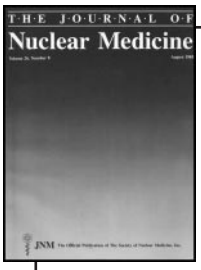
SNM Highlights as History: 1987



From the original 1987 SNM Highlights Lecture

Slices of Life

The year 1987 will be remembered as a turning point for nuclear medicine. Everyone with whom I spoke at this SNM Annual Meeting commented on the high quality of the science and the enthusiasm of all participants. Important contributions came from overseas—10% of the presentations were from Japan and 15% from Europe, contributing enormously to the overall excellence of the meeting.

Three years ago, the predominant theme of the SNM Annual Meeting was that chemistry was playing an increasing role in nuclear medicine. Two years ago, "PET was it!" Last year it became clear that "SPECT was also it!" For 1987, I propose as a theme "Slices of Life": slices indicate the steady growth of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) in nuclear medicine; life indicates our unique privilege of being able to view the chemistry of the living human body in health and disease.

Recognition Sites

A necessary function of living human beings (indeed, of all living things) is communication. Today, biomedical researchers are trying to find out how cells communicate with each other, and how these mechanisms break down in disease. Understanding how a cell recognizes molecules is a first step in understanding intercellular communication. Recognition sites on cell membranes include neuroreceptors, enzymes, and transport processes, all of which are now being studied in living human beings.

Henry N. Wagner, Jr., MD

We can see an excellent example of how the examination of recognition sites can play an important role in the practice of medicine in the work of Mark A. Mintun, MD, Michael J. Welch, PhD, and their colleagues at Washington University, St. Louis, in collaboration with John A. Katzenellenbogen, PhD, of the University of Illinois. This group, using fluorine-18 estradiol, successfully imaged receptors in primary and metastatic breast tumors, which in the past was only possible in excised tissue. Identifying the presence of estrogen receptors *in situ* provides evidence that patients can be treated with estrogen receptor antagonists, which is effective in about two-thirds of these patients.

This group's research is directed toward imaging progesterone receptors with fluorine-18 progestin, reported by Martin G. Pomper, MD. Progesterone receptors may be a better prognostic indicator than estrogen receptors, and a progesterone receptor tracer would make it possible to monitor breast tumors while the patient is being treated with drugs, such as estrogen and antiestrogen, that block estrogen receptors.

Most therapeutic drugs act by either blocking or stimulating receptors, and the ability to monitor receptors is an important new direction in clinical pharmacology.

Image of the Year

For all these reasons, my candidate for "Image of the Year" in 1987 is this group's study of estrogen receptors in metastatic breast cancer, achieved after years of in-

25 Years of Highlights

The Highlights Lectures, delivered by Henry N. Wagner, Jr., MD, at the annual meeting of the SNM every year since 1977, form a series of snapshots of the evolution of nuclear medicine. As part of the celebration of the Society's 50th anniversary, Wagner has gone back to review the original texts of these presentations. During 2003 and 2004, Newsline is presenting excerpts from the original lectures, often accompanied by present-day reflections on aspects of changing practice and technology. This month, original passages from the 1987 lecture reflect the growing interest in molecular imaging, neurocardiology, and brain chemistry. On the following page, Wagner looks back to 1987 and the origins of Japanese–U.S. cooperation on exploring the basics of brain chemistry to explain the mechanisms of war and aggression. (A number of other topics were addressed in the 1987 Highlights Lecture, for which the complete text is available at www.snm.org/pdf/highlights_lecture_1987.pdf.)

vestigation. Today's research will become tomorrow's practice, just as yesterday's research is today's practice.

Another example of using recognition sites is the work of Dean F. Wong, MD, et al. who identified dopamine receptors in pituitary tumors. If a pituitary tumor has dopamine receptors, the administration of a dopamine receptor agonist, such as bromocriptine, will often shrink the tumor to the point where surgery can be avoided. Dopamine receptors can be identified by PET imaging when plasma levels of prolactin (another test for functional pituitary tumors) are still within normal limits.

"Chemical biopsy" of adrenal masses can be carried out with iodine-131 iodomethylnorcholesterol, employed by Milton D. Gross, MD, et al. at the University of Michigan, and the Veterans Administration (VA) Medical Centers in Ann Arbor, to help determine whether such masses are benign or malignant. While hyperfunctioning adrenal masses usually indicate Cushing's disease or adrenal hyperplasia, hypofunctioning tumors are often malignant, and normally functioning masses are usually benign.

X-ray computed tomography (CT), nuclear magnetic resonance (NMR) imaging, and SPECT studies of adrenal masses by Michael G. Velchih, MD, Abass Alavi, MD, and investigators at the University of Pennsylvania again illustrate the principle of "slices of life." CT and NMR provide exquisite anatomic detail, but the images obtained during life could have been obtained even if the patient were dead. Radionuclide images, however, identify the suspicious mass as an adrenergic cell tumor, such as a pheochromocytoma, by demonstrating the accumulation of iodine-131 metaiodobenzylguanidine (MIBG) within an adrenal mass.

Radioiodinated MIBG can also be used to examine the rich adrenergic innervation of the heart. Patients with cardiomyopathy, whether it is idiopathic or caused by coronary artery disease, have problems with the autonomic innervation of the myocardium. Treating such patients with beta agonists, such as dobutamine, can improve ventricular function, as documented in a study presented by Roger A. Hurwitz, MD, and associates at Indiana University, Indianapolis. Iodine-123

Looking Back to 1987
Brain Chemistry: From Cold War to the Inner Mind

Half a century ago, Teruo Hiruma and 3 colleagues founded Hamamatsu Photonics, K.K., in Hamamatsu City, Japan. As president of the company, Hiruma recognized the increasing focus on photonics technology and understood that it was a technological breakthrough on the verge of tremendous, worldwide success. With more than 1,500 employees in 2003 and sales of hundreds of millions of dollars, the company's credits include the creation of pioneering designs and the manufacture of most photomultiplier tubes used in nuclear medicine.

I first met Hiruma in 1986, when he set his sights on designing and building the most advanced PET scanner in the world and on establishing a mind/brain imaging program. In January of that year, he met with his Hamamatsu colleagues, leaders of the National Institute of Radiological Sciences in Japan, and nuclear medicine physicians and scientists at Johns Hopkins University in Baltimore, MD, to discuss the establishment of a joint mind/brain imaging program. Hiruma was attracted to the idea that the suspicions and fears of the Cold War might be alleviated by collaborative scientific efforts in the study of brain chemistry associated with fear, violence, and war. He was particularly interested in possible applications of PET, which already was demonstrating its potential for imaging neuroreceptors in the living human brain in both health and disease.

Hiruma would later explain his motives to his friend, Nobel Physics Laureate A.M. Prokhorov, in an informal letter: "I see still big suspicion between country to country. Especially between USSR and Japan. . . . If the world continues to develop the science to kill people, in long future, the risk to destroy whole world may increase year by year. . . . When we say 'peace activity' in the past, this means propaganda against something like nuclear bomb. This is indirect. . . . We want to make peace scientifically. . . . Our peace activity is completely different from the past one. . . . Please help me and guide me if you agree with my dream."

On December 22, 1986, Hiruma, a representative from the Hopkins board of trustees, and I visited Steven Muller, president of the Johns Hopkins University, to get his approval for a collaborative effort between the university and Hamamatsu Photonics in the establishment of a joint mind/brain imaging program. The plan called for the development of a greatly improved PET scanner, better than any in existence at that time. The program was enthusiastically approved, but a problem subsequently arose because of its focus on the Johns Hopkins School of Public Health. (A widely repeated joke among Hopkins insiders at the time was that the "widest street in Baltimore" was Wolfe Street, which separated the hospital from the school of public health. Thankfully, the street has "narrowed" considerably over the years, and the 2

MIBG accumulation in such patients was found to be impaired, as reported by Jerry V. Glowniak, MD, and colleagues from the Portland VA Medical Center, Oregon Health Sciences University, and Crocker University Laboratories in Davis, California, which indicates that either myocardial autonomic nerves, themselves, or their adrenergic receptor are deficient.

To improve the specificity of assessment of the heart's autonomic innervation, Suresh G. Mislankar, PhD, et al., from the University of Michigan, synthesized an analogue of norepinephrine, fluorine-18 fluorometaraminol, a tracer that binds to catecholamine reuptake sites on presynaptic neurons. When norepinephrine or other catecholamines are secreted into a synapse, they bind to postsynaptic receptors, and are then taken back up into presynaptic reuptake sites or are metabolized by the enzyme monoamine oxidase (MAO). Fluorine-l8-labeled metaraminol can be used to indicate the functioning mass or presynaptic neurons.

Joanna S. Fowler, PhD, Alfred P Wolf, PhD, and their colleagues at Brookhaven National Laboratory synthesized carbon-11 deprenyl, a drug used to treat patients with depression, to image the distribution of MAO B in the heart. The rate of accumulation of the L-isomer was 25 times higher than that of the D-isomer, illustrating the stereospecificity of the binding. The same tracer, carbon-11 L-deprenyl, can cross the blood-brain barrier, permitting the study of MAO B enzymes within the brain. When a patient receives a therapeutic dose of deprenyl, the accumulation of subsequently administered carbon-11 deprenyl is blocked.

New Subspecialty of Neurocardiology

The use of L-deprenyl to study MAO B in both the brain and heart exemplifies the versatility of nuclear medicine. The ability to image the autonomic innervation of the heart helps to form the basis of the new subspecialty of neurocardiology, providing an approach

institutions work closely and collegially today.) In reviewing the proposed agreement, the dean of the Johns Hopkins School of Medicine wrote that "this machine should not be used for patient care and/or clinical research. . . . All patient care and/or clinical research should be done under the aegis of the School of Medicine (unless, of course, we are explicitly asked to do otherwise by our colleagues in Medicine)."

The newly created Mind/Brain Institute would subsequently be located on the Homewood campus of Johns Hopkins by Dr. Guy McKann. Today, the Mind/Brain Institute is a freestanding institute at the Hopkins with strong connections to the Krieger School of Arts and Sciences and to the School of Medicine (www.mb.jhu.edu).

On October 6, 1987, I was among 20 scientists and engineers from the United States, the Soviet Union, and Japan who went to Hamamatsu at Hiruma's invitation for a meeting on his planned initiatives. He wrote: "What we are trying to do is establish a program called 'Mind/Brain Science' as a means to a solution. . . . By undertaking a positron emission tomography project, as well as creating various photonic technologies, we hope there will be a generation of key scientific knowledge to elucidate why mankind must be in conflict at all times."

Among the attendees at the meeting was academician Natalia Bekhtereva, who succeeded Pavlov as director of the Leningrad Institute for Experimental Medicine. Bekhtereva had previously visited Hopkins, after expressing a desire to see our PET lab. In handwritten correspondence sent to me after the meeting, Bekhtereva posed a question in which she was interested: "What are the physiological changes in the brain when an emotional reaction is developing in an emotionally balanced as well as disbalanced [sic] brain?" She continued, "War for me has the ugly face of the blockage [siege] winter of 1941–1942 in Leningrad, where thousands of people died every day of bombing, hunger, and cold. I developed then a very intensive hatred toward any kind of war and this feeling never extinguished."

The 1987 meeting also marked the beginning of the development of the $80-million PET Center and Mind/Brain Imaging Program in the Hamakita Research Park, a 40-acre site owned by Hamamatsu Photonics near existing company facilities in Hamamatsu City. The following year, the first Mind/Brain International Conference was held in Hamamatsu City, with the title "Peace Through Mind/Brain Science." Numerous breakthroughs originated in this and subsequent international symposia sponsored by Hamamatsu's Research Foundation for Opto-Science and Technology.

Much remains to be done, and nuclear medicine researchers are still asking questions and finding new answers about characteristic changes in brain chemistry associated with emotions of fear, disgust, despair, and violence. Hiruma's efforts to encourage international cooperation in resolving the most basic questions that underlie shattering discord remain productive and inspiring.

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to investigating the problem of sudden death that afflicts over 300,000 Americans each year. The group at Hammersmith Hospital in London, England, previously showed that mental stress can often bring about the same degree of impaired regional coronary artery blood flow as exercise, revealing the truth in a statement made by William Harvey, the 17th-century British physician and anatomist who is credited with discovering blood circulation: "Every affection of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart."

A relation between the autonomic nervous system and substrate metabolism within the heart was illustrated by the studies of Michael E. Merhige, MD, K. Lance Gould, MD, and their colleagues at the University of Texas Health Science Center in Houston. This group found that infusions of dopamine, even when administered simultaneously with infusions of insulin and glucose, result in a shift from glucose to fatty acid metabolism.

Drs. William Wijns, J. Melin, and colleagues from the University of Louvain in Brussels, Belgium, showed that the shift to glucose metabolism in areas of "jeopardized" myocardium surrounding regions of infarctions is caused by myocyte metabolism, and not by the metabolism of accumulated leukocytes.

PET Blazes Trails for SPECT

Because so many useful radiotracers can be made with carbon-11 and fluorine-18, the cyclotron and PET are likely to remain in the forefront of nuclear medicine research. From this leading edge, advances extend to community hospital practice through the development of analogous single-photon emitting tracers, chiefly compounds labeled with iodine-123 and technetium-99m. The number of SPECT presentations doubled since last year and equaled the number of PET papers in 1987.

Tracers to study opiate, dopamine, serotonin, mucarinic cholinergic, and benzodiazapine receptors were discussed at this meeting, and several of these tracers are labeled with iodine-123. The development of tracers for studying muscarinic cholinergic and serotonin receptors began with tritiated compounds, and extended to tracers labeled first with positron emitters, and then with single-photon emitters. If PET is the heart of nuclear medicine, SPECT is becoming the muscle and bone.

Sophisticated Chemistry

An example of how sophisticated the chemistry of nuclear medicine has become was presented by John R. Lever, PhD, et al. in the labeling of diprenorphine with carbon-11. Diprenorphine is an antagonist that blocks all subtypes of opiate receptors. Compared with agonist tracers such as carbon-11 carfentanil, antagonists offer advantages for studying opiate receptors because they have far fewer pharmacologic effects, often none.

Attempts to label diprenorphine with carbon-11 in the past had produced only low yields. Dr. Lever found a new way to label the methyl group in the 6 position of diprenorphine, and synthesized a precursor that could be labeled with carbon-11 methyliodide. Methylamine in undesired positions was blocked by protective groups that were subsequently removed. His chemical yields were three times greater than the yields possible with previous methods, and the specific activity of the final product was high. Its chemical structure was confirmed by NMR spectroscopy, and the brain images obtained from a normal human subject were presented.

It is now well established that patients with partial complex (focal) epilepsy have reduced glucose metabolism at the seizure focus in the brain (often in the temporal lobe). These hypometabolic sites become hypermetabolic during seizures. Quantitative imaging of opiate receptors with carbon-11 carfentanil by J. James Frost, MD, et al. revealed that the regions of glucose hypometabolism in the temporal lobe had an increased rate of carfentanil binding compared with the unaffected side. Either the number of opiate receptors is increased or their occupancy by endogenous met-enkephalin is decreased. The increased binding showed a direct relation quantitatively to the reduction in glucose metabolism. The increased number of opiate receptors, or increased occupancy by met-enkephalin, may be a compensatory, neuronal dampening response to the hyperexcitability of the abnormal region during the seizures.

The way one goes about labeling a receptor-binding ligand with positron-emitting radionuclides was illustrated by Kazuhiko Yanai, MD et al. Carbon-11 pyrilamine, developed to examine H-1 histamine receptors, was produced with high specific activity in a synthesis time of 23 minutes. Investigators believe that H-1 histamine receptors in the cerebral cortex are involved in arousal and depression, and that these receptors in the hypothalamus are involved in appetite control, where abnormalities could cause diseases such as anorexia nervosa or obesity. Histamine receptors are involved in neuroendocrine regulation and, in the hypocampus and amygdala, are probably associated with epilepsy.