SCIENTIFIC HIGHLIGHTS OF THE EANM CONGRESS 1992

The European Association of Nuclear Medicine Congress took place from August 22-26, 1992 in Lisbon, Portugal. Prof. Dr. Eberhard Henze, director of nuclear medicine at Christian Albrechts University, Kiel, Germany, delivered the highlights lecture excerpted here. The numbers in parentheses refer to abstract numbers listed in the August 1992 issue of the European Journal of Nuclear Medicine. (Dr. Henze is publishing a more detailed review of the highlights in a forthcoming issue of EJNM.)

IN PREPARING THIS lecture I chose to focus on work that offers important and new information about new tracers and protocols available to the general nuclear medicine community. I've also emphasized new procedures that offer clinicians more sensitive and specific information by using labeled molecules for diagnosing disease, characterizing lesions and helping in treatment planning.

After three years, the labeled somatostatin derivative, octreotide, remains the most exciting tracer discussed at the annual meeting of the EANM. This peptide messenger may be labeled with iodine-123 and iodine-131, or chelated with indium-111 to make a nearly ideal tracer.

Application of Labeled Octreotide

Kwekkeboom, Krenning, and Lamberts examined more than 1,000 patients to show the diagnostic value of this tracer in imaging somatostatin receptor sites in a wide variety of neuroendocrine tumors, breast cancers, non-Hodgkin and Hodgkin lymphomas, granulomata, sarcoidosis and other diseases (#222-1). Activated T-lymphocytes also seem to carry receptors, which might enable us to image the active phase in the development of autoimmune diseases such as the ophthalmopathy of active Grave's disease. Kwekkeboom remarked that the small peptide is easy to label, has a highly specific binding to the receptors, and long lasting affinity to the receptor. No antibody formation has been observed and visualization of small tumors is possible because of high target-to-background ratios–raising the possibility of therapy with ^{131}I-labeled octreotide. Radiochemists might be encouraged to continue their efforts in labeling the many other peptide substrates that have been identified over the past years as important physiological messengers.

One group experimented with dual tracers for targeting neuroblastoma, carcinoid, and pancreatic tumors. Nokaudie and colleagues used ^{123}I-octreotide with ^{131}I-MIBG and found a good correlation between the octreotide and MIBG uptake with optimum tumor identification (#133-2). This result was confirmed in studies by van Dogen (#5P1-4) and Woltz (#133-6), who noted a disadvantage of iodinated octreotide: clearance via the gall bladder might obscure some abdominal tumors. The point of these two studies, however, is that for the first time two different tracers with a high affinity for tumors are available, both of which might be labeled with ^{131}I and used concomitantly for treatment similar to poly-chemotherapy.

Becker (#DP2-1) showed that positive ^{123}I octreotide imaging is predictive of therapeutic response with non–labeled octreotide. Verhoeff (#5P1-4) and Ivancevic (#DP1-8) showed that with ^{111}In-octreotide, high-resolution, high-contrast images can be obtained for identifying even very small lesions.

Cardiovascular Developments

The heart remains one of the foremost subjects of nuclear medicine research. FTHA, a new fatty acid analog labeled with fluorine-18 for positron emission tomography was presented by Ebert (#212-3). Oxidation of FTHA (14-[^{18}F]-fluoro-6-thia-heptadecanoic acid) is blocked by the sulfo-hetero atom, so the compound is not metabolized like a normal fatty acid and the tracer is trapped in the myocardium (Fig. 1). Prior to FTHA, only carbon-11-labeled fatty acids were available for PET imaging. Taking advantage of the longer half-life of ^{18}F, in contrast to the ^{11}C-labeled fatty acids, FTHA can be shipped to clinical PET facilities not equipped with cyclotrons. Investigators showed that uptake of FTHA in the heart correlated quantitatively to cardiac workload.

Labeled with ^{123}I, other fatty acid analogs not subject to beta-oxidation might be of great value for identifying viable myocardium. Fagret (#4P5-6) presented preliminary data using IMHA (16-[^{123}I]-iodo-3-methylhexadecanoic acid) compared to ^{18}F-fluorodeoxyglucose in 12 patients with previous myocardial infarction to determine myocardial viability within the infarcted segments. There was an impressive concordance of both imaging entities using FDG as a standard. IMHA appears to be a good indicator of myocardial viability, with a sensitivity of 97% and a specificity of 92%. IMHA seems to accumulate even better than thallium-201 after resting injection. Marie (#112-6) compared IMHA to a ^{201}Tl reinjection protocol and found that IMHA is a more sensitive indicator of viable myocardium than ^{201}Tl, which underestimated the size of the viable segments in up to 50% of patients. An additional advantage of IMHA is that only a single resting injection is needed. If further clinical studies

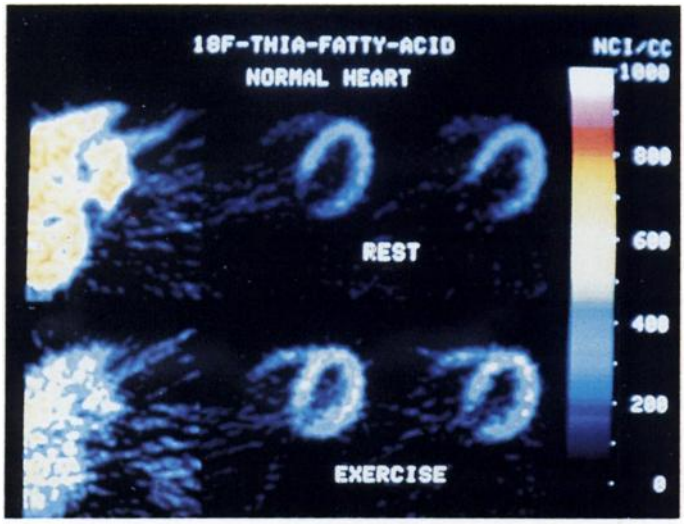

Figure 1: PET scans through the mid-section of a normal heart at rest and during exercise after intravenous administration of ^{18}F-thia-heptadecanoic acid. Note the increased uptake after exercise.

confirm these results, IMHA might become the most valuable tracer in identifying viable myocardium with conventional single-photon emission computed tomography. The studies on fatty acids are good examples of how the unique physiologic information previously obtained only with PET may be transferred to common imaging modalities.

While European PET institutions are prepared to provide routine FDG imaging for cardiology patients to evaluate viable but stunned or hibernating myocardium, conventional studies using delayed reinjection imaging with ^{201}Tl continue. Dalle Mule (#111-5) used an ingenious protocol in 32 consecutive patients who were candidates for coronary bypass surgery after having survived a myocardial infarction. He compared the reinjection/redistribution defect size to the outcome of the bypass grafting and found a positive correlation to the degree of wall thickening improvement and the time to such improvement. They proposed that ^{201}Tl reinjection imaging might predict functional recovery after bypass grafting. In Bartensteins's presentation (#112-1), the extent of redistribution correlated positively with the extent of collaterals in the area under consideration, an important finding that sheds light on the possible underlying physiology of redistribution following a second ^{201}Tl injection. Other groups tested early-reinjection protocols, such as in the Italian multi-center study presented by Baldari (#112-2) or that of van Eck-Smit (#112-5). These studies proposed more-or-less immediate reinjection of ^{201}Tl after the stress study has been completed, providing a time-saving and comfortable approach for the patient, with almost the same results as obtained by 24-hour delayed reinjection imaging.

For the first time, a dobutamine-infusion protocol has been compared with dipyridamole. Mester and colleagues (#113-2) showed that dobutamine enables testing of similar accuracy to dipyridamole when used as a substitute for exercise.

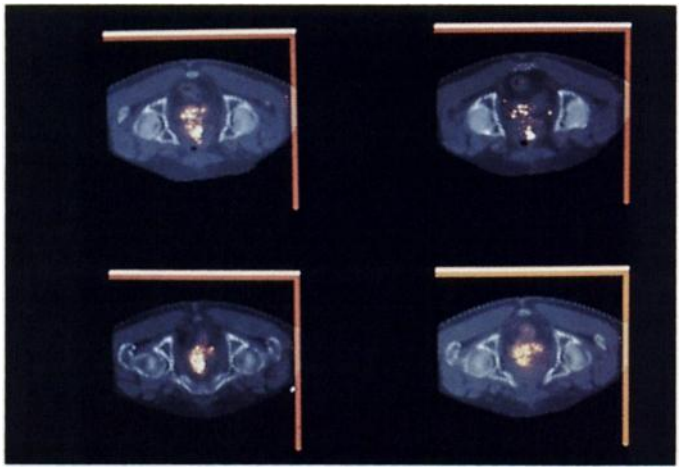

Figure 2: FDG-PET imaging in a patient with prostatic cancer. The PET study is superimposed onto an MRI, thus providing an excellent correlation of viable tumor tissue to tumor localization within the large pelvic tumor mass.

Managing Cancer

Providing high sensitivity, high specificity diagnostic tests to the oncology patient population should remain one of the major goals of nuclear medicine. Of the newer imaging modalities, FDG-PET has gained considerable interest. For the general nuclear medicine community, however, a more interesting proposition has caused greater interest: ^{201}Tl SPECT imaging might work as well as FDG-PET in the detection of viable tumor tissue. Thallium is an analog of potassium, which behaves similarly to glucose in some physiological aspects of tumor uptake, for instance, in its uptake kinetics and dependence on insulin. Thallium scans might yield information similar to imaging with labeled glucose, both in cardiology and in oncology. Investigators have known for years that ^{201}Tl is an excellent tumor imaging agent, presumably because of the relatively enhanced blood supply of tumors. Many studies at this meeting as well as at the latest Society of Nuclear Medicine meeting give evidence that the uptake of ^{201}Tl in tumors might also be due to the similarities between the kinetics of thallium (and perhaps other tracers like sestamibi) and glucose.

Summarizing the diagnostic accuracy of different imaging approaches, Haynie (#123-1) presented results obtained in 56 patients with bone or soft tissue sarcoma concomitantly using FDG-PET, CT/MRI, and conventional SPECT imaging with ^{201}Tl or ^{99m}Tc sestamibi. His summary table indicated the excellent performance of conventional SPECT imaging with ^{201}Tl or sestamibi.

Maublant (#222-5) compared the uptake of ^{201}Tl, ^{99m}Tc sestamibi and ^{99m}Tc teboroxime in neoplastic cell cultures. He showed that cellular uptake of ^{201}Tl and sestamibi increases with metabolic activity, evidence that both substances might reflect tumor growth rather than just tumor perfusion.

The combined use of ^{201}Tl and ^{131}I-MIBG imaging in neuroendocrine tumors was presented in a study by Montravers (#132-4). With 107 examinations, the study demonstrated the value of additional ^{201}Tl imaging in medullary carcinoma and in paraganglioma. Metastases did not image well with MIBG alone. In pheochromocytomas, however, thallium seemed to be of less value. This latter finding challenges the results of a study presented by Shulkin (#132-2), who investigated pheochromocytomas in which MIBG did not accumulate but FDG did. How would ^{201}Tl have performed in this setting? Nuclear medicine stands ready to offer many different and specific tracers to characterize tumors. A tumor or its metastases might be positive or negative with ^{111}In octreotide, ^{123}I-MIBG, ^{201}Tl, ^{99m}Tc-Sestamibi, labeled monoclonal antibody, or ^{18}F-FDG. We still don't know the impact of the many possible combinations. Research with multi-tracer characterization is just beginning. Conceivably, multi-tracer studies will help to sub-type tumor tissue in vivo for further applications, i.e., for proposing or designing new treatment approaches, applying differentiated treatment, or predicting different outcome and survival rates.

As for PET, Burchert (#122-5) emphasized the need for using not only qualitative image interpretation but also to correlate FDG metabolic studies to regional blood flow and to use more sophisticated processing steps to separate glucose uptake in normal liver tissues from liver metastases. Even small foci of residual tumor tissue during a treatment course can be clearly recognized where simple visual image interpretation would have failed.

A study presented by Adler (#112-3) evaluated the additional value of FDG-PET in detecting affected axillary lymph nodes in known primary breast tumor. Of 19 breast tumors, 7 positive axillary lesions were seen and this appears to be of great importance in the staging of breast tumors. Studying the differentiation of metastatic and non-metastatic prostatic carcinoma, Bares and colleagues found that metastatic prostate cancer shows a much higher glucose utilization rate in comparison to non-metastatic tumors without any correlation to tumor differentiation or proliferation (#122-4). This group optimized data presentation by superimposing the PET and NMR images, a technique that will help increase the acceptance of nuclear medicine studies by our clinical colleagues (Fig. 2).

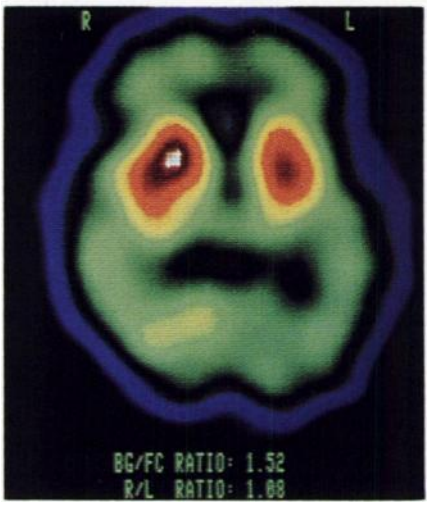

Figure 3: Imaging of the D2 receptors of the basal ganglia in a patient with Parkinson's disease, ^{123}I-IBZM SPECT shown on the left and ^{11}C raclopride PET shown on the right.

PET centers using FDG in tumor imaging and grading might be encouraged to parallel their FDG-PET studies with ^{201}Tl or ^{99m}Tc-sestamibi SPECT imaging to determine whether these or other conventional tracers are useful in tumor imaging.

Monoclonal antibodies directed towards more specific and new antigens are being developed and several convincing images were shown. Goldenberg imaged non-Hodgkin's lymphoma with LL2 monoclonal antibodies (#121-2) and reported initial results of treatment with ^{131}I-LL2 antibodies producing anti-tumor effects. Perhaps the new generation of monoclonal antibodies will do better than the first and will improve the impact of this unique imaging modality in cancer diagnosis and treatment.

Neurology and Psychiatry

In this expanding field of nuclear medicine applications, clinical studies with two new tracers were presented. The benzodiazepine receptor imaging agent ^{123}I-iomazenil was used in SPECT studies in patients with anxiety disorders. Feistel presented images of patients suffering from panic attacks (#242-1). The images revealed decreased receptor density in the left hippocampus or in the right temporal lobe. The clinical and physiologic impact of iomazenil in psychiatry and neurology will be substantial, judging from this study that seems to show for the first time that decreased receptor distribution can be documented and might be the underlying substrate of anxiety symptoms such as panic attacks.

Clinical studies with ^{123}I-iodobenzamide (IBZM), an imaging agent that allows visualization of the postsynaptic dopamine D2-receptors, revealed nearly the same information as the gold standard, ^{11}C-raclopride. Using IBZM to study patients with idiopathic Parkinson's syndrome (IPS), Tatsch found important physiologic mechanisms: drug naive IPS patients have normal or increased D2 receptor density, which is a prerequisite for positive response to dopaminergic drugs; IBZM binding to the basal ganglia seems to be asymmetric with a significantly higher accumulation at the contralateral side of disease manifestation; L-Dopa treatment does not compromise IBZM binding; and the binding capacity for IBZM fell significantly during treatment with dopamine agonists (#242-4, Fig. 3).

Similar studies by Castellano (#242-5) and Hertel (#242-6) differ slightly but

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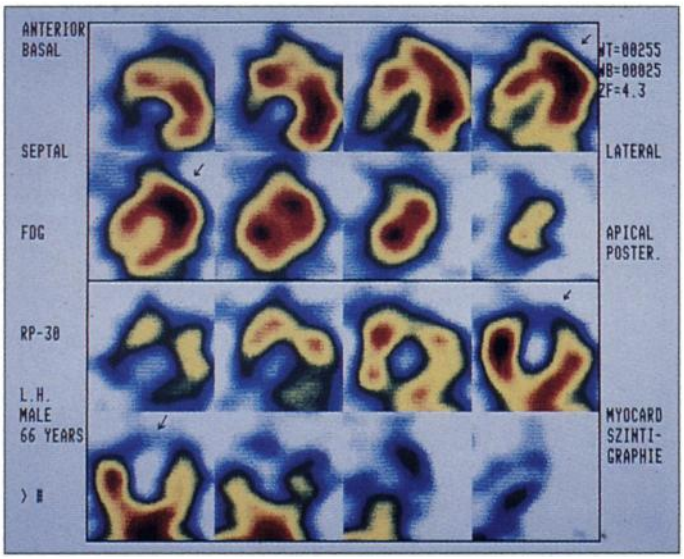

Figure 4: SPECT images of a patient with a perfusion defect apico-lateral as shown by ^{99m}Tc-sestamibi (arrow, lower panel) with well preserved glucose metabolism (arrow, upper panel) as demonstrated with ^{18}F-FDG but also using a SPECT camera.

confirm these findings, which means that a conventional D2 receptor imaging tracer is available commercially and can be used like ^{11}C-raclopride.

Resurrecting an easy-to-use but almost forgotten technique, Budihna applied first-pass gated evaluation of right ventricular function in patients submitted for lung perfusion scintigraphy with suspected lung embolism (#331-5). The additional knowledge of right ventricular function in patients with suspected pulmonary embolism seems to be clinically valuable. In patients with high probability of lung embolism (seen on the perfusion scans), the right ventricular ejection fraction was significantly depressed, averaging 47 ± 13%. The documentation of right ventricular function recovery in the follow-up of this type of patients has another clinical impact.

An ingenious new approach for quantifying shunt volume was presented by Botelho, who used ECG-gated blood pool imaging over the lung to quantify pulmonary shunts by amplitude and phase analysis of the images (#221-1). Pulmonary blood flow at greater phase angles represents the abnormal shunting volume. An excellent linear relationship (r=0.92) was found between the ECG-gated technique and the thermodilution technique.

Reporting the results of the European multi-center captopril study of patients suffering from renovascular hypertension, Fommei said the technique is useful before angiography for the detection of major stenoses, it is a highly prognostic test to predict the outcome of arteriographic interventions, and it is an excellent follow-up procedure to monitor the success of surgical intervention (#131-2). All the tracers used–DTPA, MAG3, and hippuran–seemed to have similar value.

Emerging Radionuclide Therapy

Of the many new therapy agents, samarium-153 EDTMP, seems to be stirring considerable interest. The tracer accumulates in bone as an imaging agent due to its phosphate group, but other characteristics (half-life of 46 hours, optimum beta-emission, and 103 keV gamma emission) make it suitable for therapy and imaging. The quality of scans is comparable to that of imaging with conventional bone tracers and allows a physician to document tracer kinetics in individual patients, which means more accurate estimates of radiation dose to the metastases and to the critical organs. Initial results in fifteen patients with bone metastases were presented by Ahonen (#341-3). Only two out of the fifteen patients were absolute non-responders and myelotoxicity was found in only one patient. Pain relief occurred within one week and lasted from two to seventeen weeks.

Technical Innovations

One important step in improving the performance of SPECT is attenuation correction. As a pragmatic solution, Bourguignon devised a simple method by dividing each actual pixel value of the emission projections by the average of all the attenuation factors of all voxels along the same projection line (#441-2). This method, which resembles filtered backprojection algorithms, has been applied in cardiac and cerebral scans and was reported to be to easy to use and helpful.

Technical details of a very high resolution gamma camera prototype were reported by Pani (#141-1). The innovation is based on a new type of photo multiplier with a cross-wired anode 6 cm in diameter and an intrinsic spatial resolution of about 300 microns. In impressive tomographic images of a rat brain, one could clearly separate grey and white matter even in so small a specimen.

By equipping a conventional SPECT camera with a very thick collimator, Stoll obtained SPECT images satisfactory for clinical decision making in patients injected with ^{18}F-FDG (#111-1, Fig. 4). All the advantages of the PET tracers might become possible without the expense of a PET scanner. Widespread application depends on whether industry will seize the idea and manufacture these special collimators, which may weigh up to 250 kg.

The annual meeting of the European Association of Nuclear Medicine of 1992 at Lisbon provided stimulating news in the field of clinical nuclear medicine. Many new tracers that can be used with conventional nuclear medicine equipment are commercially available in Europe. PET continues to document new physiology, stimulating the research for tracers and protocols available for general use. These exciting new tracers, ingenious methods, and novel approaches should gain widespread use in the European nuclear medicine community, for the benefit of patients and our discipline.

E. Henze, MD