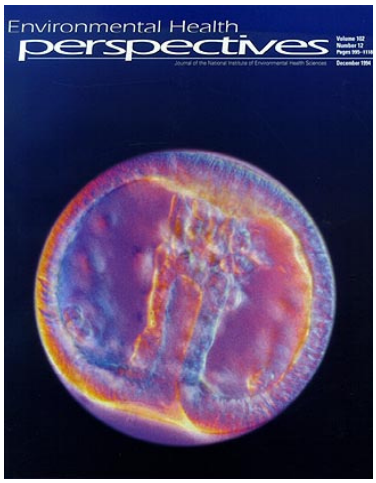
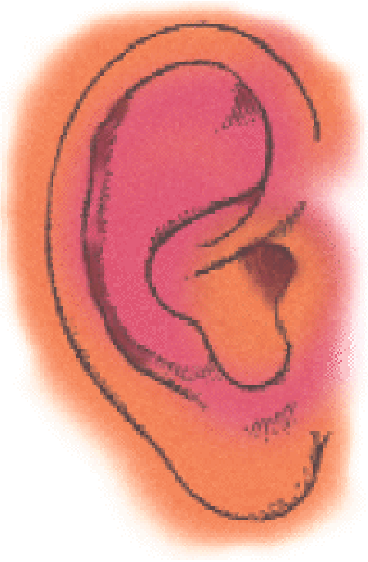
"Environmental Impact on Hearing: Is Anyone Listening?"*Environmental Health Perspectives* Volume 102, Number 12, December 1994. cited on 31 Aug 2009 http://www.ehponline.org/docs/1994/102-11/focus2.html

Environmental Health Perspectives **Volume 102, Number 12, December 1994**

http://www.ehponline.org/docs/1994/102-11/focus2.html





On The Cover: Studies of

Environmental Impact on Hearing: Is Anyone Listening?

- PubMed:Related Articles
- PubMed:Citation
- Cited in PMC
- Purchase This Issue

A look at the most recent statistics on deafness and hearing disorders in the United States reveals a startling figure: more than 28

million Americans have hearing loss, and roughly 80% of those affected have irreversible and permanent hearing damage. In addition, some six million people also suffer from tinnitus (ringing in the ears) to the extent of requiring medical attention. Some incidence figures demonstrating a progressive increase in hearing loss with age show that an estimated 15 of every 1,000 persons under age 18 have some type of hearing impairment, as do 415 of every 1,000 Americans over age 75. It seems that a tremendous audience is within range of the sounds of silence.

Apart from the aging process, causes of auditory dysfunction can be grouped under several categories: genetic errors; congenital malformation; disease states and infections; mechanical injury; auditory overstimulation; iatrogenic exposures (to certain drugs); and exposure to certain industrial chemicals and environmental pollutants. Significant progress has been made over the last decade in understanding how hearing loss may be caused by environmental factors such as noise, drugs, and other chemical toxins.

Hearing loss remains one of the most prevalent occupational diseases in the United States, as it is in most other industrialized nations. According to the Occupational Safety and Health Administration, at least one million U.S. workers in manufacturing are estimated to have sustained job-related hearing impairment, half of whom have moderate to severe hearing impairment.

"The statistics are an objective measure of the problem. But the impact of hearing loss on the individual far exceeds what we can put down in numbers," says Derek Dunn, National Institute of Occupational Safety and Health deputy director of biomedical and behavioral science. He points out that one of the major consequences of hearing loss is social isolation from friends and family as a result of the reduced ability to understand speech. "As Helen Keller once remarked, losing her sight cut her off from things. But losing her hearing cut her off from people," said Dunn.

Environmental Noise

The problem of loud and annoying environmental sound is not new. In ancient Rome, chariot driving in the evenings was forbidden by law because it created too much of a racket. (Today, visitors to the heavily trafficked Eternal City might agree to a similar ban for automobiles.) And in Elizabethan England, a man had to refrain from beating his wife at night so as not to disturb the neighbors!

To the general public, noise is merely unwanted sound, an annoyance. But call it acoustical overexposure, acoustic overstimulation, or excessive noise, sounds can be sufficiently strong, sufficiently long lasting, and involve certain frequencies so that they cause hearing loss and damage to the inner ear of humans and other species.

According to NIH estimates, more than 20 million Americans are exposed on a regular basis to industrial or recreational noise that could result in hearing loss. Such exposure is at least partially responsible for approximately 10 of the 28 million cases of hearing loss considered completely preventable.

Occupational exposure is the most common cause of noise-induced hearing loss (NIHL). It threatens the hearing of firefighters, military personnel, police officers, construction and factory workers, musicians, farmers, and truck drivers, among others. Recreational vehicles, live or recorded high-volume music, airplanes, lawn-care equipment, woodworking tools, chain saws, and some household appliances are potential sources of nonoccupational noise hazards.

OSHA estimates that about 17% of production workers or 1.6 million people have at least mild hearing loss resulting from occupational noise exposure. In addition, one million or 11% have moderate hearing impairment and nearly half a million or 5% have moderate to severe hearing loss.

Unfortunately, the generally accepted fact that NIHL is preventable in all but certain cases of accidental exposure seems to fall on deaf ears. "Even today, with increased health promotion and disease prevention, people still tend to view noise-induced hearing loss as a necessary element of a noisy occupation, although it is not inevitable," says Susan Cooper Megerson, president of the National Hearing Conservation Association. "Unfortunately, ears do not bleed [to indicate an injury] and the onset of hearing loss is insidious," she adds.

Sound Waves

Sounds may be characterized in terms of their strength (amplitude) or bandwidth (frequency expressed in cycles per second, or Hertz.) The most widely used measure of amplitude, measured by a sound-level meter, is decibels (dB). Typical conversational speech is between 65 and 70 dB. The range of frequencies audible to humans extends from about 20 Hertz (Hz), below the lowest notes on a piano, to at least 16,000 or 20,000 Hz, well above a piccolo's highest notes.

Most environmental noise includes a wide band of frequencies and, by convention, is measured through the "A" filter of a sound-level meter. These are designated in dBA units. The A-weight discriminates against low-frequency and very high-frequency sound. In effect, it "weights" the physical sound spectrum to account for the frequency response of the human ear. Thus, it serves as a reliable and readily measured estimate of loudness. To what extent, if any, sounds outside the frequency range covered by dBA measurements, including ultrasonic vibration, will damage hearing remains unclear.

Sound exposures that are potentially hazardous to hearing are usually defined in terms of sound level, frequency bandwidths, and duration. It is generally agreed that sound levels below 75 dBA will not engender permanent hearing loss, even at 4,000 Hz. At higher levels, the amount of hearing loss is directly proportional to

Sound levels and human response

Common sounds	Noise level (dB)	Effect
Boom cars	145	Beyond threshold of pain (125 dB)
Shotgun firing	130	
Rock concert (varies)	110–140	
Thunderclap (near)	120	
Stereos (over 100 watts)	110–125	Regular exposure of more than 1 minute risk permanent hearing loss (over 10 dB)
Chain saw	110	No more than 15 minutes unprotected exposure recommended (90–100 dB)
Symphony orchestra	110	
Snowmobile	105	
Jet fly-over (1,000 ft)	103	
Garbage truck/cement mixer	100	
Farm tractor	98	Very annoying level at which hearing damage begins (8 hours)
Newspaper press	97	
Subway, motorcycle	90	
Lawnmower, food blender	85–90	Annoying, interferes with conversation
Diesel truck (40 mph)	84	
Average city traffic noise	80	
Garbage disposal	80	Intrusive, interferes with telephone use
Vacuum cleaner, hair dryer	70	
Inside a car (loud engine)	70	Comfortable (under 60 dB)
Normal conversation	50–65	
Refrigerator humming	40	
Whisper	30	Very quiet
Rustling leaves	20	
Normal breathing	10	Just audible

sound level for comparable durations. A noise level of 85 dBA for an 8-hour daily exposure is potentially damaging.

On-the-Job Noise

There are two categories of hearing injury: acoustic trauma and NIHL. Exposure to an intense, short-duration noise, such as a gunshot or explosion, that may result in immediate, severe, and permanent hearing loss is classified as acoustic trauma. Acoustic trauma can damage virtually all of the structures of the inner ear, particularly the organ of Corti, which may be torn apart. Moderate-intensity exposures such as industrial noise initially cause temporary hearing loss, or temporary threshold shift. Testing within 18-24 hours after exposure reveals thresholds have returned to preexposure levels. Repeated exposures to this type of noise gradually cause permanent deterioration in auditory thresholds. Regardless of frequency content, permanent hearing loss usually begins at 4000 Hz, then spreads gradually to higher and lower frequencies. This type of injury is NIHL.

Most industrialized countries have implemented hearing conservation programs for their workers that limit daily exposure to A-weighted levels of 85-90 dB. The current OSHA noise standard in the United States is a maximum time-weighted exposure level of 90 dbA (equivalent to the sound of drilling in concrete or a power lawn mower). In 1972, NIOSH recommended an 85 dBA standard. In

1983, OSHA announced a hearing conservation amendment to its 1972 Noise Control Act. This amendment required hearing conservation programs for workplace exposures of 85 dBA or more, including worker assessments for hearing protection.

A 1990 NIH Consensus Panel on noise and hearing loss stated that the average American not exposed to industrial noise may live in an average daily exposure environment of about 73-76 dB, which is close to levels that can induce hearing loss. Many adults and schoolchildren may be getting higher-than-average exposures through leisure activities such as personal cassette players, car stereos, or arcade games. The exact incidence of sensorineural hearing loss due to these recreational activities is unknown. Cases reported immediately after an acute noise exposure are unusual. Furthermore, it is unknown whether some sounds can lead to subclinical noise damage with a sensorineural hearing loss later in life.

The Inner Ear

Current knowledge of auditory function (and dysfunction) is by no means complete and emanates largely from discoveries of structural and biophysiological changes within the inner ear that are associated with noise and other ototoxic agents.

The cochlea is a target organ for many toxic agents, including noise. Damage may be temporary or permanent, but the end result--whatever the toxin--is often similar structural damage and functional loss.

In prospective animal studies, sound exposures can be carefully controlled, and the anatomic and physiologic correlates of NIHL can be precisely defined. Although species differences with respect to the effects of absolute sound exposure may exist, the basic mechanisms that lead to damage appear to be similar in mammalian ears.

Experimentally, several different temporary or permanent impairments to the auditory system have been demonstrated after excessive exposure to noise: direct mechanical destruction, metabolic exhaustion of cochlear cells, and changes in the cochlear vascular system. Most susceptible to acoustic damage is the hair-cell receptor.

"The hair cell is the front-end detector in the hearing system, the place where mechanical actions are converted to biological actions," says James Saunders of the University of Pennsylvania Department of Otolaryngology and Human Communication. "The primary effect of that mechanical action will be actual damage to the structure of the hairs. You can indeed break them, depolymerize their cytoskeleton, and can break the so-called tip links that act on the transduction process. You can also move them back and forth excessively and cause metabolic processes within the hair cell to work overtime, leading literally to hair-cell burn out."

James Saunders -Acoustic damage can result in hair-cell burnout, leading to hearing dysfunction. *Photo:University of Pennsylvania*

The possibly neurotoxic nature of the neurotransmitter may also figure as a third process in the chain of events leading to hearing loss. "There is mounting evidence that the neurotransmitter is a glutamatelike chemical," says EPA neurotoxocologist Raelynn Janssen. "Glutamate may chemically mediate sensory transmission between hair cells and neurons of the auditory nerve." Janssen points out that a notable property of glutamate is its selective neurotoxicity in the central nervous system when present in excessive amounts. "This excitotoxicity specifically affects neurons postsynaptic to glutamatergic terminals." Janssen's work shows that glutamate administered to newborn rats is toxic to the auditory system, producing a high-frequency hearing loss peripheral

in origin. "The primary peripheral target appears to be the spiral ganglion. Cochlear hair cells presynaptic to afferent fibers of the spiral ganglion are spared," says Janssen.

Raelynn Janssen -Neuro-transmitters like glutamate may figure in hearing loss. *Photo: NIEHS*

Lawrence Fechter, director of the toxicology department of Oklahoma University's College of Pharmacy and School of Medicine, says that studies on glutamate excitotoxicity have implications beyond auditory dysfunction. "I'm more and more convinced that what we're doing in the ear is very much like what is occurring in other parts of the nervous system. If you get excessive release of glutamate from presynaptic nerve endings, this can greatly elevate the level of calcium in the cells postsynaptic to it and produce a cascade of injurious effects. This 'extra-overstimulation,' if you will, or excitotoxic action, has been identified as one of the themes in neurotoxicity. People are talking about it in respect to learning, memory, Alzheimer's disease, and to other neurotoxic diseases." Recently, Janssen demonstrated the blocking of glutamate cochlear neurotoxicity in rats through the use of glutamate receptor antagonists kynurenic acid and MK-801. Fechter is now also experimenting with MK-801. He says trimethyltin, an ototoxic and neurotoxic heavy metal, seems to work through a glutamatergic mechanism. "We've demonstrated we can protect against trimethyltin ototoxicity with MK-801," says Fechter. "We're now trying to develop candidate drugs which may be effective in preventing or reversing ototoxicity. People have been working in piecemeal fashion, identifying one chemical agent after another which is ototoxic. What's just beginning to emerge is some sense of fundamental mechanisms contributing to hearing loss which would allow us to more effectively predict new ototoxic agents and may also give us the wherewithal to protect the inner ear from injury."

Ototoxic Drugs

"Sensation is a fundamental part of the interaction of an organism with its environment," says Kevin Crofton, a research scientist in the neurotoxicology division of EPA's Health Effects Research Laboratory. "A wide variety of environmental and pharmaceutical chemicals are known to alter the structure and function of sensory systems. In fact, alterations in sensory function are frequently reported as the first signs of chemical exposure in humans."

Kevin Crofton -A wide variety of environmental chemicals and phrmaceuticals may affect hearing. *Photo: NIEHS*

Scientific awareness of ototoxicity occurred late in the 19th century with the observation that certain drugs such as quinine and acetyl salicylic acid (aspirin) could cause temporary hearing loss or tinnitus. Today, several classes of ototoxic drugs are known, including aminoglycoside antibiotics, so-called loop diuretics, certain cancer chemotherapeutic agents, and salycilates.

Aminoglycoside antibiotics. Drug ototoxicity became a recognized problem in the 1940s with reports of permanent damage to the vestibular and cochlear organs in tuberculosis patients treated with streptomycin. The aminoglycosides are perhaps the best-known and most investigated of all ototoxic agents. These agents appear to cause a similar pattern of damage to the cochlea, with some, such as streptomycin, having greater selectivity for hair cells within the vestibular system, whereas neomycin and kanamycin affect the cochlea, and gentamycin and tobramycin affect both systems of the inner ear. In terms of cochlear damage, outer hair cells of the basal end of the organ of Corti are damaged first, accompanied by high-frequency loss. With further administration of these antibiotics, there is loss of both outer and inner hair cells that progress along the basilar membrane toward its apex, accompanied by hearing loss at lower frequencies. Outer hair cells are affected before inner hair cells, and

aminoglycosides accumulate in inner-ear fluid. They also accumulate in the kidneys, which is considered another target organ for the drugs. Nephrotoxicity leads to delayed aminoglycoside excretion, which further enhances ototoxicity.

Loop diuretics . Drugs such as furosemide and ethacrynic acid produce diuresis by blocking reabsorption of sodium and chloride within the proximal tubules of the kidneys. Rarely a cause of irreversible auditory sensitivity, diuretics do affect a wide range of frequencies when taken at high enough doses. These compounds appear to interfere with ion transport within the stria vascularis rather than by directly affecting hair cells. Kidney failure prolongs drug half-life, thus increasing the risk of ototoxicity.

Salycilates . Salycilates, such as aspirin, rarely cause permanent hearing loss, but can if given in sufficiently high doses over sufficient time. Salicylate ototoxicity is often described as mild to moderate (up to 40 dB sensitivity loss in humans) and is symmetric. It is reversible usually within 72 hours after cessation of the drug. Though the mechanism of salicylate action is not fully understood, some indications are that salicylates affect cochlear outer hair cells and vascular system.

Cisplatin . A number of anticancer drugs, such as *cis* -dichlordiammine platinum (II), or cisplatin, and vincristine, can cause temporary and permanent hearing loss. Cisplatin is used in chemotherapy of ovarian, lung, and testicular cancer. The hearing loss affects the high-frequency range; severity of hearing loss depends on peak blood plasma levels. The pattern of damage to the organ of Corti is similar in many respects to that of the aminoglycosides, with similar progression of hearing loss. Disturbances of epithelium within the stria vascularis are also seen.

Nontherapeutic Chemicals

No precise accounts exist as to the number of chemicals that disrupt sensory processes, including the auditory system. An estimated 44% of chemicals reported to be neurotoxic affect some aspect of sensory functioning. Crofton says the estimates of the percentage of all known chemicals with neurotoxic effects

range from 3% to 28%. "From these admittedly crude estimates, one can presume that 1.5 percent to 16 percent of all chemicals may be sensory toxicants," says Crofton.

Organic solvents. In a recent review of volatile organic solvents having proven or probable neurotoxicities, Thais Morata and NIOSH colleagues Derek Dunn and W. Karl Silber reported five that affect the auditory system: trichloroethylene, xylene, styrene, carbon disulfide, and toluene. In several recent literature reviews of their effects on human hearing, these solvents are cited as producing auditory system abnormalities including speech discrimination problems, increased latencies of brain stem auditory evoked potentials, and hearing loss.

Trichloroethylene . Since its introduction in Germany as a grease remover during World War I, this colorless, noncorrosive solvent has been used as a dry-cleaning agent, spot remover, and in rug-cleaning solutions. Trichloroethylene (TCE) is also used as a chemical intermediary in the production of paints, waxes, pesticides, and other products, including adhesives and lubricants. NIOSH estimates that 3.5 million workers are exposed at some time to trichloroethylene. Ototoxicity associated with TCE exposure has been described as a high-frequency hearing loss in both humans and rats. Recently, an atypical and persistent mid-frequency hearing loss in rats after inhalation exposure to TCE has been identified. Crofton says similar hearing loss from exposures to other volatile organic solvents such as styrene, toluene, and mixed xylenes has also been reported. In a study of 50 workers, TCE was associated with vestibular and auditory nerve impairment. Length of exposure was associated with increased likelihood of abnormal audiograms.

"I think the significance of finding the mid-frequency hearing loss is that we have to look for a new mechanism that explains the location of hair-cell loss in the cochlea," Crofton says. He points out that any attempt to define a mechanism of action for solvent-induced ototoxicity must take into account an anatomical and/or functional process that tracks a similar nonlinear distribution of damage along the basilar membrane.

Xylene and styrene. Xylene is found in various solvent mixtures, including paints, varnishes, and thinners. It is also used in histology. Styrene is widely used in the production of various plastics, synthetic rubber, resins, and insulating materials. Statistically significant increases in hearing threshold at high frequencies have been found in workers exposed to styrene. Seven of 18 workers in a plastics boat plant with chronic exposure to styrene showed distorted speech and/or poor performance on cortical response audiometry tests. Elevated auditory brainstem thresholds were found in rats after inhalation exposure to xylene or styrene, and loss of outer hair cells have been observed in rats exposed to styrene.

Carbon disulfide. Carbon disulfide has been a recognized occupational hazard since the discovery of cold vulcanization in 1843. It can cause both acute and chronic forms of poisoning. Its effects are nonspecific, requiring a diagnosis based on confirmation of exposure, signs or symptoms, and exclusion of other diseases. Today, carbon disulfide is used in the viscose rayon textile process and as a solvent or insecticide. Auditory and otoneurologic tests revealed an increased incidence of vestibular symptoms and high-frequency sensorineural hearing losses in studies of carbon disulfide-exposed textile workers. Animal experiments have demonstrated effects on the latencies and amplitude of the auditory brainstem response.

Toluene . Toluene is the most frequently used solvent. Its industrial applications are in the manufacture of other chemicals, paints, thinners, adhesives, lacquers, rubber, and in rotogravure printing and leather tanning. Toluene exposures can occur in the home, and, like other organic solvents, it has been abused in practices such as glue sniffing and spray paint sniffing.

Much of what we know about toluene's effects on hearing come from animal studies. Toluene was first reported in 1983 by Gordon Pryor, of SRI International, to cause irreversible hearing loss in rats at frequencies of 8,000-20,000 kHz. "It appeared as though this effect was occurring in the periphery, right at the receptor in the inner ear," said Pryor. "We subsequently looked at the inner ear and, indeed, there was damage to hair cells." The results of subsequent studies

indicated that young rats are more severely affected than older rats: weanlings tending to be more sensitive to toluene than adults. "The developing nervous system may be more vulnerable to toluene exposure than the fully functioning nervous system," Pryor said.

In her recent thesis on the ototoxic effects of toluene exposure in rats, Ann-Christin Johnson of Sweden's Karolinska Institute also reported loss of auditory sensitivity that was most pronounced in the middle frequencies, with severity dependent on duration of exposure. Also reported were outer hair cell loss spread along the cochlea, with loss of inner hair cells observed six weeks after exposure. In addition, toluene-induced loss of auditory sensitivity was permanently potentiated by simultaneous exposure to acetylsalicylic acid.

Toluene primarily affects the central nervous system in both humans and experimental animals. Acute high-dose exposure provokes excitability and euphoria followed by a depressant response with disorientation, mood fluctuations, hallucinations, ataxia, and coma. Long-term occupational exposure to toluene often includes exposure to other solvents. Long-term effects of such exposures include memory and concentration deficits and disturbance of emotional and psychomotor functions.

Equilibrium disorders and cerebellar damage have been reported among toluene abusers. Ambiguous results have been reported in some studies on toluene's effects on human hearing. One study points to hearing impairment in some but not all solvent abusers. Another study reported similar audiometric inconsistencies among workers accidentally exposed to toxic vapors of toulene. Subjects who abused toluene showed dramatic hearing loss originating from central auditory pathways.

Recently, Morata and collaborators at the University of Cincinnati studied the effects of occupational exposure to solvents, including toluene and noise, among rotogravure printing and paint manufacturing workers. The results suggested a predominantly noncochlear site of damage, perhaps with central auditory pathway (brainstem) involvement.

Noise and Solvents

Because noise is the most common exogenous cause of hearing loss in humans, much recent interest has been focused on combined exposure to noise and ototoxic agents. As Johnson points out, "In work environments where solvent exposure occurs, a high level of noise exposure is also common. A critical aspect of toluene ototoxicity, therefore, is a possible interaction with noise." Combined sequential exposures to toluene and noise caused a more severe loss of auditory sensitivity in rats than exposures to toluene alone or noise alone. "When toluene exposure preceded noise exposure, a potentiation occurred at 3.15 and 6.3 kilohertz. The reversed exposure sequence caused, at most, an additive effect," said Johnson.

A study of shipyard painters found a higher degree of hearing loss than expected from noise alone. In a paper mill factory, the most severe cases of hearing loss were seen among workers exposed to solvents in the chemical department, though noise exposure was lower than in other parts of the plant. In Morata's cross-sectional study of occupational exposure to solvent mixtures and noise, audiometric testing revealed a relative risk for high-frequency hearing loss 4 times greater than controls in the noise-exposed group, 5 times greater than the group exposed only to a solvent mixture, and 11 times greater than those exposed to both either noise or toluene only.

"There is the possibility of a synergism, of an interactive-additive type of potentiation between noise and solvent exposures," NIOSH's Dunn says. "The indications of Dr. Morata and some of the others suggest we may need to take another look at proposals for protecting people from workplace hearing loss and that those proposals will have to incorporate things other than noise."

Morata adds, "If you look at pure-tone audiometry, the test commonly used nowadays for occupational studies, you cannot tell the difference between noise-induced hearing loss and a not-as-traumatic source of hearing loss. And since noise is so prevalent in almost every industry, the hearing loss is blamed on the noise and not on other factors." Dunn agrees. He points out that unless one is

told the nature of exposure--chemicals versus noise--the effects in animals, both audiometrically and even at the cellular level, appear very much the same.

What are the implications for hearing protection standards? "Right now we have no indications how to make a guideline or propose a guideline for safe exposures to the combination of chemicals and noise at the same time," Dunn says. Indeed, the situation may be even more complicated. Some studies, he explains, show that a combination of noise and solvents have an effect on hearing even at low threshold exposures. "So we really won't be able to say that if we're below the level considered safe for the chemical or below the level considered safe for the noise, then the combination will be considered safe. So it's a very exciting area for us but also one that has a whole new set of obstacles to overcome."

Heavy Metals

Arsenic. Hearing loss in humans exposed to arsenic pollution has been reported. Analysis of hair, blood, and urine of children living near a power plant burning coal with a high arsenic content (900-1200 grams per ton) revealed elevated arsenic levels. Significant hearing threshold losses were also found. Johnson notes that sodium arsenilate can induce selective hair-cell damage in the cochlea of guinea pigs and rats.

Mercury. Mercury intoxication causes hearing loss in humans and animals. In 1953, a severe neurological disorder was recognized among persons living in the vicinity of Minimata, Japan, where mercury-containing effluent flowing from a chemical manufacturing plant into the local bay contaminated shellfish. Deterioration in hearing and deafness were reported among other neurological symptoms. Findings consistent with Minimata disease have been reported in other instances of accidental mercury intoxication in Japan and Iraq. Early stages of poisoning may result in cochlear lesions, whereas hearing loss in the late stages of intoxication may result from neurological damage.

Trimethyltin. Organic tin compounds are used widely as catalysts for the manufacture of polyurethane foam and vulcanization of silicone rubber. They are also used in polyvinyl piping, siding, and window casings; marine paints, wood

preservatives, fungicides, and acaricides. Organic tin compounds are used as antiparasitics in animals. Trimethyltin is associated with structural and functional alterations of the auditory system in rats and guinea pigs. High-frequency hearing loss has been associated with damage to the basal part of the cochlea. Central nervous system damage has also been noted. The compound appears to have two distinct auditory system effects, one reversible and the other irreversible. Hearing loss initially occurs across a wide frequency range. In time, hearing recovers almost completely at lower frequencies. The irreversible high-frequency hearing loss is associated with hair-cell loss in the cochlea and marked changes in the stria vascularis.

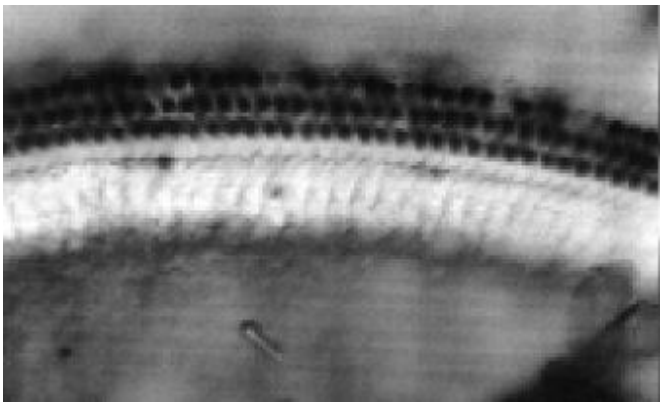
According to Leonard Rybak, a professor in the Division of Otolaryngology at Southern Illinois University School of Medicine, the possibility that organictin compounds could cause hearing loss in humans needs investigation. He recommends audiometric studies of workers with occupational exposures. "The [ototoxic] effects of lead, manganese, and other heavy metals need to be systematically studied on a large scale," Rybak says.

Cochlear Self-protection

Over the years, several laboratories have become interested in a variety of cochlear biochemical parameters associated with NIHL. Recently, interest has focused on a group of ubiquitous proteins, heat-shock proteins (HSPs), as possibly having protective properties against ototoxicity caused by noise, drugs, and trauma. Initially observed in *Drosophila* , HSPs have been found in all animals, plants, and bacteria, and are highly evolutionarily conserved. Although HSPs are commonly induced by hyperthermia, they are not stress specific and can be induced by any condition that stresses the cell, including chemical toxins. They are therefore also referred to as stress shock proteins.

"There are many different families or classes of heat shock proteins, differentially based on their denatured molecular weights. Among these are the HSP 20s, HSP 60s, 70s, 90s, and 110s. Each are conserved across many species and produced in response to stress in a wide variety of cells," says Richard Altschuler

of Michigan University's Kresge Hearing Research Institute. "HSPs can be normally present in the cell and not require stress for their expression, or they can be induced, requiring stress to be expressed, or they can both normally present and increase with stress. HSP 70 represents the most highly induced and well-studied group," says Altschuler.



Nature's ear plugs? Immunocytochemical labeling marks heat shock protein 72, which may protect hearing after noise, as black dots in outer hair cells. *Photo: Richard Altschuler*

Several studies suggest that a major function of HSPs is to facilitate cellular repair and to protect cells from further injury. HSPs are widely distributed and respond rapidly to changing conditions, a finding consistent with the basic emergency response of cells. Their protective function is supported by studies linking the induction of these proteins with an acquired thermal tolerance in cultured cells from a number of organisms.

Cells subjected to rapidly increasing temperatures died much more quickly than those that were first subjected to a modest temperature increase to induce HSP synthesis and then subjected to the higher temperature. The protective role of HSPs was more directly demonstrated by the microinjection of antibodies to the HSP 70 family of proteins into fibroblasts. Cells with the injected antibodies, which presumably inactivated HSP 70 proteins, were killed by brief heat shock, whereas control cells survived. These studies suggest that an organ about to undergo a potentially lethal condition might be protected by previous induction of heat shock proteins.

Expression of HSP 72 in the outer hair cells of the rat cochlea has been induced by acoustic overstimulation. Altschuler points out that their detection in outer hair cells and not in inner hair cells may be due to several factors. Outer hair cells are generally more susceptible to acoustic trauma than inner hair cells, and therefore more likely to express HSP 72. In addition, immunolabeling of HSP 72 was also seen in the stria vascularis, a finding that agrees with previous studies on hyperthermia and ischemic stresses. In the cochlea, localized capillary vasoconstriction as a result of noise overstimulation reduces the oxygen tension and nutrient supply to cochlear tissue, thus serving thus inducing HSP expression in the stria vascularis and microvasculature.

Could HSPs also protect the auditory periphery from damage to ototoxic drugs, as well as noise and trauma? "We're studying trauma to the inner ear in trying to determine what genes are being turned on or off under these different conditions," says Robert Wenthold of the National Insitute for Deafness and Communication Disorders "So the stress shock proteins are certainly one category that's being turned on and off, but it's only one. The ear has been so inaccessible because of its size that you must have very specific approaches," he adds. "One is to have a target like an HSP, the other is to have a very sensitive screening mechanism to see what happens, in general. Right now we're working on that latter mechanism."

Says Altschuler: "Stress shock proteins may also achieve their protective effect through mechanisms such as stabilization or refolding of other proteins. It's also possible that HSPs don't have a protective effect in the cochlea and are there for other reasons, maybe serving a role in recovery from noise-induced trauma." Altschuler also suggests that the normal presence of HSPs may have a role in both the production of and recovery from temporary threshold shift.

Individual differences in susceptibility of cochlear structures to noise, ototoxic drugs, and chemicals and their possible synergies may well exist. Marked individual variations in threshold susceptibility to intense noise by as much as 30-50 dBs have been demonstrated in both animal and human studies. However,

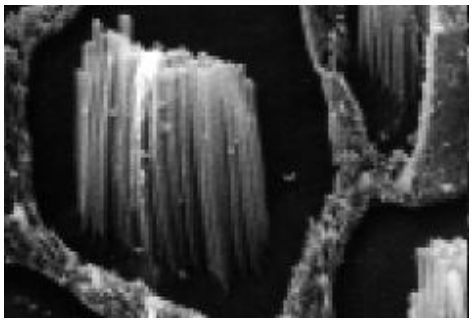
scientific knowledge remains inadequate for predicting these differences, and more research is required to understand their biological bases.

Leslie Lang

Leslie Lang is a freelance writer in Chapel Hill, North Carolina.

Of Structures Elegant, Complex, and Fragile

Knowledge of the anatomical and physiological basis of hearing has been achieved mainly in this century. Aristotle's doctrine of "implanted air," challenged seriously in the 18th century, was finally put to rest in the 19th, when modern theories of hearing began to emerge. "Unraveling the mysteries of how vibrations in the air are translated into nerve impulses in the brain had to await technological advances that have become available only since the turn of the century," says Gordon T. Pryor, director of neurosciences department at SRI International. "However, once appropriate technologies became available, progress was rapid."



Hairy ears. Hairs, such as the ones embedded in chick hair cells, amplify and transmit input to the auditory nerve. *Photo: DOE*

The advent of scanning and transmission electron microscopes made possible a detailed description of the inner ear's fine structure and its elegant geometry. The advent of biophysical and electrophysiological methods, beginning in the 1930s when it first became possible to record inner ear electrical potentials, have provided tools for recording and analyzing the earliest electrical events in the acoustical transduction process and their subsequent journey through the eighth

cranial nerve. Today, biochemical methods are just beginning to reveal the inner ear's complex molecular substrate and its functional components.

Central to the complex process of sound-wave transduction and the perception of sound is the inner ear. Located in the temporal bone, it consists of the vestibular organs and the cochlea, a snail-shaped chamber about the size of a fingertip. The cochlea, which is the organ of hearing, is a fluid-filled system of three tubular canals--scala vestibuli, scala media, and scala tympani--running parallel and coiled together in a spiral. Within the scala media is the organ of Corti, the receptor structure of hearing. Along the convoluted length of its taut basilar membrane are about 15,000 hair cells arranged in three rows of outer hair cells (OHCs) and one row of inner hair cells (IHCs). These sensory epithelial cells carry bundles of stereocilia (hairs) embedded in their cuticular plates.

External air vibrations are transmitted to the inner ear via the motions of three small bones (ossicles) of the middle ear--incus, malleus, stapes--connected in a chain stretching between the ear drum (tympanic membrane) and oval window of the cochlea. The ossicles modulate ear drum vibrations and, via the stapes, displace the fluid within the cochlear ducts, thus vibrating the basilar membrane. A traveling wave of mechanical energy passing up through the cochlea from base to apex is created, which is transduced to neural signals by the organ of Corti. The wave peaks at different parts of the basilar membrane, depending on sound wave frequency. Low frequencies cause a peak near the cochlear apex and high frequencies near the base.

Stereocilia are deflected, excited by sound waves of increasing frequency from apex to base, essentially bending back and forth thousands of times per second. This causes the opening of ion channels, thus exciting the cell and initiating synaptic transmission to afferent nerve endings that synapse on the base of the hair cells. These nerve endings are dendrites of bipolar cells located within the spiral ganglion, their bundled axons forming a major portion of the eighth cranial, or auditory, nerve.

In terms of their roles in the hearing process, IHCs and OHCs differ distinctly, Pryor explains. "Whereas the IHCs transmit the primary information about the acoustic stimulus to the afferent fibers of the eighth nerve, the OHCs are believed to modulate the transduction process."

"Ninety to ninety-five percent of fibers from the auditory nerve are receiving input from inner hair cells," says Raelynn Jannsen of EPA's neurotoxicology division. "What the outer hair cells do, to the best of our current understanding, is to serve as an active amplifier of incoming sound." This interpretation of OHC function is supported, in part, by several recent observations, including a shortening or lengthening of OHCs in response to either electrical or acoustical stimulation. These changes could alter the vibrational pattern of the basilar membrane, thereby modulating IHC tuning curves.

In terms of impulse transduction from the inner ear to the central nervous system, stereocilia movement depolarizes IHCs, which presumably leads to release of an afferent synaptic neurotransmitter, possibly glutamate or a related excitatory amino acid. An action potential is evoked in the auditory nerve. The transduced signal is subsequently mediated to the cochlear nuclei of the brain stem and via the auditory pathways to the temporal lobe, site of the auditory cortex, and thus sound is perceived.