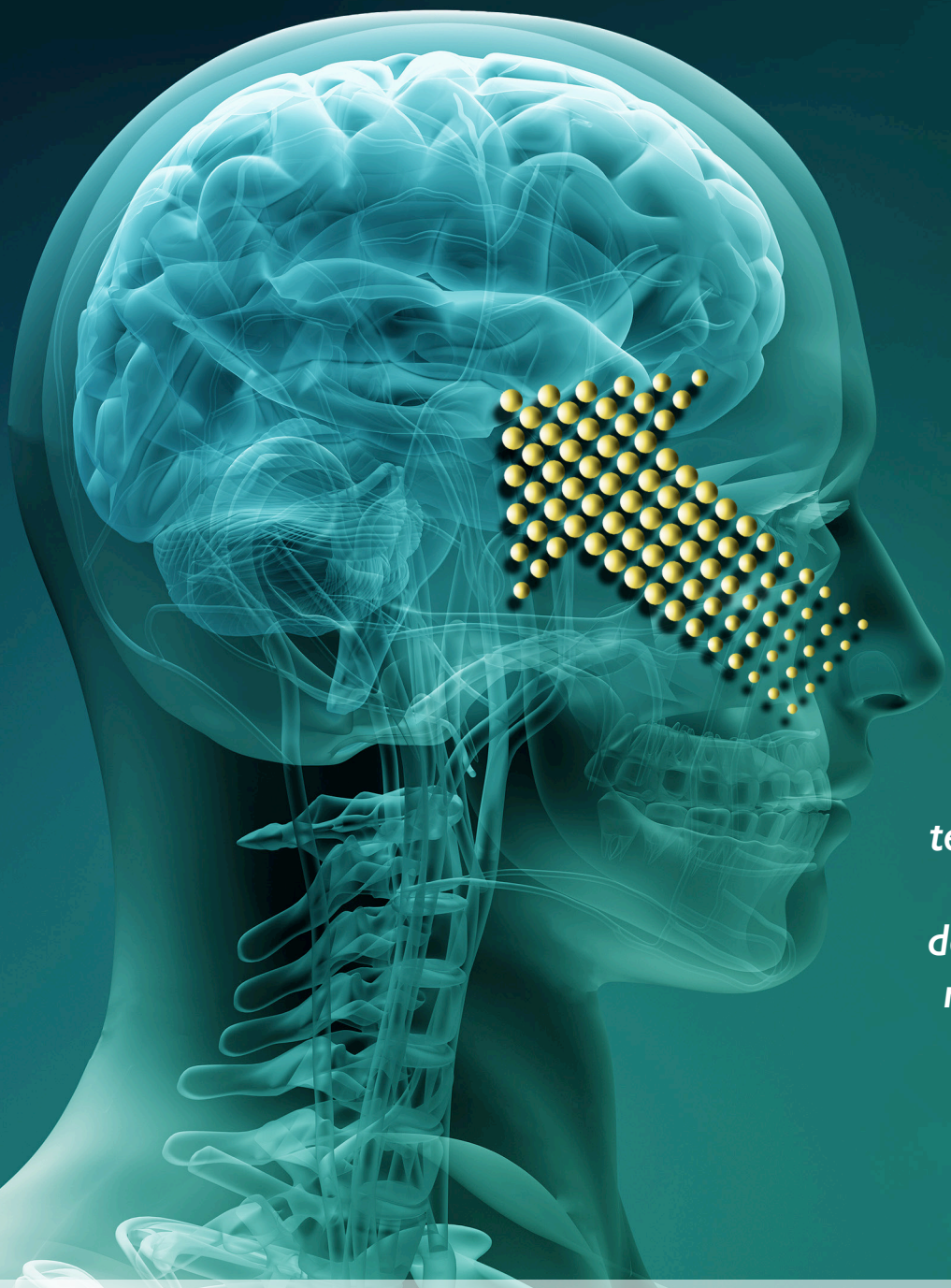
FALL 2015 ■ VOL. 12, NO. 2

NEWS FROM THE DEPARTMENT OF OTOLARYNGOLOGY AT HARVARD MEDICAL SCHOOL

# HARVARD Otolaryngology



## Crossing Over

*Rhinology Surgeon develops techniques to bypass blood-brain barrier, deliver drugs to treat neurological disease*

*(page 14)*

HARVARD MEDICAL SCHOOL | DEPARTMENT OF Otolaryngology

# HARVARD Otolaryngology

**News from the Department of Otolaryngology at Harvard Medical School**

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HARVARD MEDICAL SCHOOL | DEPARTMENT OF Otolaryngology

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## Dear colleagues and friends,

In the otolaryngology field, we spend a lot of time and surgical effort navigating complex systems through tiny spaces throughout the ear, nose, throat, head and neck. As otolaryngology physicians and researchers, we work together to push for better treatments and opportunities to improve our patients' lives.

We also rely on partners in other specialties to help us with our patients in a variety of ways. We partner with medical and radiation oncologists to help our cancer patients, with pulmonologists and gastroenterologists to help with our airway cases—every day, our work is strengthened by the collaborative network of specialists working together to deliver quality care.

We're excited about the potential of Dr. Bleier's project to help colleagues in other fields. Our cover story delves into his work that may eventually allow for the use of endoscopic skull base surgery techniques to deliver drugs to the brain and central nervous system. A few years ago, he began exploring the use of heterotopic mucosal grafting to create a "screen door" to allow therapeutic agents to cross the naturally impenetrable blood-brain barrier. He has made significant progress to date, and our hope is that there is an opportunity to apply techniques regularly used in rhinology practice to a widespread clinical dilemma of delivering drugs to treat neurological disease.

In this issue, we're excited to share our recent advances and current progress across the field with you. As you read through the pages of our Fall issue, I hope you connect with the many ways that otolaryngology physicians and researchers at Harvard Medical School are contributing to our shared success through exceptional clinical care, research and teaching advancements.

Thank you for your interest in and support of the Department's activities.

Sincerely,

D. Bradley Welling, M.D., Ph.D., FACS

*Walter Augustus LeCompte Professor and Chair*
*Department of Otolaryngology*
*Harvard Medical School*

*Chief of Otolaryngology*
*Massachusetts Eye and Ear*
*Massachusetts General Hospital*

# **Tessa A. Hadlock, M.D.,** Promoted to Professor of Otolaryngology at Harvard Medical School

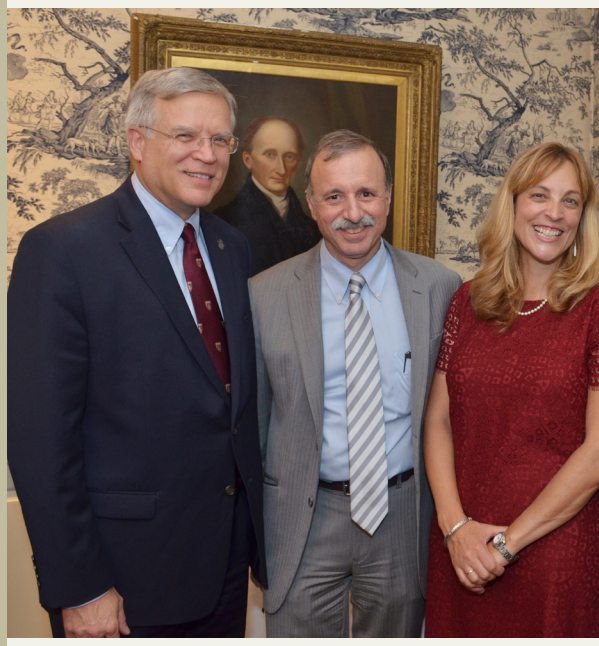
The Department recently celebrated the promotion of Tessa A. Hadlock, M.D., Division Chief of Facial Plastic and Reconstructive Surgery and Director of the Facial Nerve Center at Mass. Eye and Ear, to Professor of Otolaryngology at Harvard Medical School.

Photo by Richard Schultz.

A pioneering clinician-scientist in the facial plastic and reconstructive surgery field, Dr. Hadlock first joined Mass. Eye and Ear/Harvard Medical School as an otolaryngology resident back in 1995. She completed her undergraduate training in mathematics and biochemistry (summa cum laude) at Bowdoin College in 1990 and earned her medical degree in 1994 from the Division of Health Sciences and Technology at Harvard Medical School and the Massachusetts Institute of Technology. Soon after delving into her residency training, Dr. Hadlock developed a passion for managing facial nerve disorders, and she has since devoted her career to improving the lives of patients with facial paralysis.

In 2002, Dr. Hadlock assumed directorship of the Facial Nerve Center at Mass. Eye and Ear, a unique center of excellence exclusively dedicated to caring for patients with difficult-to-manage facial movement disorders. Under her leadership, the Center has acquired unparalleled experience with managing facial paralysis, with more than 2,000 cases seen to date. Deeply committed to advancing treatment for this patient population, Dr. Hadlock has innovated and popularized surgical, medical and physical therapy strategies that have since been embraced by colleagues in the field. The Center serves as a model for visiting physicians, many of whom return home to design and implement similar clinical environments at their institutions.

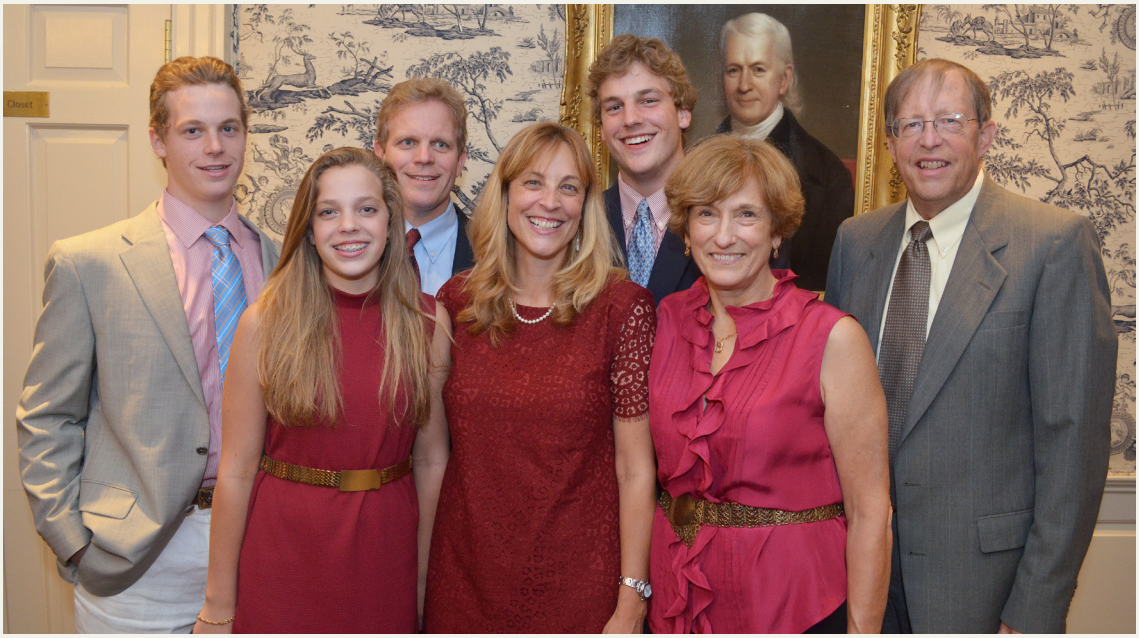
Persistently striving for new knowledge related to this complex condition, Dr. Hadlock directs a robust research program in the Facial Nerve Regeneration Laboratory, where she focuses on establishing more effective methods of regenerating facial nerve function. She is one of very few facial plastic and reconstructive surgeons in the field with funding from the National Institutes of Health. In addition to basic science work, she has published numerous clinical outcomes studies on her extensive experience. She has also developed tools to measure the efficacy of facial reanimation procedures, which are frequently referenced in international literature.

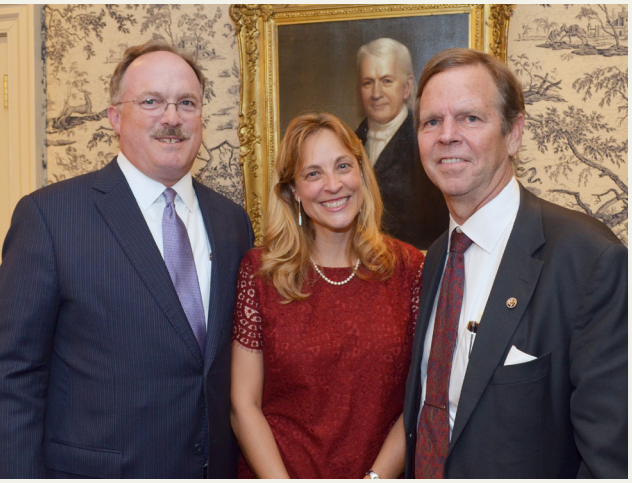


*Top Left: Drs. Brad Welling, Mark Varvares, Tessa Hadlock and Mack Cheney.*

*Top Right: Dr. Tessa Hadlock, surrounded by family.*

By sharing her expertise with others in the field, Dr. Hadlock is able to extend her impact to patients around the world. As preceptor for the clinical fellowship program in facial plastic and reconstructive surgery at Mass. Eye and Ear, she prepares young otolaryngology surgeons to manage complex facial nerve disorders in their future practices. In addition to the natural mentoring that comes along with a career in academic medicine, Dr. Hadlock is also passionate about mentoring





*Bottom Left: Dr. Hadlock with Mass. Eye and Ear President and CEO John Fernandez, and Dr. Mack Cheney.*

*Bottom Right: Dr. Hadlock with philanthropist Carmela Kletjian.*

physicians in developing countries, where she promotes global surgical activities, manages under-treated conditions and models community service as an essential component of an academic surgeon's professional mission.

"We couldn't be more proud of Dr. Hadlock," said D. Bradley Welling, M.D., Ph.D., FACS, the Walter Augustus LeCompte Chair of Otolaryngology at Harvard Medical School. "I'm certain we have only seen the beginning of landmark accomplishments yet to come. We congratulate Tessa and her supportive family on attaining this wonderful milestone in her career." ●

## An Endowed Chair for Dr. Tessa Hadlock

Patients and friends have seeded a Mass. Eye and Ear Chair for Dr. Hadlock, with philanthropic commitments totaling $750,000 to date. In order to reach a fully funded Chair, we need to raise $2 million. An endowed Chair will enable Dr. Hadlock to advance her breakthrough research and teaching in facial reanimation both here in the United States and throughout the world.

We invite others to learn more about Dr. Hadlock's work and to contribute to this effort by **contacting Irene Hammer-McLaughlin at 617-573-3388.**

# **Gregory W. Randolph, M.D., FACS, FACE,** Voted President-Elect of the American Academy of Otolaryngology–Head and Neck Surgery

***"I'm very honored that colleagues in the field have supported the election of a thyroid surgeon to Academy President. I recognize what an opportunity this is, and I'd like to use that to build better relationships with other organizations, particularly medical endocrinology and general surgical organizations, and to represent thyroid surgery as a recognized subspecialty of otolaryngology."***

—Dr. Randolph

*Top: Dr. Randolph with past clinical fellow Dr. Ashley Darr.*

*Bottom: Dr. Randolph with current President of AAO-HNS, Dr. Sujana Chandrasekhar.*

Gregory W. Randolph, M.D., FACS, FACE, Chief of the Divisions of General Otolaryngology and Thyroid and Parathyroid Endocrine Surgery at Massachusetts Eye and Ear and the Claire and John Bertucci Endowed Chair in Thyroid Surgical Oncology in the Department of Otolaryngology at Harvard Medical School, was recently elected President of the American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS), an internationally known premiere otolaryngology organization in the United States.

Dr. Randolph is serving a 3-year term that began in October, when he was recognized as President-Elect. He will take office as President in 2016, and then will serve as Past President in 2017.

Dr. Randolph has been an active member of AAO–HNS since 1993 and has contributed as a leader in many areas over the years, including his work as Coordinator for International Affairs and as a member of the Board of Directors. He also chaired the Endocrine Surgery Committee, playing an integral role in its progression from subcommittee to full committee. Dr. Randolph received the AAO–HNS distinguished honor award in 2012.

He is eager to give back to the organization that helped him to advance his burgeoning career.

"The Academy was very helpful to me early on," Dr. Randolph said. "The opportunities were formative for my career, and it connected me with physicians with similar interests around the world."

An otolaryngologist specializing in thyroid and parathyroid surgery, Dr. Randolph is the first surgeon from his subspecialty to be elected to the position, and he looks forward to the opportunity to further the evolution of endocrine surgery as part of otolaryngology.

"I'm very honored that colleagues in the field have supported the election of a thyroid surgeon to Academy President," Dr. Randolph said. "I recognize what an opportunity this is, and I'd like to use that to build better relationships with other organizations, particularly medical endocrinology and general surgical organizations, and to represent thyroid surgery as a recognized subspecialty of otolaryngology."

In addition to building ties with other medical professional organizations, as a long-standing supporter of international collegiality, Dr. Randolph would like to focus on expanding the international reach of the organization, and to foster education, research and political advocacy across the field.

"There are many important issues affecting otolaryngologists today here in the United States and around the world," Dr. Randolph said. "As an overarching body of action, the Academy serves as an educational resource and also provides much needed support through advocacy."

While Mass. Eye and Ear/Harvard Medical School alumni have held the office before, Dr. Randolph is the first otolaryngologist currently in practice at the institution to be elected to the position.

"I'm very gratified and excited," said Dr. Randolph. "I'm honored by the opportunity to represent otolaryngology at Mass. Eye and Ear and Harvard Medical School and to share our mission and values across the broad reach of the Academy."

Photos by Mary Leach.

# A New Approach in Sleep Medicine

## Physicians evaluate upper airway stimulation therapy for sleep apnea in adolescent patients with Down syndrome

Patients with Down syndrome and severe obstructive sleep apnea present unique challenges for physicians. Key characteristics of the anatomy in this population, such as larger tongues that fall back in the mouth during REM cycles, can obstruct the airway during sleep, and sensitivity to the feeling of a mask blowing air onto the face makes the traditional therapy for obstructive sleep apnea, a CPAP machine, a nightmare for these patients.

Without any favorable options to turn to and the threat of cardiovascular issues like high blood pressure and heart disease if the sleep apnea is left untreated, physicians and patients' families are sometimes left with the difficult decision to resort to life-altering tracheostomies, if the obstruction is severe to the point of not being safe.

When Christopher J. Hartnick, M.D., Division Chief of Pediatric Otolaryngology at Massachusetts Eye and Ear, first encountered a 2014 study published in the *New England Journal of Medicine* of a large multicenter clinical trial assessing the efficacy of the hypoglossal nerve stimulator—a new technology that had recently gained momentum as an alterative to CPAP therapy—in adult patients with severe obstructive sleep apnea, he saw a unique opportunity to help pediatric patients with Down syndrome and severe sleep apnea.

"We believe that the technology has a lot of potential to be applied to this population, because it is exactly that area—the large tongue base—that, most often, is causing the sleep apnea," Dr. Hartnick said. "The most compelling thing about it is the potential to help a population for which there are often no good treatments available."

By stimulating a branch of nerves in the upper airway, the hypoglossal nerve stimulator causes the tongue to move forward and out of the airway during sleep. In surgery, a cuff is placed around selective branches of the nerve, and a wire is tunneled down to a receiver in the chest, and another to a sensor below the ribs. The sensor detects breathing and sends up a signal to the stimulator cuff, which sets the whole process into motion.

Patients and their physicians can program the technology to turn on at a certain time each night, approximately half an hour after the child goes to sleep.

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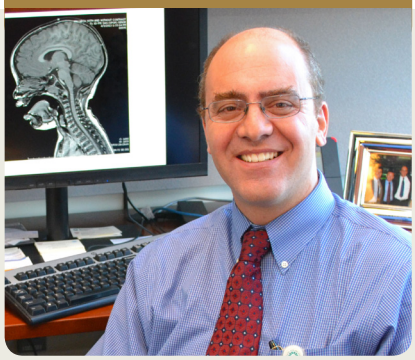


*The first subject in the clinical trial and his mother wait for surgery.*

The implant is powered by a battery that needs to be changed, which involves a minor follow-up procedure every 10-15 years. Patients with the implant are restricted from participating in MRI studies.

Keenly interesting in bringing the technology to this population, Dr. Hartnick and a team of physicians including Donald J. Keamy, Jr., M.D., John Dobrowski, M.D., and Gillian Diercks, M.D., of Mass. Eye and Ear, and Thomas B. Kinane, M.D., Allison T. Schwartz, M.D., and Brian G. Skotko, M.D., of Mass General, began an FDA-approved pilot study evaluating the safety and efficacy of the use of the hypoglossal nerve stimulator in adolescents (ages 12 to 21 years) with Down syndrome and severe obstructive sleep apnea. They received a grant from Inspire Medical Systems, Inc., in support of the study.

Photos by Mary Leach.

The team performed the first pediatric implantation in the United States on April 8, 2015. Ryan J. Soose, M.D., a sleep surgeon from the University of Pittsburgh Medical Center and author from the study published in the *New England Journal of Medicine,* traveled to Mass. Eye and Ear for the surgery.

"I think one of the advantages of academic medicine is that we work together," Dr. Hartnick said. "Ryan is an adult sleep doctor, but he was very interested in helping us by sharing the lessons he had learned and exploring the opportunity to extend the technology to this population."

One additional patient has been implanted since the first surgery was performed, and Mass. Eye and Ear has the capacity to enroll four additional subjects. Subjects in the clinical trial are being followed closely through office visits and sleep studies to thoroughly assess safety of the treatment.

The first subject's sleep study results showed a decrease of obstructive sleep apnea symptoms from an apnea hypopnea index score above 40 to below 10, and the child has subsequently been decannulated with positive results.

"At the end of this summer, he was able to go swimming for the first time," Dr. Hartnick said. "He appears to be living comfortably without a trach."

*A team of physicians began an FDA-approved pilot study to evaluate the use of the hypoglossal nerve stimulator in adolescents with Down syndrome and severe OSA. The team performed the first pediatric implantation in the U.S. on April 8, 2015.*

*"Before this technology came along, we had a population of kids who—even after removing their tonsils, adenoids and lingual tonsils—still needed treatment for severe sleep apnea. And if they couldn't tolerate a CPAP, we were faced with this terrible choice of whether to perform a tracheostomy or to just wait to see if they developed a heart problem."*
—Dr. Hartnick

Dr. Hartnick and the team are looking at many different factors to understand the safety of the device. They want to ensure that the implant is well tolerated and that patients and families will comply with their treatment plan.

"Our first child doesn't seem to notice it there, but we are wondering if the processor is bothersome," Dr. Hartnick said. "Will they pick or scratch at it? Or, will they wake up suddenly, feel it, and then be scared to use it again?"

"Though this technology has been used successfully in adults, this situation is completely different given the involvement and dependency on the parent. And when these adolescents become adults, will they still comply? These are just some things we have to follow.

As they continue to identify and enroll subjects in the trial, Dr. Hartnick and the team are gaining valuable experience in surgical technique, and also in acclimating families to the new technology.

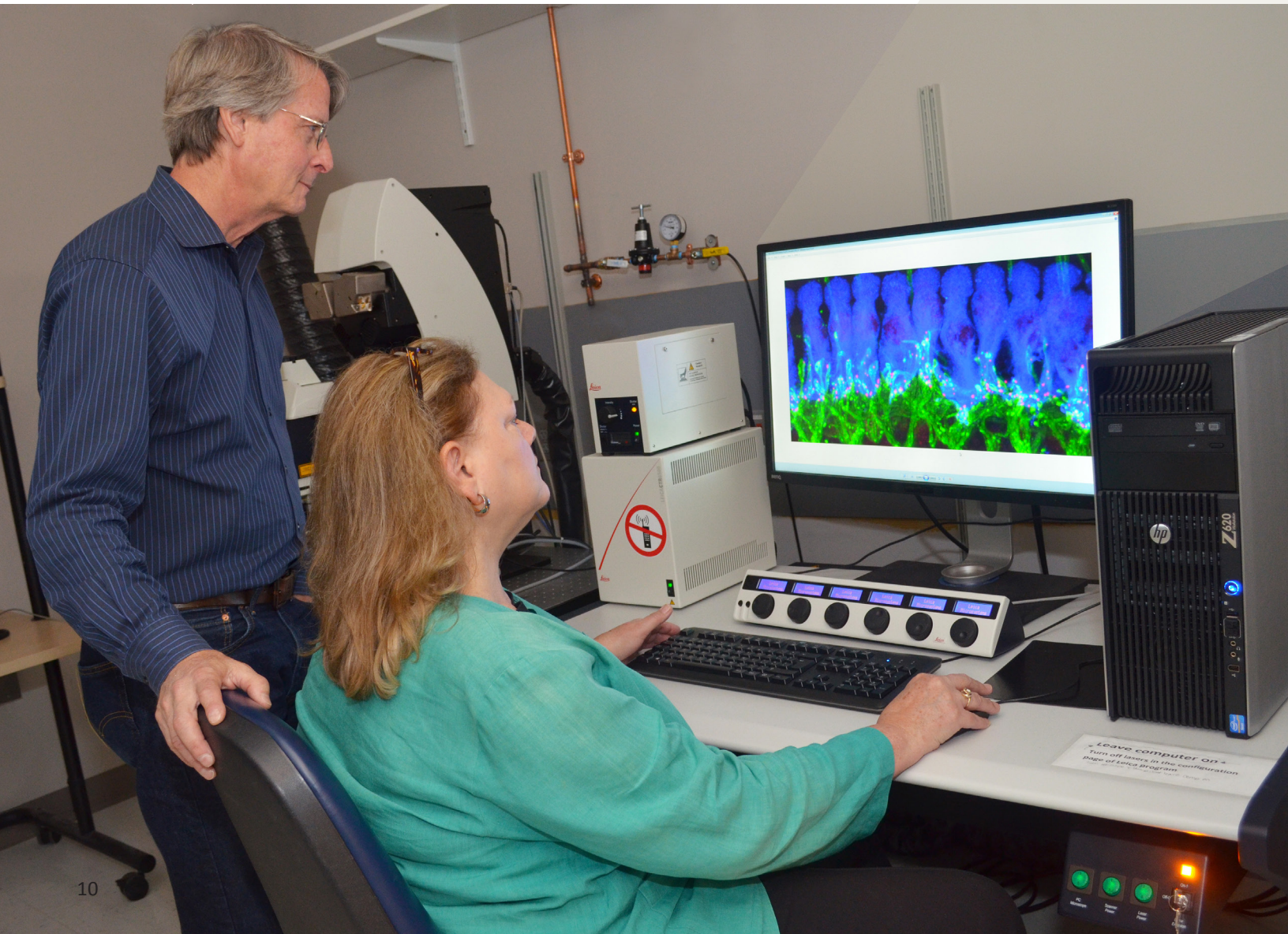
Future goals would be to expand the study to a multicenter trial.

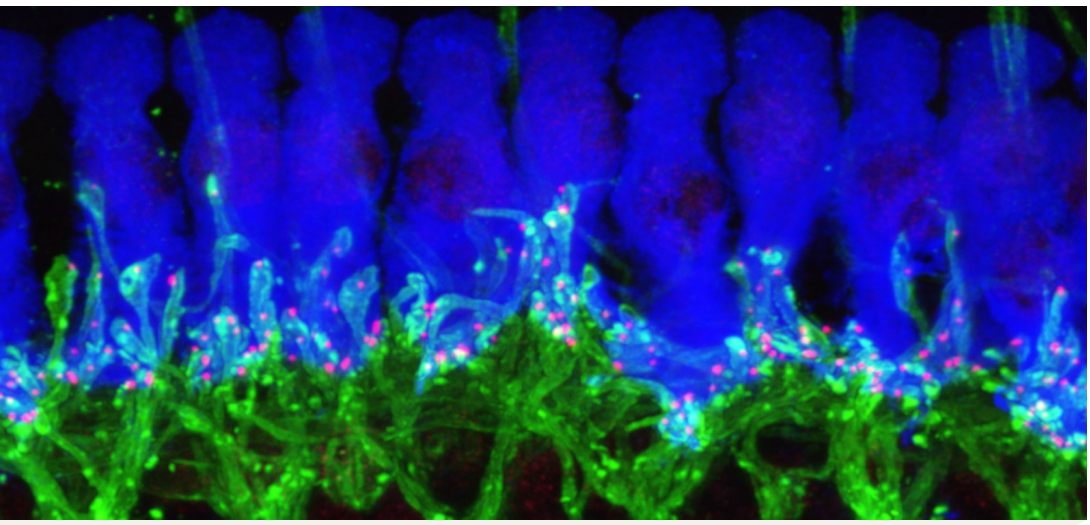
"Before this technology came along, we had a population of kids who—even after removing their tonsils, adenoids and lingual tonsils—still needed treatment for severe sleep apnea. And if they couldn't tolerate a CPAP, we were faced with this terrible choice of whether to perform a tracheostomy or to just wait to see if they developed a heart problem," Dr. Hartnick said. "If this works out, it will be a game changer for those situations."

*The first subject's sleep study results showed a decrease of obstructive sleep apnea symptoms from an apnea hypopnea index score above 40 to below 10, and the child has subsequently been decannulated with positive results.*

# HIDDEN Hearing Loss

Researchers uncover hidden damage in the inner ear, explore therapeutic options in parallel





*A normal mouse ear taken with a confocal microscope: a row of hair cells (blue), nerve terminals (green) and their synaptic contacts (red).*

It's not uncommon for patients to present with hearing disabilities that cannot be explained by a change in hearing threshold on an audiogram. In particular, a fair number of patients describe scenarios in which they have difficulties understanding conversations in noisy environments.

These are the kinds of complaints that have long eluded physicians and audiologists, and it turns out that there may be some explanation for them hidden somewhere in the inner ear.

Several years ago, a research team including Sharon G. Kujawa, Ph.D., and M. Charles Liberman, Ph.D., of Massachusetts Eye and Ear/Harvard Medical School uncovered a new type of inner ear damage that may explain these poorly understood hearing impairments that are so common among the elderly.

In a 2009 landmark publication, the researchers showed that neural synapses responsible for communication from the ear to the brain are the most vulnerable structures in the inner ear after overexposure to loud noise.

Drs. Kujawa and Liberman's finding resulted in a paradigm shift in research on hearing impairment. Conventional wisdom in the field had been that sensorineural hearing loss was largely attributed to the loss of hair cells – the sensory cells of the inner ear, and Drs. Kujawa and Liberman showed that noise first damages the synapses connecting the hair cells to the nerve fibers carrying neural signals to the brain, even when the hair cells are undamaged. The event typically results in a temporary threshold shift recorded on an audiogram; and when the audiogram returns to normal, patients are often told that no harm had been done.

"This is what everyone assumes is a benign event, " Dr. Kujawa said of temporary threshold shift. "You go to a concert, and afterward, your hearing is muffled and your ears might be ringing. Then, hours or days later, things seem to return to normal and you think, 'Wow! I've dodged a bullet.'"

Their findings show that the connections between the nerve fibers and hair cells are severed immediately after the noise exposure, and that they do not grow back. In other words, after each noise exposure, the hair cells lose some of the "wires" that connect them to the brain.

In a later study, they showed that the same process occurs in the aging ear, that the synapses are lost well before the hair cells. They speculate that this loss doesn't initially affect the ability to detect a sound, or a snippet of speech—but it can impair the ability to understand what has been said.

"What we've found is that the first event is not the loss of the hair cell or neuron per se, but the loss of the communication between them," Dr. Kujawa said. "We think it sets the stage for a subsequent series of events that ultimately result in the loss of the neuron."

Researchers have termed this condition "hidden hearing loss" for two reasons. One is that the synaptic loss does not show up on an audiogram, and the other that the damage cannot be seen with typical methods used to study the structures of the inner ear.

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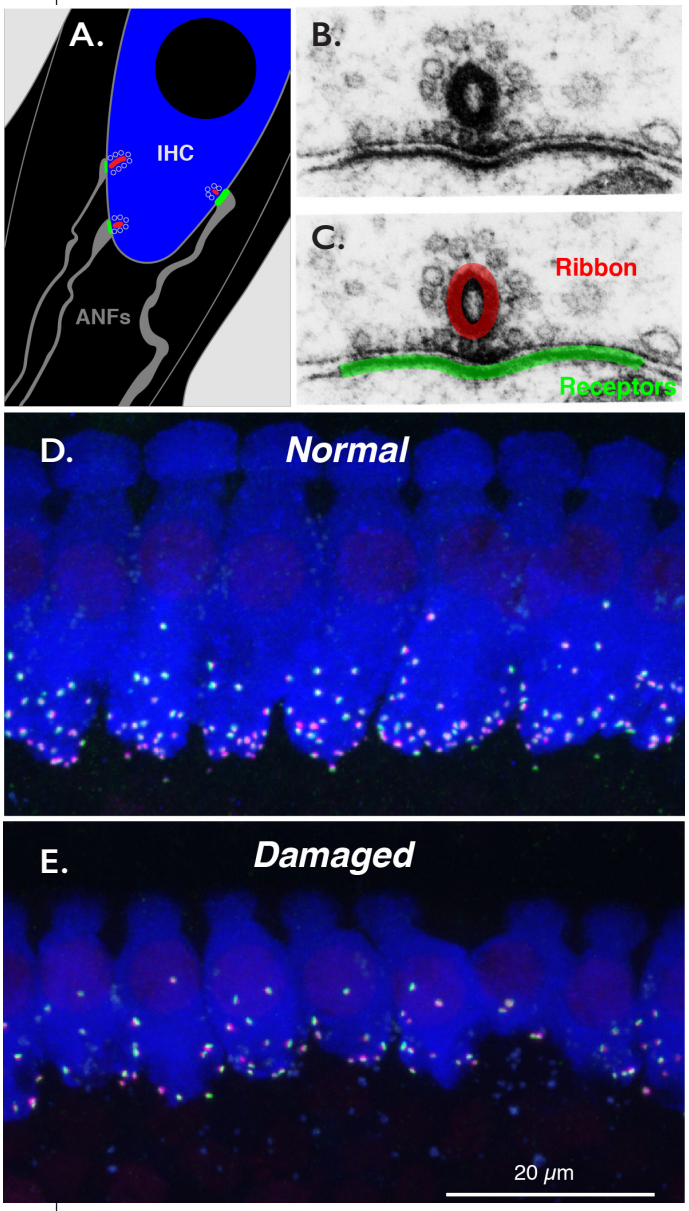
*Drs. M. Charles Liberman and Sharon Kujawa study hidden hearing loss in tissue specimens from the inner ear.*




**The assessment of hidden hearing loss in tissue specimens from the inner ear.** ***A:*** *Each auditory nerve fiber (ANF) contact a single inner hair cell (IHC), by a single synapse comprising a pre-synaptic ribbon (red, inside the hair cell) and a post-synaptic patch of neurotransmitter receptors (green, at the tip of the nerve fiber).* ***B:*** *This synaptic complex is best seen in the electron microscope, where the synaptic ribbon looks like a dense doughnut surrounded by a halo of vesicles, each of which contains neurotransmitter (i.e. glutamate).* ***C:*** *We use color-tagged antibodies that bind either to the ribbon (red) of the glutamate receptors (green) to allow us to see the synapses in the light microscope.* ***D*** *and* ***E:*** *These images, taken with a confocal microscope, each show a row of 7-8 hair cells immunostained with antibodies to synaptic ribbons (red), post-synaptic glutamate receptors (green) and a protein in hair cells (myosinVIIa, blue). The comparison illustrates the clear loss of synapses in the noise-damaged ear, despite no loss of the hair cells themselves.*

In order to really "see" the synaptopathy and quantify the damage, the researchers developed sophisticated immunostaining techniques that allowed them to visualize and count all the tiny synaptic contacts. These techniques are applied in post mortem specimens from both mice and humans.

"To look at the connections, we identified key molecular components of the synapses and then applied antibodies to these components with fluorescent tags on them, which allows us to directly see the synapses in tissue samples from the inner ear," Dr. Liberman said. "Previously, we had no way of counting these nerve connections without cutting ultrathin tissue sections and examining them in the electron microscope—a process that, in past studies, took close to a year to count the synapses on just a few hair cells."

## Looking Beyond the Audiogram

Drs. Kujawa and Liberman's finding has major implications for public health, and to many in the field, it represents a call to action.

"The message is clear—noise is more injurious than we thought," Dr. Kujawa said. "Our standard view of noise has been that you have an insult that results in a threshold shift, and if sensitivity recovers, the exposure was benign. We now know that that is frequently wrong."

Part of the difficulty in spreading this message lies in the field's dependence on the audiogram.

"Much of what we do clinically to characterize the bad things that happen to ears has been threshold-based, and that has been our view of the world for decades," Dr. Kujawa said. "But, hidden hearing loss is not a problem of hearing soft sounds, and it is not revealed by the threshold audiogram."

While further study is needed to prove that the synaptic loss they have shown in animals is also true of humans, policymakers and epidemiologists are paying attention.

"It's going to take some time to figure out what this all means to policy," Dr. Kujawa said. "But the interest is there. At the very least, it has recalibrated how we all think about noise."

*"The message is clear — noise is more injurious than we thought. Our standard view of noise has been that you have an insult that results in a threshold shift, and if sensitivity recovers, the exposure was benign. We now know that that is frequently wrong."*

—Dr. Kujawa

*"The most exciting part of our discovery is that this may be a treatable kind of sensorineural hearing impairment. We believe that there are a lot of people out there who have hair cells and ganglion cells that have been disconnected from each other who could hear better if we could reconnect them. We believe we may be able to accomplish that in the foreseeable future."*

—Dr. Liberman

## A Window of Opportunity

As they continue to explore the underlying mechanisms of the loss of neural connection in the inner ear, researchers are also looking for potential treatment strategies—for ways to re-establish those connections—in parallel studies.

And there may be a bright side. Drs. Kujawa and Liberman believe that there is a long therapeutic window for hidden hearing loss; because, while the connection is severed immediately, the hair cells often survive indefinitely and the nerve cells and their brain connections remain intact for years to decades.

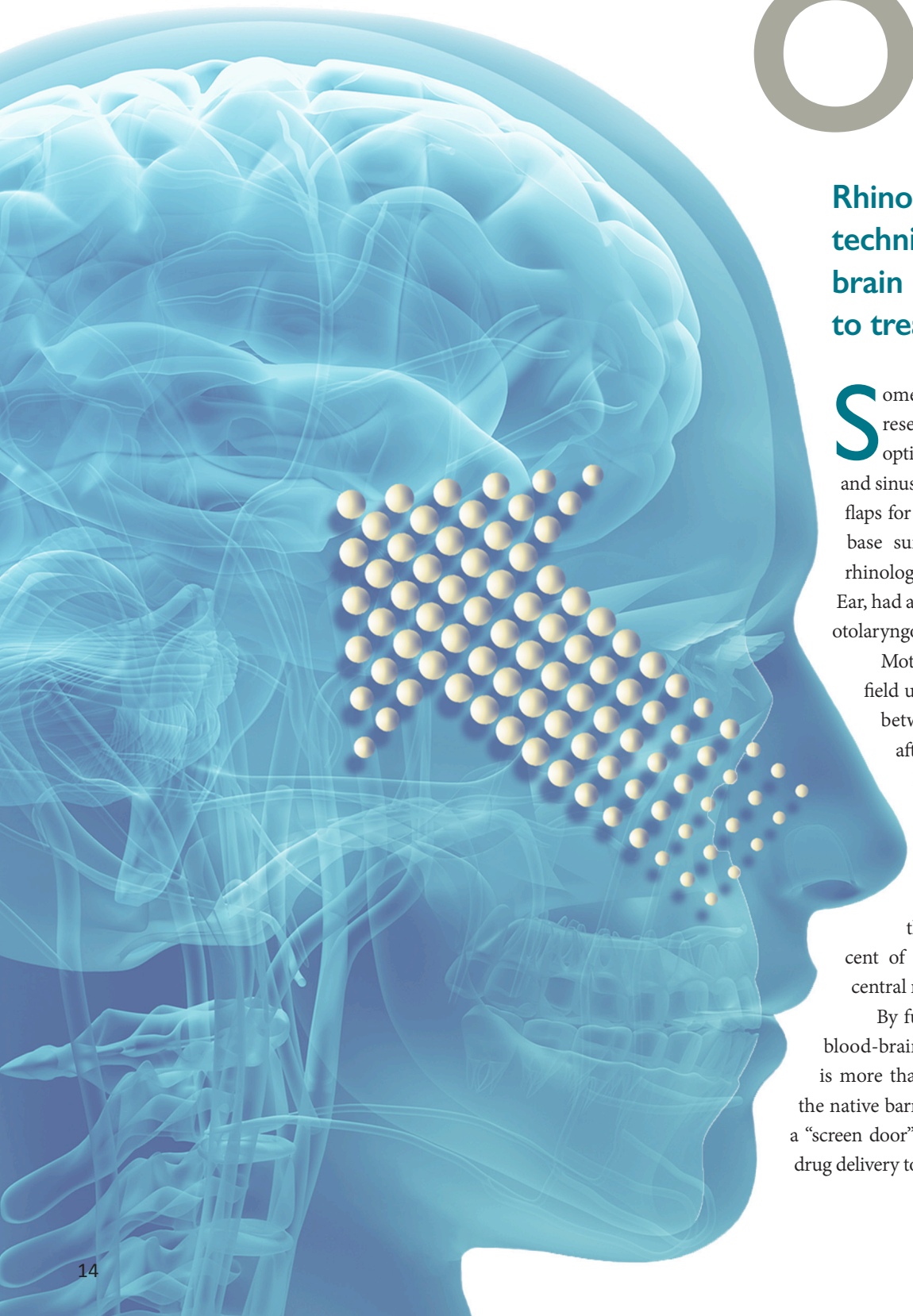
"We have a window of opportunity—and it actually may be a fairly long window, because the neuron appears to be slow to die—to reestablish the connections," Dr. Kujawa said.

Laboratories all over the world, including those at Mass. Eye and Ear, are exploring a variety of approaches to prevent damage or restore neural synapses.

Dr. Liberman's team has been applying naturally occurring neurotrophic factors to the inner ear in mice, and they have seen synaptic regeneration when applied after noise damage. Dr. Kujawa, along with Albert Edge, Ph.D., also of Mass Eye and Ear, has tested compounds that, when applied to the inner ear before exposure, protect against the synaptic damage. Both are optimistic something can be done for hidden hearing loss.

"The most exciting part of our discovery is that this may be a treatable kind of sensorineural hearing impairment," Dr. Liberman said. "We believe that there are a lot of people out there who have hair cells and ganglion cells that have been disconnected from each other who could hear better if we could reconnect them. We believe we may be able to accomplish that in the foreseeable future." ●

# CROSSING Over



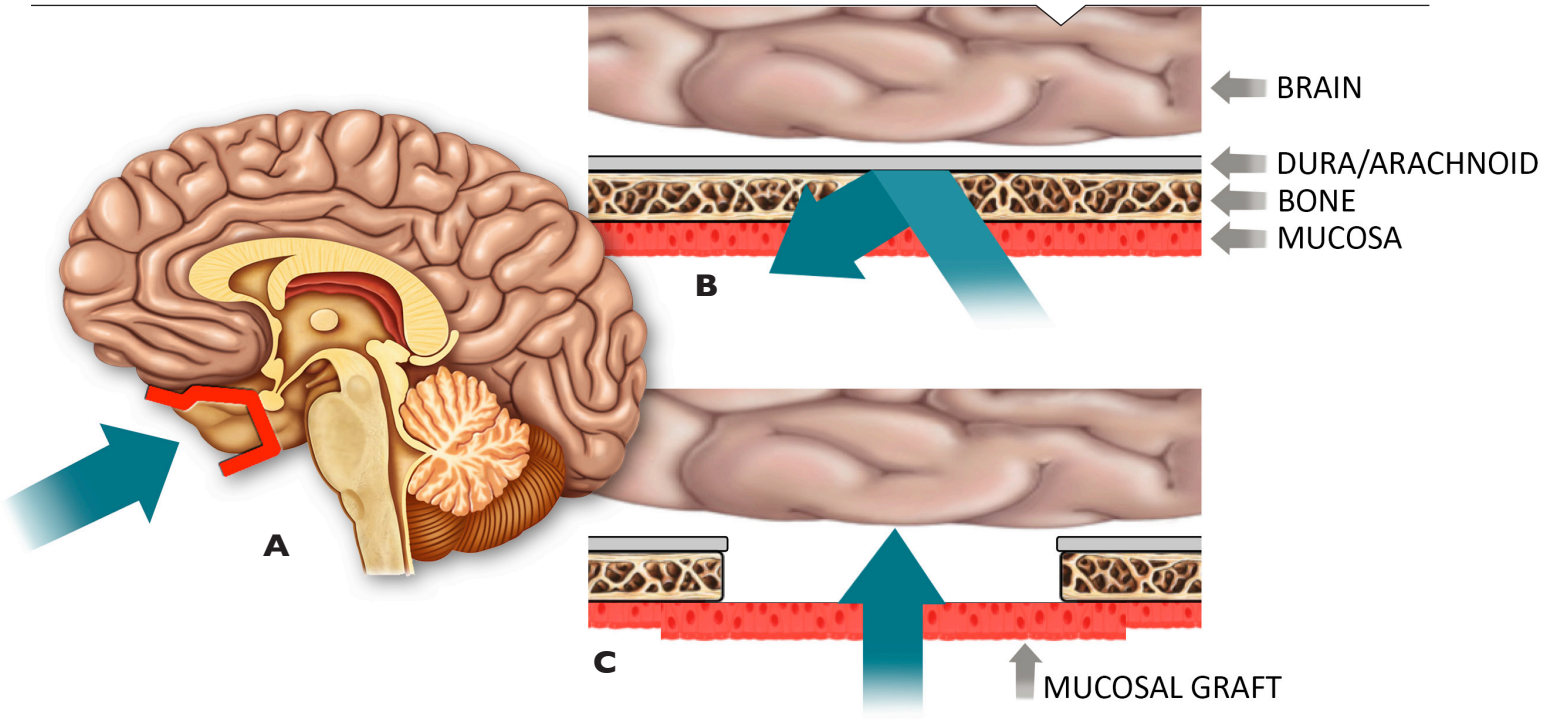
## Rhinology Surgeon develops techniques to bypass blood-brain barrier, deliver drugs to treat neurological disease

Somewhere between two separate research projects—one focused on optimizing drug distribution to the nose and sinuses, and the other designing nasoseptal flaps for reconstruction after endoscopic skull base surgery—Benjamin S. Bleier, M.D., a rhinology surgeon at Massachusetts Eye and Ear, had an idea situated pretty far outside of the otolaryngology box.

Motivated by continued success in the field using nasal mucosa to seal up the hole between the nose and the brain left behind after endoscopic skull base surgery, Dr. Bleier saw an opportunity to apply those techniques to the widespread clinical dilemma of delivering drugs across the naturally impenetrable blood-brain barrier, a mechanism that prevents approximately 98 percent of drugs from reaching the brain and central nervous system.

By functionally replacing a section of the blood-brain barrier with nasal lining, which is more than 1,000 times more permeable than the native barrier, he set out to prove he could create a "screen door" to allow for higher molecular weight drug delivery to the CNS.

*Drugs used to treat a variety of central nervous system diseases may be administered through the nose and diffused through an implanted mucosal graft (**A**, in red.) to gain access to the brain. Under normal circumstances, there are multiple layers within the nose that block the access of pharmaceutical agents from getting into the brain including bone and the arachnoid membrane, which represents part of the blood-brain barrier (**B**). After endoscopic skull base surgery (**C**), all of these layers are removed and replaced with a nasal mucosal graft, which is 1,000 times more porous than the native blood-brain barrier. Consequently, these grafts may be used to deliver very large drugs, including proteins, which would otherwise be blocked by the blood-brain barrier.*




The project has the potential to shatter a difficult roadblock in designing treatments for the large population of patients around the world with neurological disease.

"We are developing a platform that may eventually be used to deliver a variety of drugs to the brain," Dr. Bleier said. "Although we are currently looking at neurodegenerative disease, there is potential for the technology to be expanded to psychiatric diseases, chronic pain, seizure disorders and many other conditions affecting the brain and nervous system down the road."

## Preventing the development of Parkinson's disease

In 2013, Dr. Bleier and a team of otolaryngology researchers from Mass. Eye and Ear/Harvard Medical School and the biomedical engineering department of Boston University showed that nasal mucosa is capable of diffusing molecules to the brain that are up to 1,000 times larger than those excluded by the blood-brain barrier. The proof of concept paper was published in an issue of *PLOS One*.

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*Dr. Bleier performing endoscopic skull base surgery, a commonly used technique in otolaryngology practice.*

*"We are developing a platform that may eventually be used to deliver a variety of drugs to the brain. Although we are currently looking at neurodegenerative disease, there is potential for the technology to be expanded to psychiatric diseases, chronic pain, seizure disorders and many other conditions affecting the brain and nervous system down the road."*
—Dr. Bleier

Deeply encouraged by this initial finding, the team then designed further investigations to better understand the functional results of their approach.

Using a neuroprotective model, Dr. Bleier and the team showed in 2015 that their method had successfully prevented the development of Parkinson's disease in a mouse model using nasal mucosal grafting to deliver glial derived neurotrophic factor (GDNF)—a known therapeutic protein shown to delay or even reverse disease progression in Parkinson's disease—to the brain and central nervous system. They showed through behavioral and histological data capture that their delivery method was equivalent to direct injection of GDNF—the current gold standard for delivering this drug in Parkinson's disease—in diffusing drugs to the brain. Their findings were published in *Neurosurgery*.

"I was looking for diseases where there were drugs available that were effective but could not cross the blood-brain barrier," Dr. Bleier said. "GDNF has been shown to reverse the disease process in Parkinson's; however, currently, the only way to get it to the brain is through a catheter."

Direct brain infusion is the only delivery method for GDNF currently available in clinical trial for the treatment of Parkinson's disease, despite its traumatic nature and high complication rates.

While clinical trials of GDNF delivered through catheters for the treatment of Parkinson's disease in humans have raised concerns, Dr. Bleier feels confident that the nasal mucosal graft will be a much safer method for drug delivery.

"The safety and efficacy of using adjacent nasal lining in skull base reconstruction have been well established through long-term clinical outcomes studies in the field," Dr. Bleier said. "We've shown that the nasal lining protects the brain from infection just as the blood-brain barrier has done."

## Next steps

With a plan mapped out for transporting GDNF and potentially other drugs across the blood-brain barrier, Dr. Bleier's next step is to develop an effective method for applying the agents to the mucosal graft.

In early research projects, he explored implantable drug-eluting polymers to improve drug distribution in the nose and sinuses. Now, that technology may be key in diffusing drugs to the brain. When implanted over the mucosal graft, the polymers may deliver drugs to the central nervous system over time at a continuous level. Dr. Bleier recently began collaborating with colleagues in the department of pharmaceutical sciences at Northeastern University to move this idea forward.

"You can essentially fine tune the polymers to deliver the drug over the timeframes you want," Dr. Bleier said. "It slowly secretes the drug, and the patient doesn't have to do anything."

The automatic delivery of drug-eluting polymers may be especially advantageous for patients with neurodegenerative disease who struggle with compliance in following a treatment plan.

Additionally, the nasal mucosal graft approach is permanent, and would likely require very little follow up treatment.

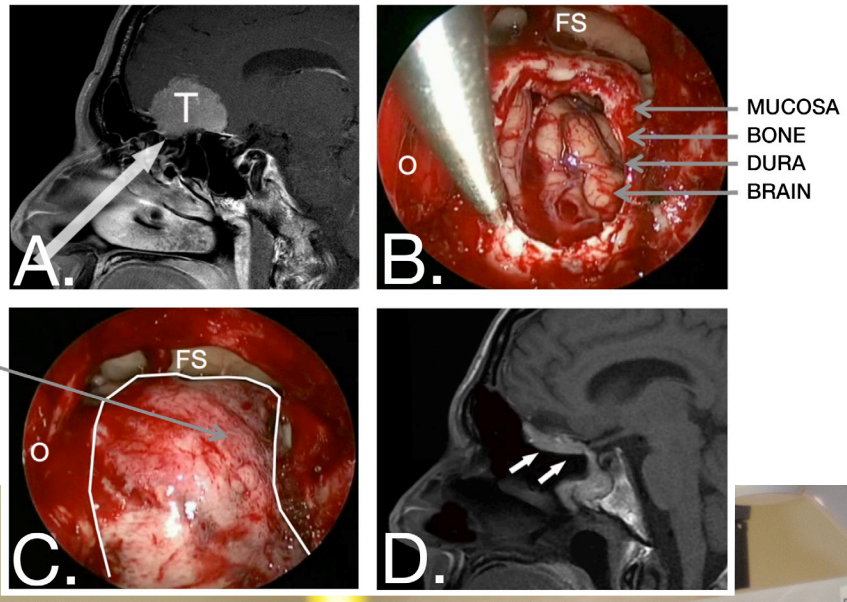
"Once you have the surgery, the graft sits there forever, and the patient lives the rest of their life with this 'screen door' to the brain," Dr. Bleier said.

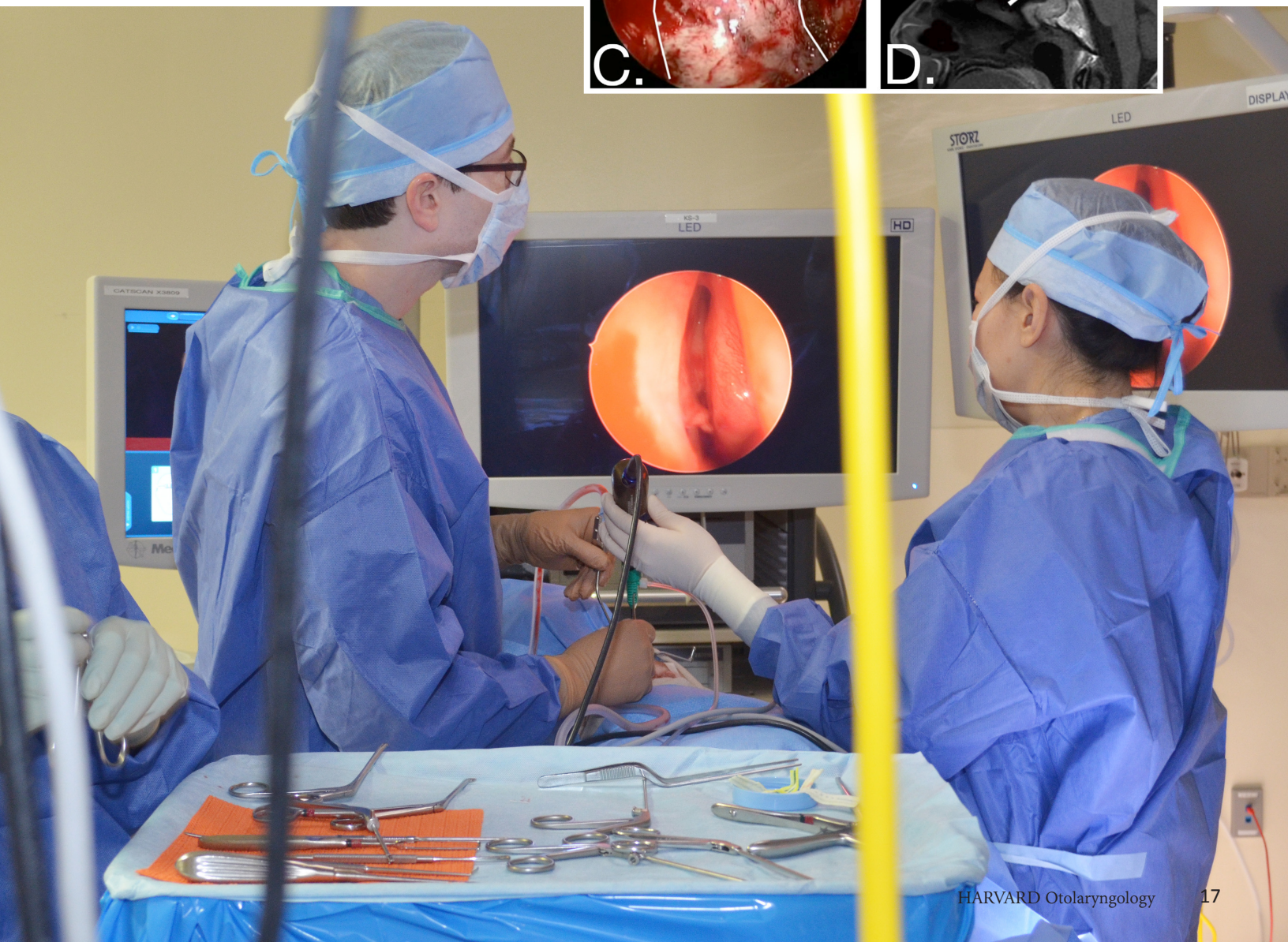
*Example of state-of-the-art endoscopic skull base surgery with mucosal graft reconstruction:* ***A:*** *MRI scan showing a typical patient with a tumor (T) that can be removed entirely through the nose.* ***B:*** *Endoscopic view after tumor removal where a large defect is created between the nose and the brain that must be reconstructed to prevent a cerebrospinal fluid leak and meningitis(O-right orbit, FS-frontal sinus).* ***C:*** *Endoscopic view of a large mucosal graft (outlined in white) which is used to reconstruct the skull base defect.* ***D:*** *Postoperative MRI demonstrating the same patient after tumor removal with a well healed mucosal graft (white arrows) sealing the defect between the nose and brain.*

The technique has the potential to benefit a large population of patients with neurodegenerative disorders, where there remains a specific unmet need for blood-brain penetrating therapeutic delivery strategies.

"We see this expanding beyond Parkinson's disease, as there are multiple diseases of the brain that do not have good therapeutic options," Dr. Bleier said. "It is a platform that opens doors for new discovery and could enable drug development for an underserved population."

*This research was supported by grants from the Michael J. Fox Foundation for Parkinson's Research.*



## Harvard Medical School Department of Otolaryngology Celebrates 2015 Graduation, 3rd Annual Meeting

Faculty and staff from the Department of Otolaryngology at Harvard Medical School gathered in Meltzer Auditorium at Mass. Eye and Ear on Friday, June 26th to celebrate the 2015 graduating class of residents and fellows.

Five chief residents and 10 clinical fellows graduated from the program. Outstanding graduates were honored in a ceremony led by HMS Otolaryngology Residency Director Stacey T. Gray, M.D., Associate Residency Director Kevin Emerick, M.D., and Walter Augustus LeCompte Professor and Chair of Otolaryngology at Harvard Medical School, D. Bradley Welling, M.D., Ph.D., FACS, among others.

***"This time of year is always bittersweet for me and the other faculty," Dr. Gray said. "We've watched the residents and fellows accomplish so much during their time here, and we are so excited to see where they are headed next. We're extremely proud that they will represent our program as they move forward in their careers as otolaryngologists."***

Keynote speaker James L. Netterville, M.D., the Mark C. Smith Professor of Otolaryngology and Director of Head and Neck Surgery at Vanderbilt University, delivered this year's graduation address, which was titled "How Heroes Shape Our Lives." In his speech, Dr. Netterville paid tribute to mentors who were influential to his medical career and life, empowering the graduates to do the same.

Prior to the graduation ceremony, the day began with the Department's 3rd Annual Meeting, an event that brings together representatives from every corner of the Department, including otolaryngology colleagues from Mass. Eye and Ear/Mass General, Beth Israel Deaconess Medical Center, Boston Children's Hospital and Brigham and Women's Hospital.

The meeting featured scientific presentations and updates from representatives from each division, with topics ranging from high-risk skin cancer management in the otolaryngology field, to combining functional and cosmetic approaches to rhinoplasty, to new techniques in endoscopic ear surgery — and much more.

The Annual Meeting provided an opportunity for thoughtful discussion among faculty and staff across subspecialties and clinical venues throughout the broader HMS Otolaryngology Department.

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## Awards and Honors

### Annual Poster Session

**Regan Bergmark, M.D.**
**2nd Place Poster Award (tie)**
"Socieoeconomic determinants of night/ weekend emergency department use of uncomplicated acute rhinosinusitis."
*Mentor: Ahmad R. Sedaghat, M.D., Ph.D.*

**Matthew Naunheim, M.D., MBA**
**2nd Place Poster Award (tie)**
"Cost benefit analysis of otolaryngology specific emergency room services using a contingent valuation system"
*Mentor: Mark G. Shrime, M.D., M.P.H., Ph.D.*

**Elliott D. Kozin, M.D.**
**1st Place Poster Award**
"Superior temporal resolution of chronos versus channel rhodopsin-2 in an optogenetic model of the ABI."
*Mentor: Daniel J. Lee, M.D., FACS*


*Dr. James Netterville, the Mark C. Smith Professor of Otolaryngology and Director of Head and Neck surgery at Vanderbilt University, delivered this year's graduation address.*

## Jeffrey P. Harris, M.D., Ph.D., Research Prize

*Presented to one of the graduating chiefs for their FOCUS research project.*

**Kyle J. Chambers, M.D.**
"Laryngeal re-innervation using a split hypoglossal nerve graft."
*Mentors: Christopher J. Hartnick, M.D., Gregory W. Randolph, M.D., FACS, FACE and Phillip C. Song, M.D.*

## Fellow Teaching Award

**Caroline A. Banks, M.D.**

## Chief Resident Teaching Award

**Allen C. Lam, M.D.**

## William W. Montgomery, M.D., Faculty Teaching Award

**Phillip C. Song, M.D.**

# Graduating Class of 2015

## Residents

Throughout her residency, **Margaret S. Carter, M.D.,** was consistently praised for her hard work, dedication and, especially, her commitment to compassionate care. As a junior resident, she would stay early and late taking care of patients. As a chief, she pitched in to help junior residents finish the work so that they wouldn't have to stay quite so early or late. In addition to her strong dedication to clinical care, Dr. Carter spent her research time during residency working on a project involving intravestibular biophosphonate distribution through stapedectomy in a guinea pig model. That project now continues on at Mass. Eye and Ear. Dr. Carter has returned to her California roots by joining Camino ENT Clinic in San Jose, where she practices general otolaryngology.

**Kyle J. Chambers, M.D.,** was extremely productive during residency. His research project, "Laryngeal re-innervation using a split hypoglossal nerve graft," resulted in an oral presentation at the American Society of Pediatric Otolaryngology meeting in 2014 and a series of publications. Dr. Chambers was actively involved in other projects that resulted in multiple posters and 6 oral presentations throughout his training.


*Top Row (L-R): Drs. Margaret Carter, Sunshine Dwojak and Kyle Chambers.*
*Bottom Row (L-R): Drs. Matthew Mori and Allen Lam.*

He was an author on 20 publications and received the John Conley resident research award for a presentation at the Triological Society Combined Sections Meeting. In the clinics and operating room, faculty noted his exceptional clinical judgment and thoughtful decision-making. Dr. Chambers recently joined Berkshire Ear, Nose and Throat in Stockbridge, Mass., where he practices general otolaryngology.

**Sunshine M. Dwojak, M.D., MPH,** joined Mass. Eye and Ear/Harvard Medical as a 7-year research track resident, and during her extra two years of training, she also earned a Master's of public health from the Harvard School of Public Health. Her research project involved outcomes, screening and awareness of head and neck cancer among American Indians—a project she created and designed independently. She received the American Head and Neck Society CORE pilot grant for the project, and she presented the work at national meetings and in three publications to date. She was also awarded the Eastern Section resident research award in the 2014 Triological Society Combined Sections Meeting. Dr. Dwojak is currently pursuing fellowship training in head and neck oncology/microvascular surgery at Vanderbilt University.

**Allen C. Lam, M.D.,** excelled in many areas throughout his residency, as he absorbed all the various practices in preparation for a career in general otolaryngology. His research project, "The effect of pro-inflammatory cytokines on expression and activity of epithelial P-glycoprotein in eosinophilic chronic rhinosinusitis without nasal polyposis," resulted in a presentation at the American Rhinologic Society meeting in 2013 and two publications. Additionally, Dr. Lam presented multiple posters at national meetings and was an author on five publications throughout his residency. An active participant in the otolaryngology field professional community, he also served on the media and public relations committee for the American Academy of Otolaryngology–Head and Neck Surgery. Dr. Lam recently joined Mass. Eye and Ear's Longwood practice as a general otolaryngologist.

Faculty members from the program describe **Matthew C. Mori, M.D.,** as a physician who is "never rattled" and "rises to every occasion." Dr. Mori's calm maturity undoubtedly contributed to his excellence in residency, where he showed ease in the operating room and dedication to his patients. His professional singing background

continued on page 20

*Drs. Inna Hussain, William Yao, Ahmad Sedaghat, Rahul Modi, Caroline Banks and Neerav Goyal.*

*Drs. Steven Hamilton, Julie Strychowsky, Victor Duarte and Heather Herrington with fellowship director at Boston Children's Hospital, Dr. Reza Rahbar.*

*Drs. Mark Varvares, Kevin Emerick, Michael Cunningham, Stacey Gray, Robert Frankenthaler, Jo Shapiro, Brad Welling and guest speaker Dr. James Netterville.*

led him to develop subspecialty interests in laryngology, and his resident research project explored the use of interarytenoid Botox® injections for vocal fold granulomas. Dr. Mori presented multiple posters at national meetings, and he was awarded second place for an oral presentation at the New England Otolaryngology Society. He also served as a member of the Laryngology and Bronchoesophagology Education Committee for the American Academy of Otolaryngology–Head and Neck Surgery. Dr. Mori is currently pursuing fellowship training in laryngology at Vanderbilt University.

## Clinical Fellows, Mass. Eye and Ear

**Caroline A. Banks, M.D.**
*Facial Plastic and Reconstructive Surgery*
*Fellowship Director:* Tessa A. Hadlock, M.D.
*Future Plans:* Remaining in the Boston area

**Neerav Goyal, M.D.**
*Head and Neck Oncology/Microvascular*
*Fellowship Directors:* Daniel G. Deschler, M.D., and Derrick T. Lin, M.D.
*Future Plans:* Assistant Professor of Surgery, Penn State University

**Inna A. Hussain, M.D.**
*Laryngology*
*Fellowship Director:* Ramon A. Franco, Jr., M.D.
*Future Plans:* Section Head of Laryngology, Rush University

**Rahul Modi, M.D.**
*Thyroid and Parathyroid Surgery*
*Fellowship Director:* Gregory W. Randolph, M.D.
*Future Plans:* Assistant Professor of Otolaryngology–Head and Neck Surgery, Bharati Vidyapeeth Medical College, India

**Ahmad R. Sedaghat, M.D., Ph.D.**
*Rhinology*
*Fellowship Directors:* Ralph B. Metson, M.D., Stacey T. Gray, M.D., and Eric H. Holbrook, M.D.
*Future Plans:* Rhinology Division, Mass. Eye and Ear

**William Yao, M.D.**
*Rhinology*
*Fellowship Directors:* Ralph B. Metson, M.D., Stacey T. Gray, M.D., and Eric H. Holbrook, M.D.
*Future Plans:* Assistant Professor of Otorhinolaryngology, University of Texas

## Clinical Fellows, Boston Children's Hospital

*Pediatric Otolaryngology*

*Fellowship Director:* Reza Rahbar, DMD, M.D.

**Victor Duarte, M.D.**
*Future Plans:* Children's Hospital of Central California

**Steven Hamilton, M.D.**
*Future Plans:* Children's Hospital of Colorado

**Heather Herrington, M.D.**
*Future Plans:* University of Vermont Medical Center

**Julie Strychowsky, M.D.**
*Future Plans:* University of Western Ontario

## The Otolaryngology Residency Program at Harvard Medical School

The Department welcomes five new residents to Mass. Eye and Ear this year, Drs. Vivek Kanumuri, Ashton Lehmann, Katie Phillips, Yen Rin and Rosh Sethi. We also welcome five new general surgery interns, Drs. Alessandra Colaianni and Natalie Justicz to Massachusetts General Hospital, Dr. Allen Feng to Beth Israel Deaconess Medical Center and Drs. Suresh Mohan and Alisa Yamasaki to Brigham and Women's Hospital.

## PGY-2 Residents

Originally from Edison, New Jersey, **Vivek Kanumuri, M.D.,** received a combined undergraduate degree in Biology with a minor in Computer Science and medical degree in the 7-year B.S./M.D. program at the College of New Jersey and Rutgers New Jersey Medical School, where he graduated magna cum laude in 2014. Dr. Kanumuri was a Howard Hughes Medical Institute Research Fellow from 2012 to 2013 and was inducted as a junior into the Alpha Omega Alpha Honor Society. He completed his general surgery internship at Beth Israel Deaconess Medical Center. Dr. Kanumuri's research interests include sinonasal tumors, endoscopic techniques, neuro-imaging and electrophysiology.

**Ashton Lehmann, M.D.,** grew up in Edina, Minn., and attended Middlebury College, where she graduated summa cum laude with high honors in neuroscience and as a Phi Beta Kappa member in 2009. She went on to pursue her medical degree at Harvard Medical School in the New Pathway program, which integrates biological, social, behavioral and clinical sciences in its curriculum. Dr. Lehmann completed her general surgery internship at Brigham and Women's Hospital.

**Katie Phillips, M.D.,** graduated magna cum laude with a degree in biochemistry from Boston College in 2009. She was a member of Phi Beta Kappa. Dr. Phillips went on to study medicine at the Ohio State University College of Medicine in Columbus, Ohio, where she had also completed an internship in the OSU Health System's Quality and Operations Improvement Department. While at the Ohio State University, she received the Viola C. Erb Scholarship Award and was Vice President of her chapter of the Alpha Omega Alpha Honor Society. Dr. Phillips completed her general surgery internship at Brigham and Women's Hospital.

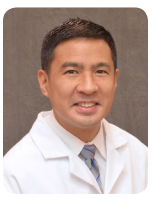
**Yen Rin, M.D., Ph.D.,** studied electrical and biomedical engineering as an undergraduate student at the Massachusetts Institute of Technology, where he earned first place in the MIT "6.270" Autonomous Robot Design competition. Dr. Ren went on to earn his medical degree through the Harvard-MIT Division of Health Sciences and Technology, a joint effort of Harvard Medical School and MIT. During that time, he also obtained a Ph.D. in medical engineering. Dr. Ren completed his general surgery internship at Massachusetts General Hospital.

Originally from Calgary, Canada, **Rosh Sethi, M.D., MPH,** graduated magna cum laude with honors in biology from Yale College, where he was a member of Phi Beta Kappa. He then pursued his medical degree and a Master's in public health degree from Harvard Medical School, in the New Pathway program, and from Harvard School of Public Health. He completed his general surgery internship at Massachusetts General Hospital. Dr. Sethi's research interests include health services research and cost-effectiveness in healthcare.

## New Clinical Fellows

### Mass. Eye and Ear

*Neskey-Coghlan Fellowship in Balance and Vestibular Disorders*
**Erez S. Davidi, M.D.**

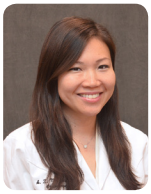


*Head and Neck/ Microvascular*
**Tjoson Tjoa, M.D.**

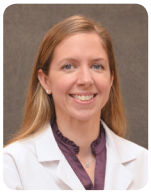
*Neurotology*
**Ruwan Kiringoda, M.D.**

*Pediatric Otolaryngology*
**Carissa Wentland, D.O.**

*Rhinology*
**Christopher D. Brook, M.D.**



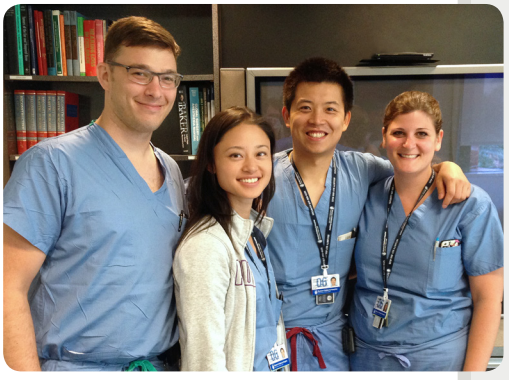
*Rhinology*
**Alice Z. Maxfield, M.D.**



*Thyroid and Parathyroid Surgery*
**Whitney E. Liddy, M.D.**

### Boston Children's Hospital

*Pediatric Otolaryngology*
**Ryan Walker, M.D.**
**Jamie Funamura, M.D.**
**David Chang, M.D.**
**Lindsay Sobin, M.D.**



# Fuxin Shi, Ph.D., Eaton-Peabody Laboratories of Mass. Eye and Ear/ Harvard Medical School, 2005–2014

*From Academia to Industry*

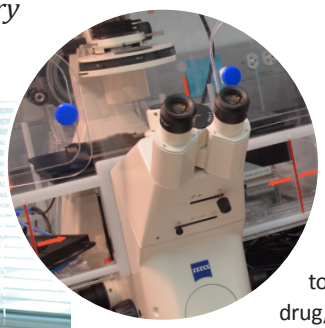
After nearly ten years in academia, Fuxin Shi, Ph.D., a research scientist investigating hair cell regeneration techniques to restore hearing, took a leap to industry.

Originally recruited as a postdoctoral fellow to the Tillotson Cell Biology Unit of the Eaton-Peabody Laboratories at Massachusetts Eye and Ear/Harvard Medical School in 2005, Dr. Shi was very productive academically in the lab working with her mentor, Albert Edge, Ph.D. She authored a number of publications related to her work on signaling pathways for hair cell regeneration, including a series of new findings on the importance of the Wnt pathway in the inner ear. Her projects were funded by grants, including one from the National Institutes of Health. In recognition of her accomplishments, she was promoted in 2012 to Instructor in Otolaryngology at Harvard Medical School.

In 2014, she was offered an opportunity to join the Novartis Institutes for Biomedical Research in Cambridge, Mass., where she now continues her research on signaling pathways for hearing as part of the company's efforts in research related to aging. Her primary goal is now to successfully develop a drug to restore hearing to those who are deaf.

"I really believe that, with the resources here, I have a great chance of bringing something to the clinic," Dr. Shi said. "They really know how to make a drug and to test for safety and efficacy."

Two years into her role at Novartis, she has found the environment to be very different from her days in academia. She currently supervises an in vivo pharmacology lab with two associates responsible for carrying out the studies she designs for three discovery projects. Carrying those projects through the discovery phase and into drug development is the clear target.



"When we're working toward developing a drug, we start with several different candidates, and we're working to bring one of those candidates to the next stage," Dr. Shi said. "After the discovery stage, we have more interaction with translational experts, showing them what we've done in research and looking for opportunities to bridge the gap to clinical trials."

She notes that the experience is a cultural departure from academia, where there is a much greater emphasis on sharing knowledge in the field through mentoring and publishing in journals. However, her experiences in academia helped her to cultivate an understanding of how to run her own lab.

"I really saw how to grow a lab working with Albert," she said. "It was the best place for me to get started."

Though she now devotes her time solely to research, Dr. Shi has a background in medicine. She received medical training at the China Medical University, where she also completed a residency in otolaryngology.

A personal move for her husband's job led her to the Netherlands, where she earned her Ph.D. in cell biology at the University of Groningen. Her doctoral training sent her down a path to joining Dr. Edge at Mass. Eye and Ear/ Harvard Medical School, and later to Novartis.

She hopes that her work as a research scientist will drive therapies for deafness, a condition that weighed heavily on her as a young physician.

"When I was a resident in China, I felt very desperate when I saw patients with deafness in the clinic and had nothing to offer them," Dr. Shi said. "It was very frustrating to me, and I always thought, if I ever had the chance, I would really try to do something about this."

# Jay T. Rubinstein, M.D., Ph.D., HMS Otolaryngology Resident, Class of 1994

*A Rewarding Combination of Research and Clinical Care*

Dr. Jay Rubinstein's interests in neural prostheses like the cochlear implant and, more recently, the vestibular implant had a lot to do with timing, as his days in the University of Washington Medical Scientist Training Program coincided with the early development of the cochlear implant.

"When I first heard about cochlear implants back when they were just a university research project, I instantly knew that it was exactly what I wanted to be doing," said Dr. Rubinstein, now the Virginia Merrill Bloedel Professor and Director of Hearing Research at the University of Washington.

"And while I was a pretty serious enthusiast for cochlear implants back then, I never dreamed that they would become the intervention that they are today," he continued. "The success really strengthened my interest in the field."

As a neurotologist and Director of the Virginia Merrill Bloedel Hearing Research Center at the University of Washington, Dr. Rubinstein has built a career balancing pioneering research with the demands of a busy clinical practice in neurotology. His primary clinical interests include acoustic neuroma surgery, cochlear implantation and vestibular surgery, and his research projects are closely tied to those interests.

Originally from New York City, Dr. Rubinstein earned his Bachelor's and Master's degrees in engineering from Brown University prior to training in the MSTP program at the University of Washington. As a medical student, he stumbled upon Dr. Hal Schuknecht's book, *Pathology of the Ear,* which ultimately led him to the otolaryngology residency program at Mass. Eye and Ear/Harvard Medical School.

"I got the last copy of the first edition from the UW bookstore in 1984, when it was just going out of print," he said. "I didn't know very much about the program at the time, but I knew that I wanted to be where Dr. Schuknecht was."

With funding from the National Institutes of Health, Dr. Rubinstein has dedicated the past several years of his research to the development of a vestibular prosthesis for patients with balance disorders for which there are currently no effective treatments. With colleague James Phillips, Ph.D., he developed a device that they tested through an FDA-approved clinical trial of four patients between 2010 and 2012. They have since retooled the device to achieve better results, and they are currently working to prepare that second generation design for humans.

When he's not working on the vestibular implant, Dr. Rubinstein is working on other funded projects including the development of a signaling processing strategy for cochlear implants to improve the perception of music, and also designing new ways of determining candidacy for and measuring outcomes from cochlear implantation. He also continues work from his doctoral dissertation—modeling the response of the auditory nerve to electrical stimulation using computational models—by mentoring a graduate student who has become involved in the project.

For Dr. Rubinstein, building his career based on a combination of research and clinical care was always very important.

"I've been fortunate enough to have been surrounded by inspiring role models during my medical training," he said. "It's why I've been able to carry that into what I do now, which is an incredibly rewarding combination of both research and clinical care."

HARVARD MEDICAL SCHOOL | DEPARTMENT OF Otolaryngology

## The Alumni Giving Society of the Department of Otolaryngology at Harvard Medical School

**The Department of Otolaryngology at Mass. Eye and Ear/Harvard Medical School established the Alumni Giving Society in 2015 to recognize faculty and alumni who make gifts of $1,000 or more during the fiscal year (October 1 – September 30). Participation is a way to stay connected and to help deliver the finest teaching experience for today's otolaryngology trainees.**

**Our alumni know from firsthand experience that support of the vital work of our students and faculty in the Department of Otolaryngology helps drive continued achievement across all areas of education, research and patient care. To date, we have 39 members whom we thank for their generosity and for partnering with us to achieve our department goals and institutional mission.**

**If you are not a member, please consider joining your colleagues today by making a gift with the enclosed envelope. As a member, you may designate your gift in the way that is most meaningful to you.**

**To learn more, please contact Julie Dutcher in the Development Office at 617-573-3350.**

### Alumni Giving Society Leadership

**D. Bradley Welling, M.D., Ph.D., FACS**
Walter Augustus LeCompte Professor and Chair of Otolaryngology
Harvard Medical School
Chief of Otolaryngology
Massachusetts Eye and Ear/
Massachusetts General Hospital

**Stacey T. Gray, M.D., '04, '05**
Program Director, Residency in Otolaryngology–Head and Neck Surgery
Harvard Medical School

### Alumni Leaders

Daniel G. Deschler, M.D.
Richard E. Gliklich, M.D., '93, '94
Donald G. Keamy, Jr., M.D.
Paul M. Konowitz, M.D.
John B. Lazor, M.D., MBA, '95, '96
Jon B. Liland, M.D., '72
Derrick T. Lin, M.D., '98, '02
Leila A. Mankarious, M.D.
William W. McClerkin, M.D., '73
Ralph B. Metson, M.D., '87
Michael M. Paparella, M.D.
Michael B. Rho, M.D., '05
Herbert Silverstein, M.D., '66

## Alumni Giving Society

**Current Alumni Giving Society members for fiscal year 2015 as of October 12, 2015 are listed below. With your gift of $1,000 or more, you will be included in the 2016 Alumni Giving Society.**

### CHAMPION
**Gifts of $25,000 or more**
Michael S. Cohen, M.D.
Donald G. Keamy, Jr., M.D.
Leila A. Mankarious, M.D.
Ralph B. Metson, M.D.

### VISIONARY
**Gifts of $10,000 to $24,999**
Nicolas Y. Busaba, M.D.
John B. Lazor, M.D.
Michael B. Rho, M.D.
Herbert Silverstein, M.D.

### INNOVATOR
**Gifts of $5,000 to $9,999**
Daniel G. Deschler, M.D.
Richard E. Gliklich, M.D.
Stacey T. Gray, M.D.
Jeffrey P. Harris, M.D., Ph.D.
Eric H. Holbrook, M.D.
Paul M. Konowitz, M.D.
Daniel J. Lee, M.D.
Joseph B. Nadol, Jr., M.D.
David E. Nash, M.D.
Fredric W. Pullen, II, M.D.
D. Bradley Welling, M.D., Ph.D., FACS

### PIONEER
**Gifts of $2,500 to $4,999**
Cliff A. Megerian, M.D.
H. Gregory Ota, M.D.
Steven D. Rauch, M.D.
Eric H. Stein, M.D.
Mark A. Varvares, M.D., FACS

### FRIEND
**Gifts of $1,000 to $2,499**
John F. Ansley, M.D.
Benjamin S. Bleier, M.D.
Daryl G. Colden, M.D.
Michael J. Cunningham, M.D., FACS
Richard R. Gacek, M.D.
Paul E. Hammerschlag, M.D., FACS
Wade W. Han, M.D.
Martin L. Hopp, M.D.
Nelson Yuan-Sheng Kiang, Ph.D.
David J. Lesnik, M.D.
Robin W. Lindsay, M.D.
Andrew A. McCall, M.D.
William W. McClerkin, M.D.
Prerak D. Shah, M.D.
Earl F. Singleton, M.D.

*News from every corner of the Department of Otolaryngology at Harvard Medical School.*

## New Leadership

**Samir Bhatt, M.D.,** will join Mass. Eye and Ear's Newton-Wellesley practice as Medical Director of Otolaryngology. Dr. Bhatt received his medical degree from Yale University School of Medicine prior to completing his otolaryngology residency training at Mass. Eye and Ear/Harvard Medical School. He has since spent much of his career as a managing partner at a busy community practice located north of Boston. Dr. Bhatt practices general otolaryngology.

## Awards, Grants and Honors

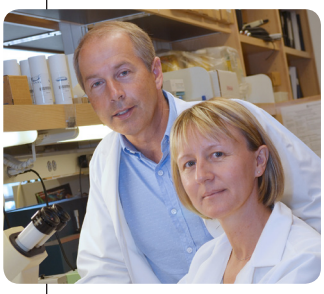
**Benjamin S. Bleier, M.D.,** received a 2015 Honor Award from the American Academy of Otolaryngology–Head and Neck Surgery Foundation, and he also received a first place video prize at the 2015 American Rhinologic Society meeting.

**Song Cheng** received a new grant award from the American Otological Society for his project entitled, "A study of the 'third window' phenomenon using inner-ear pressure measurements."

**Michael J. Cunningham, M.D., FACS,** was Commencement Speaker for the University of Cincinnati College of Medicine Otolaryngology–Head and Neck Surgery residency graduation.

**Daniel G. Deschler, M.D., FACS, Jessica Fewkes, M.D.,** and **Gregory W. Randolph, M.D., FACS, FACE,** were acknowledged in *Newsweek's* 2015 Top Cancer Doctors issue.

**Dr. Deschler,** along with **Stacey T. Gray, M.D., FACS,** and **Mark A. Varvares, M.D., FACS,** were inducted as fellows of the Triological Society.



**Gwenaelle Géléoc, Ph.D.,** and **Jeffrey R. Holt, Ph.D.,** were awarded a grant by the Kidz-b-Kidz Foundation for the purchase of new equipment to support their research on auditory function in mouse models of human deafness.

**Darlene R. Ketten, Ph.D.,** was appointed a Jefferson Science Fellow for the U.S. Department of State and the U.S. Agency for International Development. She began a one-year assignment this past August.

**Sharon G. Kujawa, Ph.D.,** was awarded a grant from the Department of Defense for her project titled, "Aging after noise: biomarkers, clinical assessment and pharmacotherapy of hidden noise injury."

**Taha Jan, M.D.,** received a CORE resident research grant award from the American Academy of Otolaryngology–Head and Neck Surgery for his project titled, "Effects of secreted factors from human vestibular schwannomas on hearing." **Dr. Tina Stankovic** is his mentor on the project.

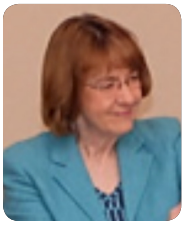
**Daniel J. Lee, M.D., FACS,** was a Visiting Professor at the University of Michigan, Vanderbilt University and University of Pennsylvania.

**Richard Lewis, M.D.,** and **Daniel Merfeld, Ph.D.,** received a new R01 grant award from the NIH for their project titled, "Employing vestibular thresholds to improve patient diagnosis."

**Dr. Lewis** was also appointed Director of the Jenks Vestibular Diagnostic Laboratory at Mass. Eye and Ear.

**Joseph B. Nadol, Jr., M.D.,** received the House-Hitselberger Lifetime Achievement Award from the American Neurotological Society.

**Dr. Nadol** was also Guest of Honor at the April 2015 American Otological Society meeting.



**Marilyn Neault, Ph.D.,** was honored at the 2015 Northeast Cochlear Implant Convention for her involvement in all ten biennial events over the past 20 years, and for serving as co-chair or program chair for the past nine.

**Sid Puram, M.D., Ph.D.,** received a CORE resident research grant award from the American Academy of Otolaryngology–Head and Neck Surgery for his project titled, "Identification of intratumoral subpopulations in oral cavity squamous cell carcinoma." **Drs. Derrick Lin** and **Brad Bernstein** are his mentors on the project.


**Nikhila P. Raol, M.D., MPH,** received the 2015 Holt Leadership Award from the American Academy of Otolaryngology–Head and Neck Surgery.

**Steven D. Rauch, M.D.,** has been appointed Professor in the Liberal Arts Department at Berklee College of Music, where he will be teaching a 15-week course on health and wellness to Berklee undergrads.

**Aaron Remenschneider, M.D., MPH,** received an award from the American Otological Society for his project titled, "Optimized 3-dimensional printed tympanic membrane prosthesis."

**Konstantina M. Stankovic, M.D., Ph.D., FACS,** received the "Benjamin's Prize" from the Collegium Oto-Rhino-Laryngologicum Amictiae Sacrum for her presentation, "Transactivation of human osteoprotegerin promoter by GATA3: Implications for therapy of sensorineural hearing loss."

**Dr. Stankovic** also received a new grant award from the Department of Defense for her project, "Preclinical validation of novel fluorescently labeled compounds to treat neurodegenerative hearing loss."

**D. Bradley Welling, M.D., Ph.D., FACS,** is the Founding Editor of a new open access journal, *Laryngoscope: Investigative Otolaryngology.*

**Dr. Welling** was also awarded a new grant from the Department of Defense for his project entitled, "Fibroblast growth factor regeneration of tympanic membrane perforations."

## HMS Promotions

**Tessa A. Hadlock, M.D.,** Professor of Otolaryngology *(See page 2 for more on Dr. Hadlock's promotion)*

**Selena Heman-Ackah, M.D., Ph.D., MBA,** Assistant Professor of Otolaryngology

**Lavinia Sheets, Ph.D.,** Instructor in Otolaryngology *(promoted from training status)*

**Phillip C. Song, M.D.,** Assistant Professor of Otolaryngology

***The following are select research advances from the Department of Otolaryngology at Harvard Medical School.***

*Jeffrey Holt, Ph.D., and Gwenaelle Gélèoc, Ph.D., of Boston Children's Hospital.*

## Basic Science

### Gene therapy restores hearing in deaf mice

A team of researchers from Boston Children's Hospital/Harvard Medical School, including **Jeffrey R. Holt, Ph.D.,** has successfully restored hearing in mice using gene therapy techniques. Their work, published online on July 8 by *Science Translational Medicine,* could pave the way for gene therapy in individuals with hearing loss caused by genetic mutations.

In earlier experiments, the researchers identified TMC1 and TMC2 as components of the hair cell transduction channel, key molecules required for auditory processing. Building upon this discovery, the team then designed a gene therapy trial for mice using viral vectors to correct mutations in TMC1.

The researchers delivered a healthy gene using an engineered adeno-associated virus 1 (AAV1) together with a promoter to the inner ears of mutant, deaf mice modeling the more common recessive form of TMC1 deafness, which causes profound hearing loss in children from a very young age. Mice that received gene therapy with TMC1 showed restored function to their inner ears – the animals' sensory hair cells began responding to sound, and their auditory brainstem responses improved. Improved hearing was shown by exposing the mice to loud tones in a "startle box," to which the mice jumped at the startling sound.

*Askew C, Rochat C, Pan B, Asai Y, Ahmed H, Child E, Schneider BL, Aebischer P, Holt JR . Tmc gene therapy restores auditory function in deaf mice. Sci Transl Med. 2015 Jul 8;7(295):295ra108.*

### Immediate and delayed cochlear neuropathy after noise exposure in pubescent mice

A team of researchers from Mass. Eye and Ear/Harvard Medical School, including **Konstantina M. Stankovic, M.D., Ph.D., FACS,** with collaborators from the University of Copenhagen, has shed further light on the acute loss of synapses on sensory inner hair cells, which contributes to hidden hearing loss. The researchers explored whether cochlear synaptopathy followed by neuropathy occurred after noise exposure in pubescence. They also defined the noise levels at which neuropathic damage occurs, and compared those levels to non-neuropathic noise levels. The data demonstrated a fine line between neuropathic and non-neuropathic noise levels associated with temporary threshold shift in the pubescent cochlea.

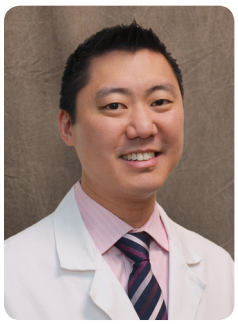
Photo by John Kent.

*For more on hidden hearing loss, please see a relevant feature story on page 10 of this issue.*

*Jensen JB, Lysaght AC, Liberman MC, Qvortrup K, Stankovic KM. Immediate and delayed cochlear neuropathy after noise exposure in pubescent mice. PLoS One. 2015 May 8;10(5):e0125160.*

### Delivery of biophosphonates to the inner ear

Researchers from Mass. Eye and Ear/Harvard Medical School, including **David H. Jung, M.D., Ph.D.,** found that bisphosphonates, potent inhibitors of bone remodeling, can be delivered directly to the mammalian cochlea without damaging the inner ear. This is potentially important for the treatment of otosclerosis, a bone metabolism disorder that results in hearing loss. The work also contributes to an understanding of where drugs go when they are delivered to the cochlea; therefore, the paper has broader implications for treatment of other ear diseases.



*Kang WS, Sun S, Nguyen K, Kashemirov B, McKenna CE, Hacking SA, Quesnel AM, Sewell WF, McKenna MJ, Jung DH. Non-Ototoxic Local Delivery of Bisphosphonate to the Mammalian Cochlea. Otol Neurotol. 2015 Jul;36(6):953-60.*

# Clinical Practice

## Establishing benchmark rates for complications after tonsillectomy

A team including **Neil Bhattacharyya, M.D.,** of Brigham and Women's Hospital/Harvard Medical School, has recently published a series of articles quantifying national benchmark rates for complications after tonsillectomy. Although tonsillectomy

is one of the most commonly performed otolaryngology procedures in the United States, it also entails a difficult recovery period, not infrequently complicated by revisits or readmissions for dehydration, bleeding, etc. These articles quantify not only the perhaps most feared complication of tonsillectomy, post-tonsillectomy bleeding, but also other issues that cause a return to the hospital. While prior studies have most commonly been institutional series, these articles present data from several geographically representative states separately for children and adults. These data are particularly timely and germane to otolaryngologists given the national focus on revisit rates after discharge from the hospital as a quality metric. In recognition of the impact of this research, the authors received the Charles Ferguson Award for Clinical Research From the American Society of Pediatric Otolaryngology in 2014. Additional work, published and ongoing, suggests that there are socioeconomic risk factors for complications after tonsillectomy as well.

*Bhattacharyya N. Rapid communication: The risk of additional post-tonsillectomy bleeding after the first bleeding episode. Laryngoscope. 2015 Feb;125(2):354-5.*

*Shay S, Shapiro NL, Bhattacharyya N. Revisit rates and diagnoses following pediatric tonsillectomy in a large multistate population. Laryngoscope. 2015 Feb;125(2):457-61.*

*Bhattacharyya N, Shapiro NL. Associations between socioeconomic status and race with complications after tonsillectomy in children. Otolaryngol Head Neck Surg. 2014 Dec;151(6):1055-60.*

*Bhattacharyya N, Kepnes LJ. Revisits and postoperative hemorrhage after adult tonsillectomy. Laryngoscope. 2014 Jul;124(7):1554-6.*

## Voice outcomes after total laryngo-pharyngectomy reconstruction

A team from Mass. Eye and Ear/Harvard Medical School, including **Daniel G. Deschler, M.D., FACS,** analyzed voice-related outcomes of more than 40 cases of reconstruction after total laryngectomy or total laryngo-pharyngectomy—the most thorough and rigorous study of tracheoesophageal voice in reconstructed patients to date. Using a strict protocol developed by this group, subjective and objective speech analysis was combined with three quality of life assessments to demonstrate that although speech in reconstructed patients was inferior to speech in patients who did not require reconstruction, reconstructed patient speech was effective and dependable. The study also demonstrated that speech was not significantly different for patients reconstructed with the radial forearm free flap compared to patients reconstructed with the jejunal free flap.

*Deschler DG, Herr MW, Kmiecik JR, Sethi R, Bunting G. Tracheoesophageal voice after total laryngopharyngectomy reconstruction: Jejunum versus radial forearm free flap. Laryngoscope. 2015 Jul 21.*

## Emergency department utilization for sinus disease

Emergency department (ED) utilization for conditions that can be readily treated at primary care offices is a source of considerable, unnecessary healthcare expenditure. Unnecessary ED utilization can reflect problems with primary care physician access, quality of care, treatment patterns, patient symptoms or other factors.

Researchers from Mass. Eye and Ear/ Harvard Medical School, including **Ahmad R. Sedaghat, M.D., Ph.D.,** have used uncomplicated acute rhinosinusitis (ARS) as a paradigm for a common condition that is most appropriately treated in the primary care setting. They previously showed that individuals with Medicaid and the uninsured are disproportionately more likely to use the ED for uncomplicated ARS. They subsequently found evidence that ED use for uncomplicated ARS by Medicaid patients may be partially related to poor access to primary care providers while ED use by the uninsured may be related to the greater severity of their ARS symptomatology.

*Bergmark RW, Ishman SL, Scangas GA, Cunningham MJ, Sedaghat AR. Socioeconomic determinants of overnight and weekend emergency department use for acute rhinosinusitis. Laryngoscope. 2015 May 27.*

# Global Surgery

## Surgical care may result in financial ruin for billions around the world

Researchers from Mass. Eye and Ear, Harvard Medical School and Boston Children's Hospital, including **Mark G. Shrime, M.D., MPH, Ph.D.,** recently set out to quantify how many people around the world would go into financial ruin when seeking surgical care.

The paper represents an important part of the *Lancet* Commission on Global Surgery, a collaborative research effort co-chaired by **John G. Meara, M.D., DMD, MBA**, of Boston Children's Hospital. Overall, the commission resulted in five key messages supported by primary research papers:

- Five billion people around the world lack access to safe, affordable surgery and anesthesia care when they need it.
- Almost 150 million more cases need to be done every year to meet that unmet need.
- Thirty-three million people around the world go into financial ruin when they have surgeries they cannot pay for, and 3.7 billion people would go into financial ruin if they needed surgery today.
- The global cost of this problem, if not addressed, would be approximately $12.3 trillion over the next 15 years.
- Surgery is an indivisible, indispensible part of a functioning healthcare system. Global health goals cannot be met without surgery.

*Shrime MG, Dare AJ, Alkire BC, O'Neill K, Meara JG. Catastrophic expenditure to pay for surgery worldwide: a modelling study. Lancet Glob Health. 2015 Apr 27;3 Suppl 2:S38-44.*

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## Innovations in Residency Training

### An increase in resident research involvement

Faculty and trainee members of the HMS Otolaryngology Residency Program, including Residency Director **Stacey T. Gray, M.D., FACS,** evaluated the changes in resident publications at their institution over an 18-year period (from 1996 to 2013) to identify factors statistically associated with publications during residency. Among the information collected to study factors associated with publication rate, resident demographics, Ph.D. degrees, training tracks and post-graduation plans were included in the study. The researchers found that there has been a substantial increase in resident publications over this period of time, and that the implementation of work hour restrictions may have been a contributing factor. Additionally, T32 grants from the National Institutes of Health was the most predictive factor in the increase in resident research involvement.

*Chen JX, Kozin ED, Sethi RK, Remenschneider AK, Emerick KS, Gray ST. Increased Resident Research over an 18-Year Period: A Single Institution's Experience. Otolaryngol Head Neck Surg. 2015 Sep;153(3):350-6.*

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#1

## Mass. Eye and Ear ranked #1 in the nation for otolaryngology care by *U.S. News and World Report.*

In a report released by *U.S. News and World Report* and the physician network Doximity, the Department of Otolaryngology at Mass. Eye and Ear/Mass General was ranked #1 in the nation for otolaryngology care.

## Upcoming Events

**MassEyeAndEar.org/ENTCalendar**

Please visit the online calendar for updated information about upcoming events in the Harvard Medical School Department of Otolaryngology.

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**News from the Department of Otolaryngology at Harvard Medical School**

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