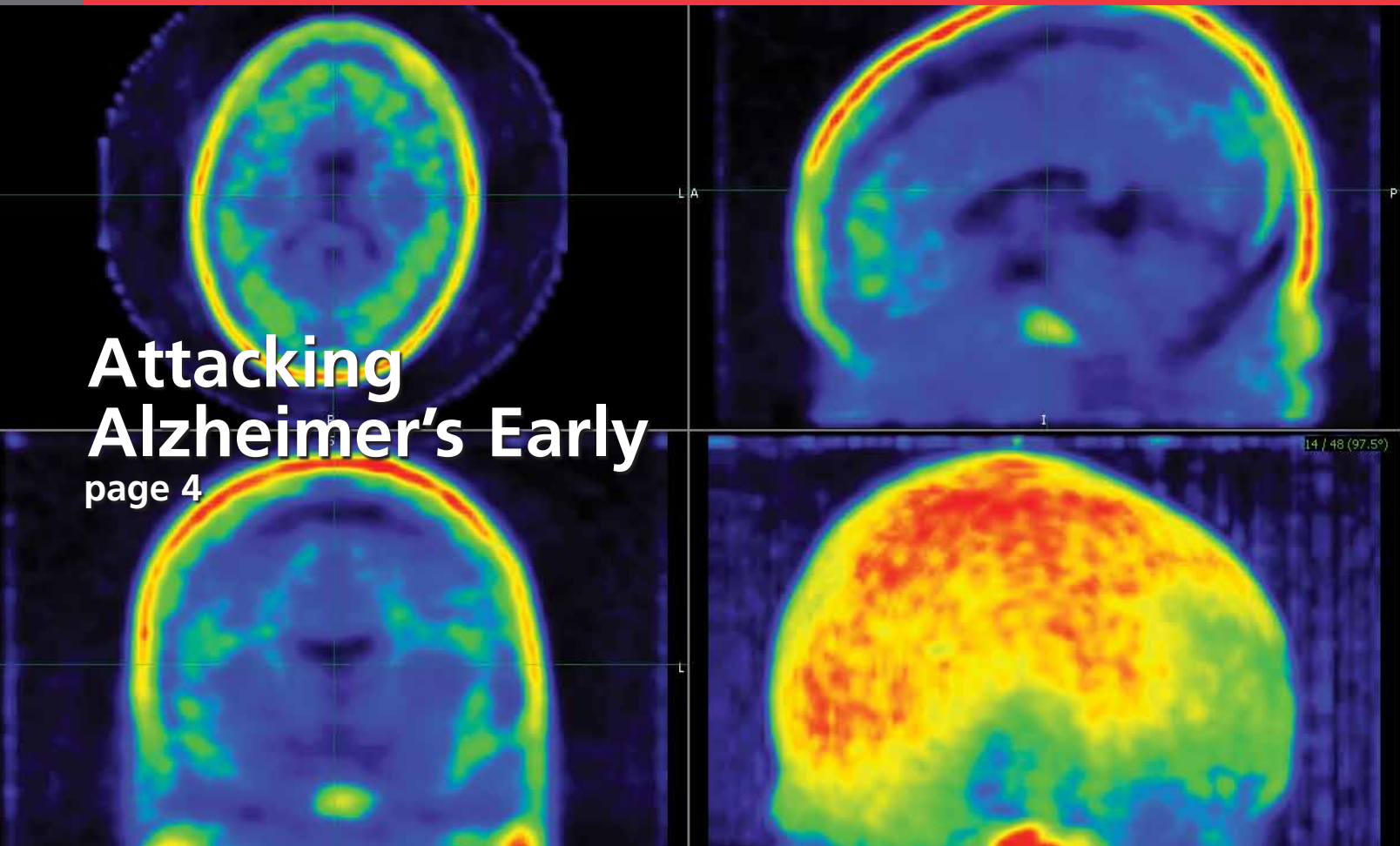


UH Innovations In Neurosciences

University Hospitals Neurological Institute



**Attacking
Alzheimer's Early**
page 4

3 How a UH neurologist solved a debilitating, perplexing illness

6 Pre-surgical evaluation of children with epilepsy

7 A physician's passion brings healing through music

Unequaled Resources and Care



As the primary affiliate of Case Western Reserve University School of Medicine, University Hospitals Case Medical Center and the UH Neurological Institute offer a depth of care and scope of expertise unmatched by any other medical center in Ohio. The University and Medical Center affiliation facilitates access to top multidisciplinary talent, emerging technologies and therapies, and unequaled research resources related to the nervous system in health and disease.

Our neurological physicians, surgeons and scientists – all members of the faculty of Case Western Reserve University School of Medicine – are leaders in their respective fields, and their ongoing research programs are at the leading

edge of medical progress. A strong emphasis on translational, or “bench-to-bedside” research, means that new and innovative treatments and technologies transfer more rapidly from the research laboratory to actual patient care.

Our integrated and multidimensional approach to innovative neurological research focused on individualized patient care continues a rich legacy of landmark medical discovery at Case Western Reserve University and University Hospitals Case Medical Center.

No case is too complex for the Neurological Institute. Our clinical excellence is the result of a comprehensive, multidisciplinary team approach that not only involves our leading specialists and skilled surgeons but also a dedicated and caring nursing staff. Our Reinberger Neuroscience Intensive Care Unit has earned the prestigious Beacon Award for Critical Care Excellence, a top honor from the American Association of Critical-Care Nurses recognizing nursing excellence.

Four other intensive care units at University Hospitals Case Medical Center have been recognized with Beacon Awards: Medical Intensive Care Unit, Cardiac Intensive Care Unit, Surgical Intensive Care Unit, and UH Rainbow Babies & Children’s Hospital’s Pediatric Intensive Care Unit. University Hospitals Case Medical Center is the *only* hospital in the state of Ohio and one of only two nationally with five or more Beacon Award-winning intensive care units.

As always, we are committed to serving the needs of you and your patients and providing excellent, innovative care.

Sincerely,

Handwritten signature of Warren R. Selman in black ink.

Warren R. Selman, MD
Director, UH Neurological Institute
University Hospitals Case Medical Center
The Harvey Huntington Brown Jr. Professor and Chair,
Department of Neurological Surgery
Case Western Reserve University School of Medicine

Handwritten signature of Anthony J. Furlan in black ink.

Anthony J. Furlan, MD
Co-Director, UH Neurological Institute
University Hospitals Case Medical Center
Gilbert W. Humphrey Professor and Chair,
Department of Neurology
Case Western Reserve University School of Medicine

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Among the nation’s leading academic medical centers, University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine, a nationally recognized leader in medical research and education.

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SCHOOL OF MEDICINE
CASE WESTERN RESERVE
UNIVERSITY

The commitment to exceptional patient care begins with revolutionary discovery. Faculty at the Case Western Reserve University School of Medicine, who also are physicians at UH Case Medical Center, are at the forefront of medical research and innovation. The School of Medicine is the largest medical research institution in Ohio and among the nation’s top medical schools for research funding from the National Institutes of Health.

A Painful Mystery Solved

A UH neurologist's thoughtful questioning, experience lead to porphyria diagnosis



Thomas C. Chelimsky, MD, Director, Autonomic Laboratory, UH Neurological Institute, University Hospitals Case Medical Center, is Chair of the American Academy of Neurology Pain Section and serves on the board of directors of the American Autonomic Society.

A 46-year-old woman complained of recurring bouts of tingling and numbness in her hands and feet. She was referred to **Thomas C. Chelimsky, MD**, for electromyography (EMG), a procedure designed to test the electrical activity of muscles and detect peripheral nerve damage. Dr. Chelimsky is Director, Autonomic Laboratory, UH Neurological Institute, University Hospitals Case Medical Center, and Professor, Neurology, Anesthesiology and Pediatrics, Case Western Reserve University School of Medicine.

EVALUATION

Dr. Chelimsky engaged the patient in conversation while conducting the EMG in an effort to keep her relaxed and comfortable. The patient described a plethora of debilitating symptoms she had suffered over several years, including acute abdominal pain, dizziness, fever, vomiting and weakness. At various times she also had chronic constipation, joint pain and an elevated heart rate. She reported that surgeons had removed her appendix, her ovaries and part of her colon in a fruitless effort to eliminate the source of her pain. During the EMG, Dr. Chelimsky detected significant nerve damage.

The patient had not come to Dr. Chelimsky for a diagnosis, but as she related her symptoms, and her physicians' inability to pinpoint the underlying disease, he began to suspect that the culprit was a rare genetic disorder: porphyria. "What clued me in that it might be porphyria was that it was extremely episodic, and the episodes sounded similar to one another," Dr. Chelimsky says.

In a typical episode, numbness and tingling in the patient's hands and feet would be followed by a drop in blood pressure and stomach pain. "To my knowledge, only two diseases have that combination of symptoms," he says. "One is familial Mediterranean fever, and that only occurs in people of Mediterranean origin, which she is not. The other is porphyria, which is characterized by pain so severe that doctors want to go in and remove the organ they think is causing it. But the pain moves around from episode to episode, so they may take out the gallbladder and then, when the pain moves down, want to remove the appendix."

DISCUSSION

Porphyria is a group of disorders that afflict fewer than 200,000 people in the U.S. A common feature of all types is the accumulation in the body of porphyrins

"Porphyria ... is characterized by pain so severe that doctors want to go in and remove the organ they think is causing it. But the pain moves around from episode to episode, so they may take out the gallbladder and then, when the pain moves down, want to remove the appendix."

or porphyrin precursors. Dr. Chelimsky characterizes porphyria as a blood disorder with autonomic manifestations. "The basic issue is that a genetic defect affects the heme pathway, which makes the molecule that's critical to oxygenation of the blood," he says. "The heme molecule is formed abnormally, and at a certain point in time – we don't really understand why – the liver starts metabolizing heme incorrectly and toxic products begin to accumulate. A crisis, or episode, is associated with very high levels of delta-aminolevulinic acid and porphobilinogen. The crisis can then lead to damaged nerves in the hands, feet and gut, and also damage to motor nerves as well."

Dr. Chelimsky suggested that the patient discuss the possibility of porphyria with her physicians. "She called me about six years later to tell me she pursued what I told her," he says. "She went home, consulted some medical books with her husband, who is a pediatrician, and saw that her symptoms matched the description of the disorder. Then they went to New York, where there's a hospital that specializes in evaluating porphyria."

OUTCOME

A *New York Times* article describing the patient's ordeal ("Perplexing Pain," Nov. 1, 2009) states that three months of testing confirmed a diagnosis of porphyria. While there is no cure, intravenous heme therapy can suppress disease activity. The patient reported that after making lifestyle changes to avoid triggering the disease, she has not experienced an episode in more than a year.

Targeting Preclinical Alzheimer's Disease

UH investigators test new amyloid imaging agents in PET scanning



Alan J. Lerner, MD, Director, University Hospitals Neurological Institute Memory and Cognition Center



Yanming Wang, PhD, Associate Professor, Radiology, Chemistry and Biomedical Engineering, and Director, Radiopharmaceutical Division, Case Center for Imaging Research, Case Western Reserve University

One in eight Americans age 65 and older – a total of 5.1 million people – has Alzheimer's disease (AD), the most common cause of dementia, according to the Alzheimer's Association. That number is expected to reach 7.7 million in 2030 and 11 million to 16 million by 2050. A recent report by Alzheimer's Disease International indicated that 1 percent of global GDP is spent in dementia care.

While researchers continue to test new treatments and explore possible avenues of prevention, an emerging focus on earlier diagnosis anticipates the day when effective treatments will slow or halt the cognitive and behavioral decline that characterizes the disease. Under the leadership of **Alan J. Lerner, MD**, Director, University Hospitals Neurological Institute Memory and Cognition Center, and Professor, Neurology, Case Western Reserve University School of Medicine, physicians at UH Neurological Institute are testing new imaging agents for positron emission tomography (PET) scanning that enable in vivo imaging of amyloid deposits in the brain.

SEARCH FOR BIOMARKERS

Researchers and clinicians have long been frustrated by the lack of either a biomarker or a reliable diagnostic test for AD. While the relationship between amyloid deposits and AD is not clearly understood, one of the hallmarks of the disease is the accumulation of amyloid plaques between neurons in the brain. Increasingly, amyloid is being viewed as a possible early biomarker of the disease. "There's been a suggestion that a certain percentage of normal individuals have significant quantities of amyloid deposit in their brains," says Dr. Lerner. "We still don't know what that means, though the suggestion is that these people are clearly at higher risk of developing Alzheimer's."

The search for a sensitive, specific biomarker for AD is not without controversy, in part because there is currently no effective treatment for AD. Dr. Lerner points out that a biomarker would be useful not only as a diagnostic tool for differentiating among types of dementia, and for selecting patients with AD for clinical trials, but also for diagnosing prodromal, or preclinical, AD. "Researchers are looking at early biomarkers because there's the sense that many of our treatments are simply too late," he says. "The theory is that maybe some of these treatments

would work if they were administered prior to cognitive decline. This is about average people – not people with end-stage disease – and what more we can be doing to help them."

AMYLOID IMAGING AGENTS

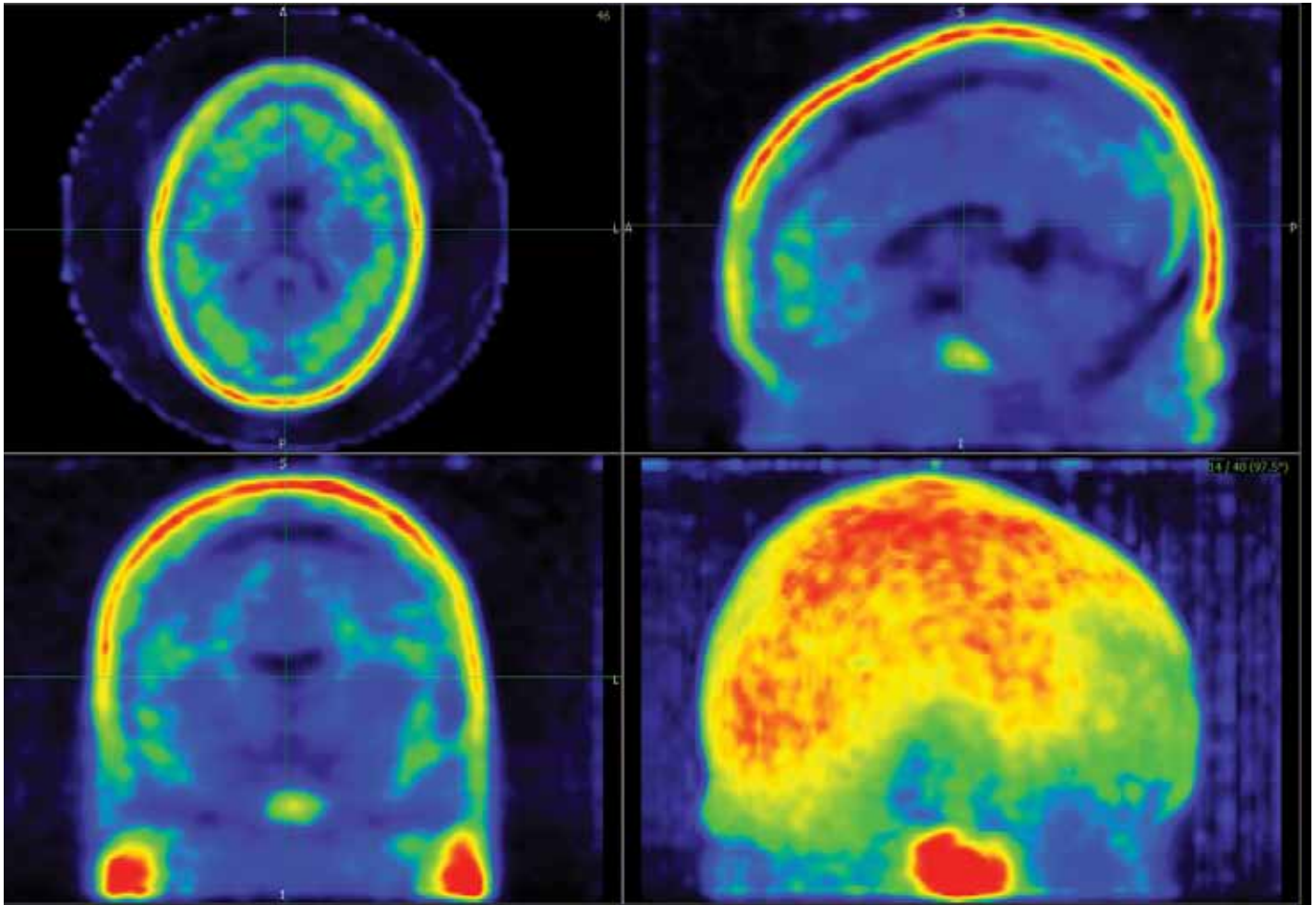
Until recently, the presence of amyloid deposits in the brain could only be detected during autopsy. Advances in radiopharmaceutical research have led to the development of agents, or radiotracers, that bind specifically to amyloid and can be safely injected into patients prior to a PET scan.

Yanming Wang, PhD, Associate Professor, Radiology, Chemistry and Biomedical Engineering, and Director, Radiopharmaceutical Division, Case Center for Imaging Research, Case Western Reserve University, was part of the team that developed the first successful amyloid imaging agent, Pittsburgh Compound B (PIB), nearly 10 years ago. Because PIB has a half-life of only 20 minutes, it is restricted to a research setting and is not commercially viable, Dr. Wang says. "The optimal agent should have minimal toxicity to the patient, it has to bind to amyloid specifically and nothing else, and if it cannot find amyloid in the brain it should also be cleared very quickly," he says. "Currently, we're trying to improve the specificity. We also are attempting to develop agents that bind to tau deposits, the other hallmark that is key to diagnosing AD."

PIB is part of a group of radiotracers labeled with carbon-11 compounds. AV-45, a newer agent belonging to the class of compounds known as fluorine-18, has a longer half-life that would permit widespread commercial distribution if it is proven effective. "The amyloid imaging agents are currently in development and available only through clinical trials," says Dr. Lerner. "Basically, all of our clinical trials now have a PET substudy, so we are testing these agents."

STARTING TO RECONSIDER

Dr. Lerner is site principal investigator for the AD Neuroimaging Initiative (ADNI), a public-private collaborative effort launched in 2004 and conducted by the National Institute on Aging. A new phase of the study will continue to track the current ADNI subjects and enroll additional patients with normal cognition,



Pictured is a positron emission tomogram (PET) using AV-45 (Avid Radiopharmaceuticals). AV-45 selectively binds to beta-amyloid and is being used in the investigation of Alzheimer's disease and mild cognitive impairment. These images were obtained from a 73-year-old woman with clinically probable AD, who was enrolled in a study of the use of gammaglobulin, intravenous for the treatment of AD.

Eli Lilly recently announced it was acquiring privately held Avid Radiopharmaceuticals for an upfront payment of \$300 million as well as \$500 million in additional payments. Payments are contingent upon future regulatory and commercial milestones for Avid's molecular imaging agent florbetapir, which is used to help detect amyloid plaque in the brain.

mild cognitive impairment or AD. PET imaging scans and spinal fluid testing for amyloid levels and tau protein will be conducted on every new patient enrolled. "These studies drive legitimate questions about cognitive aging in humans," says Dr. Lerner. "We're starting to reconsider what we've just spent the last 10 years telling people: that if you forget your keys once in a while it's not that important. Maybe it is important – we don't know. This is our window into the physiology and pharmacology of aging."

Enroll Your Patients

To inquire about ongoing clinical trials and patient referrals, call the Memory and Cognition Center at **216-464-6412** or visit **UHhospitals.org/neuro/clinicaltrials**.

AD Studies at UH

In addition to the Alzheimer's Disease Neuroimaging Initiative (ADNI) studies, investigators at the UH Neurological Institute Memory and Cognition Center are participating in three clinical trials to evaluate the following new treatments for Alzheimer's disease (AD):

- CERE-110, a viral-based gene transfer system designed to deliver nerve growth factor into the brain. UH Case Medical Center is the only site in the Midwest participating in this Phase II trial. It is enrolling subjects with mild to moderate AD.
- Latrepirdine (Dimebon), an antihistamine that improves mitochondrial function. The goal of the one-year, Phase III Concert Study, open to patients with mild to moderate AD taking donepezil, is to determine the effect of latrepirdine on cognition and memory, and self-care and daily function.
- Gammaglobulin, made from the blood of healthy adults and traditionally used to treat primary immunodeficiency disorders. Early research suggests that immunotherapy targeting amyloid may be an effective approach to treating AD. The Phase III Gammaglobulin Alzheimer's Partnership Study will examine the safety, effectiveness and tolerability of gammaglobulin in patients with mild to moderate AD.

Expert Urges Earlier Evaluation of Children with Epilepsy

Research points to cognitive gains after successful surgery



Ingrid Tuxhorn, MD, Chief, Division of Pediatric Epilepsy, UH Rainbow Babies & Children's Hospital

Surgery for young children with refractory epilepsy was once considered an avenue of last resort, appropriate only for patients whose seizures were not controlled by multiple medications. But a growing body of evidence accumulated during the past five to 10 years supports a broader spectrum of surgical candidates and earlier consideration of surgery, according to **Ingrid Tuxhorn, MD**, Chief, Division of Pediatric Epilepsy, University Hospitals Rainbow Babies & Children's Hospital.

Technologies such as positron emission tomography (PET), magnetic resonance imaging (MRI), video electroencephalography (EEG), and single photon emission computed tomography (SPECT), coupled with advances in surgical approaches, now allow pediatric epilepsy specialists to treat more types of epilepsy surgically and to perform surgery on infants who are only a few months old.

Tuberous sclerosis is one example of a disease previously thought to be treatable only with antiepileptic drugs, says Dr. Tuxhorn, who is Professor of Pediatrics and Neurology at Case Western Reserve University School of Medicine. "Patients with this disease have multiple tubers in the brain. Usually patients with multifocal epilepsy are not surgical candidates," she explains. "But there's a subgroup of patients, identified with the help of MRI, surface and invasive EEG, and functional imaging with ictal SPECT or PET, who seem to have one tuber that acts as a 'pacemaker' in the generation of focal seizures. If you remove that tuber surgically you can actually cure some of these patients or significantly reduce the seizure burden."

Approximately 60 to 80 percent of adult and pediatric epilepsy patients will respond to medical therapy with one or two drugs. The remaining 20 to 40 percent should be referred for pre-surgical evaluation to an epilepsy center with pediatric expertise, Dr. Tuxhorn says, to identify surgical options early on. This approach allows optimal timing of the surgery, which may reduce the negative impact of uncontrolled seizures on the developing brain. "Children tend to have more frequent seizures than adults. It's not unusual for a child to have daily seizures, and with catastrophic epilepsy the daily seizure frequency may be uncountable," she says. "In those cases, you're not going to hold off as long as you would with an adult who's having one or two seizures a month. If your evaluation shows that the seizures are focal, and the imaging shows you a lesion, you really should not even wait for a second or third drug."

Dr. Tuxhorn's research indicates that performing surgery early on babies and young children, rather than trying multiple drugs over the course of several years, may enable normal brain growth and improve the long-term cognitive development of children with severe, uncontrolled epileptic seizures. A study co-authored by Dr. Tuxhorn and published in *Epilepsia* (2005;46:561-7) showed that among patients who were seizure-free following surgery (33 patients out of 50), 11 patients showed gains of at least 15 IQ points, and a shorter duration of epilepsy was significantly associated with a postoperative increase in developmental quotient.

"Because the developing brain is very vulnerable to the effects of seizures, there's a very high risk that those children may lose developmental potential if they have ongoing epilepsy over a certain time period," Dr. Tuxhorn points out. "We don't really know what that period is, but there's no question that there are vulnerable phases. There's a lot of evidence that you can stabilize the progress of development and keep these kids from declining any further."

Surgical treatment of infants may require a hemispherectomy, a procedure performed at Rainbow by pediatric neurosurgeons. "This type of procedure requires extensive skill and training; the risks are higher for the smallest infants because of issues like blood loss and anesthesia," says Dr. Tuxhorn. "We try to wait until they weigh 5 to 8 kilograms. But generally the mortality risk is low, less than 1 percent. These are kids who are very sick, in intensive care because they're constantly seizing."

At the other end of the spectrum are the adolescents with more stable epilepsy. "They also need to be referred for surgical evaluation, because they're reaching a critical time of their lives when epilepsy can have a devastating impact—not just on cognitive functions like speech and memory, but also on self-esteem and social functioning," Dr. Tuxhorn says. "That's why it's so important to make sure that surgical candidates are selected early. And the only way to do it is to send them to an epilepsy center that has the requisite experience, expertise and technology."

Access Our Expertise

To schedule an appointment, please call the following numbers:

Patients: **216-UH4-KIDS**

Physicians: **216-844-PEDS**

Music Takes Center Stage

Treating musicians and promoting healing through music

A passion for music and a drive to explore the intersection of music, science and health led **Michael De Georgia, MD**, to spearhead the creation of the University Hospitals Neurological Institute's new Center for Music and Medicine. In addition to serving as the Center's Director, Dr. De Georgia is Director, Neurocritical Care Center, University Hospitals Case Medical Center, and Maxeen Stone & John Flower Professor of Neurology, Case Western Reserve University School of Medicine. He is also a percussionist with the World Doctors Orchestra and The Codes, a rock band.

COMMUNICATION AND COLLABORATION

"What struck me when I came here was the incredible depth of expertise in cognition and music on the UH campus and at CWRU. Some truly pioneering work is being done here, and at other prominent institutions in Ohio," Dr. De Georgia says. "We have a lot of resources at our fingertips, and it's in everyone's interest to collaborate. Thus, our Center serves as a hub to facilitate research and communication among experts throughout the area." Also included in the collaborative effort are arts organizations such as the Cleveland Institute of Music and the Rock and Roll Hall of Fame and Museum.

The overarching mission of the Center is to promote healing, education and research. That translates to efforts as diverse as treating injured musicians, using music to enhance patients' experiences, educating patients and physicians about the available therapies and medical resources involving music and the arts, and exploring the relationship between music, memory and dementia. Educating the public about the neurological foundations of music is a key goal. At the first annual Cleveland Music and Medicine Symposium last year, experts addressed topics such as the neurological basis for music, geographical differences in pitch perception, and the appeal of sad songs.

TREATING MUSIC-RELATED DISORDERS

As the father of three dedicated student musicians, Dr. De Georgia is particularly invested in advancing the prevention and treatment of music-related disorders. Physicians associated with the Center's Musician Wellness Program diagnose and treat amateur and professional musicians with a broad range of neuromuscular, psychological and otolaryngological disorders.

"The incidence of hearing loss is 10 to 20 percent among musicians, and it occurs in classical as well as rock musicians," explains Dr. De Georgia. "It can be a



When not serving as the Director of the UH Neurological Institute's Center for Music and Medicine, Michael De Georgia, MD, plays the drums for his rock band, The Codes.

career-ending disability. In collaboration with CWRU and Baldwin-Wallace College, we're developing and testing hearing protection devices that can actually block specific frequencies. If you're playing in an orchestra, you obviously don't want to wear earplugs and block all the sound, but you might want to wear a device that blocks the frequency of the trumpet."

Overuse syndrome, experienced by an estimated 75 percent of string players, is another focus of the Center's research. "Students and teachers need to be more aware of the incidence of these disorders and what can be done to prevent them, particularly overuse," Dr. De Georgia says. "That mantra of no pain, no gain can be especially damaging if you are a 15-year-old budding cellist. Our plan is to develop a nationwide outreach to conservatories to educate students and teachers about the importance of correct hand positions and other preventive measures."



Michael De Georgia, MD, Director, University Hospitals Neurological Institute Center for Music and Medicine, and Director, Neurocritical Care Center, UH Case Medical Center

Contact Us

A physician treating a student or professional musician who has a music-related disorder (physical, psychological or emotional) may call the Center for Music and Medicine at **1-866-UH4-CARE (1-866-844-2273)**. A staff member will arrange an appointment for your patient with a physician who has expertise in diagnosing and treating the relevant disorder.



Neurological Institute Journal

Advanced Learning & Free CME Credits

The University Hospitals *Neurological Institute Journal* provides physicians with learning opportunities surrounding innovations in surgeries, treatment options, research protocols and more gained from the bench-to-bedside methodology utilized at UH.

You can receive up to 1.5 hours of free *AMA PRA Category 1 Credits™* by reading the Spring 2010 edition of *Neurological Institute Journal*.

- Interventional Therapies for Acute Ischemic Stroke
- Neurofibromatosis Type 2: Unraveling a Challenging Disorder
- Taking Brain Health to a Deeper and Broader Level
- New Developments in Tay-Sachs Disease

To request a copy or view online, visit UHhospitals.org/NIJJournal.

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Image courtesy of Apple

University Hospitals Neurological Institute

At convenient locations throughout Northern Ohio, University Hospitals Neurological Institute delivers innovative, integrated and individualized care to patients with diseases affecting the nervous system.



We are the only Neuroscience Center of Excellence in the state of Ohio with a Stage 4-Institute Designation. Our 16 Centers of Excellence offer you premier care and access to some of the country's foremost experts in neurology, neurosurgery, neuroradiology, neuro-oncology, neuro-ophthalmology, neurotology, neuropathology, neuropsychology and related specialists. These teams work in collaboration with medical specialists at UH Rainbow Babies & Children's Hospital and the UH Seidman Cancer Center (formerly UH Ireland Cancer Center), with access to the UH Neuroscience Intensive Care Unit and Neuroscience Nursing Practice.

A relationship with UH doctors provides you:

- **Access:** 24-hour referral access for urgent cases.
- **Communication:** Keeping you informed about your patients' treatment plan and progress.
- **Professionalism:** Our goal is to return referred patients to you for ongoing care.
- **Education:** Ongoing CME learning opportunities along with explanation of treatment plans.

Whether referring patients to University Hospitals for a second opinion or treatment of complex diseases, the integration between physician specialists and researchers allows for the development of an individualized treatment plan based on patient-centered needs.

Sending your patients to the University Hospitals Neurological Institute provides:

- **State-of-the-Art Care:** Access to the Neuroscience Intensive Care Unit.
- **Personalized Treatment Plans:** Developed by a multidisciplinary team of physicians.
- **Caring Environment:** Availability of the Neuroscience Nursing Practice.
- **Cutting-Edge Advancements:** Access to research results and the latest clinical trials.

24-Hour Rapid Referral

Now connecting your patients to the UH Neurological Institute within 24 hours

Rapid Referral is the fast and convenient way to get connected to our neurological team of experts. Call the UH Rapid Referral line – and your patient will see a UH Neurological Institute specialist within 24 hours of making the appointment. **Call 1-866-UH4-CARE (1-866-844-2273) to get an appointment within 24 hours.**

PHYSICIAN ADVICE LINE

You're just one phone call away from the finest neurosurgeons, neurologists and specialists in the country. Receive immediate decision-making advice from the UH Neurological Institute team of experts by calling **216-844-1001**.