USP and PET Radiopharmaceuticals

1997 FDAMA Puts Standard-Setting Body at Center of Regulatory Process

Over the last decade, the framework for the regulation of radiopharmaceuticals for use with PET has been marked by controversy, has reached the ranks of Congress, and remains unfinished to this day. While this regulatory process evolves at the Federal level, the United States Pharmacopeia (USP) has continued its role in drug standards development and informational activities relating to PET radiopharmaceuticals. These activities are aimed at providing guidance to the profession, thereby helping to ensure maintenance of high standards of public health.

Although the USP has been involved with PET radiopharmaceuticals since 1988, its role in the regulation of these pharmaceuticals took on added importance with the passage of the FDA Modernization Act of 1997 (1997 FDAMA), which declared that PET radiopharmaceuticals would be considered adulterated if not prepared in compliance with USP standards (i.e., in compliance with standards published in USP monographs and general chapters relating to this class of drug) (1). Because this ruling is relatively new, many in the PET community are only now becoming familiar with the central role the USP now plays in PET radiopharmaceuticals.

FDA’s Draft CGMP Rule/Guidance and USP

The 1997 FDAMA also stipulates that the FDA must establish approval procedures and current good manufacturing practice (CGMP) requirements for PET radiopharmaceuticals (1). Although the FDA has not yet issued the final rule for the CGMP requirements, the draft versions of the rule and guidance for PET radiopharmaceuticals were released by the FDA in March 2002 (2,3). Both of these documents include many of the principles and concepts as stated in the general chapter “Radiopharmaceuticals for Positron Emission Tomography—Compounding” (USP 823) (4). This is because the FDA believes that USP 823 “largely reflects the consensus views of the PET community and FDA on how to properly produce PET drug products” (2,3). In addition, the draft CGMP guidance also incorporates many other general chapters and monographs from the USP to specifically address certain proposed requirements (4–7) (Tables 1 and 2). As a result, the USP has become an integral element of the regulatory framework for the preparation of PET radiopharmaceuticals, and the FDA will rely heavily on the USP in setting up the final CGMP rule and guidance.

The purpose of this article is to provide a general insight into the workings of the USP and, specifically, its role in the regulation of PET radiopharmaceuticals. In addition, it is our hope that this will serve as a stimulus to individuals within the PET community to become involved in the activities of the USP.

The United States Pharmacopeia, Inc.

The USP, Inc. is a private, nonprofit, scientific organization incorporated in the District of Columbia. Over the years since 1820, when it published a “recipe book” for 217 drugs and drug preparations, its mission has evolved into one of setting standards for drugs and providing drug information. USP standards are widely recognized as authoritative and are enforced by the FDA and state agencies. USP establishes these standards through an open participatory process with established integrity. Volunteers from all aspects of industry, education, medicine, and pharmacy carry out these activities.

The Council of Experts

Drug standards are established by the Council of Experts and by Expert Committees, USP’s scientific decision-making bodies. Membership is drawn from the scientific and health care profession communities. The USP Nominating Committee selects qualified candidates to run for election to the Council of Experts. Those elected by delegates at the USP Convention then serve as chairs of the various Expert Committees. The Nominating Committee also selects nominees for membership on the Expert Committees. Members serve 5-year terms. The USP Web site (www.usp.org/volunteers/honominate/) provides information on how to become involved in this process.

Of the 62 Expert Committees, 2 deal directly with radiopharmaceuticals. The committee charged with setting standards for radiopharmaceuticals is the Expert Committee on Radiopharmaceutical and Medical Imaging Agents, in the Noncomplex Actives and Excipients Division. Drug information related to radiopharmaceuticals is the responsibility of the Expert Committee on Radiopharmaceuticals in the Information Division.
Public Review and Comment Process for Standards Development

The USP establishes standards for drugs through a rigorous peer-review process conducted by the Council of Experts and Expert Committees, as well as through a review-and-comment process that is open to the general public. USP standards are under continuous revision. A request for revision can come from any interested entity or individual. A guideline (i.e., USP Guideline for Submitting Requests for Revision to the USP-NF [National Formulary]) on how to request revisions to the USP is available on the Web site (www.usp.org/standards/revisionguideline/index.html). This guideline also provides recommendations to sponsors on submitting information to support revisions to the United States Pharmacopeia and National Formulary (USP-NF).

Revision includes either creation of a new standard (i.e., monograph or general chapter) or revision of an existing standard. When received, the USP assigns the request for revision to a scientific liaison, who will work with the sponsor(s) to ensure that the request incorporates the appropriate information and background materials. When complete, the scientific liaison forwards the request to members of the responsible Expert Committee(s). These members evaluate the submission for technical accuracy, proper validation, and suitability. The Expert Committee(s) may approve or decline the request for revision or may request additional information. With the approval of the Expert Committee(s), the scientific liaison will prepare the request for revision for publication, submitting it for the USP’s editorial and publication process for the Pharmacopeial Forum (PF). Most requests for revision appearing in the PF are open for public comment for a period of not less than 60 days. Interested parties are referred to the USP Web site (www.usp.org/standards) for more details.

Pharmacopeial Forum

The USP publishes PF bimonthly as the working vehicle of its Council of Experts. The PF provides interested parties an opportunity to review and comment while the Council of Experts and its expert committees develop standards for the USP–NF. The USP welcomes comments and data on potential, proposed, or official standards. Comments and responses are published in the PF.

Because it is likely that the PF is not widely available within the nuclear medicine community, alternate avenues for dissemination of information on relevant activities of the USP should be developed. One such possibility would be to post PF information related to PET radiopharmaceuticals on the SNM Web site, provided that agreeable terms between the USP and SNM could be reached.

The PET community is fortunate to be a relatively small and close-knit group with multiple forums in which to exchange ideas and information. Activities of the USP should be brought into this dialogue through increased interaction with the Expert Committees via various professional nuclear medicine organizations, as well in the published literature. This article is intended as a beginning to this process.

---

**TABLE 1**

<table>
<thead>
<tr>
<th>USP general chapter</th>
<th>Citation of draft CGMP rule or guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterility Tests</td>
<td>Draft CGMP guidance: X. Finished Drug Product Controls and Acceptance Criteria</td>
</tr>
<tr>
<td>Bacterial Endotoxins Test</td>
<td>Draft CGMP guidance: X. Finished Drug Product Controls and Acceptance Criteria</td>
</tr>
<tr>
<td>Chromatography</td>
<td>Draft CGMP guidance: V. Facilities and Equipment</td>
</tr>
<tr>
<td>Radioactivity</td>
<td>Main principles and concepts for draft CGMP rule and guidance</td>
</tr>
<tr>
<td>Radiopharmaceuticals for PET-Compounding</td>
<td>Draft CGMP guidance: V. Facilities and Equipment</td>
</tr>
<tr>
<td>Automated Radio-chemical Synthesis Apparatus</td>
<td>Draft CGMP guidance: VIII. Laboratory Controls</td>
</tr>
</tbody>
</table>

**TABLE 2**

PET Radiopharmaceuticals Listed in 2004 USP-NF (5)

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>11C</td>
<td>carbon monoxide</td>
</tr>
<tr>
<td>11C</td>
<td>flumazenil</td>
</tr>
<tr>
<td>11C</td>
<td>mespiprone</td>
</tr>
<tr>
<td>11C</td>
<td>methionine</td>
</tr>
<tr>
<td>11C</td>
<td>raclopride</td>
</tr>
<tr>
<td>11C</td>
<td>sodium acetate</td>
</tr>
<tr>
<td>18F</td>
<td>fluorodeoxyglucose</td>
</tr>
<tr>
<td>18F</td>
<td>fluorodopa</td>
</tr>
<tr>
<td>18F</td>
<td>sodium fluoride</td>
</tr>
<tr>
<td>13N</td>
<td>ammonia*</td>
</tr>
<tr>
<td>15O</td>
<td>water</td>
</tr>
<tr>
<td>82Rb</td>
<td>rubidium chloride</td>
</tr>
</tbody>
</table>

* Proposed revision (6).
In addition, individuals are urged to contact Expert Committee chairs or USP staff liaisons to bring issues to the attention of a specific committee.

**USP Standards for PET Radiopharmaceuticals**

USP activities with direct impact on the practice of nuclear medicine and PET include the development of individual product monographs and general chapters that address related topics. The USP first provided standards for PET radiopharmaceuticals in 1988 and currently includes several general chapters and official monographs related to PET radiopharmaceuticals (Tables 1 and 2). The 2004 USP-NF contains 73 monographs for radiopharmaceuticals, of which 12 are PET radiopharmaceuticals (Table 2).

Monographs provide drug standards and test methodologies to be used to determine compliance with each standard. Use of alternate analytical methodologies is allowed, although all such methods must be validated against the official method. Inclusion of a particular standard in a monograph does not necessarily reflect the frequency of testing for that standard. For example, a standard for radionuclidic purity does not necessarily imply that this is a release criterion for the product. It may be possible only to show compliance with this standard after complete decay of the primary radionuclide. Currently, for PET radiopharmaceuticals, frequency of testing is dictated by USP(823), “Radiopharmaceuticals for Positron Emission Tomography–Compounding” (4), and ultimately will be dictated by CGMP regulations when finalized by the FDA.

**Active Involvement in the Development and Revision Process for USP Standards**

To ensure that the progress of PET technology will not be stifled by impractical or restrictive CGMP regulations, the PET community should be aware of current general USP chapters and monographs that are related to PET radiopharmaceuticals. In addition, it is critical for our colleagues who work in the PET field to familiarize themselves with the development and review process for USP standards. As stated previously, the FDA believes that USP(823) “largely reflects the consensus views of the PET community and FDA...” However, if USP standards are to truly reflect the views of the PET community, widespread involvement from that community in USP revision processes is necessary.

We have presented an overview and brief history of the central role the USP has played in the evolution of standards setting and regulation of PET radiopharmaceuticals. USP welcomes input from interested organizations. Members of the PET community are urged to become involved and to provide input into USP activities. Committee chairs and staff liaisons whose work is most relevant to standard setting and regulations of PET radiopharmaceuticals are:

- **Expert Committee on Radiopharmaceuticals and Medical Imaging Agents**
  Chair: Ronald J. Callahan, PhD (callahan@helix.mgh.harvard.edu)
  USP Staff Liaison: Andrzej Wilk, PhD, senior scientific associate (aw@usp.org).

- **Expert Committee on Radiopharmaceuticals**
  Chair: Barry A. Siegel, MD (siegelb@mir.wustl.edu)
  USP Staff Liaison: Denise S. Penn, RPh, senior drug information specialist (dsp@usp.org)

Colleagues from across the spectrum of nuclear medicine practice are urged to get involved in USP PET-related activities.

**REFERENCES**

DOE Announces 20-Year Science Facility Plan

In a speech at the National Press Club in Washington, DC, on November 10, U.S. Department of Energy (DOE) Secretary Spencer Abraham outlined a 20-year facility plan for the DOE Office of Science. “The plan will serve as a roadmap for future scientific facilities to support the department’s basic science and research missions,” said Abraham. The plan prioritizes the building of new scientific facilities and upgrades to current sites for a total of 28 facilities that cover the range of science supported by the DOE Office of Science, including fusion energy, materials science, biological and environmental science, high energy physics, nuclear physics, and advanced scientific computing. “This plan will be the cornerstone for the future of critical fields of science in America. These facilities will revolutionize science—and society,” said Abraham. “With this plan our goal is to keep the United States at the scientific forefront.

The Office of Science priority list for new facilities is designed to guide the department as it plans future scientific investments. The list, incorporated into a 48-page booklet titled Facilities for the Future of Science: A Twenty-Year Outlook, identifies a number of facilities and research foci of direct interest to nuclear medicine.

Twelve facilities are identified as “near-term” priorities. Rated as priority 1 is ITER (Latin for “the way”), an international collaboration to build the first fusion science experiment capable of producing a self-sustaining fusion reaction (called a “burning plasma”; see www.iter.org). Priority 2 is the implementation of an ultrascale scientific computing capability, to be located at multiple sites, that would increase by a factor of 100 the computing capability available to support open scientific research.

Among the 4 facilities tied for priority 3 is a rare isotope accelerator (RIA) that would be the world’s most powerful research facility dedicated to producing and exploring new rare isotopes not found naturally on earth. The strategic plan document notes that “RIA will involve the development of new accelerator technology to create beams of unstable isotopes that are 10 to 100 times more powerful than those available today. It will have the capability to specify, control, and precisely vary the number of protons and neutrons in atomic nuclei, and thus study not only the properties of individual nuclei, but also the evolution of these properties across the nuclear chart.”

Nuclear medicine is listed as one of the possible beneficiaries of this technology.

Another of the priority 3 facilities is a protein production and tag facility that would mass produce and characterize thousands of proteins per year. The products of this facility would support the work of a priority 7 facility for the characterization and imaging of molecular machines. This biological user facility “will provide the research community with the world’s largest assembly of sophisticated analytic and imaging instrumentation, combined with state-of-the-art computational tools, to enable users to isolate, identify, characterize, and image the molecular machines present in selected microbes under highly controlled conditions. The facility’s high-throughput capabilities will analyze thousands of molecular machines in the time it now takes to do a few.” It is envisioned that this would make a number of research fields more accessible to researchers for whom such data would otherwise be too expensive or cumbersome to collect.

Other proposed facilities of interest to the nuclear medicine community include upgrades to the Continuous Electron Beam Accelerator, Energy Sciences Network, National Energy Research Scientific Computing Center, and the Spallation Neutron Source facilities as well as the development of a second cold source for the High-Flux Isotope Reactor.

“The complete list of 28 facilities outlines to an important extent the future of science in America—and indeed the world,” Abraham said. “These facilities cover the critical areas where discoveries can transform our energy future, boost economic productivity, transform our understanding of biology, and provide revolutionary new tools to deal with disease.”

Each year, DOE science facilities are used by more than 18,000 researchers from universities, other government agencies, private industry, and other nations. The Spallation Neutron Source, scheduled to be completed in 2006, is the latest large-scale DOE user facility under construction. The DOE Office of Science prepared the priorities list during 2003 with input from the scientific community, DOE laboratories, and advisory committees. Office of Science program managers first identified 46 facilities they believe are required for world scientific leadership over the next 20 years. Six independent advisory committees reviewed the facilities, recommended 53 facilities for construction, and assessed each according to 2 criteria: scientific importance and readiness for construction. Dr. Raymond L. Orbach, director of the Office of Science, prioritized the facilities across the scientific disciplines. A number of the facilities will be located at DOE national laboratories as upgrades to existing activities. The locations of the remaining facilities will be determined through site selections open to laboratories and universities.

View the entire Future of Science document at www.sc.doe.gov.
Dates and locations have been announced for the 2004 SNM PET Learning Center weekend sessions for physicians and technologists. The successful continuing education program will expand this year to offer 22 sessions at the PET Learning Center headquarters in Reston, VA, and in Knoxville, TN, and Palo Alto, CA. Also in 2004, a series of 1-day sessions on specific aspects of PET imaging and technique will be added, including cardiac PET, neurological PET, PET radiopharmaceuticals, and PET physics.

**New One-Day Sessions on PET Topics**

The first 1-day session on “Cardiac PET: Expanding Nuclear Cardiology” will be held on January 24 at the Sheraton Wild Horse Pass Resort and Spa (Chandler, AZ), just outside Phoenix. The course is open to nuclear medicine physicians, radiologists, cardiologists, technologists, pharmacists, and affiliated health care professionals. It will provide an in-depth look at the current state of cardiac PET and its application to the diagnosis of cardiovascular disease. The program will focus on clinically established uses of PET; for example, the diagnosis of coronary artery disease and assessment of myocardial viability. Technical aspects unique to cardiac PET will be explored along with promising approaches to the identification of early coronary atherosclerosis.

Formal didactic lectures will be supplemented by clinical case studies. Participants will gain an understanding of the basic aspects of PET methodology, diagnostic approaches that expand current applications of standard SPECT myocardial perfusion imaging, and ways that these approaches can contribute to improved patient management and outcomes. The course will carry 6.25 hours of American Medical Association continuing education credit, 6.25 hours of VOICE credit, or .62 CEUs from the American Council of Pharmaceutical Education.

The 1-day Neurological PET course will be offered in Washington, DC, on April 17. Dates for additional 1-day courses are being finalized and will be announced soon.

Monitor the SNM Web site (www.snm.org) regularly for updates.

Space is limited, and all PET Learning Center classes fill quickly. Prospective attendees may register by mail, fax, on-line, or over the phone by contacting Shawneece Hennighan (shennighan@snm.org), Meeting Services Department, Society of Nuclear Medicine, 1850 Samuel Morse Drive, Reston, VA, 20190; 703-708-9000 x1229; fax: 703-709-9274.
ABNM Begins Search for New Executive Director

The American Board of Nuclear Medicine (ABNM) announced in December the opening of a search for an executive director to succeed William Blahd, MD, who, after more than 25 years of dedicated service to the ABNM, will be stepping down in 2004.

“Leading one’s specialty certification board in a position such as this is clearly an honor,” said Lawrence Holder, MD, chair of the ABNM. “In these times of change, such a charge also carries significant challenges and rewards. Working with a committed board and talented staff should provide the new executive director with great personal satisfaction and lasting professional accomplishments.”

The executive director is responsible for the management of the board offices and activities, serves as the designated representative of the board to a variety of organizations such as the American Board of Medical Specialties, and attends meetings and conferences important to the ABNM mission and operation. The executive director works closely with the administrator, who is responsible for the day-to-day operations of the board office. The executive director works with the board of trustees to determine the focus and direction of the ABNM and develops and recommends policies to the board for approval.

A candidate who has served previously on the ABNM board is strongly preferred. However, ABNM diplomates with significant experience in other national nuclear medicine organizations will be considered. He or she will be a nonvoting member of the board. The term of office is 5 years, with an opportunity for a second 5-year term. An appropriate honorarium is available. A time commitment of 35–50 days per year is projected.

Interested candidates or those who would like more information should contact Dr. Holder at P.O. Box 3216, Ponte Vedra Beach, FL, 32004-3216, or via email at leholder@earthlink.net.

Lawrence Holder, MD
Chair, ABNM
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.

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 progesterin, 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-
History

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 Cush- ing’s disease or adrenal hyperplasia, hypofunctioning tumors are often malignant, and normally functioning masses are usually benign.

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
MBG 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-18-labeled metaraminol can be used to indicate the functioning mass or presynaptic neurons.

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.

Henry N. Wagner, Jr., MD
SNM Historian
December 2003
to investigating the problem of sudden death that affects 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, muscarinic 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 methyl-iodide. 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 hippocampus and amygdala, are probably associated with epilepsy.
SNM Leadership Update

W e are busy preparing for our annual mid-winter meeting, February 7–8 at the Disneyland Hotel, Anaheim, CA. The format of this year’s meeting is the result of comments we received during the last 3 years as we experimented with the type of educational and scientific format that works best for this smaller meeting. We have redesigned the structure of the meeting based on feedback from participants and expect that this year’s meeting will be an enjoyable and profitable experience for all who join us there. Dr. Fred Fahey, SPC Associate Chair for the mid-winter meeting, has done an exceptional job in organizing our mid-winter educational symposium and was integrally involved with SNM leadership and councils in restructuring the educational program to best meet the diverse needs of our attendees while addressing several topics of importance to the nuclear medicine, radiology, and oncology communities.

This year’s meeting is structured so that presentations will not compete with each other, relieving attendees of the frustrations associated with decisions over which sessions to attend. Instead, centers and councils will present educational seminars on the latest information in their areas of interest. This year the PET Center of Excellence, in collaboration with the Brain Imaging Council, will present a 1.5-day symposium on advances in “Clinical PET: Oncology and Neurology.” The SNM Cardiovascular Council, in collaboration with the Radiopharmaceutical Science Council, Computer and Instrumentation Council, and the American Society of Nuclear Cardiology, will present 2 half-day symposia on “Nuclear Cardiology: Consolidating the Present While Moving into the Future.” The Nuclear Oncology Diagnosis and Therapy Council will also present 2 half-day symposia on “Directions in Target Radiopharmaceutical Therapy in Cancer.” On Saturday, the Technologist Section will present an all-day symposium on “Current Practice and Future Trends.”

In addition to the educational component, the mid-winter meeting is where our councils, committees, and other governance organizations hold meetings to conduct final votes on issues that have been discussed via conference call and e-mail during the previous 6 months. Last year, a major restructuring of the SNM was approved at the annual meeting, and much of our time at the upcoming mid-winter meeting will be devoted to putting the new structure in place. One aspect of that restructuring will be an increased reliance on our councils. The following mission statement for SNM councils was suggested at the Committee on Councils Retreat held in Chicago last October.

SNM recognizes the need for subspecialty interests/expertise within the field of nuclear medicine. Councils provide the expertise, professional networking, and educational programs for nuclear medicine professionals in their respective areas and serve as a resource for development and implementation of SNM policy. Their mission is to provide a forum for members with like interests, to share their expertise with the membership at large, to foster research and education in their areas of interest, to serve as a resource to SNM leadership, and to provide outreach to other professionals and organizations.

Standard operating and administrative procedures have been developed that will allow us to move from focusing on internal reorganization toward becoming a flexible, strategic organization that looks outward, embracing emerging technologies, collaborating with other organizations in areas of mutual interest, building partnerships with the radiology community, and helping practitioners maintain and expand their skills.

Interest in subspecialty organizations within the SNM continues to grow. The membership of the new PET Center of Excellence reached more than 1,200 by the end of 2003, and this month the PET Center will launch a new offering, a 1-day symposium focusing on “Expanding Nuclear Cardiology.” The symposium will be held at the beautiful Sheraton Wild Horse Pass Resort and Spa in Chandler, AZ, on January 24.

Another area currently being restructured is our bylaws. The Bylaws Committee, chaired by Dr. Warren Moore, has taken on the considerable task of a thorough review and revision of our bylaws, including writing procedures to govern the ways in which bylaws should be implemented. Last spring, the Policy and Procedures Task Force produced an initial draft of a bylaws revision and an outline of the procedures still needed to fully complete the bylaws.

International Update

Congratulations to Dr. Henry Royal, who delivered a plenary address at the 43rd Annual Meeting of the Japanese Society of Nuclear Medicine (JSNM), October 24–30, in Tokyo. Some 1,500 participants were registered for the meeting, making it the largest JSNM Annual Meeting to date. In meetings between SNM and JSNM leadership, plans were finalized for jointly sponsored educational sessions at both the SNM 2004 Annual Meeting in Philadelphia and the 2004 JSNM Annual Meeting in Kyoto. Some 920 abstracts have been received to date for the January 17–24, International Atomic Energy Agency (IAEA) symposium on nuclear oncology to be held in Porto Allegre, Brazil. This symposium marks the first time that SNM has actively partnered with the IAEA. We will be helping to produce a 4-day educational program geared toward nuclear medicine professionals in developing countries.

Virginia Pappas, CAE
SNM Executive Director
he big event in 2003 was passage of the Medicare Prescription Drug Improvement and Modernization Act which rectifies many of the problems nuclear medicine had been facing under previous reimbursement plans. As the year drew to a close we also saw publication of the 2004 Physician Fee Schedule and the 2004 Hospital Outpatient Prospective Payment System (HOPPS) rule. The Physician Fee Schedule will be updated and changes will be posted to our website. We also experienced some success in modifying 2004 HOPPS rules.

Medicare Prescription Drug Improvement and Modernization Act Of 2003

By now you all know that Congress passed and the President signed a Medicare reform act that provides prescription drug benefits in 2004 and future years. The act also contains other important provisions of interest to the medical community in general and nuclear medicine in particular.

The act enhances access to care for seniors by halting Medicare cuts to physicians and other health professionals for the next 2 years. Instead of cuts, the Medicare bill provides at least a 1.5% increase in payments in 2004 and 2005. For next year, this represents a 6% difference in Medicare payments between what was originally proposed and what was finally enacted at a time when physician practice costs are on the rise. The 2004 Physician Fee Schedule published in the November 7, 2003, Federal Register will be revised accordingly, and revisions will be posted on our website.

In May 2002, SNM wrote to the Office of Management and the Budget (OMB) regarding MCM 3060.3C—the provision requiring on-premise interpretation of images under the Medicare reassignment statute that has been in place since 1996. At the time SNM wrote, OMB had requested suggestions for streamlining agency rules. Center for Medicare and Medicaid Services (CMS) had taken the position for the better part of 7 years that a statutory amendment was necessary to amend this chapter of the manual. Section 952 of H.R. 1 will fix this problem via statute by allowing reassignment of interpretation charges by either W-2 or 1099 to physicians. Thus the facility that performs the imaging will be able to bill globally for all of the services rather than billing only for the technical component, leaving the reading physician to bill separately for the interpretation.

Payments under Medicare for many drugs used in hospitals will be revised in 2004. In general, in 2004 drug payments will be reduced to 85% of average wholesale price (AWP) and in 2005 they will shift to an average sales price or competitive acquisition system. However, radiopharmaceuticals used in hospitals are exempted and will continue to be paid at 95% of AWP for the foreseeable future (Conference Agreement, pages 152–155).

Radiopharmaceuticals used in a physician’s office will continue to be paid at 95% of AWP or invoice pricing as currently in effect (Conference Agreement, pages 161–162).

Under the HOPPS for 2003, CMS held that radiopharmaceuticals were not drugs but rather diagnostic or therapeutic procedures. Because of the application of locational wage adjustments, this had a negative impact on payments for the new Zevalin therapy. For 2004 HOPPS, CMS partially reversed itself and said that radiopharmaceuticals would be treated as drugs for the purposes of payment. The new Medicare act cures this problem under HOPPS by declaring that radiopharmaceuticals are a “specified covered outpatient drug” and will be paid as such (Conference Agreement, pages 237–238).

Many will continue for months to come to debate whether the 2003 Medicare reform act is good or bad; however, there should be no debate as to whether nuclear medicine was treated well under the new law.

2004 HOPPS Summary

The Nuclear Medicine Ambulatory Payment Classification (APC) Task Force was quite successful in obtaining most of its requested changes to the 2004 HOPPS. Some of the more important features in the final rule are:

- CMS estimates that the impact of changes will result in an overall HOPPS payment increase to hospitals of 4.5%.
- The 2004 conversion factor is $54.561, an increase from the 2003 conversion factor of $52.151.
- Although they still will not concede that radiopharmaceuticals are drugs, CMS will apply the same packaging and payment policies to radiopharmaceuticals that it applies to drugs. This will end the reduction in radiopharmaceutical reimbursement based on facility location. The Medicare reform act also positively impacts this issue.
- Consistent with the recommendations of the Commission on Radionuclides and Radiopharmaceuticals the Nuclear Medicine APC Task Force, CMS lowered the threshold for separate payment for drugs and radiopharmaceuticals from $150 to $50, thus allowing separate payment for more radiopharmaceuticals.
Fifteen radiopharmaceuticals emerged from “packaged” status as a result of the lower threshold.

In 2004, 35 radiopharmaceuticals will receive separate payment. All radiopharmaceuticals with K status in 2003 retained K status for 2004.

As proposed, CMS fundamentally restructured the previous 7 nuclear medicine APCs, creating 24 new nuclear medicine APCs based primarily on the organ or tissue being studied or treated.

The 2004 payment rates for many nuclear medicine APCs increased from 2003.

CMS adopted a number of the Task Force’s recommendations, including the recommendation to split cardiac imaging procedures into additional APCs.

As reconfigured, payment for Level I cardiac imaging procedures decreased by more than $100 and payment for the highest level, Level III cardiac imaging, increased by about $15.

The increase in payment for APC 377 Level III cardiac imaging is lower than suggested by some modeling and projections, in part because of the final procedures assigned to this APC. As finalized, APC 377 Level III cardiac imaging includes 2 procedures described by CPT codes 78461 and 78465. The median costs for CPT code 78461 ($368) are almost $150 lower than median costs for CPT code 78465 ($536). The combination of higher and lower cost procedures may have moderated the payment increase.

Total payment for complex myocardial scan procedures will increase in 2004 as a result of separate payment for the radiopharmaceutical.

CMS also adopted the Task Force’s recommendations to create Level II APCs for pulmonary and renal imaging procedures.

Payment for Level II renal imaging increased almost $200.

Payment for blood volume studies increased about $125, from $105 to $242.

CMS is considering the appropriate allocation of capital costs that may have a specific impact on nuclear medicine procedures.

Reimbursement for oncologic PET increased from $1,375 to $1,450, whereas, as expected, reimbursement for FDG decreased from $392.64 to $324.48. Total reimbursement for these procedures increased by $6.84.

Total reimbursement for myocardial perfusion PET decreased by $62.91. This change was driven by poor data reporting from facilities.

The Nuclear Medicine APC Task Force and Coding and Reimbursement Committee will continue to work with CMS on HOPPS implementation and improvement.

Energy Conference Update: Senate Adjourns Without Passing Energy Bill Conference Agreement

The Senate adjourned for the year without agreeing to the conference committee version of the energy bill. A possibility remains that after reconvening on January 20, Congress will be able to send an agreement to the President for signature.

That said, numerous hurdles remain that must be resolved before the energy bill can be enacted. The behind-the-scenes efforts to identify a compromise and cobble together the necessary votes will consume the White House and Senate leadership’s time over the next several weeks. We believe that we will see, at a minimum, the energy tax provisions enacted before Easter; however, it is still possible that Congress will once again fail to enact the Energy Bill.

William Uffelman
Director of Public Affairs
General Counsel, SNM
NCI, FDA Announce New Initiatives in Strategic Partnership

At a Friends of Cancer Research meeting in Washington, DC, on November 12, National Cancer Institute (NCI) Director Andrew C. von Eschenbach, MD, and FDA Commissioner Mark McClellan, MD, PhD, announced 2 new collaborative initiatives to facilitate the development and use of better cancer treatments. The initiatives include a new system for submitting investigational new drug (IND) applications electronically under the Cancer Biomedical Informatics Grid (caBIG) project. "In taking these important concrete steps, we are moving the NCI–FDA partnership from an idea to a working reality that will make a difference for patients," said von Eschenbach. McClellan said, "We are working to get safe and effective cancer therapies to patients as quickly and inexpensively as possible. Using modern information technologies to make our processes more efficient is a key approach to achieving this goal."

Information released by the NCI and FDA indicated that the new initiatives will:

- Link cancer researchers around the United States electronically to the FDA to reduce the time it takes for promising new drugs to be reviewed for testing in clinical trials. Electronic submission of data should allow patients earlier access to clinical trials as a result of shorter FDA processing time of IND applications; and
- Initiate cancer fellowship training programs aimed at developing a corps of physicians and scientists who are expert in clinical research, the regulatory approval process, and translation of research breakthroughs into clinical practice.

These initiatives result from ongoing work from the 2 organizations’ Interagency Oncology Task Force, which was established in May 2003 to improve the efficiency of all aspects of cancer drug development and regulatory review.

The FDA has agreed to work with NCI to develop clinical trial management software that makes it easier for cancer research groups and the FDA to work collaboratively. The 2 organizations will work to coordinate standards and develop tools to streamline regulatory interactions and accelerate the overall review process for new cancer drugs. These activities will become part of the NCI’s caBIG, in which the FDA has agreed to participate.

Under the new cancer fellowship training programs initiative, fellows will work in clinical oncology programs at NCI and in the technical and regulatory review programs at the FDA. As a result, fellows will bring state-of-the-art knowledge and technology to bear on the design, conduct, and review of clinical trials.

ASNC to Host Symposium on Cardiovascular Molecular Imaging

The American Society of Nuclear Cardiology (ASNC) is planning a symposium on cardiovascular molecular imaging at the National Institutes of Health in Bethesda, MD, May 3–4. Educational sponsors of the symposium include the SNM, ASNC, and the American College of Radiology.

Program objectives include educating the scientific community about the potential of targeted cardiovascular molecular imaging, providing an overview of critical issues related to the development of targeted radiolabeled tracers and tracer imaging technology, reviewing the imaging of cardiac reporter genes and gene expression, defining the potential of imaging in cardiac receptors and metabolism, promoting basic science research in and clinical applications of cardiovascular molecular imaging, and offering an overview of the potential of molecular imaging for improving the understanding and management of critical cardiovascular pathophysiologic processes.

A call for abstracts has been issued. Abstracts must be received by January 16. Young Investigator Awards, including a $500 travel grant, complementary registration, and certificate, will be given for the 7 best abstracts submitted by physicians or scientists who are currently in residency or fellowship training programs or are younger than 35. In addition, the registration fee will be waived for residents and fellows whose abstracts are selected for presentation. Program co-chairs include James Caldwell, MD, University of Washington (Seattle); Robert Gropler, MD, Washington University (St. Louis, MO); Lynne Johnson, MD, Brown University (Providence, RI); Leslie Leinwand, PhD, University of Colorado (Boulder); Albert Si- nusas, MD, Yale University School of Medicine (New Haven, CT); and Heinrich Schelbert, MD, PhD, University of California at Los Angeles School of Medicine. For more information see www.asnc.org.

NIH Expands Long-Distance Clinical Learning

The National Institutes of Health (NIH) Clinical Center announced on November 26 that in 2003 it had extended clinical research training programs to reach more than 1,400 physicians and other health professionals in locations as far away as Peru and Puerto Rico.

"Proper training of clinical researchers is critical to advancing medical science," said Dr. John I. Gallin, director of the NIH Clinical Center. "In the past, researchers have relied on mentors to teach them how to conduct clinical trials. We have established a formalized training pro-
HHS Announces Medical Reserve Corps Grants

On October 30 Health and Human Services Secretary Tommy G. Thompson announced 167 grants totaling more than $8 million to agencies in 40 states to help community-based organizations develop local volunteer medical emergency and public health response capabilities through the Medical Reserve Corps (MRC) program. “These awards will continue to support our communities in planning and establishing local, citizen-centered volunteer MRC units, which will include physicians, nurses and others with a broad range of skills in health and other support fields,” said Thompson.

MRC units include local citizen volunteers trained to respond to health and medical situations in support of established, local public health and emergency medical response systems. Volunteers’ responsibilities may include emergency medical care and triage, logistic or backup support for trauma units and hospitals in the event of a disaster, immunization campaigns, or public health awareness programs.

The MRC program is headquartered in the Office of the Surgeon General, which administers the grant funds and offers technical assistance to all MRC communities. For more information and a complete list of grantee agencies, go to www.medicalreservecorps.gov.

Department of Health and Human Services

Hospital Spending Increased, Nursing Shortage Temporarily Eased

The Federation of American Hospitals has released the results of 2 studies indicating that future spending for hospital services will increase substantially (despite widespread predictions that increases would be only moderate) and that the number of nurses employed by hospitals and the wages they earned grew dramatically in 2002. The results were discussed at a symposium on future demand for hospital services and supply of nursing personnel on November 12.

The data on hospital spending reported by economist Stuart Altman and colleagues from Brandeis University indicated that total real hospital spending per capita between 2000 and 2012 could increase by 75%, reflecting a predicted average annual increase of 4.8% and a substantially increased demand for hospital beds. They also found that hospital spending by baby boomers grew more rapidly than that by older individuals, a trend that indicates increased spending as now middle-aged individuals grow older. Results of the study were published in the November–December issue of Health Affairs (2003;22: 12–26).

Advocates Call for More PET in UK

At a news conference held in London on November 17, heads of health charities and medical personnel called for the British government to provide more PET facilities. They focused their comments on the effects of the current shortage on more than 38,000 UK patients diagnosed with lung cancer each year. Only 5 PET scanners are available in National Health Service hospitals in England and Wales. Charities including Macmillan Cancer Relief, the British
Lung Foundation, and CancerBACUP joined forces to urge the British government to acquire at least 10 new PET scanners in England and Wales within 5 years.

At the news conference, retired surgeon Jules Dussek, MD, said: “I would be very unhappy if I would be forced to operate on someone with lung cancer without a PET scan. I would feel naked and defenseless.” Patients reported waits as long as 8 weeks and journeys of up to 3 hours for PET services.

Several participants in the news conference suggested that lung cancer patients have received scant attention because of the stigma attached to the disease and because many patients do not survive long enough to effectively protest the quality of their care.

Professor Mike Richards, the UK’s national cancer director, was later quoted by the BBC as saying that the government was determined to prevent lung cancer through programs aimed at smoking cessation and at improving services for patients. He said as yet there was “no conclusive proof that widespread early screening was necessarily an effective use of resources” but added that a framework for PET scanning in the UK was under development.

BBC

Newsbriefs from the Literature

Dean Steps Down at NIBIB

On November 24, Donna J. Dean, PhD, deputy director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB) at the National Institutes of Health (NIH), announced that she would leave her position to become senior scholar in residence at the National Academy of Engineering (NAE). In her new capacity, she will work with the National Academies, federal agencies, academic institutions, and the private sector on issues at the interface of engineering and the life and health sciences. She will join the NAE in January.

“It was my great privilege to work with a stellar group of staff who built a firm foundation for NIBIB’s future,” she said. “I will always be proud of the pivotal role that I played in creating a new institute at NIH that has unlimited potential to foster new arenas of research. I have never had so much fun in my career, nor worked so hard, as in the past 3 years. With supportive colleagues across the NIH, in the Institute, and in the extramural community, it truly was a stimulating and exciting endeavor.”

Before becoming NIBIB deputy director in September 2002, Dean served as the NIBIB acting director during the formation and development stages of the new Institute from its beginnings in January 2001, in addition to serving as the senior scientific advisor to the NIH acting director.

National Institute of Biomedical Imaging and Bioengineering

Diagnosis

Nuclear Medicine and the Cognitive Processes of Spirituality

In 1896, when interest in the newly introduced x-ray reached a fevered pitch, a number of respected medical practitioners speculated on the possibility that the new technology might be able to visualize the human soul. For more than 100 years, these and similar efforts were cited as risible examples of early, unfettered enthusiasm. Today, however, nuclear medicine techniques promise to provide images, not of the soul, but of qualities often referred to as spiritual and previously deemed unquantifiable.

In a study published in the October issue of Perceptual and Motor Skills (2003;97:625–630), Newberg et al. from the Hospital of the University of Pennsylvania (Philadelphia) reported on the use of 11C-WAY100635 PET to measure cerebral blood flow changes during meditative prayer. The study included 3 Franciscan nuns who were experienced practitioners of “verbal-based” meditation involving internal (non-spoken) repetition of specific phrases. The volunteers were scanned before and after 50 minutes of meditation. Postmeditation scans showed increased blood flow in the prefrontal cortex (7.1%), inferior parietal lobes (6.8%), and inferior frontal lobes (9.0%) compared with premeditation (baseline) scans. A strong inverse correlation was noted between blood flow changes in the prefrontal cortex and ipsilateral superior parietal lobe. The authors also compared these results with those from a previous study of 8 Buddhist volunteers who used a different meditation technique (Psychiatry Res. 2001;106:113–122). The authors concluded that this study on a limited number of subjects “demonstrated the feasibility of studying different types of meditation with neuroimaging techniques, suggested that several coordinated cognitive processes occur during meditation, and also raised important methodological issues.”

In the November issue of the American Journal of Psychiatry (2003;160:1965–1969), Borg et al. from the Karolinska Institute and Hospital (Stockholm, Sweden) reported on the use of 11C-WAY100635 PET in assessing the relationship between serotonin-receptor density and spiritual experiences. The study included 15 healthy male volunteers who underwent PET imaging as well as assessment with the Swedish version of the Temperament and Character Inventory self-report questionnaire. As an index of 5-HT1A receptor density, binding potential was calculated for the dorsal raphe nuclei, hippocampal formation, and neocortex, and the results were correlated with responses for each of the 7 aspects, or dimensions, of the personality questionnaire. A significant inverse correlation was found in only 1 of these aspects, the “self-transcendence” di-
SPECT and Hashimoto’s Encephalitis

Zettinig et al. from the University of Vienna (Austria) reported in the November issue of Clinical Endocrinology (Oxford) (2003;59:637–643) on a study using 99mTc-ethylcysteine dimer (ECD) SPECT to evaluate brain perfusion in euthyroid patients with autoimmune thyroiditis. In part the study was designed to assess whether the encephalopathy (often referred to as Hashimoto’s encephalitis) associated with the condition actually constitutes a distinct clinical entity. The study included 41 euthyroid patients with autoimmune thyroiditis and 35 matched healthy individuals. Participants were screened for significant neurologic histories, morphologic brain abnormalities, depression, and mood disorders. All participants underwent 99mTc-SPECT imaging. Brain perfusion was quantified automatically with both a voxel-based analysis and a volume-of-interest (VOI)–based analysis of 46 predefined cortical and subcortical regions. The authors found a significant difference between patients and controls in the mean volume of perfusion defects deviating 2 SD below normal values in the voxel-based analysis. Hyperperfused areas did not differ significantly in the 2 groups. In the group of euthyroid patients, perfusion defects correlated significantly with the amount of time since diagnosis of autoimmune thyroiditis. VOI-based analysis showed that abnormal regions of perfusion were more frequent in the patient group than in the healthy volunteers, but no pattern of regional involvement emerged. Although scores on depression and mood disorder assessment instruments varied greatly between the 2 groups, these results did not correlate with perfusion patterns or abnormalities. The authors concluded that these findings of impaired brain perfusion in patients “further strengthen the hypothesis of a possible cerebral involvement in autoimmune thyroiditis in individual cases” and that “the presence of cerebral hypoperfusion suggests a cerebral vasculitis as the most likely pathogenetic model.”

Clinical Endocrinology (Oxford)

99mTc-MIBI Parathyroid Scintigraphy

In a study e-published ahead of print on November 26 in the World Journal of Surgery, Gotthardt et al. from the Philipps-University of Marburg (Germany) reported on a meta-analysis of their institution’s experience and the literature on 99mTc-methoxyisobutylisonitrile (MIBI) parathyroid scintigraphy, with special attention to previously noted discrepancies in reports on the sensitivity of the procedure. The institutional study included 139 patients who underwent parathyroid scintigraphy and subsequent surgery between 1991 and 1999. Of these, 109 were found at surgery to have primary hyperparathyroidism and 30 to have secondary parathyroidism. The sensitivity and specificity of parathyroid scintigraphy were 45% and 94%, respectively, in patients with primary hyperparathyroidism and 39% and 40%, respectively, in patients with secondary parathyroidism. These results were compared with the results of a non-statistical systematic meta-analysis of the 52 published studies about parathyroid scintigraphy. Sensitivities reported varied from 39% to 90%. The authors concluded that differing scintigraphic techniques did not account for the wide differences in reported sensitivity. Their own data and “partially unpublished” data from a number of university hospitals suggested that the sensitivity of the procedure in clinical routine may be lower than that predicted in much of the literature. They concluded that “a well-designed and properly conducted prospective study is necessary to evaluate the reasons for the differences observed.”

World Journal of Surgery

Postradiation PET Predicts Early Tumor Regrowth

Researchers from Japan reported in the December issue of the International Journal of Radiation Oncology, Biology, Physics (2003;57:1231–1238) that 18F-FDG PET performed immediately after radiation therapy can predict early tumor regrowth. The study by Koike et al. from the Yokohama City University School of Medicine (Japan) included 20 patients who received radiation for a variety of malignant tumors and who underwent PET image before and within 10 days of completing radiation therapy. Standardized uptake values (SUVs) were calculated for 26 lesions imaged in the 20 patients before and after treatment, and these were correlated with outcomes at 3 months after radiation. Retention indices (RIs) were calculated as the SUV on the posttherapy image minus that on the pretherapy image. RIs were significantly different between patients with and without residual tumor at 3 months after irradiation. All 9 lesions in 6 patients with residual tumors showed RIs >0.1, whereas none of the lesions with RIs <0.1 showed residual tumors. The authors concluded that “dual-time FDG PET imaging just after irradiation is potentially useful for predicting early regrowth of malignant tumors.”

International Journal of Radiation Oncology, Biology, Physics
Phantom Dose Measurements in SLN Lymphoscintigraphy

Researchers from Hong Kong reported in the British Journal of Radiology (2003;76:818–823) on a phantom study designed to assess the total dose to patients undergoing sentinel lymph node (SLN) lymphoscintigraphy. Law et al. from Queen Mary Hospital used an adult female phantom and a set of thermoluminescent dosimeters to measure both the transmission scan and the internal emission dose. They duplicated the protocol used in their institution, with an external transmission $^{57}$Co flood source irradiating the phantom in the posterior, left lateral, left posterior oblique, right lateral, and right posterior oblique positions. Four $^{99m}$Tc deposits as internal emission sources were used to simulate peritumoral injection. After measuring the results, the authors calculated that in their protocol, the patient with breast cancer undergoing SLN lymphoscintigraphy received a maximum effective dose of 52 $\mu$Sv for a 1-day protocol (18 MBq injection) and 204 $\mu$Sv for a 2-day protocol (74 MBq injection) when only the SLN was excised. The patient effective dose was reduced if other radioactive tissues were removed in the procedure. The authors concluded that “although the doses are low compared with other radiological examinations, the results are informative for patients concerned about radiation exposure for this new imaging technique.”

British Journal of Radiology

Intradermal Injection in SNL Mapping

Fleming et al. from St. Vincent’s University Hospital and University College Dublin (Ireland) reported in the December issue of the European Journal of Surgical Oncology (2003; 29:835–838) on a study comparing the efficacies of intraparenchymal and intradermal isotope injections in sentinel lymph node (SLN) mapping in 125 patients with histologically confirmed breast cancer. Each of 80 patients was administered radioisotope in 4 intraparenchymal injections around the tumor. Each of 45 patients received an intradermal injection at a single site over the tumor. In both groups, isosulphan blue dye was injected around tumors. Sentinel nodes were identified using a combination of lymphoscintigraphy, blue dye, and an intraoperative hand-held gamma probe. A combination of blue dye and isotope successfully located the SLN in 96% of the intraparenchymally injected group and 100% of the intradermally injected group. The authors concluded that “intradermal isotope injection in combination with intraparenchymal blue dye optimizes the localization of the SLN in breast cancer.”

European Journal of Surgical Oncology

$^{123}$I-BMIPP SPECT and Prediction of Cardiac Death

In a study published in the November issue of Circulation Journal (2003;67:918–924), Sasaki et al. from the Fujisawa Municipal Hospital (Japan) reported on a study assessing the effectiveness of $^{123}$I-methyliodophenyl pentadecanoic acid (BMIPP) SPECT in predicting cardiac death in patients with chronic heart failure. The study included 74 patients with chronic heart failure and left ventricular ejection fractions (LVEFs) <45%. All patients underwent both $^{201}$TI SPECT and BMIPP SPECT. Tracer uptake was scored in numerous cardiac segments, and heart-count-to-mediastinum (H/M) ratios were calculated. During a mean follow-up period of 660 days, 17 patients died of cardiac causes. Multivariate analysis identified H/Ms and LVEFs as independent predictors of cardiac death. The authors concluded that “analysis of the myocardial metabolism by BMIPP SPECT can predict high-risk patients with chronic heart failure.”

Circulation Journal

Gated Blood-Pool SPECT and Right Ventricular Function

Slart et al. from University Hospital Groningen (The Netherlands) reported in the October issue of the International Journal of Cardiovascular Imaging (2003;19:401–407) on a study designed to compare gated blood-pool SPECT using NuSMUGA calculation software (Northwestern University, Chicago, IL) and first-pass radionuclide angiography (FPRNA) in evaluating right ventricular ejection fraction (RVEF). The study included 22 patients in whom FPRNA and gated blood-pool SPECT acquisition were performed. RVEF calculations were performed manually and with the software, using all gated short-axis slices of the right ventricle. The authors found that the software-calculated RVEF from gated blood-pool SPECT did not correlate with that of conventional FPRNA. Mean FPRNA RVEF was 55% ± 10%, and mean gated blood-pool SPECT RVEF calculated with NuSMUGA was 32% ± 8%. Manual gated blood-pool SPECT RVEFs also did not correlate with conventional FPRNA, although they did correlate well with the software-calculated values. The authors concluded that “FPRNA and gated blood-pool SPECT calculations cannot be considered to be equivalent. Therefore, the NuSMUGA program cannot be used to calculate RVEF.”

International Journal of Cardiovascular Imaging

$^{123}$I-$\beta$-CIT SPECT and 5-Year Progression in Parkinson’s Disease

Researchers from the University of Vienna (Austria) reported in the November issue of Movement Disorders (2003;18:1266–1272) on a study of the effectiveness of $^{123}$I-2-carbomethoxy-3$\beta$(4-iodophenyl)tropane ($^{123}$I-$\beta$-CIT) SPECT in assessing the decline of striatal dopamine transporter binding over a period of 5 years in a group of patients diagnosed
with early Parkinson’s disease (PD). The study by Pirker et al. included 21 patients imaged after diagnosis at 3 intervals over a 5-year period. The authors found that when the period from the initial scanning to 26 ± 11 months (scan 2) after was compared with the period from scan 2 to 38 ± 15 months after, there was no significant difference in the rate of decline of striatal binding. The authors concluded that these data do not suggest “substantial change in the course of dopaminergic degeneration in PD within the first 5–7 years after symptom onset,” a finding that is contrary to a current assumption of rapid decline in binding capacity during early stages of the disease.

Movement Disorders

Long-Term Survival in Differentiated Thyroid Cancer

The prognostic factors relevant for long-term survival in differentiated thyroid cancer were investigated retrospectively in a large patient group by Eichhorn et al., of the Johannes Gutenberg-Universitat Mainz (Germany), and reported in the October issue of Thyroid (2003;13:949–958). The study included 484 patients (358 women; 126 men) with differentiated thyroid cancer (330 papillary; 154 follicular) who had been treated after thyroidectomy with at least 2 131I therapies and followed-up for a median of 7.6 years at the same institution. The authors found corrected cause-specific 5-, 10-, and 20-year survival rates in the whole cohort to be 0.95, 0.90, 0.83, respectively (low-risk papillary cancer: 0.99, 0.97, 0.89, respectively; low-risk follicular cancer: 0.98, 0.89, 0.89, respectively; high-risk papillary cancer: 0.89, 0.85, 0.85, respectively; high-risk follicular cancer: 0.88, 0.73, 0.52, respectively). Variables with significant negative influence on survival included distant metastases, persisting elevated human thyroglobulin levels after 1 131I therapy, age 45 years, and, in follicular cancer, sex. Locoregional external radiotherapy did not improve survival but was associated with comorbidity. The aggressiveness of the initial lymph node resection was not a prognostic factor for survival.

Thyroid

Electroporation and Radioiodine Uptake

A novel approach to enhance radioiodine uptake in a human thyroid cancer cell line was reported by Gopal et al. from the Bhabha Atomic Research Center (Mumbai, India) in the November issue of Applied Radiation and Isotopes (2003;59:305–310). The authors used electroporation, a process that involves the application of short, high-voltage electric pulses that briefly render plasma membrane permeable, to incorporate radioiodine into a noniodine-concentrating human thyroid cancer cell line (WRO). The cultured WRO cells, which usually do not incorporate iodine because of a lack of a specific transporter protein, incorporated significant amounts of radioiodine after electroporation. Factors affecting the extent of uptake by electroporation included the strength of the electric field, external concentrations of iodine, length of time of electroporation, and temperature of incubation. The incorporated radioiodine was retained over a period of 24 hours. The authors noted the promising implications of these results for thyroid cancer if validated in in vivo studies.

Applied Radiation and Isotopes

Expanding 188Re Applications in Therapy and Treatment

The advent of in-house 188Re generators has provided additional momentum to research on a growing number of radiopharmaceuticals that apply its advantageous physical and chemical properties to radiotargeted therapy and treatment of various cancers and diseases. The range of radiopharmaceuticals and potential clinical applications was surveyed in the October issue of Cancer Biotherapy and Radiopharmaceuticals (2003;18:707–717) by Jeong and Chung from Seoul National University College of Medicine (Korea). 188Re is in use in various agents aimed at the reversal of restenosis in coronary arteries, palliation of metastatic bone pain, and treatment of liver cancer, solid tumors, and rheumatoid arthritis. The authors called for research in the development of new 188Re-labeled radiopharmaceuticals to target cancerspecific monoclonal antibodies and peptides.

In the same issue of the journal (2003;18:719–726), Zhang et al. from Gunma University School of Medicine (Japan) reported on the use of 188Re-hydroxyethylidene diphosphonate (HEDP) for the palliation of bone pain in lung cancer patients. The study included 30 patients with painful osseous metastases from lung cancer who were administered 188Re-HEDP in activities ranging from 1.15 to 4.6 GBq and then followed clinically for up to 1 year. Prompt and significant relief of bone pain occurred in 80% of patients, with no significant side effects or toxicity, and 46% of patients discontinued analgesics after administration of the radiopharmaceutical.

Cancer Biotherapy and Radiopharmaceuticals

RIT in Head and Neck Squamous Cell Carcinoma

Colnot et al. from the VU University Medical Center (Amsterdam, The Netherlands) reported in the September issue of Cancer Immunology and Immunotherapy (2003;52:576–582) on the safety and other characteristics of 99mTc-labeled humanized monoclonal antibody (mAb) BIWA 4 (bivatuzumab) for radioimmunotherapy (RIT) in patients with squamous cell carcinoma of the head and neck (HNSCC). The authors evaluated the safety, tumor-targeting potential,
pharmacokinetics, and immunogenicity of $^{99m}\text{Tc}$-labeled BIWA 4 in 10 patients undergoing operations for primary HNSCC, who were treated first with doses of 25 (3 patients), 50 (4 patients), and 100 mg (3 patients). Radioimmunoscintigraphy was performed within 1 hour and after 21 hours, and patients underwent surgery at 48 hours after injection. Imaging showed targeting of primary tumors in 8 of 10 patients and lymph node metastases in 1 of 5 patients. The highest tumor uptake and tumor-to-nontumor ratios were observed in the 50-mg dose group. Tumor uptakes were 12.9/\%ID/1000\;\text{g}\;\text{kg} \; \frac{5.9}{\%ID/1000\;\text{g}\;\text{kg}}, 26.2/\%ID/1000\;\text{g}\;\text{kg}\;\frac{3.1}{\%ID/1000\;\text{g}\;\text{kg}}$, and 15.4/\%ID/1000\;\text{g}\;\text{kg}\;\frac{1.9}{\%ID/1000\;\text{g}\;\text{kg}} percentages of the injected dose (%ID)/kg for the 25-, 50-, and 100-mg dose groups, respectively, and the tumor-to-bone marrow ratios for these groups were 1.7 \pm 0.5, 3.2 \pm 1.1, and 2.0 \pm 0.6\% ID, respectively. The administration of $^{99m}\text{Tc}$-BIWA 4 was well tolerated by all patients, and no human antihuman antibody responses were observed. The authors concluded that $^{99m}\text{Tc}$-BIWA 4 can safely be administered to patients with HNSCC and that “these findings support the use of BIWA 4 for RIT studies in patients with HNSCC.”

Cancer Immunology and Immunotherapy

64Cu and Cytotoxicity in Targeted Radiotherapy

In a study published in the October 15 issue of Cancer Research (2003; 63:6864–6869), Wang et al. from the Washington University School of Medicine (St. Louis, MO) reported on a study of subcellular distribution of somatostatin analogue $^{64}\text{Cu}$-labeled 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid-octreotide (TETA-OC) and $^{111}\text{In}$-labeled diethylenetriaminepentaacetic acid-octreotide (DTPA-OC) in somatostatin receptor-positive AR42J rat pancreatic tumor cells in vitro. The purpose of the study was to investigate the mechanisms of $^{64}\text{Cu}$ cytotoxicity. Cell uptake and organelle isolation studies were conducted and compared in $^{64}\text{Cu}$-TETA-OC and $^{111}\text{In}$-DTPA-OC. Nuclear localization of each radioisotope increased over time, 19.5\% ID of the $^{64}\text{Cu}$ and 6.0\% ID of the $^{111}\text{In}$ in the cell nucleus at 24 hours. When $^{64}\text{Cu}$-TETA-OC was incubated in pulse-chase experiments with AR42J cells for 4 hours, the nuclear localization of $^{64}\text{Cu}$ increased significantly over the next 20 hours (from 9.8\% ID to 26.3\% ID). A separate control pulse-chase experiment showed that the redistribution mechanisms of $^{64}\text{Cu}$ from $^{64}\text{Cu}$-TETA-OC were different from those of the same isotope in $^{64}\text{Cu}$-cupric acetate. The amount of $^{64}\text{Cu}$ from $^{64}\text{Cu}$-TETA-OC also increased in the mitochondria over the 24 hours after administration. The authors concluded that these results suggested that “localization of substantial quantities of $^{64}\text{Cu}$ to the cell nucleus and mitochondria may contribute to cell killing with $^{64}\text{Cu}$ radiopharmaceuticals.”

Cancer Research

Hyperthermia, Ultrasound, and MicroPET

Singh et al. from the Washington University School of Medicine (St. Louis, MO) reported in the January–February issue of the International Journal of Hyperthermia (2004;20; 32–44) on the development of a microPET-compatible small animal hyperthermia ultrasound system for the heating of subcutaneously implanted tumors in studies of tumor hypoxia. They described the device and presented data from phantom and in vivo experiments indicating that the ultrasound system could produce hyperthermia to a target temperature of 41.5°C in tumors that were 8 \pm 2\;\text{mm} in diameter in mice. This temperature could be maintained within a narrow range for up to 4 h without affecting the core temperature of the animals.

International Journal of Hyperthermia