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 recently 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.

Sleep Deprivation and Dopamine

Volkow et al. from the National Institute on Drug Abuse (Bethesda, MD) and the Brookhaven National Laboratory (Upton, NY) reported in the August 20 issue of the *Journal of Neuroscience* (2008;28:8454–8461) on continued studies on the effects of sleep deprivation on the brain dopamine system. In this study, the authors used PET imaging to assess whether a single night of sleep deprivation changed dopamine activity. The study included 15 healthy individuals who underwent PET imaging with ^{11}C-raclopride (dopamine D_2/D_3 receptor radioligand) and ^{11}C-cocaine (dopamine transporter radioligand) after 1 night of rested sleep and then after 1 night of sleep deprivation. Specific binding of ^{11}C-raclopride in the striatum and thalamus was found to be reduced significantly after sleep deprivation, and the extent of this reduction correlated with increases in reported fatigue and inferior cognitive performance. Sleep deprivation did not affect specific binding of ^{11}C-cocaine in the striatum. Although the authors interpreted the decreases in ^{11}C-raclopride binding as reflecting dopamine increases with sleep deprivation, they noted that these binding decreases might also indicate decreases in receptor levels or affinity. Sleep deprivation did not affect dopamine transporters (the targets for most wake-promoting drugs), an indication that dopamine increases are likely to reflect increases in dopamine cell firing and/or release rather than decreases in dopamine reuptake. The authors concluded that given that dopamine-enhancing drugs increase wakefulness, the dopamine increase after sleep deprivation may be "a mechanism by which the brain maintains arousal as the drive to sleep increases but one that is insufficient to counteract behavioral and cognitive impairment."

Journal of Neuroscience

PET and OCD

In a study e-published on August 14 ahead of print in the the *Journal of Affective Disorders*, Olver et al. from the University of Melbourne and Austin Health (Melbourne, Australia) reported on a PET study exploring the binding of ^{11}C-SCH23390 (dopamine D_1 receptor antagonist) to D_1 receptors in the striatum of individuals with obsessive-compulsive disorder (OCD) and in healthy controls. The study included 7 drug-free patients (2 drug naïve) with OCD and 7 age-, sex-, and education-matched healthy controls. Each participant underwent ^{11}C-SCH23390 PET imaging. The D_1 receptor binding potential for ^{11}C-SCH23390 was significantly reduced in both the caudate nucleus and putamen in OCD patients compared with healthy controls. No correlations were found between binding potential and symptoms in OCD patients. The authors concluded that the downregulation of D_1 receptors in the striatum of OCD patients suggests increased nigrostriatal dopaminergic action and that, if confirmed, "this finding provides support for trials of novel treatments in OCD based on dopaminergic system blockade."

Journal of Affective Disorders

PET and MDMA Effects

McCann et al. from the Johns Hopkins School of Medicine (Baltimore, MD) reported on July 27 ahead of print in *Psychopharmacology (Berlin)* on the use of PET to explore the effect of closely spaced sequential doses of methylenedioxymethamphetamine (MDMA, "ecstasy") on dopamine transporter and 5-HT serotonin transporter (SERT) deficits and to determine whether resulting findings can be correlated with cognitive performance. The study included 16 abstinent MDMA users with a history of sequential MDMA doses (≥2 doses over a 3–12-h period) and 16 age-, sex-, and education-matched controls. Each participant underwent PET imaging with both ^{11}C-WIN-35,428 (a dopamine transporter ligand) and ^{11}C-DASB (a SERT transporter ligand). All participants also underwent formal neuropsychiatric testing. MDMA users were found to have reductions in SERT binding in several brain regions but reductions in striatal dopamine transporter binding. Memory performance over the entire study group correlated directly with SERT binding in those brain regions associated with memory function, and previous MDMA use diminished the strength of this correlation. The authors concluded that prior MDMA exposure appears to disrupt the relationship between SERT binding in areas of the brain involved in memory function, thus affecting memory performance. They also stated that "these data are the first to directly relate memory performance to brain SERT density."

Psychopharmacology (Berlin)

^{60}Cu-ATSM PET as Predictor in Rectal Carcinoma

In an article e-published on August 6 ahead of print in *Diseases of the Colon*

and Rectum, Dietz and colleagues from the Cleveland Clinic (OH) and Washington University (St. Louis, MO) reported on ^{60}Cu-diacetyl-bis-*N*-4-methylthiosemicarbazone (^{60}Cu-ATSM) PET in the detection of tumor hypoxia as a predictor of treatment response and survival in patients undergoing neoadjuvant chemoradiotherapy for rectal carcinoma. The study included 19 patients with locally invasive (T2–T4) primary or node-positive rectal cancer located $<$12 cm from the anal verge. Endorectal ultrasonography, CT, and MR imaging were used to assess pretreatment tumor size and stage, and 11 patients also underwent ^{18}F-FDG PET imaging at the request of treating clinicians. Each patient also underwent primary tumor imaging with ^{60}Cu-ATSM PET, followed within 2 wk by neoadjuvant chemoradiotherapy. Six to 8 wk later, patients underwent proctectomy, with tumors submitted for pathology and staging. Of the 17 patients evaluable, 14 had a reduction in tumor size and 13 were downstaged. The median tumor-to-muscle activity ratio (T/M) (2.6) was found to be a discrimination point between those with worse and better prognoses. Overall and progression-free survivals were worse with hypoxic (T/M $>$ 2.6) than nonhypoxic tumors (T/M $\leq$ 2.6). Two of 3 tumors with no change in size had T/M $>$ 2.6 (positive predictive value = 66%), and 6 of 14 with decreased size had T/M $>$ 2.6 (negative predictive value = 57%). Three of 4 tumors not downstaged had T/M $>$ 2.6 (positive predictive value = 75%), and 5 of 13 downstaged tumors had T/M $>$ 2.6 (negative predictive value = 62%). Mean T/M for downstaged tumors (2.2) was significantly lower than that for nondownstaged tumors (3.3). For those patients who underwent ^{18}F-FDG PET, no significant difference in mean tumor ^{18}F-FDG uptake was noted in hypoxic and normoxic tumors, and ^{18}F-FDG uptake did not correlate with ^{60}Cu-ATSM uptake. The authors concluded that the results of this pilot study suggest that "^{60}Cu-ATSM may be predictive of survival and, possibly, tumor response to neoadjuvant chemoradiotherapy in patients with rectal cancer" and called for a larger phase 2 study to validate the results.

Diseases of the Colon and Rectum

Internal Mammary Sentinel Nodes

Heus et al. from the University Hospital Maastricht (The Netherlands) reported on August 4 ahead of print in the *European Journal of Surgical Oncology* on a large study designed to determine the likelihood of finding internal mammary lymph node metastases as hotspots on lymphoscintigraphy and to evaluate the relevance of internal mammary sentinel node biopsy as a method to improve staging in breast cancer. The study included 1,008 patients with clinically node-negative operable primary breast cancer in whom both axillary and internal mammary sentinel nodes were sampled on the basis of ^{99m}Tc-nanocolloid lymphoscintigraphy, intraoperative γ-probe detection, and blue dye mapping. Lymphoscintigraphy demonstrated axillary sentinel nodes in 98% and internal mammary sentinel nodes in 20% of patients. Sampling the internal basin, based on lymphoscintigraphy results, was successful in 71% of patients, indicating metastases in 22% of these. No axillary metastases were found in 29% of patients with positive internal mammary sentinel nodes. The authors concluded that patients with internal mammary hotspots on lymphoscintigraphy have a substantial risk (22%) of metastatic involvement of the internal mammary chain and that the imaging technique allows true internal mammary node-negative patients to be spared the morbidity associated with adjuvant radiotherapy.

European Journal of Surgical Oncology

Timing of SLN Biopsy and Therapy

In an article e-published on August 5 ahead of print in the *Journal of Surgical Oncology*, Papa et al. from the Chaim Sheba Medical Center (Tel Hashomer, Israel) reported on a study designed to address optimal timing of sentinel lymph node (SLN) biopsy in patient with breast cancer undergoing neoadjuvant therapy. The study included 117 women with locally advanced cancer and clinically negative nodes treated with primary chemotherapy who were divided into 3 groups with different assessment and treatment schedules. In the first group, 31 patients underwent SLN biopsy and completion axillary lymph node dissection (ALND) in conjunction with lumpectomy/mastectomy after neoadjuvant treatment. In group 2, 58 patients underwent SLN biopsy followed by neoadjuvant therapy and then by surgery and completion ALND. In group 4, 28 patients underwent SLN biopsy followed by neoadjuvant therapy and then by surgery, but completion ALND was performed only in patients with positive SLNs. SLN identification was lowest in group 1, which also had the highest false-negative rate (15.8% compared with 0% in group 2). The authors concluded that neoadjuvant treatment lowers the SLN identification rate and increases the false-negative rate as a result of downstaging and that "SLN biopsy prior to chemotherapy could give a more accurate evaluation of axillary status, unaffected by any previous therapeutic intervention."

Journal of Surgical Oncology

PET and the Will Rogers Phenomenon

The so-called Will Rogers phenomenon occurs when an element is moved from 1 set to another and thereby raises the average values of both sets. Its name comes from that of the humorist who said, "When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states." The phenomenon made its medical debut more than 2 decades ago when researchers noted the effect that improved diagnostic technologies could have on stage migration and thereby on statistics associated with cancer prognosis (Feinstein et al. *Trans Assoc Am Physicians.* 1984;97:19–24). In the July 28 issue of the *Archives of Internal Medicine* (2008;168:1541–1549), Chee et al. from the University of California Davis Cancer Center (Sacramento, CA) looked at the question of whether the

Will Rogers phenomenon is associated with reports of PET effects on improved survival in patients with non–small cell lung cancer. The retrospective study accessed the records of 12,395 such patients in the pre-PET (1994–1998) and PET (1999–2004) eras to look for differences in staging procedures, clinical variables, and survival. The PET period saw a 5.4% decrease in the number of patients with stage 3 disease and an 8.4% increase in the number of patients with stage 4 disease. Use of PET was independently associated with better survival in patients with stage 3 and 4 but not with stage 1 and 2 disease. The authors concluded that "These data support the notion that stage migration is responsible at least in part for an apparent improvement in survival for patients with stage 3 and 4 non–small cell lung cancer in the PET scan era."

Archives of Internal Medicine

Detecting Renal Pathology in Pediatric UTI

Hamoui et al. from Children's Memorial Hospital/Northwestern University (Chicago, IL) reported on August 19 ahead of print in the *Journal of Urology* on a study to determine the agreement of ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-DMSA) scintigraphy with ultrasound findings in children with urinary tract infections (UTIs). The study included the records of 100 children (median age, 4.5 y; range, 4 mo−19 y; 84% female). Vesicoureteral reflux was identified in 74 children, and scintigraphy was abnormal (<40% differential function, global atrophy, or focal defects) in 18 patients whose ultrasound results were normal. The group of children with vesicoureteral reflux had a slightly increased incidence of abnormal scintigraphy compared with those without vesicoureteral reflux. The authors concluded that although ^{99m}Tc-DMSA scintigraphy is not part of routine practice in all children with UTIs and/or vesicoureteral reflux, it is frequently abnormal despite normal ultrasound and "should be considered in these patients to evaluate cortical defects and possibly guide further management."

Journal of Urology

THERAPY

Paclitaxel with High LET RIT

Milenic et al. from the National Cancer Institute (Bethesda, MD) reported in the August 15 issue of *Clinical Cancer Research* (2008;14:5108–5115) on a study of paclitaxel enhancement of the therapeutic efficacy of α-particle–targeted radioimmunotherapy (RIT) in a mouse model of disseminated peritoneal disease. Athymic mice with LS-174T xenografts were treated with 300 or 600 μg paclitaxel at 24 h before, concurrently, or 24 h after ^{213}Bi- or ^{212}Pb-trastuzumab administration. Groups of mice were also treated with paclitaxel alone, with RIT alone, or with ^{213}Bi-labeled immunoglobulin G (^{213}Bi-HuIgG). Mice receiving ^{213}Bi-trastuzumab alone, ^{213}Bi-HuIgG alone, paclitaxel alone, or left untreated had median survival times of 31, 21, 23, and 15 d, respectively. Paclitaxel at either dose 24 h before ^{213}Bi-trastuzumab administration provided no therapeutic benefit. Paclitaxel at either dose administered concurrently with ^{213}Bi-trastuzumab or ^{213}Bi-HuIgG resulted in median survival times of 93 and 37 d, respectively. Paclitaxel (300 or 600 μg) administered 24 h after ^{213}Bi-trastuzumab increased median survival to 100 and 135 d, respectively. Results showed the greatest improvement in median survival (198 d) with 2 weekly doses of paclitaxel (600 μg) followed by ^{213}Bi-trastuzumab. When the trastuzumab was radiolabeled with ^{212}Pb, 300 μg of paclitaxel adminisited 24 h before RIT failed to enhance therapy, but 600 μg extended median survival from 44 to 171 d. The authors concluded that "these results suggest that regimens combining chemotherapeutics and high linear energy transfer RIT may have tremendous potential in the management and treatment of cancer patients" and that "dose dependency and administration order appear to be critical factors requiring careful investigation."

Clinical Cancer Research

Fractionated ^{131}I-Anti-CEA RIT

Violet et al. from University College London (UK) reported in the August 19 issue of the *British Journal of Cancer* (2008;99:632–638) on a study of dose fractionation as a method to improve the therapeutic ratio of radioimmunotherapy (RIT). The study was conducted in mice bearing the human colorectal xenograft LS174T. Mice were administered either a single dose of 7.4 MBq ^{131}I-anti-carcinoembryonic antigen (CEA) antibody on d 1 or approximately the same total activity given as fractionated treatments of 3.7 MBq (d 1 and 3), 2.4 MBq (d 1, 3, and 5), or 1.8 MBq (d 1, 3, 5, and 8). Increased fractionation was found to significantly reduce the efficacy of therapy. Although increased fractionation decreased systemic toxicity as assessed by weight, no significant decreases in acute hematologic or marrow toxicity were noted. A significant depression of colony-forming unit counts for granulocytes and macrophages was seen in the average of all treated mice compared with that for untreated controls, indicating that treatment suppressed marrow function. The authors summarized their findings by noting that in this tumor model, "fractionated RIT causes less systemic toxicity but is also less effective at treating tumors."

British Journal of Cancer

Adenovirus-Mediated Gene Expression in Prostate Cancer

In an article e-published on August 19 ahead of print in *Molecular Therapy*, Barton et al. from the Henry Ford Health System (Detroit, MI) reported on a phase 1 study of noninvasive imaging of adenovirus-mediated gene expression in the human prostate. The study included 9 patients with clinically localized prostate cancer who were administered an intraprostatic injection of replication competent adenovirus (Ad5-yCD/utTK[SR39]rep-hNIS), armed with 2 suicide genes and the sodium iodide symporter (NIS) gene. NIS gene expression was imaged with $Na^{99m}TcO_4$ SPECT in infected cells. Gene expression was detected in the prostate in 7 (78%) patients at 1×10^{12} virus particles but not at 1×10^{11}. After

injection of 1×10^{12} virus particles in 1 cm^3, gene expression volume increased to a mean of 6.6 cm^3, representing an average of 18% of total prostate volume. Gene expression volume and intensity peaked 1–2 d after injection, and gene expression was detectable in the prostate up to 7 d after injection. Whole-body imaging showed intraprostatic gene expression, with no evidence of extraprostatic dissemination. The therapy was safe, with only grade 1 and 2 toxicities noted. The authors concluded that "the results demonstrate that noninvasive imaging of adenovirus-mediated gene therapy in humans is feasible and safe."

Molecular Therapy

MOLECULAR IMAGING

Near-Infrared Fluorescent Imaging in Pancreatic Cancer

von Burstin et al. from the Technical University of Munich (Germany) reported on August 15 ahead of print in the *International Journal of Cancer* on an investigation of novel molecular near-infrared fluorescent (NIRF) in vivo imaging techniques in clinically relevant mouse models of pancreatic cancer. Cathepsin cystein proteases and matrix metalloproteinases (MMPs) were identified by genome-wide gene expression profiling as targets for NIRF imaging. Protease activatable probes were evaluated for detection of early-stage pancreatic cancer in mice with orthotopically implanted pancreatic cancer cell lines and in control mice with pancreatitis. Whole-body in vivo NIRF imaging using activatable cathepsin-sensitive probes detected pancreatic tumors as small as 1–2 mm in diameter and showed high specificity for MMP-positive tumors. Intravital flexible confocal fluorescence laser scanning microscopy of protease activity enabled specific detection of pancreatic tumors at the cellular level. Topical application of NIRF probes markedly reduced background without altering signal intensity. The authors concluded that this combination of macroscopic and confocal laser microscopic molecular in vivo imaging of protease activity is highly sensitive, specific, and allows discrimination between normal pancreatic tissue, inflammation, and pancreatic cancer and that "translation of this approach to the clinic could significantly improve endoscopic and laparoscopic detection of early-stage pancreatic cancer."

International Journal of Cancer

NIRF Imaging of Inflammation, Angiogenesis, and Growth

In an article published on August 13 in the online journal *PLoS One* (2008;3:e2916), Gounaris et al. from the Massachusetts General Hospital and Harvard Medical School (Boston) reported on the use of inducible near-infrared fluorescent (NIRF) probes to visualize intestinal polyps in mice hemizygous for a novel truncation of the adenomatous polyposis coli gene. In vivo laser scanning confocal microscopy allowed visualization of cathepsin activity in richly vascularized benign dysplastic lesions. The authors quantified increased activities of cathepsin B and Z in the polyps using biotinylated suicide inhibitors. They found that >75% of the probe signal was localized in $CD11b^+Gr1^+$ myeloid-derived suppressor cells and $CD11b^+F4/80^+$ macrophages infiltrating the lesions. Polyposis was attenuated through genetic ablation of cathepsin B and suppressed by neutralization of tumor necrosis factor-α in mice. The authors concluded that in vivo NIRF imaging of focal cathepsin activity "reveals inflammatory reactions etiologically linked with cancer progression and is a suitable approach for monitoring response to therapy."

PLoS One

Margination of Spherical Particles in Vascular Targeting

Gentile and colleagues from the University Magna Graecia (Catanzaro, Italy) and the University of Texas M.D. Anderson Cancer Center (Houston) reported on August 15 in the *Journal of Nanobiotechnology* (2008;6:9) on a study of the propensity of circulating particles to drift laterally toward vessel walls (margination) in the microcirculation, a study with significant implications for innovative techniques in molecular imaging and nanotherapy. The authors used a parallel-plate flow chamber to study fluorescent polystyrene particles, with properties similar to those of liposomal or polymeric nanoparticles used in drug delivery and bioimaging, ranging in diameter from 50 nm to 10 micron. Confocal fluorescent microscopy was used to measure the numbers of particles marginating per unit surface, and the corresponding total volume of particles was calculated. In horizontal capillaries, margination was found to be mainly the result of gravitational forces for particles with diameters > 200 nm. In vertical capillaries, particles tended to marginate toward the walls in downward flows and toward the center in upward flows. However, these results indicated that margination would be much smaller in vertical than in horizontal capillaries. They concluded that "These results suggest that, for particles circulating in an external field of volume forces (gravitation or magnetic), the strategy of using larger particles designed to marginate and adhere firmly to the vascular walls under flow could be more effective than that of using particles sufficiently small (<200 nm) to hopefully cross a discontinuous endothelium."

Journal of Nanobiotechnology

MR and SPIO-Labeled Stem Cells

Wang and colleagues from the National Research Council Canada (Winnipeg) and Harbin Medical University (People's Republic of China) reported on July 25 ahead of print in *Magnetic Resonance Imaging* on a study designed to determine whether superparamagnetic iron oxide (SPIO) affects the viability, transdifferentiation poten-

tial, and cell-factor secretion of adipose-derived stem cells (ASCs) and whether SPIO-enhanced MR imaging detects viable stem cells. Rat ASCs were incubated in SPIO-containing cell culture medium for 2 d and then subjected to adipogenic, osteogenic, and myogenic transdifferentiation. The reverse transcription polymerase chain reaction was used to measure expression of vascular endothelial growth factor, hepatocyte growth factor, and insulin-like growth factor 1 by the SPIO-treated ASCs, and cell viability was assessed with trypan blue stain. In a separate set of in vivo experiments, SPIO-labeled ASCs were injected into 10 rat hearts that were monitored with MR imaging. The survival rate of ASCs cultured in the SPIO-containing medium was 97%−99%. These ASCs continued to express specific markers for the 3 types of transdifferentiation. Expression of cell factors was not affected by SPIO labeling. Signal voids on MR images in the living rats were associated with living SPIO-labeled ASCs in the hearts. The authors concluded that "SPIO does not affect viability, transdifferentiation potential, or cell-factor secretion of ASCs" and that MR imaging "mainly highlights living SPIO-labeled stem cells."

Magnetic Resonance Imaging

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This article is based upon multiple NIH grants and is openly accesssible through NIH and at http://jnm.snmjournals.org/.