imaging

(continued on page 1295)

COMMENTARY

into each rating. How much time and effort do these procedures take? How much emotional or mental stress do they create? How much follow-up time is required? How much preparation time is required? How are you going to factor quality control into this system? How can you factor the issues of supervision and concurrent care into these ratings?

We cannot attempt to, nor would we want to tell you how to rate procedures. However, it is vital to the future of nuclear medicine that you carefully consider the ratings you will give to each procedure. How does it relate to the base procedure, and how does it relate to other procedures on the list? Honest ratings of these procedures are essential. This cannot be dashed off quickly. We urge that significant thought be given to the ratings by those contacted.

Careful attention to this survey will help avoid the errors in the data base that plague the Radiology RVS. We would like to avoid all the problems we have encountered during the recent Radiology RVS by having our practitioners understand and accurately complete the Harvard RBRVS questionnaire.

Full cooperation with the Harvard group is required to enable them to gather data that will be valid for use in structuring the nuclear medicine RBRVS.

Robert E. Henkin, MD
President-Elect
American College of Nuclear Physicians

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device will be by the side of every surgeon at the operating table.

Another novel approach to instrumentation is the study from Ulm, FRG, by Henze et al. (No. 444), who have provided quantification techniques to tell the dentist or the radiologist looking at dental x-rays the metabolic activity associated with various structural abnormalities in the mandible and the maxilla.

Pharmaceutical Research Centers

The combined use of PET/SPECT imaging and magnetic resonance spectroscopy (MRS) offer a whole new approach to drug design, development, and evaluation. Wolf et al. from the University of Southern California and Siemens Medical Systems demonstrated how MRS with fluorine-19 5-fluorouracil can be used to select specific patients in whom therapy with this drug is likely to be effective (No. 352). They found that when there was trapping of unmetabolized drug, there was a better response than when this did not occur.

The use of PET/SPECT in pharmacology raises the question of dedicated animal scanners. A group from Brookhaven National Laboratory, Hammatsu Photonics, University of Massachusetts, Worcester, and Jiangsu Institute of Nuclear Medicine, Peoples Republic of China, is developing a device to look at iodine-125, but problems of sensitivity must still be solved (No. 280). Digby and Hoffman from UCLA presented design considerations and simulation studies of an animal PET scanner with a spatial resolution of 2.5 mm (No. 688).

The Future

Three decades ago, we began to use rectilinear scanners, with three to five inch crystals in order to obtain anatomical information about organs such as the thyroid, kidneys, spleen, and liver that could not be seen in x-rays. This meeting documents the tremendous progress that has been made since that time.

In 1668, John Locke said: "Anatomy is absolutely necessary to a surgeon, but that anatomy is likely to afford any great improvement in the practice of physics, I have reason to doubt. All that anatomy can do is show us the gross and sensible parts of the body." When we are able to map the entire human genome, we will have the ultimate in anatomy, but it still will be only anatomy.

Almost 500 years ago, Paracelsus said: "The body is a conglomeration of chemical reactions. When these are deranged only chemical medicines can correct them." Imaging *in vivo* chemistry remains the most fundamental principle of nuclear medicine. Why not?

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