Can 'Hair Cells' Unlock Deafness?

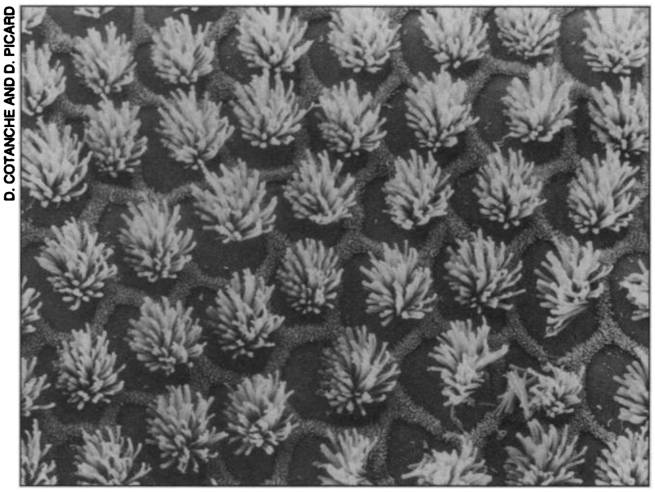
Recent results show that–contrary to received wisdom–these key sensory cells of the inner ear can regenerate in some animals, perhaps opening the way to curing many cases of deafness

Of the more than 18 million cases of deafness or hearing impairment in the United States today, some 80% are examples of sensorineural deafness—"nerve deafness"—most often due to the malfunctioning of the hair cells of the inner ear. These cells, which line the snail-shaped cochlea, convert sound waves into electrical impulses that are passed on to the brain. Until now, even the most advanced medical technology didn't hold much hope for the hearing loss that results when hair cells die from aging, infection, or noise damage: The received wisdom was that hair cells don't regenerate, and anyone with nerve deafness—including the many elderly people with hearing loss—was condemned to a life of silence. But new results, based on studies of fish, birds, and mice, suggest the received wisdom needs an overhaul: The ear's hair cells may indeed be capable of regeneration. Concludes Jeffrey Corwin of the University of Virginia, a leader in the current work: "We shouldn't think of nerve deafness as a permanent deficit, one that can't possibly be reversed."

Maureen Hannley, former head of NIH's hearing research program and director of research development at the American Academy of Otolaryngology, Head, and Neck Surgery, calls the new research into hair cells and their potential for regeneration in adults "one of the most exciting things happening in science now." Although researchers caution that the possibility of relieving deafness remains remote, what has been discovered recently is impressive. A few years ago researchers studying chickens and quails found these birds could regenerate hair cells, an ability it was thought no warm-blooded creatures had. Most recently, investigators have been pinning down exactly where these new cells come from, puzzling over what triggers the regeneration, and hoping to make the transition to mammals in their research studies. If they can make that key step—and many in the field believe this is a real possibility—many deaf people might have a chance at regaining the world of sound.

All this is a far cry from where hair cell research stood in 1974, when Corwin, then a graduate student, was soaking up the sun at the University of Hawaii. Scientists studying fish and amphibians knew that an organ called the lateral line can regenerate. The lateral line contains hair cells that enable these organisms to sense changes in water motion. But hair cells in the inner ear of the same organisms, it was thought, could not regenerate. As part of a study of the hearing ability of sharks, though, Corwin made a startling finding: A certain part of the inner ear of an adult shark typically held 240,000 hair cells, while the same part in young sharks averaged only 20,000. The obvious implication was that hair cells continue to form in the ear throughout the animal's lifespan. This was not regeneration of damaged tissue, but it was the first evidence, at least in cold-blooded animals, that hair cells could be produced after birth.

Until the mid-1980s, hair cell regeneration remained largely a curiosity, thought to be limited to cold-blooded creatures. But work on birds over the past 5 years has laid that notion to rest and galvanized the field. In 1985, for example, Doug Cotanche of Boston University Medical Center began studying how acoustic overstimulation damaged the ears of young chickens. In his work, Cotanche normally examined the birds' ears and their hair cells immediately after exposure to harmful noise. But in one series of experiments, Cotanche heeded a colleague's suggestion and allowed the birds some recovery time. And after 10 days, the ears showed little sign of damage—indeed, they appeared almost completely healed.



D. COTANCHE AND D. PICARD

Audible forest. Stereocilia sprout from the tops of hair cells in the chick cochlea. Each cell is some 5 micrometers across.

Working a similar vein at about the same time, otolaryngology resident Raul Cruz and surgeon Paul Lambert in Edwin Rubel's lab at the University of Virginia were studying how chicks responded to large hair cell loss induced by high doses of the antibiotic gentamicin. Over a period of 3 weeks, after the hair cells had been decimated by the drug, Cruz documented a gradual increase in their number. Taken together, these two studies, published in 1987, suggested that the recovery process included formation of new hair cells—and not just the repair of damaged ones. "This was a tremendous departure—to realize you could destroy or injure hair cells and get them back. It was astonishing!" recalls Hannley.

After a pair of findings like that, the field was bound to fill up quickly—and it did. By the next year, several groups had reported success in finding definitive evidence for regeneration (*Science*, 24 June 1988, p. 1772 and 1774). Cotanche teamed up with Corwin to continue his studies on chicks, while Rubel and Brenda Ryals, a clinical audiologist now at James Madison University, decided to examine adult quails. Both teams picked a radioactive form of thymidine, one of the four DNA bases, as a marker for following the recovery process and proving that the hair cells they were seeing were in fact new. This radioactive tracer would be incorporated into cells only if they were synthesizing DNA, a clear sign of new cell production. Corwin and Cotanche reported that at the sites where the ear was damaged—and nowhere else—hair cells and the supporting cells that surround them contained the radioactive tracer. Ryals and Rubel found essentially the same thing in their adult quail, showing that the phenomenon was not limited to young birds. The two groups concluded that the damage to the avian ears had prompted a dormant pool of stem cells to proliferate, and that some of the progeny had differentiated into supporting cells and hair cells.

Proving that hair cells in warm-blooded animals could regenerate was startling, but it wasn't enough. Researchers then had to identify the precursor cells from which the new hair cells had sprung. On the basis of their thymidine-labeling studies, Corwin and Cotanche proposed that the regeneration starts when the supporting cells directly below the damaged hair cells, responding to some unknown cue, reenter the cycle of cell division and begin to proliferate. But it was also possible that the new hair cells and supporting cells were derived from preexisting hair cells. To confuse matters further, work by Douglas Girod in Rubel's lab suggested another possibility: that a third group of cells, known as hyaline cells, which are near the hair cells but not directly in contact with them, were the precursors.

For a time, the field revolved around this issue, as researchers disputed the roles of hyaline cells and supporting cells. To settle the question, Corwin, along with Kenneth Balak, now at Western Kentucky University, focused an ultraviolet laser microbeam on the lateral line organs of salamander tails to remove hair cells from a well-defined area, leaving only the supporting cells. And still the researchers observed regeneration. In fact, through time-lapse video recording, Corwin and his colleague Jay Jones watched as the supporting cells divided once, then a second time, and then, in places where hair cells were missing, differentiated into replacement hair cells rather than supporting cells. To explain how new cells chose their fate, Corwin hypothesizes that "the newborn cell is programmed to become a hair cell unless it's touching another hair cell."

Additional work has since backed up the initial laser studies by extending the observations to chicks, and labs using other methods to chart the recovery process have seen a similar pattern. As a result, most in the field have crowned supporting cells the hair cell precursors—though Rubel, now in Seattle at the University of Washington, has not completely backed away from his initial interest in hyaline cells. "It's still an open question," he says, arguing that they, too, may be precursors to hair cells.

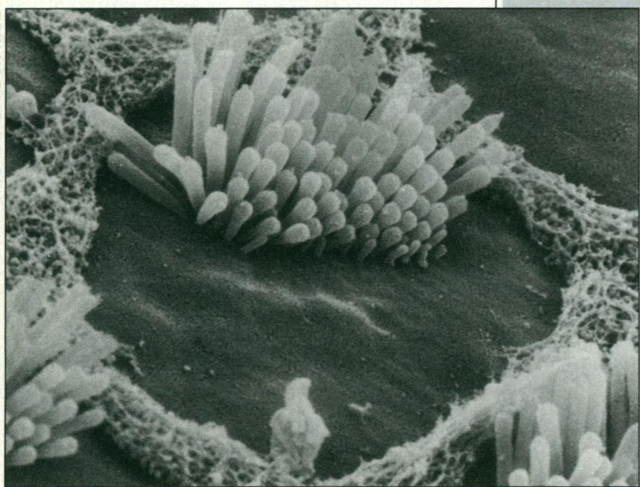
But researchers who do accept that supporting cells are the hair cell parents are already moving on to a new question: What chemical signals prompt the supporting cells to break out of their dormant state and begin proliferating? "It could be a single signal or a brew of signals," says Rubel. Researchers are also asking what events trigger such chemical cues. Must the hair cells be completely killed, or just damaged to some threshold level, before the signals for regeneration kick in? The answers to these questions are likely to be years down the road, say most in the field. In this area, "there's a lot of theory and no evidence for anything," Ryals told *Science*.

The biggest question, of course, is the extent to which the findings about regeneration apply to humans. So far, no one has found evidence for mammalian regeneration, and some believe the human ear is too complex ever to exhibit such behavior. Still, researchers are starting to work on mammals, and some intriguing clues are popping up. Graduate student Matt Kelley and Corwin, for example, have been investigating the effect on hair cells of retinoic acid, a chemical increasingly implicated in differentiation throughout the developing embryo (*Science*, 19 October 1990, p. 372). They use a method developed by the University of Wisconsin, Madison's Hanna Sobokowicz to maintain embryonic mice cochlea in culture. When the cochleas were treated with retinoic acid, they developed more than the three or four rows of hair cells typical for a mammalian ear, Kelley and Corwin reported at a meeting earlier this year. This is not regeneration, they emphasize, but the differentiation of precursor cells into hair cells has increased, suggesting that this process is regulated by chemicals in the cell's environment.

Even if mammals can regenerate hair cells, that might not be enough for recovery of hearing. Cotanche points out that hearing loss often involves additional damage to structures around the hair cells that would also have to be repaired. And any new hair cells would have to develop functional connections to the brain—an issue that Ryals, who along with Cotanche was among the first to look at effects of acoustic overstimulation on birds, is now investigating. Despite such caveats, the early work has been encouraging. There has been research on birds with either drug-induced or noise-induced hearing damage, in which they seem to recover auditory function as hair cells regenerate; other studies indicate that new hair cells do indeed transmit information to the brain.

So, are the dreams of these researchers really so far-fetched? Given the lack of evidence that mammals can regenerate hair cells after birth, let alone that doctors could trick the adult human body into doing so, hair cell researchers are always quick to caution that therapeutic success—if any—remains decades down the road. Still, for the moment, this research appears to be the only avenue to a cure for many people afflicted with hearing loss due to damaged hair cells. Despite remarkable advances, hearing aids can only do so much. Says Rubel, "We're the only game in town. If you can't regenerate hair cells, there's little chance you will ever truly restore hearing for the seriously impaired or deaf." Slowly, the odds for that monumental task may be improving.

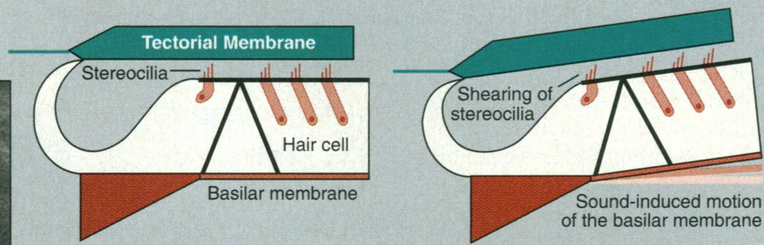
–**John Travis**



D. COTANCHE AND D. PICARD

Organ pipes. A higher powered electron micrograph of a single hair cell from the chick.

Eerie Sensations



Inner sanctum. Deep within the inner ear, thousands of hair cells, named for the 100 or so thin projections—called stereocilia—that extend from the top of each cell, line the helical Organ of Corti. In human beings, hair cells are divided into an inner row and three or four outer rows, all of them resting on an acellular sheet called the basilar membrane. Making contact with the tips of the stereocilia of the outer rows is an acellular mass, the tectorial membrane, which lies like a flap over the hair cells *(left)*. As sound waves make their way into the inner ear, their energy moves the membranes. This shearing action shifts the stereocilia *(right)*, triggering the hair cells to produce electrical impulses that are conveyed to the brain and interpreted as sound. Source: H. Davis/*Laryngoscope*; adapted by D. Cotanche.