From the original 1984 SNM Meeting Highlights

1984 will be remembered as the year in which emission computed tomography, both positron emission tomography and single photon emission, moved into the mainstream of nuclear medicine; a movement at a time of considerable confusion concerning the relative roles of the plethora of imaging modalities, extending all the way from digital subtraction angiography to NMR imaging. Both PET and SPECT will contribute significantly to the future of nuclear medicine, which is bright because of the soundness of its basic principles, it being a science concerned with the changes in the spatial and temporal distribution of the physical and chemical constituents of the human body.

The practice of medicine in the decade of the 1970s emphasized diagnosis. The emphasis of the 1980s is on better treatment. A significant number of papers presented at this meeting were concerned with monitoring and thereby improving treatment, but there should be many more if nuclear medicine is to keep up with the times. It is not good to reach a turning point and not turn....

Tomography and Brain Chemistry

The growth of positron emission tomography is documented by the almost fourfold increase over the past two years in the number of papers and posters involving PET. Of the 85 PET reports, 49 were concerned with brain chemistry. Hippocrates said, “It is disgraceful in every art and, more especially, in medicine, after much trouble, much display, and much talk to do no good after all.” The transition from science to service is exemplified by the UCLA group studies of patients with focal epilepsy. These investigators reported that there are at least 5000 patients in the United States who are potential candidates for surgical therapy of epilepsy. During a focal seizure, the focus of the seizures can be identified by the fact that there is increased glucose metabolism at the site of the origin. Between seizures, the involved foci are hypometabolic. Such studies of brain chemistry stand in sharp contrast to the first radionuclide uptake test performed by Joseph Hamilton in Ernest Lawrence’s laboratory in 1941. Even though the radionuclides and instruments are different, the detecting of increased or decreased organ function remains a basic principle of nuclear medicine. Every new measurement of a function results in at least two diseases; one in which that function is abnormally high and the other in which it is abnormally low. The 1984 SNM meeting documents that Hamilton was right when he said that the discovery of artificial radioactivity and the development of the cyclotron have given the biologist the most useful tool for research since the discovery of the microscope.

...The study of brain chemistry by PET extends greatly the contributions of x-ray computed tomography and nuclear magnetic resonance imaging. In addition to the presentations concerned with brain bioenergetics by means of deoxyglucose and oxygen, we heard papers describing new ligands that make possible the assessment of dopamine, serotonin, benzodiazapine, muscarinic cholinergic, and opiate receptors in the brain. Fourteen presen-
tations were concerned with the study of neurotransmitters and neuroreceptors. The former are chemical messengers bringing us information about the outside world; the latter determine how we react to this information. The combined effects of the chemical binding of the neurotransmitters and the neuroreceptors eventually determines our behavior.

Wong and his associates reported the use of carbon-11 methylspiperone to study dopamine and serotonin neuroreceptors in over 100 persons. While the Hopkins group used carbon-11 methylspiperone to study dopamine and serotonin receptors, the group at Brookhaven, under the direction of Wolf, prefers fluorine-18 as a tracer. Its half-life of 110 minutes makes it possible to extend the studies over four hours, or even longer. The use of fluorine-18 rather than carbon-11 also facilitates the production of the tracer, since a single run with fluorine-18 can provide enough tracer for several studies on the same day.

In the Hopkins study, normal men were found to have a dramatic fall in dopamine receptor activity in the caudate and putamen with increasing age. This finding illustrates that important changes occur in dopamine and serotonin receptors and that they can be measured by PET. Another finding was that the fall in receptor activity in normal aging women was only half as fast as that of men. Between the ages of 20 and 70 years, men had a 46% decrease in dopamine receptor binding, while women had only a 25% decrease. This suggests that hormonal factors may be influencing dopamine receptor activity. Serotonin receptor binding also fell with age; 30% in men and 19% in women between the ages of 20 and 70 years.

At this meeting, the first studies of opiate receptor imaging in a living human being were reported. $^{11}$C-carfentanil was the tracer and accumulation was observed in the caudate nucleus and the putamen, and the frontal and temporal parietal cortex. The distribution of regional glucose metabolism observed in a sensory-deprived person resembled the distribution of opiate receptors. The absence of opiate receptors in the primary sensory areas suggests the hypothesis that sensory data are first processed in the primary sensory areas and then passed on to areas containing opiate and other receptors where emotional connotations are superimposed.

We can anticipate that over the next few years, we will be hearing answers to the questions of whether there are neuroreceptor abnormalities in various neuropsychiatric diseases, such as Parkinson’s disease, Huntington’s disease, and schizophrenia. We will learn whether receptor activity changes as a person develops one of these diseases. The UCLA group reported studies of regional glucose metabolism in persons who are at risk for the development of Huntington’s disease. Persons who are at risk of developing Huntington’s disease seem to have reduced glucose metabolism in the basal ganglia even before they develop symptoms.

In a group of 17 patients with Alzheimer’s disease, Friedland, Budinger, and associates found reduced glucose metabolism in the temporal parietal region, a region rich in mus-

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**Looking Back: Thoughts on Tracer Regulation and Production**

In 1984, Niels K. Jerne, Georges J.F. Köhler, and César Milstein won the Nobel Prize in Medicine and Physiology for their work in cell culture to produce antibodies of predefined specificity. This would lay the foundation for what is today among the most exciting areas of nuclear medicine: radioimmunodiagnosis and -therapy. At the same time, advances in PET and SPECT were opening the way for new radiotracers in both animal research and clinical applications.

At the 1984 SNM meeting, as at other venues where educated individuals gathered that year, there was much talk of George Orwell’s predictions in his 1949 novel *Nineteen Eighty-Four*. He described a futuristic bureaucratized state in which uniformity and regulations stifled the human spirit of inquiry. The book remains a reminder that we must constantly strive to keep government from becoming all-powerful. In nuclear medicine, conversations about the author’s predictions inevitably centered on the role that government had come to play in the regulation of many aspects of medical practice.

Some of us remember the early days of nuclear medicine, when radiopharmaceutical development took place under a blanket waiver granted by the Atomic Energy Commission. Later, in the 1970s, many of us resisted efforts to lift this waiver and place radiopharmaceutical development under the aegis of the U.S. FDA, a process that we were able to forestall for almost a decade. Representatives of the FDA maintained that “Radiopharmaceuticals have all the same problems as stable drugs, plus those related to radioactivity.” This and similar statements ignored the fact that the amount of injected material in a radiopharmaceutical is so low that no biological or pharmacological effect is caused. Instead, the important qualitative considerations in readying radiopharmaceuticals for routine use are radiation safety and purity. Since the waiver was revoked in the 1980s and radiopharmaceuticals came under regulation by the FDA, nuclear medicine has faced serious problems in dealing with the amount of time required for new radiopharmaceutical approval.

In 1984, expenditures for health care in the United States amounted to $384.3 billion, and the figure tops $1 trillion today. Expenditures for health research and development totaled only $11.8 billion—less than half
carinergic cholinergic axons coming from the nucleus basalis of Meynert. The patterns of glucose metabolism in patients with moderate or severe Alzheimer’s disease are different from the patterns in patients with other dementias. The characteristic pattern of regional glucose metabolism in patients with severe Alzheimer’s disease is reflected in the distribution of regional blood flow. The distribution of impaired blood flow and glucose metabolism in patients with Alzheimer’s disease resembled that of normal persons under conditions of sensory deprivation, with the most pronounced reductions being in the primary sensory areas.

....Oncology is another important area of development of positron and single photon tomography, even though far fewer persons are affected by brain tumors when compared to the thousands of persons afflicted with schizophrenia, Parkinson’s disease, and Alzheimer’s disease. Measurement of $^{11}$C-methionine appears to be the best way to non-invasively assess the degree of malignancy of a brain tumor. The use of tracers such as gallium-68 EDTA and rubidium-82 raises the question about the translatability of PET studies into community hospitals. Will there be a place for PET scanners in institutions that don’t have cyclotrons based on the use of these tracers, plus tracers provided by regional cyclotrons? Should every major university medical center plan on a cyclotron/PET capability within the next 5 years? Will service-oriented community hospitals in the future rely primarily on SPECT and technetium-99m or iodine-123 labeled compounds?

**Iodine-123**

Iodine-123, a radionuclide that has offered promise for many years, finally seems to be moving ahead as an important radionuclide, although technetium-99m is likely to remain the workhorse of nuclear medicine. The availability of carbon-11 and fluorine-18 greatly enhances our chemical capabilities, but iodine-123 and technetium-99m labeled compounds permit the extension of the successes of positron tomography into widespread clinical practice. The brilliant chemists in our field reported important advances in developing useful technetium-99m and iodine-123 labeled compounds for heart, brain, and kidney. Twenty-five presentations involved iodine-123, most describing IMP or HIPDM for the study of regional cerebral blood flow. Many of the monoclonal antibody papers involved I-123 as well. Other compounds illustrating that I-123 can play an important role include radioiodinated QNB for studying muscarinic cholinergic receptors and metaiodobenzilguanidine for detecting pheochromocytomas. Evidence that manufacturers and governmental agencies now believe that I-123 can play an important role in nuclear medicine is that one radiopharmaceutical company is building a large cyclotron to produce I-123 and the Brookhaven linear accelerator (BLIP) will be able to produce 10 curies of I-123 per week within the next year.

Today’s current budget for the National Institutes of Health alone. Rising costs drive the direction of innovation in our current medical climate, and this is clear in choices made by the pharmaceutical industry. The industry prefers to develop therapeutic agents, which have potential profits far greater than those for diagnostic radiopharmaceuticals. This preference is exacerbated by a process that demands the same levels of clinical trials, outcomes data, and extended waiting periods for both diagnostic and therapeutic drugs.

The number of new drugs of all types coming onto the market peaked in the mid-1990s. In 1996 and 1997, after high-level criticism for tardiness in the approval process, the agency approved more than 120 new drug applications. By 2002, the number of annual new drug approvals had dipped to 78. In the special category of “new molecular entities” (NMEs; chemicals not previously used in medications), the decline has been even steeper. The annual number of approved NMEs went from a high of 53 in 1996 to only 9 in 2002—the lowest yearly number of NME approvals since the 1980s. The FDA has in place policies under which “exciting new drugs” can be deemed “priorities” and approved within 6 months. Surely many of the new diagnostic and therapeutic agents involving radioactive tracers should be considered for this special treatment, but the types of evaluations needed for new radiopharmaceuticals remain demanding.

In 1984, there was much discussion about evaluations needed for approval of new diagnostic radiopharmaceuticals. Case studies, consensus development, and non-randomized and randomized clinical trials are the mainstays of research and development. However, in the case of diagnostic agents, a solid judgment of the “success” of the agent can be made almost immediately after procedures by determining whether the information provided was useful. Once the agent has been proven safe for patients, evaluations of effectiveness are based on the accuracy of the diagnostic information revealed, not on the outcomes of subsequent management decisions made on the basis of this information. For all of us in nuclear medicine, the question of regulation of radiopharmaceuticals remains as topical today as it was 20 years ago.

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