FDA Unveils Product Development Priorities

Health and Human Services (HHS) Secretary Mike Leavitt and the Food and Drug Administration (FDA) released on March 16 an initial list of priority research projects aimed at advancing innovation in medical products. The Critical Path Opportunities List, part of the FDA Critical Path Initiative, outlines 76 initial projects to bridge the gap between the quick pace of new biomedical discoveries and the slower pace at which those discoveries are currently developed into therapies. In a press release accompanying the announcement, FDA officials noted that, “If accomplished, the new tests and tools developed under the Critical Path Initiative will modernize the drug development process by 2010 and help to get new medical discoveries to patients faster and at a lower cost.”

“Right now, researchers are trying to bring 21st century medical innovations to market using 20th century tools to evaluate them. Under the Critical Path Initiative, we anticipate being able to dramatically increase the success rate in moving products from the lab to the patient,” said Dr. Andrew C. von Eschenbach, then acting FDA commissioner. “The keys to a smarter more modern medical product development process are the standardization of new tools to test potential products along with the unprecedented integration of information within government, industry, and academic partnerships.”

The Critical Path Opportunities Report is organized into 6 broad topic areas: development of biomarkers, clinical trial designs, bioinformatics, manufacturing, public health needs, and pediatrics. In compiling the list, FDA administrators indicated that priority efforts will focus on accelerated biomarker development and streamlining clinical trial design, each of which have direct implications for nuclear and molecular medicine researchers. “Most researchers agree that a new generation of predictive biomarkers would dramatically improve the efficiency of product development, help identify safety problems before a product is on the market (and even before it is tested in humans), and facilitate the development of new types of clinical trials that will produce better data faster,” said Janet Woodcock, MD, deputy commissioner for operations and head of the FDA Critical Path Initiative. “Similarly, researchers stressed that (Continued on page 30N)

JNM Editor, SNM Members Receive Imaging Awards

At the Academy of Molecular Imaging (AMI) annual conference March 25 to 29 in Orlando, FL, awards were made to 3 SNM Members, including the editor-in-chief of The Journal of Nuclear Medicine (JNM), for outstanding contributions in molecular imaging.

Heinrich R. Schelbert, MD, PhD, George V. Taplin Professor of Nuclear Medicine at the David Geffen School of Medicine of the University of California at Los Angeles and editor-in-chief of JNM, was presented with the 2006 Peter Valk Distinguished Clinical Science Award. His major research interest has been the development and validation of noninvasive radionuclide imaging techniques for the study of cardiovascular function and the application of these novel techniques in the study of functional and metabolic consequences of coronary artery disease. Major accomplishments include the discovery of the specific pattern of blood flow and metabolism in chronically dysfunctional myocardium that is predictive of potential reversibility and the development and validation of PET-based techniques for measuring regional myocardial blood flow in absolute units using $^{15}$N-ammonia. He has edited several books on cardiovascular imaging, published more than 300 peer-reviewed articles, and serves as a regular reviewer for numerous cardiology and nuclear medicine journals. He is a 2-time recipient of the Georg von Hevesy Prize from the World Federation of Nuclear Medicine and Biology and has been recognized with the Georg de Hevesy Nuclear Medicine Pioneer Award by SNM and the Distinguished Scientific Achievement Award by the American Heart Association.

The 2006 Distinguished Basic Science Award was presented to Ralph Weissleder, MD, PhD, a professor at Harvard Medical School, director of the Center for Molecular Imaging Research at Massachusetts General (Continued on page 50N)
The William G. Myers, MD, PhD, Collection at the Medical Heritage Center (MHC) of The Ohio State University (OSU) is set to open later this month in Columbus to honor one of the pioneers in the applications of radioisotopes in medical diagnosis and treatment. On May 25, as part of the opening festivities, historian and long-time Myers associate Henry N. Wagner, Jr., MD, will lecture on Myers’s role in the development of nuclear medicine and related fields. The opening will be accompanied by public programs designed to enhance awareness of the availability of these nuclear medicine–related materials for scholarly research. In addition, the MHC Web site will feature a Myers virtual exhibit and a new MHC digital library with the Myers Collection serving as the pilot project.

The collection documents the personal life and many professional achievements of Myers (1908–1988). In 1940, just 1 year after Ernest O. Lawrence won the Nobel Prize for development of the cyclotron, Myers attended a lecture by Ernest’s brother John H. Lawrence on the potential uses of the cyclotron in medicine. The description of potential uses for radioisotopes in medicine ignited Myers’s interest in what was to become his life-long research pursuit: applying the cyclotron to the development of radioactive isotopes for novel medical applications.

Myers was instrumental in bringing a cyclotron to the Physics Department at OSU in 1941. In 1948, he introduced $^{60}$Co as a substitute for radium in cancer treatment, and, in 1952, he and Benjamin H. Colmery introduced $^{198}$Au as a replacement for $^{222}$Ra in permanent seed implantation for cancer therapy (Fig. 1). Myers is said to have introduced more radioisotopes into nuclear medicine than any other individual (Table 1).

The Myers Collection contains photographs, correspondence, news clippings, report cards, and other ephemera that document his early life. Myers was born in Toledo, OH, to a farmer father and factory worker mother. His parents divorced when he was quite young, and he was placed in an orphanage for several years. His father remarried and reunited the family on a homestead in Alberta, Canada. Young Bill helped to build the log house and support the family by hunting and fishing. After a brief stint away from high school, Myers graduated from Wauseon High School in Ohio and won a competitive scholarship to OSU. The Myers Collection contains his master’s thesis, dissertation, and course work that document his years at the university, where he supported himself as a barber and a teaching assistant in chemistry. By attending for 39 consecutive quarters, Myers earned his doctorate in physical chemistry in 1939 and his medical degree in 1941.

Photograph courtesy of The Ohio State University Photo Archives.

Figure 1. Myers with radioactive gold seeds for permanent seed implantation in cancer therapy.

A highlight of the Myers Collection is the group of letters he wrote in 1946 to Florence Lenahan, his new bride, describing his experience as a radiation security officer and radiation monitor during Operation Crossroads. This joint Army and Navy nuclear weapons test series took place in the Bikini Atoll of the Marshall Islands and included the first post-WWII nuclear bombing tests. The series consisted of 2 tests, Able and Baker, each using the same type of MK 3A fission bomb that was dropped on Nagasaki. Able was the first test designed to study the effects of the atomic bomb on naval vessels, planes, and animals. Utilizing an airburst-type detonation, Able produced radiation contamination that quickly dissipated. Baker, on the other hand, employed a subsurface burst and yielded very different results: an explosion that bathed the fleet in radioactive mist and debris and required almost a year of decontamination efforts. This experience cemented Myers’s interest in what would soon be called the “atoms for peace” movement.

Containing approximately 16,000 letters, memos, and postcards, the Correspondence Series of the Myers
Collection is especially strong. Myers cultivated professional and personal relationships with Nobel Prize winners and other important figures in the fields of chemistry, physics, and nuclear medicine at hospitals and research centers throughout the world. The collection includes letters from many important figures in nuclear medicine and physics, including Paul Aebersold, John Lawrence, Rosalyn Yalow, Hal Anger, Irene Curie, and Glenn T. Seaborg. Myers made copies of letters he sent, so that the collection contains an unusually complete record of his written communications. Correspondence with various United States government agencies is also represented, including the U.S. Atomic Energy Commission.

The correspondence also provides information about Myers’s interest in the history of nuclear medicine. An early member of the SNM, Myers remained active in the organization throughout his long career and served as the Society’s historian for 13 years (1973–1986). During this time, he published many articles documenting the history of nuclear medicine in The Journal of Nuclear Medicine and in Newsline.

The Photographs Series of the Myers Collection is particularly rich and includes approximately 3,840 photographic prints, 4,508 negatives, and 18,400 slides. Myers was an avid photographer and an active member of the faculty photography club. His photographic subjects include nuclear medicine pioneers, historical OSU Medical Center events, and nuclear medicine equipment. Perhaps the most fascinating photographs in the collection are those made during the early days of nuclear equipment production, when changes occurred rapidly and the previous year’s innovations were quickly outdated and discarded. To better catalog these equipment images, the MHC is working on a photograph identification project with specialists in nuclear medicine who are familiar with this early equipment.

Other series, such as Associations and Conferences; Publications; Research, Speeches and Exhibits; Teaching; and Equipment, Laboratories, and Supplies document Myers’s more than 4 decades in nuclear medicine. The Association and Conferences Series contains more than 3 linear feet of civil defense–related materials. As a faculty member at the OSU College of Medicine, he researched and taught for more than 40 years. He taught the university’s first radiation biology course (the first such course to be taught by a physician); held faculty positions in the departments of Medicine, Physiology, and Radiology; and earned emeritus professor status in 1979. He served as a visiting professor of biophysics at the University of California, Berkeley, in the 1970s, and Cornell University (Ithaca, NY) in the 1980s. He also conducted extensive research with larger cyclotrons at the Lawrence Berkeley National Laboratory and the Memorial Sloan–Kettering Cancer Center. Myers was a prolific author, publishing more than 200 articles.

Throughout his career, Myers championed the cyclotron. With Myers as its backer, OSU acquired one of the first cyclotrons in the world and was among the first universities to make short-lived radionuclides for medical use. As Myers’s career progressed, he studied radionuclides with progressively shorter half lives and was among the first to champion the notion of hospitals installing their own cyclotrons. Wagner, the current historian of the SNM and coauthor of the soon-to-be-published book Atoms for Life: A Personal History of Nuclear Medicine, calls Myers the “godfather of the cyclotron.”

Mary Manning, MA, MLIS
Medical Heritage Center
The Ohio State University
Columbus, OH

For more information on the opening event or on conducting research in the collection, please contact the Myers archivist, Mary Manning MA, MLIS, at manning.84@osu.edu or 614-292-9966 or visit the MHC online at http://mhc.med.ohio-state.edu.
By the 1960s and 1970s it was clear that nuclear medicine techniques showed promise in a number of applications. What was not immediately clear was how these techniques should be applied in children. Perhaps the most basic tenet of all pediatric practice is that children are not merely miniature adults, with diagnoses and treatments titrated down by metrics of size and weight. This was especially true in nuclear medicine, where the potential effects of radioisotopes added a separate dimension to concerns about specialized approaches in children.

Pediatric nuclear medicine faced a number of challenges in its developing years. First was the obstacle of critical mass: only a few practitioners specialized in the area, and no professional organization or meeting venues focused solely on their concerns. This difficulty was compounded by deeply ingrained public misconceptions about radiation and its effects and by a complex and sometimes frustrating system of regulatory requirements and constraints. At the request of Conrad Nagle, editor of Newsline, I have prepared this look back at some of the efforts from this period in which I was directly involved.

The Pediatric Nuclear Medicine Club

With the increasing use of radioisotopes in children in the mid 1960s, pediatric nuclear medicine practitioners naturally gathered at larger professional meetings to discuss common problems and exchange experiences. As pediatric nuclear medicine practice increased, it became obvious that these communications could be better accomplished through a more formalized organization. With support from individuals such as S. Ted Treves, MD, at the Boston Children's Hospital and David Gilday, MD, at the Hospital for Sick Children in Toronto, Ontario, I organized the first meeting of pediatric nuclear medicine practitioners at the 1974 Annual Meeting of the SNM in San Diego, CA. I posted homemade signs (Fig. 1) around the meeting hall, with the goal of developing a pediatric interest group within the SNM. The leadership of the society expressed their concern to me that our special interest group meeting was being convened to create another society that would be in competition with the SNM, a prospect that the founders of the club did not envision then or later. Approximately 40 individuals attended the initial meeting, including physicians, technologists, physicists, nurses, pharmacists, and industry representatives. The goals for the pediatric club were established. I was chosen to serve as the spokesperson for the group, and Sue Weiss, CNMT, was elected secretary.

Several ambitious goals were proposed at this meeting, including a formal request for recognition of a pediatric nuclear medicine group by the SNM. A major objective was to petition the SNM for a formal representative on the program committee and for a specific time slot on the scientific program for a pediatric nuclear medicine category at the annual meeting. Several technologist members of the club, including Weiss, Royal Davis, CNMT, and Elizabeth Kilburn, RTNM, also succeeded in securing a pediatric track for the technologist section programs at the SNM annual meetings. Another initial goal was to pool data and information for the purposes of peer-reviewed publication by the membership. The club members agreed to cooperate and coordinate research studies and to conduct conjoint phase III safety and efficacy studies to obtain U.S. Food and Drug Administration (FDA) approval for various radiopharmaceuticals in children. Another goal was to promote the use of nuclear medicine in other pediatric subspecialty organizations and to referring pediatricians.

At the 1975 Annual Meeting of the SNM in Philadelphia, PA, the interest group was formally named the Pediatric

From the Newsline Editor:

This is the second in a 3-part series from James J. Conway, MD, a distinguished pioneer in pediatric nuclear medicine and past president of the SNM. In the first part of the series (J Nucl Med. 2006;47:N12–N20), he recalled the individuals and early advances that contributed to the introduction of pediatric applications into the mainstream of nuclear medicine practice. In this installment, he looks at the establishment and evolution of the Pediatric Nuclear Club within the SNM and at the challenges faced by the subspecialty in its formative years. In the final installment, he will provide a fascinating and highly personal memoir of his own experiences as a researcher, clinician, and educator.

Conrad Nagle, MD
Nuclear Medicine Club of the SNM. The club has met at every SNM annual meeting since and regularly presented pediatric scientific papers followed by a business meeting and a member’s miscellany of interesting cases. From the beginning, many international members have participated in the club’s activities.

In 1975, I suggested that one of the definitive educational goals for the club could be the publication of a bibliography of pertinent pediatric nuclear medicine literature. At the time, literature searches were often laborious and difficult. It was proposed that the discipline was sufficiently new that such an undertaking would not present a formidable task for the fledgling group. Volunteer compilers were accepted from those in attendance, and categories of interest were assigned. The volunteers and their assigned topics included Kilburn, for pediatric nuclear medicine technology; Gilday, for the central nervous system; Henry Wellman, MD, for the thyroid; Treves, for cardiac medicine technology; Gilday, for the central nervous system; and Eugene L. Saenger, MD, for radioimmunoassay; Massoud Majd, MD, for skeletal imaging; Hirsch Handmaker, MD, for liver, abdomen, and spleen; Robert G. Brown, MSc, for radiopharmaceuticals; and Jerold M. Lowenstein, MD, and Michael J. Gelfand, MD, for radiobiology and dosimetry. The result was the compilation of a bibliography of 1,659 references pertinent to pediatric nuclear medicine from more than 2,500 contributors. The Pediatric Nuclear Medicine Club’s A Bibliography of Pediatric Nuclear Medicine Literature was published in 1976 by Searle Radiographics, Inc. and distributed free to nuclear medicine practitioners (1). It should be remembered that the sophistication of the Internet and a computerized Index of Medical Literature for medical reference searches were undreamed of at this time. The compilation of this specialized bibliography on pediatric nuclear medicine simplified research for many authors by providing a well-codified means of access to historical and other pertinent references in the literature.

In 1990, membership in the Pediatric Nuclear Medicine Club had grown to more than 100. According to the bylaws of the SNM, a minimum of 100 members was necessary for recognition of the club as an SNM council. I recommended that the club petition for SNM council status at the 1990 meeting. Although several members feared that we would lose the sense of purpose and fellowship generated at yearly meetings, the group voted to seek council status. The petition for recognition was submitted to the SNM Board of Trustees, and council status was granted on June 10, 1991.

In June, 1992, the Society of Pediatric Radiology (SPR) conducted a survey. Of 65 pediatric radiology facilities in the United States, only 36 responded to the survey. Of these, only 11 had 50% full-time equivalent pediatric nuclear medicine practitioners (2). Of additional interest, a significant number of pediatric nuclear medicine practitioners, both then and now, have not joined the SNM. At least 250 individuals participate in Gelfand’s pediatric nuclear medicine e-mail community (3), yet the SNM Council on Pediatric Imaging currently has only 120 official members. Gelfand’s list server has been a major link for communication and interaction of practitioners, especially in the intervals between meetings, and he should be lauded for bringing this freely available site to fruition.

Important functions of the SNM Pediatric Council have been representation on the SNM Board of Trustees and later in the House of Delegates. Perhaps more important has been representation on the program committee for the annual meetings. Members have served as reviewers for pediatric articles for The Journal of Nuclear Medicine (JNM) and the Journal of Nuclear Medicine Technology (JNMT) as well as for many other journals. Pediatric Council members have had professional and social get-togethers at the annual meetings of the SNM and of the European Association of Nuclear Medicine. At the meetings of the World Federation of Nuclear Medicine and Biology, we have had well attended pediatric nuclear medicine tracks and even “College Bowl” challenges in Toronto, Ontario; Sydney, Australia; and Berlin, Germany. The 120 members of the Pediatric Imaging Council of the SNM today include technologists, basic scientists, radiopharmacists, nurses, industry members, and nuclear medicine physicians from the United States and around the world.

**Combating Radiation Hysteria**

The growing subspecialty had much to overcome, both in the culture and in dealing with sometimes contradictory and constraining regulatory efforts. Radiation hysteria was a pervasive force in the 1960s and 1970s. Much of the public’s perception of “radiation risk” was rooted in the after-effects of the Hiroshima and Nagasaki bombings and was supplemented by the widely publicized risk data that emerged gradually during the 1960s. These data were derived primarily from...
exposures resulting from massive and instantaneous single exposures, often associated with early deaths. Soon the longer-term effects from lesser exposures began to manifest themselves as a variety of cancers and chronic illnesses. It was natural for these findings to have a significant effect on the public’s perception of risk from medical imaging and therapeutic procedures employing radiation.

Other long-term radiation risk data had been made public earlier with the poisoning of radium dial painters, overexposures in radiotherapy (especially in pediatric applications), and in contrast agents, such as thorotrast, found to have deleterious effects. Much of the published data on radiation risks was being determined from these most egregious incidents of overexposure and then extrapolated to estimates of risk from clinical radioisotope studies.

Various “theoretical risks” were being determined by scientific bodies, such as the International Commission on Radiological Protection (ICRP) and the National Commission on Radiological Protection (NCRP). Those organizations conceptualized and debated different models of risk that could be extrapolated from a threshold level to a no-threshold level. The concept of radiation risk was being developed and modified with each release of data and estimated known exposures. These open debates confused the public and provided fodder for the antiradiation activists.

Compounding the problem, self-proclaimed radiation risk “experts” (often with axes to grind) devised their own data interpretations, sometimes for promotion of their publications. These individuals were spotlighted in the national radio and television media. One “scientist expert” proclaimed on the Phil Donahue Show that a single unit of radiation, the rad, delivered to the brain would result in 1 out of 200 children developing brain cancer within his or her lifetime. This telecast reached more than 25 million viewers throughout the world. Such proclamations had serious detrimental effects on the public’s perception of radiation risk. After this show aired, a distraught mother called me about her son, who had recently undergone a brain scintigram. I spent several hours with the mother, attempting to dispel her fears that she had approved a study that had “a very high chance” of causing her son’s death. I protested to Donahue’s staff that the presentation on his show of the risks of radiation to children was highly exaggerated and created fears in many parents that might prevent them from allowing their children to undergo necessary radiologic and nuclear medicine studies or treatments. A number of months later, Donahue invited me to present my side of the story on his show. Fortunately, I had been trained previously in television presentations at the Home Box Office studios in New York City, through an American College of Nuclear Physicians (ACNP)—sponsored program of media training for its leadership. I believe that I succeeded in dispelling a great many public fears about radiation risks while on the Donahue show. I placed radiation risk and benefits from radiologic and nuclear medicine procedures into a proper perspective, emphasizing the real risks from disease processes. I was selected subsequently to participate on Committee 3, the medical committee, of the ICRP, where I am proud to have contributed to the development of 2 important radiation protection documents for the patient (4) and for the worker in radiology and nuclear medicine (5).

Some popular mythologies about radiation are particularly persistent. In film after film, exposure to radiation created giant mutations or resurrected unlikely prehistoric behemoths. More than 30 popular comic book and cartoon characters, including Spiderman, the Hulk, the Beast, and even Captain America, owed their special powers to inadvertent exposure to radiation. It was ingrained in many of us as children that radiation is a dangerous and (perhaps more important) evil force (6).

All of these revelations, real or unreal, served to impede the general acceptance of the use of radioisotopes in children, despite the fact that many nuclear medicine studies delivered lower absorbed radiation doses than comparable radiographic studies. At the same time, as a profession, we also came to know that radiation has a greater effect upon children and so we adopted the principles of the ICRP, the NCRP, and the Nuclear Regulatory Commission (NRC) to administer absorbed radiation doses that are “as low as reasonably achievable” to provide a satisfactory study.

Meeting the Challenge of Government Regulation

Perhaps the greatest impediment to the growth of pediatric nuclear medicine encountered in the early years was government regulation in all its forms. Regulations arose from the many national and local government agencies and from the “self-imposed regulations” that originated in medical organizations. At the government level there were at least 20 national organizations that included the NRC, FDA, DOE, DOT, FTC, BRH, EPA, APA, CRS, and the JCAHO—an alphabet soup of regulatory bodies that do not need spelling out for most readers of this journal. Similar bodies at the state and local level have included the IDNS, EPA, CBH, and RSC. For everyone practicing nuclear medicine, the submission of complex applications and reporting forms, along with frequent and often unannounced inspections, became a way of life. At our institution, we finally had to insist that no more than 1 agency could inspect on any single day, because the inspectors sometimes bumped into one another and disrupted clinical work.

Effective voluntary self-regulation arose from the creation of hospital institutional review boards and Radioactive Drug Research Committees. The ACNP and the American College of Radiology also provided self-regulation guidelines. In addition, the American Academy of Pediatrics issued its recommendations for the use of drugs in children (7). The U.S. Department of Health, Education, and Welfare (today Health and Human Services) issued its own regulations in General Considerations for the Clinical Evaluation of Drugs in Infants and Children (8). Both of
these documents imposed restrictions on the use of non-FDA-approved drugs in children. At the time, none of the commercially available radiopharmaceuticals had undergone clinical testing in children or secured FDA approval for these applications. However, we could still prescribe radiopharmaceutical drugs on an individual basis.

The most serious impediments to the growth of pediatric nuclear medicine came from the NRC and the FDA, although many of the other agencies influenced the direction of research and practice. A classic example of a regulatory impediment was the approval of $^{99m}$Tc-pertechnetate for radionuclide cystography. In the late 1960s, Donald Blaufax, MD, and I, working independently and unknown to each other, were developing a gamma camera technique to study vesicoureteral reflux in children (9–10). C.C. Winter, MD, had successfully documented vesicoureteral reflux in children using radioisotopes and a scintillation probe detector in 1965 (11). Our first radionuclide cystogram at the Children’s Memorial Hospital (CMH) in Chicago, IL, was performed in January 1970. We performed some 70 studies in the following year on a $3,000 research grant from the general research program at CMH. Table 1 summarizes the long regulatory scenario that ensued. In short, 15 years would pass before final FDA and NRC approval would allow practitioners to instill 1 mCi of $^{99m}$Tc-pertechnetate into the bladder of a child.

An especially aggravating role in this process was played by the NRC. In spite of the 1980 FDA approval of $^{99m}$Tc-pertechnetate for radionuclide cystography, some NRC inspectors, attempting to protect the public from unnecessary radiation, cited practitioners for performing radionuclide cystography by a route of administration not described in the FDA package insert. Thus, although we had gained approval for the routine use of $^{99m}$Tc-pertechnetate in children, the interpretation by NRC inspectors was that it was not approved for administration into the bladder—or any other orifice for that matter. The result was that practitioners were forced to use x-ray cystography, which delivered significantly higher absorbed radiation doses to children.

This regulatory impediment required the filing of a New Drug Application (NDA) supplement for the instillation of $^{99m}$Tc-pertechnetate into the bladder for radionuclide cystography. I persuaded Joe Goldstein of Medi-Physics Corporation and H.C. McCleary, Jr., Andrew Bass, H. Maroon, and Michael Swiatocha of E.R. Squibb and Sons to conduct limited phase III clinical trials with instillation of $^{99m}$Tc-pertechnetate into the bladder and to submit supplements for their NDA-approved radiopharmaceuticals to satisfy the NRC’s interpretation of the route of administration rule. Letty Lutzker, MD, and I conducted the limited phase III clinical trials and filed all of the necessary paperwork with the FDA. This goal was finally met in 1985—15 years after the first radionuclide cystography with a gamma camera was performed. I remain convinced that without constant badgering by members of the FDA Radiopharmaceutical Drugs Advisory Committee (RDAC) and its chairs Ralph Robinson, MD, and Barry Siegel, MD, that $^{99m}$Tc-pertechnetate might still not be fully approved for radionuclide cystography.

Another example from the early regulatory difficulties makes it easier to understand the frustration experienced by early practitioners of pediatric nuclear medicine. The U.S. Atomic Energy Commission (AEC; precursor to the NRC) had assumed control of radioisotopes for medical purposes

### TABLE 1
Innovation to Approval: Regulatory Saga of $^{99m}$Tc-Pertechnetate in Pediatric Radionuclide Cystography

<table>
<thead>
<tr>
<th>Action</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>First radionuclide cystogram at Children’s Medical Hospital</td>
<td>January 1970</td>
</tr>
<tr>
<td>First presentation of 100 cases at a professional meeting</td>
<td>September 1971</td>
</tr>
<tr>
<td>First scientific publication</td>
<td>August 1972</td>
</tr>
<tr>
<td>Rejection by FDA for placement on “Well Established List”</td>
<td>February 1975</td>
</tr>
<tr>
<td>Petition for a Medi-Physics NDA* supplement</td>
<td>July 1975</td>
</tr>
<tr>
<td>100 cases collected at 4 pediatric centers to prove safety and efficacy</td>
<td>April–June 1976</td>
</tr>
<tr>
<td>Squibb NDA supplement submission</td>
<td>January 1977</td>
</tr>
<tr>
<td>Medi-Physics data filed</td>
<td>June 1978</td>
</tr>
<tr>
<td>Squibb data filed</td>
<td>March 1979</td>
</tr>
<tr>
<td>Medi-Physics inquiry</td>
<td>May 1979</td>
</tr>
<tr>
<td>FDA Medi-Physics approval</td>
<td>December 1980</td>
</tr>
<tr>
<td>NRC restricts “route of administration”</td>
<td>April 1982</td>
</tr>
<tr>
<td>FDA Squibb approval</td>
<td>August 1982</td>
</tr>
<tr>
<td>Additional clinical trials for “route of administration”</td>
<td>1983–1984</td>
</tr>
<tr>
<td>NRC acceptance of the “route of administration”</td>
<td>1985</td>
</tr>
</tbody>
</table>

*New Drug Approval status*
after World War II. Radiopharmaceuticals were exempted from the requirements of the Food, Drug, and Cosmetics Act of 1962, because they were under the control of the AEC. The FDA took back responsibility for some radiopharmaceuticals in 1965 by placing the most commonly used radioisotopes, such as $^{131}$I, on the “Well Established List.” The FDA accepted data from the literature as support for the safety and efficacy of certain commonly used radiopharmaceuticals and to secure approval for routine clinical use. However, the FDA determined that pediatric indications for these same radiopharmaceuticals had not been “documented in the literature” and thus were not accepted in the approval process for the well-established list. As a consequence, the so-called “orphan clause” was included on all package inserts (12). The orphan clause stated that the radiopharmaceutical had not been proven safe and effective for clinical use in children. A practitioner who used the radiopharmaceutical in a child did so on an individual prescription basis (as is the right of a licensed physician). The practitioner thus accepted any risks that might be associated with the nonapproved drug. The result was an understandable reluctance in some institutions to apply even the most common nuclear medicine techniques in children, despite clear evidence of the effectiveness of these techniques in diagnosis and treatment.

In an effort to remove the orphan clause from package inserts, I persuaded volunteers from the Pediatric Nuclear Medicine Club to conduct limited clinical trials and submit additional supporting data from the literature to document the safety and efficacy of the more common radiopharmaceuticals for specific pediatric indications. Pediatric nuclear medicine practitioners who expended considerable time and effort with me on this endeavor included Traves, Handmaker, Gelfand, Lutzker, Judith Ellen Ho, MD, Howard Ted Harcke, Jr., MD, Sidney Heyman, MD, Diane Duszynski, MD, and George Sfakianakis, MD. Of course, none of the work could have been accomplished without the technological assistance of pediatric nuclear medicine technologists, such as Weiss at CMH, Davis at Boston Children’s Hospital, and many others.

A number of individuals in the radiopharmaceutical industry provided significant resources and service for this pediatric indications project. They included Edward Holmes, Sam Barker, James Finn, Linda Drachman, and Len S lootmaker. Without the tremendous amount of effort and paperwork in submitting the class action petitions, the orphan clause might still be included in all of our common radiopharmaceutical package inserts. In all instances, the cost of these limited controlled phase III clinical trials was borne by the volunteer individuals and their institutions.

In the early 1980s, members of the SNM and the ACNP again answered the call to document substantial evidence of safety and efficacy for “unusual” radionuclide procedures in children and adults based upon literature data. I served as the chair and organizer of an ad hoc group of volunteers to develop class action petitions that were submitted with the encouragement of the FDA for their medical review as testimony of the safety and efficacy for these new indications and routes of administration. Among the individuals who worked on the “new indications” projects were Leon Malmud, MD, and myself for oral $^{99m}$Tc-sulfur colloid for gastroesophageal reflux; Wellman, Aslam Siddiqui, MD, and Bruce Mock for intrathecal $^{99m}$Tc radiopharmaceuticals for radionuclide cisternography; Ed Suprenant, MD, and Michael Hayes, MD, for $^{99m}$Tc-diethylenetriaminepentaacetic acid lung aerosol; Tapan Chaudhuri, MD, for radionuclide dacrocystography; Jim Wolfenden, MD, and Dennis Patton, MD, for cutaneous blood flow measurements with intradermal injection of $^{133}$Xe; and Gregory Gergans, MD, for lymphoscintigraphy. Other individuals who worked on projects included Alderson and Barbara Y. Croft, MD. Many physicists at the participating institutions provided absorbed dosimetry calculations for the package inserts. Sue Flint of the New England Nuclear Corporation volunteered her company’s bibliographic resources for the members of the ad hoc committee.

Because of the rapidly increasing use of radiopharmaceuticals in children, the FDA appointed pediatric nuclear medicine practitioners to the RDAC to address the use of nonapproved radiopharmaceutical drugs in children. I was appointed to the committee in 1976 and served until 1985. Gilday and Traves were among other early members. Through the use of limited prospective phase III clinical trials at a number of institutions, retrospective reviews of the literature, and the cooperation of manufacturers, $^{99m}$Tc-pertechnetate and many other radiopharmaceuticals were finally approved for use in children. Another pediatric project initiated by the RDAC that assisted the FDA in the drug approval process was the determination of pediatric absorbed dosimetry calculations under the guidance of Traves as subcommittee chair. These volunteer efforts resulted in additional FDA approvals for a number of commonly used radiopharmaceuticals in children.

**A Note on Industry Partners**

I would be remiss in not acknowledging the role of industry in the development of pediatric nuclear medicine. In the very early years, the Nuclear–Chicago Corporation sponsored free symposia in numerous cities both in the United States and abroad. Academicians and other practitioners were invited to present lectures about their developing pediatric practice. These 1-day symposia were well attended by those eager to learn about techniques and tailored approaches.

In the ensuing years, numerous manufacturers, including the Picker Corporation, Mallinckrodt Inc., General Electric Corporation, Medi-Physics, and Syncor, sponsored educational programs both locally and at SNM annual meetings. The instrument manufacturers were especially helpful in modifying their equipment to conform to the imaging needs of small children. Pediatric practitioners were

(Continued on page 30N)
faced with the challenge of imaging children who might weigh 1 pound or 250 pounds, and ingenuity was often needed. Our hospital carpenters manufactured a wooden table with a cutout that fit the camera’s collimator. We were then able to place the infant or small child directly on the collimator for better resolution.

The pharmaceutical manufacturers played a major role in the development of indications for pediatric use for many of the commonly used radiopharmaceuticals. Although the FDA encouraged manufacturers to sponsor phase III clinical trials in children, the high cost of such trials was a burden that some radiopharmaceutical manufacturers could not assume, considering the relatively low volume of such agents sold for pediatric applications. However, the need for data led to the formation of fruitful investigative partnerships between industry and pediatric nuclear medicine specialists, with many of these relationships lasting now for decades.

REFERENCES

(Continued from page 28N)

the primary research, evaluation, approval, and medical treatment delivery and reimbursement divisions of HHS, including the FDA, National Institutes of Health, Centers for Medicare & Medicaid Services, and Agency for Healthcare Research and Quality. The FDA is currently identifying several priority Critical Path research opportunities. Some of the projects in the list could be undertaken by a single organization, whereas others will require collaborations coordinated and supported by the FDA. For example, a major Critical Path undertaking also announced on March 16, which seeks to develop guidance on the use of standard biomarkers to predict safety in drug development, will be coordinated by the Critical Path Institute and carried out by a newly formed Predictive Safety Testing Partnership including Bristol-Myers Squibb, Johnson & Johnson, Merck, Novartis, and Pfizer. The FDA, although not a member of the partnership, will assist it in an advisory capacity.

“It is important to note that the list released today is meant to spur a continued dialog among industry, academia, patient, and professional groups and government organizations about the research priorities that need to be accomplished in our effort to modernize the medical product development process,” added Woodcock. “We believe it is crucial to build a national infrastructure to support and continually improve the Critical Path Initiative. Therefore, we must reach beyond specific opportunities and build collaborations to work together to encourage continued development of the Critical Path sciences.”

More information about the Critical Path Initiative is available at www.fda.gov/oc/initiatives/criticalpath/

U.S. Food and Drug Administration
Imagine. Discover. Reveal.

If you think you know what educational programs SNM has to offer, you need to take another look—they are increasingly comprehensive, flexible, and cutting edge. Our Learning Center’s innovative curriculum both increases your knowledge of current practice and prepares you for the future. New online courses and modules debut almost every week to make it easy for you to explore the treatments, procedures, and diagnostic tools you need to be a front-runner in your profession. With a growing list of online Lifelong Learning and Self-Assessment Program (LLSAP) modules, the debut of our easy-to-navigate educational Web portal, and the first self-paced online courses based on our most popular workshops, it is clear that SNM’s focus is truly on your educational needs.

**Imagine** . . . multiple society resources to cultivate medical imaging professionals with modern knowledge and concepts to improve human health. New skill sets need to be developed as molecular imaging continues its rise in examining the body’s physiology to monitor, detect, treat, and eventually predict and prevent disease before symptoms develop. As more work is done at the cellular level—and to prepare for an expected expanded role in medical care—a new breed of imaging professional must be capable of using many different imaging modalities both alone and in combination to offer the most accurate diagnostic assessments and measurements of treatment response. These new directions in medicine create new educational horizons for SNM.

**Discover** . . . all our educational offerings through SNM’s highly anticipated online education portal. This one clear, easily recognizable and accessible Web page, debuting soon, will allow you to easily and intuitively find pertinent information about our educational opportunities, whether it’s our LLSAP modules, new online programs, CT or PET/CT case studies or workshops, or our annual and midwinter educational meetings.

An imaging professional anywhere in the world can sit at a laptop and utilize our LLSAP modules, a number of which have been approved for self-assessment credit to satisfy the maintenance of certification requirements for physician diplomates of either the American Board of Nuclear Medicine or the American Board of Radiology. SNM’s peer-reviewed modules allow health care practitioners to assess their medical knowledge and competency in patient care, in systems-based practice, and in practice-based learning and improvement. Over the year, our program will offer new Web-based self-assessment modules covering recent developments in nuclear medicine and correlative imaging in the specialty fields of oncology, cardiology, neurology, endocrinology, pulmonology, gastroenterology, musculoskeletal and genitourinary disorders, and basic sciences. The topics addressed will address the technical aspects and evaluation and treatment of patients using PET, CT, PET/CT, SPECT, and SPECT/CT. Program participants can move through these online modules at their own pace.

SNM alone offers DICOM (Digital Imaging and Communications in Medicine) images—a standard protocol used for handling, storing, and transmitting information in medical imaging among computer systems—creating a virtual workstation experience for participants.

Sitting at that same laptop, an imaging professional can now engage in a new, hour-long overview presentation about PET or breast cancer, as SNM brings to life the first of about 20 self-paced, online courses based on SNM Learning Center workshops and symposia. These highly interactive courses with illustrative slides will eventually provide a wide scope of courses covering systems/acquisitions, clinical applications, lung cancer, lymphoma, melanoma, correlative imaging, PET protocols, cardiac PET/CT, and brain PET. As with our LLSAP modules, once an online test is passed, credit for continuing education is automatically recorded.

In the near future, about 500 interactive, diagnostic CT cases and SPECT cardiology cases with DICOM figures will be offered through our Learning Center and can be used to gain experience as set out in suggested on-the-job guidelines from SNM, the American College of Radiology, and the Society of Computed Body Tomography and Magnetic Resonance.

In addition, the Learning Center offers weekend workshops and focused symposia, continuing a focus on CT topics for physicians and technologists alike. Our annual and midwinter educational meetings will continue to address future directions and the latest medical research results.

**Reveal** . . . ways to implement medical education innovation and medical care development for patient care. Your work may be over at the end of each day, but your education—never. SNM stands with you and continues to bring future medical revelations over the next 5, 10, and more years. To learn more, visit SNM’s education Web page: www.snm.org; click on Education.

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*Virginia Pappas, CAE
Chief Executive Officer, SNM*
Exciting FDA Events at SNM Annual Meeting

Continuing an exciting and highly beneficial tradition, Food and Drug Administration (FDA) staff members will host a continuing education session on FDA issues at the 2006 SNM Annual Meeting in San Diego, CA. Presenters and topics tentatively scheduled include George Mills, MD, MBA, who will speak on Imaging Biomarkers and Imaging Standardization for Clinical Trials; Alex Gorovets, MD, who is scheduled to discuss the Development of Imaging Product: Regulatory Perspective; Kaye Kang, who will discuss Highlights of Standard Meetings with the Medical Imaging Division; Tiffany Brown, who will speak on Navigating the Process of Imaging Submissions; Florence Moore, who will present the Comparison of BLA and NDA Regulatory Requirements for Biotechnology Products; and Tushar Kokate, who is scheduled to speak on Exploratory IND Studies in Humans: Preclinical Requirements. The exact time and date of the session had not been announced as Newline went to press.

The FDA staff will also host a separate business meeting on the morning of June 5 (Monday) tentatively featuring discussions from Ravindra Kasliwal, PhD, on Chemistry, Manufacturing and Controls for PET Drugs and Thuy Nguyen on the Administrative Steps to Submitting a PET-FDG NDA. A discussion with FDA staff about the Radioactive Drug Research Committee process will follow these presentations.

NRC NARM Regulations
The Nuclear Regulatory Commission (NRC) naturally occurring and accelerator-produced nuclear materials (NARM) regulations required by Section 651(e) of the Energy Policy Act of 2005 should be available for public comment by the time you receive this issue of The Journal of Nuclear Medicine, according to the NRC timetable. SNM is interested in how the NRC proposes to regulate cyclotron products and whether the commission will attempt to assume authority over everything activated by the production process, including the accelerators themselves.

Basic Nuclear Medicine Research Funding
SNM staff and consultants are continuing to work toward finding a permanent home for basic scientific research pertaining to nuclear medicine within the Department of Energy (DOE), National Institutes of Health, or some another agency. Hill meetings between SNM staff, consultants, and Senate and House appropriators for Health and Human Services and Energy and Water issues are held on a regular basis, and the various appropriations subcommittees are currently holding preliminary hearings to discuss the fiscal year 2007 budget, so we are hopeful that the research appropriations cut from the DOE budget will find a home in another agency.

RadCARE Bill (S 2322)
On February 17, the RadCARE bill (S 2322)—the Senate version of the Consumers Assurance of Radiologic Excellence bill (HR 1426)—was introduced in the 109th Congress by Senator Michael B. Enzi (R-WY) and by Senator Edward M. Kennedy (D-MA), chair and ranking minority member of the committee of jurisdiction, the Health, Education, Labor and Pensions Committee. This is extremely good news for the nuclear medicine technology community, as the legislation on the Senate side is now far more likely to move through committee than ever before.

CARE Bill (HR 1426)
At this writing, the CARE bill has 118 cosponsors in the House of Representatives.

ASRT “RT in DC” Meeting
The annual “RT in DC” meeting (March 12–14) went exceptionally well with solid representation from the nuclear medicine technology community. The event featured an educational session on grassroots advocacy from DC-area lobbyists and Capitol Hill staffers, followed by a day of legislative appointments as approximately 130 radiologic and nuclear medicine technologists converged on Capitol Hill to advocate for the CARE legislation. Two senators were added to the cosponsor list for Senate bill and 5 representatives were added to the cosponsor list for the House version as a result of the American Society of Radiologic Technologists-sponsored event.
National Oncologic PET Registry Launch Delayed

During the first week of March, the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) notified the leadership of the National Oncologic PET Registry (NOPR) that it may require the NOPR to change its procedures related to Institutional Review Board (IRB) approval. Hopes for a quick launch of the registry had been high after the February 10 Centers for Medicare & Medicaid Services (CMS) announcement of an agreement with NOPR to collect data regarding PET scans. NOPR was given an exemption to the human protection regulations, with the understanding that the scans were acquired for medically necessary (not research) reasons and that the accumulation of associated patient data was the only risk to which patients were exposed. The OHRP reviewed the submitted materials and issued a position statement indicating that the NOPR does not qualify for exemption under the human protection regulations.

The immediate challenge posed by this restriction is that it threatens the broad representation of cases regarded as important in the registry. Many smaller imaging facilities do not have their own IRBs and, even after approval, the necessary consent procedures might be so cumbersome as to discourage participation by some practitioners. The NOPR is managed by the American College of Radiology (ACR) and the ACR Imaging Network in collaboration with the Academy of Molecular Imaging (AMI). The SNM and the American Society of Clinical Oncology have played key roles in guiding the project’s development.

Speaking at the AMI annual meeting on March 26, Barry Siegel, MD, from the Mallinckrodt Institute of Radiology (St. Louis, MO) and cochair of the NOPR Working Group, presented an update on the status of the project to attendees. At present, all infrastructure and processes necessary for operation of the NOPR, in accordance with the original design of the registry, are in place. The NOPR is working to understand any new requirements under consideration and to plan support for NOPR participating sites should new requirements be confirmed. The NOPR is committed to activating the registry as soon as possible and to fulfilling its original objectives to “assess the effect of PET on referring physicians’ plans of intended patient management across a wide spectrum of cancer indications that are currently not covered by the Medicare program, and in relation to cancer type, indication, performance status, physician’s role in management, and type of PET,” Siegel said. “The goal is to acquire data that can be used to evaluate PET in a manner that does not interfere with patient clinical care and minimizes the burden to the patient, PET center, and referring physician.”

CMS and OHRP are working to resolve the question of whether individual IRB review and approval will be required for participation in the registry. When a final determination is reached, NOPR will post this information on its Web site and notify all registered facilities and those on its e-mail broadcast list. Until this issue is settled, the NOPR cannot accept patient registrations or finalize facility registrations. Meetings to resolve the IRB issues were scheduled for April, although no resolution had been announced at Newsline press time.

American College of Radiology

Dynamic Bladder Software Tool Available

The Medical Internal Radiation Dose (MIRD) Committee of the SNM announced in March that an interactive, Windows-based computer program written in Visual Basic 6.0 has been released as an educational and research tool for radiopharmaceutical dosimetry investigators. The program automates the model described in A Dynamic Urinary Bladder Model for Radiation Dose Calculation (MIRD Pamphlet No. 14 revised; 1999). The Dynamic Bladder Software Tool includes kinetic models for 20 standard radiopharmaceuticals and can accommodate user-entered data for new radiopharmaceuticals to produce graphs and tables of bladder wall surface doses for 7 initial bladder volumes, 9 initial void times, and 3 urine production rates.

The program allows comparison of the ways in which urinary bladder wall doses change as a function of the model variables for different radiopharmaceuticals. Data are displayed on the screen or may be sent to a printer or file, from which they can be exported into other programs for further analysis. Users may modify the kinetic models for the supplied standard radiopharmaceuticals should updates to the biologic parameters become available. The program provides convenient extension of the model for user-entered radiopharmaceuticals not included in the standard list, accommodating up to 4 separate components describing whole-body urinary elimination. The Dynamic Bladder Software Tool may be downloaded from: http://interactive.snm.org/index.cfm?PageID=4309.

SNM Medical Internal Radiation Dose Committee

Mallinckrodt Resumes 99mTc Generator Production

On April 5, Mallinckrodt, Inc./Tyco Healthcare resumed manufacture and shipment of its Ultra-TechneKow Technetium Generator. The move was announced in a March 23 letter to customers. The company voluntarily recalled the generator on November 19, (Continued on page 42N)
NIH Provides $24 Million to Support Research Network

The National Center for Research Resources (NCRR), a part of the National Institutes of Health (NIH), announced on March 17 that it will provide $24.29 million over 5 years to the University of California, Irvine (UCI) for continued support to the Biomedical Informatics Research Network (BIRN). Currently a consortium of 28 universities and 37 research groups, BIRN is leveraging and sharing distributed tools, software applications, techniques, data, and expertise that extend beyond the boundaries of individual laboratories. This major NCRR initiative, involving both basic and clinical investigators, is initially concentrating on research involving neuroimaging, but the tools and technologies developed will ultimately be applicable to other disciplines.

UCI is leading the part of the project known as Function BIRN, which brings together researchers at 14 institutions for the common purpose of developing and testing interdisciplinary techniques for integrating efforts in functional magnetic resonance imaging (fMRI) across multiple sites. The award will allow the Function BIRN team to improve calibration of imaging equipment across sites, develop robust protocols for cognitive assessment, formulate methods for analysis of resulting data, and develop a scalable technology toolkit to support such complex studies. A test project will interpret fMRI datasets from more than 200 subjects scanned at facilities across the country.

“Through this effort, we are creating new models for collaboration among researchers who study diseases at multiple sites with different equipment,” said Elaine Collier, MD, Assistant Director of NCRR’s Division of Clinical Research. “Function BIRN’s utilization of emerging technology for collaborative research and sharing of knowledge gained will accelerate scientific discoveries by allowing researchers to tackle complex questions and large-scale research projects that were not previously possible.”

In its initial phase, the Function BIRN focused on developing a shared data storage infrastructure and standard imaging methods for the multiple sites. The project entailed a set of 5 research participants who traveled to 9 sites around the country for brain scans using a common protocol. This formed the first calibration dataset of its kind in the world for systematically studying intersite variability. Software tools were developed to reduce such variability, to automatically correct image distortions, and to manage data for large and diverse neuroimaging research projects. The open-source data and tools are available at www.ncbi.nlm.nih.gov/ncrr/birn.

Function BIRN’s director is Steven G. Potkin, MD, a professor of psychiatry and the Robert R. Sprague Director of Brain Imaging at UCI. “One of our most significant accomplishments is that through Function BIRN we have begun to create the sociology and culture for data sharing among researchers,” Potkin said. “By working together with top researchers at many sites, we can simultaneously test a variety of approaches to a problem and compare results, which has greatly accelerated the progress we are able to make.”

Another goal of Function BIRN is to encourage the research community to make use of the tools, data, and lessons learned. Collaborations have already begun with other NIH-supported organizations such as the Neuroimaging Informatics Technology Initiative, the Treatment Unit on Research for Neurocognition in Schizophrenia, and NCRR-funded General Clinical Research Centers located around the country. In addition to Function BIRN, the overall BIRN initiative comprises: the BIRN Coordinating Center, the primary software development and computational hub; Morphometry BIRN, which is investigating whether structural differences in the brain correlate to symptoms of neuropsychiatric illnesses; and Mouse BIRN, which is studying animal models of diseases such as multiple sclerosis, schizophrenia, Parkinson’s disease, and brain cancer.

With the infrastructure in place and the lessons learned from the neurology projects, NCRR plans to expand BIRN to support other types of large-scale, collaborative investigations, including the incorporation of other imaging modalities. BIRN is expected to eventually incorporate distributed computing resources, mechanisms for the integration of interoperable software tools, and linkage of data through the federation of databases.

For more information about BIRN, visit www.ncbi.nlm.nih.gov/ncrr/birn.

Berkeley Lab Dedicates Molecular Foundry

A new research center to be known as the Molecular Foundry was officially dedicated at the Lawrence Berkeley National Laboratory in Berkeley, CA, on March 24. The facility is the first of 5 proposed U.S. Department of Energy (DOE) Nanoscale Science Research Centers and is an $85-million, 6-story, 94,500-square-foot, steel-and-glass building. As a DOE national research facility, the resources at the Molecular Foundry will be made available to qualified researchers.

**Lawrence Berkeley National Laboratory**

**Model Cancer Center at City of Hope to Include RIT**

City of Hope Cancer Center (Duarte, CA) announced on March 9 the receipt of a $20 million grant to establish the Arnold and Mabel Beckman Center for Cancer Immunotherapeutics and Tumor Immunology. The center will provide space and resources for scientists in City of Hope’s Division of Cancer Immunotherapeutics and Tumor Immunology (CITI). Within the center, scientists will research new treatment ideas, manufacture biologic agents on site, and conduct preclinical testing and clinical trials.

“We are pleased that the Arnold and Mabel Beckman Foundation is continuing its longstanding commitment to scientific discovery at City of Hope,” said Andrew Raubitschek, MD, CITI chair. “This new facility will strengthen our basic science efforts in areas such as tumor immunology, while speeding the outstanding work of our scientists directly to the hands of physicians to benefit patients more quickly than ever before.”

The wide array of disciplines represented at the center, from hematology to molecular biology, will promote collaboration and innovation. CITI researchers will bring together their expertise to focus on 4 key investigational areas: radioimmunotherapy, cellular immunotherapy, molecular immunotherapy, and vaccine immunotherapy.

**City of Hope Cancer Center**

**CMS Opens New Pay-for-Quality Models**

The Centers for Medicare & Medicaid Services (CMS) announced on March 22 that it is making available the shared savings payment model and quality measurement and reporting processes. "We are making the shared savings model and quality reporting tools available so physician groups and health care systems can focus their resources on system redesign to improve patient safety, enhance quality, increase efficiency, and reduce scientific uncertainty and unwarranted variation,” said CMS Administrator Mark B. McClellan, MD, PhD.

The PGP Demonstration shared savings model provides additional financial support for physicians to improve the quality and efficiency of health care services delivered to Medicare fee-for-service beneficiaries. Under the model, physician groups are eligible for performance payments derived from savings from better care management designed to anticipate patient needs, prevent chronic disease complications and avoidable hospitalizations, and improve quality of care. In turn, physicians can use these savings to invest in health technology, care coordination, and other steps to improve care and reduce costs.

Physician groups, integrated delivery systems, and regional coalitions are eligible to use the PGP model. Newly formed regional coalitions of smaller physician groups could come together for demonstration purposes to participate in the MHCQ Demonstration using the PGP model. Applicants using the PGP model are required to meet all MHCQ goals and objectives (e.g., improve patient safety, enhance quality, increase efficiency, and reduce scientific uncertainty and unwarranted variation) and have 150 or more physicians. Industry analysts point out that although imaging groups may be reluctant to participate in such programs, the introduction of required pay-for-performance metrics across the board in medical practice are almost certainly on the CMS horizon within the next decade. Nuclear medicine, along with other imaging specialties, will be
challenged to develop metrics that adequately represent quality, patient-centered practice while at the same time not imposing unreasonable restrictions or record-keeping burdens on practitioners.

MHCQ-PGP Model applications must be received on or before September 29, 2006. More information can be found on the MHCQ Demonstration webpage at www.cms.hhs.gov/DemoProjectsEvalRpts/.

Centers for Medicare & Medicaid Services

CMS Minority Outreach Demonstration Sites

The Centers for Medicare & Medicaid Services (CMS) announced on March 24 the selection of sites for 6 demonstration projects to improve the early detection and treatment of cancer and reduce health disparities among minority Medicare beneficiaries.

“Medicare has the best coverage ever for preventing deaths through earlier detection and treatment, but we still have a big gap in using these treatments, especially for our minority beneficiaries,” said CMS Administrator Mark McClellan, MD, PhD. “These new programs will support our key goal of better quality of care and reduced health disparities for people with Medicare.”

Minority groups (and selected institutions) in the demonstration include American Indians (Huntsman Cancer Institute, Salt Lake City, UT); Asian Americans and Pacific Islanders (Molokai General Hospital, Hawaii); African Americans (Johns Hopkins University, Baltimore, MD; and Josephine Ford Cancer Center, Detroit, MI); and Hispanic Americans (University of Texas, Houston; and the New Jersey Medical School, Newark).

The demonstration projects will help more than 13,000 minority Medicare beneficiaries “navigate” the health care system in a more timely and informative manner. The services provided under this demonstration will help participants overcome barriers to 3 components of cancer care: screening, diagnosis, and treatment. Project sites will provide services to help participants schedule timely appointments for cancer screening and, if needed, follow-up diagnostic testing. Other services that may be provided include assistance with transportation, translation or interpretation, and care coordination.

Centers for Medicare & Medicaid Services

Slight Slowdown in Health Care Spending Predicted

Health care spending in the United States is projected to grow 7.4% in 2005 and 7.3% in 2006, surpassing $2 trillion, according to a report released on March 15 by the Centers for Medicare & Medicaid Services (CMS). Projections are updated each year based on the most recent available data (currently 2004 data). The 7.4% growth rate is 0.5 percentage points less than the 7.9% growth observed in 2004 and represents the third consecutive year of decelerating growth, a trend that is expected to continue in 2006.

Underlying the slowdown in national health spending in 2005 and 2006 is an expected drop in personal health care spending. Influenced by legislated Medicare payment adjustments that are to be implemented in 2007, growth in personal health care spending is projected to fall to 7.0% that year. In 2008, growth is expected to rebound to 7.5%, but then gradually slow over the remainder of the 10-year projection. Over the coming decade, however, with the aging of the population scale and also describes changes at the local and even family level, examining, for example, important changes in family structure as a result of divorce.

Among the findings explored in the document are:

• The United States population aged 65 and over is expected to double in size within the next 25 years.
• Although the health of older Americans is improving, many are disabled and suffer from chronic conditions.
• The financial circumstances of older people have improved dramatically, although there are wide variations in income and wealth.
• Higher levels of education, which are linked to better health, higher income, more wealth, and a higher standard of living in retirement, will continue to increase among people 65 and older.
• As the United States as a whole grows more diverse, so does the population aged 65 and older.
• Changes in the American family have significant implications for future aging.

The 65+ report is a project of the NIA’s Behavioral and Social Research Program, which supports the collection and analysis of data in several national and international studies on health, retirement, and aging. The program’s director, Richard M. Suzman, PhD, suggested that, with 5 years to go before the baby boom begins to turn 65, “Many people have an image of aging that may be 20 years out of date. The very current portrait presented here shows how much has changed and where trends may be headed in the future.”

The 243-page compendium examines in detail 5 key areas: growth of the older population (changes in age and racial/ethnic composition); longevity and health (life expectancy and causes of death); economic characteristics (income and household wealth); geographic distribution (by population and race); and social and other characteristics (marital status, living arrangements, and voting patterns).


U.S. Census Bureau

UNSCEAR at 50

The first full session of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) opened on March 14, 1956, and the committee recently celebrated its golden anniversary as the UN scientific body responsible for documenting our radiation legacy. UNSCEAR’s first 2 substantive reports, submitted to the UN General Assembly in 1958 and 1962, provided initial international consensus summaries on the state of scientific knowledge on human radiation exposure. Together the reports laid the scientific grounds on which the Partial Test Ban Treaty on the prohibition of nuclear weapon testing in the atmosphere was negotiated and signed in 1963. Over the decades, UNSCEAR became the official international authority on the levels and effects of radiation used for peaceful as well as military purposes and derived from natural and artificial sources.

According to a press release marking the anniversary, UNSCEAR’s findings and influence include: the recognition that medical diagnostic and therapeutic exposures were a major component of artificial radiation exposure globally; periodic published reports that have influenced the programs of international bodies, such as the International Atomic Energy Agency (IAEA), International Labor Organization, World Health Organization, and the International Commission on Radiological Protection; regular evaluations of the evidence for radiation-induced health effects from studies of the survivors of the atomic bombings in Japan in 1945 and other exposed groups; and assessment and updates of the radiologic consequences from the 1986 Chernobyl accident. The Committee also participates in the Chernobyl Forum, which the IAEA and partner organizations launched to document the accident’s health and environmental effects.

UNSCEAR’s work today is taking on added dimensions, noted its secretary, Malcolm Crick. “Countries are confronting important decisions that involve radiation effects,” he says. “They include new medical uses of radiation, environmental restoration, waste disposal, and the nuclear power option—all areas in which UNSCEAR is called upon to provide authoritative scientific information.” Over the coming year, the committee plans reviews of the risks from radon, epidemiological studies of radiation and its cancer and noncancer effects, and cellular responses to radiation exposure. UNSCEAR, with a membership that includes 21 countries, will hold its annual meeting later this month in Vienna.

United Nations Scientific Committee on the Effects of Atomic Radiation

When Patients Know About Physician Compensation

In a study published in the March 27 edition of the Archives of Internal Medicine (2006;166:623–628), Pearson et al. from Harvard Medical School and Harvard Pilgrim Health Care (Boston, MA) investigated the effects of disclosure of physicians’ financial incentives to patients. The randomized trial was conducted among 8,000 adult patients at 2 multispecialty group practices in Boston and Los Angeles, CA. These patients received a compensation disclosure letter written by the chief medical officer of their physician group and then responded 3 months later to a survey. The authors found that patients who had received the disclosure letter were significantly more capable of correctly identifying the compensation models of their primary care physicians and also had more confidence in their ability to judge the possible influence of incentives on their own health care than were patients who received no disclosure. Although the “disclosure intervention” did not change the perceived level of trust in primary care physicians overall, almost one-fourth of patients who remembered receiving the disclosure indicated that it had increased their trust either greatly or somewhat. Less than 5% of patients responded that the information decreased trust. Patient loyalty to physicians was found to be higher among disclosure patients. The authors concluded that, “This study suggests that regulators, policy makers, and physician groups themselves should renew their consideration of disclosure as an instrument to advance the best interests of patients and physicians.”

Archives of Internal Medicine
Each month the editor of Newsline selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Many selections come from outside the standard canon of nuclear medicine and radiology journals. This month the literature contained a remarkable number of articles on the utility of PET and other nuclear medicine techniques in assessment of orthopedic conditions and treatments. Several of these are included in this review. Note that although we have divided the articles into diagnostic and therapeutic categories, these lines are increasingly blurred as nuclear medicine capabilities expand. Many diagnostic capabilities are now enlisted in direct support of and, often, in real-time conjunction with therapies. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role.

**Diagnosis**

**18F-Fluoride PET and Fatigue-Induced Bone Damage**

In an article e-published on March 10 ahead of print in *Bone, Silva et al. from the Washington University School of Medicine (St. Louis, MO)* reported on the use of 18F-fluoride PET to describe the time course of bone response to fatigue. The study involved inducing fatigue (at 30%, 45%, 65%, or 85% of fracture displacement) in 1 forelimb of adult rats. The other forelimb in each rat served as the control. Rats were imaged with 18F-fluoride and small animal PET at 4 hours and at 2, 4, 7, 9, 11, 18, 24, and 30 days after the fatigue event. Significant increases in tracer uptake were found in the fatigued forelimbs on the first day and reached peak levels 4–9 days later. The level of uptake was significantly related to the level of fatigue displacement. On the basis of these results and accompanying histologic findings, the authors concluded that “a single bout of fatigue loading leads to a transient increase in the uptake of 18F-fluoride, that the uptake is in proportion to the level of initial damage and is associated with increased vascularity and woven bone formation in the first week after loading.”

**18F-FDG PET and Skeletal Blood Flow in Exercise**

Kalliokoski et al. from the Bispebjerg Hospital (Copenhagen, Denmark) reported on March 23 ahead of print in the *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology* on an 18F-FDG PET study designed to elucidate the role of nitric oxide and prostaglandins in local skeletal muscle blood flow during exercise. The study included 7 healthy young men who underwent near infrared spectroscopy and 18F-FDG PET imaging with and without local blockade of nitric oxide and prostaglandins (by L-NAME and indomethacin infusion directly into muscle) at rest and during dynamic knee-extension exercise. Blood flow and tracer uptake were measured. The results indicated that local blockade during exercise decreased blood flow only locally. Muscle glucose uptake showed no differences in response to the blockade. The authors noted that these results suggest that nitrous oxide and prostaglandins in healthy young men “synergistically contribute to the local regulation of blood flow in skeletal muscle independently of muscle glucose uptake.” The vasodilators can play a role in regulating microvascular blood flow in localized regions of muscle without influencing regional glucose uptake. The implied conclusion was that “local substrate uptake in skeletal muscle can be regulated independently of regional changes in blood flow.”

**18F-FDG PET in Prosthetic Loosening Assessment**

In the March 3 issue of *BMC Musculoskeletal Disorders (2006;7:20), Delank et al. from Cologne University (Germany) reported on a study of the clinical value of 18F-FDG PET in preoperative assessment of inflammation and loosening in hip and knee joint prostheses. The study included 27 patients who were scheduled for surgical procedures to correct prothetic loosening. Each patient underwent 18F-FDG PET imaging and multiphase bone scintigraphy (27 hips and knees plus 9 additional intact prosthetic joints within the PET field of view). Imaging findings were compared with results from surgery, histopathology, and microbiology. PET and bone scintigraphy were approximately equal in their abilities to correctly identify loosening (76.4% and 75% of cases, respectively). PET was 100% sensitive for septic cases and 45.5% sensitive in cases of increased abrasion and aseptic foreign-body reactions. PET was not able to reliably distinguish between abrasion-induced and bacterial-caused inflammation. The authors concluded that 18F-FDG PET provides a highly accurate prediction of periprosthetic septic inflammatory tissue, so that “a negative PET result in the setting of a diagnostically unclear situation eliminates the need for revision surgery.” However, they cautioned that a positive PET result cannot provide reliable information on the cause of inflammation.
Specialty Bias in Interpretation of Orthopedic Images

In an article published in the March/April issue of Spine Journal (2006;6:177–184), Mulconrey and colleagues from the University of Nebraska Medical Center (Omaha) reported on the effect of subspecialty bias on the interpretation of various imaging modalities in the assessment of patients with complaints of low back or leg pain. The retrospective review included a random selection of 17 patients who presented to an orthopedic spine specialist with complaints of mechanical low back or leg pain. Each had undergone a thorough clinical workup, including MR imaging, bone scans, and SPECT. A team of orthopedists and radiologists interpreted the studies and responded to a multi-item questionnaire about the findings. The results were compared with a “group consensus.” Interobserver reliability between the 2 groups of specialists was high for identification of a degenerative disc, spondylolisthesis, and Modic change ($\kappa = 0.773, 0.728,$ and 0.669, respectively). The level of agreement was lower for bone scintigraphy and SPECT ($\kappa = 0.539$ and 0.460, respectively). Averaged reviewer-predicted bone scan results showed a positive predictive value of 68% and a negative predictive value of 84%. SPECT results were similar (positive predictive value of 66%, negative predictive value of 84%), although SPECT identified 24% more lesions in the lumbar spine than did the bone scan. The ability to interpret MR scans of the lumbar spine was comparable between the specialties. The authors concluded that, “the presence of MRI changes enables an accurate prediction of bone scan or SPECT scan findings” and that the SPECT scan “demonstrates an increased sensitivity in the detection of spinal abnormalities and the ability to localize a lesion when compared with planar bone scan.”

Spine Journal

Comparison of Imaging Techniques in Prosthetic Loosening

Temmerman et al. from the VU Medical Centre (Amsterdam, The Netherlands) reported on March 18 ahead of print in the Archives of Orthopaedic and Trauma Surgery on a study comparing the relative utility of plain radiography, subtraction arthrography, nuclear arthrography, and bone scintigraphy in identifying aseptic femoral component loosening. The retrospective study assessed the diagnostic accuracy and interobserver reliability of these techniques in 78 patients referred for evaluation of femoral hip prostheses using all 4 of the imaging modalities. Results were compared with findings on surgery or over clinical follow-up. The sensitivity and specificity of plain radiography, subtraction arthrography, nuclear arthrography, and bone scintigraphy (81% and 74%, 47% and 78%, 69% and 76%, and 88% and 50%, respectively) were recorded. Considerable interobserver variability was found in the results. Among the authors’ conclusions was that “bone scintigraphy and nuclear arthrography together made a significant contribution to the diagnosis when used in combination with plain radiography and are, when plain radiography is inconclusive, useful additional diagnostic techniques for the detection of femoral component loosening.”

Archives of Orthopaedic and Trauma Surgery

Leptin Plasma Levels in Obese Patients

Schindler et al. from the University of California at Los Angeles reported in the March 21 issue of the Journal of the American College of Cardiology (2006;47:1188–1195) on a study using $^{13}$N-ammonia PET to evaluate the effects of obesity, insulin resistance, and inflammation on coronary circulatory function and to look at the relationship between these results and leptin levels. The study included 72 patients divided into 3 groups based on body mass index (BMI): controls ($20 \leq \text{BMI} < 25$), overweight ($25 \leq \text{BMI} \leq 30$), and obese ($\text{BMI} > 30$) individuals. Each patient underwent assessment of myocardial blood flow (MBF) response by cold pressor test and $^{13}$N-ammonia PET imaging to measure pharmacologic vasodilation. BMI was found to be significantly correlated to the Homeostasis Model Assessment Index of insulin resistance and C-reactive protein levels. The cold PET Looks at Muscle EMG and Perfusion in the Knee

Laaksonen et al. from the University of Turku (Finland) reported in the March issue of Clinical Physiology and Functional Imaging (2006;26:99–105) on a PET study designed to investigate the association between muscle blood flow and electromyographic (EMG) activity in different compartments of the quadriceps femoris (QF) muscle. The study included 12 healthy male participants, who were imaged with $^{15}$O-water PET during 2 submaximal exercise sessions of different intensities. Force of knee extensors and muscle EMG activity in the vastus lateralis (VL), vastus medialis (VM), and rectus femoris (RF) muscles were also recorded. The exercise intensity and average force production were higher during the second exercise session than the first, but average EMG activity was slightly lower or unchanged. PET indicated that perfusion was unchanged in the second exercise period when measured over the entire QF muscle. However, individual changes in muscle perfusion were closely correlated to changes in muscle EMG activity in the VL and VM, but poorly correlated in the RF muscle. The authors concluded that “the different associations between muscle perfusion and EMG activity in different QF muscles suggest a specific functional role of the vasti muscles and the RF muscle.”

Clinical Physiology and Functional Imaging

Leptin Plasma Levels in Obese Patients
PET and Lung Inflammation in Cystic Fibrosis

Chen et al. from the Washington University School of Medicine (St. Louis, MO) reported ahead of print on March 16 in the American Journal of Respiratory and Critical Care Medicine on a study designed to determine whether 18F-FDG PET can be used as a noninvasive method to quantify lung inflammation in patients with cystic fibrosis (CF). The study included 20 patients with CF and 7 healthy volunteers, each of whom underwent PET imaging. A subset of 7 volunteer patients also underwent bronchoalveolar lavage. Patients were grouped by rate of pulmonary function decline as stable, intermediate, or rapidly declining. Tracer uptake (net influx rate constant) was significantly elevated in the CV patients when compared with healthy volunteers and most elevated in the group with rapidly declining pulmonary function. Tracer uptake also correlated positively with the number of neutrophils present in lavage fluid. The authors concluded that not only can 18F-FDG PET be used to assess inflammatory burden in patients with CF, but the elevations in tracer uptake “may be able to identify patients with more aggressive disease and may be useful in monitoring changes in inflammatory burden in response to novel treatments.”

American Journal of Respiratory and Critical Care Medicine

Elevated Splenic SUVs in PET Imaging of Malaria

Kawai and colleagues representing a group of medical schools and imaging centers in Japan reported in the March issue of the American Journal of Tropical Medicine and Hygiene (2006;74:353–360) on a study correlating the results of 18F-FDG PET imaging with pathology changes observed in a primate model of severe human malaria. The researchers performed whole-body PET imaging in Plasmodium coatneyi-infected Japanese macaques in the acute phase of disease development. The imaging results showed increased splenic tracer uptake, indicating marked enhancement of glucose metabolism. Standardized uptake values for the spleen were significantly higher in infected monkeys than in controls. Subsequent pathology indicated splenomegaly in all infected monkeys, hyperplasia of lymphoid follicles in white pulp, a large number of activated macrophages, and congestion of parasitized red blood cells and malaria pigments in red pulp. The authors concluded that an “increase in splenic glucose uptake may thus be closely related to activation of the splenic clearance system against blood-stage malarial parasites.”

American Journal of Tropical Medicine and Hygiene

PET and Preclinical AD Markers in CSF

In the March issue of the Annals of Neurology (2006;59:512–519), Fagan et al. from the Washington University School of Medicine (St. Louis) reported on a study to determine whether the mean decrease observed in cerebrospinal fluid (CSF) amyloid-β(42) in dementia of the Alzheimer’s type may reflect plaques acting as “sinks,” hindering transport of amyloid-β(42) between brain and CSF. Pittsburgh Compound B (PIB) PET imaging was used to characterize the brain amyloid load, and these results were then compared with CSF amyloid-β(42) and other measures in a group of 24 clinically characterized research subjects. The results divided the participants into 2 clearly distinguished groups: those with positive PIB binding and lowest CSF amyloid-β(42) levels, and those with negative PIB binding and the highest CSF amyloid-β(42) level. PIB binding did not correlate with other measures, including CSF amyloid-β(40) tau, phospho-tau(181), plasma amyloid-β(40), or plasma amyloid-β(42). The most intriguing finding was that PIB binding and low CSF amyloid-β(42) did not correspond with clinical diagnoses in all patients. Three individuals who were assessed as cognitively normal were PIB-positive with low CSF amyloid-β(42), which the authors noted as evidence of preclinical Alzheimer’s disease (AD). They concluded that the results “suggest that brain amyloid deposition results in low CSF amyloid-β(42), and that amyloid imaging and CSF amyloid-β(42) may potentially serve as antecedent biomarkers of (preclinical) AD.”

Annals of Neurology

SPECT and Frontotemporal Dementia

McMurtray et al. from the University of California at Los Angeles reported in the February 28 issue of Neurology (2006;66:517–522) on a study characterizing the presenting clinical features of frontotemporal dementia (FTD) and contrasting these with the degree of frontal and temporal hypoperfusion on SPECT imaging.
The investigation included 74 patients who were first evaluated with neurologic work-ups and SPECT and either met the criteria for the FTD form of frontotemporal lobar degeneration (excluding primary progressive aphasia and semantic dementia) at initial evaluation (25 patients) or progressed to meet these criteria during a 2-year follow-up period (49 patients). Initial neurologic features were compared with observed variations in regional SPECT hypoperfusion. Patients with FTD were found to have more hypoperfusion in the right frontal lobe than in other regions, with those so diagnosed at initial evaluation having the highest degree of right frontal hypoperfusion. Right frontal lobe involvement was associated with apathy and could predict loss of insight, environmental dependency, and stereotyped behaviors. Left frontal hypoperfusion was associated with a decline in personal hygiene, and left temporal hypoperfusion with compulsions and mental rigidity. The authors concluded that FTD at initial presentation is “disproportionately a right frontal disease evident on behavioral measures and on SPECT,” but added that patients with FTD can also present initially with other regional differences in clinical diagnostic features.

18F-FDG PET and Traumatic Diffuse Brain Injury

In an article e-published on March 20 ahead of print in the Journal of Neurology, Neurosurgery, and Psychiatry, Nakayama et al. from the Kizawa Memorial Hospital (Japan) reported on an 18F-FDG PET study using statistical parametric mapping (SPM) analysis to investigate the cerebral metabolism of chronic-stage patients with traumatic diffuse brain injury (TDBI). The study included 52 patients with TDBI without large focal lesions, who were divided into 3 groups based on consciousness or cognitive function: (A) patients in a state with higher brain dysfunction (22); (B) patients in a minimally conscious state; and (C) patients in a vegetative state (17). Patterns of regional cerebral metabolism for each individual were assessed with PET and compared on SPMs with those of healthy volunteers. Hypometabolism was noted in the patient group bilaterally in the medial prefrontal regions, the medial frontobasal regions, the cingulate gyrus, and the thalamus. Hypometabolism was greatest in group C. The authors concluded that these results suggest that bilateral hypometabolism in the areas noted may “reflect the clinical deterioration of TDBI, which is due to functional and structural disconnections of neural networks rather than to direct cerebral focal contusion.”

Journal of Neurology, Neurosurgery, and Psychiatry

Long-Term Follow-Up on Radiation Release

Several studies appeared in the medical literature in March reporting on continued assessments of medical sequelae to radiation-release events, including the 1986 accident at Chernobyl and the World War II bombing of Japanese cities. Ivanov et al. from the Russian Academy of Medical Sciences (Obninsk, Russia) reported on March 17 ahead of publication in Radiation and Environmental Biophysics on thyroid cancer incidence among children and adolescents in the Bryansk oblast area in the 1991–2001 follow-up period. Statistical analyses showed significant radiation risk only for those exposed as children between the ages of 0 and 9 years. For girls whose age at exposure was 0–4 years, the excess relative risk per 1 Gy for the study period was 45.3 (with internal control) and 28.8 (with external control). The corresponding figures for boys whose age at exposure was 0–9 years were 68.6 and 177.4. Jacob et al. from the GSF-Institute of Radiation Production (Neuberger, Germany) reported in the March issue of the Journal of Radiological Protection (2006;25:51–67) on a similar statistical study among Ukrainians and Belarusians who were children or adolescents at the time of the Chernobyl release. The authors identified a baseline of thyroid cancer incidence in these regions and correlated these data with location, gender, and age. They determined that the baseline cases contributed about 70% to the thyroid cancer incidence in Ukraine and about 40% to the incidence in Belarus. Tondel et al. from Linkoping University (Sweden) reported in the March issue of the American Journal of Industrial Medicine (2006;49:159–168) on the increased incidence of malignancies in individuals across a wide age spectrum after the fallout of 137Cs over Sweden after the Chernobyl accident in 1986. The study included 1,137,106 inhabitants who were 0–60 years old in 1986 and lived in 8 counties of Sweden with the highest levels of radioactive fallout. Using sophisticated maps and satellite technology, each individual was ranked for exposure to 137Cs. The authors identified an average excess relative risk per 100 nGy/hour of 0.042, with the possibility of additional levels of risk for thyroid cancer and leukemia.

In a study published on March 1 in the Journal of the American Medical Association (2006;295:1060–1062), Imaizumi et al. from the Radiation Effects Research Foundation (Nagasaki, Japan) evaluated the prevalence of thyroid diseases and radiation-dose responses in atomic bomb survivors. The survey study included 4,091 individuals. Thyroid diseases were identified in 1,833 (44.8%) of the total participants. In the subgroup of 3,185 participants (which excluded individuals exposed in utero, who were out the city at the time of the atomic bombings, or who experienced unknown radiation doses), the incidences of all solid nodules, malignant tumors, benign nodules, and cysts were 14.6%, 2.2%, 4.9%, and 7.7%, respectively. The prevalence of positive thyroid antibodies, antithyroid antibodies, positive hypothyroidism, and Graves disease was 28.2%, 3.2%, and 1.2%, respectively, in this same group. The authors estimated that about 28% of
all solid nodules, 37% of malignant tumors, 31% of benign nodules, and 25% of cysts in the overall group were associated with radiation exposure at a mean and median thyroid radiation dose of 0.449 Sv and 0.087 Sv, respectively. They concluded that “a significant linear radiation dose response for thyroid nodules, including malignant tumors and benign nodules, exists in atomic bomb survivors,” but added that no significant dose response is apparent for autoimmune thyroid diseases.

**Radiation and Environmental Biophysics**

**Journal of Radiological Protection**

**American Journal of Industrial Medicine**

**Journal of the American Medical Association**

### Pretargeted RIT in Thyroid Carcinoma

In an article e-published ahead of print on March 20 in the *Journal of Clinical Oncology*, Chatal and colleagues from France and the United States reported on a study of the efficacy of pretargeted radioimmunotherapy (RIT) with a bispecific monoclonal antibody (BsmAb) and a radiolabeled bivalent hapten in patients with metastatic medullary thyroid carcinoma (MTC). The study included 29 patients with advanced, progressive MTC, who received an antcarcinoembryonic antigen (CEA)/anti-diethyleneetriamine pentaacetic acid indium BsmAb, followed 4 days later by a $^{131}$I-labeled bivalent hapten.

The authors looked at overall survival in this group and a group of 39 patients with MTC who were not treated. They found that the overall survival was significantly longer in high-risk, treated patients than in high-risk, untreated patients. Patients defined as biologic responders (47% of those treated) experienced significantly longer survival than either nonresponders or untreated patients. Treated patients with bone/bone-marrow disease had longer survival times than patients without such involvement. These and accompanying laboratory findings led the authors to conclude that short serum calcitonin doubling times and bone-marrow involvement appear to be prognostic indicators in MTC patients who undergo pretargeted RIT.

*Journal of Clinical Oncology*

### Measles Virus Therapy in Ovarian Cancer

Hasegawa et al. from the Mayo Clinic College of Medicine (Rochester, MN) reported in the March 15 issue of *Clinical Cancer Research* (2006;12:1868–1875) on a virotherapy study with 2 oncolytic measles viruses: MV-CEA, which is being tested in patients with ovarian cancer and which can be monitored by measuring blood carcinoembryonic antigen (CEA) levels; and MV-NIS, which codes for the thyroidal sodium iodide symporter (NIS) and can be monitored by serial radiiodine imaging. The authors performed combined therapy in a mouse model of ovarian cancer and determined that not only is the dual therapy with MV-CEA and MV-NIS superior to treatment with either virus alone, but it “allows noninvasive monitoring of virotherapy via soluble marker peptide and gamma camera imaging.” They pointed to the important implications for the clinical development of oncolytic measles viruses.

*Clinical Cancer Research*

(Continued from page 15N)