diagnosis, and therapy purposes. The WRAMC hospital and other facilities at the Washington site are expected to shut down by September 15.

Participants in the session indicated that most of the radioactive materials remaining on site are related to nuclear medicine and radiation therapy activities. The NRC is overseeing all the decommission-associated tests at Walter Reed. Col. Casmere H. Taylor, chief of health physics at the hospital, told local news radio WTOP that staff has conducted "scoping surveys" to determine which buildings contain radioactive material. Testing involves removing tiles in renovated areas and assessment of floors, walls, benches, sinks, and sewer lines. Much of the cleaning will take place after all patients are moved at the end of August. "We still will continue some of the decommissioning work probably until the end of the year," Taylor said. After the cleanup, another series of surveys will be conducted to ensure that radioactive material has been removed and properly disposed. Plans for the decommissioned WRAMC site have not yet been finalized, but the District of Columbia has indicated that mixed-use applications (retail and residential) will be favored. Documents related to WRAMC decommissioning plans are available in the NRC's electronic documents systems at www.nrc.gov/reading-rm/adams.html.

Nuclear Regulatory Commission
WTOP News

FDA and Nanotechnology Regulation

The U.S. Food and Drug Administration (FDA) on June 9 released draft guidance to provide regulated industries with greater certainty about the use of nanotechnology. The guidance outlines the agency's view on whether regulated products contain nanomaterials or involve the application of nanotechnology. The draft guidance, "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology," is available online and open for public comment. In the document, the agency named certain characteristics (such as the size of nanomaterials used and the exhibited properties of those materials) that may be considered when attempting to identify applications of nanotechnology in regulated products. "With this guidance, we are not announcing a regulatory definition of nanotechnology," said Margaret A. Hamburg, MD, Commissioner of Food and Drugs. "However, as a first step, we want to narrow the discussion to these points and work with industry to determine if this focus is an appropriate starting place."

For products subject to premarket review, the FDA intends to apply the points contained in the draft guidance, when finalized, to better understand the properties and behavior of engineered nanomaterials. For products not subject to premarket review, the FDA will urge manufacturers to consult with the agency early in the product development process so questions related to the regulatory status, safety, effectiveness, or public health impact of these products can be adequately addressed. In 2006, the FDA formed the Nanotechnology Task Force, charged with identifying and addressing ways to better enable the agency to evaluate possible adverse health effects from FDA-regulated nanotechnology products. The agency issued a report by the task force in 2007 that recommended that the FDA create additional guidance and take steps to address potential risks and benefits of drugs, medical devices, and other FDA-regulated products using nanotechnology. FDA will develop additional guidance documents related to specific products or product categories in the future, as needed.

U.S. Food and Drug Administration

MedPAC and Prior Authorization

The Medicare Payment Advisory Commission (MedPAC) on June 16 issued a report to Congress recommending that Medicare implement a prior authorization program for clinicians who order greater numbers of advanced imaging studies than their peers. Citing the rapid volume growth of advanced imaging services over the past decade (including MR, CT, and nuclear medicine imaging), the recommendation was designed to give the Centers for Medicare and Medicaid Services (CMS) "a tool to improve payment accuracy for and ensure the appropriate use of advanced imaging services." The stated rationale was that targeting "outlier" practitioners, rather than all providers, would reduce administrative costs and the burden on practitioners and beneficiaries.

The commission recommended additional changes to the current payment model to address inappropriate pricing and reduce financial incentives for investing in ancillary services. These additional recommendations urged CMS to bundle payments for multiple services that are often furnished together and to reduce payment for the professional component of diagnostic imaging services provided by the same practitioner in the same session. The entire MedPAC report is available at http://medpac.gov/documents/Jun11_EntireReport.pdf.

Medicare Payment Advisory Commission

FROM THE LITERATURE

Each month the editor of Newsline selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. 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. We have added a special section on molecular

imaging, including both radionuclide-based and other molecular imaging efforts, in recognition of the extraordinary activity and promise of diagnostic and therapeutic progress in this area. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in the briefs presented here. We have also added a small section on noteworthy reviews of the literature.

MOLECULAR IMAGING/ THERAPY

"FDG Signature" in Breast Ca Subtypes

In an article e-published on June 6 ahead of print in *Cancer Research*, Palaskas et al. from the University of California at Los Angeles reported on a study designed to explore the molecular determinants of varying glucose metabolism and resulting ^{18}F-FDG retention in different types of cancers. The research group investigated the transcriptomes of human cancer cell lines and primary tumors for 95 metabolic pathways associated with ^{18}F-FDG uptake. The glycolysis and several glycolysis-related pathways showed the greatest transcriptional enrichment, providing what the authors called an "FDG signature." This accurately predicted FDG uptake in breast cancer cell lines and overlapped with established gene expression signatures for both the basal-like breast cancer subtype and MYC oncogene–induced tumorigenesis in mice. In additional studies, human breast cancers with nuclear MYC staining and high RNA expression of MYC target genes showed high FDG uptake on PET. This FDG signature was also associated with MYC gene copy gain, increased MYC transcript levels, and elevated expression of metabolic MYC target genes in a human breast cancer genomic dataset. The authors concluded that these findings "link clinical observations of glucose uptake with a pathologic and molecular subtype of human breast cancer" and "suggest related approaches to derive molecular determinants of radiotracer retention for other PET imaging probes."

Cancer Research

NIRF Imaging of Coronary Inflammation/ Injury

Jaffer et al. from the Massachusetts General Hospital/Harvard Medical School (Boston) reported in the June 21 issue of the *Journal of the American College of Cardiology* (2011;57: 2516–2526) on the development of a method for 2-dimensional (2D) intravascular near-infrared fluorescence (NIRF) molecular imaging of inflammation in atherosclerosis and stent-induced vascular injury. The article described the engineering of a novel catheter for optimized 360° views in intravascular NIRF imaging. Initial phantom studies confirmed submillimeter axial resolution, nanomolar sensitivity to NIR fluorochromes, and relatively low NIRF light attenuation through sera. Images were acquired using the cysteine protease–activatable imaging reporter Prosense VM110 in rabbit aortas with atherosclerosis or implanted 3.5-mm coronary bare-metal stents at d 7 after implantation. Intravascular ultrasound was coregistered to provide anatomical images of arteries. Ex vivo studies included NIRF imaging, fluorescence microscopy, and histologic and immunohistochemical analyses. The authors found that the combination of 2D NIRF, intravascular ultrasound–NIRF fusion, microscopy, and immunoblotting studies in the model of atherosclerosis provided insight into the spatial distribution of plaque protease activity. In the stent-implanted vessels, real-time imaging demonstrated an edge-based pattern of stent-induced arterial inflammation. These results suggested that this imaging strategy could provide "high-resolution in vivo spatial mapping of arterial inflammation in coronary-sized arteries" and revealed "increased inflammation-regulated cysteine protease activity in atheromata and stent-induced arterial injury."

Journal of the American College of Cardiology

Imaging Early Pancreatic Cancer

In an article published in the June 14 issue of the *Proceedings of the National Academy of Sciences of the United States of America* (2011; 108:9945–9950), Eser et al. from the Technische Universität München (Germany) reported on a novel approach to in vivo molecular imaging and diagnosis of murine pancreatic intraepithelial neoplasia, with implications for clinical applications in early-stage pancreatic ductal adenocarcinoma. The researchers combined a cathepsin-activatable near-infrared probe with flexible confocal fluorescence laser microscopy in experiments conducted in a genetically defined mouse model of pancreatic ductal adenocarcinoma. They were able to successfully detect and grade murine pancreatic intraepithelial neoplasia (a precursor for pancreatic ductal adenocarcinoma) in vivo and in real time. The technique proved to be highly sensitive and specific, as well as superior to clinically established fluorescein-enhanced imaging. The authors concluded that "translation of this endoscopic technique into the clinic should tremendously improve detection of pancreatic neoplasia, thus reforming management of patients at risk for pancreatic ductal adenocarcinoma."

Proceedings of the National Academy of Sciences of the USA

Mitochondrial Events as Imaging Biomarkers

Yivgi-Ohana et al. from the Weizmann Institute of Science (Rehovot, Israel) reported on June 2 in the online journal *Cell Death & Disease* on a method for utilizing mitochondrial events as biomarkers for imaging apoptosis. Current tools for imaging apoptosis in living cells focus either on caspase activity or on phosphatidyl serine in the outer leaflet of the cell membrane. Here, the authors focused

on detection of a specific mitochondrial event during apoptosis: translocation of the apoptosis-promoting gene Bax to mitochondria and release of cytochrome c. The technique involved bimolecular fluorescence complementation imaging expression of split yellow fluorescent protein (YFP) fragments that had been fused to Bax and cytochrome c. The result was robust induction of YFP fluorescence in the mitochondria of apoptotic cells. In vivo expression of split YFP protein fragments could be imaged in liver hepatocytes, and in vivo imaging of subcutaneous tumors showed elevated YFP fluorescence at the time of apoptosis induction. The authors concluded that this YFP complementation technique "could be applied for high-throughput screening and in vivo molecular imaging of mitochondrial events during apoptosis."

Cell Death & Disease

TOF Spectrometry and the Lens Capsule

In an article e-published on June 13 ahead of print in the *Journal of Proteome Research*, Ronci et al. from Flinders University (Bedford Park, Australia) reported on studies using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry imaging (MALDI-MSI) analysis to provide new information about the distribution of proteins on the excised ocular lens. MALDI-MSI is used to elucidate the spatial distribution of small molecules, peptides, and proteins within tissues. The authors found that trypsin digestion carried out on tissue improved MALDI-MSI analysis of human lens capsules and afforded high repeatability of results. MALDI-MSI showed a concentric distribution pattern of proteins, including apolipoprotein E and collagen IV α-1 on the anterior surface of surgically removed lens capsules, which they concluded "may indicate direct or indirect effects of environmental and mechanical stresses on the human ocular lens" and warrants further exploration using this technique.

Journal of Proteome Research

THERAPY

NIS-Mediated Antitumor Approach

In an article e-published on June 22 in the *Journal of Clinical Endocrinology and Metabolism*, Riesco-Eizaguirre et al. from the Consejo Superior de Investigaciones Científicas y Universidad Autónoma de Madrid, the Hospital Universitario La Paz, and the Instituto de Salud Carlos III (all in Madrid, Spain); the Instituto Aragonés de Ciencias de la Salud (Zaragoza, Spain); and the Institut National de la Santé et de la Recherche Médicale (Nantes, France) reported on a new broad-spectrum sodium-iodide symporter (NIS)–mediated approach for in vivo radionuclide treatment of cancer. The authors investigated the NIS-mediated therapeutic effect of telomerase promoters in a wide variety of human cancer cells, including lines derived from melanoma (M14), breast (MDA-MB-231), colon (HT-29), lung (H460), ovarian (OVCAR-3), and thyroid (TPC-1) carcinomas. Fragments from the telomerase promoters hTERT or hTR were used to drive the expression of NIS in these cell lines, with a series of assays performed to confirm NIS functional expression as well as radionuclide-mediated cytopathic effects after exposure to ^{131}I. In in vivo studies, tumor xenografts in mice were infected with hTERT and hTR and then treated with ^{131}I. Both promoters were found to be selectively active in cancer cells that were effectively killed by exposure to radioiodine. A single 1-mCi dose of ^{131}I markedly suppressed tumor growth of melanoma-derived tumor xenografts, with less pronounced results in colon cancer-derived xenografts. The therapeutic effect of the hTR promoter was found to be stronger than that of the hTERT promoter. The authors concluded that these results indicate that "telomerase-driven expression of NIS could potentially have applications for ^{131}I therapy of a wide variety of cancers."

Journal of Clinical Endocrinology and Metabolism

Practical Quantitative ^{177}Lu SPECT

Beauregard et al. from the Centre Hospitalier Universitaire de Québec and Laval University (Quebec City, Canada) and the Peter MacCallum Cancer Centre and University of Melbourne (Australia) reported in the June 15 issue of *Cancer Imaging* (2011;11: 56–66) on quantitative ^{177}Lu SPECT imaging using a commercially available SPECT/CT system. They described the development of a method in which serial SPECT images of ^{177}Lu sources ranging from 89 to 12,400 MBq were acquired with multiple contiguous energy windows along with coregistered CT images and then reconstructed using an iterative algorithm with attenuation and scatter correction. Camera sensitivity and dead time were resolved by nonlinear curve fit computations. With this method, SPECT datasets could be converted to what authors called a "QSPECT" dataset allowing quantitation in Becquerels/cubic centimeter or standardized uptake values. Phantom studies were performed for validation, followed by proof-of-principle studies on 5 patients who were administered therapeutic doses of ^{177}Lu-octreotate. The results included high accuracy in both the phantom model and in patients. The authors concluded that this approach "has the potential to yield more accurate dosimetry estimates than planar imaging and facilitate therapeutic response assessment" and that "validating this method with other radionuclides could open the way for many other research and clinical applications."

Cancer Imaging

DIAGNOSIS

Uptake vs Clearance in Bone Turnover

In an article e-published on June 13 ahead of print in *Bone*, Blake et al. from King's College (London, UK) compared the utility of information yielded by bone tracer uptake and bone plasma clearance as metrics for

whole-skeleton bone turnover. Data for the study were taken from 2 clinical trials of the bone anabolic agent teriparatide. The first study included 20 women with osteoporosis who underwent ^{18}F-fluoride PET imaging of the lumbar spine at baseline and after 6 mo treatment with the agent. Bone uptake in the lumbar spine was expressed as standardized uptake values (SUVs), and blood samples were used to evaluate plasma clearance. Spine plasma clearance was found to have increased by 23.8% at 6 mo, during which period SUVs increased by only 3.0%. The second study included 10 women who underwent ^{99m}Tc-methyl diphosphonate (^{99m}Tc-MDP) scans at baseline and at 3 and 18 mo after initiation of teriparatide therapy. In each woman, blood sampling was performed for whole-skeleton plasma clearance and bone uptake was calculated. Whole-skeleton plasma clearance was found to have increased by 37.1% at 19 mo, during which period the 4-h whole-skeleton uptake increased by only 25.5%. During treatment in the 2 studies, ^{18}F plasma concentration decreased by 20% and ^{99m}Tc-MDP concentration decreased by 13%, which the authors indicated was sufficient to account for differences between the uptake and plasma clearance results. They concluded that "measurements of response to treatment using bone uptake and plasma clearance gave different results because the effects of teriparatide on bone resulted in a sufficiently increased demand for radionuclide tracer from the skeleton that the concentration in the circulation decreased." They added that similar effects are likely to occur with other therapies that have sufficiently strong effects on bone metabolism, in which cases changes in bone plasma clearance may give a more accurate assessment of response to treatment than those in SUV or uptake.

Bone

SPECT and PEs

Morris et al. from the University of California, San Diego reported on June 16 ahead of print in the *American Journal of Respiratory and Critical Care Medicine* on a method for diagnosis of acute pulmonary embolism (PE) with SPECT and ^{99m}Tc-anti-D-dimer (DI-80B3) monoclonal antibody Fab' fragments. The study included 42 patients with moderate-to-high clinical probability of PEs or a positive D-dimer test who underwent both a contrast-enhanced multidetector thoracic CT and thoracic ^{99m}Tc-DI-80B3 SPECT. Separate and independent readers, unaware of histories or the study purpose, interpreted the SPECT and CT scans using established criteria. Thoracic CT identified 21 patients with PE and 21 without. Against this standard, ^{99m}Tc-DI-80B3 SPECT was found to have a sensitivity of 76.2% and a specificity of 90.5%, with no treatment-related serious adverse events. This acceptable safety profile and the avoidance of exposure to contrast led the authors to conclude that ^{99m}Tc-DI-80B3 SPECT may provide a viable clinical alternative in patients with suspected PE.

American Journal of Respiratory and Critical Care Medicine

Phenotyping of Abdominal Fat

In an article e-published on June 9 in *Obesity (Silver Spring)*, Thomas et al. from the Imperial College London/Hammersmith Hospital (UK) reported on a study designed to calculate a reference range for total and regional adipose tissue as well as ectopic fat in liver and muscle in healthy subject. The study was initiated as a result of numerous reports indicating that individuals with greater intra-abdominal adipose tissue and hepatic fat than predicted by clinical obesity indices (i.e., larger fat deposits despite relatively "normal" subject weight and size) are at increased risk of metabolic diseases. The researchers used whole-body MR imaging to analyze relationships among age, body mass, body mass indices, waist circumference, and the distribution of adipose tissue in 477 volunteers (243 male, 234 female). Proton MR spectroscopy was also used to determine intrahepatocellular and intramyocellular lipid content. The variables that proved to offer the strongest individual correlation for adiposity and ectopic fat stores were waist circumference in men and body mass index in women. Large variations in intra-abdominal adipose tissue, abdominal subcutaneous adipose tissue, and intrahepatocellular depots were identified and were not fully predicted by clinically obtained measurements of obesity. The gender- and age-specific patterns of regional adiposity in this large cohort and the variables that best predicted individual adiposity and ectopic fat stores led the authors to propose a "thin-on-the-outside fat-on-the-inside" subphenotype for individuals at increased metabolic risk.

Obesity (Silver Spring)

Visualizing Hepatic Integrin $\alpha_v\beta_3$ Expression

Li et al. from Fudan University (Shanghai, China) reported on May 26 ahead of print in *Hepatology* on the potential of ^{99m}Tc-labeled cyclic arginine-glycine-aspartic acid pentapeptide (cRGD) as a SPECT radiotracer to image hepatic integrin $\alpha_v\beta_3$ expression and thereby reflect hepatic stellate cell activity in fibrotic livers. The researchers used rat models of liver fibrosis to study the expression and distribution of integrin $\alpha_v\beta_3$ during fibrotic progression or regression and assessed the binding activity of ^{99m}Tc-cRGD to integrin $\alpha_v\beta_3$ in liver sections. In vivo SPECT was then performed in rats to assess hepatic integrin $\alpha_v\beta_3$ expression at different stages of liver fibrosis. Protein and messenger RNA levels of integrin α_v and β_3 subunits were found to increase as fibrosis progressed, with activated hepatic stellate cells found to express the majority of integrin $\alpha_v\beta_3$ in fibrotic livers. Activated hepatic stellate cells showed high receptor-coupling affinity and an abundant receptor capacity, with binding highest in advanced fibrosis. ^{99m}Tc-labeled cRGD SPECT showed that the radioactivity ratio of liver to heart increased in direction relation to the severity of hepatic fibrosis. The

authors concluded that "hepatic integrin $\alpha_v\beta_3$ expression in fibrotic liver reflects hepatic stellate cell activity, and its imaging using ^{99m}Tc-labeled cRGD as a SPECT radiotracer may distinguish different stages of liver fibrosis in rats."

Hepatology

PET, Aortic Stenosis, and Inflammation

In an article published in the June 21 issue of the *Journal of the American College of Cardiology* (2011; 57:2507–2525), Marincheva-Savcheva et al. from the Massachusetts General Hospital (Boston) investigated whether FDG uptake on ^{18}F-FDG PET is increased in the aortic valve in aortic stenosis, which is known to be associated with valvular inflammation. The retrospective study focused on PET/CT data from 84 patients (ages 73 ± 9 y; 42 with aortic stenosis and 42 age-matched control individuals). Researchers assessed FDG uptake in the aortic valve on PET without knowledge of the patient's stenosis/nonstenosis status. Target-to-background ratios were calculated as valvular/blood activity. Stenosis severity was determined on echocardiography, and aortic valve calcification was assessed by CT. The aortic valve tissue-to-background ratio on PET was increased in the group with aortic stenosis but only in the mildly and moderately stenosed valves. When subjects were categorized according to aortic valve calcification, valvular FDG uptake was increased in mildly and moderately calcified but not severely calcified valves, compared with noncalcified valves. The authors concluded that these results support "the hypothesis that aortic stenosis is an inflammatory condition and suggests that inflammation may be reduced in late-stage disease," a finding that may have significant implications in the design of studies assessing the effect of therapeutic agents on modifying the progression of stenosis.

Journal of the American College of Cardiology

PET and Pervasive Development Disorder

Shandal et al. from the Wayne State University School of Medicine and Children's Hospital of Michigan (both in Detroit) reported on June 2 ahead of print in the *Journal of Child Neurology* on a study designed to evaluate the cerebral protein synthesis rate of language brain regions in children with developmental delay with and without pervasive developmental disorder. The study included 16 children categorized as developmentally delayed (8 with pervasive developmental disorder [mean age, 6 y 3.25 mo] and 8 without [mean age, 6 y 5.25 mo]) who underwent L-[1-^{11}C]-leucine PET imaging. Higher protein synthesis rates in the children with pervasive developmental disorder were found in the left posterior middle temporal region, a region in which a significant correlation of the Gilliam Autism Rating Scale score with the protein synthesis rate was identified across all participants. Significant asymmetric protein synthesis (right > left) was observed in the middle frontal and posterior middle temporal regions in children without pervasive developmental disorder. The authors concluded that "abnormal language area protein synthesis in developmentally delayed children may be related to pervasive symptoms."

Journal of Child Neurology

REVIEWS

Review articles provide an important way to stay up to date on the latest topics and approaches by providing valuable summaries of pertinent literature. The Newsline editor recommends several reviews accessioned into the PubMed database in late May and in June. In an article e-published on June 12 ahead of print in the *Journal of Ethnopharmacology*, Li et al. from the Zhejiang University School of Medicine and the Zhejiang Chinese Medical University (China) provided an overview of "Current applications of molecular imaging and luminescence-based techniques in traditional Chinese medicine." On June 8, ahead of print in *Leukemia & Lymphoma*, Tan et al. from the National Institutes of Health (Bethesda, MD) described "Current and future imaging modalities for multiple myeloma and its precursor state." During et al. from the New York University School of Medicine (NY), reported on June 1 ahead of print in *Neurological Sciences* on "The concept of FDG-PET endophenotype in Alzheimer's disease." In the June issue of the *Journal of Cell Physiology* (2011;226:1444–1452), Welling et al. from the Leiden University Medical Center (The Netherlands) reviewed "In vivo biodistribution of stem cells using molecular nuclear medicine imaging." New and Aikawa, from Brigham and Women's Hospital/Harvard Medical School (Boston, MA), in the May issue of *Circulation Research* (2001;108:1381–1389), provided an article on "Molecular imaging insights into early inflammatory stages of arterial and aortic valve calcification." Kunjachan et al. from the Mahatma Gandhi University (Kerala, India), University Hospital RWTH- Aachen (Germany), Birla Institute of Technology and Science (Rajasthan, India), and the Utrecht Institute for Pharmaceutical Sciences (The Netherlands) reviewed on June 1 ahead of print in *Fundamental & Clinical Pharmacology* the "Physicochemical and biological aspects of macrophage-mediated drug targeting in anti-microbial therapy."