

*An estimated half of all Americans will lose at least some of their hearing by the time they retire. By age 75, about half of us will also suffer from balance problems. Currently, in addition to hearing loss, about 10 million to 15 million Americans suffer from tinnitus severe enough to seek medical help.*

*Although the causes of hearing loss, balance disorders and tinnitus can be wide-ranging, a frequent common denominator can be found in the cells within our inner ear that mediate our senses of hearing and balance: sensory hair cells.*

## Can We Regenerate the Inner Ear by Teaching Old Cells New Tricks?



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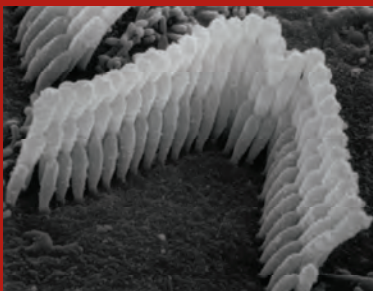
### How hair cells work

Our perception of sounds starts with our external ear capturing sound waves. Next, the three tiniest bones in our body pass them across the middle ear and convey them to the cochlea. This spiral cavity is the auditory portion of the inner ear and contains about 15,000 hair cells. We call them hair cells because of the tiny hair-like projections that stick up from each cell's surface like organ pipes. As sound waves travel along the cochlea, they stimulate these projections, which cause the hair cells to become electrically active (Fig. 1). A nerve cell connects each hair cell to the brain, which then interprets these electrical signals as sound.

Hair cells are incredibly mechanically sensitive. It has been estimated that a movement as little as the diameter of a few atoms can stimulate their hair-like projections. Put on a human scale, we can compare this amount of movement to moving the very tip of the Empire State Building by a few inches. This sensitivity allows us to hear extremely soft sounds, such as a whisper, the sound of a pin dropping or the softest of orchestral pianissimos.

This exquisite sensitivity of hair cells comes at the price of vulnerability. In addition to the aging process, a variety of insults and injuries can damage hair cells – principally loud noises (Fig. 2). Chemicals, such as certain kinds of antibiotics or chemotherapy drugs, also cause damage. We consider these chemicals "ototoxic." A person can perceive ringing in the ears as one of the first signs of damage to hair cells. For some, this may progress to full-blown tinnitus.

Damage to hair cells can ultimately lead to their death. The hearing loss that results can be gradual, as is commonly seen in the wear-and-tear of old age. It can also be immediate and catastrophic, such as deafness resulting from explosions or gunshots. In either case, the hearing loss is permanent, as the human body never replaces the lost hair cells. However, this is not true for other animals. We have known for more than 20 years that birds, frogs and fish can naturally regenerate their hair cells. A bird that has been deafened by exposure to loud noises or drugs that kill hair cells is able to grow back its entire complement of hair cells and hear perfectly  
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*Figure 1: The surface of a single cochlear hair cell. The hair-like projections sticking up from the surface of the cell form a V. Movement of these tiny projections cause hair cells to become electrically active.*

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again in a matter of weeks. However, mammals apparently lost the ability to regenerate hair cells at some point over the last 200 million years when their ancestors separated from the ancestors of modern birds and reptiles.

## How birds regenerate hair cells

Every bird hair cell is surrounded by four to seven less elaborate "supporting cells" to form a repeating mosaic pattern. The death of a bird hair cell triggers one of its neighboring supporting cells to divide, creating two "daughters." One of the daughter cells then turns into a hair cell. (Fig. 3, top). This process of division, followed by transformation into a hair cell, restores the mosaic of hair cells and supporting cells back to their original state. This happens all the time in many parts of the mammalian body, such as our skin, the bone marrow that produces blood cells and our digestive system. We lose about 10 billion cells from the lining of our gut every day and will continue to do so until the day we die. Intriguingly, this process of division and transformation even occurs in parts of the mammalian brain thought to play a role in short-term memory. However, although mammals,

like birds, also have supporting cells surrounding their hair cells, there is almost no regeneration of hair cells after damage (Fig. 3, bottom).

## Why can't mammals do what birds do?

There are a number of possible explanations for the failure of hair cells to regenerate in mammals. For example, mammalian supporting cells might simply have lost the ability to divide and make hair cells at some point in our evolution. Alternatively, they might still be able to regenerate hair cells, but the signal to trigger regeneration might be blocked or missing.

To test these possibilities, my colleagues and I at the House Ear Institute carried out a conceptually simple but technically difficult experiment. We developed ways of purifying supporting cells from the ears of newborn mice, a time when all the cell types of the cochlea are formed and in place. We also devised ways of keeping the supporting cells alive in a culture dish to study their ability to divide and make hair cells. After several years of trial and error, we were able to show that in a culture dish, supporting cells of a newborn mouse could behave like those of

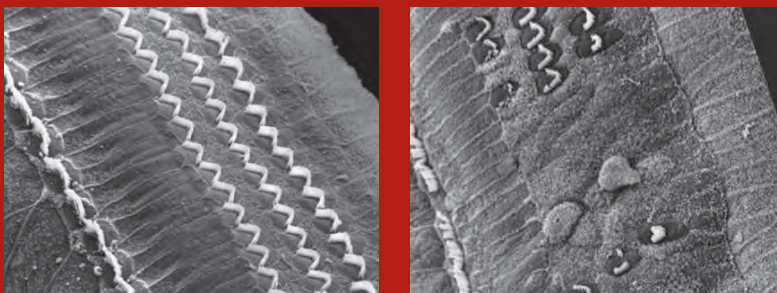


Figure 2: (Left) The surface of a mammalian cochlea showing three rows of outer hair cells and a single row of inner hair cells. (Right) A mammalian cochlea damaged by sound. Many of the hair cells have been destroyed, and will never regenerate, leading to permanent hearing loss.

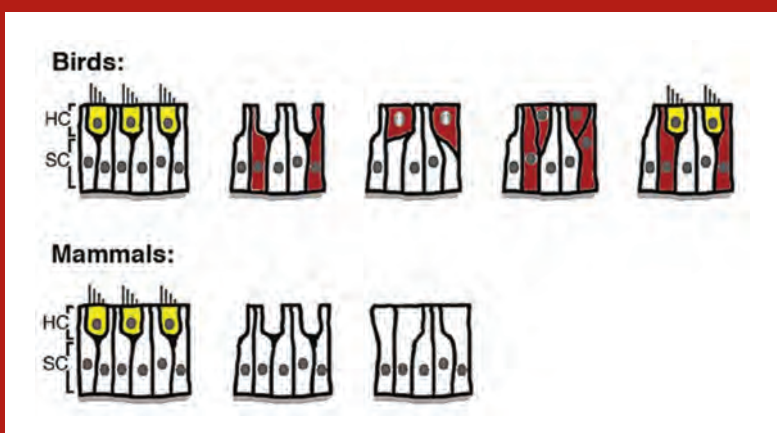


Figure 3: (Top) When bird hair cells (HC, in yellow) are killed, some of the supporting cells (SC) are triggered to divide into 'daughter cells' (in red). One of the two daughter cells turns back into a hair cell, restoring the system back to normal. (Bottom) In damaged mammals, the supporting cells almost never divide or make new hair cells.

birds – they were able to divide, and their daughters were able to turn into hair cells.

## Do genes play a role?

We then started to ask why the mouse supporting cells were able to divide in a dish, but not in the intact mouse ear. Cells in our bodies have about 25,000 genes, which pass on genetic characteristics encoded in our DNA. One family of genes acts to stop cells from dividing when they are not meant to. These genes serve an extremely important role, as their malfunction can lead to inappropriate cell growth and sometimes to cancer. Mouse supporting cells express one such growth-blocking gene with the rather unimaginative name of p27. We found that when we took supporting cells out of the mouse ear and grew them in a dish, about half the supporting cells switched off the p27 gene within 12 hours. These are the cells that started dividing.

So far, so good. However, we had conducted our experiments in newborn mice and, unlike humans, mice do not start to hear until about two weeks after birth. We decided to repeat our experiments in 2-week-old mice and, to our surprise, the purified supporting cells were now unable to switch off the p27 gene and therefore unable to divide. Our results suggested that the ability to switch off the p27 gene seemed to correlate with the ability to divide.

We settled the issue by using a genetic trick to switch off the p27 in 2-week-old mice – and once again, their supporting cells were able to divide. Learning how to switch the p27 gene off in the right place at the right time might help human supporting cells divide and transform into hair cells.

## What has all this told us?

We now believe that mammals may have the capacity for hair-cell regeneration, but that this capacity is normally blocked. In our quest to trick the mammalian ear into behaving more like a bird's, our experiments have raised one possible target – the p27 gene. However, we are a very long way from attempting to try such experiments in humans. We need to find answers to many more basic questions, such as, how do we trigger just the right amount of supporting cell division and transformation into hair cells? The cochlea is an extremely mechanically sensitive structure, and it is likely that producing too many hair cells may do more harm than good. Despite these challenges, it is clear that birds are showing us the way ahead and only time (and a lot more research) will tell if we will be able to follow their cue. ☺☺☺

*Born in London, England, Andy Groves received his bachelor's degree at the University of Cambridge and his Ph.D. from the Ludwig Institute for Cancer Research in London. He subsequently moved to the California Institute of Technology to study the development of the nervous system. Dr. Groves began working at the House Ear Institute in 1999, where he works on the embryonic development of the inner ear and on developing new approaches to regenerate the ear after damage.*

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**Dr. Hoover** is a Fellow of the American Academy of Otolaryngology, Board of Allergy & Environmental Medicine and Royal Society of Medicine, London, and a Diplomat of the Royal College of Surgeons of England. Dr. Hoover has served the Houston area for 25 years, spoken in over 26 countries and published in numerous medical journals, such as:

- International Rhinology. Supplement 2.all.1987
- Tinnitus & Allergy. Proc II International Tinnitus Seminar, Munster, Germany. 1987. Publisher, Harch V. Karlstruhe
- The Journal of Japan Rhinologic Society. Vol 30,1(1991)

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