Hearing Health Hour: One Ear, Two Systems: The Relationship Between Balance and Hearing
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Lead Presenters: Jennifer Stone, Ph.D., and James Phillips, Ph.D.

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DR. LALWANI - Welcome to our Hearing Health Hour webinar. I'm Dr. Anil Lalwani and I appreciate you joining Hearing Health Foundation for another I'm sure will be fantastic Hearing Health Hour webinar. Today's topic is a hot one, inner ear hair cells regeneration, but there's a slight twist. Today we will discover the interconnectedness between both hearing and balance hair cells. Now this event has a live captioner and you can enable closed captions by clicking the CC button at the tool bar on the bottom of your screen. Now, if you need any other assistance using Zoom, follow the link to the technical guide shared in the chat.

Again, my name is Dr. Lalwani and I'm a board member at Hearing Health Foundation. I oversee the Emerging Research Grants, so the ERG program. The ERG is a competitive program that awards funds to researchers conducting cutting edge research in the hearing and balance systems. I'm also a professor and vice chair for research in the department of otolaryngology-head and neck surgery, as well as the associate dean for student research here at Columbia University's Vagelos College of Physicians and Surgeons in New York.

Today, we will hear from Dr. Jennifer Stone of the University of Washington, who is not only an alumna of the ERG program, but is also part of our other major research program the Hearing Restoration Project or HRP. The HRP is a consortium of scientists working collaboratively to advance cures for hearing loss and tinnitus. She's joined by her colleague, Dr. James Phillips, also of University of Washington, who is a researcher as well as a clinician. They will introduce themselves in more detail. Together they'll speak about the vestibular or balance system as well as the auditory or the hearing system and how these two systems are alike and different. And how advances in the research in one system can contribute to understanding of the other.

HHF's two research programs, the ERG and the HRP, are only possible through the generosity of supporters like you. And if you'd like to support our work on hearing loss, tinnitus, and related conditions you can do so today at hhf.org/donate. Now we'll move to the presentation "One Ear, Two Systems: The Relationship Between Balance and Hearing." Please do hold your questions for Drs. Stone and Phillips until the end for the Q and A session. Dr. Stone, Dr. Phillips.

DR. STONE - Okay great. Thank you very much Anil. I'm going to start by sharing my screen. All right. Well, it's a delight to be here today, and I'd like to start by having Jim and I introduce ourselves and tell you a little bit about what we do. My name is Jenny Stone. I'm a researcher, I'm a research professor in otolaryngology at the University of Washington. And I work at the Virginia Merrill Bloedel Hearing Research Center. For 33 years, I performed research on our sense of hearing and on our sense of balance, which we'll also refer to as the vestibular sense today. I also teach students and clinicians how to conduct research studies. My goals are to expand our fundamental knowledge about how hearing and vestibular systems work and how they degenerate and how they are repaired, and to train new people to carry on this work in the future. Jim?

DR. PHILLIPS - Hi, my name is Jim Phillips. I am a research professor in the same department as Dr. Stone, the department of otolaryngology and head and neck surgery at the University of Washington. I'm also the director of the Dizziness and Balance Center at the University of Washington Medical Center. And I also direct the vestibular diagnostic laboratory, which is the vestibular testing laboratory at the University of Washington Medical Center and a similar service at Seattle Children's Hospital. I'm a vestibular neurophysiologist and my research interest is in understanding the mechanisms that allow us to process the vestibular sensory information and to generate useful reflexes and responses to those stimuli. I'm also doing translational research, looking at new diagnostic modalities and also treatments for vestibular disorders.

DR. STONE - Great. Well, thanks, Jim. So we're really delighted to be here today. We're honored to be invited by the HHF to talk to you about disorders of the vestibular system. I'm a huge fan of HHF. When I was starting out my career, as Anil said, I was awarded an early research grant and that was in 1999. That funding was instrumental to launching my career and getting federal funding and developing a stable research program. So I'm very grateful for all that HHF does to promote hearing in areas that are near and dear to me, and also are critical for our human health, for our hearing health.

So why are we speaking today about that vestibular system? While we wish to raise awareness of vestibular disorders, as we will explain, we feel that more research in this important area is badly needed to improve the health of millions of Americans who have the similar deficits. And importantly, to share with you that promoting vestibular research will also have major impacts on hearing health. So what are these two sensory systems? The auditory system is our sense of hearing. It allows us to communicate and also to sense sound, to apply sounds in the environment. And both of these functions are critical for, for our wellbeing.

The vestibular system is mainly required for maintaining our balance. We typically think of that, but also helps us orient ourselves in space, navigate in our environment, and a lot more, which Jim will talk about. And our vestibular sense like our hearing sense is crucial for our wellbeing. So similar to the auditory system, the vestibular system is highly prone to damage at any age. And when this happens, it causes significant sensory deficits and degradation of our quality of life.

In our talk, we will address how the vestibular system works and how when it stops working, there's not only a devastating and dangerous loss of motor functions, but also changes in our thought processes, our orientation and our surroundings and our levels of anxiety. It's understandable then that deficits in our vestibular system often have profound effects on how we feel minute to minute and also impact our work productivity, as well as our relationships with other people.

Vestibular deficits impact a huge number of people. A study from Johns Hopkins found that around 35% of people, 35% over the age of 40, will experience a balance disorder. Yet, despite how common these deficits are, we still understand very little about the underlying causes of vestibular problems: how to diagnose specific types of vestibular problems, how to treat them, or how to prevent them. So today we hope to turn heads toward this problem and to promote more research in this area.

The last thing I'll mention before I jump into my slides is especially important to many of you listeners, which is people who have hearing loss are much more likely to have balance disorders than those who do not have hearing loss. This is in large part because the primary organs for hearing and balance are both located in the inner ear in a common space and they share similar biological and physiological features. So importantly, the same things that cause hearing loss also induce vestibular deficits and vice versa. But the good news is that if we can develop solutions to these problems, it's likely that they will also have impacts on the other system.

Okay, so this is going to be the overview of our talk today. We're going to discuss, I'm going to start by discussing the anatomy and function of the vestibular system. And then Jim's going to talk about vestibular disorders from a patient's perspective and a clinician's perspective. And then we'll talk about research areas that we think are really important to emphasize. And also the cross talk that happens between auditory and vestibular research. This talk is going to focus much more broadly than on hair cell regeneration itself, but talk about the vestibular problems in general. And I'll come around to talk about regeneration eventually.

All right, so the sensory organs for hearing, which I've said is our auditory sense, and for balance, which I'm going to refer to as our vestibular sense, are located in the inner ear. This diagram shows here, you can see the two external ears drawn here on the left and right, the middle ear is shown here. And then our inner ear is shown in green here. And what I want to point out is that the left and right in our ears have mirror symmetry. And they project nerves, branches of the cranial--eighth cranial nerve--to the brain and the brain processes information from these two organs, from all the different areas of these organs, and then helps us with our sense of hearing and our sense of balance.

Over here is a diagram from "Grey's Anatomy," just showing you what a single inner ear looks like. I want to point out the different regions. The cochlea is our organ of hearing, that's here in the lower right. The vestibule is this area in the center region. And this is where the vestibular organs are housed. The semicircular canals are located in the top part of the diagram there. And you can see three different semicircular canals that although it's hard to see in two dimensions actually project—actually are oriented—in very different planes, right angles to each other for two of them, and then at an orthogonal plane.

This entire structure, the inner ear, is based in fluid. And as we move our ear these semicircular canals transmit the fluid and the fluid is shared with all the other organs in the same space of the inner ear. So the auditory and vestibular sensory organs have distinct structures that reflect their different functions, and I'd like to illustrate this here.

What is the cochlea? The cochlea is at the bottom there, it's that coiled structure. And there's one of them on each side, and it senses sounds. There are five organs on each side that help us with the sense of--our vestibular sense. Three of them are called the cristae and those are at the top and they're each located in the semicircular canal. They sense rotations of our head. The two organs that have otoconia, which I'll come back to in a minute, are called the maculae. They sense static head position and the linear motions of the head, and they're located in the region indicated by the arrow.

So the two senses work in very different ways, but they also have important commonalities, which I'd like to share with you now. How does the cochlea sense our hearing function? Well, if you look in the diagram on the left, you can see this coiled structure. And along that coil is a sensory epithelium, which looks basically like a strip, that strip sits on a membrane, which is illustrated on the right. And this membrane, if you sort of unroll this strip, you can see it has a different structure along its length. And when sound waves hit the middle ear—hit the eardrum— this is transmitted into the inner ear and it causes this membrane to vibrate and results in a traveling wave along that membrane which is shown in the diagram here.

Now, the sensory cells for hearing and for balance are called hair cells. And they're named hair cells because of this specialized structure called a hair bundle that's made of multiple hair-like structures. There are thousands of hair cells in each cochlea that are distributed along that membrane. And when, if you look on the diagram on the right, when that traveling wave is large enough underneath the hair cells, it will cause them to have their bundle deform or deflect in the direction of the arrow. That causes the hair cell to become electrically excited—activated—and to cause the nerve to fire, in this case the cochlear branch of the eighth nerve to fire a signal to the brain to communicate. And that's how it communicates with the brain.

Importantly, information from one cochlea may enable us to communicate with each other, but two cochleae, two cochleae are required for us to optimally localize sounds and sound localization is one of the critical functions that allows us to identify where sounds are located and to identify dangerous cues, et cetera. But then also these two cochleae working together also help us to understand speech in noisy environments.

How do vestibular organs sense head motion or head position? Well, as I mentioned, there are five of them. There are the maculae organs, which are shown in blue, and reside in this position. The saccule and the utricle. And then there are three cristae, which are shown here. I'll start by talking about the maculae. The maculae sense linear head motion. An example of this is head tilt to one side. When our head moves, well, I should mention that this, the hair cells themselves, have their bundles embedded in this membrane. And on top of that membrane lie these ear stones, or otoconia that I'm sure you've heard of before, which I'm showing in gray here in this diagram.

So when the head moves in a linear direction, as shown by the top arrow there, above there, the otoconia movement happens in the opposite direction. Now, if you look back to the diagram on the right, this is very similar to what happens in the cochlea. The otoconia deflect the stereocilia without that bundle of hairs on top of the hair cell, and then the hair cell is activated and it sends a nerve signal in this case along the vestibular branch of the eighth nerve. Now the saccule and utricle are located at right angles to each other. And so they're both sensitive to different types of head motions. The cristae have a different type of stimulation.

The hair cells there are located inside the organ, this ampulla that sits at the end of each semicircular canal and when we rotate our heads in different directions, the fluid in the semicircular canals moves ever so slightly, and it causes those hair cell bundles to be deflected. The head rotation occurs in one direction. The fluid motion happens in the other.

And if again you look at the right side, you'll be reminded of a similar kind of mechanism where the fluid causes the hair bundle to be deflected, and that causes the hair cell to be excited and the nerve to send a signal to the brain. So the integration, you can tell that each of these five organs has different functions, okay, it senses different types of head motions in different directions. And so it's the integration of these five organs that's really important for how the vestibular system works.

So when the brain receives information from these five organs, it becomes integrated. And then it also compares information from both sides, from the five vestibular organs on both sides to understand—to optimally understand—how we are oriented in space and how we are moving. So both ears—like for hearing—are really important for our vestibular sense.

I just want to point out anatomically that the vestibular and auditory branches of the eighth nerve carry information from each sensory system to the brain and that's shown there in the bottom. The auditory component of the nerve is shown in purple and the vestibular component and shown in pink. And these nerves travel together through the temporal bone, to the brain, as shown there. And so pathologies such as tumors can affect both these sensory systems. And so it's not uncommon with tumors of the inner ear to have both hearing and balance problems.

Also importantly, the sensory organs in our inner ear, vestibular and auditory, have a common embryonic origin, so a single gene mutation may disrupt development of both sensory systems. And this is illustrated here, how the ear develops is illustrated here, in these beautiful images from Doris Wu's lab in which she used a white paint to fill the inner ear, to look at its structure. And I'm showing development of the inner ear, with the early forming ear on the left, and that primordium of the ears called the otocyst, and the nearly mature ear on the right. And what I hope you can appreciate is that the otocyst is a fairly nondescript structure on the left and as the ear develops and the vestibular and auditory areas specialize, and those organs specialize all from that common origin.

So if there are mutations that affect the early phase of ear development, it's going to affect both hearing and balance. And even later mutations, mutations that affect later stages of development, will have impacts on both sensory systems. Vestibular and auditory sensory organs are also composed of very similar elements. I touched on this when I talked about sensory hair cells, which are shown here for the auditory system on the left and vestibular system on the right. We're looking down on the surface of those hair bundles.

And if you look at the diagrams at the bottom, you can see that the hair cells, their bundles project up into the fluid spaces and their body cell bodies are located at the top of the epithelium. But also there's another important cell type called supporting cells that are also present in both epithelia and they serve important functions such as they provide structural support for both the epithelial types. And they regulate the chemical environment of the cochlea. And also they have potential to form new hair cells in some organisms and that's what regeneration is all about. We rely on supporting cells for regeneration.

And finally before I turn things over to Jim I want to emphasize that similar things cause damage to the hearing and vestibular systems. I talked about mutations before that are inherited, those impact both sensory systems. Ototoxic drugs also can injure the hair cells in the sensory organs and sometimes the neurons. Antibiotics like gentamycin and streptomycin are common causes of ototoxicity, antitumor drugs, such as cisplatin, and there are probably other unknown ototoxins that affect both systems that we should explore as well. Now we all know that exposure to prolonged or intense noise causes hearing damage, but there's also emerging evidence that these sorts of stimuli may also cause damage to the vestibular organs, particularly when noise is a very high pressure or concussive such as what's experienced by the military sometimes.

And microbial infections like CMV, Epstein-Barr virus, or meningitis also cause a loss of balance and hearing functions. And of course, I'm growing all too familiar with the fact that aging affects my hearing and my balance function. And this is what we refer to as presbycusis in the case of aging and presbystasis in the case of the balance system. I hope that helps you understand a bit more about how these two systems are intertwined and how they each function differently and similarly, and I just want to summarize by saying the auditory and vestibular sensory systems have different functions, but they share important features. And importantly as Jim will talk too about, they often fail together. Okay, Jim.

DR. PHILLIPS - Thank you, Jenny. May I have the next slide? Great. My job here is to tell you a little bit about vestibular disorders. As Jenny mentioned, they're quite common. And that study that you mentioned looked with just a normal aging study, they did a simple vestibular test, a balance test on adults aged 40 and older, and found that roughly a third of those adults had vestibular dysfunction. And in fact, that was true, about 32% had vestibular dysfunction, even if they had no history of self-reported dizziness or vertigo.

Most vestibular complaints that people have when they see a physician—and that's roughly a third of us actually will visit a physician with a primary complaint of a balance problem or a vestibular problem—most of these complaints are transient and they in fact many times don't require any treatment at all. Many are easily treated.

So benign paroxysmal positional vertigo, which is when the structures of the inner ear deteriorate, can be treated sometimes with simple repositioning maneuvers which can be performed in the office and provide almost immediate treatment. However, a significant number of vestibular disorders become chronic debilitating issues and importantly for this group—and Jenny has mentioned it before—individuals with vestibular function are really significantly more likely to have hearing loss and vice versa suggesting that those structures of the inner ear often play an important role and often share pathology in common. Next slide please.

So I wanted to tell you a little bit of what you might experience. If you have a vestibular disorder, if you have an acute unilateral loss of the vestibular function, the primary thing that you'll experience is a sense that something is horribly wrong. And the reason for this is we don't appreciate the importance of the vestibular sense until the vestibular sense itself is compromised. And then you have an appreciation for its profound significance to your everyday life. If you have a long-term progressive loss, vestibular disorders can sneak up on you for producing progressive changes in balance and vision and orientation that you might just associate with normal aging.

If you have a vestibular disorder, you're likely to experience one of these things. Dizziness: which is sort of an altered sense of spatial orientation. Vertigo: which is a false sense of movement, a sense that you or the world are moving. And often this is in a very compelling way and you can't reason your way out of it. Imbalance: it's an inability to maintain your posture, difficulty walking, and of course falls, which are a leading cause of death in older adults. In that study that Jenny mentioned, and that I've mentioned as well, loss of vestibular function was associated with eight times the likelihood of falls in that normal aging population.

Oscillopsia is something that patients experience with vestibular disorders. This is the sense actually of the motion of the visual world and blurred vision when your head moves. And this is caused by the fact that there's a steady-cam system built into your brain that compensates for head movement by moving your eyes so that your eyes remain fixated on objects of interest. When that system fails, you lose vision, your vision becomes blurred, and the world moves dramatically.

Cognitive challenges: patients with balance disorders and dizziness associated with the vestibular loss have trouble concentrating and they have trouble with memory. They experience brain fog, and it's one of the most frequently encountered complaints when a patient comes in with a chronic vestibular disorder. Depression and anxiety: there's a high correlation between vestibular loss and psychopathology. And this is not just reactive. It's true that vestibular disorders are debilitating and they're isolating. And so it's logical that people would experience depression or anxiety and an association with them but there actually is an anatomical substrate for this as well.

And finally, autonomic dysfunction: people with vestibular disorders experience nausea, vomiting, changes—difficulty—with blood pressure regulation, et cetera. And while primary orthostatic hypertension can produce dizziness because you're not perfusing your brain adequately, actually vestibular disorders can cause orthostatic hypotension, inability to regulate blood pressure, because your vestibular sense contributes to the activation of constriction of blood vessels and so on, which allow you to appropriately distribute blood to your brain. Next slide, please.

This is the anatomical substrate of all of this stuff. And I'm just going to briefly mention it. It's a slide that Jenny gave me, which is modified from something that Carey Balaban presented. The vestibular nuclei and the center of this are the primary recipient zone in the central nervous system for vestibular information from the inner ear.

This is a displaced cerebellar nucleus actually. And it receives a lot of information from a lot of different sensory systems, most importantly, visual and proprioceptive senses through the cerebellum as well, and uses that to produce an integrated sense of where you are in space. And then it uses that information to distribute that information to structures, which have a variety of different functions. For example, it sends information to the oculomotor nuclei, the spinal cord, and cerebellum to generate movements that stabilize the body in the eyes.

It sends information to your cerebral cortex so you'll have a percept of your location in space, and it's kind of an integrated perceptive space in general. It sends information to the limbic system and the structures that are responsible for assigning subjective and emotional value to experience. It sends information to structures that ultimately project to the vagus nerve to control autonomic responses.

And importantly, it sends a lot of information to the hippocampus and structures that are involved in your ability to encode information, lay down new memories, and also your sense of conscious awareness. So the vestibular nuclei and the vestibular system are intimately involved in all of these. Next slide, please.

Vestibular disorders can affect one or both ears. Both ears contain five vestibular end organs, as Jenny said. And that's a good thing because there's a certain degree of redundancy there. The vestibular nerves themselves are tonically active. They're constantly, the hair cells are constantly secreting neurotransmitter and the afferent fibers are constantly discharging. They modulate their discharge based on motion inputs.

So for a rotation, there are actually matched pairs of end organs that have opposite directional sensitivity in the two ears. If I turn my head to the right, the afferents from the lateral semicircular canal in the right ear increase their discharge and the afferents from the comparable canal in the left side, left ear, decrease their discharge. And vice versa.

This means not only does the vestibular system have redundancy but to operate optionally, both ears need to provide some sort of balanced information to the brain. No difference between these matched inputs from each ear tells your brain that you are stationary.

When you turn your head, there's a difference between the two ears and that difference tells your brain that you are turning. Acute unilateral loss reduces the output from one ear, and that then tells your brain that you're turning rapidly toward the other ear. It produces whirling vertigo, and it's a sensation that you can't talk your brain out of. You have to work over time to recover from that.

Bilateral vestibular loss doesn't produce whirling vertigo, but it can be insidious. Patients who are receiving aminoglycoside therapy often don't know that they have complete bilateral loss of the vestibular function until they recover from the illness that required their aminoglycoside therapy. And then they try to get up and walk around and they realize that something is again horribly wrong. There is no whirling vertigo, just profound imbalance, disorientation, and cognitive challenge. Next slide please.

How do patients recover from vestibular loss? Recall that I said that most vestibular disorders are self limited. This may mean that the primary cause of the dysfunction has resolved, that the labyrinthitis or neuronitis has resolved and the hair cells and nerve fibers are sending the same information that they did before. Often however this is not the case. Rather, the central nervous system actually engages compensatory mechanisms to restore function based on input, which is still impaired. This is true for many of us.

These compensatory mechanisms are: compensation: the central nervous system restores symmetry to the activity of central structures based on this unbalanced unilateral input relying on commissural connections from one side of the brain to the other. Adaptation: the brain monitors the activity of central circuits and the resulting behaviors like the reflexes that stabilize the eye and adjust them to restore function. Despite the fact that the input is still impaired. And finally substitution: the brain substitutes inputs from vision, somatosensation, kinesthetic sense, and touch and hearing to restore function. These strategies frequently work. Sometimes you feel fine afterward. They are imperfect, they don't fully compensate for your loss, and often they fail completely. Next slide please.

So patients really do need new vestibular therapies. They desperately need these. Currently there are no non-experimental restorative therapies for the loss of vestibular hair cells. Auditory and vestibular scientists are using comparable approaches to treat these problems and advances in one field also potentially benefit both groups of patients because people, because researchers in the other field can rely on those advances to move forward in their own area. And I'd just like to point out one such advance and commonality.

This is called a vestibular neuro-prosthesis, it looks like a cochlear implant. This is from our laboratory, but similar devices are being developed at Johns Hopkins and also in Europe. This device has multiple arrays, electrode arrays, on—the sort of big electrode array in the middle— goes into the cochlea to restore hearing function. And then the three smaller arrays at the top, each of those go into one of the semicircular canals close to the ampulla to restore balance function. And then there's a remote ground.

So the device is sending motion information to the balance portion of the inner ear and sound information to the hearing portion of the inner ear. These are currently implanted in patients and this field is advancing rapidly and you can see I think the commonality between hearing and balance in this example. Jenny.

DR. STONE - Great. Thank you. That's one example of how research development in one area and development of therapies has impacted the other. My personal research focuses on trying to identify ways to restore the hair cells that we lose due to these various things that I mentioned. In humans, both auditory and vestibular hair cells degenerate due to ototoxins, injury, infections, and the aging process.

This is just a pictorial example of how profound a hair cell loss can be in individuals who are not really that old. This shows, this is a study from Andy Forge—or an image from Andy Forge—on the left just showing you what a young adult guinea pig utricle looks like—one of the vestibular organs—for reference. You can see all those white structures are the hair cell bundles that sort of project up out of the epithelium into the space. And then on the right are two human utricles that are from otherwise fairly healthy people. What I hope you can appreciate is in the picture in the middle for an 80-year-old woman, she only has one remaining hair cell in that field. And for the 65-year-old man, I don't see a single remaining hair cell there.

So this is quite a profound loss of critical cell type. And Jim was just mentioning compensation, one wonders how well they could compensate from such a problem. But I also think one also wonders how many of us are walking around with profound loss and don't realize it and also don't know how better things could be, maybe, if we had them replaced.

So I look at regeneration, I think regeneration, and a lot of us feel that it has a potential to improve or reverse hearing or vestibular deficits. If you can replace the hair cells, maybe you'll have better function. So what have we been looking at is: does regeneration happen? And can we determine how to promote it if it doesn't.

And so this is another study from Andy Forge, which he conducted in young adult guinea pigs. It shows what happens in the auditory organs. Mammals, as far as we know, mammals can regenerate auditory hair cells in maturity. They may do so when they're very young, but once they've matured, there's very little capacity for auditory hair cell regeneration. That's illustrated here where you can see all the normal hair cells at the top. Then weeks after treatment, all you see is a scar of supporting cells.

In contrast, in the same study, Andy looked at the vestibular organ of the guinea pigs, which also had damage, and what he saw like a couple of weeks after damage was that middle panel on the right there. But weeks later, about eight or 12 weeks later, some hair cells had been replaced, which was really exciting in a mammal. This wasn't enough to restore vestibular function, but it indicated to us that there was a potential to work with us, or at least there was some capacity for regeneration.

Subsequent studies from Andy's group and studies from other people's groups, looking at autopsies have shown that humans may also be able to regenerate some vestibular hair cells. So the point of what I'm showing you is that because a vestibular system has natural capacity for regeneration, it provides a very important opportunity for us to study how this small degree of regeneration is regulated. My lab has really switched from studying the hearing organ to the vestibular organ because of the potential that the system offers. But we also have to keep looking at how that auditory organ responds so that we can know what blocks regeneration in that system.

I'm going to move to my next and last slide now to just try to summarize why we think it's important to promote research on the vestibular system. The main reason is that there's still so much that we don't know. And when you don't know how to treat a system, you don't know fundamentally how it works, or what goes wrong with it, where the lesion is, et cetera. It really slows development of better medicine, It really, really delays treatments. We really need more research on the following critical topics.

I want to remind you this work will help us understand both sensory systems. Understanding the fundamental biology of how the vestibular system develops, functions, and degenerates, building better diagnostics for improving genetic testing, imaging of the inner ear, tests of the vestibular function, preventing ototoxicity and other forms of damage, fixing the injured systems, perhaps through stem cells, gene therapy, or perfusing pharmaceutical agents into the ear, or even better, maybe we could identify systemic treatments or building better treatments, such as improving the vestibular implant or finding better ways to rehabilitate someone with vestibular loss.

What's the best way to promote vestibular research? Well, obviously we need to fund more projects on the auditory and vestibular systems. We need to recruit more people into the field. One way to do that is through HHF's ERG program, which provides more training to young investigators and also may stimulate crossover from other disciplines because it stimulates people to do new types of research, new ideas. We can leverage insights and technology from auditory research, and cross-foster ideas and approaches and vice versa, and also take novel approaches to problem solving such as this consortium research model that the HRP uses. So I'd like to stop there and move to your questions. And I hope that this has provided a better perspective for you on where the field of the vestibular disorders is and what we might do to make it better.

Dr. LALWANI - Dr. Stone, Dr. Phillips, that was terrific, really a lot of interesting stuff, how hearing and balance are interconnected. You outlined a pretty aggressive agenda in terms of what kind of research needs to be done. How is this research funded now? Are there opportunities for funding out there?

DR. STONE - Oh yes. The National Institutes of Health, for instance, fund multiple projects on vestibular and auditory research and organizations like the Department of Defense also are very invested in funding balance research--research on the vestibular system. But there aren't as many applications that come into the National Institutes of Health on vestibular system. In fact, there are many fewer grants that are funded compared with auditory research, and the NIH would like to fund more projects and they keep telling us to send in more grants. But I don't think we can do that until we recruit people into the field and get people interested in new ideas and new approaches to doing things. And so that's where Hearing Health Foundation may be very helpful.

DR. LALWANI - Dr. Phillips, there's a question for you and maybe for Dr. Stone as well. Can one—and I think he partially alluded to it in one of your earlier slides—can one train vestibular function to escape the disorder? Can you train yourself out of a problem?

DR. PHILLIPS - The short answer is yes, sort of. The brain is capable of altering the reflex functions that are contingent on the vestibular input and modifying what it does with the information that it gets. But there are certain things that the brain cannot compensate its way out of.

For example, if you lose all inner vestibular function, you are going to have oscillopsia, the brain can't solve that problem. The reason for that is that the reflexes that move your eye that are contingent on information from the ear are incredibly quick--they take about 10 milliseconds to be activated. Whereas if you use visual information to stabilize your eye in the world, it takes more like a hundred milliseconds or 120 milliseconds to extract visual motion information and generate eye muscle activations that can produce compensatory eye movements. Those are much too slow to eliminate the motion of the visual world and the blurring of the visual world that results.

DR. LALWANI - It is interesting that some physical therapy for balance leads to some improvement of symptoms is something similar true for hearing as well. Can rehab for hearing lead to better function overall? What are your thoughts about that? It's a very broad question.

DR. PHILIPPS - Is that a question for me?

Dr. LALWANI - Either one. I think as you alluded to the similarities between the two systems, this may be one of those differences between the two systems, I guess.

DR. PHILLIPS - So I think one of the things about vestibular rehabilitation is that because there are so few other strategies for treating the vestibular system and vestibular loss, there's been an enormous investment into the development of vestibular rehabilitation strategies. However, I would say that auditory rehabilitation is a very real and important field. A lot of it has to do with optimizing some of the aids, for example, the amplification technologies and so on, so that patients receive maximum benefit from those. But yes, absolutely the rehabilitation professionals can provide significant benefit in both areas.

DR. LALWANI - There's a question from an anonymous viewer, "Since I can't regenerate those cells, is there anything I can do in addition to avoiding loud noise and other toxic drugs to prevent deterioration?" I'm going to turn it toward the vestibular system, even though I suspect the question is really about the auditory. There are things you can do in the auditory system to avoid toxicity. Is there something similar in the vestibular system that you can do to avoid deterioration of the vestibular system over time?

Dr. STONE - I guess it depends on the type of deterioration that happens. I mean, yes, you can limit noise exposure if you're trying to prevent hearing loss that may keep your hair cells happier for longer. I think if you don't have any choice but to use antibiotics and cisplatin to treat severe illness, there's nothing that we know right now that can protect the ear from those structures.

Those research areas are well underway though, I mean this is an active area of research. People are trying to understand, for instance, how cisplatin injures the ear at the same time that it's killing tumor cells and trying to find ways to block that. I don't believe there's any reason to think that rehabilitation affects the inner ear in any meaningful way, but it certainly—if you build, if you build the compensation adaptation needed to manage things—then as deterioration proceeds, as we lose our hair cells because of aging or other reasons, then you're kind of, you're one step up and you're better off. You're probably better off managing it. But I'll defer to Jim to ask for that answer too.

DR. PHILLIPS - What I would say is that, although there really aren't good strategies to prevent the loss of hair cells with time and there's something sort of akin to presbycusis, which is called presbystasis which occurs in older adults where you lose hair cells over time, your best defense against having a symptomatic vestibular problem is to remain active because that actively engages all of the mechanisms that I described to keep the brain sort of abreast of changes in the peripheral sensory input and optimizing whatever information it's receiving to perform well.

And people when they compensate, when they're well compensated to a loss which is not complete, they actually feel pretty much their normal selves, although perhaps their performance is deteriorating a little bit. And certainly if they came into a vestibular laboratory, we could demonstrate that they had a loss. So remaining active and actively utilizing all of that information in the context in which you ordinarily encounter those sensory inputs in your everyday life-- that's absolutely essential to maintaining good health.

DR. STONE - That is challenging because sometimes when you have a vestibulopathy or a problem, the last thing you want to do is move, right? But it's the best thing for helping your body to adapt to that.

DR. LALWANI - Yeah. Dr. Stone, I think that's a very important point for our audience to understand this--often recovery from an insult like that, the initial part can be more symptomatic, that you get more dizzy early on before you get better. And that's not a sign of something getting worse. There's a really interesting question: if the HRP is successful in discovering the mechanisms for auditory hair cell regrowth, with this new knowledge, would there be immediate transfer value of the regrowth of the vestibular hair cells, or will your research effort be necessary? This is right up the alley of your talk actually today, the interconnectedness

DR. STONE - Yeah, it's a great question. I would actually probably have to flip that around because I think we're probably going to figure out how to regenerate the vestibular hair cells before we can regenerate auditory cells. And I mean that as a field, not just the HRP, but a lot of people are working, they understand the power behind having a system that regenerates a little bit, that we can ratchet that up. It's easier to ratchet something up than start something that's completely stalled.

And it really looks like the supporting cells, those progenitors to new hair cells in the auditory organs, become very silenced and heavily inhibited from forming new hair cells, from regenerating hair cells. So in some, I mean, obviously I think anything that we learn in either system that tells us the best way to restore function in the inner ear and within that system, the least deleterious way to make new hair cells make the most new hair cells and make the specific types of hair cells that we need for—which I didn't really go into, but we have different subtypes of hair cells that are important functionally—is going to help the other system.

But each system has unique challenges and that relates to the fact that in the cochlea we have inner and outer hair cells, and they are very distinct from each other and distinct from vestibular hair cells. In the vestibular system, we have type one and type two hair cells, which are very distinct from outer and inner. So understanding how those cell types specifically can be made again and how they can get incorporated into the system is a unique challenge to each system. But yes, there's a lot of translation potential.

DR. LALWANI - Are there any gene therapy trials in the vestibular system regeneration or the vestibular system period, right now that we know of?

DR. STONE - Gosh, I should let you answer that Anil. I think the only trial that I was aware of was to promote regeneration has been that transcription factor ATOH1. I don't know if that was targeted specifically to people with hearing loss or also to people with vestibular balance disorders.

DR. LALWANI - Mostly hearing loss. I'm sorry it was just an audience question it wasn't really meant for you, it wasn't meant directed from us.

DR. STONE - No no, I think honestly, I don't—I can't speak to the outcome of that trial very well, but I'm pretty certain there are not any other trials that are active now toward hair cell regeneration.

DR. LALWANI - And as there's an auditory brainstem implant, is there a vestibular brainstem implant or somebody working on that area as well, one of the other questions from an audience member.

DR. PHILLIPS - Yeah. That's an excellent question. There are certainly a lot of patients who would potentially benefit from such an implant. What I can say is that several groups have considered it and have written about it sort of hypothetically, but there have been, as far as I know, no trials, either in animals or in human subjects of such a device. I think that the technology, I mean, comparable technology to the auditory brainstem implant could easily be employed in the vestibular system.

One of the problems or challenges that you face with a vestibular implant is that in the periphery, there's a nice organization of directional sensitivities and so on for afferent activation of afferent fibers. And so electrical stimulation can selectively activate afferents in a way that should produce a coherent sense of motion. In the brainstem, that typography is much more complicated. So it will be challenging to do this.

DR. LALWANI - Somewhat related, how many electrodes are there in the vestibular implant that you're working on, Dr. Phillips.

DR. PHILLIPS - All right so among the three groups, the number of electrodes range from one to three in each end organ. However, those multiple electrodes are actually not there to differentially activate, for example, afferents within a single ampulla. The reason that they're there is, or at least the hope is that by doing bipolar or tripolar stimulation, you can reduce current spread and control the activation of afferents and limit it to a single ampulla, as opposed to having it spread to other ampullae and produce crosstalk between inputs.

DR. LALWANI - Well, we have a lot more excellent questions, but we've kind of run out of time at this point. So I will bring our webinar to a close. I want to thank all of you for attending, especially Drs. Stone and Phillips for this really informative research presentation on the vestibular or balance system, and how it's interconnected to the auditory system. We're very fortunate HHF is to be able to fund this important research with your help. Remember that you can donate to our efforts to advance better treatments and cures for hearing and balance disturbance at hhf.org/donate. Again thank you. Have a great evening, thank you again.

DR. STONE - It was our pleasure. Thank you Anil, and thank you HHF, and thank you audience.