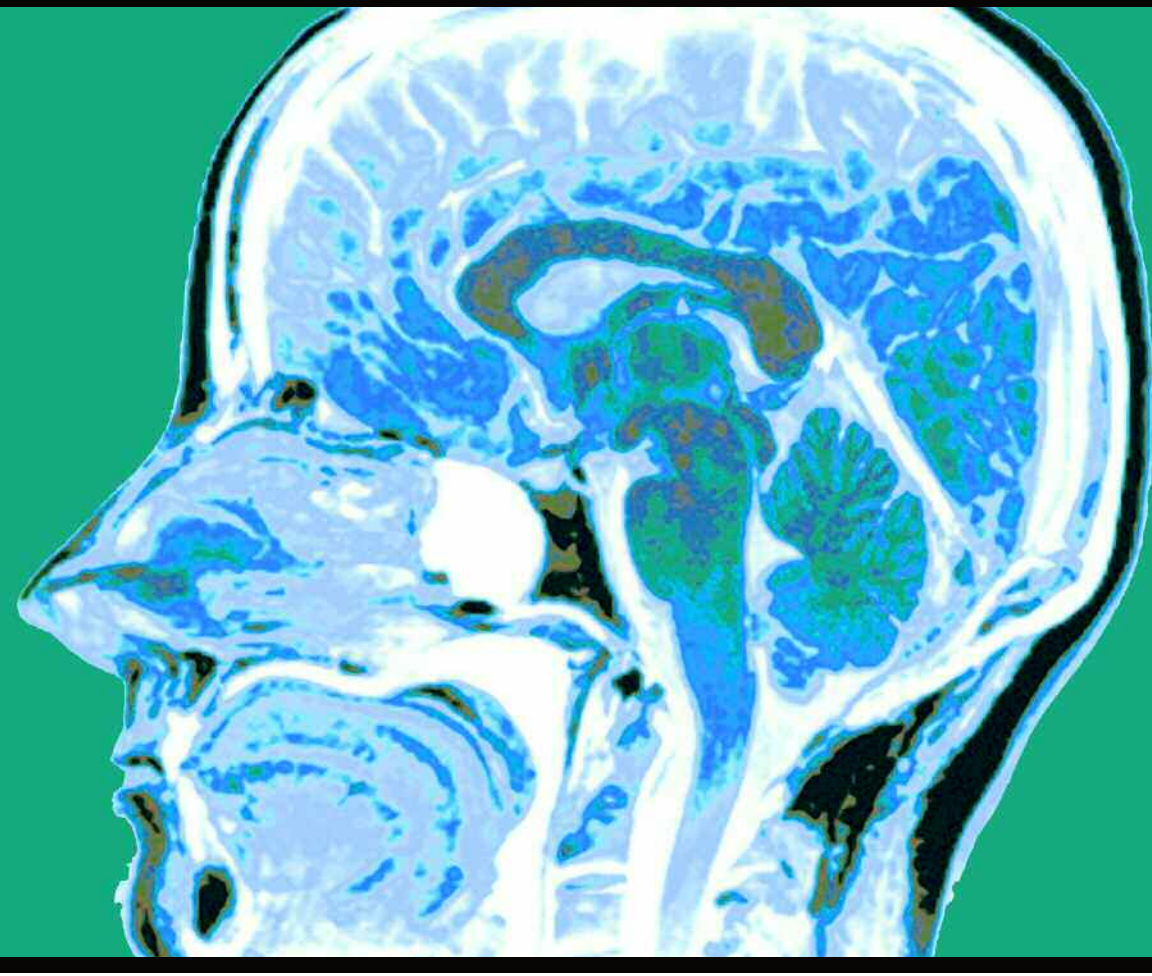
INNOVATIONS | 2008 EDITION



Neurology and Neurosurgery

JOHNS HOPKINS MEDICINE

JOHNS HOPKINS
MEDICINE

Mission

The mission of Johns Hopkins Medicine is to improve the health of the community and the world by setting the standard of excellence in medical education, research and clinical care. Diverse and inclusive, Johns Hopkins Medicine educates medical students, scientists, health care professionals and the public; conducts biomedical research; and provides patient-centered medicine to prevent, diagnose and treat human illness.

Vision

Johns Hopkins Medicine provides a diverse and inclusive environment that fosters intellectual discovery, creates and transmits innovative knowledge, improves human health, and provides medical leadership to the world.

Core Values

Excellence & Discovery
Leadership & Integrity
Diversity & Inclusion
Respect & Collegiality

Table of Contents

NEUROLGY AND NEUROSURGERY

Department Overview 4

Demonstrating Clinical Innovation and New Discoveries 11

Patient Safety and Quality Measures 40

The Patient Experience 48

Our Faculty 55

How to Refer a Patient 58

Locations 58

Referral Assistance 59

Johns Hopkins Medicine Overview 61

Neurology and Neurosurgery

Dear Colleague:

JUSTIN MCARTHUR, M.B.B.S., M.P.H.

HENRY BREM, M.D.

Every aspect of our professional life at Johns Hopkins is devoted to patient care. Both our clinical work and our research are designed to clarify conditions and diseases to develop enhanced treatments for our patients.

We are pleased to share with you a glimpse into our ongoing efforts, innovations and discoveries on the journey to superior patient care. Inside, you'll find some of our latest research that is helping to translate into better patient outcomes, innovations that bring treatments to a new level and steps we're taking every day to improve quality, outcomes and patient safety.

Each patient we care for remains our first priority. When you refer to us, you've placed tremendous confidence and trust in us, and we'll work with you to ensure the best possible results.

Finally, we are committed to excellence in everything we do. This book is part of an ongoing initiative to relay information about activities in our departments, report on innovations and discoveries in the field of neurology and neurosurgery, and enhance patients' access and experience. We are looking forward to continuing this important initiative.

Warm regards,

Justin McArthur, M.B.B.S., M.P.H.
Director (interim)
Department of Neurology
Professor of Neurology, Pathology and Epidemiology

Henry Brem, M.D.
Director
Department of Neurosurgery
Harvey Cushing Professor of Neurosurgery Oncology and Ophthalmology

You may refer a patient to any member of our faculty by calling 410-955-9441 (Neurology) or 410-955-2248 (Neurosurgery) or e-mail us at neuroaccess@jhmi.edu.

For urgent referrals or consultation, call the Hopkins Access Line (HAL) at 1-800-765-5447.

For more information about Johns Hopkins Neurology and Neurosurgery, visit our Web site at www.hopkinsneuro.org.

Overview of Neurology and Neurosurgery at Johns Hopkins

Opened in 1889, The Johns Hopkins Hospital is not a particularly old institution, but it has what might be called a very long history. It was here in the early 1900s that Harvey Cushing, "the father of neurosurgery," performed the first successful operations for brain tumors; here, in 1937, that Walter Dandy performed the first aneurysm clipping.

Our team quickly emerged as leaders with research on how the brain reacts to injury and with innovations like the use of X-rays to guide brain surgery. The field of neurocritical care was brought to life at The Johns Hopkins Hospital. Here, our neurologists, anesthesiologists and neurosurgeons pioneered one of the first dedicated neurological critical care units in the nation.

Since that time, we are pleased that our program is consistently recognized by peers around the country and ranked among the best for both pediatric and adult neurology and neurosurgery by *U.S. News & World Report.*

One of our goals is to develop the next generation of leaders in neurology and neurosurgery. Our clinical training programs—unique in their depth in areas like neuroimmunology, acute-care neurology, spine, vascular, tumors and cognitive neuroscience—guide our residents and fellows as they build an academic career.

Our faculty, strengthened by our tradition of sharing ideas across disciplines and melding laboratory-based and clinical research, can offer patients new and exceptional diagnostic capabilities and therapies.

For brain tumor patients, for example, they can choose from not only standard treatments, but also novel ways to deliver radiation, chemotherapy, vaccines and gene therapy. All patients are assessed by expert teams that cross multi-specialties. Our patients have access to the best current therapies as well as to clinical trials that bring the newest experimental treatments to those who need them most.

2008 Highlights

In this booklet, we've showcased some of our recent clinical innovations, discoveries, and safety and quality measures. We've also included sections that illustrate the patient experience at Johns Hopkins. Published research is listed throughout. Here are some of the clinical and research highlights for 2008:

- Centers of excellence for encephalitis (*page 47*), adult hydrocephalus (*page 25*) and pituitary tumors (*page 17*).
- New cancer treatment delivery methods for brain and spinal tumors (*page 27*).
- Novel techniques in cerebrovascular neurosurgery (*page 12*).
- The role of stem cells in brain tumors (*page 34*).
- Repairing injured peripheral nerves (*page 48*).
- Genetic targets for tumor therapy (*page 30*).
- Measuring the onset of Alzheimer's disease (*page 36*).

Safety and Quality Measures

Protocols for briefing and debriefing in each OR case, for reducing surgical site infections and for assuring optimal stroke outcomes—these are examples of the initiatives we've undertaken. Our electronic medical record and provider order entry enhance patient safety. Our nursing staff is specially trained and specialty certified to ensure the best management and patient outcomes. Some of the safety and quality initiatives we highlight in this booklet are:

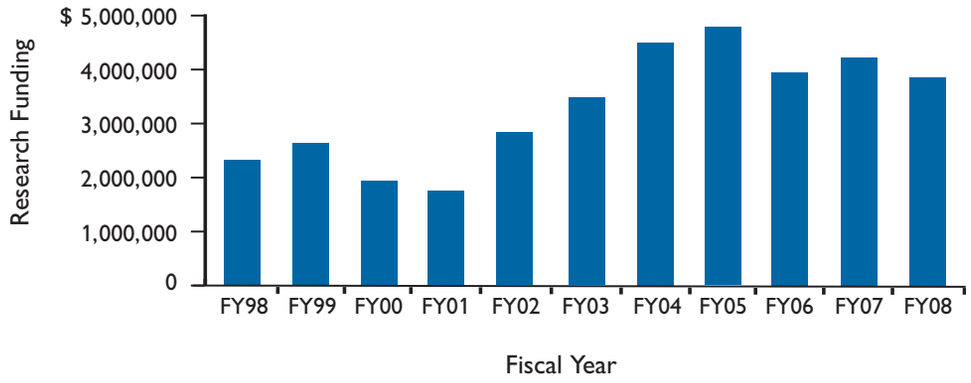
- Reducing infection rates in pediatric hydrocephalus (*page 40*).
- Diagnosing encephalitis (*page 47*).

Research

In the past decade, we have seen our funding from the National Institutes of Health as well as from other private sources double. Our young investigators are pursuing novel science. Many are engaged in entrepreneurial, privately sponsored research initiatives.

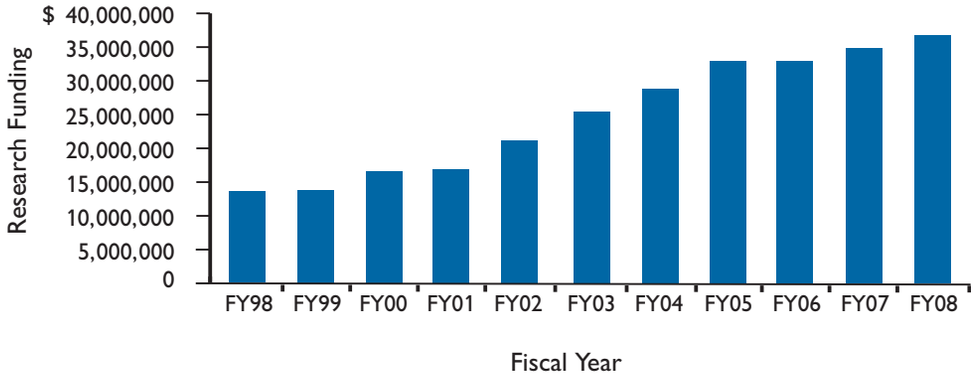
Department of Neurosurgery

Sponsored Project Revenue



Department of Neurology

Sponsored Project Revenue

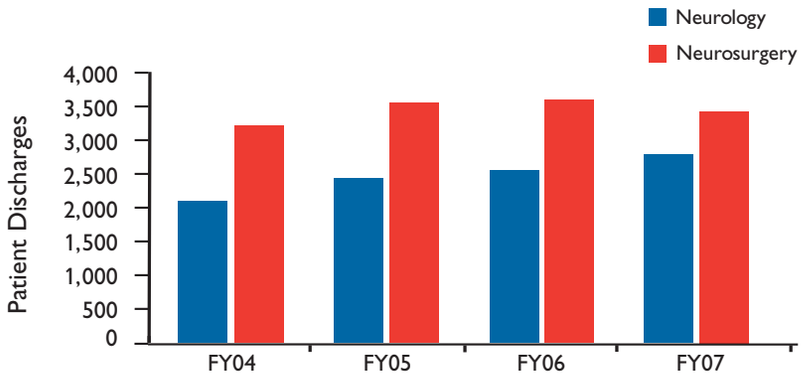


Experience and Outcomes

Neurology and Neurosurgery work together to diagnose and treat the full range of adult and pediatric neurological diseases. Each year we provide more than 30,000 outpatient consultations, admit approximately 5,000 inpatients, and perform over 4,000 brain tumor, vascular, spine and pediatric neurosurgery operations. Our NCCU remains one of the most comprehensive in the country; our two certified stroke units have some of the lowest stroke mortality rates in the nation, while our patients often have an extremely complex mix of medical problems underlying their neurological diseases.

Total Inpatient Discharges

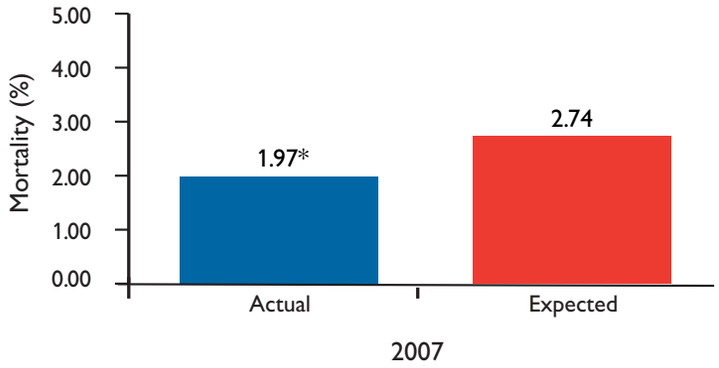
(includes The Johns Hopkins Hospital and The Johns Hopkins Bayview Medical Center)



Our mortality rates are between .77 and 2.47 percent lower than expected mortality rate for neurology and neurosurgery patients treated at comparable academic medical centers.

Mortality Rates – Neurology

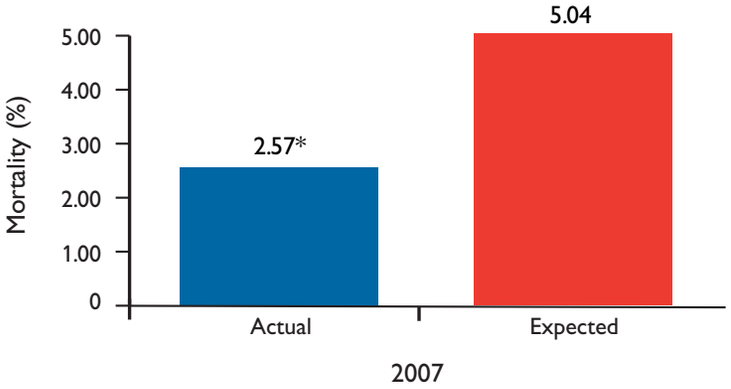
Source: University HealthSystem Consortium



In 2007, The Johns Hopkins Hospital recorded a 1.97 percent mortality rate for all neurology inpatient discharges, which is .77 percentage points lower than the expected mortality rate for neurology inpatients treated at an academic medical center. *Significant difference from expected at .05 level of significance.

Mortality Rates – Neurosurgery

Source: University HealthSystem Consortium



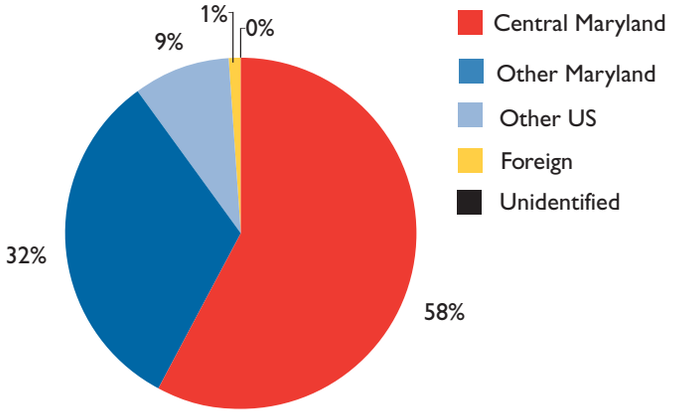
In 2007, The Johns Hopkins Hospital recorded a 2.57 percent mortality rate for all neurosurgery inpatient discharges, which is 2.47 percentage points lower than the expected mortality rate for neurosurgery inpatients treated at an academic medical center. *Significant difference from expected at .01 level of significance.

Patient Origin

While many of our patients are from our local community, others comes from all over the world for treatment. Last year, about half of our neurology and neurosurgery adult inpatients were from outside of the Baltimore region and Maryland.

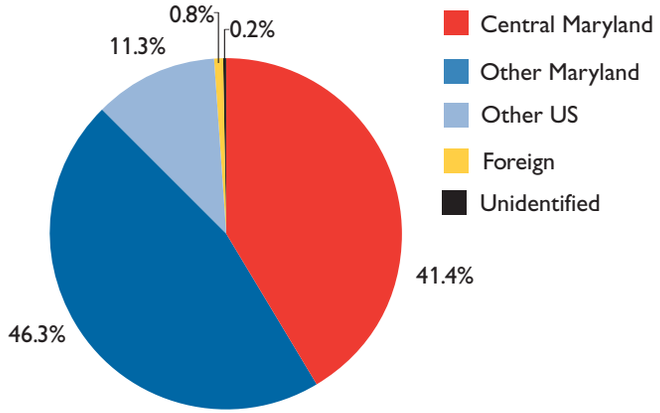
Adult Neurology Patient Origin

FY2007



Adult Neurosurgery Patient Origin

FY2007

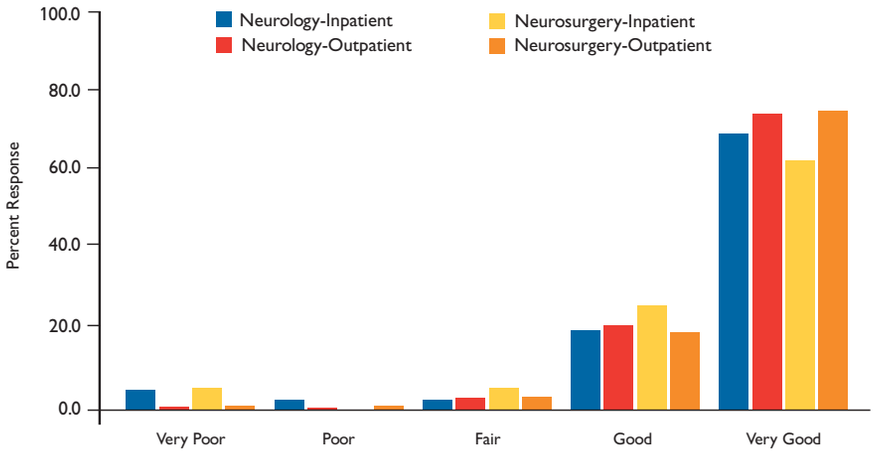


Patient Satisfaction

In our efforts to provide our patients with the best treatment and care, we continually solicit patient feedback and use this infomation to help improve the patient experience. Results from our most recent patient satisfaction surveys, July 2007 to May 2008, indicate that the majority of patients would recommend the practice and feel the quality of care is good or very good.

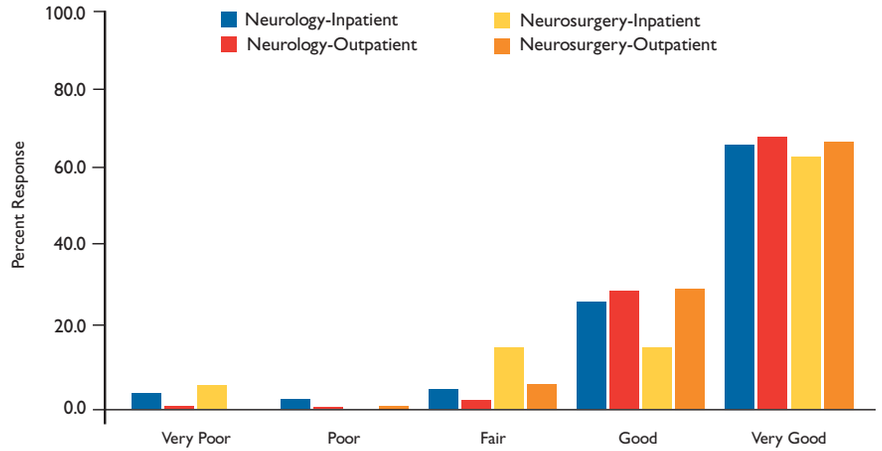
Likelihood to Recommend Practice

July 2007 – May 2008



Overall Quality of Care

July 2007 – May 2008



Demonstrating Clinical Innovation and Moving Discovery Forward

Learn on the following pages how we are breaking new ground in patient care.

Demonstrating Clinical Innovation

- Aneurysm Expertise
- A Surgical Approach to the Odontoid
- Managing Pituitary Tumors: It Takes a Team
- Reversing the Blindness of Central Retinal Artery Occlusion
- Skin Punch Biopsy to Assess Neuropathy and Nerve Regneration
- Dietary Therapy for Seizures
- Attacking Adult Hydrocephalus

Moving Discovery Forward

- A Promising Treatment for Brain and Spinal Tumors
- Probing Genetic Changes for New Brain Tumor Treatments
- The Role of Stem Cells in Brain Tumors
- Who Will Develop Alzheimer's Disease? What Drugs Will Help?
- Stem Cells that Undo Nerve Damage
- Nanofibers with Protein Regenerate Damaged Nerves

Demonstrating Clinical Innovation

Aneurysm Expertise

Johns Hopkins cerebrovascular surgeons approach brain surgery much like a chess team approaches a tournament: *with a strategy to win.* "We incorporate innovative solutions to treating aneurysms and other conditions and end up with excellent outcomes," says **Rafael Tamargo**.

Tamargo, head of cerebrovascular neurosurgery, has built one of the largest centers for aneurysm treatment in the United States. His team treats about 170 aneurysms a year, both surgically and endovascularly. Volumes like those are exceptional for a state like Maryland. "There is only one hospital in the entire state of New York that treats more than 100 aneurysm cases a year, and New York has a far greater population than Maryland," Tamargo says.

"At Hopkins, a team of neurosurgeons, neurologists and neuroradiologists evaluates every case to determine the best way to treat patients," Tamargo says. This is one of a handful of centers in which giant and complex aneurysms are repaired under hypothermic cardiopulmonary bypass. Cardiac surgeons lower the body temperature, stop the heart and halt the flow of blood to the brain for up to 45 minutes. With the blood flow reduced, the aneurysm softens, buying time for neurosurgeons time to map out a plan for clipping the aneurysm.

Twenty percent of aneurysm patients have multiple aneurysms, often on opposite sides of the brain. Traditionally, surgeons perform two separate operations, one for each side of the brain. Tamargo is among a handful of surgeons worldwide to use a one-surgery, contralateral approach. He first clips the aneurysm on one side. Then, through the same opening, he dissects a safe pathway to the other side of the brain and reaches the other aneurysm sites.

Another innovation helps avoid hydrocephalus, a major complication of aneurysm surgery. This build-up of fluid usually requires implanting a shunt—and a second surgery. Hopkins neurosurgeons have shown that making an opening in the lamina terminalis reduces the incidence of hydrocephalus from 15 percent to less than 2 percent in patients with aneurysmal subarachnoid hemorrhage.

In a recent discovery, published in December 2007, our neurosurgeons found that some people may be genetically predisposed to developing vasospasm, or the narrowing of vessels after hemorrhage. With these insights, Tamargo says, doctors will be better equipped to avoid vasospasm in those at risk.

Finally, Hopkins is one of a few centers nationwide to treat cerebrovascular insufficiency from intracranial disease, which can lead to stroke. To increase blood supply to the brain, our neurosurgeons connect an artery that typically supplies blood to the scalp to an artery in the brain.

RESEARCH PUBLISHED:

Chaichana K, Levy A, Miller-Lotan R, Shakur S, Tamargo R. Haptoglobin 2-2 genotype determines chronic vasospasm after experimental subarachnoid hemorrhage. *Stroke.* 2007 Dec;38(12):3266-71.

Huang J, McGirt M, Gailloud P, Tamargo R. Intracranial aneurysms in the pediatric population: case series and literature review. *Surgical Neurology* 2005;63:424.

Tuffiash E, Tamargo R, Hillis A. Craniotomy for treatment of unruptured aneurysms is not associated with long-term cognitive dysfunction. *Stroke* 2003;34:2195.

Komotar R, Olivi A, Rigamonti D, Tamargo R. Microsurgical fenestration of the lamina terminalis reduces the incidence of shunt-dependent hydrocephalus after aneurysmal subarachnoid hemorrhage. *Neurosurgery* 2002;51:1403.

Chiang V, Gailloud P, Murphy K, Rigamonti D, Tamargo R. Routine intraoperative angiography during aneurysm surgery. *Journal of Neurosurgery* 2002;96:988.

Oshiro E, Rini D, Tamargo R. Contralateral approaches to bilateral cerebral aneurysms: a microsurgical anatomical study. *Journal of Neurosurgery* 1997;87:163.

Miller N, Monsein L, Debrun G, Tamargo R, Nauta H. Treatment of carotid-cavernous sinus fistulas using a superior ophthalmic vein approach. *Journal of Neurosurgery* 1995;83:838.

A Surgical Approach to the Odontoid

A minimally invasive surgical approach developed by a Johns Hopkins neurosurgeon has been shown to safely allow access for resection of the odontoid and decompression of the brain stem and spinal cord in patients with a rare condition known as basilar invagination. Compared to traditional approaches, it may also reduce the risks of complication and infection.

Basilar invagination occurs when the odontoid, the second vertebra of the neck, migrates upward through the opening in the skull where the spinal cord joins the brain stem, putting pressure on the spinal cord or the brain stem. The condition can cause difficulty swallowing or speaking, headache, muscle weakness, numbness in the neck or hands, and in extreme cases, sudden death. It may be congenital or develop in those with bone diseases such as rheumatoid arthritis. It can also be caused by injuries from vehicular accidents or falls.

The standard operation to correct basilar invagination is complex because gaining access to the site is so difficult. Traditional methods require traversing the oral cavity. This approach, though, offers a limited operative view and requires an intimate understanding of oral and pharyngeal anatomy. Other methods may increase morbidity rates during the operation, as well as postoperative complications, infections and scarring.

Jean-Paul Wolinsky, assistant professor of neurosurgery, has developed an endoscopic transcervical odontoidectomy, an alternative to traditional techniques that use a transoral or a transmandibular/transoral approach.

Image courtesy of the Journal of Neurosurgery.

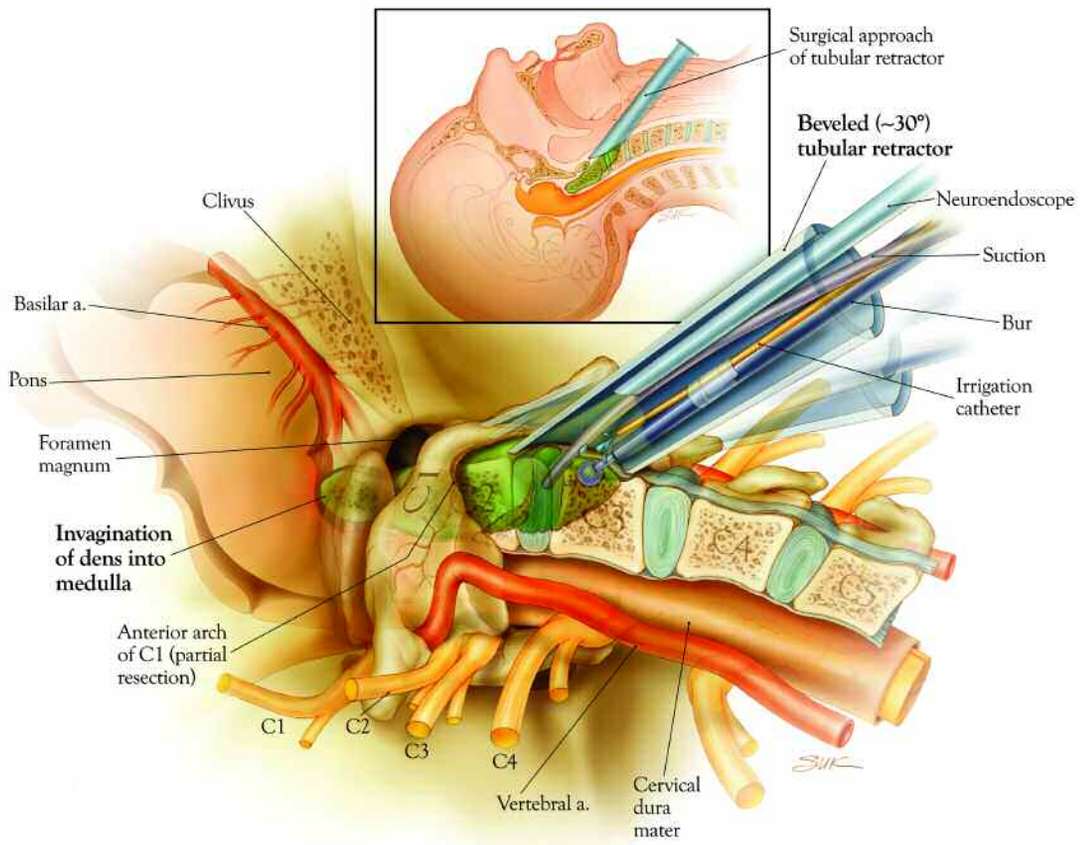


Figure 1: Artist's rendition showing the tubular retractor placed against the anterior cervical spine acting as a working channel for instruments and endoscope. The inset shows the orientation of the patient in the operating room. (a = artery)

"The image-guided endoscopic transcervical odontoidectomy has many advantages over the conventional techniques. Most importantly it allows surgeons to avoid traversing the oral cavity," says Wolinsky. It also gives surgeons a better angle of view. For patients, it reduces the need for prolonged intubation and tube feeding, causes less postoperative pain and produces better cosmetic results. In addition, there's a decreased risk for infections and other complications because recovery time is shorter.

Wolinsky and his team worked out the approach based on their experience with the placement of odontoid screws and with other skull-base procedures and endoscopic neurosurgery. They created a table-mounted tubular retractor system that is inserted while the patient is supine with the neck gently extended (see Figure 1). After performing several feasibility studies on foam models and then on cadavers, the team used the method in patients. Ten patients (including four children) have had the procedure so far; all experienced complete decompression with no serious complications.

Says Wolinsky, "The technique is safe and effective and opens up a new surgical route for this complex surgery."

RESEARCH PUBLISHED:

Wolinsky JP, Sciubba DM, Suk I, Gokaslan ZL. Endoscopic image-guided odontoidectomy for decompression of basilar invagination via a standard anterior cervical approach. Technical note. *Journal of Neurosurgery: Spine* 2007;6:184.

Managing Pituitary Tumors: It Takes a Team

It may be no bigger than a pea, but the tiny pituitary has a tall order to fill. From its lofty position deep within the skull, this master gland oversees most of the body's other endocrine glands, regulating and controlling the secretion of hormones they produce.

Pituitary tumors, though usually benign, can wreak real havoc. They can bring on conditions like gigantism or acromegaly, hypothyroidism and Cushing syndrome. Even tumors that don't produce hormones, or nonfunctioning tumors, can cause headaches, nausea and vision problems as they grow and interfere with neighboring structures in the brain. Not surprisingly, making the differential diagnosis is difficult.

"Because these tumors affect so many different areas, we developed the Johns Hopkins Pituitary Tumor Center. Now patients have in one place all the resources they need for successful treatment," says neurosurgeon **Henry Brem**, who works closely with Roberto Salvatori, center director.

Henry Brem (seated) confers with endocrinologist Roberto Salvatori.

The Pituitary Tumor Center is managed by a team of neurosurgeons, endocrinologists, neuro-ophthalmologists, neuroradiologists, radiation therapists and specialized nurses. Treatments, tailored to tumor type and size as well as the patient's age and overall health, include medical management, radiotherapy and surgery. Whatever the approach, the goal is to normalize hormonal secretion and halt the progression of neurological defects and other symptoms.

For many patients, hormone replacement therapy may control tumor growth. For those who need surgery, the center offers a combination of microsurgery and endoscopic surgery. Brem and his colleagues have refined the transsphenoidal approach with intraoperative MRI and computer navigation, techniques that make it possible to monitor progress throughout the intricate operation. A direct endonasal approach, versus the conventional sublabial approach, allows the mass to be removed via an incision in the lining of the nose.

Multiple radiation options are available, including Gamma Knife. Treatments are individually tailored to each patient.

The Pituitary Tumor Center team also collaborates with Hopkins researchers who are studying ways to control excessive hormone secretion and shrink tumors. Collaborative efforts like these, says Brem, are already improving patient outcomes.

Reversing the Blindness of Central Retinal Artery Occlusion

It is sudden, painless and profound. And loss of vision in one eye—essentially a "stroke" of the eye or central retinal artery occlusion—is of special interest to stroke specialist **Eric Aldrich**.

The neurologist and his team are perfecting a technique to improve visual acuity following CRAO. Building on research by physicians in Europe, Aldrich and neuro-ophthalmologist **Neil Miller**, reviewing a series of Hopkins cases from 2000 to 2007, found that 42 patients who had intra-arterial thrombolysis using small amounts of the clot-busting tPA had better results than standard therapy.

The European trial used continuous infusion—a microcatheter was placed in the neck for up to an hour to deliver the tPA. The Hopkins technique involves using the microcatheter to deliver a slow injection by hand over two minutes, removing the catheter for five to 10 minutes, and then repeating the slow injection. Aldrich attributes much of the technique's success to interventional neuroradiologists

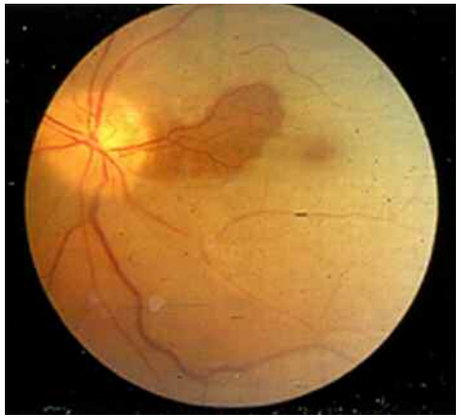
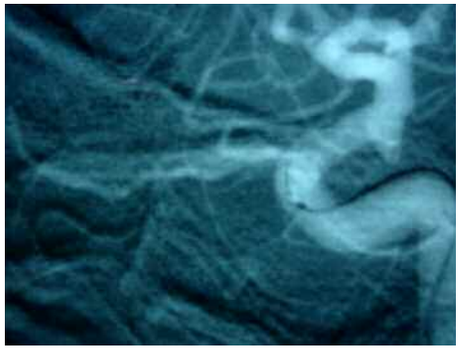


Image courtesy of New England Retina Associates (www.retinamd.com).

Normal retina orange-red in appearance (full of blood); with CRAO, pale white (absence of blood)



Angiogram image of catheter in ophthalmic artery

Phillipe Gailloud was able to insert a 1 millimeter catheter into a 1 millimeter artery during a cerebral angiogram and guide it to within a half-inch of the clot.

Minimizing the time the catheter sits in place reduces the risk of stroke, Aldrich says. "We've improved the technique and replicated the European results." Those results showed that 76.4 percent of patients who received tPA treatment improved in visual acuity versus 33 percent who received standard therapy alone.

Standard therapy involves paracentesis, or inserting a needle in the eye to withdraw fluid and decrease pressure so that the clot moves away from the retina. Patients also inhale carbogen, a mixture of oxygen and carbon dioxide, to dilate the arteries and force the clot to shift. "Those treatments are rarely curative," Adrich says, "and nothing new has been explored until now."

At follow-up, one-third of the patients in the Hopkins study who received the tPA treatment improved by three lines or more on the Snellen chart versus only 4.8 percent in the control group. "Statistically, you are 13 times more likely to have a three-line improvement in visual acuity—a substantial jump in vision—if you receive this treatment," says Aldrich.

FDA guidelines state that the sooner tPA is administered, the better the results. During a stroke, the window of opportunity is three hours. For artery occlusion, Aldrich has found, it is 15 hours.

A phase II trial is planned.

IN PRESS:

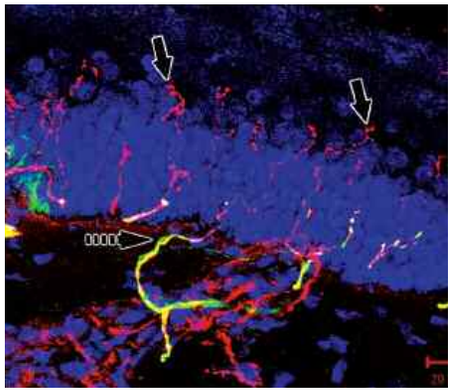
Aldrich E, Lee A, Chen C, Gottesman R, Bahouth M, Gailloud P, Murphy K, Wityk R, Miller N. Local intra-arterial fibrinolysis administered in aliquots for the treatment of central retinal artery occlusion: The Johns Hopkins Hospital Experience. *Stroke* 2008; June 39 (6):1746-50. Epub 2008 Apr.17

Skin Punch Biopsy to Assess Neuropathy and Nerve Regeneration

In 1995, a skin punch biopsy developed by Hopkins neurologists became clinically available to assess the early onset of neuropathies. Since then, our neurologists have evaluated more than 17,000 biopsy specimens from around the country. To meet the demand, they created the Johns Hopkins Cutaneous Nerve Lab and trained physicians at five other facilities around the country to also evaluate these biopsies.

Skin punch biopsy allows physicians to measure the loss of the small sensory nerve fibers that supply the skin's surface and conduct information about pain and temperature. "It helps us quantify the severity of a neuropathy," says **Justin McArthur**, co-director of the cutaneous nerve lab and co-developer of the minimally invasive technique. The biopsy is useful in making the differential diagnosis.

Previous methods of evaluating neuropathies tested damage only to the large-fiber nerves. They could be invasive, requiring excision of larger nerves in the leg. Skin punch biopsy is minimally invasive, sensitive to minor nerve changes, and can be easily repeated.



Double-stained confocal images of the panaxonal marker protein gene product 9.5 with the schwann cell marker p75 in cutaneous nerves in human controls. PGP 9.5-stained epidermal nerve fibers (arrows) (red) extend into the epidermis but schwann cells (broken arrow) stop at the junction between epidermis and dermis.

McArthur and colleague **Michael Polydefkis**, co-director of the nerve lab, are also using the biopsies to follow changes in nerve fiber densities in clinical trials testing promising neuroregenerative and neuroprotective agents. They are involved in several trials focusing on diabetic neuropathy, HIV

neuropathy (an NIH-funded trial) and chemotherapy neuropathy.

In addition, Polydefkis is researching nerve regeneration using a method he and his team developed in which they slightly damage nerve fibers in normal skin to watch how fast they grow back. They found that the chemical capsaicin—which causes a mild burning sensation and is safe and well-tolerated in humans—doesn't destroy nerve fibers but merely trims them away from the skin. The team can then measure the rate at which they regenerate.

This model is more accurate than others at determining the rate of nerve growth. "We're able to detect even miniscule improvement in nerve regeneration," says Polydefkis. The model also allows the team to compare nerve regrowth in healthy subjects with that in people with diabetes and prediabetes, and to determine whether a drug accelerates regrowth. Even diabetics who had no other signs or symptoms of neuropathy, had reduced rates of regeneration. This suggests that neuropathy-free subjects with diabetes could be included in trials of regenerative agents.

The skin punch biopsy model is an objective tool, Polydefkis says. Physicians read the biopsy by counting nerve fibers on a piece of tissue without knowing the status of the patient. He hopes the research will soon identify a drug to cure neuropathy. "We're continuing to refine the process, and as we move forward, skin punch biopsy will be a big part of our strategy."

RESEARCH PUBLISHED:

Gibbons CH, Griffin JW, Polydefkis M, Bonyhay I, Brown A, Hauer PE, McArthur JC. The utility of skin biopsy for prediction of progression in suspected small fiber neuropathy. *Neurology* 2006;66:256.

Lauria G, Cornblath DR, Johansson O, McArthur JC, Mellgren SI, Nolano M, Rosenberg N, Sommer C. EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy. *European Journal of Neurology* 2005;12:747.

Polydefkis M, Hauer P, Sheth S, Sirdofsky M, Griffin JW, McArthur JC. The time course of epidermal nerve fibre regeneration: studies in normal controls and in people with diabetes, with and without neuropathy. *Brain* 2004;127:1606.

Dietary Therapy for Seizures

Over the past 40 years, the John M. Freeman Pediatric Epilepsy Center has helped develop and promote the ketogenic diet, the high-fat, low-carbohydrate, adequate-protein regimen that controls seizures in at least half of the patients who fail drug treatments. The Johns Hopkins protocol for initiating and maintaining the diet is in use at centers around the world.

Now, Hopkins researchers have found that the ketogenic diet may be just as effective as medications in treating new-onset epilepsy—specifically, a rare form of epilepsy known as infantile spasms. "To our knowledge, this is the first described use of the ketogenic diet for the initial treatment of a specific childhood epilepsy syndrome," says **Eric Kossoff**, medical director of the Johns Hopkins Ketogenic Diet Program.

In a retrospective, case-cohort study, Kosoff and his group demonstrated that the diet was generally as effective as the standard medication, adrenocorticotrophic hormone (ACTH), with fewer side effects and seizure recurrences and a much lower cost. They are now designing prospective studies on the diet for new-onset infantile spasms as well as other causes of seizures.

With all its advantages, the ketogenic diet does have its drawbacks. It is restrictive and requires a major change in lifestyle that most adults are unwilling to accept. Moreover, scientists are still not sure exactly why the ketogenic diet works, says **Adam Hartman**, an assistant professor of neurology and pediatrics. They do know, however, that it mimics the effects of fasting and produces ketones, which may inhibit seizures and have other neuroprotective properties.

Hartman is researching the mechanisms of the diet and its potential benefits in other neurological illnesses. "By isolating the relevant mechanisms of its effects, we hope to optimize the diet as it is currently administered and identify other neurological indications that dietary

therapy may improve," he says. "We also hope to find a way to achieve similar effects more conveniently, in such a way that would not require the major lifestyle change that typically accompanies dietary therapy of any sort."

A pill form would be ideal, Kossoff and Hartman say. The modified Atkins diet, which was developed as a treatment for epilepsy in 2002 by Kossoff and other neurologists at Johns Hopkins, has recently been demonstrated to be therapeutic for both children and adults. This diet does not restrict calories, fluid or protein and can be started without a fast or first admitting the patient to the hospital.

Both Kossoff and Hartman agree: As further studies of this alternative diet for adults continue, the potential for the ketogenic diet is wide open.

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Attacking Adult Hydrocephalus

Weeks after Selvin Madow banged his head in an automobile accident, he thought he'd completely recovered. But every morning he awoke with a strange feeling of fullness in his head.

Madow was eventually diagnosed with adult hydrocephalus, or normal pressure hydrocephalus (NPH), the condition in which cerebrospinal fluid accumulates in the ventricles of the brain.

Hopkins neurosurgeon **Daniele Rigamonti** wanted to place a shunt to drain the fluid, but Madow resisted, believing he would improve with time. Finally, his wife implored him to do something about his peculiar gait, one of the chief symptoms of his disorder, and Madow had the shunt placed. Today, the retired Baltimore shoe manufacturer is back to normal.

At the Johns Hopkins Hydrocephalus Center many specialists work together to help patients like

Daniele Rigamonti checks the shunt Selvin Madow received after developing hydrocephalus resulting from a head injury.

Madow. People suspected of having NPH are evaluated in a single outpatient visit. Diagnosis is a challenge because two of NPH's three chief symptoms—gait problems and dementia (the third is urinary incontinence)—are also signs of diseases like Parkinson's and Alzheimer's disease.

Gait and vestibular specialist **David Solomon** and **Abhay Moghekar**, who specializes in cognitive disorders, have joined Rigamonti in the center. Together they offer the gold standard for a definitive evaluation for shunt surgery. Candidates are admitted to the hospital for a rigorous evaluation during which more than 300 milliliters of CSF is drained over a period of three days. The team applies quantitative assessments before, during and after the lumbar drainage to discover if shunt surgery would be beneficial.

"We're continuously working together to modify our protocol," Solomon says. "We review the accumulated experience from Johns Hopkins, and we incorporate best practices from published guidelines. We see more than 100 new patients a year, so we're able to truly test new hypotheses for treatment and diagnosis."

The three specialists see patients from all over the world and have added a program coordinator to help guide and educate patients about NPH. Patients who need complex and long-term management of nonfunctioning shunts are often referred to the center, Moghekar says.

"By refining diagnosis and treatment, we're selecting appropriate patients for surgery and helping a large number of elderly people who would otherwise go into a nursing home at a large cost to society," says Rigamonti.

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Moving Discovery Forward

A Promising Treatment for Brain and Spinal Tumors

A new therapy for treating brain and spinal tumors is being taken from the laboratory to the bedside. A drug delivery treatment system that has been shown to be safe and effective for brain tumors now also looks promising for metastatic spinal disease, which has not had many effective chemotherapy options to date, Hopkins physicians say.

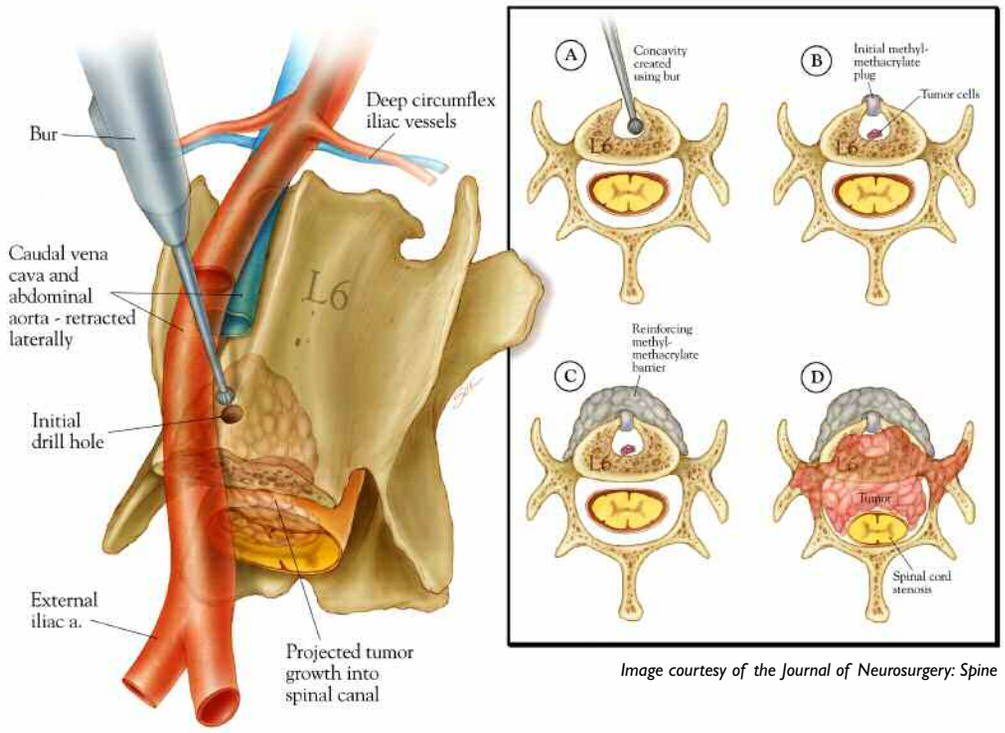

Image courtesy of the Journal of Neurosurgery: Spine

Artist's rendering of the landmarks for the L-6 vertebral body in rodent model. Inset: The drilling and sealing procedure: the concavity is created using the burr (A); the initial PMMA plug is inserted (B); the reinforcing PMMA barrier is applied (C); and as the tumor grows, it causes spinal cord compression (D). A = artery.

The OncoGel delivery system allows for the slow release of anticancer drugs over several weeks when it is injected directly into the tumor or into the tumor resection cavity. Biodegradable and thermosensitive, OncoGel is liquid when cool but forms a gel when body temperature warms it. The system can be tailored to deliver various agents at different rates, releasing drugs 3 to 5 centimeters from the initial injection spot. Since gliomas recur at or near the primary tumor site, placement of OncoGel into the tumor resection cavity may prevent or prolong time to tumor recurrence.

Henry Brem, director of neurosurgery, explains that new FDA-approved drugs for treating brain cancer and tumors are rare because it is so difficult to get drugs past the blood-brain barrier. In fact, the first FDA-approved drug in 20 years, the Gliadel wafer, was developed in Brem's lab. It delivers chemotherapy directly to the brain. It was approved by the FDA in 1994 and is now the standard therapy for malignant brain tumors all over the world.

Two years ago, Brem's lab started working with OncoGel. "With OncoGel, we can get through the blood-brain barrier to target the brain directly to enhance exposure to medication while minimizing side effects," he says. The data generated in the Brem lab has been reviewed by the FDA and is the scientific basis for an ongoing, multicenter phase I clinical trial. Several patients have been enrolled to date.

Hopkins researcher **Betty Tyler** says the investigators hope to mimic results found in rats that showed OncoGel combined with radiation therapy was more effective than either OncoGel or radiation therapy alone.

Ziya Gokaslan, director of the Hopkins Spine Division, is looking at OncoGel for treating metastatic spinal tumors and cancer, which affect thousands of people a year. Treatment options are minimal, and the outlook for those patients is not positive.

Gokaslan's team developed an animal model for metastatic spinal tumors. As with human spinal metastases, the tumors extended into the spinal canals, and the animals gradually developed weakness in their legs. The researchers then tested surgery, radiation therapy and local chemotherapy using OncoGel. Animals treated with radiation had significant delay in their time to paralysis. Those treated with OncoGel implantation achieved similar outcomes. A combination of the two treatments further prolonged time to paralysis and in some animals completely eradicated the tumor.

"Our researchers plan to use a similar strategy in patients with breast metastases to the spinal column," Gokaslan says. "They are applying for internal review board approval and hope to start human trials soon."

Gokaslan and his team have already introduced fundamentally new successful surgical treatments for spine cancers that have previously been thought of as inoperable.

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Probing Genetic Changes for New Brain Tumor Treatments

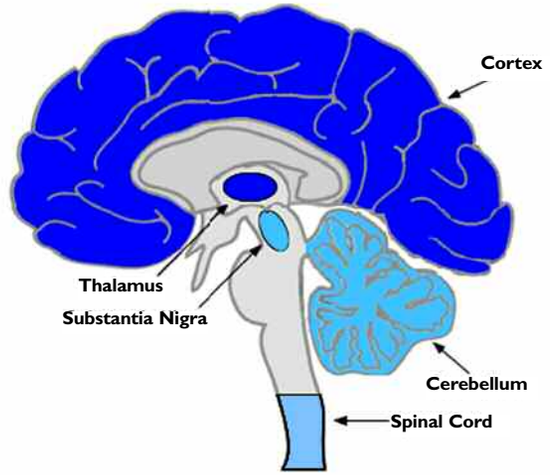
Approximately 44,000 new cases of primary brain and central nervous system tumors are reported each year in the United States; more than 13,000 people die of these cancers each year. In the Brain Cancer Biology and Therapy Research Laboratory, directed by **Gregory Riggins**, researchers are working to locate the genetic and genomic changes that occur in brain cancers. "Understanding these mutations and other molecular events can help us develop better treatments," Riggins says. "For example, we're looking at mutating proteins and changes in genetic DNA to discover what process changes a normal cell into a cancer cell. Those are our targets for therapy."

Researchers seek small molecules (biologically active substances or drug candidates) that can block the genes' actions to test as possible therapies. New drug candidates, Riggins says, have been identified and are under development.

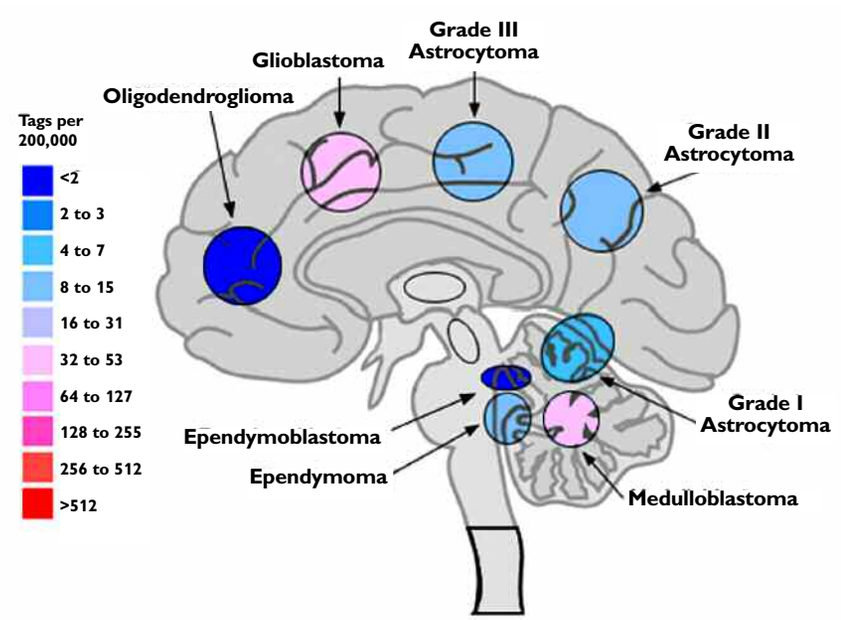
Neurosurgeon **Gary Gallia**, along with other full time brain tumor neurosurgeons, is working closely with Riggins to make these new therapies available to patients.

SAGE Brain Anatomic Viewer Results

The SAGE Genie anatomic viewer tool developed by Riggins' lab and the National Cancer Institute is a cancer research tool available on the Web used to determine what genes are expressed in cancer.



Normal



Cancer

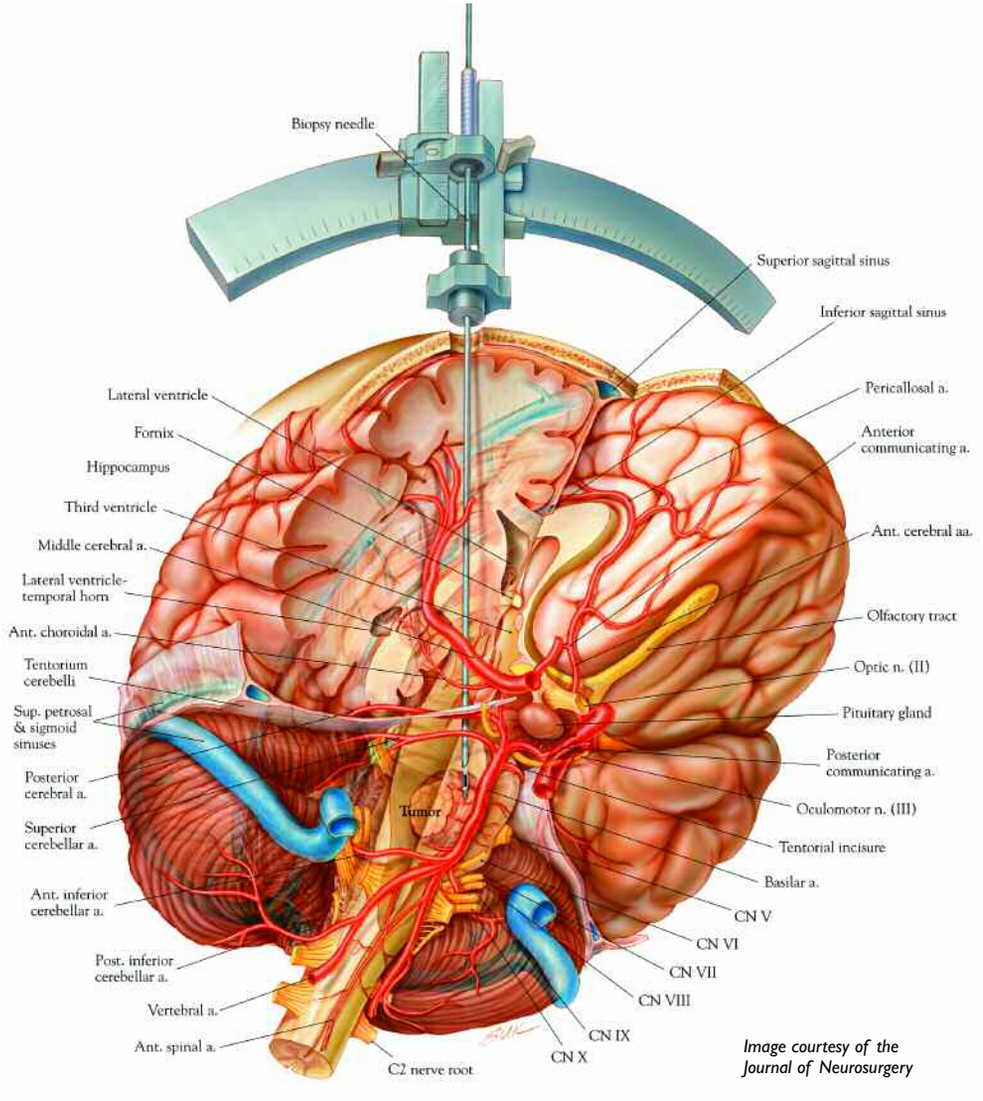
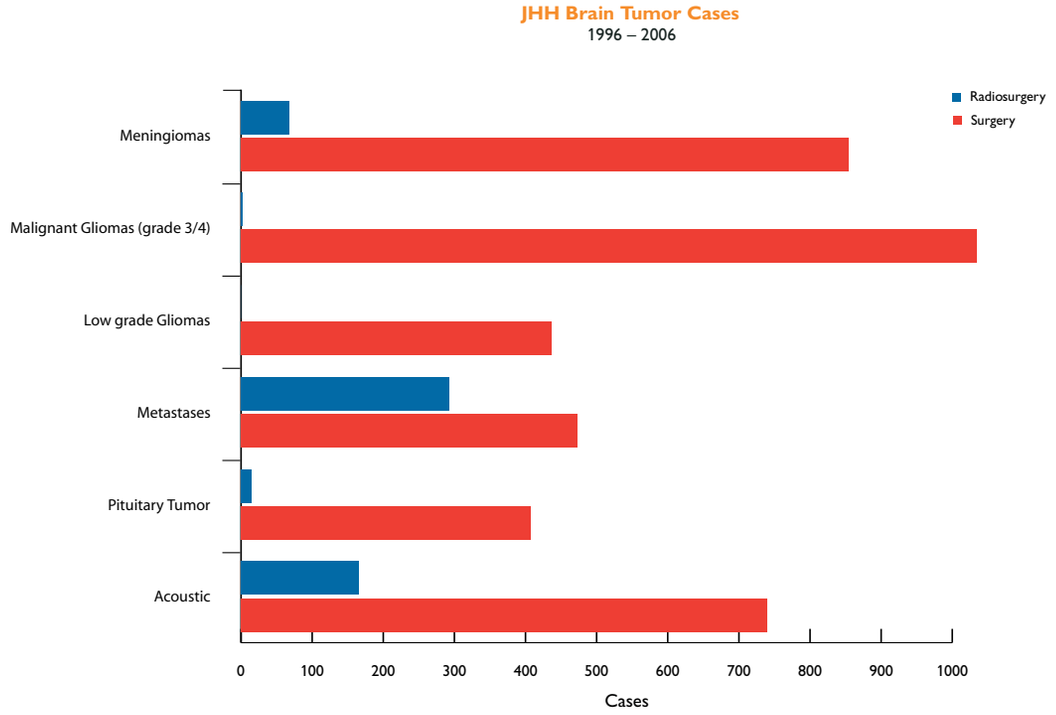


Image courtesy of the Journal of Neurosurgery



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The Role of Stem Cells in Brain Tumors

Using their knowledge of the properties of stem cells, investigators are searching for answers to some elemental mysteries about the human brain. How do cells migrate? What is the cell-of-origin for brain tumors? This work, says neurosurgeon **Alfredo Quiñones-Hinojosa**, aims to gain a new understanding of the brain's potential and its ability to regenerate or produce abnormal pathologies.

Research indicates that brain tumor stem cells may be derived from neural stem cells and that both of these cell populations may originate in an area of the brain known as the subventricular zone, or SVZ. The SVZ contains astrocytes, cells known to produce growth factors critical to the regeneration of damaged neural tissue. Astrocytes potentially serve as brain stem cells. Quiñones is now developing the first comprehensive map of the SVZ in the adult human brain.

Because human and animal SVZs are very different, Quiñones says, the challenge was to create a viable model. Thanks to a method his lab developed, human tumor and healthy brain tissue discarded from the operating room after surgery can be kept alive for up to two weeks, time enough to study neural and brain tumor stem cell migration.

"These discoveries and our increasing understanding of the human brain could help pave the way for a number of therapeutic treatments for brain cancer, neurodegenerative diseases and brain damage," says Quiñones.

Alessandro Olivi, Director of the Johns Hopkins Neurosurgical Brain Tumor Program and colleagues have recently discovered that bone morphogenetic proteins (BMP) can inhibit the growth of brain tumor stem cells and thus may prove extremely important in the development of new treatments to brain cancer.

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Human and rodent subventricular zone (SVZ)

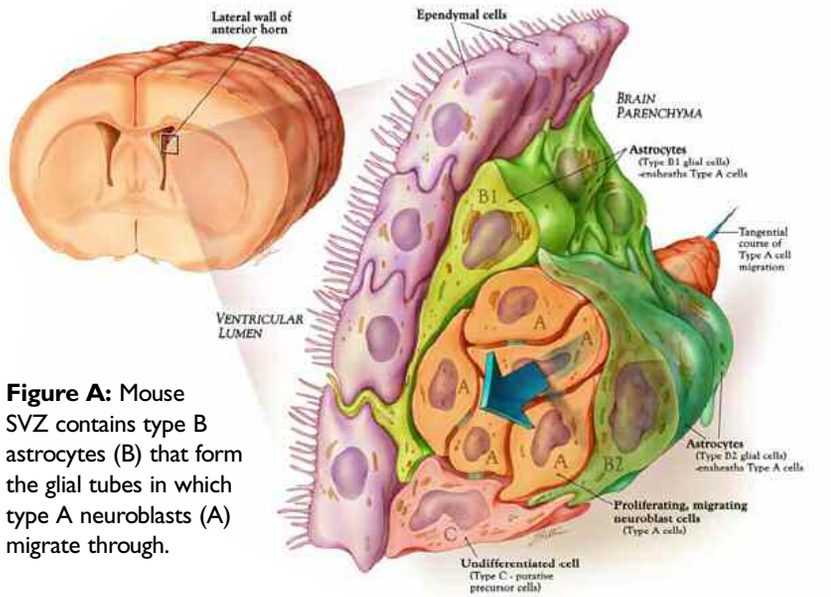
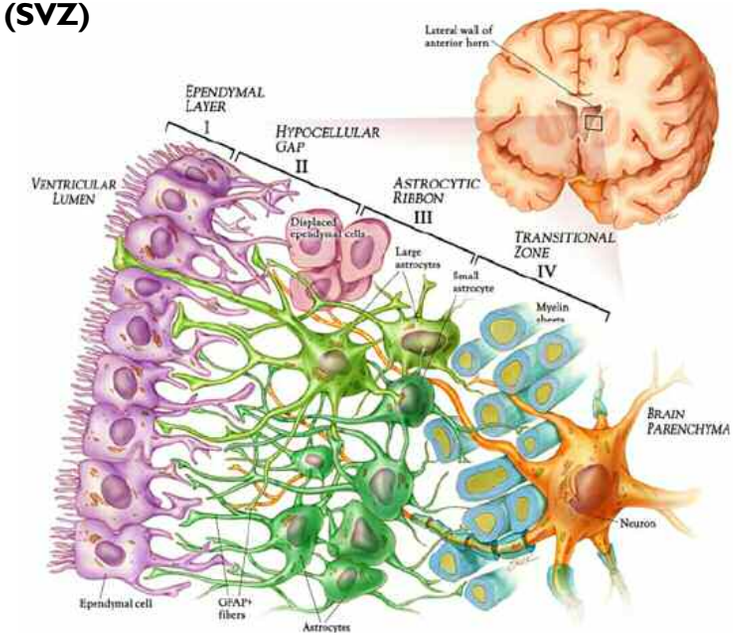


Figure A: Mouse SVZ contains type B astrocytes (B) that form the glial tubes in which type A neuroblasts (A) migrate through.

Figure B: Human SVZ with four layers that are absent in mice (I-ependymal layer, II-hypocellular gap, III-astrocytic ribbon, IV-transitional zone). These cells are separated from the lateral ventricles (LV) by a monolayer of ependymal cells (E).

Images courtesy of Experimental Neurology



Who Will Develop Alzheimer's Disease? What Drugs Will Help?

Marilyn Albert, director of the Division of Cognitive Neuroscience, is researching measurements that could predict who is going to develop Alzheimer's disease. She's exploring whether these measures can be used in clinical trials to assess the effectiveness of new medications.

"We know there are changes in the brain that precede the full-blown symptoms of the disease by at least as long as a decade," Albert says. "Using MRI scans of the brain, we've been following people who have mild symptoms to see what measures or biological markers are going to predict who will progress to dementia. Once we find such measures, we look to see if they might be useful in evaluating new medications."

A measurable biomarker would provide a more accurate way to tell whether a drug treatment is working. Collaborating with researchers in biomedical engineering and radiology, Albert developed an automated labeling system for analyzing MRI data images. The system combines different measurements to form a more accurate picture of what changes are occurring in the brain over time.

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Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 2006; 31:968. Epub March 10, 2006.

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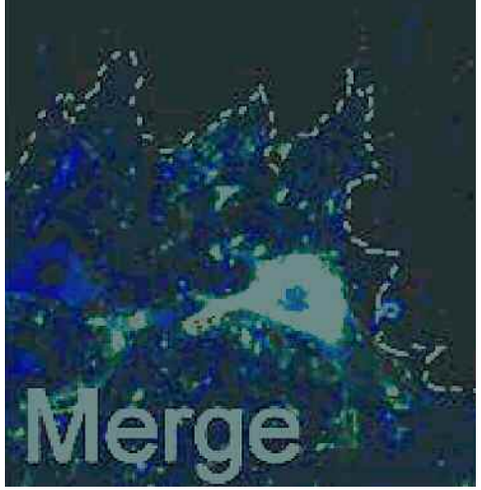
Stem Cells That Undo Nerve Damage

Using mouse embryonic stem cells, a team of Johns Hopkins scientists has engineered new, complete, fully working motor neuron circuits stretching from spinal cord to target muscles in paralyzed adult rats. Now they're using human embryonic stem cells in larger mammals to see how well the technique applies to human nerve recovery. The research could lead to an approach to repair damage from ALS (Lou Gehrig's disease), multiple sclerosis, transverse myelitis and traumatic spinal cord injury, the investigators say.

This team has found that stem cells can be made to retrace complex pathways of nerve development long shut off in adult mammals. By injecting embryonic stem cells at the right time and place, physicians might restore the biological memory for growing neurons.

There will be several years of testing and thorough data evaluation before human clinical trials could begin, says **Douglas Kerr**, the neurologist who is leading the research, but "this is proof that we can recapture what happens in early stages of motor neuron development and use that to repair damaged nervous systems."



Embryonic stem (ES) cell-derived motor axons reach skeletal muscle targets at three months after transplantation. Arrowheads denote transplant-derived motor neurons. Dashed line denotes the gray/white matter junction.

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Nanofibers with Protein Regenerate Damaged Nerves

Nerves damaged in accidents or other trauma cannot repair themselves. Currently, surgeons transplant the patient's own nerves (usually taken from the leg) to guide regrowth, but the technique is not very effective. Research into speeding the repair of injured peripheral nerves could one day benefit 100,000 people with this problem each year.

Led by **Ahmet Höke**, Johns Hopkins neuroscientists found that nanofiber nerve guides, laced with human glial cell-derived neurotrophic factor (GDNF) and other proteins, improve tissue regeneration in rats. Biomedical engineer **Kam Leong**, Höke's longtime collaborator, created artificial nerve guides from biodegradable polymer. The guides bridge the damaged nerves. Höke and Leong manufactured the circular tubes of polymer—much thinner than a human hair—with nanofibers (or nano-spaghetti, see photo) infused with GDNF and other proteins to speed the process of regeneration.

"The polymer allows nutrients from the blood to pass through and pick up the GDNF to encourage regrowth of nerves," Höke says. The next step, he adds, is research with primates. If that is successful, human testing could follow.

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"Nano-spaghetti": Nanofibers aligned along the length of the tube, fill up artificial nerve guides like spaghetti in a box and provide a substrate for peripheral nerves to regenerate more efficiently.

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Patient Safety and Quality Measures

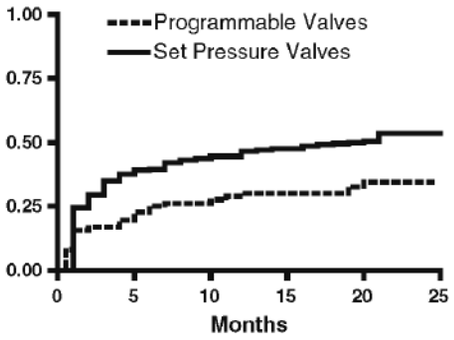
Infection Rates Plummet in Pediatric Hydrocephalus

Shunt infection rates for pediatric hydrocephalus patients at Johns Hopkins have fallen from 12 percent to 2 percent thanks to a new protocol for draining the cerebrospinal fluid (CSF) from the brain through an antibiotic-impregnated shunt.

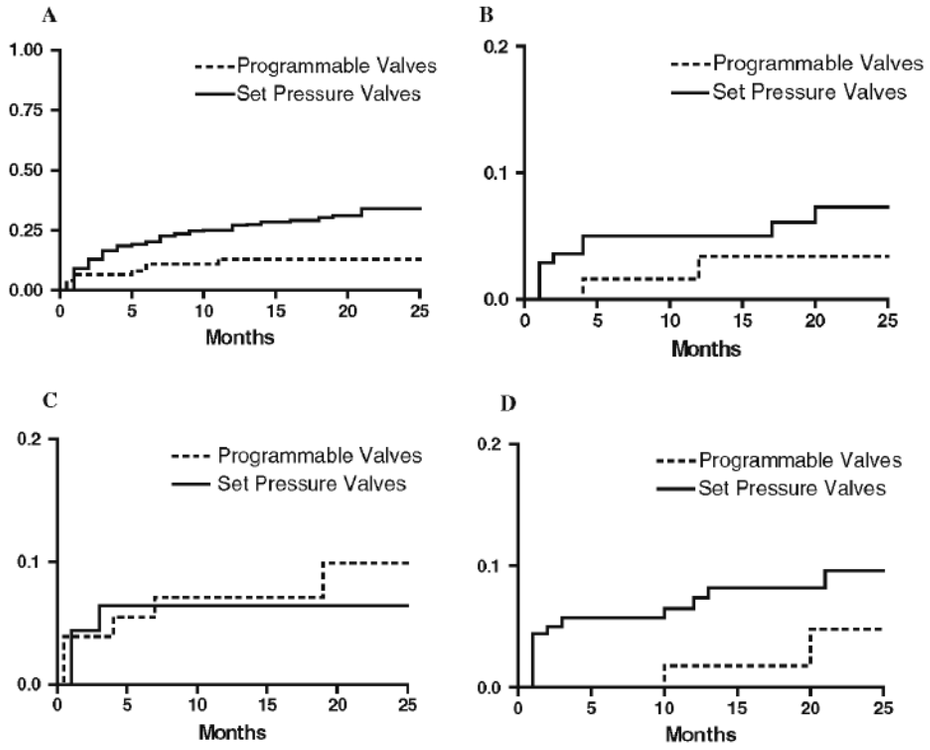
Treatment for hydrocephalus, the condition that occurs when an excessive amount of CSF builds up in the ventricles of the brain, often includes implanting a shunt system to divert the flow of CSF to another area of the body where it can be absorbed.

About one in 10 implanted CSF shunts becomes infected, and that can be a severe, life-threatening complication, says pediatric neurosurgeon **George Jallo**. Most shunt infections occur within six months of placement.

To combat that risk, antibiotic-impregnated shunt systems were developed; the technology is an outgrowth of the Hopkins techniques for using brain polymers to deliver chemotherapy. The new antibiotic-loaded shunts were found to significantly reduce incidence of shunt infection in children. "These catheters deliver a slow-release, low-dose antibiotic that almost completely erases the risk of infection," Jallo says. "As a result, we're using them with excellent outcomes."



Kaplan–Meier analyses comparing shunt revision rates as a function of programmable vs set-pressure valve systems. By 24 months after shunt placement, 26 (35 percent) programmable valve shunt catheters had failed compared to 109 (54 percent) set-pressure valve catheters. Patients receiving programmable valve shunt catheters were 1.5-fold less likely to require shunt revision for the first 25 months after shunt insertion ($p<0.05$).



Kaplan–Meier analyses comparing etiology of shunt failure as a function of programmable vs set-pressure valve systems. **a** *Proximal obstruction* By 24 months after shunt placement, proximal obstruction had occurred in only 9 (12 percent) programmable valve shunt catheters compared to 58 (29 percent) set-pressure valve catheters. Patients receiving programmable valve shunt catheters were 2.5-fold less likely to experience proximal shunt obstruction ($p<0.01$). **b** *Distal obstruction* There was no risk reduction for the occurrence of distal obstruction in patients receiving programmable vs set-pressure valve shunt catheters [relative risk (95 percent CI); 0.69 (0.22–2.28); $p=0.56$]. **c** *Shunt infection* There was no risk reduction for the occurrence of shunt infection in patients receiving programmable vs set-pressure valve shunt catheters [relative risk (95 percent CI); 1.31 (0.47–3.79); $p=0.585$]. **d** *Valve change* There was a trend toward decreased valve changes [relative risk (95 percent CI); 0.34 (0.15–1.27), $p=0.121$) in patients receiving programmable vs set-pressure valve shunt catheters.

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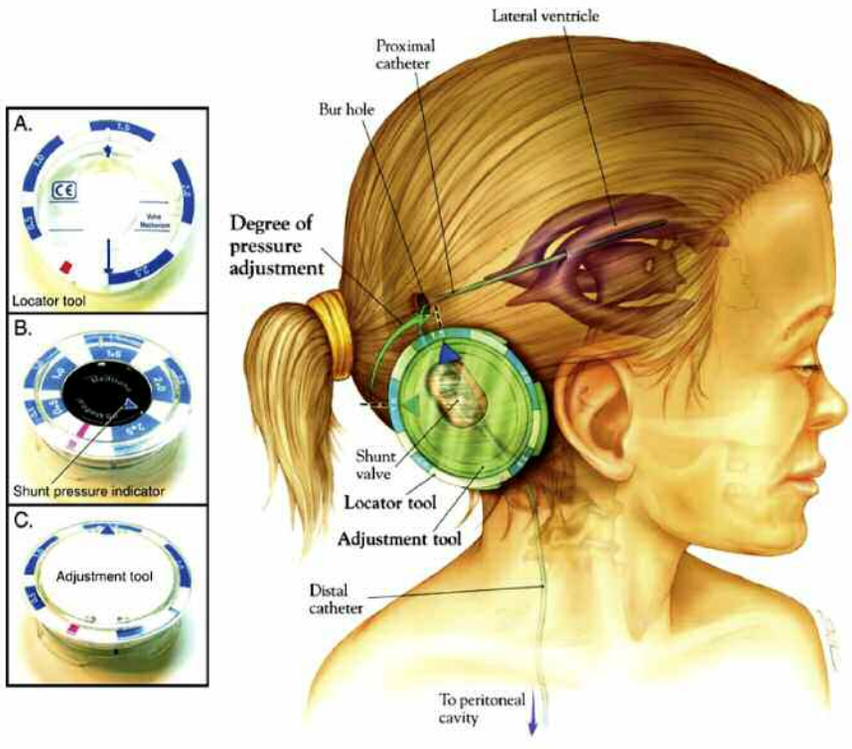
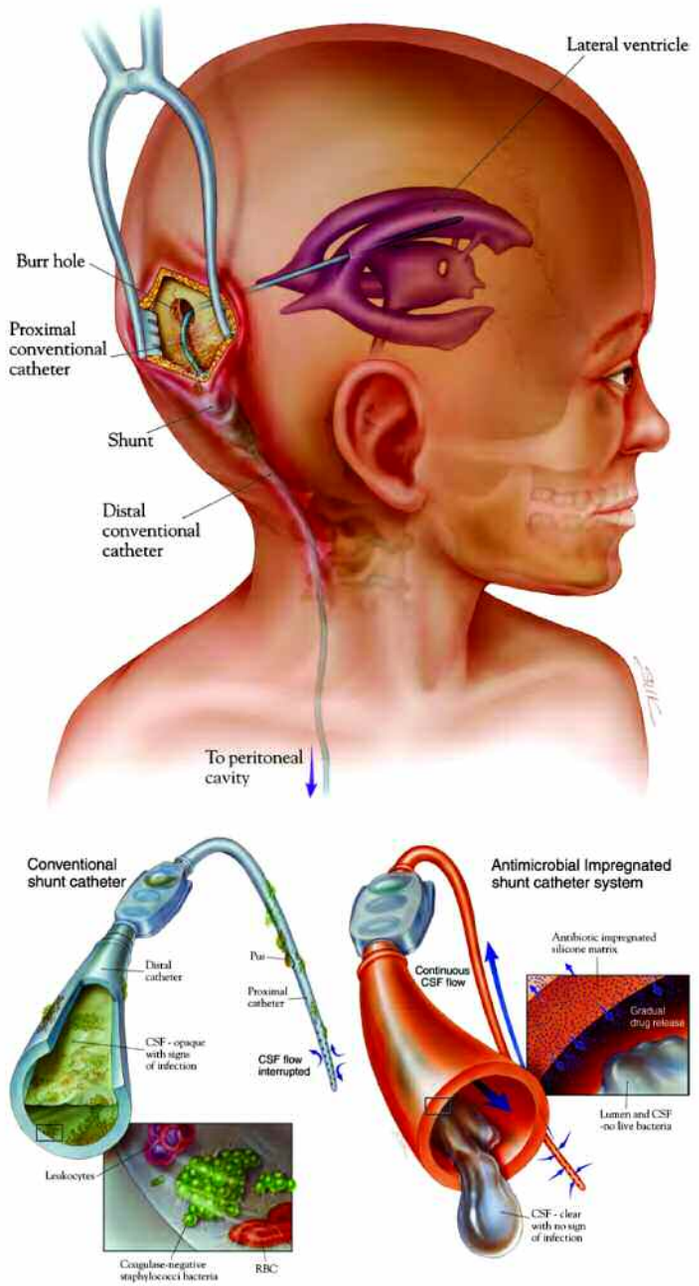


Illustration depicting the Medtronic Shata© valve system. Adjustment of valve pressure from 1.0 to 1.5 allows a noninvasive increase in the opening valve pressure.

Image courtesy of Child's Nervous System



Illustrations of the AIS catheters and the traditional shunt system.

Upper: The surgeon's preference for placement of a VP shunt.

Lower left: Traditional catheter with valve assembly.

Lower right: The AIS catheters attached to the valve assembly.

Image courtesy of the Journal of Neurosurgery: Pediatrics

D.M. Sciubba, et al.

Research in the Neuro ICU

In the Johns Hopkins neurosciences critical care unit, physician and nurse specialists work together to improve patient outcomes through extensive collaboration, constant monitoring and integration of research.

"The NCCU manages the entire patient medical profile. Once a patient is admitted to the unit, all care and decisions are transferred to the NCCU team," says **Marek Mirski**, director of the neurosciences critical care division.

Johns Hopkins has two neuro-ICUs. One, at Hopkins Hospital, is directed by Mirski; the other, at Johns Hopkins Bayview Medical Center, is directed by **Romergryko Geocadin**. Both are managed by the same faculty on a rotating basis. The y work closely with faculty in neurosurgery, neurology and highly specialized nursing colleagues. Together, they admit more than 1,700 patients a year.

The units champion expert clinical bedside management as well as the integration of research and patient care. "Every day, our team brings a scientific eye to improving care," Geocadin says. "When we encounter a clinical question, we take it to the lab, create an animal model to study, get the answers and bring them to the bedside."

Geocadin, for example, has a $2.8 million NIH grant to study a novel application of the EEG. Using the EEG, he is trying to understand how the brain regains consciousness after a comatose state such as cardiac arrest. Geocadin studied animal models and tested his findings on 30 patients. Now, he and his team are participating in a multicenter study with 100 patients.

"We're getting EEGs as close to cardiac arrest as possible to help determine the neurological status of the patient," says Geocadin. "Our eventual goal is to help clinicians make therapeutic decisions that will improve patient outcomes."

The NCCU team also studied the management of massive brain swelling associated with severe brain injuries. To reduce swelling and pressure, they raised the level of salt concentration in the brain. The approach, which originated with clinical observation and progressed with further study in the laboratory by Mirski and others, now is in use in the NCCU and has significantly reversed brain swelling, reduced brain pressure and improved survival.

These examples illustrate the importance of taking a problem from the bedside to the bench and back again. Says Geocadin, "It's the only way to advance the field."

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Toward Better Encephalitis Diagnosis

Hopkins neurologists and neurosurgeons in the newly created Johns Hopkins Encephalitis Center are defining protocols to more accurately diagnose acute encephalitis.

There are about 20,000 cases of acute encephalitis a year in the United States. Up to 70 percent of cases have no identified cause. In the past eight years, there has been an increase in viral encephalitis, especially the type associated with the West Nile virus.

"Determining the cause of encephalitis is the real challenge," says center director **Benjamin Greenberg**. "Treatment varies widely, and it is imperative to diagnose the cause correctly in order to save patients."

Even after extensive evaluations, many patients do not have firm diagnoses right away, and some get sicker. So the focus is on making a diagnosis within three days to two weeks, says **Romergryko Geocadin**, director of the neurosciences critical care unit at Johns Hopkins Bayview Medical Center. "We're reviewing all the literature and organizing a list of protocols with the appropriate testing in the right order. We want to maximize the window of time in which to diagnose and treat this condition."

The neurocritical care units at Bayview and Hopkins Hospital collaborate with the encephalitis center to provide care. The center has all the resources to perform full diagnostic evaluations. "Although still young," says Jana Goins, executive director of the encephalitis center, "our center has the groundwork in place."

The Patient Experience

Life After Brachial Plexus Injury

Today, Denise McCreery, 34, enjoys rock climbing, swimming and playing with her 4-year-old niece. She also just moved back into a home of her very own. But it has taken time to get to this point. Two and a half years ago, an accident forced McCreery to quit a job she loved and move back home with her parents, who helped her through months of rehabilitation to regain movement in her paralyzed arm.

In March 2005, the Leesburg, Va. resident, a director and instructor at a local college, was driving north on I-95 heading to New Jersey. She remembers a continuous flow of traffic—and then waking up in the driver's seat of her car, covered in glass from a broken windshield. She'd been injured by a brake drum that had broken off a truck ahead. Bouncing off the asphalt, it hurtled through the window and penetrated her left shoulder, slicing through the intricate brachial plexus area of her upper torso.

It cracked three vertebrae and broke her collarbone, two ribs and six other vertebrae, paralyzing her left shoulder and arm down to the wrist. "My arm just hung there, useless," she recalls. After weeks of physical therapy, a specialist near her home told her, "I'm afraid there's no way you're going to get your arm back."

Such predictions are all too common, says neurosurgeon **Allan Belzberg**. What happens then is that patients don't seek out proper help quickly. "Don't wait," Belzberg says. "The earlier we get the patients, the better our results."

Belzberg did not see McCreery until about three months after the accident. When the surgical team opened McCreery's brachial plexus structure, they had to navigate around already formidable stretches of inflexible scar tissue that had rendered some portions of nerve material unusable. Still, they found working nerve portions they could repair.

During the 11-hour operation, the team rewired and designed an alternate nerve pattern for the part of the brachial plexus that had been pulled from the spinal cord. They redirected one nerve headed for the scapula to a shoulder muscle, another nerve headed for the triceps to a second shoulder muscle, and a third nerve headed for the hand to the biceps muscle.

Denise McCreery with physical therapist Kristin Ameraron, MSPT, OCS.

For a time, Belzberg explains, the transplanted nerves "remember" their old functions. At first, McCreery had to think "make a fist" to bend her elbow. But with time, the nerves adapt and movements come automatically.

McCreery put in many hours of hard work and physical therapy to help those movements along. Her determination has paid off. Now, though she'll be on medicine for nerve pain for a few more years, people don't even know she was in an accident.

"I've had the best physicians and family support," McCreery says, unpacking boxes in her new place. "I'm finally getting my life back."

Managing a Complex Brain Tumor

Ten years ago, when Tom Roberts and Patti Mallin married, they envisioned a future full of adventure, travel and eventually, children. Never did the path they pictured include a brain tumor. Now Roberts, 39, can't imagine going through tumor treatment, rehabilitation and recovery without his wife. "She's my strength," he says. "We're doing this together."

In May 1999, Roberts, an Internet and Web specialist at the National Academy of Sciences, was training for the Marine Corps marathon. He chalked up his unsteady gait and difficulty running to the challenging training. Then he had a grand mal seizure.

"We were stunned. I was young, healthy and had no history of seizures," says the Takoma Park, Md., resident. Testing revealed a large tumor mass in his brain called an oligodendroglioma. He immediately had surgery at a large regional hospital in the D.C. area and then opted to have his ongoing treatment managed at Johns Hopkins.

Patti Mallin and Tom Roberts

At Hopkins, specialists in neurology, neurosurgery, neuro-oncology. neuro-radiation therapy, neuro-radiology, neuro-pathology nursing and physical and occupational therapy review complex cases weekly and weigh in on each treatment decision. "We provide a thoughtful approach to balance attacking the cancer with aggressive therapies while maximizing quality of life," says **Jaishri Blakeley**, Roberts' neuro-oncologist. "We don't give up, and as a result, we've seen good long-term outcomes."

Roberts continued to work until April 2006, when MRI scans indicated new tumor growth, prompting a second round of radiation, more chemotherapy and a second craniotomy in January 2007. Recently though, he received good news: The tumor mass had decreased. Now the team is treating the damage to the brain resulting from radiation and chemotherapy.

"Currently, we're juggling medication to maximize my level of activity and minimize fatigue from the brain tumor treatment over the years," Roberts says. He continues occupational therapy exercises and attends physical therapy sessions, and he's working to surpass plateaus and to recognize when he's reached his limit. "There are lots of things I can't do, but more that I can."

All in all, he counts himself lucky. "I wouldn't do anything differently in my current treatment," he says. "I have terrific support and resources both at home and at Hopkins."

Throughout the "adventure," as he calls it, Roberts and his wife have educated themselves on all aspects of his diagnosis and tried to live as normally as they could. Camden, their daughter, was born in the midst of treatment. She is now 6.

An Experimental Drug for MS

Kathy Gewain knows something about longevity: last year, the Rockville, Md. insurance representative helped her parents celebrate their 50th wedding anniversary, and she herself has been married for 28 years. Unfortunately, her illness knows something about longevity as well.

Her symptoms started in 1988 when she awoke one morning and couldn't feel her feet. Gewain dealt with slowly progressing symptoms, until finally in 2000, an MRI clearly showed multiple sclerosis, the disease that occurs when the immune system attacks the central nervous system.

Gewain came to Hopkins, where over the next four years she tried treatment after treatment with disappointing results. That is not surprising, because of the 400,000 people in the United States who have MS, 40 percent to 50 percent simply do not improve with conventional therapy, says neurologist **Douglas Kerr**. "Current MS therapies are only modestly effective, with significant side effects and risks, and many patients continue to accrue disability even with treatment."

Kerr is leading clinical trials for Revimmune, an experimental high-dose treatment for MS made by Accentia Biopharmaceuticals. "Revimmune is an aggressive, chemo-based therapy that we're testing in patients who are failing standard therapy," Kerr says. It uses a one-time, ultra-high intensity course of an approved drug, cyclophosphamide, delivered intravenously for four hours a day over four days.

Gewain met the rigid criteria as a candidate and had the treatment in June 2004. Although the aggressiveness of the treatment made her nervous, she never got sick. She stayed in Baltimore during and for two weeks after the therapy so doctors could monitor her progress. She returned for neurological testing every three months.

Six months later, she was able to walk up the stairs to watch her son graduate from college. More than 36 months post-Revimmune and on no other medications, Gewain says she still feels occasional numbness in her feet and the heat still bothers her, but otherwise she hasn't had any recurrence of MS symptoms. She's back to walking the mall, grocery shopping and climbing ladders to paint her walls.

This new treatment could benefit thousands, Kerr says. To date, 11 patients have received the treatment at Hopkins, with excellent results, and doctors plan to treat more patients in the near future. "Most patients have shown substantial improvement, and many have a complete elimination of signs of the disease even after two years," says Kerr. He is recruiting for a multicenter, phase II clinical trial.

CLINICAL TRIAL:

MS Clinical Trial: High-Dose Cyclophosphamide in Multiple Sclerosis. Investigating the use of high-dose cyclophosphamide (HiCy) in the treatment of multiple sclerosis. HiCy uses an ultra-high intensity, short-course of an intravenous formulation of cyclophosphamide to "reboot" a patient's immune system, thereby eliminating autoimmunity.

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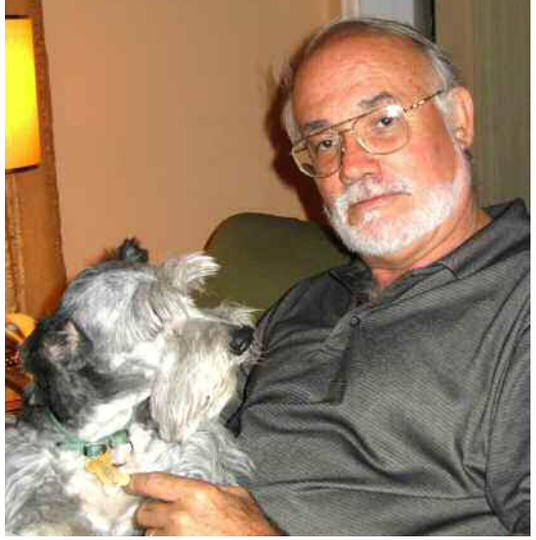
Kathy Gewain

A Stroke Treatment That Speaks for Itself

Author and political science professor Robert (Dan) Tschirgi was not yet 60 when he had an ischemic stroke that robbed him of his speech and vocabulary—in all three languages he speaks fluently. But Tschirgi, a resident of Cairo and Cozumel, recovered his ability to speak English, Turkish and Spanish after undergoing an investigational treatment for stroke at Johns Hopkins.

Tschirgi, who is also proficient in several other languages, awoke one day in August 2005 with impaired vision and problems with his coordination. By that night, he was in a Cozumel clinic, where he was diagnosed as having had a stroke. His wife made arrangements to transport him to Johns Hopkins.

By the time he arrived, Tschirgi had suffered occlusions in both carotid arteries, triggering a small stroke in his left hemisphere, says **Argye Hillis**, Hopkins professor of neurology and medicine and co-director of the cerebrovascular division. But the real problem was the low blood flow in the bigger region of his left hemisphere, causing severe aphasia, a common neurological symptom when the stroke is in that region.



Dan Tschirgi

But Tschirgi was in the right place: Hillis had just completed a randomized trial that showed treating appropriate stroke candidates with medically induced hypertension resulted in better outcomes for neurologic functions when compared to conventional care.

"Animal studies had shown that increasing blood flow to ischemic tissue that was not yet dead resulted in improved outcomes," she says. "So we augment the blood pressure for a short time to boost blood flow to that area until we see improvement."

Research shows that this method can even be helpful more than 24 hours after stroke onset, Hillis says. "Dan had been having symptoms for well over 24 hours, and he was getting worse. But he started improving as soon as we started the blood pressure augmentation."

Our Faculty

Henry Brem is the Harvey Cushing Professor of Neurosurgery, a professor of oncology and ophthalmology, and director of the Department of Neurosurgery at the Johns Hopkins University School of Medicine.

Dr. Brem graduated from Harvard Medical School with honors and trained in neurosurgery at Columbia University's Neurological Institute. He completed a fellowship in neurosurgery and ophthalmology at Johns Hopkins and then joined the faculty in 1984. Dr. Brem rose to the rank of full professor and helped build one of the leading brain tumor centers in the United States. He also directs the Hunterian Research Laboratory, which has introduced new therapies for brain tumors. In 1998, Brem was elected to the National Academy of Sciences' Institute of Medicine. He is one of the few neurosurgeons in the country to be named to this national organization. In 2000, Dr. Brem was appointed the Harvey Cushing Professor, neurosurgeon-in-chief and chairman of the Department of Neurosurgery at Hopkins.

Dr. Brem focuses his clinical practice on the surgical treatment of pituitary tumors, meningiomas, gliomas, acoustic neuromas, skull-base tumors and other solid brain tumors. He has developed new clinical treatments for brain tumors, including the delivery of chemotherapy directly to the brain through the Gliadel wafer, anti-angiogenesis therapies, computer navigation systems used during surgery and brain tumor vaccines. Dr. Brem is board-certified in neurological surgery.

Henry Brem, M.D.

Justin McArthur is a professor of neurology, pathology and epidemiology and interim director of the Department of Neurology at the Johns Hopkins University School of Medicine. He is also the director of the Johns Hopkins/National Institute of Mental Health Research Center for Novel Therapeutics of HIV-associated Cognitive Disorders.

Dr. McArthur received his medical degree from Guys Hospital Medical School in London, England. He completed an internship and residency in internal medicine at The Johns Hopkins Hospital. Dr. McArthur continued his education at Hopkins by completing a residency in neurology and earning his master's degree in public health.

Now the interim director of the Department of Neurology, Dr. McArthur is nationally and internationally recognized for his work in studying the natural history, development and treatment of HIV infection, multiple sclerosis and other neurological infections and immune-mediated neurological disorders. Dr. McArthur has also developed a technique to use cutaneous nerves to study sensory neuropathies, including those associated with chemotherapy, HIV and diabetes.

Justin McArthur, M.B.B.S., M.P.H.

As director of the Johns Hopkins/National Institute of Mental Health Research Center for Novel Therapeutics of HIV-associated Cognitive Disorders, Dr. McArthur leads his interdisciplinary research team in translating discoveries of the pathophysiological mechanisms into novel therapeutics for HIV-associated dementia (HIV-D). Dr. McArthur is board-certified in neurology and internal medicine.

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How to Refer a Patient

For urgent physician-to-physician referrals or consultation, please call the Hopkins Access Line (HAL) at 1-800-765-5447.

You may also refer patients to Neurology faculty by calling 410-955-9441 or e-mail neuroaccess@jhmi.edu. To refer patients to Neurosurgery faculty call 410-955-2248.

For more information about Johns Hopkins Neurology and Neurosurgery, visit our Web site at www.hopkinsneuro.org.

Locations

Johns Hopkins Neurology and Neurosurgery offers patient consultations in offices throughout the Baltimore metropolitan area, including the Outpatient Center at The Johns Hopkins Hospital, Johns Hopkins Bayview Medical Center, and ambulatory outpatient centers at Green Spring Station and Cedar Lane in Howard County. For directions and maps, please visit our Web site at www.hopkinshospital.org/directions.

Referral Assistance

Hopkins USA

Hopkins USA provides one point of contact for our out-of-town patients. Our staff can help patients identify appropriate physicians or specialists, coordinate multiple medical appointments, arrange second opinions, and obtain general information on Johns Hopkins' numerous services. In addition, Johns Hopkins USA staff can provide information regarding transportation, lodging and other travel needs. Call 410-735-HUSA (4872) to talk with Hopkins USA. For family accommodations on the patient floor, see information regarding the Marburg Pavilion on page 60.

Johns Hopkins Medicine International

The professional staff of International Services coordinates all aspects of international patients' medical care, paying special attention to personal, cultural, and travel-related needs. The staff will arrange consultations, second opinions or treatments and coordinate appointments in a timely manner. The staff also provides medical records reviews before the patient travels to the United States, language interpreters, cost estimates and assistance with travel arrangements. For more information, call 410-955-8032. From outside the country, call +01-410-955-8032 or visit the website, www.jhintl.net.

Accommodations Assistance

Accommodations Office

The Johns Hopkins Hospital has arranged special rates (and shuttle service in some instances) at local hotels for patients and their families. A full-service travel agency is available to help patients and their families with air, hotel or ground accommodations. It is open Monday through Friday, 8:30 a.m. to 5 p.m. Please call 1-800-225-2201 or 410-614-1911 for assistance.

Marburg Pavilion

Located in the historic Marburg Building, the Marburg Pavilion offers deluxe accommodations for adult patients. A limited number of private rooms and two-room suites are available for an additional charge and feature fine wood furniture, private baths, entertainment centers and an array of services such as expanded dining menus and overnight sleeping accommodations for family members. For more information call 410-614-4777.

Patient Relations

Patient Representatives are available to help resolve any concerns about patient care, interpret the policies and procedures of the hospital, and arrange for services patients may need. At The Johns Hopkins Hospital, call 410-955-CARE (2273) to speak with a patient representative. Hours are 8:30 a.m. to 5 p.m. and the office is located in the hospital at Carnegie 100.

At Johns Hopkins Bayview Medical Center, call 410-550-0626 to speak with a patient representative about any patient care concerns. Hours are 8:30 a.m. to 5 p.m. The office is located in the Bayview Medical Office on the main level.

Sign Language

Deaf and hearing-impaired patients can arrange for interpreters or use the TTY in the patient relations offices at both The Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center. They can also arrange for interpreters, sign language interpreters for deaf and hearing impaired patients.

For more information, call **410-955-2273** at Hopkins Hospital or **410-550-0626** at Bayview, or visit the JHH website at **www.hopkinsmedicine.org** or Bayview's website at **www.hopkinsbayview.org**.

For patient information and visitors guide to The Johns Hopkins Hospital, visit **www.hopkinshospital.org/patients/index.html.**

Johns Hopkins Medicine Overview

Johns Hopkins Medicine, established in 1995 to unite Hopkins biomedical research, clinical teaching and business enterprises, brings together the Johns Hopkins University School of Medicine and its faculty with the facilities and programs of The Johns Hopkins Health System. The Health System, which has its origins in the founding of the world famous Johns Hopkins Hospital, now comprises three hospitals, as well as other elements of an integrated system, from a community physicians group to home care. The components of Johns Hopkins Medicine consistently are named at the top of national rankings for best hospital and best school of medicine, and its faculty consistently win the largest share of NIH research funds. Results of this research continue to advance efforts to diagnose, treat and prevent many diseases.

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