neurotransmitter

A MAGAZINE OF THE GEORGE WASHINGTON INSTITUTE FOR NEUROSCIENCE AND
THE GEORGE WASHINGTON UNIVERSITY HOSPITAL'S NEUROLOGICAL INSTITUTE

spring 2018

The Spring 2018 edition of *Neurotransmitter* demonstrates that the rigorous fields of the basic and clinical neurosciences have spiritual and artful sides.

Since its inception, *Neurotransmitter* has been decorated with art that plays off the subjects of its articles. This edition produces its own art. Within these pages, you can see a beautiful microscopic image of nerve bodies and their supporting cells taken by first-year MD student Aslam Akhtar, PhD, as part of his research studies of the olfactory bulb, an area of the brain critical to the sense of smell. His photo could hang in any Washington, D.C., gallery, but it also educates about the complexity of the brain.

James L. Griffith, MD, chair of the Department of Psychiatry and Behavioral Sciences and Leon M. Yochelson Professor of Psychiatry and Behavioral Sciences, was honored for his lifetime of work leveraging the power of religious belief in psychiatric therapy, especially for those of us suffering profound traumas.

You also can read about virtual reality technology that allows our neurosurgeons to map complex surgeries to remove tumors or treat blood vessel abnormalities before they enter the operating room. Here again, the images demonstrate the beauty and complexity that is the human brain.

Director of the George Washintgon University (GW) Institute for Neuroscience Anthony-Samuel LaMantia, PhD, professor of pharmacology and physiology, was honored recently in two ways. First, the sixth edition of LaMantia's textbook, Neuroscience, was published. The book has become the standard for the field and is the source for budding neuroscientists to receive their education. Second, GW's School of Medicine and Health Sciences (SMHS) acknowledged his excellence by naming him the Jeffrey Lieberman Professor of Neurosciences. Joining LaMantia as an endowed professor is GW resident alumnus Brandon Kohrt, MD, PhD, RESD '13, associate professor of psychiatry and behavioral sciences, who became the Charles and Sonia Akman Professor in Global Psychiatry. Not only is an endowed professorship a prestigious appointment at any academic institution, but it also provides financial support of neuroscience research at GW and honors the donor in perpetuity. Such endowments are the lifeblood of universities from the time they were first established at Oxford University centuries ago.

Neurotransmitter further spans the breadth of the neurosciences with stem cell treatments for multiple sclerosis and brain stem physiology that could lead to potential therapies for sleep apnea. As you will appreciate, discoveries occur through the collaboration of many scientists and physicians. This is the strength of GW Hospital, GW Medical Faculty Associates, and SMHS.

ANTHONY CAPUTY, MD
Chair, Department of Neurosurgery,
and Hugo V. Rizzoli Professor
of Neurological Surgery

HENRY J. KAMINSKI, MD
Chair, Department of Neurology,
and Meta Amalia Neumann
Professor of Neurology

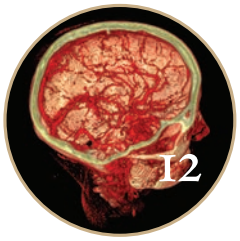
JAMES L. GRIFFITH, MD
Chair, Department of
Psychiatry and Behavioral Sciences,
and Leon M. Yochelson Professor of
Psychiatry and Behavioral Sciences

ANTHONY-SAMUEL LAMANTIA, PhD
Director, GW Institute for Neuroscience,
Jeffrey Lieberman Professor of Neurosciences,
and Professor of Pharmacology and Physiology

ROBERT H. MILLER, PhD
Senior Associate Dean for Research,
Vivian Gill Distinguished Research Professor,
and Professor of Anatomy and Regenerative Biology

neurotransmitter *spring 2018*

contents



THE NEUROSCIENCES INSTITUTE (NI) at the George Washington University Hospital is a premier neurological center. Patients come for comprehensive interdisciplinary care by the Institute's internationally recognized team of experts. The team treats patients for a wide range of neurological problems and provides expert care for patients with the most complex disorders that affect the nervous system. The NI consists of neurosurgeons, neurologists, emergency room physicians, critical care specialists, physiatrists, psychiatrists, neuro-radiologists, neuro-pathologists, and neuro-interventional specialists as well as outstanding allied health service providers in nursing, speech therapy, physical therapy, occupational therapy, and neuro-rehabilitation. The NI combines medical and surgical services, along with research and education, under unified leadership to optimize the health of our patients now and into the future through a multidisciplinary approach, state-of-the-art technology, and innovative treatment trials. To learn more, visit **www.gwhospital.com/hospital-services/the-neurosciences-institute-at-the-george-washington-university-hospital**.

Co-Directors: **ANTHONY CAPUTY**, MD, FACS; **HENRY KAMINSKI**, MD; and **KIM RUSSO**, MS, MBA, CEO/managing director of George Washington University Hospital

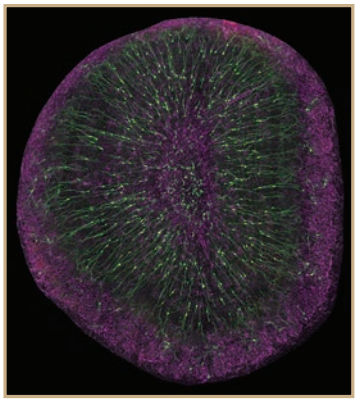
GW MFA Neurology
202-741-2700
www.gwdocs.com/neurology

GW MFA Neurosurgery
202-741-2750
www.gwdocs.com/neurosurgery

GW MFA Psychiatry
202-741-2888
www.gwdocs.com/psychiatry

CLINICAL CENTERS:
Cognitive Neurology Center
Deep Brain Stimulation Center
Epilepsy Center
Headache / Migraines Center
Interventional and Therapeutic Neuroradiology Center
Multiple Sclerosis Center
Neuro Imaging Center
Neuro-Oncology Center
Neuro Trauma Critical Care Center
Neuromuscular Disorders Center
Parkinson's Disease Center
Sleep Center
Spine Center
Stereotactic and Radiosurgery Center
Stroke Treatment Center
Translational Research Center

CONTEST HIGHLIGHTS THE ART OF SCIENTIFIC RESEARCH AT SMHS



THE BEAUTY OF SCIENCE
First-year MD student Aslam Akhtar, PhD, is the inaugural grand prize winner of the George Washington University School of Medicine and Health Sciences Art of Science Contest. Akhtar's image was selected from the 12 images submitted for consideration.

Looking at a winning submission for the first-ever George Washington University (GW) School of Medicine and Health Sciences (SMHS) Art of Science Contest, one might not know the bright purple and green colors represent olfactory bulb interneurons and astrocytes in the brain, but that's the beauty of art: there's more to it than meets the eye.

The contest shows off the amazing research medical students, graduate students, and post-doctoral fellows are conducting "through dynamic and beautiful images," said Alison Hall, PhD, associate dean for research workforce development and professor of neurology at SMHS.

The four contest winners – chosen by a team of SMHS deans, students, and staff – will have their images displayed in the SMHS Dean's Suite in Ross Hall.

Grand prize winner and first-year MD student Aslam Akhtar, PhD, said a push from classmates and class discussions about the olfactory bulb neurons – the neurons responsible for our sense of smell – led him to enter his image in the contest.

"I hope when someone walks by they reflect more about the deeper meaning," Akhtar said, adding hopefully "it will create an appreciation for the complexity of the brain and the lifelong impacts that diseases of the brain can have."

The image, he added, arose from his neurodevelopmental research into how neurons in the brain develop from neural stem cells after birth. "There are only a few regions of the brain where neurons are generated after birth, the olfactory bulb being one of these regions," he said. "If we can better understand the characteristics of the stem cells that generate these neurons, we can apply that knowledge toward replacing or supporting cells lost in neurodegenerative diseases."

This year, 12 images were submitted for consideration, and Hall said she hopes even more images, reflecting even broader approaches to research, are submitted in the years to come. The contest will be an annual event.

Winner Shabnum Patel, PhD, a post-doctoral fellow with the GW Cancer Center, submitted an image showing her immunotherapy research. "For this image, we were focused on making Mucor-specific T-cells to fight the fungal infection Mucormycosis," she said. "We thought [the contest] would be a nice way not only to display a beautiful picture, but also to get people interested in the type of research that we do."

Hall added that the beauty of the entries is what makes the contest so interesting.

"[When choosing a winner,] we didn't ask 'Is this an important scientific advancement?' or 'Is this technique important?' We were really just looking at how attractive it was," Hall said. "But beneath these pretty images are major advances in our understanding of biomedical science and potential medical advances."

> "[When choosing a winner,] we didn't ask 'Is this an important scientific advancement?' or 'Is this technique important?' We were really just looking at how attractive it was. But beneath these pretty images are major advances in our understanding of biomedical science and potential medical advances."
>
> **Alison Hall**, PhD

> "I hope when someone walks by they reflect more about the deeper meaning. [Hopefully] it will create an appreciation for the complexity of the brain and the lifelong impacts that diseases of the brain can have."
>
> **Aslam Akhtar**, PhD, first-year MD student

SETTING THE STANDARD FOR NEUROSCIENCE, RESEARCHERS RELEASE SIXTH EDITION OF ACCLAIMED TEXT

Academic publisher Sinauer Associates announced this fall the release of the sixth edition of Neuroscience, co-authored and co-edited by Anthony-Samuel LaMantia, PhD, director of the George Washington University (GW) Institute for Neuroscience (GWIN), Jeffrey Lieberman Professor of Neurosciences, and professor of pharmacology and physiology at GW's School of Medicine and Health Sciences (SMHS). Since its initial publication, the comprehensive text has grown to become a standard in the dynamic field of neuroscience, spanning topics from cellular signaling to cognitive function.

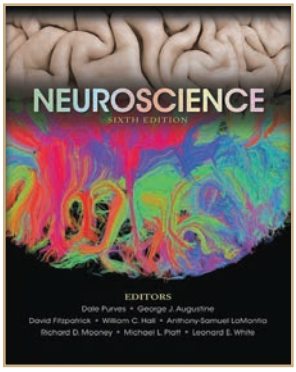
The best-selling and most widely used text for medical and undergraduate neuroscience courses has been a combined effort over its many years, according to LaMantia, and features co-authors and editors from Duke Institute for Brain Sciences; Duke University School of Medicine; Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; the Max Planck Florida Institute for Neuroscience; and the University of Pennsylvania.

> "It's an interesting time for this aspect of academic science, education, neurosciences, and academic publishing."
>
> Anthony-Samuel LaMantia, PhD

This recent edition is also the first published since Sinauer became a subsidiary of Oxford University Press. "That means that the book … has a larger audience as part of the Oxford University Press orbit," said LaMantia.

"I think everyone is very enthusiastic," he added. "It's an interesting time for this aspect of academic science, education, neurosciences, and academic publishing."

New to this edition is an expanded cognitive neuroscience unit, with chapters on attention, decision-making, and evolution of cognitive functions; an updated neural signaling unit; and new clinical applications boxes and web essays.



A NEW RELEASE
The sixth edition of Neuroscience, co-authored and co-edited by Anthony-Samuel LaMantia, PhD, was released by Sinauer Associates, a subsidiary of Oxford University Press, in the fall of 2017. Since its initial publication, the textbook has become the most widely used text for medical and undergraduate neuroscience courses. It is now a standard in the dynamic field of neuroscience.

WHERE RELIGION MEETS PSYCHIATRY
James L. Griffith, MD, received the American Psychiatric Association's Oskar Pfister Award. The award, which is named after a Lutheran minister, is presented to individuals who have made outstanding contributions to the understanding of the interplay between religion and psychiatry.

DRAWING STRENGTH FROM THE SPIRITUAL SIDE

James L. Griffith, MD, chair for the Department of Psychiatry and Behavioral Sciences and Leon M. Yochelson Professor of Psychiatry and Behavioral Sciences at the George Washington University School of Medicine and Health Sciences, received the Oskar Pfister Award from the American Psychiatric Association during the association's Institute on Psychiatric Services: The Mental Health Services Conference in New Orleans.

The award – named in honor of Oskar Pfister, a Lutheran minister who studied and used psychoanalytic principles in his work – is presented annually to individuals who have made outstanding contributions to the understanding of the interplay between religion and psychiatry.

Over the course of his career, Griffith has focused on helping clinicians learn how to draw from patients' spiritual resources when helping them to cope and sustain resilience in the face of disease, disability, and suffering. He has become a global mental health leader, providing psychiatric treatment for immigrants, refugees, and survivors of political torture.

At the meeting, Griffith also delivered the Oskar Pfister Award Lecture, "Hope Modules: Brief Psychotherapeutic Interventions to Counter Despair from Chronic Adversities." Griffith described his work developing brief interventions to help patients sustain hope despite demoralizing life circumstances and methods for teaching trainees and other clinicians.

GW Expands Presence at Neuroscience 2017

Neuroscience 2017 drew more than 30,000 scientists from throughout the world to Washington, D.C.

The George Washington University (GW) had an enhanced presence at one of the largest neuroscience conferences in the world, The Society for Neuroscience 2017 Annual Meeting, held at the Walter E. Washington Convention Center in mid-November.

The meeting drew more than 30,000 scientists from throughout the world to Washington, D.C., for a week of presentations and intellectual exchanges about the brain, how it works, how it develops, and the challenges of solving brain diseases.

Anthony-Samuel LaMantia, PhD, director of the GW Institute for Neuroscience, Jeffrey Lieberman Professor of Neurosciences, and professor of pharmacology and physiology at GW's School of Medicine and Health Sciences (SMHS), said the meeting comes to Washington, D.C., every three years, and this year GW's presence was expanded to include satellite sessions held on the GW Foggy Bottom campus.

LaMantia added that both the promise and challenge of having such a prominent role at the meeting is to continue to expand GW's neuroscience community to be a part of all the changes happening in the field. The last several years have brought robust growth to neuroscience research at GW, and there is a commitment to continue to grow in this critical area of biomedical research.

Throughout the meeting, GW neuroscientists from SMHS, the Columbian College of Arts and Sciences, and the Milken Institute School of Public Health at GW presented nearly 60 research posters.

SMHS faculty also spoke at the event, including Robert H. Miller, PhD, senior associate dean of research, Vivian Gill Distinguished Research Professor, and professor of anatomy and regenerative biology; Vittorio Gallo, PhD, associate dean for child health research and professor of pediatrics; and Kevin Pelphrey, PhD, director of the GW Autism and Neurodevelopmental Disorders Institute and Carbonell Family Professor in Autism and Neurodevelopmental Disorders.

One of the main takeaways from the event, LaMantia said, is the growth in addressing translational issues of neuroscience. "I think we want to develop more aspects of translational research at GW, because that is something more and more being featured in the field," he said. Recent progress, attendees reported, hold promise for new approaches to disorders that previously were thought insoluble. These include neurodegenerative disorders like Alzheimer's and neurodevelopmental disorders like autism spectrum disorder.

"I think it will be interesting in 2020, when Neuroscience returns to D.C., to see [what direction research has taken the profession]," LaMantia added. "The field has grown, but it's also changed. I am hopeful that will continue, and that we will even have a bigger presence in 2020."

THE MEETING OF PEERS
The Society for Neuroscience 2017 Annual Meeting was held at the Walter E. Washington Convention Center in mid-November. The conference, one of the largest neuroscience conferences in the world, will return to Washington, D.C., in 2020.

Brandon Kohrt Installed as Charles and Sonia Akman Professor in Global Psychiatry

CHANGING THE LIVES OF CHILDREN
Brandon Kohrt, MD, PhD, RESD '13, (right) was recently installed as the Charles and Sonia Akman Professor in Global Psychiatry. In his career, Kohrt has worked to reduce stigma among youth and adults affected by mental illness, political violence, and physical illness in countries such as Nepal, Liberia, South Africa, Ethiopia, Mongolia, Haiti, and India.

Sangeeta, Ramesh, Asha. Those are names of children whose lives were restored thanks to the efforts of global mental health expert Brandon Kohrt, MD, PhD, RESD '13, associate professor of psychiatry and behavioral sciences at the George Washington University (GW) School of Medicine and Health Sciences (SMHS). Kohrt shared their stories at his installment as the Charles and Sonia Akman Professor in Global Psychiatry.

"We are all part of the George Washington University because of the dedication to improving the quality of the human experience and to reducing human suffering through research, education, and service," Kohrt said. "I am deeply grateful … for the opportunity to pursue this mission to its fullest extent."

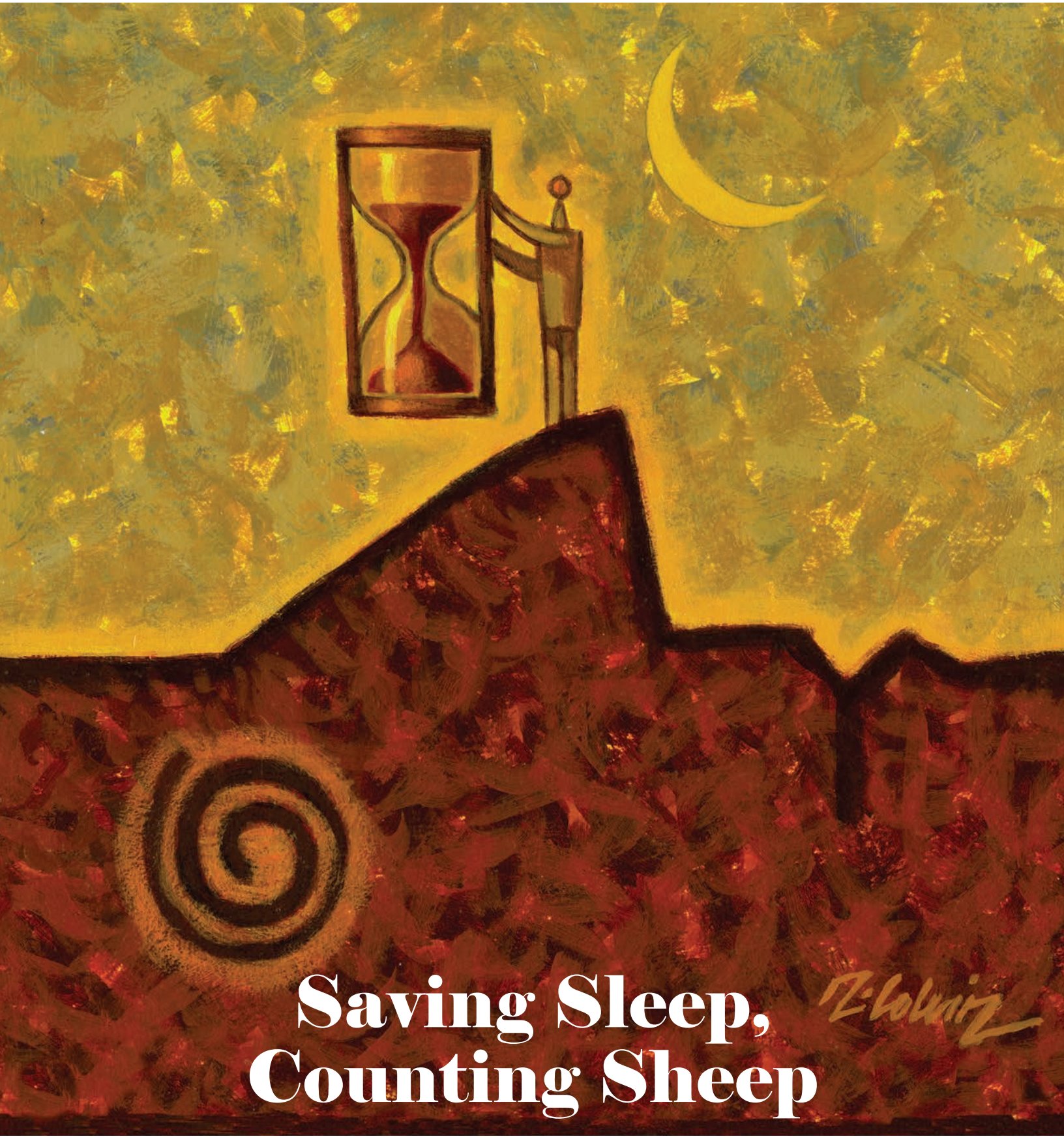
The endowed fund was made in memory of the parents of Leonard C. Akman, MD '43, a pioneer in heart transplantation and cardiac catheterization and cousin to Jeffrey S. Akman, MD '81, RESD '85, vice president for health affairs, Walter A. Bloedorn Professor of Administrative Medicine, and dean of SMHS. When Leonard Akman passed away, he left SMHS a $3.2 million gift to support a variety of initiatives, the choosing of which he left to his cousin.

Kohrt has worked on mental health in Nepal since 1996 and as an adviser to the Transcultural Psychosocial Organization in Nepal since 2006. He also has collaborated with The Carter Center Mental Health Program in Liberia since 2010, and he has investigated the mental health consequences of and designed interventions for child soldiers and earthquake survivors in Nepal.

In addition, Kohrt collaborated on the development of a Nepali school-based youth suicide prevention program. And, in Liberia, Kohrt designed programs to reduce stigma among youth and adults affected by mental illness, political violence, and the Ebola outbreak. "He has worked in South Africa, Ethiopia, Mongolia, Haiti, and India," said Forrest Maltzman, provost and executive vice president for academic affairs at GW. "He is changing the world, and he is never sleeping."

"We are all part of the George Washington University because of the dedication to improving the quality of the human experience and to reducing human suffering through research, education, and service."

Brandon Kohrt, MD, PhD, RESD '13



Saving Sleep, Counting Sheep

GEORGE WASHINGTON MEDICAL FACULTY ASSOCIATES CENTER FOR SLEEP DISORDERS FOCUSES ON HELPING PATIENTS CATCH SOME Zs

BY **KATHERINE DVORAK**

We've all been there at some point, tossing and turning and counting down the minutes before the alarm goes off and the day begins. For more than a third of the American population, however, sleep disorders such as insomnia, sleep apnea, narcolepsy, and restless legs syndrome make those struggles a nightly occurrence, often putting those precious seven to eight hours of sleep out of reach.

Insufficient sleep is more than an inconvenience; it can cause serious long-term cardiac and neurological problems, including increased risk of hypertension, stroke, and even cognitive impairment, according to David Mendelowitz, PhD, vice chair and professor of pharmacology and physiology at the George Washington University (GW) School of Medicine and Health Sciences (SMHS).

"More work is beginning to touch on the hypothesis that sleep apnea might be involved in more long-term problems, such as Alzheimer's disease."

David Mendelowitz, PhD

Mendelowitz says there's growing recognition of the intersection between conditions such as obstructive sleep apnea and serious neurologic disorders. "More work is beginning to touch on the hypothesis that sleep apnea might be involved in more long-term problems, such as Alzheimer's disease," he says.

One of Mendelowitz's efforts is finding novel treatments for obstructive sleep apnea, a chronic condition involving an intermittent blockage of the upper airway during sleep, which is associated with snoring, pauses in breathing, and excessive sleepiness. More than 18 million adults in the United States suffer from the disorder, according to the National Sleep Foundation.

"There are very significant cardiovascular consequences of sleep apnea. We're interested in what changes in the central nervous system, particularly in the brain stem, occur during sleep apnea to initiate and/or sustain these cardiovascular diseases," Mendelowitz says. "At the same time, we want to identify targets of opportunity for treating sleep apnea to reduce the dysfunction of the cardiovascular system and reduce the risks of adverse cardiovascular events."

However, sleep apnea is often underdiagnosed. The closure of the airway, says Vivek Jain, MD, medical director of the GW Medical Faculty Associates' (MFA) Center for Sleep Disorders and associate professor of medicine at SMHS, often goes unnoticed during sleep. "Most patients won't recognize they have sleep apnea," Jain says. "For every patient [with sleep apnea] we see in the clinic, or in general in the country, I think there are probably two out there who haven't been tested."

Jain adds that the symptoms of sleep apnea – fatigue, daytime sleepiness, or interrupted sleep – usually are what drive patients to the Center for Sleep Disorders.

Patients diagnosed with sleep apnea are often prescribed a continuous positive airway pressure

For more than a third of the American population, sleep disorders such as insomnia, sleep apnea, narcolepsy, and restless legs syndrome make getting enough sleep a nightly struggle.

therapy (CPAP) device. The machine, which includes a plastic mask that fits over a user's nose and sometimes mouth, is worn during sleep and helps to increase air pressure so the airway doesn't collapse when a person inhales. CPAP machines are 100 percent effective when patients use them, notes Jain. Unfortunately, he adds, they have low compliance.

"At least 50 percent of the patients who are prescribed CPAP machines discontinue their use or use them for less than four hours a day," Mendelowitz says. "It's extremely uncomfortable, awkward, and it's not the sexiest thing in the world to be sleeping with a mask on your face."

Currently there are no pharmacological treatments for the disorder, he notes. But, Jain and Mendelowitz are collaborating on translational research in the hope of discovering such an option.

"Two graduate students in my lab … were looking at a pathway from the hypothalamus to neurons that are important in autonomic control. They found that there's a specific population of neurons in the paraventricular nucleus of the hypothalamus that releases oxytocin, which in turn excites autonomic parasympathetic neurons to the heart and restores autonomic balance," Mendelowitz explains. "We found in our work that activation of these oxytocin neurons prevented the hypertension that occurs in an animal model with sleep apnea."

After the discovery, Mendelowitz approached Jain about conducting a pilot project to test if oxytocin would be beneficial in patients with sleep apnea. Eight patients diagnosed with sleep apnea presented for a sleep study and received a dose of oxytocin via a nasal spray before bed.

Their initial findings were positive, Jain and Mendelowitz say, showing that oxytocin may play a role in shortening apnea duration and lessening nighttime arousals. "These patients did subjectively feel better. [It's an] uncontrolled, non-blinded, non-randomized placebo control study, but it's a good beginning," Jain says.

While sleep apnea is one of the main disorders for which patients seek out the sleep center, it's not the most common, Jain says. Although people may not see it as a disorder, sleep deprivation is one of the most prevalent sleep conditions, he notes, and insomnia, the inability to fall asleep or return to sleep in the night, comes in second.

In addition, says Mendelowitz, a lot of these conditions can be overlapping; someone can have both sleep deprivation and sleep apnea.

Another sleep disorder, which affects 10 percent of U.S. adults, is restless legs syndrome. Elias Karroum, MD, PhD, assistant professor of neurology at SMHS and a neurologist at the MFA, whose research focuses on the condition, notes that restless legs syndrome differs from other sleep disorders be-

SIGNS OF SLEEP APNEA

- Snoring that's interrupted with periods of quiet
- Snoring that resumes with a loud sound as breathing restarts
- Morning headaches
- Frequently falling asleep during the day
- Being easily irritated
- Depression
- Difficulty remembering things

> "People talk about impairment of alcohol, but we should also open the conversation on impairment due to sleep problems."
>
> Vivek Jain, MD

cause it happens while a person is awake.

Also known as Willis-Ekbom Disease, the disorder causes uncomfortable sensations in the legs and an irresistible urge to move them. It happens to people in the evening or at night while they are still awake and can prevent people from falling asleep, which can lead to insomnia, says Karroum.

"I like to think of it as a resting wakefulness disorder with a core sensory component of feeling the need to move the limbs," he explains. In addition, in up to half of the patients, the abnormal sensations are not only unpleasant, but also quite painful. Karroum says one reason he is studying this disorder is because there is still a lot to learn about it, including what causes the sensations and pain in these patients.

Two to 3 percent of U.S. adults experience moderate to severe cases of restless legs syndrome, in which the sensation occurs two to three times a week and negatively affects a patient's daily life, Karroum says. For those patients, he'll recommend a small dose of dopamine agonists, which mimic the neurotransmitter dopamine in the brain.

Jain says while research on sleep has picked up in the last 20 years, "there's still more to be done."

"People may blow a lack of sleep off, saying 'oh, I get six hours of sleep at night,' and they don't even bat an eye. But six hours of sleep is not right. It really has its own independent negative effects on health, including many cardiovascular diseases, obesity, and diminished cognitive awareness," he says. "People talk about impairment of alcohol, but we should also open the conversation on impairment due to sleep problems."

WHAT TO EXPECT AT THE SLEEP CLINIC

When arriving at the MFA Center for Sleep Disorders, patients give detailed histories of their sleep patterns. Some of the questions asked include: What time do you go to bed? How many minutes does it take you to fall asleep? Do you fall asleep at inappropriate times? Do you snore?

If overnight monitoring is deemed necessary to diagnose the right sleep disorder, a patient will either be brought to the lab – located at 2021 K St., NW – for a sleep study, or given monitors to take home.

At home: Home monitors are not as extensive as those used in clinic-based sleep studies. These devices simply record breathing and oxygenation. If the home monitor shows a mild case of a disorder such as sleep apnea, then an in-lab study may be requested to confirm the findings.

In the lab: Patients spend the night in a hotel-like setting to have their sleep monitored. Study arrival time is 8:30 p.m., at which point a patient is prepped for a polysomnography test, which takes about 45 minutes. The test looks at brain-wave patterns and physiologic function during sleep. Sensors are placed on the face and scalp to measure electrical activity in the brain, a sensor by the nose records respiration rates, and oxygenation is measured using a finger probe, and belts on the chest and abdomen measure breathing effort.

While it's expected that patients won't have a perfect night's sleep in the lab – people rarely do when not in the comfort of their own beds – disorders like sleep apnea will surface even if subjects only get a few hours of shut eye.

"Even if you sleep on the Metro, or fall asleep at home on the couch, you will have sleep apnea," says Jain. "It's a sleep phenomenon; it's not a stress-related phenomenon or environment-related phenomenon."

Insufficient sleep can cause serious long-term cardiac and neurological problems, including increased risk of hypertension, stroke, and even cognitive impairment.

Of Mice and MSCs

MESENCHYMAL STEM CELL RESEARCH OFFERS PROMISE AND PUZZLES

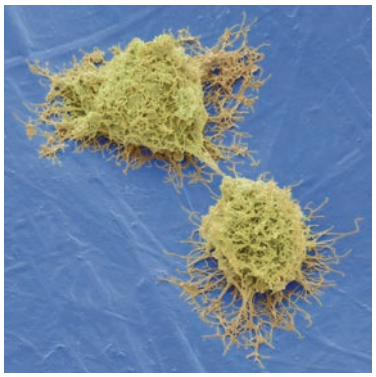
BY **STEVE GOLDSTEIN**

Robert H. Miller, PhD, senior associate dean for research, Vivian Gill Distinguished Research Professor, and professor of anatomy and regenerative biology

Cell therapy is number one on the research rock charts. The practice of transferring intact, live cells into a patient to help lessen or cure a disease is rapidly expanding, and in the United States alone, there currently are more than 15,000 active clinical trials in the field.

One of the most promising therapies is the transplantation of mesenchymal stem cells (MSCs), which are multipotent cells present in multiple tissues including umbilical cord, bone marrow, and fat. MSCs give rise to bone, cartilage, muscle, and adipocytes (fat cells), which promote marrow adipose tissue. These versatile cells are particularly suited as a cellular therapy for autoimmune diseases, including multiple sclerosis (MS), and they have immunosuppressive and tissue repair properties that lend themselves to therapy for inflammatory diseases. Based on their success in treating animal models of MS-like experimental autoimmune encephalomyelitis (EAE) – a brain-inflammatory disease of the central nervous system that erodes the myelin sheath protecting nerves – MSCs have moved rapidly into clinical trials for MS.

Such a trial is described in a research paper co-authored by Robert H. Miller, PhD, senior associate dean for research, Vivian Gill Distinguished Research Professor, and professor of anatomy and regenerative biology at the George Washington University School of Medicine and Health Sciences. Despite the hope and promise resting on MSCs, the clinical trial failed to show significant improvement, resulting in the conclusion that central nervous system damage diminishes the therapeutic function of bone marrow MSCs.



LOOKING FOR A TREATMENT FOR MULTIPLE SCLEROSIS
Robert H. Miller, PhD, led a clinical trial to transplant mesenchymal stem cells (right). These versatile cells are particularly suited as a cellular therapy for autoimmune diseases, including multiple sclerosis.

"This is a pretty interesting cell therapy – it's one of the most interesting of the therapies around," Miller says. "There are something like 27 MSC clinical trials going on now."

In the paper, Miller reports that bone marrow MSCs derived from mice with encephalomyelitis weren't as effective at treating the disease as those from uninfected mice. Similarly, the cells derived from MS patients showed less therapeutic efficacy in treating EAE, and researchers also observed the secretion of higher levels of some pro-inflammatory proteins. The results, showing diseases such as EAE and MS reduce the therapeutic effectiveness of bone marrow MSCs, are leading researchers to rethink the use of a patient's own MSCs as a potential MS treatment.

Despite the outcome, Miller is upbeat about the therapeutic value of MSCs, recalling how, before this study, they found human mesenchymal stem cells were very effective in reducing the disease burden in animals. "When we got that data, I went to see Jeff Cohen at the Cleveland Clinic … and he put the clinical trial together with 12 patients – all of whom had MS," says Miller.

As Miller explains in the paper, MSCs are defined experimentally as a population of cells that "stick to things" and can generate the major connective tissue derivatives, such as fat and mesenchymal tissues. They also are self-renewing, so they can divide.

"We know they live in bone marrow, and we know they live in fat and adipose tissues, and some people think they are parasites that live around vasculature in many organs," Miller explains. "They are relatively hard to isolate."

Putting human MSCs into mice, according to Miller, was effective at reducing disease, and putting mouse cells into mice is also effective at reducing disease. In human trials, however, the treatment has not proven to be as effective in reducing disease. "What this paper argues is that it's not necessarily true that the human MSCs are bad or that the human disease is different – although we don't know that," Miller says. The outcome was determined by what happened to the bone marrow before cells were isolated. In the trial, patients came in, had bone marrow taken from their hips, the MSCs were isolated, and they were expanded in a dish and then reinfused into the vasculature. "All the clinical trials had used that paradigm because the FDA feels quite strongly about the possibility of rejection," says Miller. "The studies in mice were done using normal human-derived cells – not MS-derived cells."

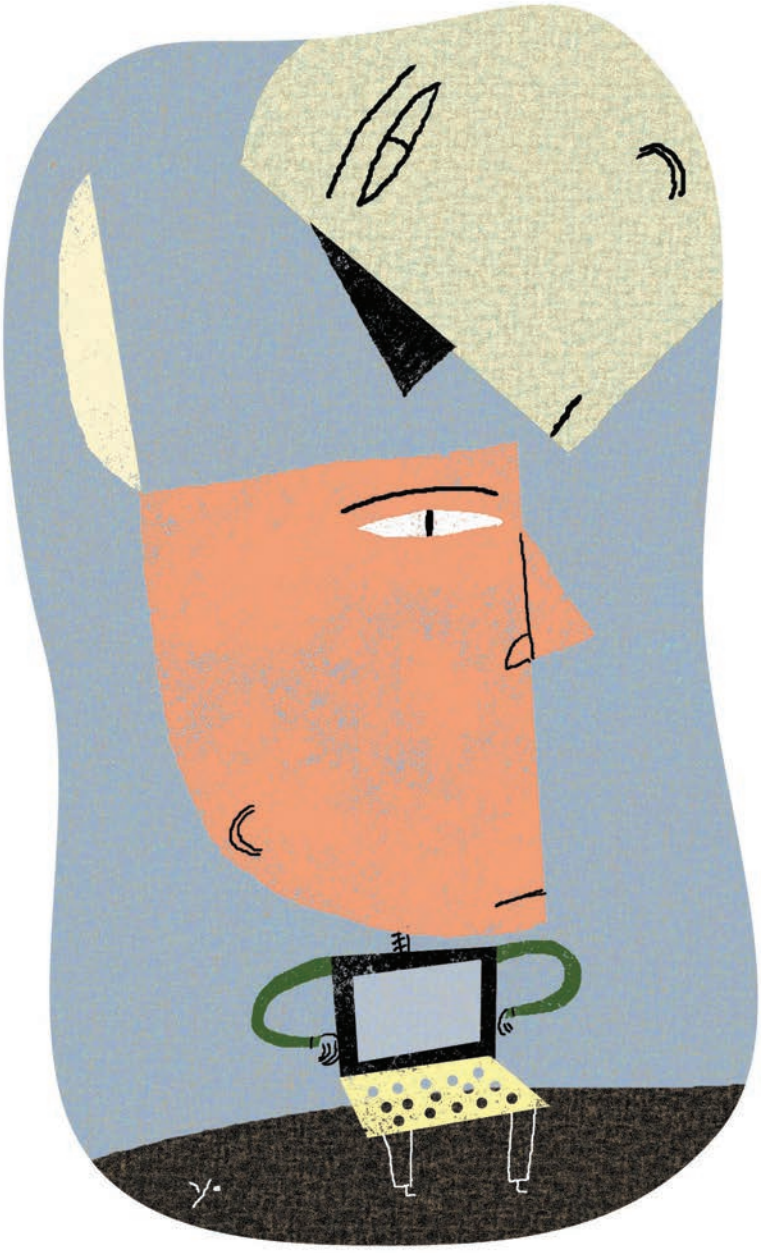
Thus, according to Miller, the reason the clinical trials didn't work can be traced to the source of the cells. "We were starting off with defective cells, in effect, and the clinical trial was proof of that hypothesis," says Miller. When diseased mice were infused with normal cells and cells derived from MS patients, the MS-derived cells "didn't work nearly as well." An experiment to test the influence of genetics also proved negative. Again, the effect of diseased and normal MSCs in genetically identical mice was compared. It clearly isn't genetics, asserts Miller, "so it says something about the disease has compromised the capability of those cells, and that's why I think the clinical trials failed."

Miller is sanguine about the trials. "This is the way translational science works. You make an observation in the laboratory. You put it into a clinical trial. The clinical trial tells you something. You go back to the laboratory based on that knowledge, and then you redesign the clinical trial based on that new information." He concedes, however, that he was "really disappointed when the trials didn't work because we felt sure it was going to work – based on the animal data."

Still, next steps are planned based on the outcome of the failed trials. Miller suggests that "if Jeff Cohen had taken my cells and put them in an MS patient, I hypothesize they would have worked." But allergenic transplants are frowned upon by the FDA because they carry a higher rate of rejection, and thus more risk for people in trials.

"Will this ever be the best way to treat MS? I don't know," says Miller. "But I'd rather have an MSC transplant, even an allergenic MSC transplant, than a whole bone marrow transplant, which is what some people are doing now for some MS patients."

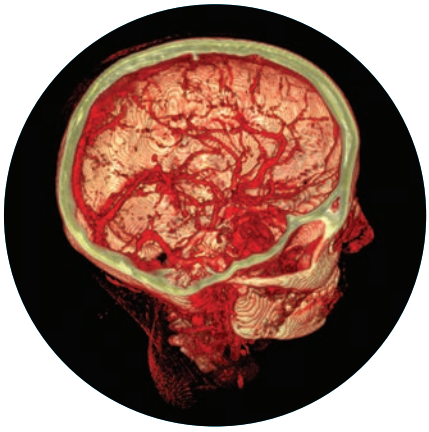
There are currently more than 15,000 active cell therapy clinical trials in the United States.



A Virtual Reality Check

USING TECHNOLOGY FOR EDUCATION AND PREOPERATIVE PLANNING

BY **CAROLINE TRENT-GURBUZ**



The black and bulky headset fits snugly, though Aalap Herur-Raman, senior virtual reality program lead from Surgical Theater, can adjust the straps as needed. When he taps on the keyboard in front of a pair of computer screens, it's impossible not to peer through the binocular-like eyepiece as the image – upside down, per the surgical point of view – zooms into a skull, revealing a maze of colorful vasculature and brain matter.

"There are the blood vessels," points out Anthony Caputy, MD, chair of the Department of Neurological Surgery and Hugo V. Rizzoli Professor of Neurological Surgery at the George Washington University (GW) School of Medicine and Health Sciences (SMHS), on the corresponding computer screens. Herur-Raman adjusts the opacity of the brain matter – thick and gray – until it fades away. "You can always add some of the brain matter back in," Caputy continues, "so you can see where the brain is in relation to the blood vessels. You can even see where the tumor is in relation to the blood vessels."

VIRTUAL REALITY
Through Precision Virtual Reality, a product based on an F-16 flight simulation program, medical professionals can see abnormalities in the brain, such as the tumor appearing behind the left eye socket in the patient scan above.

The tumor, a bright green mass appearing behind the left eye socket, is the target of the unique device, which provides medical professionals and patients a 3-D glimpse of a specific condition.

Precision Virtual Reality (VR), a product of Ohio-based company Surgical Theater, is based on an F-16 flight simulation program. A chance meeting at a coffee shop with a neurosurgeon led the company's founders – both Israeli Air Force officers – to tweak their simulator program for neurological surgery.

"[It's] actually not terribly complex," explains Todd Goldberg, vice president of sales at Surgical Theater. "We are essentially a VR studio; instead of making music or movies, like you think of studios in entertainment, we make personalized medical content that's useful for patients and surgeons. The components consist of a very high-powered computer, with the latest, greatest, and most advanced graphics processing unit, or GPU, and the latest and greatest Intel chip. But the real brain of the system is the software itself."

That software, which identifies potential surgical paths for brain and spinal conditions, is key for the SMHS Department of Neurological Surgery's approach to patient outcomes. "It's a huge part of this three-pronged process: education, patient engagement, and surgical planning," says Jonathan Sherman, MD, associate professor of neurological surgery at SMHS, who, as a longtime proponent of the tool, led the campaign to bring it to GW Hospital.

Right now, budding neurological surgeons have access to the Ammerman Lab, a microsurgical lab in SMHS' Ross Hall that focuses on skull base, minimally invasive, microvascular, and spine surgeries, as well as basic science research. There, residents can literally get a "feel" for surgery – the texture of tissues, vibrations, additional movements – but with Precision VR, they get a more in-depth understanding of the structural aspects of the brain and spine.

From a patient perspective, Precision Virtual Reality is a powerful tool for edification and engagement.

AT A GLANCE
Anthony Caputy, MD, discusses the results of the Precision Virtual Reality with patient Danielle Collins. At the age of 27, Collins was diagnosed with a ruptured arteriovenous malformation, an abnormal connection between the arteries and veins.

"[When it comes to] the education of residents and students, even professionals, Precision VR will help them better understand what we'll encounter in surgery and the risks of the surgery," Caputy says. "You can show [them], here's the anatomy, here's the motor pathways, here's the sensory pathways, here's the optic pathways. You can cut everything out around the pathway you want to show, whereas before, you would show it with brain slices. Their mind would have to put the 3-D together."

Those complementary aspects, he adds, are critical to education. "We need both of those labs to train people."

From a patient perspective, the tool is equally powerful for edification and engagement.

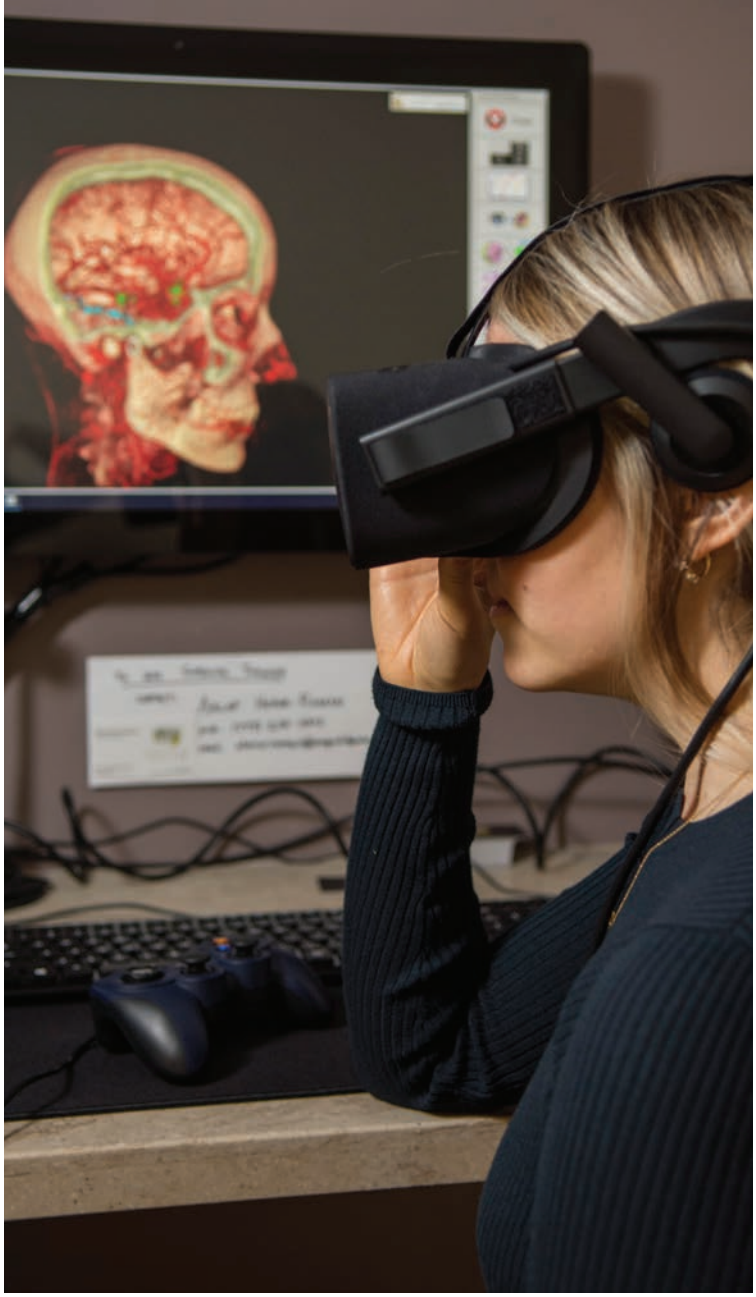
"Looking at an MRI or a CAT scan, patients almost tune you out because they don't quite understand everything that's going on, and they think they have to be a physician or health care professional to interpret a CAT scan or MRI," says Michael Rosner, MD, vice chair of the Department of Neurosurgery and professor of neurological surgery at SMHS. "To be able to take all that data and just put it in the three-dimensional model is … very, very helpful."

GW Hospital patient Roodelyne Jean-Baptiste, for example, previously had two surgeries to treat brain tumors, which were "brutal," she says. Last winter, she was told she needed a third surgery, but she balked, thinking her tumor was relatively small. Her physician (Sherman) insisted, however: "He said, 'No, we can't hold off because of the size.' We had to move so fast because it was already affecting me. The tumor was making me unable to eat and dizzy."

After her surgery, Sherman used Jean-Baptiste's MRIs and Precision VR to explain the complexity of her tumor. "He actually showed me exactly what he was talking about when he had to avoid a cut and what he had to stay away from when he went into the brain,"

IN THEATER
Michael Rosner, MD, addresses an audience at the George Washington University School of Medicine and Health Sciences on the topic of Surgical Theater.

she recalls. "If I had had [the 3-D image] from the first time I encountered the procedure, I would have never hesitated to do it. You can actually see what the doctor is saying instead of agreeing with them just to agree with them."



While Jean-Baptiste was able to get a better handle on her specific tumor, Sherman and his fellow neurological surgeons gained insight into what surgical strategies worked best. With a tumor, for example, Precision VR includes arrows for possible surgical entries, and surgeons get a clear view of what obstacles they may need to navigate around to ensure a successful procedure.

"Now, we can plan out ahead of time and really see the anatomy," Sherman says. "It helps us get a better perspective on what we're going to do surgically. We can use this technology to plan surgical [techniques], and then in the OR, we can actually use it to navigate to what we're doing."

Caputy agrees, adding that by visualizing the environment, surgical teams can identify areas of concern ahead of time. "Surgeons can devise a strategy that best allows them to achieve their goal: tumor removal and the preservation of functions," he says. "You want the most effective approach, and Precision VR can help you plan for that."

GW Hospital was the first hospital in the mid-Atlantic region to offer the tool, a boon for local patients and surgeons. "This is yet another way that we are moving the care standard higher at GW Hospital," says Kimberly Russo, MBA, MS, CEO and managing director of GW Hospital.

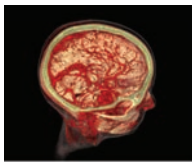
Although the tool is primarily geared toward neurology-related conditions and procedures at GW Hospital, its potential extends far beyond its technological appeal. As Goldberg explains, health care has a tendency to create silos; Precision VR, however, promises to break down those divisions and allow for better collaboration.

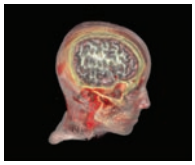
"This is one of those rare technologies that has come along that builds bridges among different members of the health care team, among different departments of the hospital, and certainly among patients and their families," Goldberg says.

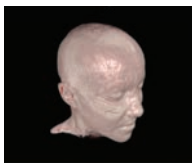
Sherman likewise believes that the tool's value isn't limited to neurological surgery. "Ultimately, we're [trying] to get this across disciplines," he explains. "My goal is that this isn't just a neurosurgical tool; this is … something we can use for all areas of subspecialty in surgery. We're just touching the tip of the iceberg of what our potential is with this technology."

A PEEK INTO THE BRAIN

Patient Danielle Collins peeks into her brain through the Precision Virtual Reality headset. Collins said the device provided a tangible way to understand the surgical plan, and made her feel like she was a part of the process. She said being able to see something that is undetectable by sight took away part of the fear of the unknown.







Taking Away the Fear of the Unknown

VIRTUAL REALITY GIVES PATIENTS THE INFORMATION TO ACT

BY **KATHERINE DVORAK**

A MIGRAINE TURNS OUT TO BE LIFE-THREATENING

A sharp pain in her head forced Danielle Collins to leave a Pilates class early. After two days of pain, Collins decided to seek medical help. The pain she was feeling stemmed from life-threatening bleeding in her brain due to a ruptured arteriovenous malformation, an abnormal connection between the arteries and veins.

On a Monday in early June 2017, Danielle Collins went to Pilates like any other day. But during the class, she felt a sharp pain in her head, forcing her to leave early. She chalked it up to a bad migraine, but after two days of suffering through the pain, Collins decided to see a doctor, only to discover she was experiencing life-threatening bleeding in her brain.

Collins, who works as a realtor at Chevy Chase, Maryland-based Wydler Brothers Real Estate, found out at 27 years old that her brain was bleeding due to a ruptured arteriovenous malformation (AVM), an abnormal connection between the arteries and veins.

"I was running 8 miles five times a week before this happened," Collins says, adding that she has always been health conscious. "I hadn't taken Advil, hadn't had a drink of alcohol, hadn't had anything in almost seven years. So I didn't take Aleve or Excedrin … which would have thinned my blood and probably killed me."

Collins soon found herself at the George Washington University (GW) Hospital looking at images of the inside of her brain. The device used, Precision Virtual Reality (VR), offers 3-D views of medical conditions and helps identify possible surgical paths.

"It provided a tangible way to understand the surgical plan, and made me feel like I was truly a part of the process," she says. "When you have an injury on your body, like a gash on your arm, you can see that. But when something is undetectable by sight, to provide sight to the areas that would be blind to you is incredible. It took away part of the fear of the unknown."

Over the next 10 days at GW Hospital, Collins received two angiograms, an MRI, CAT scans, and a craniotomy. She expressed sincere thanks for everyone who helped her during her time at GW, including Anthony Caputy, MD, chair of the Department of Neurological Surgery, and Wayne Olan, MD, director of interventional and endovascular neurosurgery at GW's Comprehensive Stroke Center."This was the best thing that ever happened to me," she says. "No day is a bad day to me anymore; I woke up this morning."

Only months removed from her surgery, Collins was back at work and back to her morning runs. "Running is time to clear my head," she says. "I run because I want to live a long life, I want to have a healthy body."

Collins adds that she found peace in a Bible passage from 2 Timothy 1:7 that says: "For God has not given us a spirit of fear, but peace (love), power, and a sound mind."

"On June 12, 2017, God, with the team of surgeons and everyone at GW, gave me a sound mind, and it was something I never even knew I needed because I had no prior knowledge of the AVM," she says. "It's amazing what minds collectively put together were able to do to save my mind."

ANTHONY-SAMUEL LAMANTIA, director of the George Washington University (GW) Institute for Neuroscience and professor of pharmacology and physiology at the GW School of Medicine and Health Sciences, has become the inaugural Jeffrey Lieberman Professor of Neurosciences.

A Measure of Success

ANTHONY-SAMUEL LAMANTIA HONORED FOR WORK DEFINING THE ORIGINS OF A DEVASTATING NEURODEVELOPMENTAL DISORDER

"If one is to achieve any measure of success in his or her professional and personal journey, that success is built upon the love, support, and guidance of family, friends, and colleagues. They make the journey possible."

Anthony-Samuel LaMantia, PhD

In what he called a "milestone in an odyssey from the Midwest to the mid-Atlantic," Anthony-Samuel LaMantia, director of the George Washington University (GW) Institute for Neuroscience and professor of pharmacology and physiology at the GW School of Medicine and Health Sciences (SMHS), became the inaugural Jeffrey Lieberman Professor of Neurosciences during an installation ceremony. Surrounded by colleagues, family, and friends, LaMantia beamed as he thanked them for the moment.

"If one is to achieve any measure of success in his or her professional and personal journey, that success is built upon the love, support, and guidance of family, friends, and colleagues. They make the journey possible," he said.

LaMantia has played a pivotal role in expanding the GW neurosciences faculty and has been a catalyst for partnerships and collaborations across the school, the university, and with Children's National Health System, said Jeffrey S. Akman, MD '81, RESD '85, vice president for health affairs, Walter A. Bloedorn Professor of Administrative Medicine, and dean of SMHS.

At the outset of LaMantia's distinguished career, he explored the organization and development of axon pathways that connect the two hemispheres of the cerebral cortex and helped develop new methods for observing neural circuits in living animals over time. While an assistant professor of neurobiology at Duke University, he demonstrated that the forebrain, which mediates learning, memory, and cognition, is built with the same molecular tools that build limbs, hearts, and facial bones. He used this work as a foundation for studying the pathogenesis of DiGeorge, or 22q11 Deletion Syndrome, a genetic disorder that comes with the highest known genetic risk for autism and schizophrenia, as well as heart, face, and limb malformations.

LaMantia worked with the professorship's namesake, Jeffrey A. Lieberman, MD '75, now the Lawrence C. Kolb Professor of Psychiatry and chair of the Department of Psychiatry at the Columbia University College of Physicians and Surgeons, while the two were at the University of North Carolina (UNC) at Chapel Hill.

"I think it represents the tying together of so many threads in my life," Lieberman said, reflecting on the coincidence of LaMantia being picked as the first recipient of the professorship. It was "unbeknownst to Jeff [Akman] when he orchestrated this," he added, but "Anthony was at Duke when I was at UNC, and I actually played a big role in recruiting him to UNC."

THE GEORGE WASHINGTON UNIVERSITY
School of Medicine and Health Sciences
Department of Neurology
2150 Pennsylvania Avenue,
9th Floor, Room 9-400
Washington, D.C. 20037

School of Medicine & Health Sciences
THE GEORGE WASHINGTON UNIVERSITY

THE GEORGE WASHINGTON UNIVERSITY MEDICAL FACULTY ASSOCIATES MFA

THE GEORGE WASHINGTON UNIVERSITY HOSPITAL