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BY SALLY POBOJEWSKI • PHOTOS BY LIN JONES

"What did you say?"

I come from a long line of people whose favorite question was: "What did you say?"

My great-grandmother couldn't hear a word we said, unless we spoke directly and loudly into the trumpet horn she carried around with her. My grandmother's contributions to family conversation could strike us as hilarious, because she often had no idea what we were talking about. My father, now in his 70s, has hearing aids but says they make his ears itch, so he doesn't always wear them.

And then there's me. I'm the middle-aged woman who has to hold the TV remote so I can control the volume. The one who smiles and nods a lot at parties, because I can't understand what anyone is saying. The one whose audiologist says of my hearing test results: "It's not bad enough for hearing aids yet, but you'll be back."

I have age-related hearing loss, which doctors call presbycusis, and I have lots of company. According to the National Institutes of Health, about one-third of Americans over age 60 have lost enough of their hearing to affect their ability to understand conversational speech. The older you get, the more likely you are to have trouble hearing. If you make it past 80, your chances of experiencing significant hearing loss are more than 50 percent.

For an elderly person with hearing loss, communicating can be awkward and embarrassing. After asking someone to repeat something for the third time, frustration escalates and it's just easier to forget about the entire conversation. Talking on the telephone — especially a cell phone — is difficult. Dinner in a noisy restaurant is more an ordeal than a pleasure. The inability to hear can make elderly people avoid social interaction and new experiences, leading them into isolation at a stage of life when activity and social networks are more important than ever.

Hearing aids can help, but many people have trouble adjusting or find them uncomfortable. The best ones are expensive and not covered by most insurance plans.

Surveys conducted by the National Center for Health Statistics show that the number of Americans with hearing loss has doubled since the 1970s. One big reason for this increase is that we are living so much longer than we used to. Every part of the body deteriorates with age and the ear is no exception. But what intrigues scientists is why some people are affected so much more, and so much earlier in life, than others.

"Hearing loss in the elderly has a whole variety of different causes. Nearly everyone has some hearing loss, but it's not uniform," says Glenn E. Green, M.D., assistant professor of otolaryngology in the U-M Medical School. "Some people have normal hearing, despite being elderly, and some people are profoundly deaf with no clear-cut cause."

Like most medical disorders and diseases common in industrialized countries today, age-related hearing loss is caused, scientists believe, by complex interactions between our genes and environment. This makes it difficult to sort out how much of hearing loss is genetic and how much is caused by the way we live.

Take me, for example. Given my family history, I've obviously inherited some mutated genes that predispose me to progressive hearing loss. But how much of it is the result of blasting my ears at all those rock concerts back in the '60s? And what about all those antibiotics — some of which are known to cause hearing loss — I received as a child?

Glenn Green

"Everyone has a different exposure to noise, drugs, infections, industrial solvents, smoking, diabetes and vascular diseases — they all can cause hearing loss," says Jochen Schacht, Ph.D., professor of otolaryngology in the Medical School and director of the U-M Kresge Hearing Research Institute. "In a human, it's just about impossible to sort this out."

Part of what makes it so difficult to study the genetics of human deafness is that the inner ear is incredibly complicated. Scientists estimate there could be between 150 to 200 genes that, when mutated, can directly cause hearing loss in humans. Factor in the impact of an unknown number of modifier genes that influence the activity of hearing-related genes, and the picture gets even murkier.

Scientists know of at least 4,519 human genes that are active, or expressed, in the human inner ear, according to Green. Since the most recent estimate of the number of genes in the human genome is nearly 24,000, it means that more than 18 percent of our genes are involved in some way in our ability to hear.

"The auditory system is the most genetically complex organ in the human body," Green says.

Turning sound waves into electrical impulses that can be "heard" by the brain requires specialized cells found nowhere else in the body. One of the most intriguing is called an auditory hair cell. Human beings are born with about 20,000 of these cells lining the inside of a snail-shaped bony organ, located deep in the inner ear, called the cochlea (COKE-lee-ah).

When sound waves hit the eardrum, vibrations are transferred to fluid inside the cochlea. Moving fluid triggers the movement of tiny projections called stereocilia on hair cells. When stereocilia move, hair cells respond by generating electrical impulses, which are carried by the auditory nerve to a part of the ➤

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brain called the cochlear nucleus, and eventually relayed to the auditory cortex. During this process, the signals are interpreted in a way that allows us to "hear" them as sound.

Defects at any step in the process can interfere with hearing, but hair cells seem to be especially vulnerable to damage and sensitive to the effects of genetic mutations. And unlike most types of human cells, auditory hair cells cannot regenerate.

Yehoash Raphael, Ph.D., associate professor of otolaryngology in the U-M Medical School, has used gene therapy to stimulate the growth of new hair cells in guinea pigs. But until this new treatment is shown to be safe and effective for use in people, the hair cells we are born with are all the hair cells we'll ever have. When they're gone, they're gone forever.

Jochen Schacht

From Mouse to Human

Much of what scientists know about the function of genes associated with human deafness, they've learned from mice. So far, scientists have identified 58 genes with mutations that directly cause hearing loss in humans. Mutations in most of these genes are also known to cause hearing loss in mice.

The easiest way to study the effects of mutations on human inner ear cells would be to take a biopsy, grow the cells in a culture dish and see what happens. Unfortunately, Mother Nature has a lot invested in the inner ear and has gone to extraordinary lengths to protect it. Completely surrounded by bone, it's small and difficult to access surgically. It's impossible to take a cell sample from a living person without destroying their hearing, and cell samples from autopsies don't grow well in culture.

The good news is that nearly all genes in mice and people are closely related, and the structure and function of the inner ear is similar in both species. So, a genetic mutation that causes deafness in mice is very likely to also cause deafness in humans.

"Working with mice allows us to see the earliest physical effects associated with defective genes," says David Kohrman, Ph.D., associate professor of otolaryngology and of human genetics in the U-M Medical School. "We can study mice with a specific mutation and control the animal's environment, so we can be certain that the effects we see in the mouse are caused by that mutation."

Kohrman works with strains of experimental mice that are made-to-order for genetic research. Some have "natural" or spontaneous mutations that affect their ability to hear, in addition to causing problems with balance. Kohrman also can knock-out — or remove — genes, add new ones, turn genes on and off, and study the effects on cells and tissue in the inner ear.

Kohrman is one of 10 U-M scientists who are part of a new research study funded with a $6.9 million grant from the National Institute on Aging. Directed by Jochen Schacht, three teams of U-M scientists — including geneticists, aging experts and biologists who specialize in the workings of the inner ear — will try to unravel the complex genetic and environmental factors responsible for hearing loss associated with aging.

"We've had a lot of success identifying obvious recessive mutations in genes that cause congenital hearing loss," Kohrman says, "but in this study the research team will be looking for subtle, later-onset effects. It's a way to get at genes involved in age-related hearing loss, which is a genetically messy problem."

David Kohrman

Margaret Lomax

Living in the 21st century means our hair cells are assaulted every day with much louder and more sustained noise than anything our ancestors had to deal with. Many scientists believe this could be one reason for the increased incidence of age-related hearing loss.

Stressed-Out Cells

Many scientists believe that diseases and degenerative changes we associate with aging are the result of stress-related damage to cells, proteins or DNA.

We think of stress caused by an angry boss or a screaming toddler, but cells have their own set of stressors to deal with. To auditory hair cells in the inner ear, the most damaging type of stress comes in the form of noise. Close exposure to a very loud noise — an explosion, gunshot or a jet engine — can literally flatten the stereocilia on hair cells or rupture the cells themselves, causing immediate hearing loss which can be permanent. But prolonged exposure to noise over 90 decibels — like city traffic, lawnmowers and loud music — can be just as damaging.

The inner ear can repair some damage to auditory hair cells, as long as the damage isn't too severe. But over a lifetime, the cumulative effects of noise can kill hair cells and cause permanent hearing loss. Living in the 21st century means our hair cells are assaulted every day with much louder and more sustained noise than anything our ancestors had to deal with. Many scientists believe this could be one reason for the increased incidence of age-related hearing loss.

Another type of stress that may be a factor in age-related hearing loss is something scientists call oxidant stress. In this case, cell damage comes from oxygen radicals — atoms of oxygen with an extra unpaired electron. Oxygen radicals are a toxic by-product of the chemical reactions cells use to generate energy. They also are found in cells exposed to alcohol, drugs or pollutants.

Atoms with extra electrons are like hyperactive children. They race around the cell, bashing into things, searching for a protein or molecule with an extra electron they can bind to. In the process, they do a lot of damage to cell membranes, DNA and other large molecules.

According to Schacht, scientists have found damage from oxidant stress in the inner ears of animals, but don't know exactly how it's related to the loss of hair cells and deafness commonly seen in older animals. Determining the nature of that relationship is one of the goals of the NIH-funded research project.

"We know there is oxidant stress in the ear and we know it begins about the same time animals are losing their ➤

By mapping the genetic variance in the mice and comparing their genes to those of mice that spent their lives in a quiet environment, Richard Miller hopes to find out whether the genes that control loss of hair cells after noise exposure are the same as genes that regulate loss of hair cells with aging.

hearing," Schacht says. "But we don't know whether oxidant stress is what causes the hair cells to die."

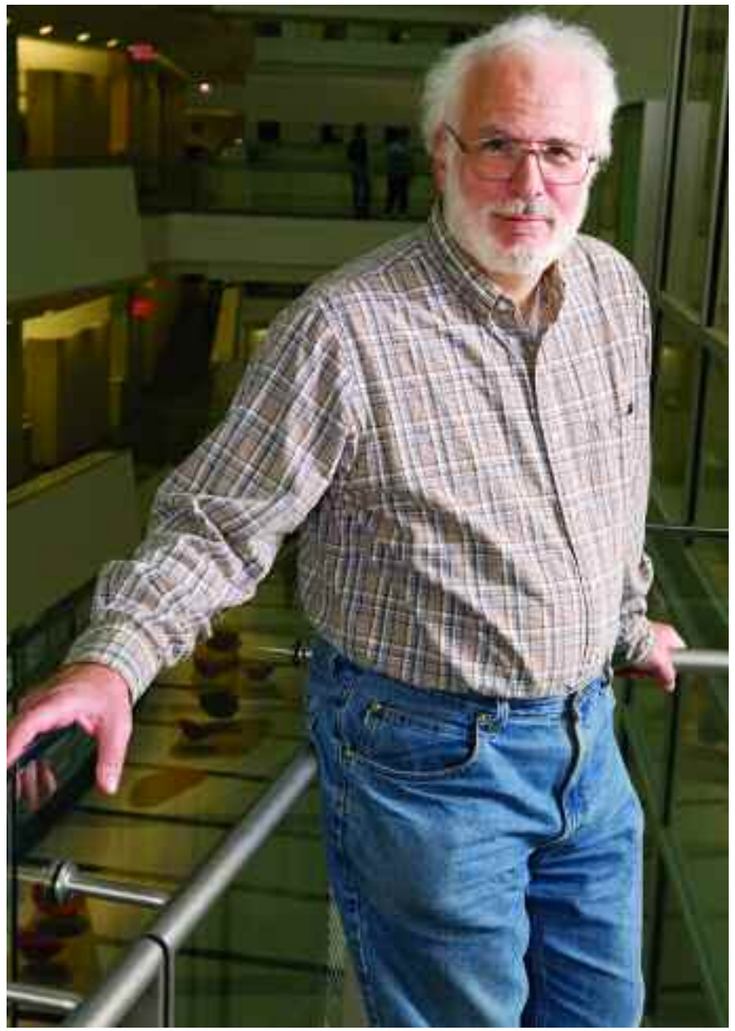
To find out, some of the mice in Schacht's research study will be fed a diet high in antioxidants, like glutathione and Vitamin C, which bind to free radicals and prevent them from rampaging through vulnerable cells. As the mice age, U-M scientists will analyze cells and tissue to see whether mice fed high doses of antioxidants have less stress-related damage to auditory hair cells than animals that don't get antioxidants. The mice will be protected from loud noises, so "all the changes we observe will be due to the aging process and will not be noise-related," Schacht says.

Margaret Lomax, research professor in the Kresge Hearing Research Institute, will direct another part of the NIH study. Her focus is on heat shock proteins — which cells use to protect themselves from stress — and how they may be related to hearing loss.

"Cells under stress shut down their normal production of protein to generate a flood of heat shock proteins that bind to regular proteins, protect them during the stressful period, and help them recover afterwards," Lomax explains.

Scientists know that the biochemical pathway triggering the production of heat shock proteins becomes less active in animals as they age, and they know that heat shock proteins are found in inner ear cells. "We want to determine whether the decrease in this protective pathway contributes to age-related hearing loss," Lomax says.

The third part of the NIH study is directed by Richard A. Miller, M.D., Ph.D., professor of pathology in the Medical School and research scientist at the VA Ann Arbor Healthcare System. Miller and his research team will try to identify the genes that control hearing loss late in life. To do this, they are creating a new strain of research mice by interbreeding four different mouse strains that have normal hearing at birth, but start to lose it in early middle age. For a mouse, that's about 18 months old.



Richard Miller

By the end of the five-year study, David T. Burke, Ph.D., a collaborator in the study and professor of human genetics in the Medical School, will have identified key DNA sequence data from an extended family of 600 mice, all related to each other as siblings. By the time the mice reach middle-age, Miller expects some will have perfect hearing, some will have an average amount of hearing loss, and some will be prematurely deaf.

"We'll take DNA from every mouse and figure out which genes it got from its mother and which genes it got from its father," Miller says. "Then we'll take the deaf mice and see whether there is a specific gene or loci [part of a chromosome] you have to have in order to lose hearing late in life."

To identify genes associated with noise-induced hearing loss, one group of four-way-cross mice will be exposed for two hours to high-intensity noise — "the kind of noise exposure you'd get if you were foolish enough to go to a rock concert without ear plugs," Miller says.

Based on previous research, U-M scientists expect some of the mice will recover part or all of their hearing, while others will have permanent damage. By mapping the genetic variance in the mice and comparing their genes to those of mice that spent their lives in a quiet environment, Miller hopes to find out whether the genes that control loss of hair cells after noise exposure are the same as genes that regulate loss of hair cells with aging.

If U-M scientists can pin down the specific genes involved in age- and noise-related hearing loss, it's possible that future gene therapies or cell-based therapies could be developed to treat some types of inherited age-related hearing loss.

There's also the prospect of genetic testing for genes associated with hearing loss. Knowing you carry mutations that make you especially vulnerable to noise-induced hearing loss, for example, might make you think twice about pursuing a career as a construction worker, a jet pilot or a rock musician.

But don't throw away the hearing aids just yet, because as Jochen Schacht emphasizes, the benefits of all this research are unknown and many years in the future.

"Prevention is better than trying to repair damage after the fact," he says. "If I can do something now to prevent or slow down hearing loss, that is absolutely the best strategy."

It's too late for me to prevent damage to my own auditory hair cells, so I'm saving up for hearing aids and doing everything I can to preserve the hair cells I have left. I live in the country where my ears enjoy long periods of silence. I'm compulsive about turning off televisions, radios and CD players. No more loud concerts or sporting events without earplugs for me. And don't even think about giving me an iPod.

Because some day, when I dance at my grandson's wedding, I want to be able to hear the music.

Sally Pobojewski, who lives in quiet Chelsea, Michigan, is a senior science writer in the U-M Medical School and serves as science editor of Medicine at Michigan.

On the Web:

Studying inherited deafness in humans is far more difficult than with mice. U-M researchers Marci Lesperance and Glenn Green explain why:

www.medicineatmichigan.org/magazine

For more information on age-related hearing loss:

http://nihseniorhealth.gov/hearingloss/faq/faqlist.html
www.nidcd.nih.gov/health/hearing/older
www.niapublications.org/agepages/hearing.asp

For more information on noise-induced hearing loss:

www.nidcd.nih.gov/health/hearing/noise.asp