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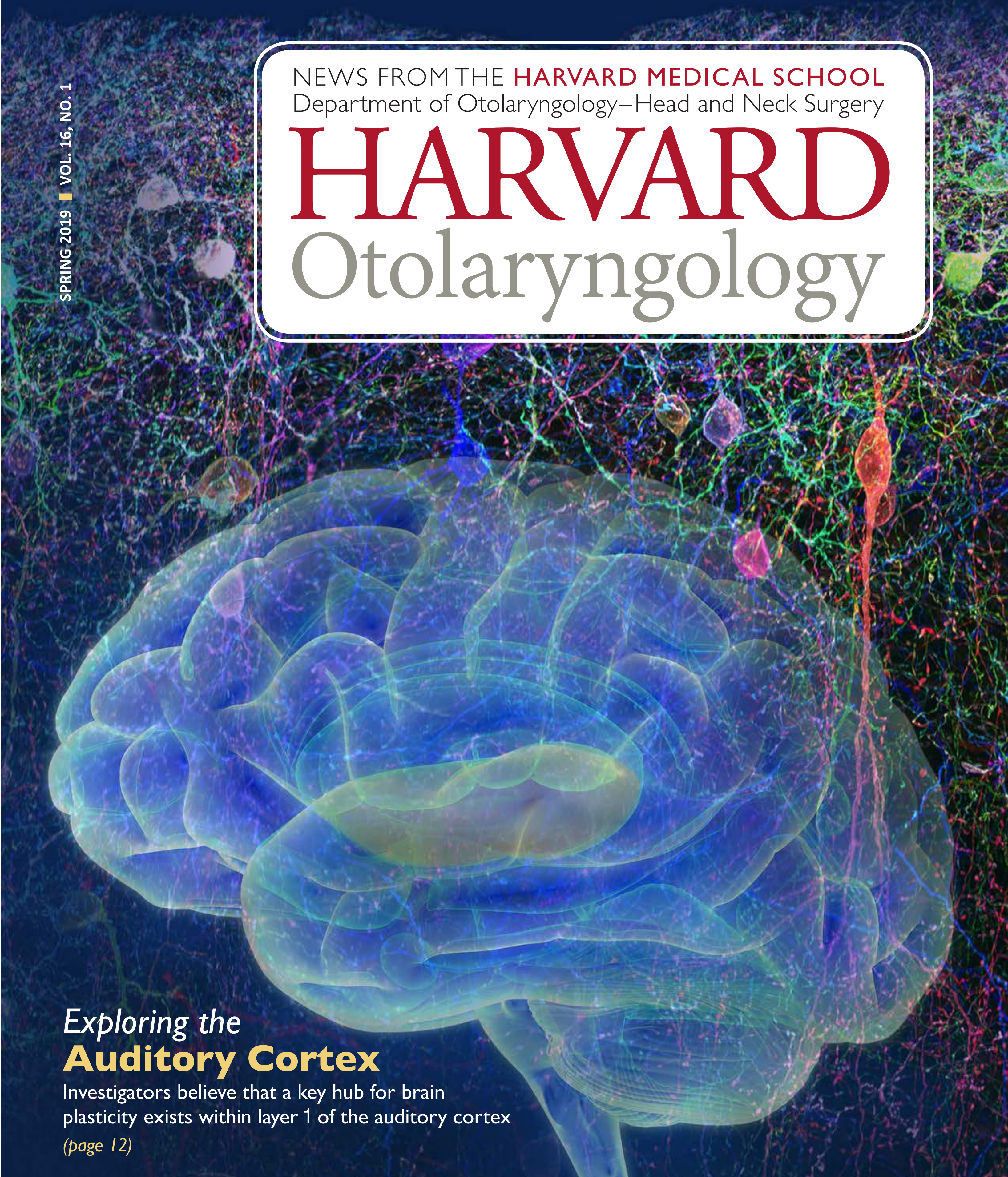
NEWS FROM THE HARVARD MEDICAL SCHOOL
Department of Otolaryngology–Head and Neck Surgery

HARVARD Otolaryngology



Exploring the **Auditory Cortex**

Investigators believe that a key hub for brain plasticity exists within layer 1 of the auditory cortex

(page 12)

HARVARD MEDICAL SCHOOL | Department of Otolaryngology Head and Neck Surgery

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News from the Harvard Medical School Department of Otolaryngology–Head and Neck Surgery

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HARVARD MEDICAL SCHOOL | Department of Otolaryngology Head and Neck Surgery

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Contents

Dear colleagues and friends,

As medical professionals, we aim to have an impact on the development of new treatments for patients through our research efforts. Translating basic science into therapies or procedures can be instrumental to our field—and life altering for patients.

At Harvard Medical School, we have many ongoing initiatives with bench-to-bedside potential. In our cover story, we highlight the work of Anne E. Takesian, PhD, of the Eaton-Peabody Laboratories at Massachusetts Eye and Ear. She has recently identified neurons within the first layer of the brain's auditory cortex that could act as hubs for triggering adaptive plasticity. Starting on page 12, we discuss how this new knowledge may lead to novel therapies for developmental conditions such as autism spectrum disorder.

In this issue, we also highlight work that has discovered that electrodes in the nose can produce smell through electronic stimulation. This proof of concept finding may be the foundation needed to create devices for smell restoration. Additionally, we discuss a novel approach to remove the thyroid gland through the floor of the mouth.

We're excited to share more with you about our research advances and current progress across the field. Thank you for your interest in and support of the department's activities.

Sincerely,

D. Bradley Welling, MD, PhD, FACS

Walter Augustus Lecompte Professor and Chair
Department of Otolaryngology–Head and Neck Surgery
Harvard Medical School

Chief of Otolaryngology–Head and Neck Surgery
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Head and Neck Cancer Research Center Named at Massachusetts Eye and Ear

A generous donation helps establish a research center dedicated to curing head and neck cancer

With the goal of creating better outcomes for head and neck cancer patients, the Mike Toth Head and Neck Cancer Research Center at Massachusetts Eye and Ear launched earlier this year. Made possible by a gift from Michelle and Bob Atchinson in honor of their close friend, Mike Toth, the center is committed to developing new treatments and finding cures for cancers of the head and neck.

The opportunity to help doctors and scientists combat head and neck cancer hits close to home for the Atchinsons, who are longtime friends of Mass. Eye and Ear. They watched Mike, their dear friend and Mass. Eye and Ear patient, courageously battle tongue and throat cancer for 10 years.

"Mike was one of the most unique and special people we have ever known. He was a visionary and a creative genius," said Mrs. Atchinson. "He exuded life. Even as the cancer robbed him of his ability to speak and eat, he continued to draw people to him with his humor and optimism."

When the Atchinsons learned of the growing incidence of head and neck cancer and Mass. Eye and Ear's plan to launch a one-of-a-kind head and neck cancer research center, they were inspired to help.

"At Mass. Eye and Ear, we are uniquely positioned to make a real impact in advancing head and neck cancer research," said Derrick T. Lin, MD, FACS, Director of Head and Neck Surgical Oncology at Mass. Eye and Ear and the Daniel Miller Associate Professor of Otolaryngology–Head and Neck Surgery at Harvard Medical School.

With a large patient population and a sizable tumor bank—both of which are critical for testing potential new therapies—Mass. Eye and Ear has ambitious plans to recruit scientists, build laboratories, and invest in research. Through the Toth Center, these plans will all be made possible. By introducing a new hub for collaboration, this center will forge relationships in order to bring emerging research strategies to head and neck cancer, which can ultimately expedite breakthroughs in treatment.

Photos by Pierce Harman.

"As part of one of the most research-rich medical communities in the world, we can harness the power of strategic collaborations with experts in immunology, genetics, and cancer to elevate the standard of care and create better outcomes for people with head and neck cancer," Dr. Lin continued.

Two investigators specializing in head and neck cancer research, Srinivas Vinod Saladi, PhD, and Daniel L. Faden, MD, have recently been recruited by the center. Dr. Saladi's research focuses on understanding the mechanism by which epigenetic reprogramming contributes to cellular plasticity in tumors. Dr. Faden is interested in examining how acquired genomic alterations and viral infection affect head and neck cancer initiation, growth, and response to treatment.

Both investigators are working to dissect the mechanisms contributing to head and neck cancer in order to find and develop therapeutic opportunities.

Top left:
From left to right: Bob Atchinson, Mass. Eye and Ear President John Fernandez, Susan Toth, and Michelle Atchinson.

Middle:
Mass. Eye and Ear Chief of Otolaryngology–Head and Neck Surgery Dr. Brad Welling at the Toth Center dedication reception.

Top right:
The Toth Family (left to right) Zack Toth, Frances Carr Toth, Susan Toth, Rachel Toth, and Max Toth.

Bottom right:
Head and neck cancer faculty (left to right) Drs. Vinod Saladi, Derrick Lin, and Jeremy Richmon.

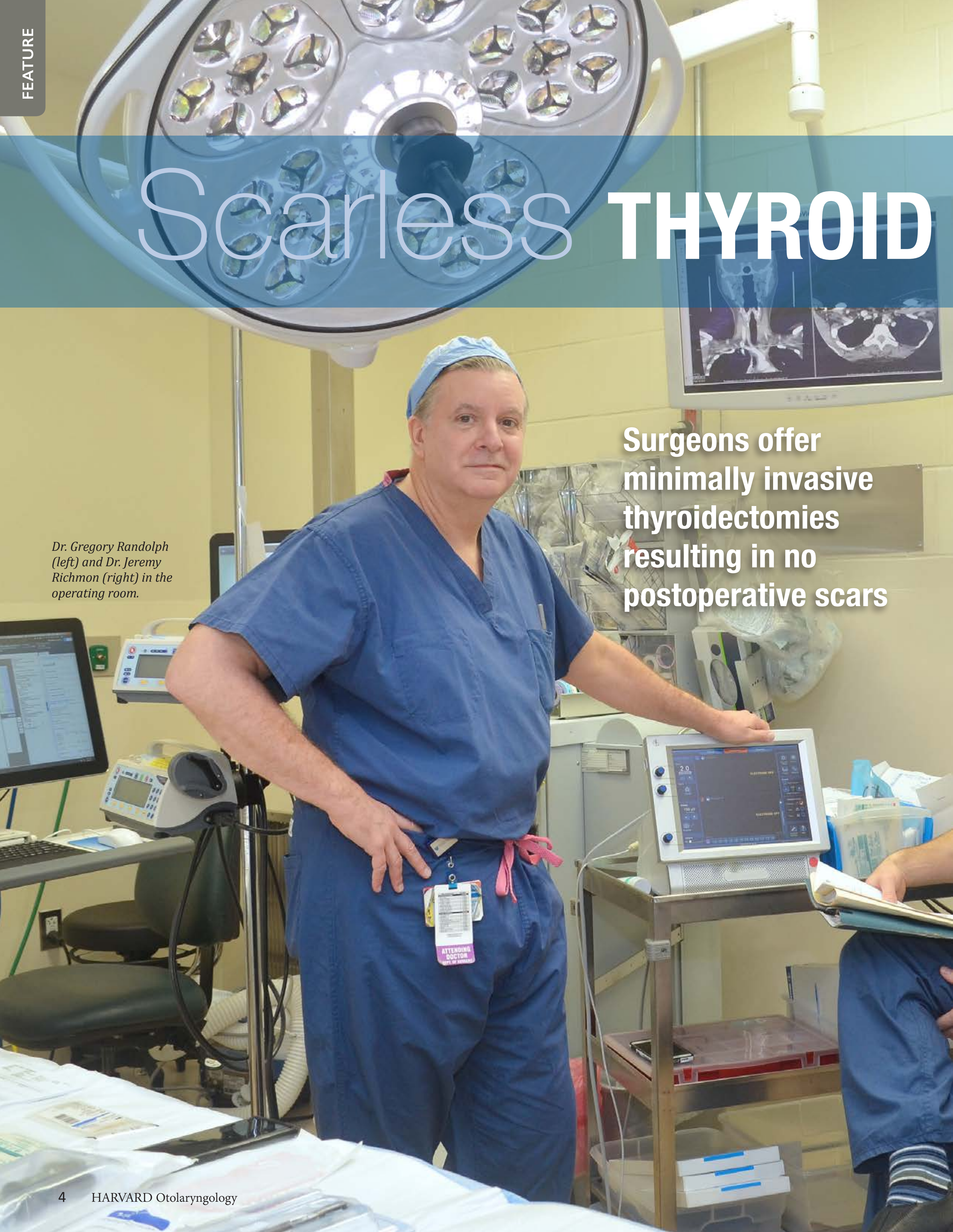
The establishment of this center is the first step toward creating the nation's premier head and neck cancer research enterprise. Going forward, the center aims to attract additional philanthropic support to recruit more investigators and fund new research initiatives.

"The Toth Center will take the lead in the research and treatment of head and neck cancer. It will be a focal point of innovation, uniting the incredible talent in the Boston medical community. It is only right that it be named after a gifted man who lived his life for others," said Mr. Atchinson.

Want to learn more about how you can help advance research at the Mike Toth Head and Neck Cancer Research Center? Contact **Melissa Paul** at **617-573-4168** or **melissa_paul@meei.harvard.edu**.

Scarless **THYROID**

Surgeons offer minimally invasive thyroidectomies resulting in no postoperative scars



Dr. Gregory Randolph (left) and Dr. Jeremy Richmon (right) in the operating room.

SURGERY

The adverse effects of a neck scar, a de facto result of a conventional thyroidectomy, can be distressing for some patients. A thyroidectomy is currently the standard approach to removing the thyroid gland, a butterfly-shaped organ that sits in the base of the neck, through a neck incision. While it is effective, the permanent scar left behind has motivated both patients and surgeons to seek alternative approaches.

Not all patients mind having a scar, but, for those who do, their quality of life may be negatively impacted. This is particularly prevalent in cultures that have stigmas against visible scars and in patient populations who place a higher emphasis on their physical appearance.

Various remote-access approaches to the thyroid have been developed over the years with the goal of avoiding a visible scar. The most recent and promising development in this arena has been the transoral approach.

> *"If the patient's goal is to avoid a permanent scar, we've determined that a transoral approach could be an appropriate alternative for them."*
>
> –Dr. Richmon

A transoral thyroidectomy, which can be performed with minimally invasive endoscopic or robotic technology, accesses the thyroid gland through the lower lip. By making incisions inside of the mouth instead of the neck, the procedure is completed without leaving any visible postoperative scars.

"We've found that the transoral approach is the ideal remote-access approach for thyroid surgery," said Jeremy D. Richmon, MD, Associate Professor of Otolaryngology–Head and Neck Surgery at Harvard Medical School and Director of Robotic Surgery at Massachusetts Eye and Ear. "There is less flap dissection during the procedure and no postoperative scars, which makes it a good option for patients who desire to optimize aesthetics."

A safe and feasible alternative

Dr. Richmon has been involved in remote-access thyroid surgery since 2010. With a team at the Johns Hopkins University School of Medicine, he has explored various approaches through the chest, neck, and most

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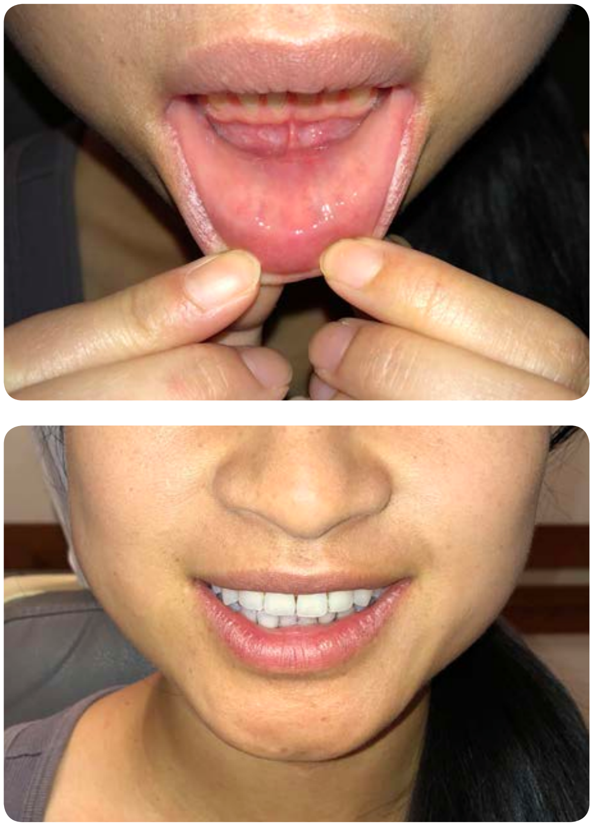
Photos by Dr. Jeremy Richmon.



Lower lip incision sites and appearance of a patient six weeks after surgery.

recently, mouth. His group was the first to describe the transoral approach in 2011.

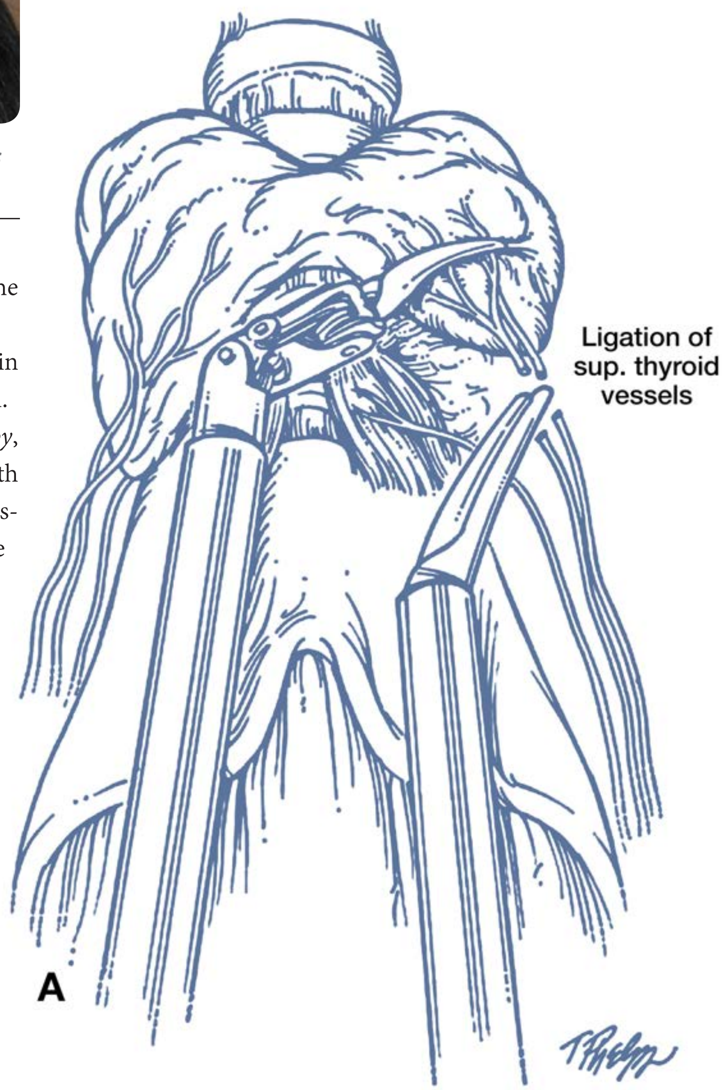
This approach was further explored by surgeons in Asia, which has led to its growing widespread adoption.

In a 2017 study published in *Surgical Endoscopy*, Dr. Richmon and colleagues from Thailand and South Korea evaluated 200 patients who had undergone transoral thyroid surgery to demonstrate that it can be done in an acceptable surgical duration with minimal pain scores. Overall, it has been determined to be a safe and feasible alternative to a conventional thyroidectomy.

"We understand that this procedure won't be for everyone," said Dr. Richmon, who was the first person in the United States to perform this procedure with a robot in 2016 and has continued to be instrumental in its development. "But we think it is important to have options for those patients whose quality of life might suffer as a result of having a neck scar. If the patient's goal is to avoid a permanent scar, we've determined that a transoral approach could be an appropriate alternative for them."

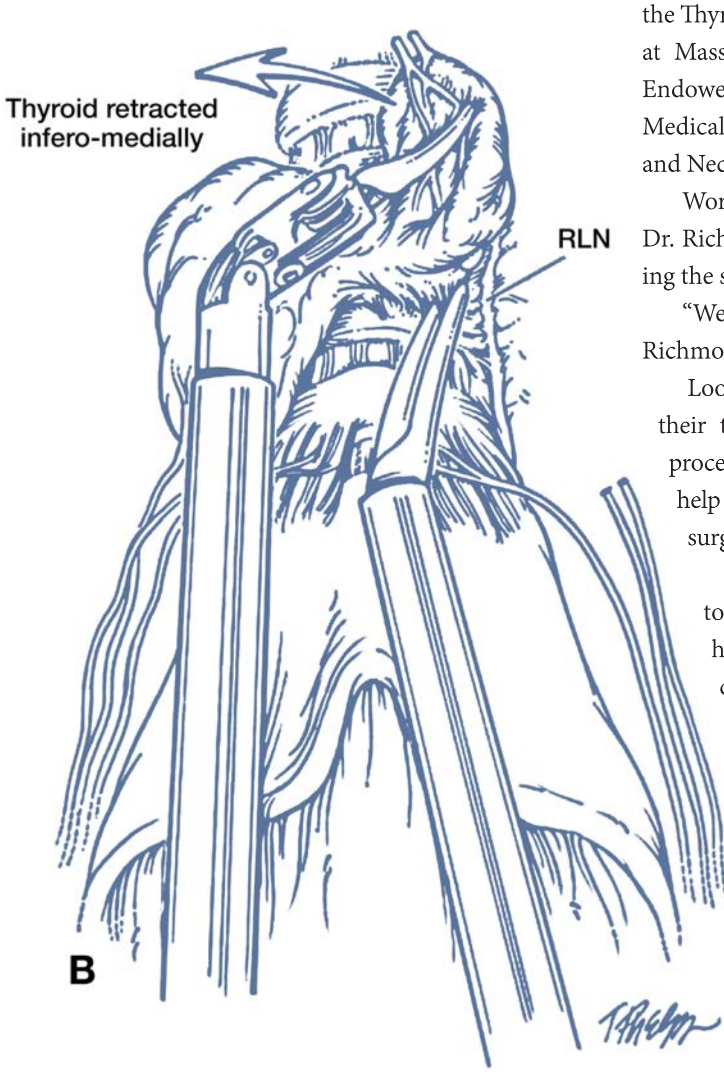
Unlike a traditional thyroidectomy, transoral procedures start with three lower lip incisions. The distance between the lip and thyroid gland is relatively short and requires less tissue dissection than other remote-access approaches, making it an optimal location. After the incisions are made, laparoscopic instruments and an endoscope or surgical robot are inserted and tunneled around the jaw until the thyroid gland is reached.

Once the thyroid gland is exposed, surgery advances in a similar fashion as a traditional, open thyroidectomy would, but with high-definition magnification. The critical nerves and surrounding structures are identified using this magnification and preserved as the thyroid gland is freed and ultimately removed through the lip incision.



The incisions are then closed with absorbable stitches, and patients are transferred to the recovery room. Recovery is similar to that of open thyroidectomy. Most patients are able to start on an oral diet and be discharged the same day as surgery. Risks that are unique to this procedure include lower lip swelling, bruising, and temporary numbness, which usually resolve after a few weeks.

"Most remote-access approaches require more tissue dissection and are limited in their extent to treat contralateral disease," said Dr. Richmon. "With the transoral approach, however, there is a direct pathway to the thyroid with equal access to both sides of the neck and a superb view of the anatomy with the scope. The magnified view is arguably better than what you can see with the naked eye."



Schematic representation from the surgeon's point of view detailing two critical intraoperative steps.

Used with permission from John Wiley & Sons, Inc. Richmon JD, Pattani KM, Benhidjeb T, Tufano RP. Transoral robotic-assisted thyroidectomy: A preclinical feasibility study in 2 cadavers. Head Neck. 2011 Mar;33(3):330–3.

An expectation to grow

Although the transoral thyroidectomy is an attractive option for patients looking to avoid a neck scar, there are still many hesitations to it becoming a widely used procedure. Only about 55 centers worldwide have treated patients with this approach to date. Additionally, patients with smaller nodules or cancers without lymph node involvement are the ones who've been deemed the most appropriate candidates.

Surgeons do expect these numbers to grow, however, as this surgery has been determined to be reproducible for selective high volume endocrine centers.

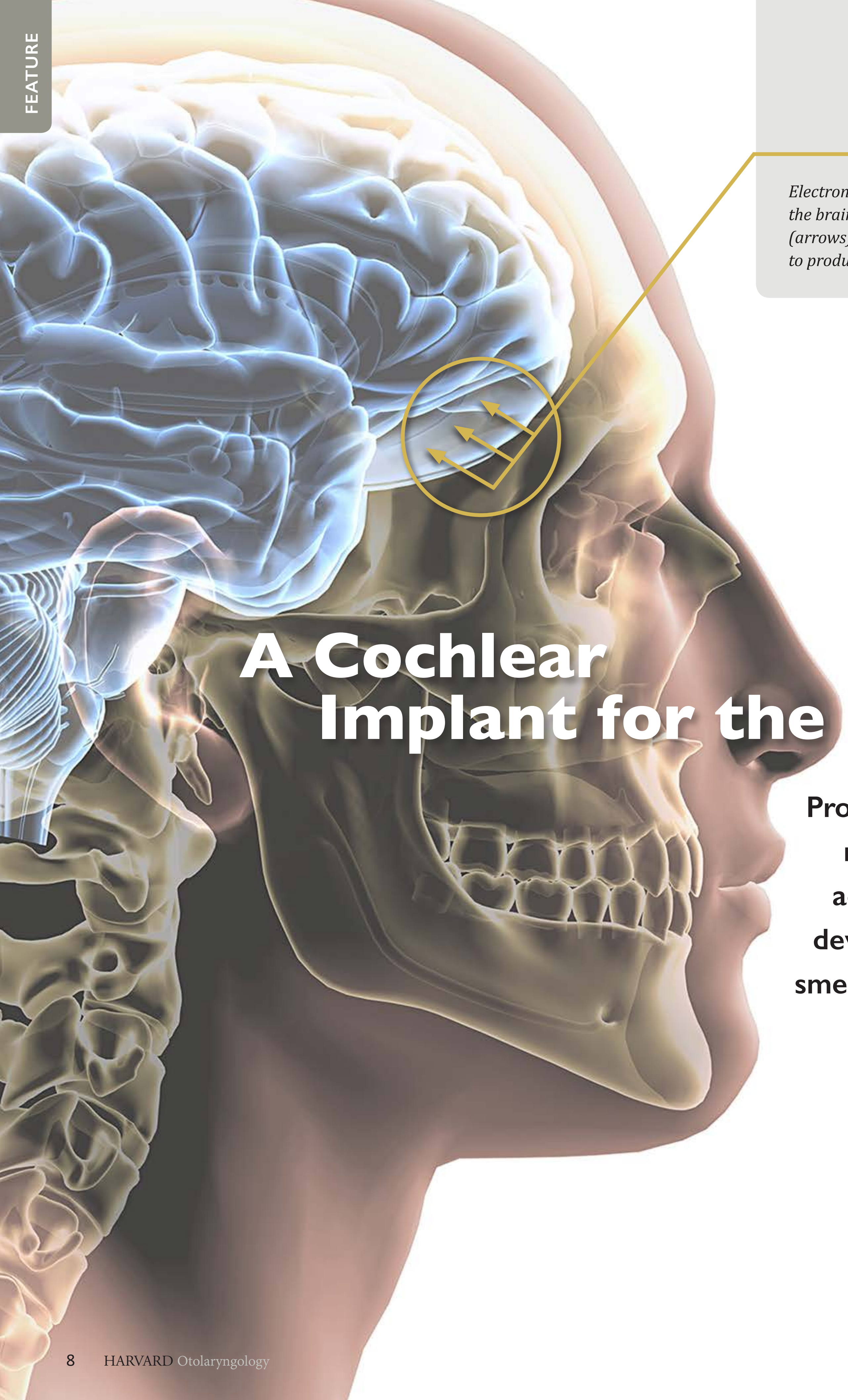
"Nearly 600 thyroid and parathyroid surgical cases are performed at Mass. Eye and Ear each year by more than 20 surgeons. Dr. Richmon's work on transoral thyroidectomy expands the hospital's offering for appropriate patients and builds on our worldwide reputation for neural monitoring and safe thyroid surgery," said Gregory W. Randolph, MD, FACS, FACE, Director of the Thyroid and Parathyroid Endocrine Surgery Division at Mass. Eye and Ear, the Claire and John Bertucci Endowed Chair in Thyroid Surgical Oncology at Harvard Medical School, and Professor of Otolaryngology–Head and Neck Surgery at Harvard Medical School.

Working with Dr. Randolph and other colleagues, Dr. Richmon has co-authored recent guidelines governing the safe introduction of this technology.

"We are proud to be moving forward with Dr. Richmon's pioneering work," Dr. Randolph added.

Looking forward, Dr. Richmon, Dr. Randolph, and their team will continue to refine and enhance the procedure so that more institutions can offer it. This will help ensure that more patients have access to this surgical option.

"For the right person, the transoral thyroidectomy is a tremendous advance that may ultimately help preserve their quality of life," Dr. Richmon concluded.



Electronically stimulating the brain's olfactory bulb (arrows) has been proven to produce a sense of smell.

A Cochlear Implant for the Nose

Proof of concept research may accelerate the development of smell restoration technology

Estimated to occur in five percent of the population, anosmia is a phenomenon that reduces and/or eliminates a person's ability to smell.

Like the loss of any sensory input, a loss of smell comes with its hardships. Our sense of smell contributes to our enjoyment of life, from smelling our favorite meals cooking on the stove to appreciating the fresh scent of spring. Our perception of flavor even relies heavily on smell.

Smell is also important to daily safety and well-being. We rely on it to alert us of hazards such as smoke, gas, or spoiled food. It's understandable why many people who suffer from smell loss also suffer from a diminished quality of life.

In some instances of smell loss, there is a treatable, underlying cause that's easy to pin down, such as sinus disease. Treating that underlying cause typically restores the ability to smell. In other cases, however, anosmia is caused by damage to the sensory nerves and, unfortunately, there are currently no proven therapies for this.

"We don't have effective forms of therapy for many cases of smell loss," said Eric H. Holbrook, MD, Director of Rhinology at Massachusetts Eye and Ear and Associate Professor of Otolaryngology–Head and Neck Surgery at Harvard Medical School. "We attribute such cases to the nasal cavity (olfactory) nerves, which are responsible for detecting odors, either not working properly or not being present at the same numbers they once were. This is something that's shown to be challenging to fix."

Nasal sensory smell nerves do have the ability to regenerate on their own, but they can fail to do so, especially in older populations. One of the therapeutic potentials is to replace or enhance the regenerative

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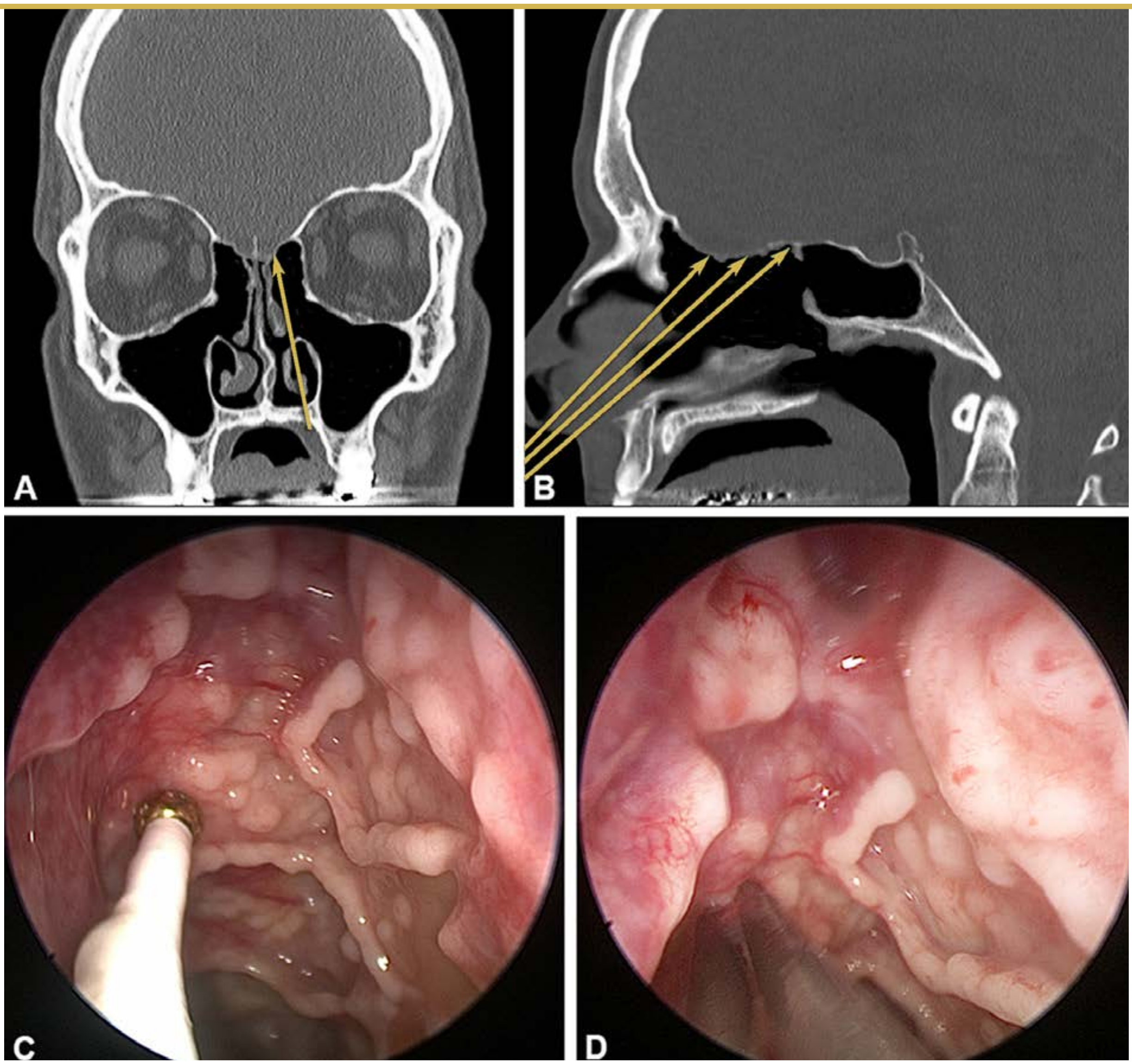
"We wanted to address the question of whether or not electrical stimulation of the olfactory bulb could produce a sense of smell. Our goal was to determine if artificial electrical stimulation was feasible as a future therapeutic modality."

–Dr. Holbrook

Photo by John Earle.



***Approximate location of electrode positioning in the ethmoid sinus cavity. Panels A** and **B** are CT scan renditions in the coronal and sagittal plane, respectively. The yellow arrows demonstrate the approximate location of electrode positioning at the skull base for delivery of the electrical stimulation. **Panels C** and **D** are endoscopic photos of the monopolar **(C)** and bipolar **(D)** electrodes positioned in the ethmoid cavity for electrical stimulation.*

Used with permission from John Wiley & Sons, Inc. Holbrook EH, Puram SV, See RB, Tripp AG, Nair DG. Induction of smell through transethmoid electrical stimulation of the olfactory bulb. Int Forum Allergy Rhinol. 2019 Feb;9(2):158–164.

capacity of the basal cells of the epithelium. The hope is that by stimulating these stem cells, they will begin to divide and produce new neurons, which could re-establish a sense of smell.

"Similar to hearing investigators attempting to regenerate hair cells in the inner ear to help those hear who cannot, we are searching for a means to restore the nerves of the nose to induce smell," said Dr. Holbrook. "Work of James Schwob, MD, PhD, and Tufts University School of Medicine has brought us closer to harnessing the olfactory stem cells and manipulating them for future regenerative therapy, but also like regenerating hair cells, actually restoring smell in humans will take time."

Electrically stimulating the nose

While investigators work on hair cell regeneration, patients with profound hearing loss do have the option of cochlear implants. These are surgically implanted devices that electrically stimulate the auditory nerve to restore hearing.

Taking the cochlear implant as inspiration, Dr. Holbrook's colleagues from the Virginia Commonwealth University (VCU) School of Medicine, Richard M. Costanzo, PhD, and Daniel Coelho, MD, FACS, have been testing the idea of an olfactory implant system that uses electrodes to stimulate the olfactory bulb, a neural structure involved in smell, in mice.

While investigators at VCU work to develop a system for artificial electrical stimulation of smell, Dr. Holbrook, alongside his colleagues at Mass. Eye and Ear and Massachusetts General Hospital, assessed the possibility of bringing this technology to humans. In doing so, Dr. Holbrook and his team became the first to apply this concept through the human nasal cavities and sinuses.

"We wanted to address the question of whether or not electrical stimulation of the olfactory bulb could produce a sense of smell. Our goal was to determine if artificial electrical stimulation was feasible as a future therapeutic modality," he said.

In a recent study published in *International Forum of Allergy & Rhinology*, Dr. Holbrook described the feasibility of trans-nasal electrode stimulation. Through endoscopic positioning of electrodes in the sinus cavities against the thin bone of the cribriform plate, a bone separating the olfactory bulb from the nasal and sinus cavities, he tested the ability to electrically stimulate a smell in five patients with an existing ability to smell. Having a working sense of smell was important in order to confirm the viability of using electrical stimulation to produce a smell.

Three of the five patients described sensations of smell (including reports of onion, antiseptic, sour, and fruity aromas) as a result of the stimulation.

"Our work shows that smell restoration technology is an idea worth studying further," said Dr. Holbrook. "The development of cochlear implants, for example, didn't really accelerate until someone placed an electrode in the cochlea of a patient and found that the patient heard a sound of some type."

A proof of concept established

The idea of electrical impulse-based smell restoration isn't completely new. People have thought about stimulating the olfactory bulb for years. In fact, past research in animals suggests that this technology is attainable. Unfortunately, past attempts at nasal stimulation in humans have not resulted in a subjective perception of smell.

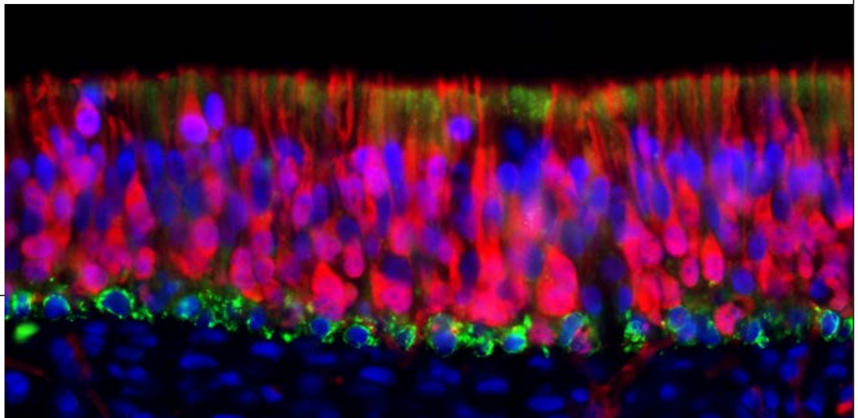
The animal research and prior neurosurgical reports of direct brain stimulation in humans is what encouraged Dr. Holbrook and his team to attempt electrically inducing a subjective perception of smell.

"When using animals, they might respond in some way, but you never quite know if it's a result of true smell or some other sensation. That is why it is important to try this in humans," Dr. Holbrook explained.

With success in humans, Dr. Holbrook and his team have established proof of concept. Their future work will extend the trials to include subjects without a sense of smell. They will also work to develop more consistent, objective measurements of smell perception.

This breakthrough in human patients opens the door for a 'cochlear implant for the nose' to be developed in parallel with the work on nerve regeneration—though Dr. Holbrook and his team caution that the concept of an olfactory stimulator is more challenging than existing technologies.

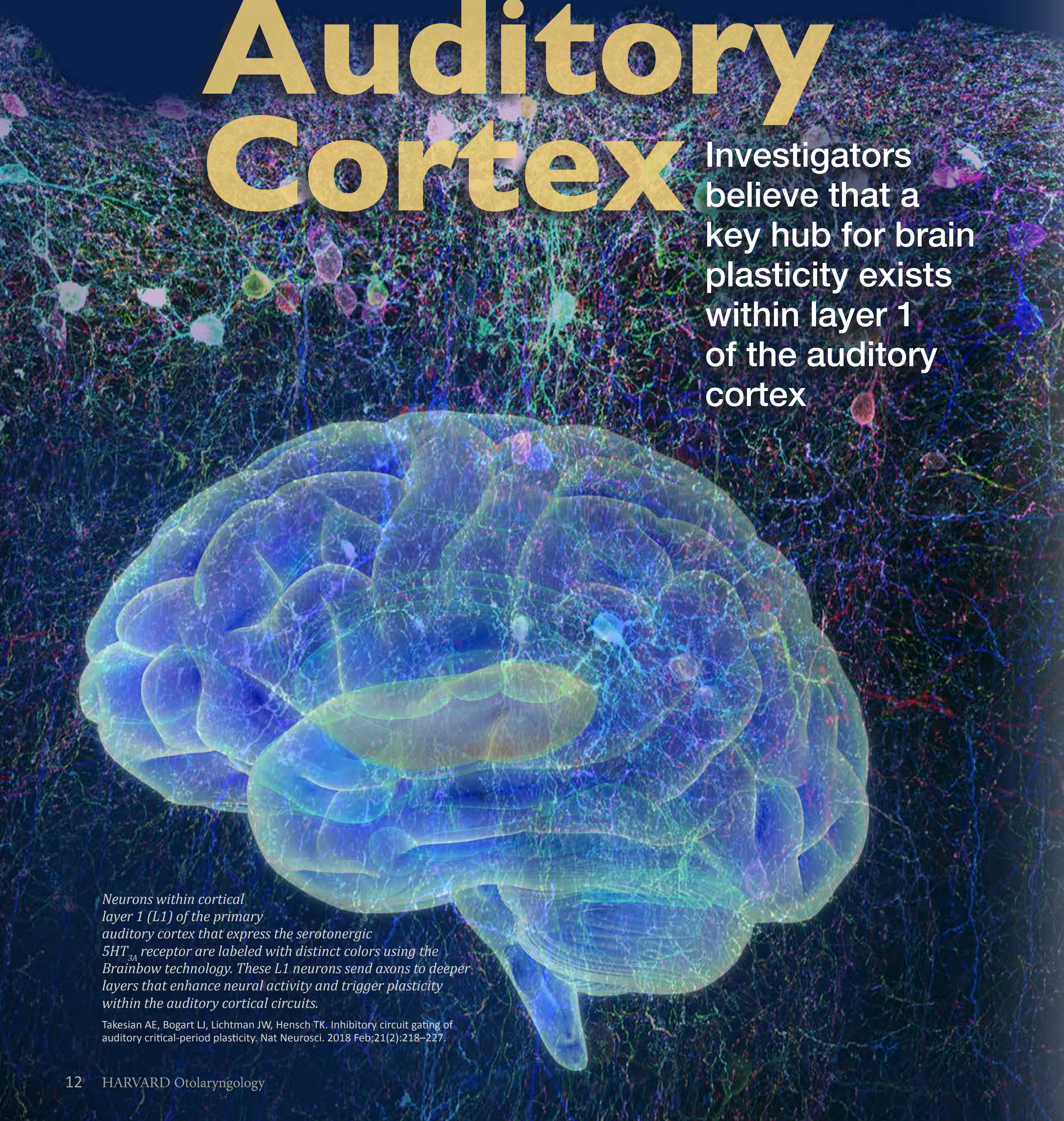
"There's currently so little that we can do for patients with smell loss, and we hope to eventually be able to re-establish their sense of smell," Dr. Holbrook said. "Now we know that electrical impulses to the olfactory bulb can provide a sense of smell—and that's encouraging."



Microscopic view of a section through normal olfactory epithelium. *Using antibodies to label specific cells in a thin section of the human olfactory epithelium obtained from the nasal cavity, we can see the multiple layers of olfactory neurons labeled* ***red*** *and one population of the basal stem cells labeled* ***green*** *that may be manipulated to restore absent neurons in patients with smell loss.*

Exploring the Auditory Cortex

Investigators believe that a key hub for brain plasticity exists within layer 1 of the auditory cortex



Neurons within cortical layer 1 (L1) of the primary auditory cortex that express the serotonergic $5HT_{3A}$ receptor are labeled with distinct colors using the Brainbow technology. These L1 neurons send axons to deeper layers that enhance neural activity and trigger plasticity within the auditory cortical circuits.

Takesian AE, Bogart LJ, Lichtman JW, Hensch TK. Inhibitory circuit gating of auditory critical-period plasticity. Nat Neurosci. 2018 Feb;21(2):218–227.

L1

Over the course of our lives, our brains evolve due to neuroplasticity. This remarkable ability supports everything from our development of basic motor skills to cognitive processes such as language. Although this function exists throughout adulthood, it's been deemed most active in early life.

Developing brains readily adapt to the surrounding sensory environment by forming new connections between neurons and eliminating others. It's thought that the neural circuits sculpted by our experiences in infancy and early childhood are reflected in some of our adult abilities and behaviors.

Neuroscientists are working to better understand brain plasticity and how it might relate to therapies for neurological and developmental disorders. Understanding the changes that occur within the brain, especially those between childhood and adulthood that cause a loss of plasticity, could give us insights into *why* and *how* certain disorders happen. It could also lead to the development of treatment strategies that use brain plasticity to reverse damage.

Neuroscientist Anne E. Takesian, PhD, Assistant Professor of Otolaryngology–Head and Neck Surgery at Harvard Medical School and an investigator in the Eaton-Peabody Laboratories (EPL) at Massachusetts Eye and Ear, is initiating projects to identify specific neural targets to reopen windows of brain plasticity beyond early life in order to recover auditory function.

"Neurological disorders, brain injury, and peripheral hearing loss can all affect our brain's ability to process sounds. Harnessing the brain's natural mechanisms for plasticity to improve hearing could influence a significant percentage of the world's population," she said.

Work led by Dr. Takesian has recently brought us a step closer to understanding brain plasticity. Published in *Nature Neuroscience*, her work has identified neurons within layer 1 (L1) of the auditory cortex as centers that trigger adaptive plasticity.

Fundamentally, there's potential that these L1 neurons could be targeted to activate plasticity within the auditory cortex, a part of the brain that processes sound information and plays a key role in speech comprehension.

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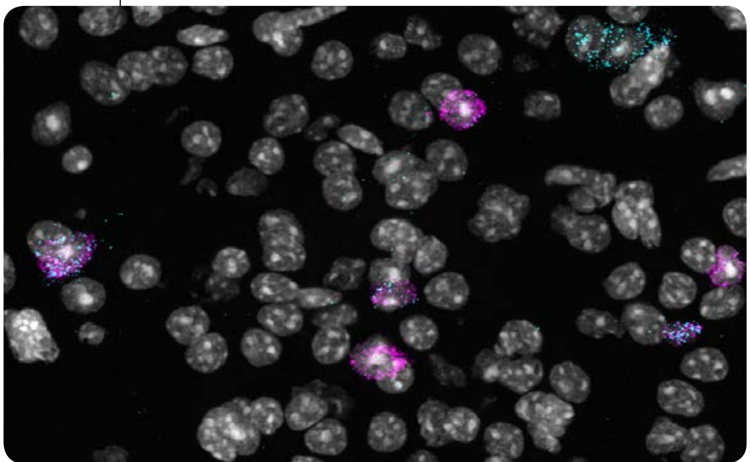
"Finding new ways to leverage the brain's inherent ability to rewire will have widespread impacts. We hope that the results of our research will offer novel strategies to tap into L1 circuits and trigger brain plasticity to improve auditory perception following neurological disorders, injury, or hearing loss."

–Dr. Takesian



A subtype of L1 interneurons identified by the expression of a specific marker (VIP, magenta) co-express serotonin receptors (HTR3A, cyan) using fluorescent in situ hybridization.

A hub for neuromodulators

Historically, little has been understood about the first layer of the cortex. Positioned underneath the skull, this layer has been overlooked due to its small number of neurons.

However, Dr. Takesian and a team of investigators from the laboratory of Takao K. Hensch, PhD, at Boston Children's Hospital found the few neurons within this layer to be powerfully responsive to neuromodulators, which are nervous system chemicals such as acetylcholine and serotonin that are involved in attention, memory, and learning.

How neuromodulators work in the auditory cortex has been a mystery that Dr. Takesian, as well as many others, has been trying to solve.

"We and others recently learned that some of the cells most responsive in the auditory cortex to acetylcholine and serotonin are those up in cortical L1," Dr. Takesian said. "When silencing these L1 neurons, we found that this abolishes the ability of the auditory cortex to reorganize in response to sounds during periods of heightened plasticity in early development."

It has been long thought that sensory input from the thalamus, the part of the brain that relays motor and sensory signals to the cerebral cortex, mostly targets the deeper cortical layers such as layer 4. However, Dr. Takesian showed that topographically organized inputs from the thalamus also synapse onto L1 neurons. This has identified L1 as a key hub where both neuromodulatory and sensory inputs meet to tune the cortical layers below.

"Our study suggests that many fast neuromodulatory and sensory signals converge onto the L1 neurons. These neurons reach down to specific types of neurons within the lower layers of the cortex, enhancing neural activity and the ability of these circuits to undergo plasticity. Exploiting these neuromodulatory pathways may be the key to developing transformative therapies that stimulate plasticity in the adult brain," Dr. Takesian explained.

Stimulating brain plasticity

By identifying changes in the activation of L1 neurons that could modulate the auditory cortex's susceptibility to plasticity, Dr. Takesian found a possible avenue for the use of existing drugs to target the neuromodulatory pathways that activate L1 neurons.

The signaling pathways of acetylcholine and serotonin are targeted by available therapeutic drugs used to treat depression and Alzheimer's disease. Investigators are already finding that these drugs can be used in other parts of the brain to augment plasticity.

Since both are able to activate L1 cells in the auditory cortex, there is potential to use existing drugs such as selective serotonin reuptake inhibitors to activate brain plasticity and improve hearing.

"Serotonin signaling is classically associated with mood disorders like depression or anxiety, but here we are posed to investigate its promise in promoting experience-based learning, which would have widespread implications across many conditions," said Carolyn Sweeney, PhD, a postdoctoral fellow in the Takesian Lab who is leading a study on modulation of L1 neurons with Jacob McLennan, Emma He, Benjamin Glickman, and Ana Castro, MPH.

"Further understanding brain plasticity could have implications in helping to enhance and quicken adults' ability to learn or even rebuild cognitive function in stroke and trauma patients," she continued.

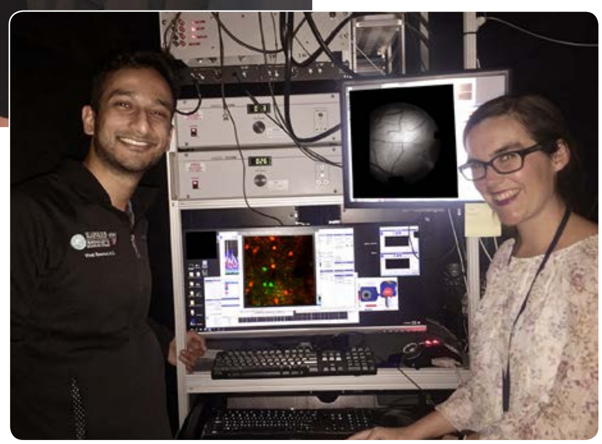
Discoveries on the horizon

Although cortical L1 has emerged as a key player in controlling brain activity and plasticity, neuroscientists are just beginning to understand the mysterious, sparse population of neurons that populate this layer.

As a next step, the Takesian Lab is forming a new model of the L1 neurons as a diverse population composed of various cell types that respond to respective neuromodulators such as serotonin, acetylcholine,

Left: *Members of the Takesian Lab from left to right: Christine Junhui Liu, Dr. Carolyn Sweeney, Angela Zhu, Dr. Anne Takesian, Jacob McLennan, Ana Castro, Benjamin Glickman, and Dr. Dongqin Cai.*

Bottom: *Dr. Vivek Kanumuri (left) and Dr. Carolyn Sweeney (right) team up from the Takesian and Lee/Brown laboratories to explore the* in vivo *function of specific cortical neurons in auditory plasticity and learning.*



Inset photo by Dr. Anne Takesian.

and stress hormones. Using cutting-edge neuroscience technologies in genetics, optical imaging, and electrophysiology, their goal is to unravel the complex circuitry within this layer to understand how each component is involved in the function and plasticity of the auditory cortex.

The Takesian Lab has also teamed up with Daniel B. Polley, PhD, and Dongqin Cai, PhD, also of the EPL, to understand how exploiting various mechanisms in the auditory cortex could reverse pathological activity following hearing loss. This work could provide insight into new therapies to reverse tinnitus and abnormal sound perception.

In collaboration with Dr. Polley and Bernardo L. Sabatini, MD, PhD, from Harvard Medical School, Dr. Takesian is also studying circuits involved in developmental disorders, specifically autism spectrum disorder. Their goal is to harness L1 neurons to elicit plasticity in order to change the neural circuits that increase the hyperexcitability of auditory pathways in autism patients.

Lastly, she is working with EPL investigators Daniel J. Lee, MD, FACS, M. Christian Brown, PhD, Vivek Kanumuri, MD, and Angela Zhu to discover new ways to target L1 neurons to help auditory brainstem implant and cochlear implant users adjust more quickly and efficiently to their devices. "Patients must learn to interpret complex sound signals through these implants. Taking advantage of the neuroplasticity in the cortex may result in better overall outcomes," said Dr. Kanumuri.

"Finding new ways to leverage the brain's inherent ability to rewire will have widespread impacts," said Dr. Takesian. "We hope that the results of our research will offer novel strategies to tap into L1 circuits and trigger brain plasticity to improve auditory perception following neurological disorders, injury, or hearing loss." ●

Dr. Takesian's work is supported by the National Institute on Deafness and Other Communication Disorders (NIDCD), the Nancy Lurie Marks Family Foundation, the Lauer family, the Bertarelli Foundation, and the Jacobs Foundation.

Alumni Profile

Jeffrey P. Harris, MD, PhD, FACS, HMS Otolaryngology Resident, Class of 1979

Becoming a leader in otolaryngology

At a young age, Jeffrey P. Harris, MD, PhD, FACS, developed a recurring ear infection that led to the discovery of a cholesteatoma. It was surgically removed at Massachusetts Eye and Ear and, by chance, this procedure became his first link to his eventual career.

Although the surgery itself did not instill an immediate interest in the field of otolaryngology in Dr. Harris, it did draw the attention of two of his instructors during medical school at the University of Pennsylvania Perelman School of Medicine.

"I didn't come into medicine thinking I would be a surgeon," said Dr. Harris, who is a Distinguished Professor and the Chief of Otolaryngology–Head and Neck Surgery at the University of California, San Diego (UCSD). "I was more interested in immunology, pathology, and infectious disease. However, when my instructors, James B. Snow, Jr., MD, and Herbert Silverstein, MD, FACS, who are both Mass. Eye and Ear alumni, learned that I received care there, they set out to sell me on surgery."

Dr. Snow and Dr. Silverstein took a special interest in Dr. Harris. It was their mentorship that eventually led to his pursuit of a career in otolaryngology. He is now a practicing neurootologic and skull base surgeon.

A native of Massachusetts, Dr. Harris returned to Boston for his residency training in otolaryngology after medical school. Being in the Mass. Eye and Ear/Harvard Medical School program was important to him, as he admired the prospect of studying under otolaryngology leaders such as Harold F. Schuknecht, MD, William W. Montgomery, MD, Joseph B. Nadol, Jr., MD, and many others.

"I got to know Dr. Schuknecht well during my residency, especially after he relied on my editorial revisions for many of his manuscripts," said Dr. Harris. "Learning from him and others meant a lot to my education. On one special occasion, Dr. Schuknecht took me to the 21 Club while attending a meeting in New York City. He told me that Julius Lempert, MD, had taken him there when he was a young, up-and-coming otologist and he thought he should pass along this tradition."

Following residency, Dr. Harris joined the faculty at UCSD. This appointment shifted his clinical focus, inspiring an increased interest in neurotology and skull base surgery. It also led him to complete advanced fellowship training in these areas at the University of Zürich in Switzerland.

In 1986, at the age of only 37, he became the Chief of Otolaryngology–Head and Neck Surgery at UCSD. Now 33 years into his tenure as chief, he has become one of the longest-standing otolaryngology department chiefs in the nation.

Under his leadership, his department has greatly expanded with more than 30 faculty members, 14 residents, two neurotology fellows, and a pediatric fellow. It is now the largest division in surgery at UCSD and is home to a joint doctoral program in audiology with San Diego State University.

As a surgeon, Dr. Harris performed the first cochlear implant surgery in San Diego and continues to have an active clinical practice today. As for research, his interests began in immunology when receiving his MD/PhD from the University of Pennsylvania. Those interests have since evolved into investigating the causes, diagnoses, and treatments of deafness and other inner ear disorders.

Over time, he has contributed more than 200 publications, five books, and numerous book chapters. With his work, he also pioneered new methods of drug delivery to the inner ear, which inspired him to co-found the biopharmaceutical company, Otonomy, Inc.

During his career, Dr. Harris has been the president of both the American Otological Society (AOS) and the Association for Research in Otolaryngology. He is also the recipient of the Award of Merit and Presidential Citation from the AOS. As a member of the Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum, he was awarded the Shambaugh Prize.

Notably, in honor of the education he received at Mass. Eye and Ear/Harvard Medical School, he established the Jeffrey P. Harris, MD, PhD, Research Prize, which is presented to one of the graduating Harvard otolaryngology chief residents for their research project at graduation.

Of all of his successes, however, his greatest pride comes from the achievements of his former trainees.

"When I look back at my career, what's most remarkable to me is what my graduates have achieved in their careers," said Dr. Harris. "They are now department chairs both in the United States and abroad, leaders in our specialty societies, and out doing great work in their communities. It's what makes me most proud."

Bradford C. Backus, PhD, Eaton-Peabody Laboratories of Massachusetts Eye and Ear/Harvard Medical School, 1997–2005

Offering more to cochlear implant users

Building speakers and playing the jazz trumpet in high school put Bradford C. Backus, PhD, on the path to becoming a hearing scientist.

Now primarily a Translational Research Manager for Oticon Medical's cochlear implant division, Dr. Backus' work helps people with cochlear implants listen, hear, and communicate the best they can.

"My family always encouraged a connection to music growing up," said Dr. Backus, who is also the Founder and Managing Director of Audio³ Ltd., a London-based electrical engineering and acoustics consulting company. "Because of that, I have always had an interest in sound and wanted to improve sound enjoyment for others."

As an electrical engineering student at Dartmouth College, Dr. Backus quickly found himself drawn to music cognition and the intersection between sound and psychology. This led him to complete an internship at Bose Corporation, where he worked on passive acoustics, including spatial sound in car audio.

After graduation and 180 days on skis in Colorado, Dr. Backus began his graduate work in the MIT/Harvard Medical School Speech and Hearing Bioscience and Technology (SHBT) graduate program.

"The moment I was accepted into the SHBT program, the most influential seven years of my life began," he said. "During those years, I got to work with some of the best minds in all of hearing science."

With an interest in acoustics, Dr. Backus began working under the guidance of John J. Guinan, Jr., PhD, of the Eaton-Peabody Laboratories at Massachusetts Eye and Ear. Together, they used stimulus frequency otoacoustic emissions to study the basic properties of the human medial olivocochlear reflex, which is thought to protect the cochlea from acoustic damage. Dr. Backus' idea was to characterize the time course of this neural reflex using in-ear acoustical measurements. The result remains the seminal work on this topic.

"The great thing about the training I received at Mass. Eye and Ear was that not only are you working with first-rate scientists who are superb mentors, but they also give you a sense of what it means to be a scientist and the ethics that you need to put in place to succeed. The training really paints a full picture of how to be a scientist," said Dr. Backus.

After completing a short postdoc at Mass. Eye and Ear, Dr. Backus left Boston to begin a postdoc at the University College London (UCL) Ear Institute. There, he studied noise-induced hearing loss under the guidance of David T. Kemp, PhD, FRS. He also designed a low-noise amplifier for recording brain signals. Toward the end of his tenure at UCL, he helped write and manage a collaborative four million European-wide FP7 grant to design advanced binaural cochlear implants.

"Running this grant was a big growth moment for me," he mentioned. "There were a lot of managerial skills that had to be acquired through that process. It also sent me on the path to looking more closely at cochlear implants. At the time, I was traveling to different clinics helping people tune their cochlear implants, but with my training from Mass. Eye and Ear, it was obvious that I could do more."

In 2007, Dr. Backus used his strong background in sound and electrical engineering to establish Audio³. Along the way, he won the UCL Bright Ideas Award and a Rising Star Award for London entrepreneurship.

Today, Audio³ produces consumer and industrial products for sound applications and provides engineering consulting services. The company always seeks to understand how we hear and uses that knowledge to produce sound reproduction, hearing health, and acoustic measurement instruments. Audio³ was responsible for developing the Arcam rCube and the soundBadge® personal noise dosimeter.

Dr. Backus also serves on the boards of several United Kingdom acoustics companies and provides translational research for Oticon Medical. At Oticon, his aim is to improve binaural cochlear implants and make the experience for users more enjoyable. Much of his work today involves solving common problems with cochlear implants (e.g., hearing in noisy environments) and incorporating virtual reality into training programs for users.

"You take someone who cannot easily operate in the world and turn them into someone who can carry on a perfect conversation on the phone," said Dr. Backus. "Through my work, I can help someone go from being very isolated to being able to communicate. Having that kind of impact gives me a great source of pride." ●

HARVARD MEDICAL SCHOOL | Department of Otolaryngology Head and Neck Surgery

The Alumni Giving Society of the Department of Otolaryngology–Head and Neck Surgery at Harvard Medical School

The Department of Otolaryngology–Head and Neck Surgery at Massachusetts 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–Head and Neck Surgery helps drive continued achievement across all areas of education, research, and patient care. To date, we have 24 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.

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Chief of Otolaryngology–Head and Neck Surgery, Mass. Eye and Ear/Massachusetts General Hospital

Michael B. Rho, MD, FACS, '05
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Medical Director, Otolaryngology, Mass. Eye and Ear, Stoneham

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Paul M. Konowitz, MD, FACS
John B. Lazor, MD, MBA, FACS, '95, '96
Jon B. Liland, MD, '72
Derrick T. Lin, MD, FACS, '98, '02
Leila A. Mankarious, MD
William W. McClerkin, MD, '73
Ralph B. Metson, MD, '87
Michael M. Paparella, MD
Herbert Silverstein, MD, FACS, '66

From left to right: Drs. Ashton Lehmann, Nicholas Dewyer, Alisa Yamasaki, Ralph Metson, Brad Welling, Katie Phillips, and Rosh Sethi.

Alumni Giving Society

Current Alumni Giving Society members for fiscal year 2019 from October 1, 2018, to May 21, 2019, are listed below. With your gift of $1,000 or more, you will be included in the 2019 Alumni Giving Society.

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Herbert Silverstein, MD, FACS
Phillip C. Song, MD
Feodor Ung, MD

News from every corner of the Harvard Medical School Otolaryngology–Head and Neck Surgery Department.

New Faculty

Julie G. Arenberg, MS, PhD, has joined Mass. Eye and Ear as the Associate Director of Clinical Research and Education for Audiology. Previously, she worked at the University of Washington, directing their clinical audiology doctorate program and Cochlear Implant Psychophysics Laboratory. She earned her master's degree in audiology at San Francisco State University and PhD in neuroscience at the University of Michigan. She completed her clinical training at Stanford Hospital and Clinics. Her interests include children and adults with severe hearing loss who can benefit from cochlear implants. She also conducts research focused on improving speech perception outcomes and quality of life for cochlear implant users.

Fouzi Benboujja, PhD, is an Instructor in Otolaryngology–Head and Neck Surgery at Harvard Medical School. With a doctorate from Polytechnique Montréal and postdoctoral training from Mass. Eye and Ear, his work focuses on accelerating innovation in healthcare with new intraoperative guidance systems. He is particularly interested in investigating ways to improve surgical interventions with advance photonics technologies. Overall, his research aims to create theragnostic systems to diagnose and treat laryngeal dysfunctions.

Jennifer A. Brooks, MD, MPH, will join the Boston Children's Hospital Department of Otolaryn-gology and Communication Enhancement in July. Fellowship-trained in both pediatric otolaryngology (Boston Children's Hospital) and thyroid and parathyroid surgery (Mass. Eye and Ear), Dr. Brooks will treat pediatric patients with thyroid disease and salivary gland dysfunction in addition to general ear, nose, and throat disorders. She earned her medical degree from and completed residency training in otolaryngology–head and neck surgery at the University of Southern California. She also has her masters in public health from Dartmouth Medical School.

Bridget D. Burgess, MD, will join Mass. Eye and Ear's Weymouth and Duxbury locations in August. With a subspecialty interest in laryngology, Dr. Burgess will see adult and pediatric patients with voice, swallowing, and breathing disorders in addition to seeing comprehensive otolaryngology patients. She earned her medical degree from Loyola University Chicago Stritch School of Medicine before completing her residency training in otolaryngology–head and neck surgery there. She is now completing her fellowship in laryngology at Johns Hopkins Hospital.

Phillip Huyett, MD, will join the Mass. Eye and Ear Division of Sleep Medicine and Surgery in August. He is board-eligible in sleep medicine and otolaryngology, and will see patients at Mass. Eye and Ear's main campus and Longwood locations. Dr. Huyett earned his medical degree from Tufts University School of Medicine before completing his residency training in otolaryngology–head and neck surgery at the University of Pittsburgh Medical Center. He is now completing his fellowship training in sleep medicine and surgery at the University of Southern California Keck Hospital.

Louis F. Insalaco, MD, will join Mass. Eye and Ear's Stoneham location in August. He will practice comprehensive otolaryngology, seeing both adult and pediatric patients. Dr. Insalaco is a Massachusetts native who earned his medical degree from Tufts University School of Medicine before completing his residency training in otolaryngology–head and neck surgery at Boston Medical Center. He then went on to complete a fellowship in pediatric otolaryngology and facial plastic surgery with the University of Minnesota Medical Center and Children's Hospitals and Clinics of Minnesota. His clinical interests include general and pediatric otolaryngology and facial plastic surgery.

Elise Lippmann, MD, will join Mass. Eye and Ear in September. She will practice comprehensive otolaryngology, seeing both pediatric and adult patients in Boston. She will also be a member of the Mass. Eye and Ear Emergency Department. Dr. Lippmann earned her medical degree from Loyola University Chicago Stritch School of Medicine before completing her residency training in otolaryngology–head and neck surgery at the University of Illinois at Chicago. Her clinical interests include working with a wide range of patients in areas such as hearing loss, thyroid disorders, and sinus disease.

HMS Promotions

Linda N. Lee, MD, FACS, Assistant Professor of Otolaryngology–Head and Neck Surgery

Faisal Karmali, PhD, Assistant Professor of Otolaryngology–Head and Neck Surgery

Adrian J. Priesol, MD, Assistant Professor of Otolaryngology–Head and Neck Surgery

Sunil Puria, PhD, Associate Professor of Otolaryngology–Head and Neck Surgery

James Naples, MD, will join the Beth Israel

Deaconess Medical Center Division of Otolaryngology/Head and Neck Surgery in August. He earned his medical degree from the University of Connecticut School of Medicine, where he also completed residency training in otolaryngology–head and neck surgery. He is now completing his fellowship training in neurotology at the Perelman School of Medicine at the University of Pennsylvania. Clinically, he is interested in cochlear implants, vestibular disorders, and skull base surgery. He has research interests in intratympanic therapies and ototoxicity, and enjoys learning about medical history.

Anju K. Patel, MD, has joined Brigham

and Women's Hospital as a surgeon and member of their voice program. A graduate of The George Washington University School of Medicine and Health Sciences, Dr. Patel completed residency training in otolaryngology–head and neck surgery at Tufts Medical Center. Subsequently, she completed her fellowship in laryngology and care of the professional voice at Emory University. Her clinical interests include management of voice and swallowing disorders, minimally invasive surgical techniques, and in-office laryngeal procedures. Her research interests include the development of novel treatments for vocal cord paralysis, diagnosis and management of upper esophageal pathologies, and use of health literacy to improve patient outcomes.

Aravindakshan Parthasarathy, PhD,

is an Instructor in Otolaryngology–Head and Neck Surgery at Harvard Medical School. With a doctorate in biological sciences from Purdue University and postdoctoral training from Purdue University and Mass. Eye and Ear, his work focuses on studying changes in hearing due to pathologies associated with aging and noise exposure. He aims to understand how changes in the peripheral auditory system and the central auditory pathway contribute to hearing loss using a combination of electrophysiological, histological, and computational techniques in clinical populations and animal models of hearing loss.

Cher (Xue) Zhao, MD, will join Mass. Eye

and Ear as a pediatric otolaryngologist in August. Dr. Zhao earned her medical degree from the University of Michigan Medical School before completing her residency in otolaryngology–head and neck surgery there. She is now finishing her pediatric otolaryngology fellowship at Boston Children's Hospital. Her clinical interests include pediatric head and neck masses, endoscopic ear surgery, salivary gland disorders, aerodigestive disorders, sleep surgery, and sinus disease.

New Leadership

Thomas L. Carroll, MD, has been named Medical Director of ENT Clinic Operations at Brigham and Women's Hospital.

John M. Dobrowski, MD, FACS, has been named Associate Director of the Sleep Medicine and Surgery Division and Director of Adult Sleep Medicine and Surgery at Mass. Eye and Ear.

Donald G. Keamy, Jr., MD, MPH, has been named Director of Pediatric Sleep Medicine and Surgery at Mass. Eye and Ear

Paul M. Konowitz, MD, FACS, has been named Vice Chair for Strategic Network Development at Mass. Eye and Ear.

Noah S. Siegel, MD, has been named Director of the Sleep Medicine and Surgery Division at Mass. Eye and Ear.

Awards, Grants, and Honors

Dunia E. Abdul-Aziz, MD, has been awarded a grant from the American Neurotology Society for her work, "Targeting epigenetic modifying enzymes for hair cell regeneration."

Jeffrey Tao Cheng, PhD, received an SBIR Phase II grant from the National Institutes of Health's National Institute on Deafness and Other Communication Disorders. The central focus of this project is to develop a clinically viable multimodal endoscopic imaging system to enable detailed imaging of cellular pathology in the cochlea.

Michael J. Cunningham, MD, FACS, was the honored guest for pediatric otolaryngology at the 10th Annual George Washington University Cherry Blossom Conference in March.

Daniel L. Faden, MD, received a grant from the North American Skull Base Society for his work, "Dissecting etiologic oncogenic programs in sinonasal squamous cell carcinoma."

William C. Faquin, MD, PhD, has been selected as editor-in-chief of *Cancer Cytopathology*. He also received the L.C. Tao Educator of the Year Award at the 2019 Annual Meeting of the United States and Canadian Academy of Pathology.

Stacey T. Gray, MD, has been named the associate editor of *International Forum of Allergy & Rhinology*.

David H. Jung, MD, PhD, FACS, and **Linda N. Lee, MD, FACS**, were elected as Fellows of the American College of Surgeons.

Elliott D. Kozin, MD, the Mass. Eye and Ear Neskey-Coghlan Fellow in Neurotology, recently gave grand rounds at the University of Pennsylvania Department of Neurosurgery on traumatic auditory injury. He also received a grant from the American Otological Society for his work, "Cochlear changes following mild traumatic brain injury in a porcine head injury model."

Daniel J. Lee, MD, FACS, received a grant from the Swiss National Science Foundation for his work, "Neuroprosthetic platform for personalized and implantable systems: Application to reverse paralysis and restore hearing." This four-year grant will develop and test novel conformable spinal cord and auditory brainstem implant electrode arrays in non-human primates. He also recently received a two-year SBIR Phase II grant from the Department of Defense to develop and test a novel endoscopic assisted drug delivery device for acute inner ear pathologies.

Richard F. Lewis, MD, is supervising a new study at Mass. Eye and Ear, funded by Sanofi Genzyme. Its goal is to determine if changes in eye movements can be used to track progression of two rare lysosomal storage diseases, late onset Tay-Sachs and Sandhoff disease.

Stéphane F. Maison, PhD, delivered the keynote lecture at the 11th Speech in Noise Workshop in Belgium. He also delivered the keynote lecture for La journée étudiante en Audiologie – Edition 2019 at the University of Québec in Montréal.

Suresh Mohan, MD, Mass. Eye and Ear/ Harvard Medical School resident, received a new F32 grant from the National Institute of Dental and Craniofacial Research and National Institutes of Health for his work, "Enhancement of axonal penetration through cross-facial nerve grafts." His mentors for the award are **Nate Jowett, MD, FRCSC**, and **Tessa A. Hadlock, MD**.

Hideko Heidi Nakajima, MD, PhD, is the recipient of an R01 grant from the National Institutes of Health and National Institute on Deafness and Other Communication Disorders for her work, "Implantable microphones for fully implantable hearing prosthetics."

Aaron K. Remenschneider, MD, MPH, the Neskey-Coghlan Neurotology Fellow **Elliott D. Kozin, MD**, and PhD student **Nicole Black** created PionEar, a tiny bio-inspired, 3D-printed ear tube that reduces scarring and the need for repeated insertion surgery. This work recently won top honors at the Collegiate Inventors Competition®, receiving the gold award worth $10,000.

Yin Ren, MD, PhD, received the Humanitarian Grant from the American Academy of Otolaryngology–Head and Neck Surgery to fund a mission trip to Kathmandu, Nepal. He spent three weeks there in December of 2018, learning about cleft lip and palate surgery at the Nepal Cleft and Burn Center.

Srinivas Vinod Saladi, PhD, and **Daniel L. Faden, MD**, were the recipients of the 2018 Norman Knight Leadership Development Award at Mass. Eye and Ear. **Dr. Saladi** was also recently awarded a grant from the Melanoma Research Foundation for his work, "Characterizing the role of the hippo pathway during melanoma immunotherapy."

Jo Shapiro, MD, FACS, was awarded the American Board of Internal Medicine Foundation's Professionalism Article Prize for her work, "Confronting unprofessional behavior in medicine."

David A. Shaye, MD, FACS, was named the surgical team leader for the Doctors Without Borders Noma Project in Northern Nigeria. Noma is a disfiguring disease of the face that affects the severely malnourished, mostly in the "Noma Belt" of Africa.

Kristina Simonyan, MD, PhD, Dr med, received a new multisite grant from the Department of Defense as part of their Bilateral Academic Research Initiative. Her project aims to develop an innovative approach to creating novel frameworks for humans and machines to be collaborative teammates. Dr. Simonyan has also been named an associate editor of *Otolaryngology and Movement Disorders: Laryngoscope Investigative Otolaryngology* and *Journal of Clinical Movement Disorders*.

In late 2018, a Mass. Eye and Ear team led by **Jeremy D. Richmon, MD** (far left), and **Derrick T. Lin, MD, FACS** (third from the right), performed their first surgery for head and neck cancer using Mass. Eye and Ear's new surgical robot. The robot helps surgeons reach tumors in the back of the throat in a minimally invasive way, allowing patients to avoid long hospital stays and extensive rehabilitation.

The following are select research advances from the Harvard Medical School Department of Otolaryngology–Head and Neck Surgery.

Basic Science

Improved TMC1 gene therapy restores hearing and balance in mice with genetic inner ear disorders

Fifty percent of inner ear disorders are caused by genetic mutations. To develop treatments for genetic inner ear disorders, a team of researchers including **Jeffrey R. Holt, PhD**, and **Gwenaelle S. Géléoc, PhD**, from Boston Children's Hospital/Harvard Medical School designed gene replacement

therapies using synthetic adeno-associated viral vectors to deliver the coding sequence for transmembrane channel-like (*Tmc*) 1 or 2 into sensory hair cells of mice with hearing and balance deficits due to mutations in *Tmc1* and closely related *Tmc2*.

The team reported restoration of function in inner and outer hair cells, enhanced hair cell survival, restoration of cochlear and vestibular function, and in collaboration with **Daniel B. Polley, PhD**, and **Jennifer Resnik, PhD**, from Mass. Eye and Ear/Harvard Medical School, restoration of neural responses in the auditory cortex. They also found that inner ear *Tmc* gene therapy restores behavioral responses to auditory and vestibular stimulation, breeding efficiency, litter survival, and normal growth rates in mouse models of genetic inner ear dysfunction.

The data suggest that *Tmc* gene therapy may be well-suited for further development and perhaps translation to clinical application.

Nist-Lund CA, Pan B, Patterson A, Asai Y, Chen T, Zhou W, Zhu H, Romero S, Resnik J, Polley DB, Géléoc GS, Holt JR. Improved TMC1 gene therapy restores hearing and balance in mice with genetic inner ear disorders. Nature Commun. 2019 Jan 22;10(236).

Exosomes "swarm" to protect against bacteria inhaled through the nose

How the airway protects itself from infection from the bacteria we breathe in has largely remained a mystery—until now. A Mass. Eye and Ear/Harvard Medical School research team led by **Benjamin S. Bleier, MD, FACS**,

recently discovered that when bacteria are inhaled, exosomes, or tiny fluid-filled sacs, are immediately secreted from cells that directly attack the bacteria and also shuttle protective antimicrobial proteins from the front of the nose to the back along the airway, protecting other cells against the bacteria before it gets too far into the body.

The team found that when cells at the front of the nose detect a bacterial molecule, they trigger a receptor called TLR4, which stimulates exosome release. When that happens, an innate immune response occurs within five minutes. First, it doubles the number of exosomes that are released into the nose. Second, within those exosomes, a protective enzyme, nitric oxide synthase, also doubles in amount. The exosome "swarm" process gets an assist from another natural mechanism of the nose: mucociliary clearance. Mucociliary clearance sweeps the activated exosomes over to the back of the nose, along with information from cells that have already been alerted to the presence of bacteria. This process prepares the cells in the back of the nose to immediately fight off the bacteria, arming them with defensive molecules and proteins.

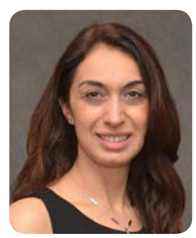
Along with this new understanding of the innate immune system, these findings may have implications in the development of new methods of delivering drugs through the airway. More specifically, as natural transporters, exosomes could be used to transfer inhaled packets of therapeutics to cells along the upper airway—and possibly even into the lower airway and lungs.

Nocera AL, Mueller SK, Stephan JR, Hing L, Seifert P, Han X, Lin DT, Amiji MM, Libermann T, Bleier BS. Exosome swarms eliminate airway pathogens and provide passive epithelial immunoprotection through nitric oxide. J Allergy Clin Immunol. 2019 Apr; 143(4):1525–1535.e1.

A separation of innate and learned vocal behaviors defines the symptomatology of spasmodic dysphonia

Spasmodic dysphonia (SD) is a neurological disorder characterized by involuntary spasms in the laryngeal muscles. It is thought to selectively affect speaking while other vocal behaviors remain intact. However, the patients' own perspective on their symptoms is largely missing, leading to partial understanding of the full spectrum of voice alterations in SD.

A Mass. Eye and Ear/Harvard Medical School team led by **Kristina Simonyan, MD, PhD, Dr med**, asked 178 SD patients to rate their symptoms on the visual analog scale based on the level of effort required for speaking,



singing, shouting, whispering, crying, laughing, and yawning. Speech production was found to be the most impaired behavior, singing required nearly similar effort as speaking, and shouting showed a range of variability in its alterations. Other vocal behaviors, such as crying, laughing, whispering, and yawning, were within the normal ranges across all SD patients.

These findings widen the symptomatology of SD, which has predominantly been focused on selective speech impairments. The team suggests that a separation of SD symptoms is rooted in selective aberrations of the neural circuitry controlling learned, but not innate, vocal behaviors.

Guiry S, Worthley A, Simonyan K. A separation of innate and learned vocal behaviors defines the symptomatology of spasmodic dysphonia. Laryngoscope. 2018 Dec 24.

Toward the bionic face: A novel neuroprosthetic device paradigm for facial reanimation

Facial palsy is a devastating condition potentially amenable to rehabilitation by

functional electrical stimulation. A team of researchers including **Nate Jowett, MD, FRCSC**, and **Tessa A. Hadlock, MD**, of Mass. Eye and Ear/Harvard Medical School, recently characterized a novel paradigm for unilateral facial reanimation via an implantable neuroprosthetic device and demonstrated its feasibility in a live rodent model.

The paradigm comprises use of healthy-side electromyography activity as control inputs to a system whose outputs are neural stimuli to effect symmetric facial displacements. The vexing issue of suppressing undesirable activity resulting from aberrant neural regeneration (i.e., synkinesis) or nerve transfer procedures is addressed using proximal neural blockade. The researchers implanted epimysial and nerve cuff electrode arrays in the faces of rats, and delivered stimuli to evoke blinks and whisks of various durations and amplitudes. The dynamic relation between electromyography signals and facial displacements were modelled and facial nerve blockade in awake behaving animals was achieved without detrimental effect, noted from long-term continual use.

The researchers note that use of proximal neural blockade coupled with distal functional electrical stimulation may have relevance to rehabilitation of other peripheral motor nerve deficits.

Jowett N, Kearney RE, Knox CJ, Hadlock TA. Toward the bionic face: A novel neuroprosthetic device paradigm for facial reanimation consisting of neural blockade and functional electrical stimulation. Plast Reconstr Surg. 2019 Jan;143(1):62e–76e.

Peripheral vestibular system histopathologic changes following head injury without temporal bone fracture

Balance problems are among the most commonly reported chronic symptoms after a head injury. While vestibular dysfunction

following a temporal bone (TB) fracture may be expected, less is known about histologic changes to the peripheral vestibular system following head injury. A team of Mass. Eye and Ear/Harvard Medical School investigators including the Neskey-Coghlan Neurotology Fellow **Elliott D. Kozin, MD**, and postdoctoral student **Renata M. Knoll, MD**, studied specimens of the peripheral vestibular system from the Otopathology Laboratory at Mass. Eye and Ear of patients who sustained head injury without a TB fracture.

In patients with history of head injury without evidence of TB fractures, distinct vestibular pathology was found, including a decrease of Scarpa's ganglion cell population and degeneration of vestibular membranous labyrinth. This study provides an analysis of rare human temporal bone data that may help elucidate the pathophysiology of vestibular dysfunction following head injury.

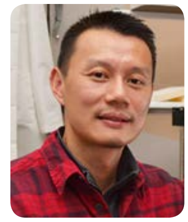
Knoll RM, Ishai R, Trakimas DR, Chen JX, Nadol JB Jr, Rauch SD, Remenschneider AK, Jung DH, Kozin ED. Peripheral vestibular system histopathologic changes following head injury without temporal bone fracture. Otolaryngol Head Neck Surg. 2019 Jan;160(1):122–130.

Tympanic membrane surface motions in forward and reverse middle ear transmissions

Characterization of tympanic membrane (TM) surface motions with forward and reverse stimulation is important for understanding how the TM transduces acoustical and mechanical energy in both directions. Such information can be used to test numerical middle ear models and guide the design of tissue-engineered TM-like materials.

In a study led by **Jeffrey Tao Cheng, PhD**, and **John J. Rosowski, PhD**, of the Eaton-Peabody Laboratories at Mass. Eye and Ear/Harvard Medical School, stroboscopic opto-electronic holography (OEH) was used to quantify motions of the entire TM surface in human cadaveric ears from 0.25 to 18.4 kHz.

The forward sound stimulus was coupled to an anatomically realistic artificial ear canal that allowed optical access to the entire TM



surface. The reverse mechanical stimulus was applied to the body of the incus by a piezoelectric stimulator. The results showed clear differences in TM surface motions evoked by the two stimuli.

In the forward case, TM motion was dominated by standing-wave-like modal motions that are consistent with a relatively uniform sound pressure load over the entire TM surface. With reverse mechanical stimulation, the TM surface showed more traveling waves, consistent with a localized mechanical drive applied to the manubrium embedded in the TM. With both stimuli, the manubrium moved less than the rest of the TM, consistent with the TM acting like a compliant membrane rather than a stiff diaphragm and with catenary behavior due to the TM's curved shape.

Cheng JT, Maftoon N, Guignard J, Ravicz ME, Rosowski JJ. Tympanic membrane surface motions in forward and reverse middle ear transmissions. J Acoust Soc Am. 2019 Jan;145(1):272–291.

Clinical Practice

Genomic correlates of exceptional response to ErbB3 inhibition in head and neck squamous cell carcinoma

Precision medicine involves using genetic information specific to a patient's tumor

to choose the most efficacious therapy for that individual. Identifying mechanisms that make certain tumors responsive to a particular drug, but not others, known as biomarker discovery, is vital to precision medicine approaches.

Daniel L. Faden, MD, of Mass. Eye and Ear/Harvard Medical School, uses translational genomic approaches to study biomarkers and precision medicine in head and neck cancer. Recently, Dr. Faden and colleagues examined specimens from a clinical trial in

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which patients received a novel drug, CDX-3379, prior to surgery. This allowed them to compare alterations in the DNA and RNA of the tumor before and after exposure to the drug. By examining the tumor of a patient with advanced oral cavity cancer, who experienced a near-complete response after only two doses of the drug, Dr. Faden became the first to demonstrate that amplification and overexpression of the gene FZD3 may lead to sensitivity to CDX-3379.

Utilizing a bedside-to-bench approach, Dr. Faden and his colleagues then studied this mechanism of sensitivity in the laboratory using head and neck cancer cells. This work can be found in the most recent edition of the *Journal of Clinical Oncology-Precision Oncology*.

Faden DL, Gomez-Casal R, Alvarado D, Duvvuri U. Genomic correlates of exceptional response to ErbB3 inhibition in head and neck squamous cell carcinoma. JCO Precision Oncology. 2019:3,1–5.

Postoperative ibuprofen and the risk of bleeding after adenotonsillectomy

Ibuprofen is an effective painkiller after adenotonsillectomy (T&A) but concerns exist about whether or not it increases postoperative hemorrhage. In a multicenter, randomized double-blinded trial led by **Gillian R. Diercks, MD, MPH**, and **Christopher J. Hartnick, MD, MS**, of Mass. Eye and Ear/ Harvard Medical School, physicians observed 741 children aged two to 18 undergoing T&A using monopolar cautery to determine the effect of ibuprofen on post-tonsillectomy bleeding.

The study was the first randomized double-blinded trial powered to specifically evaluate rates of severe bleeding requiring a return to the operating room when postoperative ibuprofen is used. The team found that the difference in bleed rate between treatment groups surpassed the three percent non-inferiority margin for overall bleeding as well as bleeds requiring a return to the operating room. Thus, the study could not rule out a higher risk of bleeding when ibuprofen is used for analgesia postoperatively. This presents a dilemma for surgeons and other professionals who manage children after T&A. The team notes that resources should be devoted toward identifying and developing safe, effective analgesics for children after T&A. Additionally, developing decision support algorithms to help clinicians make evidence-based choices about which postoperative analgesics to prescribe based on surgical indications and patient factors is recommended.

Diercks GR, Comins JJ, Bennett K, Gallagher TQ, Brigger M, Boseley M, Gaudreau P, Rogers D, Setlur J, Keamy D, Cohen MS, Hartnick CJ. Comparison of ibuprofen vs. acetaminophen and severe bleeding risk after pediatric tonsillectomy: A noninferiority randomized clinical trial. JAMA Otolaryngol Head Neck Surg. 2019 Apr 4.

Autologous tissue grafting in primary and revision rhinoplasty

Rhinoplasty is one of the most commonly performed surgeries by facial plastic surgeons. Cartilaginous and bony grafting is a critical surgical technique required in many primary and revision rhinoplasty cases. In cases where autologous grafting is performed from the patient's ear or rib, there is an additional surgical site with the potential to affect healing time and postoperative pain.

A team of surgeons from Harvard Medical School, including **Linda N. Lee, MD, FACS**, of Mass. Eye and Ear and **Neil Bhattacharyya, MD, FACS**, of Brigham and Women's Hospital, led a study evaluating autologous extra-nasal grafting in primary and revision rhinoplasty. The data showed that revision rhinoplasty cases had more than twice the likelihood of requiring a secondary source of grafting (24.4 percent and 11.1 percent). Additionally, they found that auricular cartilage grafts are the most commonly used source in both primary and revision rhinoplasty cases (7.1 percent and 14.4 percent) followed by costal cartilage (1.1 percent and 7.1 percent).

This is the first study to examine percentages of site-specific autologous grafting from auricular and costal donor sites for primary and revision rhinoplasty cases. Gender- and age-specific trends associated with specific grafting sites were also identified. These data are important to help guide patient and physician preoperative counseling and informed consent for all rhinoplasty surgeries.

Lee LN, Quatela O, Bhattacharyya N. The epidemiology of autologous tissue grafting in primary and revision rhinoplasty. Laryngoscope. 2018 Nov 8.

Laryngomalacia causing recurrent respiratory issues and/or feeding difficulty in children: Are we missing anything?

Laryngomalacia, a condition involving collapse of supraglottic tissue due to excess mucosa or reduced laryngeal tone, is the most common laryngeal anomaly. While it is commonly associated with stridor in children, related recurrent respiratory issues and/or feeding difficulties may pose a threat to the well-being of the affected child. A research team from Boston Children's Hospital/Harvard Medical School, including **Reza Rahbar, DMD, MD**, described the prevalence of aspiration, the passage of fluids into the airway, in pediatric patients with laryngomalacia who present with recurrent respiratory issues and/or feeding difficulty.

Of 395 patients diagnosed with laryngo-malacia at Boston Children's Hospital in 2015, 142 patients (35.9 percent) presented with additional recurrent respiratory issues and/or feeding difficulties and underwent a modified barium swallow (MBS) study in the same year. One hundred twenty-eight (90.1 percent) patients had swallowing dysfunction documented during the MBS. Aspiration was identified in 60 (42.3 percent) patients and silent aspiration (aspiration without a cough response) was documented in 59 (98.3 percent) of these patients. Epilepsy/ seizures, laryngeal cleft, and premature birth were significantly associated with abnormal MBS study findings.

Swallowing dysfunction and aspiration are common findings in these patients; therefore, silent aspiration deserves special consideration from clinicians who treat them.

Irace AL, Dombrowski ND, Kawai K, Watters K, Choi S, Perez J, Dodrill P, Hernandez K, Davidson K, Rahbar R. Evaluation of aspiration in infants with laryngomalacia and recurrent respiratory and feeding difficulties. JAMA Otolaryngol Head Neck Surg. 2018 Dec 27.

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