

MS: More than Counting Lesions

“It’s one of the great frustrations in treating patients with MS,” says neurologist **Peter Calabresi**. “You get a high-quality scan. You see the white spots that signify lesions in the brain,” he says. “But that doesn’t always correlate with what you see happening to your patient.”

A patient could, for example, have neuralgia’s electric shocks running down both arms and suffer the numbing fatigue of a flare-up, yet clinicians might see no change from the last imaging.

This *clincoradiological paradox* isn’t unusual, says Calabresi, head of Hopkins’ Multiple Sclerosis Center. And not only can it keep the severity of MS out of sync with how aggressively to treat it, but more cosmic effects can follow. Pharma companies, for example, are less likely to invest the millions needed to test new drugs because it’s so hard to verify their effects in a reasonable time.

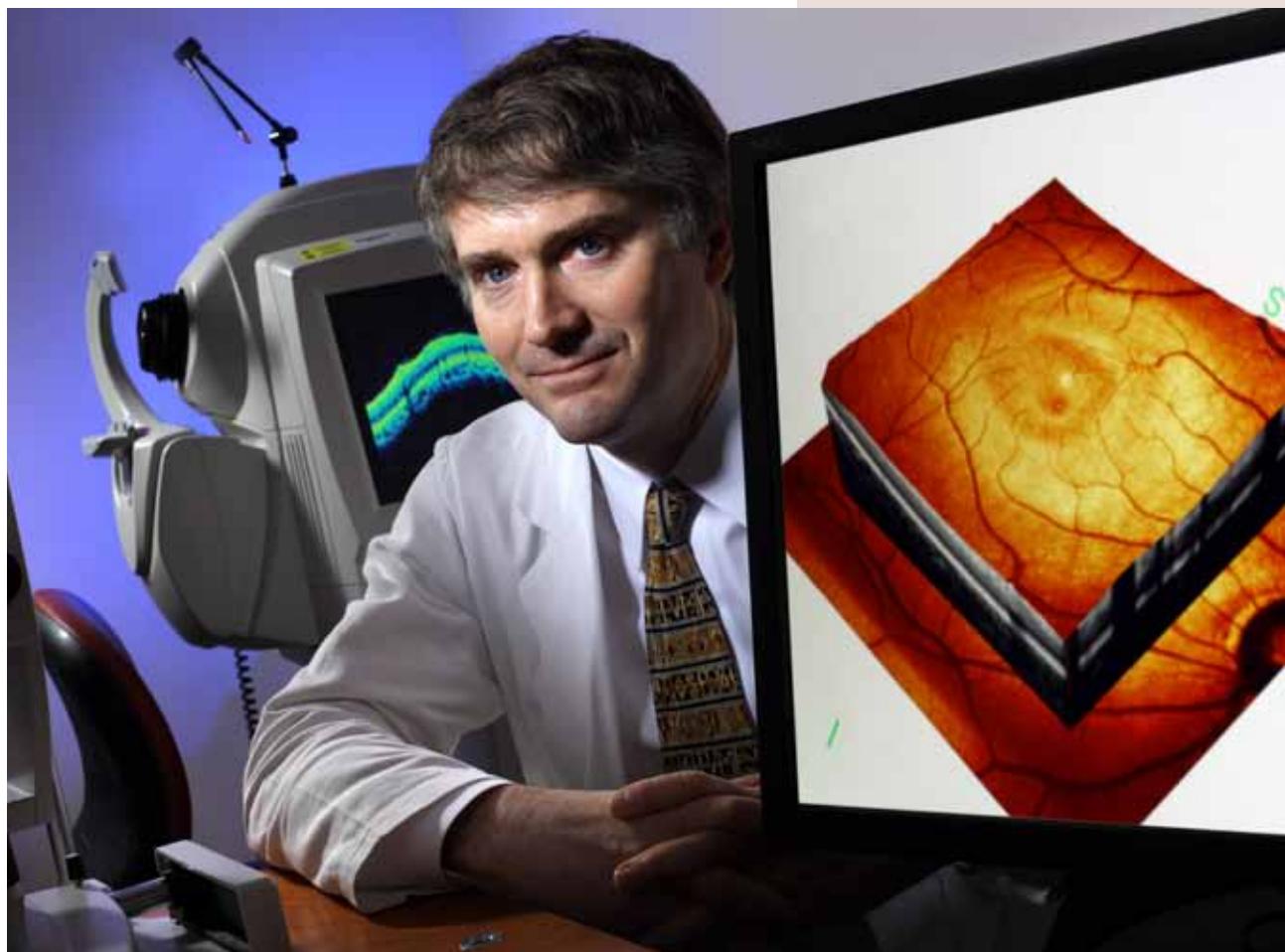
The problem is that lesions don’t always define the underlying pathology in MS. Calabresi and his colleagues, however, are finding ways around that. One method, optical coherence tomography (OCT), is newly pulled from ophthalmic clinics where it’s used to assess retinal damage from glaucoma or macular degeneration. Now OCT is poised to turn the eye into an easy, reliable window into MS. “It’s ready for prime time,” says Calabresi.

In an OCT scan, a beam of infrared light plays across the retina and the resulting data on the “bounce-back” gets crunched by a microprocessor

“WHAT WE HOPE IS THAT BOTH TECHNOLOGIES WILL PREDICT WHO’S GOING TO HAVE BRAIN ATROPHY.”

into a meaningful readout. It’s like ultrasound, only with light. Within 10 minutes, in the comfort of a neurologist’s office, Calabresi says, you can measure the thickness of the retinal nerve fiber layer. And that’s becoming a valuable metric.

“Originally,” he explains, “we used OCT just to assess the optic neuritis that’s common with MS.” But there’s been a sea change in the way medicine views MS, with the realization that the lasting damage comes from neurodegeneration as well as autoimmune attacks on myelin. So Calabresi and colleagues track a patient’s thinning retina as a finger on degeneration’s



OCT is poised to turn the eye into a reliable window into MS, says Peter Calabresi.

pulse. It goes beyond counting brain lesions. “The inflammatory attacks are just the tip of the iceberg,” he says.

But it’s one thing to say *Now we can measure the loss of naked axons in the eye* and another to prove that reflects a whole demyelinating disease. So Calabresi and colleagues on a select multicenter team have, for five years, followed MS patients with OCT. They’ve shown, for example, that the retinal layer thickness is in sync with how patients do on clinical tests of vision loss—a true structure-function link. They’ve also found that the more progressive the MS, the more rapid the thinning.

Most important is that Calabresi’s team showed a significant tie between retinal changes and increased brain atrophy, the MS hallmark. “These matches,” he says, “are better than we could have hoped for.”

“At Hopkins, we’re at a point where we’re using OCT cautiously in clinical practice. We have the newest generation machine. Its resolution is spectacular.”

This isn’t, however, to dismiss the usefulness of MRI, Calabresi emphasizes. Great strides have been made recently with that method, particularly with diffusion tensor imaging. “It’s important,” he adds, “to be able to check the integrity of entire nerve fibers.” What we hope,” he says, “is that both techniques will help predict who’s going to have brain atrophy. Then we might intervene before the brain is greatly affected.” ■

Information: The Johns Hopkins Multiple Sclerosis Center at 410-614-1522

Inside



2

New Eye on the “Small” Stuff in Traumatic Brain Injury



3

iCT: It’s better than OK for the OR



4

Could Stem Cells Fill the Pituitary Gap?

The following clinical trials are actively recruiting patients.

Epilepsy

Double-blind, randomized, historical control study of the safety and efficacy of eslicarbezepine acetate monotherapy in subjects with partial epilepsy not well controlled by current antiepileptic drugs. Trial for subjects who experience partial seizures and are stable on no more than 1 and 2/3 (standard dose) of other antiepileptic drugs. *Info: Gregory Krauss, MD, P.I.; Amanda Cole, coordinator, acole12@jhmi.edu, 410-614-8628.*

Parkinson Disease

LCIG (Levodopa-Carbidopa Intestinal Gel)
We are enrolling patients in an open-label, multi-center safety and efficacy study of an investigational medication for patients with severe motor-fluctuations despite optimized treatment with available parkinson disease medications. *Info: Joseph Savitt, P.I., jsavitt@jhmi.edu; Melissa Gerstenhaber, coordinator, mgerste1@jhmi.edu; 410 614-1242.*

Multiple Sclerosis

Relapsing Remitting MS(RRMS)-A multicenter trial evaluating whether oral treatment with estriol, the major estrogen of pregnancy, decreases relapses in relapsing remitting multiple sclerosis (RRMS) subjects when used in combination with injectable Copaxone®. *Info: Peter Calabresi, MD, P.I.; Stephanie Syc, coordinator, ssyc1@jhmi.edu, 410-502-2488.*

RRMS

A multicenter trial evaluating whether the efficacy and safety of PEGylated Interferon Beta-1a (BIBo17) in subjects with RRMS when given either every 2 weeks or every 4 weeks versus placebo. *Info: Peter Calabresi, MD, P.I.; Kristie Albright, research nurse, kalbrig2@jhmi.edu, 410-502-6867.*

Primary Progressive Multiple Sclerosis

A double-blind, randomized, multicenter, placebo-controlled, parallel-group study comparing the efficacy and safety of 1.25mg fingolimod (FTY720) administered orally once daily versus placebo in patients with primary progressive multiple sclerosis (PPMS). *Info: Julius Birnbaum, MD, P.I.; Alpa Uchil, research nurse, apalich2@jhmi.edu, 443-287-6079, or Regina Brock-Simmons, research coordinator, rrock1@jhmi.edu, 410-502-7220.*

Acute Optic Neuritis

A multicenter trial to determine whether Copaxone® is neuroprotective in Acute Optic Neuritis (AON). Participants must be randomized within 9 days of visual disturbance. *Info: Peter Calabresi, MD, P.I.; Stephanie Syc, coordinator, ssyc1@jhmi.edu, 410-502-2488.*

Atkins Diet

Open-label trial of modified Atkins diet for adults (18 years of age and over) with at least weekly uncontrolled seizures. Study is done via the internet. *Info: Eric Kossoff, MD, P.I.; Mackenzie Cervenka, co-investigator, mcerven1@jhmi.edu, 410-955-1270.*

Intracerebral Hemorrhage and Intraventricular Hemorrhage

A Phase III randomized clinical trial (RCT) to compare a policy of early extraventricular drain (EVD) use and recombinant tissue plasminogen activator (rt-PA, Cathflo® Activase® Genentech, Inc., San Francisco, CA) with EVD use and placebo (normal saline) for the treatment of subjects with intracerebral hemorrhage (ICH) and intraventricular hemorrhage (IVH) with obstruction of the 3rd or 4th ventricles by blood. *Info: Wendy Ziai, MD, and Daniel Hanley, MD. PIs; Shannon LeDroux, study coordinator, 410-502-6367, sledrou1@jhmi.edu Study pager: 410-283-6772.*

Intracerebral Hemorrhage

Phase II trial is to determine the safety of using a combination of minimally invasive surgery and clot lysis with rt-PA to remove ICH. *Info: Judy Huang, MD, and Daniel Hanley, MD. PIs; Shannon LeDroux, study coordinator, 410-502-6367, sledrou1@jhmi.edu Study pager: 410-283-6772.*



Tommy Martinson's chat with neurointensivist Robert Stevens is a testament to the enlightened persistence of several NCCU teams.

Why White Matter Matters in TBI

When 21-year-old Tommy Martinson eased out of a coma in Hopkins' neurocritical care unit, two months had passed since a stranger leaving a bar hammered him with a left temporal punch. Fortunately for Martinson, he was "out" while successive teams administered what neurointensivist **Robert Stevens** calls "the full weight of neurological critical care."

The young man had a subdural hematoma, a subarachnoid hemorrhage and an internal brain hemorrhage—not unheard of with the concussive and acceleration-deceleration injuries that mark severe traumatic brain injury (TBI). He developed resistant status epilepticus that only a pharmacologically induced coma and antiseizure meds relieved. Then came the severe pneumonia and hypoxic respiratory failure that demanded high levels of ventilator support. The wages of survival, though, was acute kidney injury, and Martinson went on dialysis. "That's not to mention the pulmonary embolism and multiple infections," Stevens adds.

The fact that a grateful Martinson is now back in college and has picked up his old life, "shows, by any measure, a spectacular recovery," Stevens adds. Amazingly, his new classmates wouldn't begin to suspect what he's been through. It's only by Martinson's own reports that lingering symptoms first came to light.

"My reaction time has changed some," Martinson explains, "in that I take a little longer to 'get' something." He also has trouble interpreting where sounds come from. Those quieter, cognitive problems, Stevens believes, may come when axons are sheared as the brain decelerates suddenly.

Immediate life-threatening injuries, of course, take priority in neurointensive care, but Stevens'

team also has a new focus on this subtler damage—diffuse axonal injury(DAI)—in the brain's white matter. Relieving it he says, would bring a huge change in brain trauma therapy.

"White matter damage is definitely prevalent," Stevens explains. "Virtually all brain trauma patients have it in some form." They don't need to suffer severe trauma—people can experience it after a concussion, a fleeting loss of consciousness, he says.

Symptoms of DAI include difficulties in consciousness, executive function, memory or attention that can last months to years after injury. And though there are therapies such as cognitive rehab, stimulants and psychotherapy, for example, none cure it.

But change is coming, Stevens believes, in part from a wealth of imaging techniques his team plans to apply to brain injury. Among them is diffusion tensor imaging (DTI), a way to view the white matter tracts that connect brain to brain. Stevens collaborates with Hopkins' "father of DTI," neurophysicist Susumu Mori, both to advance research on white matter damage and explore DTI as a diagnostic tool.

"We are exploring a link between white matter injury, the functional disruption of the tracts and specific cognitive changes," says Stevens. If there is such a tie, he adds, "we could, perhaps, find ways to reconnect the tracts." Though that may seem so much pie-in-the-sky just now, Hopkins is committed to finding care that goes beyond the supportive. ■

For information: 410-955-7481

When Numbers Reveal the Bleeding Obvious

Brain hemorrhage, we know, is the most lethal form of stroke, particularly for patients with both intracerebral and intraventricular bleeding, where reported mortality rates range from 50 to 80 percent. It's a medical shock-and-awe that so many die, let alone that such variability exists.

Dan Hanley, however, has put both his conviction and expertise behind a powerful tool that can help improve those odds: data.

Hanley oversees a massive, multicenter randomized study called CLEAR III (Clot Lysis Evaluating Accelerated Resolution) to examine the use of the clot-dissolver, tissue plasminogen activator (t-PA) for speeding away brain hematomas. The data collected from the 40-plus centers involved in the study, he says, will confirm or deny that the method saves more lives and offers better health outcomes than other forms of treatment.

It's just one of several studies coordinated by the Johns Hopkins Brain Injury Outcomes Services (BIOS) Division, which Hanley directs. For 10 years, the group has served as the organizational hub for outcomes research aimed at brain injury. The division not only helps design and conduct such studies, but also advises on analyzing the mass of data they generate.

Besides Clear III, the team has coordinated multicenter trials on adding ultrasound to clot-busting drugs in treating brain hemorrhages, for example, or

on a treatment for induced hypertension in acute stroke. Some drugs and devices that BIOS studies have been part of practice for years, Hanley says.

But medicine has lacked rigorous trials to validate them. Brain hemorrhage, he adds, is an especially egregious example: "Even guidelines from the American Stroke Association point out the lack of well-designed studies." This new one, he hopes, will change that.

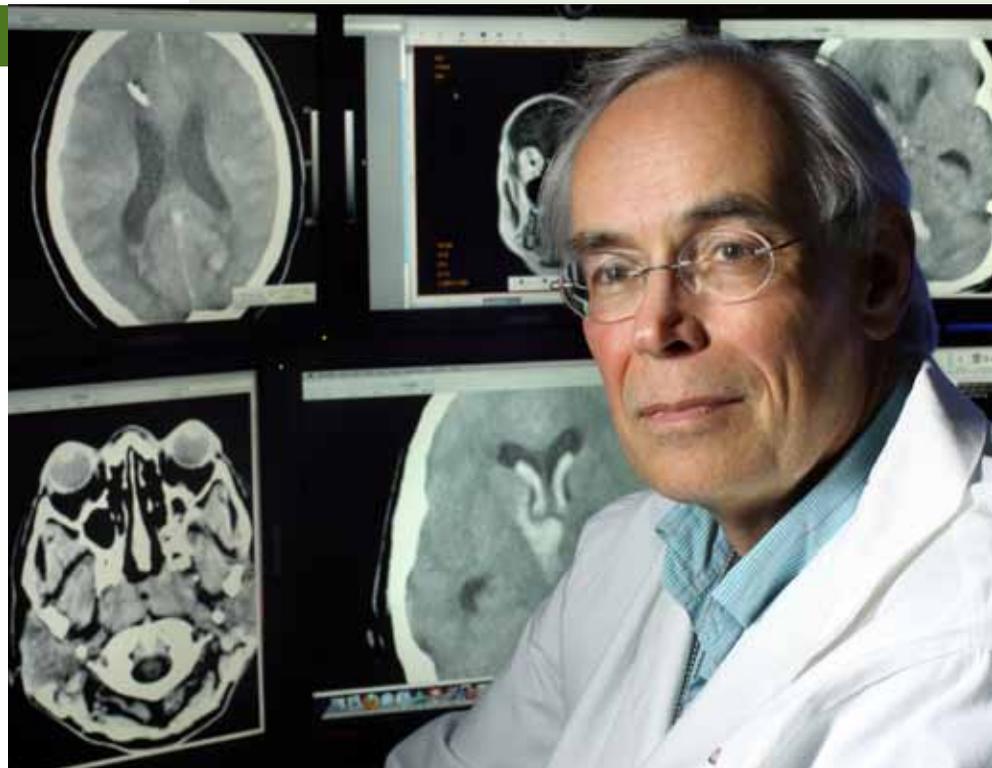
Earlier versions of CLEAR have shown t-PA's safety and best dosage. This latest one examines any benefits of quickly clearing clotted blood from brain ventricles—an idea animal studies support. Extraventricular drainage alone—using a catheter to drain the blood clot—hasn't proved greatly helpful. So BIOS suggested a look into supplementing that approach with tPA.

With this technique, surgeons insert an intraventricular catheter once the hemorrhage ends. They then irrigate the clot with t-PA, and allow it to drain over several days. Phase II CLEAR showed a six-month mortality of 20 percent—far lower than

anything ever before. In addition, a striking half of the study's patients regained ability to care for themselves. Safety was high.

If this larger, phase III trial confirms earlier benefits, Hanley says, they'll have found the first real approach for intraventricular hemorrhage to save lives and counter disability. ■

Neurologist Dan Hanley banks on the power of outcomes research.



A HIGH-TECH DIFFERENCE



"Having this permits far safer brain or spinal surgery," says Ali Bydon. "We're hooked on it now."

On Site CT is Outta Sight

This winter, Hopkins became the first of only a handful of U.S. centers to adopt an intraoperative CT that's so sophisticated it would be at home in a Star Wars movie. Called BrainSuite iCT, it's the most accurate surgical visualization system available. "In a word, it's *phenomenal*," says neurosurgeon **Ali Bydon**, who's had ample time to befriend it.

Newly installed at Johns Hopkins Bayview Medical Center, iCT offers Hopkins neurosurgeons the benefits of versatile, precise, on-site imaging and navigation. Having both available during surgery dispels the traditional cloud of uncertainty that descends when patient anatomy or internal tissue relationships shift during brain or spine surgery.

"An iCT scan before the patient leaves the OR allows you to

confirm the adequacy of your job, to see how well nerve roots or the spinal cord are decompressed, for example," says Bydon, a specialist in spinal reconstruction. The bone-to-tissue contrast is so high that you can easily check that pedicle screw placement is away from nerves, he adds. If a brain tumor's not removed completely, if clots or small areas of a calcified disc remain, you know it right away.

In short, it shrinks that perennial problem in neurosurgery, having to take patients back to the operating room. "The system reduces the take-back rate almost to zero," says Bydon. And that obviously lowers infection risk.

Equally impressive is the accurate navigation it brings to surgery. The new software is able to integrate patient brain or spine images taken beforehand by CT, MRI or PET with those

made later, during the operation. During surgery, the CT scanner and accompanying touch screen instrument panel—they're housed in a wall common to two operating rooms—roll out on a floor-based track. Patients stay *in situ*, not needing to be moved, much less wheeled to a distant imaging suite. The whole process typically takes two minutes.

What's displayed in the OR—on a wall-mounted screen that's like a very large iPod where images are whisked open, closed or enlarged with a touch—is a clear, accurate, anatomical roadmap, Bydon says. "The iCT is like the global positioning system in a car. It eliminates the need to stop and ask for directions." ■

For information: 410-614-6996

For information: 410-550-0939

A New Take on Cushing's Idea

In 1911, a middle-aged man walked into Hopkins because his GP thought that neurosurgeon Harvey Cushing might be his best hope. The patient had signs of a pituitary tumor and lost pituitary abilities: the headaches, the halved visual fields, increased thirst, urine, and a deep hunger for sleep.

Cushing—celebrated even then—offered him the most advanced treatment of the day, surgically relieving the man's intracranial pressure and injecting him with ground whole pituitary gland. The patient rallied but couldn't tolerate the injections. That prompted Cushing's drastic step: he twice transplanted a fetal pituitary gland into the patient's *cortex*, hoping it would take root.

Today, a century later, neurosurgeon **Alfredo Quiñones-Hinojosa** also carries out pituitary surgeries at Hopkins. His approach is often the endonasal and transphenoidal one Cushing used, but “the procedure, overall, is a far cry from the old outcomes here,” he says, when 25 percent of patients died in pituitary surgery. Because pituitary tumors are so common—in perhaps 10 percent of the population—Quiñones-Hinojosa's surgical skill and that of Hopkins colleagues is well-honed. They see some 100 patients a year in the OR. It's that, along with MRI navigation, neuroendoscopy and other



New stem cell work, says neurosurgeon Alfredo Quiñones-Hinojosa, channels pioneer Harvey Cushing.

advances that has whittled the mortality figures.

Still, what Cushing tried to do with his implants has never left Quiñones-Hinojosa's mind. “I began thinking about it when I was a resident,” he says. Having healthy implanted cells in the brain to replace its missing growth hormone, for example—especially in the setting of a patient's own internal

feedback loops and time tables—would clearly rule.

To that end, Quiñones-Hinojosa heads a team of neuroscientists and cell biologists to advance what looks increasingly possible. Their hope, unlike Cushing's, lies in stem cells.

No one has isolated the “pituitary stem cell” that could, in theory, regenerate the whole gland or its chosen parts, though most say it probably exists. But the Hopkins team believes, meanwhile, there's much to learn from a subgroup of “brain tumor stem cells” that they tease from the noncancerous pituitary adenomas that Quiñones-Hinojosa resects in the OR. Put in the right medium, he says, the cells differentiate to produce the various hormones.

Though “regenerative medicine” for pituitary illness is some time away, other benefits of studying the stem cell cultures may be closer. “There's a potential to discover what lets the adenomas keep dividing,” he says. “Our immediate hope is to find a simple way to reregulate that abnormal growth.” ■

Information: The Pituitary Center at Johns Hopkins 410-955-4526

Pituitary Pathology, Subtle to Obvious

“Not all pituitary tumors are visible by imaging, even with MRI,” explains endocrinologist **Roberto Salvatori**, with the Pituitary Center at Johns Hopkins.

Diagnosis, then, can depend on being adept at interpreting motley signs—often subtle ones that cross multiple systems. A rise in body fat, a drop in muscle mass and raised total cholesterol, for example, might not be picked up as a pituitary matter. But as a specialist, Salvatori is alert to the ways a wash of growth hormone signals a somatotrophic adenoma in an adult patient.

The Pituitary Center maintains a staff of 16 clinicians who excel in delivering highly specialized, patient-specific care for pituitary pathology. Patients are triaged by one of two endocrinologists and nurse coordinator **Rita Pach**, who arranges single-day visits. Pach also sets up as-needed appointments with the center's neurosurgeons, neuroophthalmologists, otolaryngologist or specialized radiation oncologist.

The clinicians are quick to work with a patient's referring physicians—from gynecologists to dentists—who have found the suspected “incidentalomas,” as Salvatori calls them, or confirmed the tumors that then send patients to Hopkins.

The center also has a reputation for its extended follow-up care.

For information: 410-955-4526

NeuroLogic

Johns Hopkins Medicine
901 S. Bond Street/Suite 550
Baltimore, Maryland 21231

This newsletter is published for the Departments of Neurology and Neurosurgery by Johns Hopkins Medicine Marketing and Communications.

Departments of Neurology and Neurosurgery

Justin McArthur, *Director of Neurology*
Henry Brem, *Harvey Cushing Professor and Director of Neurosurgery*

Marketing and Communications

Dalal Haldeman, Ph.D., M.B.A., *vice president*
Marjorie Centofanti, *managing editor, writer*
Melissa Hendricks, *writer*
Max Boam, *designer*
Mary Ann Ayd, *copy editor*
Keith Weller, *photographer*

With questions or comments, contact:
mcentofanti@jhmi.edu or 410-955-8725

© 2010 The Johns Hopkins University and
The Johns Hopkins Health System Corporation.

WWW.HOPKINSMEDICINE.ORG/NEURO

Non-Profit Org
U.S. Postage
PAID
Permit No. 5415
Baltimore, MD