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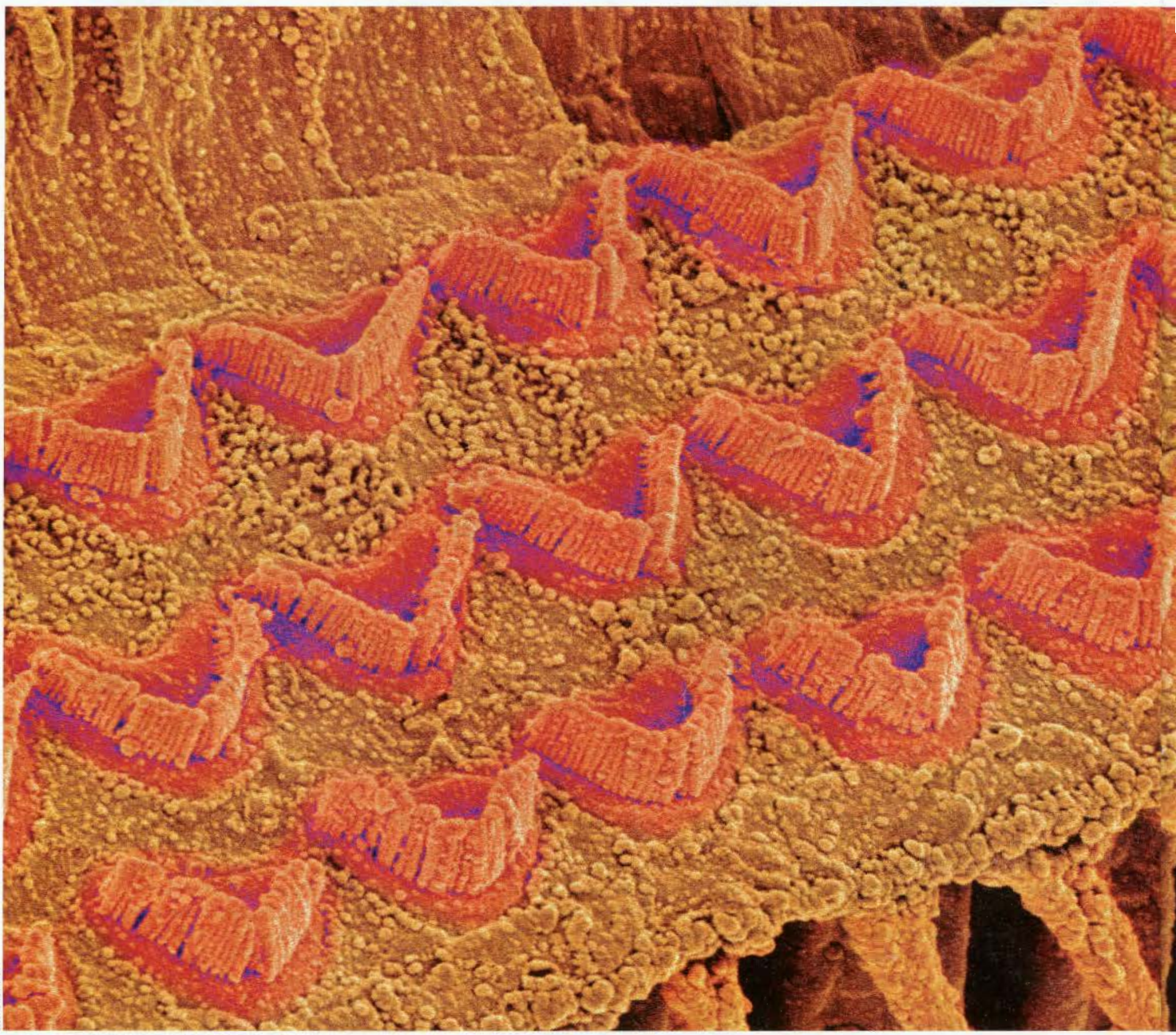
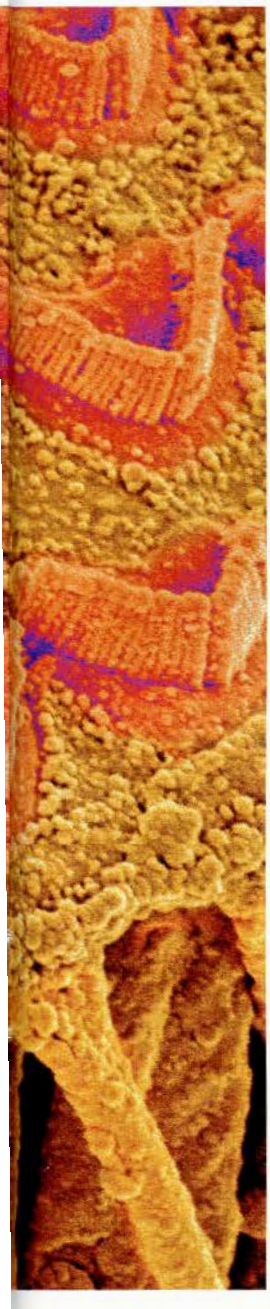


SOUHRI NISHINAGA

hear tomorrow

if we could grow new ones? **Michael Tennesen** investigates



Those bundles of microscopic hairs in your inner ear are trying to tell you something

WHAT'S that you say? Hearing problems are more common these days? Perhaps you've noticed that your mother asks you to speak up more often. Or that you have to crank up the TV louder than before, or find it harder to follow conversations in noisy bars.

According to the World Health Organization, some 278 million people worldwide have moderate to profound hearing loss in both ears. The condition afflicts an estimated one-third of people older than 60 and half of those over 85. The vast majority of severe cases are caused by damage to the inner ear or to the nerves between the ear and the brain. "It is the most prevalent sensory deficit in the population," says Yehoash Raphael, a specialist in the neurobiology of hearing at the University of Michigan, Ann Arbor.

The leading cause of profound hearing loss is injury to tiny structures in the auditory portion of the inner ear called hair cells. These convert acoustic waves in the inner-ear fluid into electrical signals that are then relayed to the brain. Once they are damaged by ageing, loud noise, disease or medication, these exquisitely sensitive cells do not recover or grow back. Not in humans, anyway. If you were a bird, it would be a different story: they would regrow naturally in about three weeks. In fact, a host of other animals have the ability to regenerate hair cells, but we mammals just don't.

Or do we? Somewhere down the evolutionary line mammals lost the ability to regain their hearing, but new research is showing that the regeneration mechanism might still be there, and it might just be possible to reawaken it. Now the race is on to exploit this and develop new types of therapy. Although much still needs to be worked out, hair cell regeneration has passed some crucial tests and could become a viable option some years down the road. No one is talking about a "cure" for deafness yet, but the approach could conceivably restore hearing and at least complement other interventions such as cochlear implants.

The idea goes back to the 1980s, when biologists discovered that birds, bony fish and some amphibians grow new hair cells throughout their lives. In 1988, Jeff Corwin and Doug Cotanche, then at the University of Hawaii in Honolulu, published a paper in *Science* showing that chickens could regenerate auditory hair cells after being deafened. Around the same time, Ed Rubel

278m

Number of people worldwide with moderate to profound hearing loss

of the University of Washington in Seattle demonstrated similar results in other birds. "Virtually all vertebrates except for mammals regenerate hair cells," says Rubel.

So why can't we? Nobody knows for sure, but Rubel thinks our early mammalian ancestors may have exchanged the ability to regenerate hair cells for the capacity to hear the higher-frequency pitches they needed to find prey and avoid predators; as sensory cells become more specialised they may lose the ability to divide and morph into new cells. Other researchers think the ability may have disappeared when mammals started living longer: since advanced age brings a greater risk of cancer, nature may have switched off some types of cell regeneration to ward ▶

off tumour growth. Whatever the reason, researchers reckoned that if other animals can regenerate hair cells, then mammals might retain that capacity too.

First they had to find out how new hair cells were produced. In humans and other mammals, hair cells are found in a fluid-filled spiral structure called the cochlea, and surrounding them are numerous supporting cells (see Diagram, right). Rubel's experiments in the 1980s showed that when a hair cell is destroyed in a bird, a nearby supporting cell receives a signal to divide, creating one new hair cell and one new supporting cell to take its place. In the early 1990s, Raphael reasoned that it was a specific gene that was issuing the orders, but which one?

Divide and rule

Working with rodent ears over the next few years, Raphael's team singled out a gene called *Atoh1* as a likely candidate. This was one of many genes important in determining whether a cell in the inner ear grew up to be a hair cell or a supporting cell, and it seemed to be on the side of the hair cells.

That's exactly what the researchers found in their tests. In 2003, they injected the gene into the inner ears of guinea pigs. Two months later, they discovered what looked like new hair cells growing just outside the auditory portion of the inner ear. They also noticed that auditory nerve fibres were extending towards the cells. This was exciting: it suggested that regenerated hair cells might automatically integrate into the auditory system and be able to send signals to the brain.

Raphael and his collaborators repeated the experiment in 2005 with deafened guinea pigs and showed that cell regeneration could occur in the appropriate area of the ear (*Nature Medicine*, vol 11, p 271). They also recorded the electrical activity in the auditory brainstem of the animals and concluded that some hearing had been restored.

The results were not without their problems, however. For a start, in many cases the new cells looked like hybrids rather than pure hair cells or supporting cells; some had hair bundles, or stereocilia, but grew in places usually reserved for supporting cells. Also the genes were delivered using virus particles derived from the common cold, which, although they worked well in lab animals, might prove less successful in the outside world; most humans and animals have developed immunity to pathogens, and this can cause trouble if you introduce a virus. Raphael is now testing molecules that may be able to bind to receptors on the supporting cells and induce regeneration without the viral delivery.

More crucially, the researchers need to find out the quality of hearing that can be regained. Raphael suspects that in his tests the animals' restored hearing was rather distorted compared to normal. If they were human, he says, they might even have preferred deafness. "Until scientists develop ways to determine the functional outcome of the procedure on mice and guinea pigs, we won't be trying this on humans," he says. In addition to measuring electrical activity in the brainstem, they might perform behavioural tests or measure acoustic signals in the ear canal, in the way clinicians test the hearing of infants.

To study the supporting cells more closely, another team, led by Neil Segil and Andy Groves at the House Ear Institute in Los Angeles, has tried a slightly different approach. The researchers knew from previous work that the gene *p27Kip1* was important for keeping supporting cells from dividing, so they decided to culture the cells in the lab. That way they could isolate the genetic pathways that control how they divide.

12m

Number of Americans with tinnitus, or persistent ringing in the ears

When they did this using supporting cells from the inner ear of a newborn mouse, something surprising happened. About half of the cells switched off *p27Kip1* all by themselves and went through natural division, producing supporting cells and hair cells (*Nature*, vol 441, p 984). It was the first time this had been shown in mammals. "What we wanted to do was get the supporting cells to divide," says Groves. "The fact that we got hair cells out of this was gravy."

100k

Estimated number of cochlear implant users worldwide

They tried the same thing with supporting cells from mice that were 2 weeks old, and the results were not nearly as good. The cells didn't switch off *p27Kip1*, and only about 2 per cent divided. This suggests that some biochemical process occurs after birth to block this ability permanently. When they knocked out *p27Kip1* and looked at the cells from 2-week-old mice, they found that 11 per cent of them divided. This suggests that other blockers of cell division, along with *p27Kip1*, switch on as an animal gets older, making the task even harder.

Nevertheless, Segil and Groves reckon they have proved that mammalian cells do indeed have the latent capacity to regenerate hair cells. What's more, they feel that researchers now possess the tools and methods to tease out the suite of genetic signals in the mammalian ear that suppress this ability. "We can begin to pick apart the pathways that lead to regeneration," says Segil.

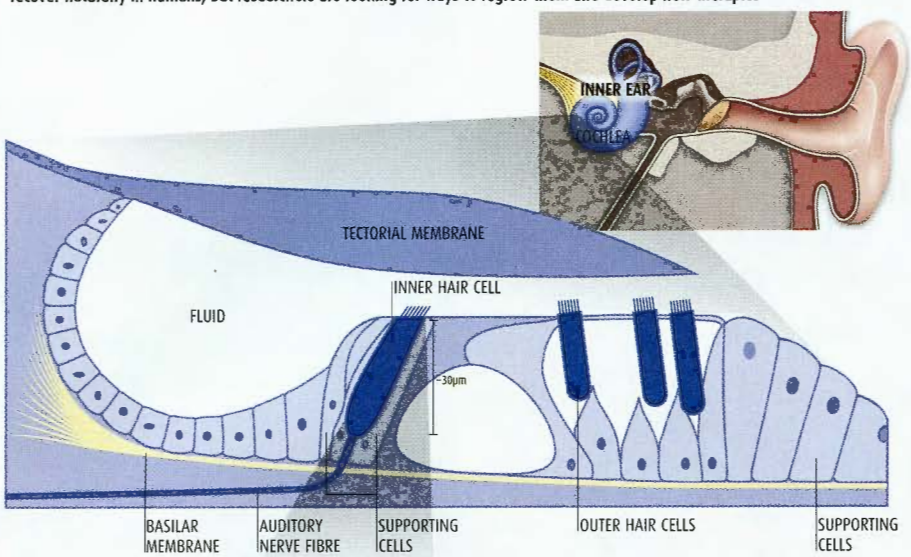
Of course, experiments in a Petri dish are a long way from restoring human hearing, but learning the fundamental biology is the first order of business. "Biological problems take longer to solve than you think. Tech problems take less time than you think," says Groves. "If we can uncover the molecular pathways, we can turn this over to the drug companies to identify pharmaceuticals that could manipulate the process."

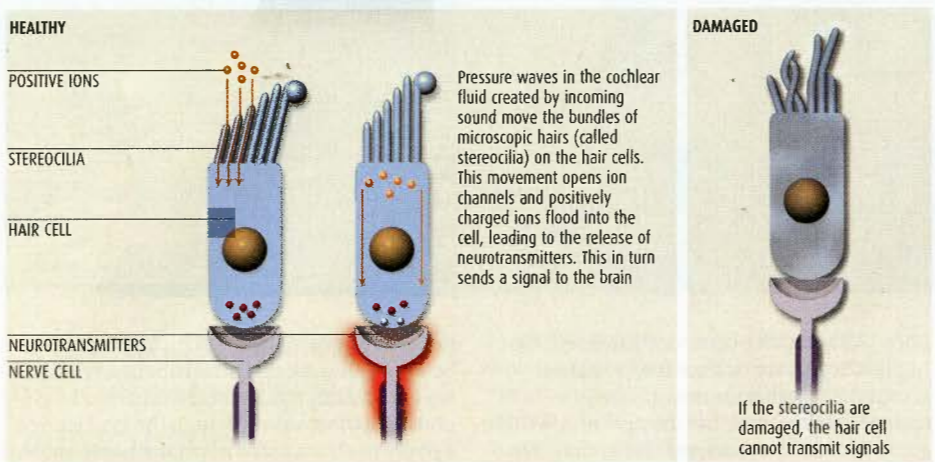
A third team has tried yet a different tactic. Instead of targeting the supporting cells, Zheng-Yi Chen of Harvard Medical School and the Massachusetts General Hospital in Boston has been trying to make hair cells themselves divide. He has done this by turning off *retinoblastoma*, or *RB*, a gene that suppresses tumours and also seems to play a role in how cells mature into their final forms. "When *RB* is on, cells cannot divide and grow," says Chen. This may be great news for combating cancer, but not for restoring hearing.

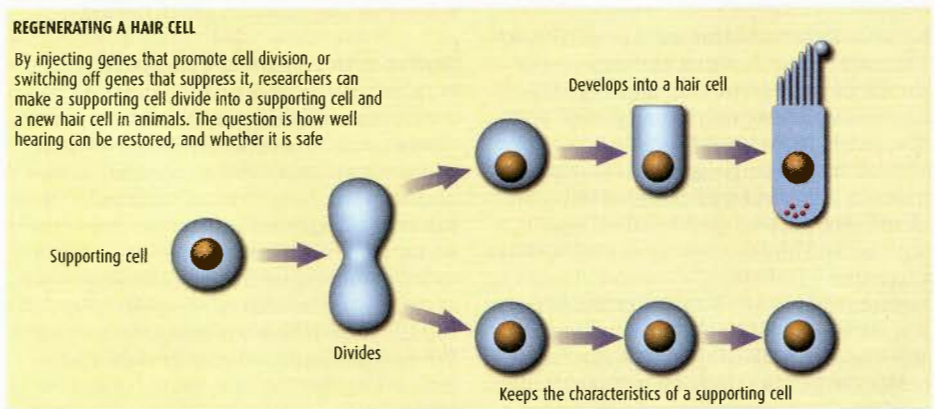
When Chen and his colleagues knocked *RB*

RESTORING HEARING

The leading cause of deafness is damage to the sensitive hair cells of the inner ear, from noise exposure or ageing. Hair cells do not recover naturally in humans, but researchers are looking for ways to regrow them and develop new therapies







out of mouse embryos, they found that mature hair cells were able to cycle and produce new and functioning hair cells (*Proceedings of the National Academy of Sciences*, vol 103, p 7345). Unfortunately this effect was only temporary: though the cells grew, they did not mature properly and within three months they had died, leaving the mice with no hearing. That means *RB* is probably needed for auditory hair cells to mature.

Turn it on

The challenge now is to extend the life of those hair cells – crucial for any prospective therapy. Chen thinks he might be able to do this by switching *RB* off for only a couple of weeks, and then turning it back on. One way to do this might be to inject a special sequence of RNA that blocks the gene but degrades over time. Alternatively, the researchers might make use of the fact that vestibular hair cells from the balance portion of the inner ear seem to survive without *RB*; this could yield further clues about which signals are needed. "Once hair cells regenerate, they can stay functional for life," says Chen.

When might all this lead to a working therapy for profound hearing loss? "Decades sounds dispiriting, but I think we are talking double figures," Groves says. Raphael agrees. "It will take some serendipity, some luck," he says. "Hopefully there will be many people working along with us, because it is not something we can or want to do ourselves."

Other researchers are more optimistic. Chen believes it may be possible to achieve therapeutic hair cell regeneration in humans – with some amount of hearing restored, though nobody can say how much – in 10 years. "The whole field is very exciting right now," he says. "If we can identify the molecules that are responsible in the human ear and avoid side effects, we will be on the way."

Whatever the timetable, we now know it is possible for hair cells to regrow, and this opens up the amazing possibility that people might one day be able to regain hearing that can help them in daily life. As Rubel says: "It's no longer a question of if, but when." ●

Michael Tennesen is a science writer based in Lomita, California