

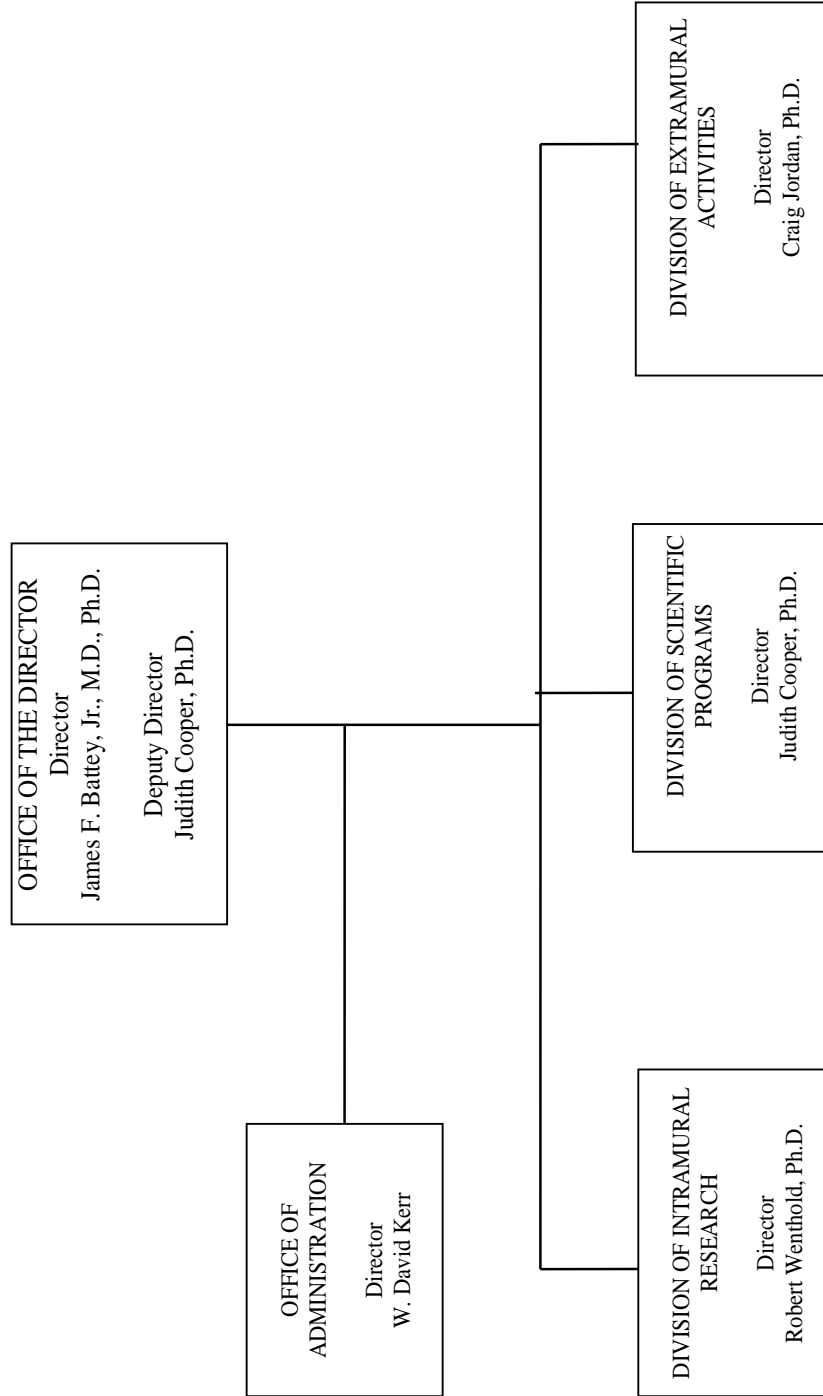
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

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**NATIONAL INSTITUTES OF HEALTH
National Institute on Deafness and Other Communication Disorders**



NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

For carrying out section 301 and title IV of the Public Health Service Act with respect to deafness and other communication disorders, [~~\$397,432,000~~] *\$391,556,000* .

[Department of Health and Human Services Appropriations Act, 2006]

**National Institutes of Health
National Institute on Deafness and Other Communication Disorders**

Amounts Available for Obligation 1/

Source of Funding	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Appropriation	\$397,507,000	\$397,432,000	\$391,556,000
Enacted Rescissions	(3,247,000)	(3,974,000)	0
Subtotal, Adjusted Appropriation	394,260,000	393,458,000	391,556,000
Real transfer under NIH Director's one-percent transfer authority for Roadmap	(2,492,000)	(3,516,000)	0
Comparative transfer from OD for NIH Roadmap	2,492,000	3,516,000	0
Subtotal, adjusted budget authority	394,260,000	393,458,000	391,556,000
Unobligated balance lapsing	(89,000)	0	0
Total obligations	394,171,000	393,458,000	391,556,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:

FY 2005 - \$1,646,000 FY 2006 -\$1,920,000 FY 2007 - \$2,000,000

Excludes \$72,000 in FY 2006 and \$94,000 in FY 2007 for royalties.

Justification

National Institute on Deafness and Other Communication Disorders

Authorizing Legislation: Section 301 of the Public Health Service Act, as amended.

Budget Authority:

FY 2005		FY 2006		FY 2007		Increase or	
Actual		Appropriation		Estimate		Decrease	
<u>FTEs</u>	<u>BA</u>	<u>FTEs</u>	<u>BA</u>	<u>FTEs</u>	<u>BA</u>	<u>FTEs</u>	<u>BA</u>
140	\$394,260,000	140	\$393,458,000	141	\$391,556,000	1	\$(1,902,000)

This document provides justification for the Fiscal Year 2007 activities of the National Institute of Deafness and Other Communication Disorders, including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2007 HIV/AIDS activities can be found in the NIH section entitled “Office of AIDS Research (OAR).” Detailed information on the NIH Roadmap for Medical Research may be found in the Overview section.

INTRODUCTION

Why Young People are at Risk: Music, Movies, and Video Games, Oh My!

Young people live in a loud and noisy world. In this age of the escalating use of personal stereo systems, hands-free cell phones, and portable movie/game systems, American youth are exposed to harmful levels of noise every day. This exposure can lead to permanent noise-induced hearing loss (NIHL). It is estimated that approximately 10 percent (or 22 million) of American adults between 20-69 years old may have suffered permanent damage to their hearing from exposure to loud sounds or noise at work or in leisure time activities.¹ To help address this growing problem, the NIDCD will continue to increase awareness of NIHL by (1) encouraging the use of appropriate ear protection and (2) reducing the number of individuals who suffer from noise-induced hearing loss through research and public education activities. By focusing on children and teens and addressing key topics such as the use of personal stereo systems, the NIDCD hopes to teach young children and teens learn to protect their hearing while still enjoying their music, movies, and video games.

Human communication disorders are disorders that affect hearing, balance, smell, taste, voice, speech, or language. These disorders often compromise social, recreational, emotional, educational, and vocational aspects of an individual’s life. The mission of the NIDCD is to support basic and clinical research and research training focused on understanding the normal processes and disorders of human communication. While science and technology have increased our capacity and need for communication, many aspects of contemporary life remain profoundly difficult for individuals with communication disorders.

¹ Based on NHANES 1999-2000 with noise “notches” and noise exposure history.

Story of Discovery: Can We Help the Ear Repair Itself?
Scientists hope to “re-start” the ear’s developmental machinery.

NIDCD-supported scientists are identifying the genes necessary for forming the ears and enabling them to detect sound. They hope that a good understanding of normal development will enable them to correct or prevent hearing and balance disorders in children. As the Baby Boomer generation gets older, scientists hope their knowledge will help them develop therapies to restore hearing and balance lost due to infection, injury, noise, and the aging process.

How does the ear detect sound? Auditory hair cells are a vital part of the ear’s ability to detect sound. Located in the inner ear, hair cells have microscopic hair-like projections that protrude from their tops. The surfaces of these hairs contain pores, or channels, that open after the hair-like projections are subjected to mechanical force. Inside the ear, the force comes from a sound wave that moves through the fluid underlying the hair cells, lifts them up, and drives them into an overlying membrane. The channels open and release small molecules in a chemical chain reaction that ultimately tells the auditory nerve to tell the brain that sound has been detected.

Signals Controlling Hair Cell Development. In 1993, five scientists at the University of Virginia wrote a review article addressing an important question for developmental biologists: how do the ears take shape from an identical mass of unspecified cells to an organized pattern of hair cells and supporting cells? Cutting-edge research in simple models like the fruit fly described how a system called “lateral inhibition” is used to specify different kinds of cells, such as neurons and non-neuronal cells in other developing systems. Based on this, the group proposed that mammalian ears use a similar system of organization.

The lateral inhibition theory proposes that individual cells begin to take on the identity of one cell type, such as a nerve cell. The developing nerve cells, or neurons, then inhibit neighboring cells (located at their sides, or laterally) from also becoming neurons. This theory explains how a group of identical cells can develop into a mixture of neurons surrounded by non-neurons.

Scientists began using lateral inhibition as a framework for posing questions about how the ears develop. This approach has led to the discovery of some very important mechanisms determining how mammalian ears organize themselves – and these basic details of development may one day show scientists how to help individuals with hearing loss to hear sound once again.

If an auditory hair cell is keeping its neighbors from becoming hair cells, then destroying it should result in loss of the inhibition. That is, the neighboring cells may then become hair cells in its place. That was exactly what graduate student Matthew Kelley observed in 1995, when he used a laser to destroy selected mouse auditory hair cells. After the hair cells were destroyed, time lapse photos showed neighboring supporting cells migrating into the hair cell layer and developing as new hair cells. Although these studies suggested that lateral inhibition was indeed at work, nobody yet knew what genes might be involved in this process. Once again, a breakthrough came through use of the fruit fly as a model for investigation.

Molecular Detective Work: From Flies to Mice. Fruit flies use a primitive structure called the chordotonal organ to detect sound, and mutant flies missing a gene called *atonal* lack these organs. Scientists began searching for a gene similar to Atonal (an ortholog) that is responsible for mammalian ear development. They discovered that a candidate gene, called *Math1*, or *Atoh1*, was able to restore chordotonal organs in *atonal* mutant flies. When NIDCD-supported scientists “knocked out” or removed the *Math1* gene, the mutant mice suffered a wide range of problems, including deafness and balance problems. In 2002, a different group of NIDCD-supported scientists reported that the fruit fly gene can “rescue” or prevent the defects of mice lacking the *Math1* gene. This research demonstrated an amazing similarity between the mouse and fruit fly auditory systems, and also established the importance of *Math1* in mouse ear development.

Encouraged by these fly/mouse similarities, one laboratory searched for more fruit fly gene orthologs in the mouse ear. The group was led by Matthew Kelley, now heading up his own laboratory in the NIDCD intramural program. Fruit fly neurons express a gene called *delta* during lateral inhibition. In a 1999 publication, the laboratory reported that a mouse ortholog of *delta*, known as *Jag2*, was expressed in the right place and at the right time to play a role in lateral inhibition in mouse hair cell specification. Mutant mice that lack *Jag2* produce far too many hair cells – more evidence that lateral inhibition is at work.

In 2005, the Kelley lab reported that not only do developing hair cells inhibit their neighbors from becoming hair cells, but also send signals that recruit nearby cells to develop as supporting cells. This means that if scientists use these genes to try to stimulate the development of extra hair cells (to replace those missing or damaged), they will not “use up” all the supporting cells, as had been feared. Each group of developing hair cells appears to organize itself in an appropriate pattern and to recruit the supporting cell types needed to maintain the group’s sound-detecting function.

Also in 2005, NIDCD-supported scientists at Harvard University, Northwestern University, Tufts, and the University of Virginia identified a gene that prevents the regeneration of hair cells. The group knew that a gene called “retinoblastoma” or *Rb1*, forces cells to exit the so-called “cell cycle,” meaning that they stop dividing and begin to mature. They also knew that *Rb1* is expressed in mouse ears during the time they are generating hair cells. Based on this knowledge, they looked at the number of hair cells in mice lacking *Rb1*, and found that they have extra hair cells. Blocking *Rb1* expression in cultured hair cells, they reactivated the cell cycle – causing the hair cells to begin dividing once again. This critical discovery provides scientists with a more detailed understanding of the genes controlling the development of hearing. If we want to make more hair cells, we must both activate hair cell “On” genes, and inactivate hair cell “Off” genes – such as *Rb1*.

Working to Restore Hearing. If an individual’s hearing loss is due to hair cell death, the only way to restore normal hearing is to replace the lost hair cells. However, under normal circumstances, mammals cannot replace hair cells. Due to years of intense and dedicated basic research, we now know some of the many genes important for ear development and hearing. How can we use this information to help those who are deaf?

Hijacking a Virus for a Good Cause – Gene Therapy. Viruses that have been altered to remove disease-causing elements and to include a gene of interest are a useful way for scientists to “deliver” genes to cells and tissues – the virus passes the inserted gene along when it infects the tissue. NIDCD-supported scientists at the University of Michigan used their knowledge of the ear’s gene expression programs to recruit cells in a deaf ear to become hair cells. They treated deafened guinea pig ears with a virus carrying the gene *Math1/Atoh1*, and found evidence that new hair cells were generated. More importantly, the treated animals showed functional evidence of partial restoration of their hearing. This is the first successful demonstration of gene therapy that improves hearing in formerly deaf animals. Scientists hope to one day use this type of gene therapy to restore hearing in humans.

Improving Gene Therapy Methods - Cow Virus Is Powerful New Tool. Even though scientists can use viruses to deliver important genes to the ear, sensory tissue of the ear is particularly challenging to infect. The viruses currently used are able to infect only a relatively small number of cells. NIDCD and NICHD intramural scientists collaborated to develop a new type of virus to deliver important genes to ear tissues. In 2005, the group reported that they had successfully used a modified cow virus to deliver genes to the ear tissues of rats. The virus infected nearly all hair cells and supporting cells, making it an attractive new tool for recruiting new hair cells within a damaged ear.

Scientists hope to use their combined knowledge of the ear’s developmental program and gene therapy techniques to restore hearing to those who become deaf. Such important scientific advances are based upon scientists’ ability to build on past discoveries in a wide ranging collection of animal model systems.

Citations: Di Pasquale G, Rzadzinska A, Schneider ME, Bossis I, Chiorini JA, Kachar B, A novel bovine virus efficiently transduces inner ear neuroepithelial cells. Mol Ther 11: 849-855, 2005.

Izumikawa M, Minoda R, Kawamoto K, Abrashkin KA, Swiderski DL, Dolan DF, Brough DE, Raphael Y, Auditory hair cell replacement and hearing improvement by *Atoh1* gene therapy in deaf mammals. Nat Med 11: 271-276, 2005.

Woods C, Montcouquiol M, Kelley MW, *Math1* regulates development of the sensory epithelium in the mammalian cochlea. Nat Neurosci 7: 1310-1318, 2004.

SCIENCE ADVANCES

HEARING RESEARCH

Genes that Direct Ear Formation

Background: The inner ear is a complex organ that detects sound and helps maintain balance. Problems with establishing the developing ear's orientation (left-right, top-bottom, front-back) compromise its functions and may lead to deafness or balance disorders. Although previous studies demonstrated that the orientation of the inner ear relies on signals from nearby tissues such as the hindbrain, scientists had little information about the mechanisms involved.

Advances: NIDCD intramural scientists studied two animal models: (1) mice lacking the gene *Gbx2* and (2) developing chicken embryos whose hindbrain had been rotated (front to back) or flipped (top to bottom). Their experiments suggest that *Gbx2* and another gene, sonic hedgehog (*SHH*), play important roles in establishing the developing ear's orientation.

Implications: Understanding the genetic mechanisms that underlie the normal development of the inner ear will help scientists understand how certain mutations cause human deafness and balance disorders and design strategies to prevent or treat these disorders.

Citations: Bok J, Bronner-Fraser M, Wu DK, Role of the hindbrain in dorsolateral but not anteroposterior axial specification of the inner ear. *Development* 132: 2115-2124, 2005.

Lin Z, Cantos R, Patente M, Wu DK, *Gbx2* is required for the morphogenesis of the mouse inner ear: a downstream candidate of hindbrain signaling. *Development* 132: 2309-2318, 2005.

Link to publications: <http://dev.biologists.org/cgi/content/full/132/9/2115> and <http://dev.biologists.org/cgi/content/full/132/10/2309>

Proteins That Help the Ear Detect Sound

Background: Many of the tiny structures important for hearing are built from proteins or require proteins to function. In 2005, NIDCD-supported scientists made some critical discoveries about how proteins help the ear detect sound.

Advances: Stereocilia on a single auditory hair cell are bundled together in a staircase shape that is needed for normal hearing and balance. By studying what goes wrong in mice that inherit defective genes, NIDCD scientists have discovered how two proteins work together to build normal stereocilia. The MyoXVa (myosin 15a) protein binds and transports the whirlin protein from the main part of the hair cell (the cell body) out to the tips of developing stereocilia. The stereocilia “grow” by adding proteins to their ends. When mice inherit defective genes for MyoXVa or whirlin proteins, their stereocilia do not develop into the normal staircase pattern, and the mice are deaf. However, gene therapy that reintroduces normal copies of the mutant genes can “rescue” normal stereocilia formation.

Individuals who inherit mutated copies of another myosin gene, *MyoVIIa*, are deaf and have balance problems, which constitute a syndrome called Usher Type 1B. Until recently, scientists

did not know how the mutation caused these problems. NIDCD-supported scientists identified the fruit fly equivalent of *MyoVIIa*, known as *crinkled*. Flies with mutant copies of *crinkled* suffer symptoms similar to human Usher 1B Syndrome. The fruit fly equivalents of hair cells in the mutants develop in a disorganized manner and cannot detect sound. Scientists can now study this insect model of Usher 1B Syndrome to help them understand the human disorder.

Finally, NIDCD-supported scientists have identified yet another protein that is critical to our ability to detect sound. A fine filament called a tip link connects the tips of adjacent hair cell stereocilia, and tip links pull on channels in the hair cell membranes to open them. Charged ions rushing through these channels change the voltage inside the cells and set off an electrical current (nerve impulse) that travels to the brain and is detected as sound. Now NIDCD-supported scientists have found the protein that forms the hair cell channels. TRPA1 is made by hair cells, is located in the tips of stereocilia, and is necessary for hair cells to respond to sound. It also forms an unusual extended elastic chain that may pull and open the channel. When the scientists blocked TRPA1 formation in animals, their hair cells were unable to conduct electrical current, suggesting that ions could not enter the stereocilia.

Implications: These studies help scientists understand how genes and their associated proteins function in normal ears to help detect sound. This detailed understanding at the molecular level may help scientists develop gene therapies for some forms of hereditary deafness in humans.

Citations: Corey DP, Garcia-Anoveros J, Holt JR, Kwan KY, Lin SY, Vollrath MA, Amalfitano A, Cheung EL, Derfler BH, Duggan A, Geleoc GS, Gray PA, Hoffman MP, Rehm HL, Tamasauskas D, Zhang DS, TRPA1 is a candidate for the mechanosensitive transduction channel of vertebrate hair cells. Nature 432: 723-30, 2004

Belyantseva IA, Boger ET, Naz S, Frolenkov GI, Sellers JR, Ahmed ZM, Griffith AJ, Friedman TB, Myosin-XVa is required for tip localization of whirlin and differential elongation of hair-cell stereocilia. Nat Cell Biol 7: 148-56, 2005.

Todi SV, Franke JD, Kiehart DP, Eberl DF, Myosin VIIA defects, which underlie the Usher 1B syndrome in humans, lead to deafness in Drosophila. Curr Biol 15: 862-868, 2005.

Link to publications:

<http://www.nature.com/nature/journal/v432/n7018/abs/nature03066.html;jsessionid=50EF80DCB9C175BC62BFCA37ED0A00BB>,
<http://www.nature.com/ncb/journal/v7/n2/abs/ncb1219.html;jsessionid=4508BB77EE6A2378A215FAB258A409FE>, and <http://www.current-biology.com/content/article/abstract?uid=PIIS0960982205003921>

Link to press release: <http://www.nih.gov/news/pr/feb2005/nidcd-10.htm>

Improper Use of Modifiers: Not just a Grammatical Error Anymore

Background: According to Section 28 of Healthy People 2010², genetic mutations are estimated to cause at least half of all cases of inherited or childhood-onset hearing loss. Individual variations in the severity of hearing loss are common and typically attributed to environmental factors and modifier genes – genes that can alter the impact of a mutation in another gene but do not by themselves cause hearing loss. Modifier genes in the genetic background of an individual can affect the severity of hearing loss caused by a mutation.

Advance: NIDCD-supported scientists have identified a genetic variation in humans that affects the severity of hearing loss caused by a mutation of another gene. In a study of a single large family, five adult siblings had a mutant form of the gene that encodes for the protein, cadherin 23, which is required for regulating the amount of calcium both around and within sensory hair cells. Calcium is important for hair cell structure and nerve impulse transduction. However, the degree of hearing loss among the siblings varied. While three of the five individuals had severe to profound deafness, the other two had hearing loss only in the higher frequencies. This variability suggested the action of a modifier gene.

Implications: Clinical genetic testing for modifier genes would provide valuable information for predicting the severity and progression of hearing loss associated with advanced age, exposure to loud noise, and mutations in other deafness genes. Understanding how modifier genes work would also provide a critical entry point for the design and testing of biological interventions to modify the severity of hearing loss. For example, since calcium pumps are excellent targets for drug development, this discovery reveals an opportunity to devise and test potential therapies to prevent or slow progressive hearing loss.

Citation: Schultz JM, Yang Y, Caride AJ, Filoteo AG, Penheiter AR, Lagziel A, Morell RJ, Mohiddin SA, Fananapazir L, Madeo AC, Penniston JT, Griffith AJ, Modification of human hearing loss by plasma-membrane calcium pump PMCA2. *NEJM* 352: 1557-1564, 2005.

Link to publication: <http://content.nejm.org/cgi/content/abstract/352/15/1557>

Link to press release: http://www.nidcd.nih.gov/news/releases/05/4_13_05.asp

Testing in Infants for Prevention and Diagnosis of Hearing Loss

Background: Because hearing loss is among the most common human birth defects and the importance of early intervention during the early critical period for learning language (<18 months of age), states have adopted Early Detection and Hearing Intervention (EHDI) programs. Since EHDI began, more than 70 hearing impairment genes have been identified. Mutations in two of these genes, which code for proteins known as connexins (GJB2 and GJB6) account for over half of the cases of genetic hearing loss in some populations. Cytomegalovirus (CMV) is another common cause of congenital (at birth) infection and a leading cause of progressive hearing loss in children in the United States. Approximately 10% to 15% of children with congenital CMV infection have some degree of hearing loss that has delayed onset and worsens

² U.S. Department of Health and Human Services. *Healthy People 2010*. 2nd ed. With Understanding and Improving Health and Objectives for Improving Health. Two vols. Washington, DC: U.S. Government Printing Office, November 2000.

during childhood. Combining EHDI newborn hearing screening with genetic and CMV testing has the potential for rapidly diagnosing the cause and extent of hearing impairment in children.

Advances: NIDCD-supported scientists have taken the first step towards assessing the benefit of widespread inclusion of genetic testing in the EHDI process. Data suggest that children who have GJB2-related hearing impairment will benefit from cochlear implantation, so it is probable that it will become an important addition to current EHDI protocols. GJB2/GJB6 genetic testing will help to determine whether or not hearing impairment is part of a clinical syndrome, or is instead non-syndromic (not associated with any other condition) because individuals with GJB2/GJB6-related hearing impairment do not show any other disease conditions. Once clinicians are sure that hearing impairment is non-syndromic, there is no need to continue testing for other conditions that are part of common syndromes that include hearing impairment.

In another study, NIDCD-supported investigators determined the relationship between CMV virus burden (amount of CMV DNA in the blood) and CMV related hearing loss in infancy. The amount of infectious CMV in urine and the quantity of CMV DNA in blood were determined in a group of children with congenital CMV infection and were followed for approximately 3 years. Scientists observed that a high virus burden during the first month of life is associated with hearing loss. These findings imply that it may be possible to identify children with asymptomatic CMV infection at increased risk for hearing loss by measuring virus burden during infancy.

Implications: At present, genetic testing for deafness genes is limited. However, future tests will be able to screen dozens of hearing impairment genes using complex genetic screening techniques, like microarrays. Now that GJB2/GJB6 and CMV diagnosis is theoretically achievable, scientists and policy makers should decide how best to incorporate these genetic tests into the EHDI protocol. Combining the protocols could streamline the evaluation process and avoid additional testing and recurrent evaluations.

Citations: Boppana SB, Fowler KB, Pass RF, Rivera LB, Bradford RD, Lakeman FD, Britt WJ, Congenital Cytomegalovirus Infection: Association Between Virus Burden In Infancy and Hearing Loss. *J Pediatr* 146: 817-823, 2005.

Schimmenti LA, Martinez A, Fox M, Crandall B, Shapiro N, Telatar M, Sininger Y, Grody WW, Palmer CG, Genetic Testing as Part of the Early Hearing Detection and Intervention (EHDI) Process. *Genetics in Medicine* 6: 521-525, 2004.

Link to publications: http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WKR-4GFTYC7-1D&_coverDate=06%2F30%2F2005&_alid=313870635&_rdoc=1&_fmt=&_orig=search&_qd=1&_cdi=6913&_sort=d&_view=c&_acct=C000000150&_version=1&_urlVersion=0&_userid=10843&_md5=3449f521983c3ba2465e669ad6d86671 and <http://www.geneticsinmedicine.org/pt/re/gim/abstract.00125817-200411000-00010.htm;jsessionid=DqRnpMYhqi0RawBe7Ypcw69kdjZ12LBo9GPao1jsvsbGvBo2ZBrl!1277578804!-949856144!9001!-1>

Research Advances in Vaccines Against Middle Ear Infection

Background: Nontypeable *Haemophilus influenzae* (NTHi) and *Moraxella catarrhalis* are two major bacteria that cause middle ear infection (otitis media) in children. Antibiotics are usually prescribed to treat this infection but there is a need to develop a vaccine against the microbes that are involved in otitis media. Previously, scientists identified and used a major surface component of NTHi, called lipooligosaccharide (LOS), to develop a conjugate vaccine against NTHi. LOS is also a possible virulence factor in the pathogenesis of human infections caused by *M. catarrhalis*, however, information about the roles of the oligosaccharide chain from LOS in *M. catarrhalis* infection remains limited.

Advances: NIDCD intramural scientists have made advances in improving the quality of these conjugate vaccines by developing a new carrier protein purified from the outer membrane of NTHi and are testing if the new carrier would be useful for sugar-based conjugate vaccines. Using an outer membrane protein, P6, as a new carrier for NTHi LOS conjugate vaccines, scientist determined that P6 could serve as an effective carrier for conjugate vaccines and have a potential to generate better immune responses against NTHi in animal models.

In another advance, NIDCD intramural scientists have identified a *kdtA* gene that appears to play a role in LOS biosynthesis in *M. catarrhalis*. When scientists developed a mutant strain of *M. catarrhalis* that lacked the specific gene, the bacteria showed reduced resistance to a series of chemical compounds and were susceptible to attack by cell in normal human serum. It also could not adhere as efficiently to human epithelial cells in the respiratory tract easily, and was more easily cleared from the nose, throat, and lungs of a mouse that was exposed to the mutant strain. These data suggest that the gene responsible for synthesizing LOS is important for the biological activity of the LOS and the virulent capability of the bacteria.

Implications: Learning how the *kdtA* gene functions in LOS biosynthesis and the bacterial virulence in *M. catarrhalis* or identifying a new protein carrier that can be used for production of sugar-based conjugate vaccines against NTHi are providing new insights into novel vaccines or therapeutic interventions against bacteria that cause otitis media.

Citations: Peng D, Choudhury BP, Petralia RS, Carlson RW, Gu XX, Roles of 3-deoxy-D-manno-2-octulosonic acid transferase from *Moraxella catarrhalis* in lipooligosaccharide biosynthesis and virulence. *Infect Immun* 73: 4222-4230, 2005.

Wu T, Chen J, Murphy TF, Green BA, Gu XX, Investigation of Nontypeable *Haemophilus influenzae* outer membrane protein P6 as a new carrier for lipooligosaccharide conjugate vaccine. *Vaccine* Epub, 2005.

Link to publications: <http://iai.asm.org/cgi/content/full/73/7/4222?view=long&pmid=15972513>
and
http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TD4-4GJV96N-3&_coverDate=07%2F06%2F2005&_alid=313551920&_rdoc=1&_fmt=&_orig=search&_qd=1&_cdi=5188&_sort=d&_view=c&_acct=C000000150&_version=1&_urlVersion=0&_userid=10843&md5=fd0a3ffdd78f071b8c0d39ee7e1c5d81

Better Hearing in Real-Life Situations: Advances in Cochlear Implants

Background: Using state-of-the-art technology, cochlear implants (CIs) provide electrical stimulation directly to the auditory nerve, bypassing the damaged cochlea, which is usually the cause of deafness. Although the vast majority of CI users can understand speech in a quiet room, and report improvement in quality of life, they still report having continued difficulties locating sounds and understanding speech in everyday noisy environments. Given the growing population of CI users (approx. 96, 000 worldwide), a key challenge is to improve CI users' ability to localize sound and understand speech in noisy environments. In the past year, several groups of NIDCD-supported scientists have addressed these issues by improving the quality of the sound input into the brain and promoting the health of the existing auditory nerve cells and fibers.

Advances: One group of NIDCD-supported scientists is clinically testing a new CI design with a shorter electrode that is inserted into the base of the cochlea to restore hearing at high frequencies, while preserving residual low frequency hearing in the top of the implanted cochlea. The scientists observed that residual hearing is preserved with the use of this electrode. In addition, individuals implanted with the short electrode showed better speech recognition in a noisy environment than individuals with the traditional long electrode.

Another group investigated the benefits of bilateral cochlear implantation (Bi-CI) (a cochlear implant in each ear) in both adults and children. Results show that they are significantly better at localizing sounds and hearing speech in a noisy room when they wear Bi-CIs compared with a single CI. In addition, within 1 to 2 years, children with Bi-CIs learn how to locate sounds, and the majority of Bi-CI children can now localize sounds better with two ears than one.

Finally, another group developed a new CI design capable of delivering drugs to the inner ear. A drug called brain derived neurotrophic factor (BDNF) provides significant enhancement of auditory nerve function when delivered into the inner ear of guinea pigs. This finding suggests that BDNF delivery might be used to counteract the degeneration of the auditory nerve typically seen following hearing loss. Neural sensitivity to electrical stimulation (ES) was significantly improved in animals receiving this drug as compared to those receiving electrical stimulation alone; sensitivity to ES is an important factor for the successful function of a cochlear implant. Based on these promising results, future cochlear implant designs could include a drug delivery system in order to improve the long term health of the auditory nerve and thus maximize the individual's ability to hear with this device.

Implications: Individuals who are deaf with a CI work hard in order to be able to hear, learn, and play in a hearing world. Improving sound localization (with Bi-CIs) and preservation of the residual hearing and nerve health is important for improving life for hearing impaired individuals.

Citations: Gantz BJ, Turner C, Gfeller KE, Lowder MW, Preservation of Hearing in Cochlear Implant Surgery: Advantages of Combined Electrical and Acoustical Speech Processing. Laryngoscope 115: 796-802, 2005.

Litovsky R, Johnstone P, Godar S, Agrawal S, Parkinson A, Peters R, Lake J, Bilateral Cochlear Implants in Children: Localization Acuity Measured with Minimum Audible Angle. Ear and Hearing In press, 2005.

Shepherd RK, Coco A, Epp SB, Crook JM, Chronic depolarization enhances the trophic effects of brain-derived neurotrophic factor in rescuing auditory neurons following a sensorineural hearing loss. J Comp Neurol 486: 145-158, 2005.

Link to Publications: <http://www.laryngoscope.com/pt/re/laryngoscope/abstract.00005537-200505000-00009.htm;jsessionid=DqCLLV1CNFDwF0QqhHxOZ84OV9RVDObus4nqZTdObcgq9BmYEcHe!514292530!-949856145!9001!-1> and <http://www3.interscience.wiley.com/cgi-bin/abstract/110474059/ABSTRACT>

Take Two After Each Rock Concert to Protect Your Hearing

Background: Exposure to loud sounds or noise can lead to noise-induced hearing loss (NIHL) by damaging and/or destroying the inner ear's sensory hair cells. Scientists believed that NIHL damaged the hair cells by the pure force of the loud sound vibrations. In that case, the only NIHL prevention was to reduce the sound exposure and/or use ear protectors. Recent studies, however, have found that noise exposure triggers the formation of molecules (free radicals) known to cause hair cell death. Therefore, scientists may be able to dampen or prevent NIHL by using antioxidants that scavenge free radicals. Antioxidants, however, were thought to prevent noise-induced cell death only when given prior to the noise exposure.

Advance: Recently, NIDCD-supported scientists have demonstrated that antioxidants, salicylate (aspirin) and Trolox (vitamin E), could be administered as much as 3 days after noise exposure and still significantly reduce hearing loss. In this study, guinea pigs were exposed to noise at 120dB (equivalent to the noise level of a jet engine) for 5 hours and given antioxidants by injection from 3 days prior to 5 days after the noise exposure. The study showed that earlier treatment was more effective than delayed treatment. Aspirin and Vitamin E administration up to 3 days after noise exposure significantly reduced the extent of hearing loss, hair cell damage, and the amount of free radicals produced following noise exposure.

Implications: These results detail a window of opportunity for rescue from noise trauma. Given the probable safety of aspirin and vitamin E and their use in the prevention of other major disorders, scientists hope to begin clinical trials on their efficacy in humans, with the goal of reducing NIHL.

Citation: Yamashita D, Jiang HY, Le Prell CG, Schacht J, Miller JM, Post-exposure Treatment Attenuates Noise-Induced Hearing Loss. Neuroscience 134: 633-642, 2005.

Link to publication: http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T0F-4GD4SSY-D&_coverDate=12%2F31%2F2005&_alid=313850968&_rdoc=1&_fmt=&_orig=search&_qd=1&_cdi=4861&_sort=d&_view=c&_acct=C000000150&_version=1&_urlVersion=0&_userid=10843&md5=e8266ae2b207496a9aeed8335f08e458

BALANCE RESEARCH

Hearing and Balance Development Give Mixed Signals

Background: During development of the mammalian inner ear, specification of cells to form distinct sensory structures for hearing is known to depend on two important signaling molecules called Shh and Wnt. Earlier research showed that Shh was critical for the development of the auditory cavity or sac into the cochlea for hearing, but little was known about what signaled the development of the vestibular organs necessary for balance. Is Wnt responsible?

Advance: NIDCD-supported scientists created mouse embryos containing a transgene that was modified so that cells activated by the Wnt molecule were distinguishable under the microscope. Wnt signaling was active in the top portion of the inner ear vesicle, turning on genes known to be important for balance formation. An interesting role was discovered for Shh, which initiates gene expression in the bottom vesicle; it was found to also restrict the signaling of Wnt within the top portion of the vesicle. Opposing signals between the Shh and Wnt molecules result in different gene expression between the top (balance) and bottom (hearing) components of the inner ear.

Implications: Balance disorders involving the inner ear include vertigo, loss of balance, and loss of appropriate eye movement control. The proper function of the normal adult vestibular system depends on correct developmental processes to produce the needed structural details of the inner ear. This research shows a balance between Shh and Wnt signaling activities in the embryo and provides critical insight for understanding how molecular mechanisms initiate development of the hearing or balance systems.

Citation: Riccomagno MM, Takada S, Epstein DJ, Wnt-dependent regulation of inner ear morphogenesis is balanced by the opposing and supporting roles of Shh. Genes & Devel 19: 1612-1623, 2005.

Link to publication: <http://www.genesdev.org/cgi/content/full/19/13/1612>

OLFACTORY (SENSE OF SMELL) RESEARCH

An Odor Like No Other: Unique Proteins Involved in Smell Recognition

Background: The sense of smell is necessary for mammals to communicate with their environment. The sensory nerve receptors of the vomeronasal organ (VNO) in the nose plays an essential role in the detection of chemical signals secreted by mammals that influence gender, reproductive status, and social dominance. It has been difficult for scientists to define the molecular nature of such signals. One possibility is proteins of the major histocompatibility complex (MHC) class I molecules. MHC molecules play an important role in defining an individual's tissue type by providing a specific cellular marker that is unique for each individual.

Advance: NIDCD-supported scientists have discovered that peptides derived from MHC proteins could provide a special signal that exerts its action via the activation of sensory receptor neurons of the vomeronasal system. When MHC peptides are not kept on cell surfaces and are

released in bodily secretions, they represent a previously unknown family of chemosensory stimuli that can influence social behavior and individuality within a species.

Implications: Pheromones serve as hormones that communicate fundamentally different information and activate the olfactory system in a different way than the smell of food or other airborne compounds. Pheromones convey a variety of socially relevant cues, ranging from the mating status of a female to secretions released during territorial scent marking. These findings demonstrate that MHC peptides activate receptors of the VMO and function as a chemosensory signal, which provides additional information about the genetic status of an individual and allows an animal to uniquely identify another animal as friend or foe.

Citation: Leinders-Zufall T, Brennan P, Widmayer P, Chandramani P, Maul-Pavicic A, Jager M, Li XH, Breer H, Zufall F, Boehm T, MHC Class I Peptides as Chemosensory Signals in the Vomeronasal Organ Science 306: 1033-1037, 2004.

Link to publication: <http://www.sciencemag.org/cgi/content/full/306/5698/1033>

TASTE RESEARCH

Common Worldwide Variation Discovered In Human Taste Receptor Genes

Background: Differences in our sense of taste may have a profound impact on which foods we choose to eat, so it is important to understand the basis of these differences. Recent advances in chemosensory science have led to the identification of taste receptors, located on the surface of taste cells that reside on the taste buds on the tongue. These receptors bind to tastants released from food and initiate signals to the brain, where the specific taste is recognized. It has been known that the *T2R* gene family is involved in detecting bitter taste in humans. This gene family contains 25 different genes, encoding different receptors that allow humans to taste a wide variety of different bitter substances.

Advance: In studying the individual difference in bitter taste sensation, NIDCD intramural scientists discovered that all 25 human bitter taste receptor genes exist in a variety of different forms in the population. These genes encode for different receptor proteins. Evolutionary genetic analyses suggest the different forms of these genes have occurred in high frequencies in the population under the influence of natural selection. This implies that the different forms of each receptor functions to sense different bitter substances. Given the many different forms of each receptor discovered, it is clear that each person is endowed with an almost unique set of bitter-sensing abilities. In addition, for some bitter receptors, different forms are found to be present at higher frequencies in different populations.

Implications: These findings reveal how inherited factors affect taste perception and food preferences in different individuals. These preferences can have major implications for dietary choices each person makes. Obesity and Type 2 diabetes are known to be caused by a combination of genetic and environmental factors. The variations found in taste receptor genes may represent a portion of the underlying causes of these disorders, and additional research is warranted. In addition, the discovery that different forms of a particular gene exist at high frequency in different populations may provide information about ethnic differences in food

preferences and dietary choices, and may allow reveal more about health disparities between different groups of individuals.

Citation: Kim U, Wooding S, Ricci D, Jorde LB, Drayna D, Worldwide haplotype diversity, and coding sequence variation at human bitter taste receptor loci. Human Mutation 26: 199-204, 2005.

Link to publication: <http://www3.interscience.wiley.com/cgi-bin/abstract/110577356/ABSTRACT>

Love for Sweets Isn't Only Based On Your "Sweet Tooth"

Background: Most humans enjoy eating candy and sweets. Sweet-tasting compounds in foods include large proteins (brazzein), as well as smaller carbohydrates (glucose) and artificial sweeteners (saccharine). Taste buds on our tongue contain receptors that are responsive to sweet-tasting compounds. The sweet taste receptor gene family consists of only 3 members. Two of the 3 members are responsible for the production of a separate sweet receptor protein and these two proteins, T1R2 and T1R3, function as a combined complex called a protein dimer. Scientists conclude that the sensitivity and selectivity of the receptor to a wide variety of sweet-tasting compounds must reside in the nature of the interaction between a particular sweet-tasting compound and the different extracellular sites and transmembrane domains within the receptor molecule.

Advances: Scientists have recently found that the molecular basis for sensitivity to the sweet protein, brazzein, depends on a site within a region of the human T1R3 taste receptor but T1R2 is not involved in the binding. Moreover, this site differs from the site needed for the sensitivity to other smaller sweet-tasting molecules.

In another study, scientists have discovered that a mutation in the gene that encodes for T1R2 renders the receptors in cats non-functional; therefore, felines are unable to taste sweet compounds. This is an unusual example of the loss of function of a single gene leading to a specific change in a relatively complex behavior, namely the loss of preference for sweet-tasting compounds. In this case, the loss is selective for sweet taste but other elements of food intake remain normal.

Implications: Taste preference shapes diet, nutrition, and health. The underlying genetic bases for food preferences have significant health implications. This is most apparent in the realm of sweet consumption and the origins of obesity and diabetes. Since preference to sweets appear to have substantial genetic underpinnings, genetic variations, deletions or over-expression become potential behavioral modifiers with important long-term health consequences. It is important to understand sweet taste receptor function at the molecular level in order to design more effective low- and non-caloric sweeteners and sugar substitutes.

Citations: Li X, Weihua L, Wang H, Cao J, Maehashi K, Huang L, Bachmanov AA, Reed DR, Legrand-Defretin V, Beauchamp GK, Brand J, The Cysteine-Rich Region of T1R3 Determines Responses to Intensely Sweet Proteins. J Bio Chem 279: 45068-45075, 2004.

Jiang P, Ji Q, Liu Z, Snyder LA, Benard LMJ, Margolskee RF, Max M, Pseudogenization of a Sweet-Receptor Gene Accounts for Cats' Indifference Toward Sugar. *PLoS Genetics* 1: 27-35, 2005.

Link to publications: <http://www.jbc.org/cgi/content/full/279/43/45068> and <http://genetics.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pgen.0010003#s6>

SPEECH RESEARCH

The Complexities of Singing and Song Learning

Background: Animal models provide neuroscientists with solid evidence on the structure and function of the brain. For example, it is observed that the adult brain may be able to add nerve cells (neurogenesis). Hence understanding the neural circuitry of animals that vocalize (e.g., songbirds) is relevant to the understanding of the neural basis of human speech, given the similarities of structures and abilities in brains of birds and mammals, including humans.

Advance: NIDCD-supported scientists have examined and described the structure and function of nerve cells (neurons) involved in learning, planning, and execution of complex movements. Specifically, scientists are studying the high vocal center (HVC) portion of the brain that is involved in singing and song learning in zebra finch birds and how their nervous system involves movement and hearing associated with learned vocalization. It was observed that during singing, the finch's projection neurons (HVC/RA) send scattered impulses. During song playback, another set of projection neurons (HVC/X) are involved and are essential in vocal plasticity. These local interactions between neurons, including inhibition of other neurons, shape highly selective responses that distinguish the role of HVC in vocalization.

Implications: Research has shown that several neuronal features are likely to be involved in motor and auditory functions of the HVC in song-related activity. Neurons excite interneurons that inhibit other neurons, providing a feed-forward inhibitory mechanism. Interneurons connect to a variety of projection neurons to coordinate their activity. Understanding the complexities of the finch's HVC and how it learns to sing may be relevant to understanding how humans process speech.

Citation: Mooney R, Prather JF, The HVC Microcircuit: the Synaptic Basis for Interactions between Song Motor and Vocal Plasticity Pathways. *J Neurosci* 25, 1952-1964, 2005.

Link to publication: <http://www.jneurosci.org/cgi/content/full/25/8/1952>

VOICE AND LANGUAGE RESEARCH

Uncovering New Language in an Ancient Land

Background: The goal of all language scholars is to uncover the fundamental nature of human language. One way of doing this is to observe the emergence of a new language arising without influence from other languages. This is difficult to do, because humans have been using language for tens of thousands of years, and there are no new languages spoken today. However,

the sign languages used by deaf individuals do not have the same histories as spoken languages. In fact, sign languages are the only natural languages that can still be studied in early stages of development.

Advance: Recently, NIDCD-supported scientists witnessed such an instance of emerging language. Researchers have been investigating a new sign language that arose in isolation in a Bedouin village in Israel with a very high proportion of individuals who are deaf, and their language has been caught in time to document its characteristics and structure just one generation after it first appeared. The researchers found, that in the space of just one generation, a language was born which conveys a wide range of information important to any community. Researchers have also discovered that this new language quickly developed a grammatical structure – specifically, a means for encoding the relations between the do-er of an action, the action itself, and the recipient of the action. Al-Sayyid Bedouin Sign Language (ABSL) encodes this information through the order of words in a sentence, which is Subject, Object, and Verb (e.g., *mother daughter feed*, meaning ‘The mother fed the daughter’). This order was conventionalized by this small language community in a short time, and surprisingly, it differs from that of any of the other languages in the area – Arabic, Hebrew, or Israeli Sign Language. Researchers are exploring the roots of this new structure, its other characteristics, and how the language is changing with each new generation of signers.

Implications: Using this novel approach, a significant basic trait of human language has been identified, that is to develop systematic syntactic structure very early in the course of human communication. The results of this study will also be useful in designing basic natural communication systems for children with language disorders.

Citation: Sandler W, Meir I, Padden C, Aronoff M, The emergence of grammar: Systematic structure in a new language. PNAS 102, 2661-2665, 2005.

Link to publication: <http://www.pnas.org/cgi/content/full/102/7/2661#SEC3>

A Snapshot of Parkinson's Disease

Background: Parkinson’s disease (PD) is a neurological illness that has profound, disabling effects on motor control, speech, voice, and language. The mainstay of treatment since the 1960s has been administration of drugs that replace or mimic the neurotransmitter dopamine in the basal ganglia, which has been lost in the neurodegenerative process that characterizes this disorder. Antiparkinsonian drugs have well-recognized temporal effects, and often lose their effectiveness in alleviating the symptoms of Parkinson’s disease over time. Until recently, brain imaging studies have not attempted to map drug effects as they change over time in PD individuals.

Advance: NIDCD intramural scientists, traced the effects of the drug apomorphine, which mimics the action of dopamine in PD individuals with positron emission tomography (PET). They found that early changes in brain activity may support nonspecific effects on arousal, attention, and mood. On the other hand, later effects, more closely associated with reversal of Parkinsonian symptoms, were seen in those portions of the brain that involve movement. These effects were expected, but dramatic changes were also detected in other portions of the brain, usually not affected with movement. These findings were unexpected because, although changes

in activity were strongly associated with clinical improvement, these latter brain regions (cerebellum and sensory cortices) are not part of the current model for PD, nor have they been thought to play a role in dopamine's actions in the normal brain.

Implications: These results demonstrate that unexpectedly, antiparkinsonian drugs evoke changes in brain activity that occur well outside circuits traditionally thought to underlie symptom production in PD. The fact that these changes occur at the time of maximal clinical improvement suggests that the current model of PD may be over simplified, and needs to be modified. A greater role for the centers of the brain known to control movement in this disorder is consistent with state-of-the-art neuroimaging studies that have only very recently demonstrated a close (and similarly unexpected) interconnection between other sections of the brain.. The foregoing may precipitate a shift in our understanding of how dopamine regulates movement and speech in the normal brain and of the functional consequences of dopamine loss in PD. These studies should provide a baseline for the evaluation of newer drug treatments for PD and novel surgical interventions such as deep brain stimulation.

Citation: Hosey LA, Thompson JL, Metman LV, van den Munckhof P, Braun AR, Temporal dynamics of cortical and subcortical responses to apomorphine in Parkinson disease: an H₂¹⁵O PET study. Clin Neuropharmacol 28: 18-27, 2005.

Link to publication: <http://www.clinicalneuropharm.com/pt/re/clnneupharm/abstract.00002826-200501000-00005.htm;jsessionid=DpAQLb1EMjujE81SSALNgjpi0Pa6lxR2wqEnd1GgpoY8XpNNYG9b!1971627109!-949856144!9001!-1>

PET Portrays Pictures of the Brain During Vocalization

Background: Voice is an essential function needed for spoken language and in itself transmits important information – about emotional state, intentionality, and arousal – that significantly enriches human communication. Until recently, neuroimaging methods had not been used to evaluate how the brain produces and regulates vocalization – how it organizes and monitors vocalization in the course of speech production. Understanding brain mechanisms that support this process is important because impaired vocalization is a part of a host of human communication disorders.

Advance: Using positron emission tomography (PET), NIDCD intramural scientists have discovered that during phonation, humans activate the older portions of the brain. This same system is used by a wide variety of lower animals when they produce species-specific vocalizations (alarm or mating calls, for example). What makes humans different is that this system appears to have come under voluntary control of more recently evolved regions of the brain. These latter regions are coactivated and strongly coupled with activity in the older regions when humans vocalize. In addition, there are marked differences in the brain regions that humans use in hearing their own voice during speaking as opposed to hearing the voice of others. Moreover, robust functional connections between the hearing and speech systems appear when the brain monitors and corrects speech.

Implications: Identifying and characterizing the human vocalization system at the functional level provides intriguing insights into the evolution of vocal control. Older brain mechanisms

appear to have been recruited and placed under voluntary control during the evolution of speech. Breakdown of these control processes may be important in the understanding disorders characterized by an inability to voluntarily regulate voice and speech, for example, stuttering, spasmodic dysphonia, Tourette's syndrome, and post-stroke dyspraxia. Brain imaging methods may provide a way of evaluating treatments aimed at ameliorating these disorders.

Citation: Schulz GM, Varga M, Jeffires K, Ludlow CL, Braun AR. Functional Neuroanatomy of Human Vocalization: An H215O PET Study. Cereb Cortex Epub doi:10.1093/cercor/bhi061, 2005

Link to publication: <http://cercor.oxfordjournals.org/cgi/content/short/bhi061v2>

NIH ROADMAP

The NIDCD is proud to have one of its premier grantees, Erich D. Jarvis, Ph.D., named among 13 recipients of the 2005 NIH Director's Pioneer Award. The NIH Director's Pioneer Award is a key component of the NIH Roadmap for Medical Research. The NIH Director's Pioneer Award Program supports scientists of exceptional creativity who propose highly innovative approaches to major contemporary challenges in biomedical research. Dr. Jarvis is an associate professor in the Department of Neurobiology at Duke University Medical Center. His research focuses on the molecular basis of how songbirds learn how to communicate. His research project combines molecular, behavioral, electrophysiological, and computational tools to understand how songbirds learn and produce vocalizations. He plans to use his Pioneer Award to pave the way for research on repairing speech and voice disorders in humans.

NIH NEUROSCIENCE BLUEPRINT

The Blueprint is a framework to enhance cooperation among fifteen NIH Institutes and Centers that support research on the nervous system. The Blueprint continues to add new resources for technology and training. It also promotes conceptually integrative advances by improving how resources and information are shared across the research community, and it encourages new research into translational and clinical domains. Those affected by sensory and communication disorders will particularly benefit from NIDCD's participation in the Blueprint. As the Blueprint evolves, feedback from the research community will help guide plans for Blueprint activities.

In FY 2006, NIDCD is contributing to the trans-NIH Neuroscience Blueprint Core Centers grants. This program provides core Neuroscience-related research facilities that are not otherwise available in order to further the understanding of the functions and disorders of the nervous system. Support of the Neuroscience Blueprint Core Centers is expected to assure a greater productivity than would be possible from the separate projects alone. NIDCD's support of these centers reflects its interest in encouraging collaboration among neuroscientists to help us understand ways to restore cells lost in the brain, including the sensory hair cells of the inner ear and cells within the central auditory system.

FY 2007 INITIATIVES

Title: Developmental R24 Grant for Patient Oriented Research and Phased infrastructure R21/R33 Grant for Patient Oriented Research

Mechanism of support: RFA

New or significant expansion: New

Objective: These two RFAs are designed to encourage partnerships (among researchers and interested organizations, e.g., academia, health care organizations, industry, and patient organizations) and support infrastructure needs for patient-oriented research in the NIDCD mission of hearing, balance, smell, taste, voice, speech and language.

Description: The RFAs were developed to provide support for the creation of innovative partnerships to conduct developmental and planning activities for future research applications including the groundwork for research grant applications (R01s, R21s, and P50s). In addition, the RFAs were intended to supply infrastructure such as bioinformatics and data management systems, support for regulatory compliance and management, support for patient recruitment, informed consent and IRB issues, and biostatistical support. The outcomes of the RFAs should be designed with a larger goal to share program outcomes with other institutions.

Title: NIDCD Translational Research Grants

Mechanism of support: PAR

New or significant expansion: New

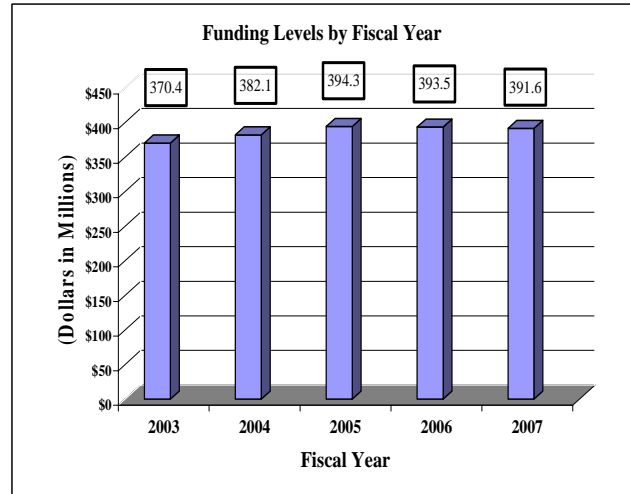
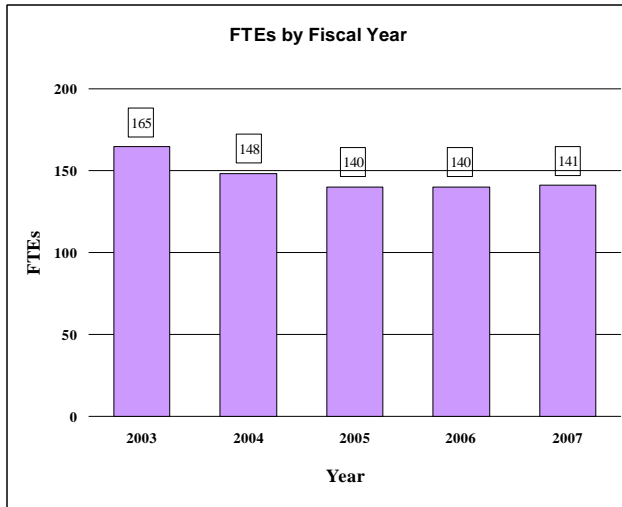
Objective: The PAR hopes to provide a new avenue for basic scientists and clinicians or clinical scientists to jointly explore, initiate, and conduct translational research projects in the NIDCD mission areas of hearing, balance, smell, taste, voice, speech, and language.

Description: A bench-to-bedside approach to translational research requires collaborations and interactions between basic scientists (delivering new information and ideas) and clinical scientists (providing observations about the nature, progression, and treatment of disease). The scope of this PAR includes a range of activities to encourage translation of basic research findings to have a practical impact on the diagnosis, treatment, and prevention of communication disorders.

Budget Policy

The Fiscal Year 2007 budget request for the NIDCD is \$391,556,000, a decrease of \$1,902,000 and 0.5 percent versus the FY 2006 Appropriation. Included in the FY 2007 request is NIDCD's support for the trans-NIH Roadmap initiatives, estimated at 1.2% of the FY 2007 budget request. A full description of this trans-NIH program may be found in the NIH Overview.

A five year history of FTEs and Funding Levels for NIDCD are shown in the graphs below. Note that as the result of several administrative restructurings in recent years, FTE data is non-comparable.



NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while pursuing new research opportunities. We estimate that the average cost of competing RPGs will be \$299,000 in FY 2007. While no inflationary increases are provided for direct recurring costs in noncompeting RPGs, where the NIDCD has committed to a programmatic increase for an award, such increases will be provided.

NIH must nurture a vibrant, creative research workforce, including sufficient numbers of new investigators with new ideas and new skills. In the FY 2007 budget request for NIDCD, \$360,000 will be used to support 2 awards for the new K/R "Pathway to Independence" program.

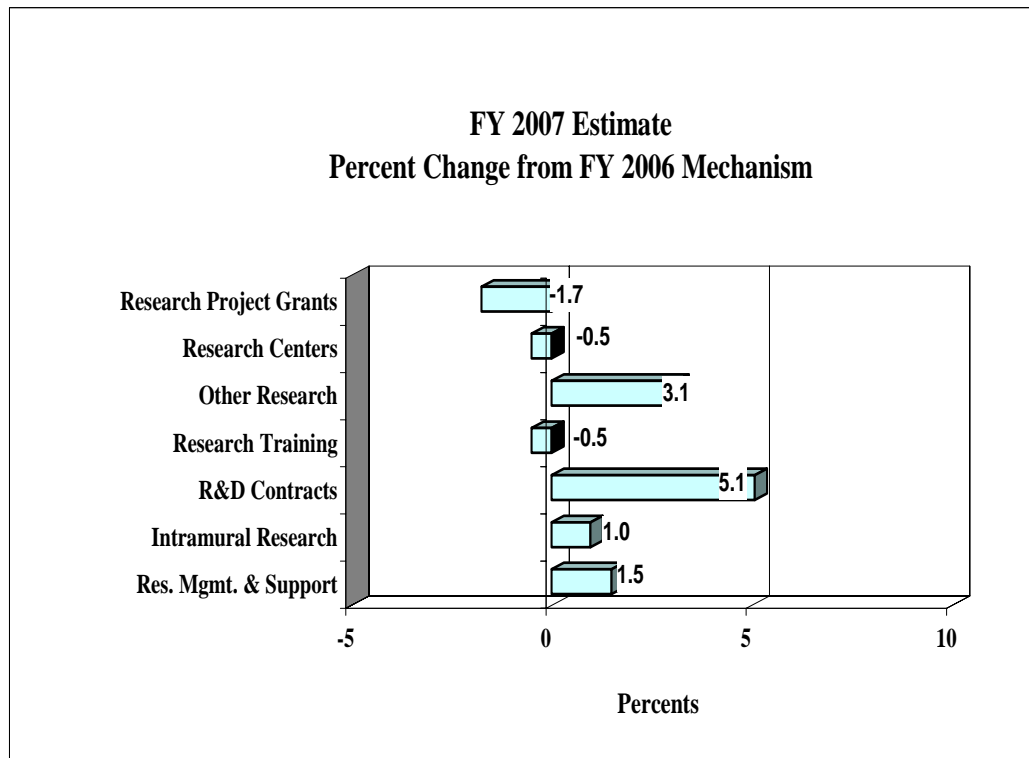
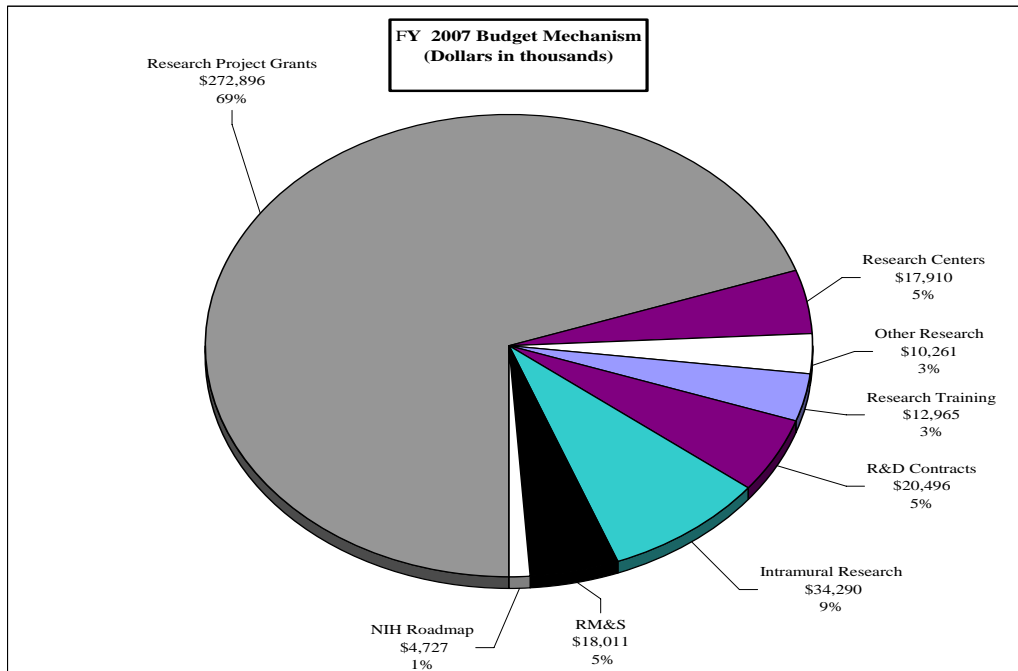
NIDCD will also support the Genes, Environment, and Health Initiative (GEHI) to: 1) accelerate discovery of the major genetic factors associated with diseases that have a substantial public health impact; and 2) accelerate the development of innovative technologies and tools to measure dietary intake, physical activity, and environmental exposures, and to determine an individual's biological response to those influences. The FY 2007 request includes \$676,000 to support this project.

In the FY 2007 request, stipend levels for trainees supported through the Ruth L. Kirschstein National Research Service Awards will remain at the FY 2006 levels.

The FY 2007 request includes funding for 20 research centers, 65 other research grants, including 43 career awards, and 54 R&D contracts. Intramural Research increases by 1.0 percent. Research Management and Support increases by 1.5 percent.

Necessary administrative savings in Research Management and Support will be achieved by reducing the number of scientific workshops sponsored and limiting the number of new publications.

The mechanism distribution by dollars and percent change are displayed below:



NATIONAL INSTITUTES OF HEALTH
National Institute on Deafness and Other Communication Disorders

Budget Mechanism - Total

MECHANISM	FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
<u>Research Projects:</u>						
Noncompeting	683	\$212,189,000	641	\$203,434,000	630	\$202,695,000
Administrative supplements	(23)	757,000	(23)	750,000	(23)	750,000
<u>Competing:</u>						
Renewal	63	23,098,000	68	24,800,000	67	25,000,000
New	138	36,927,000	148	39,642,000	135	35,351,000
Supplements	0	0	0	0	0	0
Subtotal, competing	201	60,025,000	216	64,442,000	202	60,351,000
Subtotal, RPGs	884	272,971,000	857	268,626,000	832	263,796,000
SBIR/STTR	32	9,317,000	45	9,125,000	45	9,100,000
Subtotal, RPGs	916	282,288,000	902	277,751,000	877	272,896,000
<u>Research Centers:</u>						
Specialized/comprehensive	21	17,039,000	20	18,000,000	20	17,910,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	100,000	0	0	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	21	17,139,000	20	18,000,000	20	17,910,000
<u>Other Research:</u>						
Research careers	42	7,251,000	41	7,100,000	43	7,425,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	0	0	0	0	0
Other	18	2,189,000	22	2,850,000	22	2,836,000
Subtotal, Other Research	60	9,440,000	63	9,950,000	65	10,261,000
Total Research Grants	997	308,867,000	985	305,701,000	962	301,067,000
<u>Research Training:</u>	<u>FTEs</u>		<u>FTEs</u>		<u>FTEs</u>	
Individual awards	147	5,531,000	144	5,500,000	143	5,473,000
Institutional awards	190	7,677,000	183	7,530,000	182	7,492,000
Total, Training	337	13,208,000	327	13,030,000	325	12,965,000
Research & development contracts (SBIR/STTR)	54 (0)	18,818,000 (21,000)	54 (0)	19,506,000 (21,000)	54 (0)	20,496,000 (0)
<u>Intramural research</u>	<u>FTEs</u>		<u>FTEs</u>		<u>FTEs</u>	
Intramural research	72	34,166,000	72	33,960,000	73	34,290,000
Research management and support	68	16,709,000	68	17,745,000	68	18,011,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Buildings and Facilities		0		0		0
NIH Roadmap for Medical Research	0	2,492,000	0	3,516,000	0	4,727,000
Total, NIDCD	140	394,260,000	140	393,458,000	141	391,556,000
(Clinical Trials)		(2,245,000)		(2,890,000)		(2,890,000)

NATIONAL INSTITUTES OF HEALTH
National Institute on Deafness and Other Communication Disorders

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2005		FY 2006		FY 2007		Change	
	Actual		Appropriation		Estimate			
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
<u>Extramural Research:</u>								
Deafness and Other Communication Disorders		\$340,893		\$338,237		\$334,528		(\$3,709)
Subtotal, Extramural research		340,893		338,237		334,528		(3,709)
Intramural research	72	34,166	72	33,960	73	34,290	1	330
Res. management & support	68	16,709	68	17,745	68	18,011	0	266
Cancer Control & Prevention	0	0	0	0	0	0	0	0
NIH Roadmap for Medical Research	0	2,492	0	3,516	0	4,727	0	1,211
Total	140	394,260	140	393,458	141	391,556	1	(1,902)

NATIONAL INSTITUTES OF HEALTH
National Institute on Deafness and Other Communication Disorders

Summary of Changes

FY 2006 Appropriation		\$393,458,000	
FY 2007 Estimate		391,556,000	
Net change		(1,902,000)	
CHANGES	FY 2006 Appropriation		Change from Base
	FTEs	Budget Authority	FTEs Budget Authority
A. Built-in:			
1. Intramural research:			
a. Within grade increase		\$10,314,000	\$133,000
b. Annualization of January 2006 pay increase		10,314,000	81,000
c. January 2007 pay increase		10,314,000	174,000
d. Payment for centrally furnished services		5,535,000	83,000
e. Increased cost of laboratory supplies, materials, and other expenses		18,111,000	362,000
Subtotal			833,000
2. Research Management and Support:			
a. Within grade increase		8,262,000	137,000
b. Annualization of January 2006 pay increase		8,262,000	65,000
c. January 2007 pay increase		8,262,000	141,000
d. Payment for centrally furnished services		2,592,000	39,000
e. Increased cost of laboratory supplies, materials, and other expenses		6,891,000	138,000
Subtotal			520,000
Subtotal, Built-in			1,353,000

NATIONAL INSTITUTES OF HEALTH
National Institute on Deafness and Other Communication Disorders

Summary of Changes--continued

CHANGES	FY 2006			
	Appropriation		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	641	\$204,184,000	(11)	(\$739,000)
b. Competing	216	64,442,000	(14)	(4,091,000)
c. SBIR/STTR	45	9,125,000	0	(25,000)
Total	902	277,751,000	(25)	(4,855,000)
2. Research centers	20	18,000,000	0	(90,000)
3. Other research	63	9,950,000	2	311,000
4. Research training	327	13,030,000	(2)	(65,000)
5. Research and development contracts	54	19,506,000	54	990,000
Subtotal, extramural				(3,709,000)
6. Intramural research	<u>FTEs</u> 72	33,960,000	<u>FTEs</u> 1	(503,000)
7. Research management and support	68	17,745,000	0	(254,000)
8. NIH Roadmap for Medical Research	0	3,516,000	0	1,211,000
Subtotal, program		393,458,000		(3,255,000)
Total changes	140		1	(1,902,000)

NATIONAL INSTITUTES OF HEALTH
National Institute on Deafness and Other Communication Disorders

Budget Authority by Object

	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	140	141	1
Full-time equivalent of overtime & holiday hours	0	0	0
Average ES salary	\$152,200	\$155,200	\$3,000
Average GM/GS grade	12.4	12.4	0.0
Average GM/GS salary	\$88,706	\$90,658	\$1,952
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	\$136,179	\$139,175	\$2,996
Average salary of ungraded positions	95,154	97,247	2,093
OBJECT CLASSES	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	\$8,480,000	\$9,114,000	\$634,000
11.3 Other than Full-Time Permanent	4,020,000	4,260,000	240,000
11.5 Other Personnel Compensation	314,000	340,000	26,000
11.7 Military Personnel	129,000	0	(129,000)
11.8 Special Personnel Services Payments	2,174,000	2,217,000	43,000
Total, Personnel Compensation	15,117,000	15,931,000	814,000
12.0 Personnel Benefits	3,390,000	3,445,000	55,000
12.2 Military Personnel Benefits	42,000	0	(42,000)
13.0 Benefits for Former Personnel	27,000	30,000	3,000
Subtotal, Pay Costs	18,576,000	19,406,000	830,000
21.0 Travel & Transportation of Persons	520,000	524,000	4,000
22.0 Transportation of Things	32,000	32,000	0
23.1 Rental Payments to GSA	0	0	0
23.2 Rental Payments to Others	100,000	101,000	1,000
23.3 Communications, Utilities & Miscellaneous Charges	675,000	680,000	5,000
24.0 Printing & Reproduction	150,000	150,000	0
25.1 Consulting Services	170,000	168,000	(2,000)
25.2 Other Services	1,280,000	1,285,000	5,000
25.3 Purchase of Goods & Services from Government Accounts	32,719,000	33,095,000	376,000
25.4 Operation & Maintenance of Facilities	490,000	495,000	5,000
25.5 Research & Development Contracts	8,850,000	9,498,000	648,000
25.6 Medical Care	1,424,000	1,425,000	1,000
25.7 Operation & Maintenance of Equipment	1,070,000	1,075,000	5,000
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	46,003,000	47,041,000	1,038,000
26.0 Supplies & Materials	3,230,000	3,091,000	(139,000)
31.0 Equipment	1,925,000	1,772,000	(153,000)
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	318,731,000	314,032,000	(4,699,000)
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	0	0	0
44.0 Refunds	0	0	0
Subtotal, Non-Pay Costs	371,366,000	367,423,000	(3,943,000)
NIH Roadmap for Medical Research	3,516,000	4,727,000	4,727,000
Total Budget Authority by Object	393,458,000	391,556,000	1,614,000

NATIONAL INSTITUTES OF HEALTH
National Institute on Deafness and Other Communication Disorders

Salaries and Expenses

OBJECT CLASSES	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	\$8,480,000	\$9,114,000	\$634,000
Other Than Full-Time Permanent (11.3)	4,020,000	4,260,000	240,000
Other Personnel Compensation (11.5)	314,000	340,000	26,000
Military Personnel (11.7)	129,000	0	(129,000)
Special Personnel Services Payments (11.8)	2,174,000	2,217,000	43,000
Total Personnel Compensation (11.9)	15,117,000	15,931,000	814,000
Civilian Personnel Benefits (12.1)	3,390,000	3,445,000	55,000
Military Personnel Benefits (12.2)	42,000	0	
Benefits to Former Personnel (13.0)	27,000	30,000	3,000
Subtotal, Pay Costs	18,576,000	19,406,000	830,000
Travel (21.0)	520,000	524,000	4,000
Transportation of Things (22.0)	32,000	32,000	0
Rental Payments to Others (23.2)	100,000	101,000	1,000
Communications, Utilities and Miscellaneous Charges (23.3)	675,000	680,000	5,000
Printing and Reproduction (24.0)	150,000	150,000	0
Other Contractual Services:			
Advisory and Assistance Services (25.1)	170,000	168,000	(2,000)
Other Services (25.2)	1,280,000	1,285,000	5,000
Purchases from Govt. Accounts (25.3)	13,901,000	13,910,000	9,000
Operation & Maintenance of Facilities (25.4)	490,000	495,000	5,000
Operation & Maintenance of Equipment (25.7)	1,070,000	1,075,000	5,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	16,911,000	16,933,000	22,000
Supplies and Materials (26.0)	3,227,000	3,087,000	(140,000)
Subtotal, Non-Pay Costs	21,615,000	21,507,000	(108,000)
Total, Administrative Costs	40,191,000	40,913,000	722,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS COMMITTEE REPORTS

FY 2006 House Appropriations Committee Report Language (H. Rpt. 109-143)

Item

Hearing loss.--The Committee encourages NIDCD to further research in the area of early identification of hearing loss and interventions strategies. The Committee urges the NIDCD to continue to support research in the areas of inner ear protection, rescue, and regeneration, such as noise-induced hearing loss, ototoxicity and hair cell regeneration, as well as research on the central auditory system. In addition, the Committee encourages the NIDCD to continue research on rehabilitative technologies and strategies, leading to improved prevention, treatment, and management of hearing loss, tinnitus, and dizziness. The Committee recommends that the NIDCD maintain support for the translation of basic research discoveries into better clinical diagnostic techniques and treatments (p. 89).

Action taken or to be taken

Early identification of hearing loss: NIDCD supports a robust research portfolio on early identification strategies, including hearing screening systems for measuring auditory brainstem responses (ABR) and otoacoustic emissions (OAE) and interventions. NIDCD supports research that will assist clinicians as they characterize auditory performance in a newborn who fails hearing screening, as well as research that designs intervention strategies to optimize communication success.

Inner ear protection and noise-induced hearing loss: NIDCD-supported scientists are making new discoveries that will help prevent noise-induced hearing loss (NIHL). They have demonstrated that antioxidants, salicylate (aspirin) and Trolox (vitamin E), could be administered as much as 3 days after noise exposure and still significantly reduce NIHL. NIDCD will continue to increase awareness of NIHL by (1) encouraging the use of appropriate ear protection and (2) reducing the number of individuals who suffer from noise-induced hearing loss through research and public education activities such as the WISE EARS! campaign.

Hair cell regeneration and ototoxicity: NIDCD is continuing its dedicated support of research to regenerate hair cells within the inner ear. NIDCD-supported scientists have also learned how gene therapy may help restore lost hearing. In FY 2005, they reported the first successful demonstration of gene therapy that improves hearing in formerly deaf animals. They hope to use this type of gene therapy to restore hearing in humans. Other NIDCD-supported scientists have improved gene therapy for the ear by developing a new type of virus to deliver important genes to ear tissues. The virus infected nearly all hair cells and supporting cells, making it an attractive new tool for reestablishing new hair cells within a damaged ear. Scientists also identified genes responsible for increased susceptibility to ototoxic drugs, such as aminoglycosides. This knowledge may provide a key to preventing hearing loss caused by antibiotic therapies.

Management of hearing loss, tinnitus, and dizziness: NIDCD is sponsoring a workshop on Tinnitus in FY 2006. The workshop will bring together experts working in the field to identify common research areas that require more investigation. NIDCD will use the recommendations from this workshop to develop targeted research funding opportunities in order to improve our ability to prevent, treat, and manage tinnitus.

NIDCD is also conducting two clinical trials to (1) identify genes and mutations causing hereditary disorders of hearing, balance, or both and (2) test how well exercise therapy can help restore visual sharpness to individuals with balance disorders that suffer from blurred vision when they move their heads.

Translation of basic research discoveries into better clinical diagnostic techniques and treatments: Using recommendations generated by a 2004 workshop, the NIDCD has developed several initiatives in translational research. These initiatives, including the recently released “Dissemination and Implementation Research in Health”, will encourage collaborative research to hasten translation of basic research findings into practical guidelines to improve treatment and prevention of deafness and other communication disorders. NIDCD has also placed greater emphasis on translational research by creating a new branch within the Division of Scientific Programs to coordinate extramural translational research for the institute. NIDCD recruited a chief for this branch in FY 2005.

Item

Early hearing detection and intervention (EHDI).--The Committee encourages the NIDCD to enhance its EHDI research, especially as it pertains to the genetics of hearing loss, the causes of late-onset and progressive hearing loss, the benefits of early identification, and the identification of and effective intervention for children with monaural and milder degrees of hearing loss. To avoid duplication, the NIDCD should coordinate its efforts with other institutes and agencies conducting EHDI activities (p. 90).

Action taken or to be taken

Research on early hearing detection and intervention is an active and important area of the NIDCD’s research portfolio. Infants who are born deaf or hard-of-hearing have a better chance of learning language if the hearing loss is found immediately after they are born and if they learn a spoken or signed language as early as possible. Better understanding of late-onset and progressive hearing loss continues to be a priority research area for NIDCD.

Congenital cytomegalovirus (CMV) infection is thought to be responsible for a significant proportion of late-onset and progressive childhood hearing loss. In FY 2005, NIDCD awarded a major new contract entitled “The Natural History of CMV related Hearing Loss and the Feasibility of CMV Screening as Adjunct to Hearing Screening in the Newborn.” The goals of this seven year study are (1) to correlate CMV status at birth with the presence of permanent and/or progressive sensorineural hearing loss and (2) to determine the extent to which CMV screening can improve detection and predictions of either existing or progressive hearing loss if combined with physiological metrics already in use for newborn hearing screening. Hearing loss of genetic origin is responsible for approximately 50% of childhood hearing loss. NIDCD is

supporting multidisciplinary research to understand how to use genetic information in the clinical management of children and infants with hereditary hearing impairment.

NIDCD was an active participant in the planning and conduct of a July 2005 CDC-sponsored National Workshop on Mild and Unilateral Hearing Loss. The goal was to assemble a knowledgeable group of individuals that represented research and practice to develop plans to respond to research needs and objectives in areas such as screening for hearing loss, diagnostic evaluation and follow-up technology and early intervention.

NIDCD continues to interact with other institutes and agencies conducting EHDI activities and participated in a May 2005 meeting on “Closing the Gaps in Programs and Services for Infants and Young Children with Hearing Loss.” This initiative addresses the goals and objectives of the New Freedom Initiative for Americans with Disabilities and the Healthy People 2010 Objectives for the Nation.

Item

Neurofibromatosis (NF) – NF accounts for approximately five percent of genetic forms of deafness. Unlike other genetic forms of deafness, NF-associated deafness is potentially preventable or curable if tumor growth is halted before damage has been done to the adjacent nerve. Research is now being conducted to cure deafness in NF mice through gene therapy, with important implications for patients suffering from meningiomas and other tumors. The Committee encourages NIDCD to strengthen its NF research portfolio through all suitable mechanisms including RFAs and clinical trials (p. 90).

Action taken or to be taken

Neurofibromatosis Type 2 (NF2) is a group of inherited disorders in which non-malignant tumors grow on several nerves that usually include the hearing and vestibular (balance) nerve. Ongoing research at the NIDCD on NF2 includes studying the mechanism by which the NF2 gene is regulated in a mouse model, which will provide information as to how tumor formation can be prevented. The long-term objective is to further identify and understand factors that affect the development and/or growth of NF2 tumors. These studies will hopefully lead to the development of novel therapeutics toward the cure of NF2 tumors.

The NIDCD continues to support technologies to enhance the successful treatment of individuals with NF2. Individuals with NF2 may be required to undergo surgery to remove the acoustic neuroma. However, this procedure may result in damage to the auditory nerve and lead to deafness. NIDCD is supporting a R&D contract to develop a cochlear nucleus auditory prosthesis (Auditory Brainstem Implant or ABI) for individuals who have lost their hearing from NF2. This implantable device would be a benefit to deaf individuals that are unable to gain benefit from a conventional cochlear implant. The ABI has been in clinical trials for both adults and children with NF2 for several years. Additionally, scientists have successfully implanted patients with a new modified version of the ABI called the Penetrating Electrode Auditory Brainstem Implant (PABI). The PABI, a prosthetic device currently in Phase I clinical trials, has an additional assembly of microelectrodes designed to penetrate into the auditory portion of the brainstem (cochlear nucleus). The ABI and PABI, based on cochlear implant technology, stimulates the hearing portions of the brain to restore some degree of hearing function to people

deafened by bilateral tumors on their hearing and balance nerves. If successful, physicians will have a viable means to restore hearing function to individuals with NF2.

Moreover, in conjunction with NINDS, the lead institute at the NIH for NF research, NIDCD is participating in a trans-NIH Program Announcement soliciting applications for the establishment of National Centers for Neurofibromatosis Research. Recent discoveries have created important opportunities for basic, translational, and clinical research on the neurofibromatoses. The purpose of this Program Announcement is to encourage the formation and development of research centers that can capitalize on these opportunities, and ultimately develop therapeutic intervention for individuals with neurofibromatosis. These new centers are intended to provide focused expertise and resources, and establish a multi-disciplinary environment that will accelerate research progress.

FY 2006 Senate Appropriations Committee Report Language (S. Rpt. 109-103)

Item

Balance Disorders.--The Committee is aware that over 124 million Americans have experienced dizziness or a balance problem, and the cost of medical care for individuals with balance disorders exceeds \$1,400,000,000 annually. Over 50 percent of elderly individuals interviewed at home complain of balance disorders. Despite research into the organization and function of these balance receptors located in the inner ear, there is a need to study the genes expressed in these tissues in order to understand why receptors commonly fail or become dysfunctional. Gene discovery techniques including cDNA libraries and microarray expression profiling are likely to lead to new drugs to treat or prevent vestibular disorders and greater understanding of how these systems work. The Institute is urged to expand its support of research in this promising area (p. 135).

Action taken or to be taken

Although a multitude of genes have been identified in which mutations can cause hearing loss, molecular mechanisms underlying familial disorders affecting peripheral vestibular function appear to be rare and have not been well described. Ongoing research at NIDCD includes characterizing genes essential to normal development and function in the vestibular system. The genetic bases of several inherited cerebellar syndromes of imbalance and un-coordination are being investigated, as well. In addition, NIDCD is currently recruiting individuals for a clinical trial to investigate the genetic analysis of hereditary disorders of hearing loss or balance disorders. This clinical trial will attempt to (1) define and characterize phenotypes and natural histories of subjects in the trial; (2) identify the underlying causative mutations and genes by linkage, positional cloning, and/or candidate gene mutation analysis; and (3) correlate observed phenotypes with the corresponding mutations and functions of the underlying genes. In addition to the trial and basic research, NIDCD recently supported the Fifth International Symposium on Ménière's Disease and Inner Ear Homeostasis Disorders. Scientists presented papers at the meeting that addressed the genetics of Ménière's disease, which can involve vertigo and balance dysfunction. NIDCD remains committed to investigating all causes of balance disorders, and is enthusiastic about continuing its research and learning more about genetic influences in balance disorders.

Item

Environmentally-induced Hearing Loss -- The Committee continues to be concerned by the number of Americans who suffer from chemical and noise-induced hearing loss and strongly supports the expansion of NIDCD's Wise Ears! Campaign among school-age children. The Committee also supports expanded research on prosthetic and pharmacological therapies for hearing loss from noise stress and ototoxic drugs (p. 136).

Action taken or to be taken

NIDCD's WISE EARS!® national campaign efforts focus especially on the prevention of noise-induced hearing loss in children and workers in noisy environments. For more than 5 years, NIDCD has built a coalition network with nearly 100 organizations nationwide to promote awareness about protecting our hearing for a lifetime. For elementary school teachers and students NIDCD has developed the "I Love What I Hear" classroom activity and video for Grades 3 through 6, along with a web-based interactive sound ruler and a "How Loud Is Too Loud" bookmark. Recently, this educational outreach video aired on a news program that reaches 8 million students in 12,000 schools. NIDCD also developed a middle school curriculum supplement, "How Your Brain Understands What Your Ear Hears." Students in Grades 7 and 8 learn to develop healthy hearing habits and to avoid excessive exposure to loud noise that can lead to hearing loss. These materials are available on the NIDCD Web site, along with a Kids and Teachers Web page that has become a major resource for information about noise-induced hearing loss (NIHL) prevention. Students, teachers, and parents have access to interactive quizzes, learning tools, and videos that are available in English and Spanish. Print materials also are available for teachers without Web resources. Later in 2006, NIDCD is planning to participate in a national conference on Noise-Induced Hearing Loss in Children and Youth at Work and Play and explore new partnerships to expand the WISE EARS!® campaign objectives to reach younger audiences.

NIDCD supports basic research directed towards developing pharmacological therapies for hearing loss, including deafness resulting from excess noise or ototoxic drugs. Recent studies have shown that loud noise exposure triggers the formation of molecules (free radicals) known to cause hair cell death and using antioxidants may dampen or prevent NIHL by purging free radicals. Antioxidants were thought to prevent noise-induced cell death only when given prior to the noise exposure, however, NIDCD-supported scientists recently demonstrated that antioxidants, salicylate (aspirin) and Trolox (Vitamin E), could be administered soon after noise exposure and still significantly reduce hearing loss. The study showed that earlier treatment was more effective than delayed treatment. Aspirin and Vitamin E administration up to 3 days after noise exposure significantly reduced the extent of hearing loss, hair cell damage, and the amount of free radicals produced following noise exposure. These results detail a window of opportunity for rescue from noise trauma. Given the probable safety of aspirin and vitamin E and their use in the prevention of other major disorders, scientists hope to begin clinical trials on their efficacy in humans, with the goal of reducing NIHL. There is also research underway in animals to study the possible use of gene therapy to prevent the death of sensory hair cells and spiral ganglion neurons following exposure to certain antibiotics that are toxic to the structures of the inner ear.

In addition to these studies, NIDCD supports many research projects that supports applied research to develop improved hearing aids and other prosthetic devices for individuals with

hearing loss. For example, research is being conducted to develop directional microphones for hearing aids that can better determine speech in a noisy environment. Scientists are also studying ways to improve electrode technology and speech processing strategies for cochlear implants.

Item

Hearing Devices for Children.--Everything that is known about hearing aids and cochlear implants is based on adult needs. Hearing aids also need to be optimized for children's needs, because there are so many differences between adults and children. Therefore, the Committee encourages NIDCD to support a collaborative effort of researchers to participate in a multi-center, longitudinal research project to track auditory development and speech perception in hearing-impaired infants. In addition, the Committee encourages the NIDCD to explore the feasibility of electrical stimulation applied to the vestibular system (analogous to the cochlear implant) to treat balance disorders (p. 136).

Action taken or to be taken

NIDCD is supporting and encouraging new research that would improve the benefits of hearing aids and cochlear prostheses for children with profound hearing loss as well as provide benefits for those with less-than-profound hearing loss. New studies are investigating the benefits of binaural cochlear implantation (a cochlear implant in each ear), the use of a cochlear implant in one ear and a hearing aid in the other (bimodal stimulation), and the development of new listening and training paradigms to increase the performance of current cochlear implant users.

In addition to these ongoing activities, NIDCD awarded several new grants in FY 2005 in response to a Request for Applications on Speech Processor Optimization for Cochlear Implants. This initiative seeks to stimulate innovation in the design of cochlear implants to provide gains in user benefit, especially under noisy condition (typical of children's daily exposure) that are currently correlated with poor user performance. In addition, NIDCD awarded two contracts with strong emphasis and relevance to pediatric issues to investigate the effects of electrical stimulation in animal models of the developing auditory system. These contract awards will examine neural changes dependent upon the type and duration of electrical stimulation; studies in young animals are specifically required by the contract statement of work. The scientists supported by the contract will acquire data from neonatal deafened animals that will guide future decisions on the care of pediatric individuals with severe to profound hearing loss

NIDCD supports several ongoing longitudinal research projects (both single-center and multi-center) to track auditory development and speech perception in hearing-impaired infants. These multidisciplinary research grants are studying the auditory capacity of hearing-impaired children to understand how age-of-identification and communication mode affect spoken language, and cognitive and psychosocial development in young children with hearing loss. This research could lead to the development of new behaviorally based methodologies that will give clinicians new tools to optimize auditory processing skills in hearing-impaired and deaf infants before and after hearing aid fitting and cochlear implantation.

NIDCD sponsored a workshop on Electrical Stimulation of the Vestibular Nerve on June 2004. Presentations were given by extramural scientists to identify opportunities for development of

neural prostheses to electrically stimulate the vestibular portion of the eighth nerve. Roundtable discussions were held to discuss needs for further basic research, technology platforms for research and development, safety concerns, and to identify clinical populations that would benefit from initial applications of this technology. NIDCD recently issued a Request for Proposals for the development of devices analogous to the modern cochlear implant, which stimulates the vestibular nerve.

Item

Hereditary Hearing Loss.--The Committee applauds the remarkable progress towards understanding the molecular basis for hereditary hearing impairment and encourages NIDCD to continue to support research to identify the structure, regulation and function of genes whose mutation results in human communication disorders, including deafness. The Committee continues to encourage efforts to screen for the single and multi-genetic bases of hearing loss through contemporary techniques, including diagnostic gene chips. The Committee encourages the development of animal models to better assess how gene mutations result in impaired central auditory function (p. 136).

Action taken or to be taken

NIDCD Division of Intramural Research has several major efforts aimed at identifying genes that cause deafness in both humans and in animal models as well as programs to characterize the function and regulation of these genes. These genes generally affect the peripheral auditory system, but provide information and models for studying changes that occur in the central auditory system as a result of these peripheral changes.

NIDCD also encourages the use of new state-of-the-art molecular techniques to improve our understanding of underlying pathology causing deafness and for improving diagnostic capabilities. For example, NIDCD is supporting work to uncover the pathophysiological mechanisms of human auditory diseases by analyzing mouse genetic models using proteomic and genomic approaches. NIDCD-supported scientists are developing a subtractive strategy in which digitized abundance of transcripts and proteins in mutant mice with lost inner ear structures is subtracted from those of control mice with normal inner ear structures. Transcript comparisons between mutants and controls are being made by cDNA microarray analysis. The identified differences will be useful for developing strategies for prevention and treatment human ear diseases. Genes, proteins and their molecular pathways that are identified become potential targets of drug therapies for hearing loss.

NIDCD is supporting work to improve molecular diagnostic capabilities of hearing loss. For example, despite the discovery of genes for nonsyndromic hearing loss, very few genetic tests have been developed, primarily due to the enormous cost of offering full sequencing of these genes with few known common mutations. To address this problem, NIDCD is currently funding research, which utilizes state-of-the-art techniques to begin to develop a Deafness GeneChip starting with eight genes known to be involved in recessive nonsyndromic hearing loss. The number of genes on the chip will increase as the technology is refined. This is a promising and cost-effective way to expand genetic testing for hearing loss. This methodology is new to clinical diagnostics and is being validated in a rigorous manner.

Item

Inner Ear Hair Cell Regeneration.--The Committee applauds past support of regenerative studies, such as those in guinea pigs, and urges NIDCD to continue to give a high priority to new and important directions in restoring hair cells of the cochlea, such as gene therapy, adenovirus vectors, and stem cells. The Committee also encourages NIDCD to request more collaborative applications among scientists working on the isolation of stem cells in the brain and scientists working in the inner ear hair cell field (p. 136).

Action taken or to be taken

NIDCD is continuing its support of research to restore hair cells to the cochlea of the inner ear. For example, the Institute is participating in a trans-NIH effort to understand how stem cells interact with their immediate environment inside the body by participating in an initiative called "Interactions between Stem and Progenitor Cells and the Microenvironment *in vivo*." NIDCD's interest in funding this research is based on the idea that if we wish to use stem cells as therapy to restore lost function, such as hearing loss, we must first understand how stem cells function in their normal environment.

In FY 2005, researchers supported by NIDCD have made significant progress towards understanding how hair cells of the inner ear are produced and function. They identified several genes that control the development of hearing. This knowledge is a critical precursor to being able to reactivate the developmental programs that produce the inner ear's hair cells.

NIDCD-supported scientists have also learned how gene therapy may help restore lost hearing. In FY 2005, they reported the first successful demonstration of gene therapy that improves hearing in formerly deaf animals. Scientists hope to use this type of gene therapy to restore hearing in humans. Other NIDCD-supported scientists have improved gene therapy for the ear by developing a new type of virus to deliver important genes to ear tissues. The virus infected nearly all hair cells and supporting cells, making it an attractive new tool for reestablishing new hair cells within a damaged ear.

Item

Learning Disabilities.--The Committee is pleased that the NIDCD continues to support research activities focused on speech processing and on the development of expressive and receptive language. The Committee encourages continued activity and looks forward to learning the results of this work as they hold significant promise for individuals with learning disabilities. The Committee encourages the Institute to continue to coordinate with other Institutes working on related activities (p. 137).

Action taken or to be taken

NIDCD has a longstanding commitment to, as well as continuing support of, research into identification and outcomes of early language disorders. In addition, NIDCD encourages research into the school-aged academic difficulties of children with specific communication disorders, such as hearing loss or Specific Language Impairment (SLI). Research currently is focused on ways to improve speech perception, speech production, and understanding and use of

language in these populations, thereby lessening and perhaps avoiding the academic problems associated with preschool language disorders. One of the anticipated benefits of cochlear implantation in children is improved acquisition of spoken language. NIDCD supports a variety of research investigations into the language acquisition characteristics of children who have received implants, as well as their long-term outcomes related to academic performance.

NIDCD continues to engage in collaborative activities with other institutes at NIH, in particular, NICHD (which supports the majority of NIH-funded research in learning disabilities), NIMH, and NINDS. NIDCD and NICHD recently developed and co-sponsored a request for applications (Typical/Disordered Language: Phenotype Assessment Tools) which resulted in the funding of several outstanding research projects focused on the assessment of childhood language and language disorders. This research is likely to have a significant impact on the identification and treatment of language and learning disabilities in children.

Item

Pharmaceutical Research.--Recognizing the promise of new technologies to deliver pharmaceutical agents to the inner ear, the Committee encourages NIDCD to initiate molecular studies analyzing effectiveness of drugs, genes and gene products on cell death pathways and cascades, followed by trials to assess safety and benefits of pharmaceuticals to prevent and better treat sensorineural hearing loss from various causes (p. 137).

Action taken or to be taken

NIDCD has long supported molecular studies to investigate the importance of cell death pathways and hearing loss. Because hair cells are highly specialized and extremely sensitive to death from a variety of stresses, such as aging, noise trauma, and certain therapeutic drugs, the identification of genes and proteins involved in apoptotic signaling continues to be a strongly supported component of NIDCD portfolio. Currently supported research studies explore comparative animal models combined with high throughput chemical analog screens to identify and discern the effects of putative therapeutic compounds and hearing function. In addition, research is strongly supported in areas of auditory development as a means to better understand cell cycle regulation, which provide key molecular time frames regulating the decisionary process of apoptotic pathways. Recently, NIDCD held a “Molecular Therapies” workshop to gather the necessary expertise to move such significant research findings into real clinical applications. These efforts, in combination with the recently established NIDCD Translational Research Branch (TRB), should enable further expansion of more clinical trial-based programs.

NIDCD also supports research to assess the effectiveness of drugs that specifically promote the survival and function of auditory neurons in damaged ears that lack hair cells, since these neurons are essential for the operation of a cochlear implant. Ongoing contract research is underway to identify candidate drugs and assess their action on the auditory nerve in different animal models. A novel cochlear implant design has been developed that incorporates both a drug delivery system for the cochlea along with the stimulating electrodes. Preliminary results from this approach are promising, although there is concern that the drug delivery system could provide a route for infection into the cochlea. Further research is underway to determine the efficacy of this approach in different animals, over long periods, and effects on nearby cochlear structures. Efforts are also underway to support the development of a device optimized for

administering bioactive compounds directly to the inner ear. One project seeks to develop a programmable drug delivery system for the long-term administration of compounds to the inner ear in order to treat a variety of disorders.

The current clinical trials program seeks to expand to include sponsorship of all stages of clinical trials. Investigators are responding to an initiative to do Phase I/II trials to test drugs that may be otoprotective in those receiving ototoxic chemotherapy, or animal studies that will lead to Phase I trials to test otoprotectants for aminoglycoside-induced hearing loss.

Item

Presbycusis – Presbycusis, the gradual loss of hearing from aging, is the most prevalent type of hearing loss and the third leading chronic disease (following hypertension and arthritis) in people over 65. It will become more common as the Nation’s population grows older. To improve the quality life of millions of senior citizens, the Committee encourages research into declining stria vascularis metabolism, an important factor, as well as continuing studies on the central mechanisms of presbycusis (p. 137).

Action taken or to be taken

There is a strong relationship between age and reported hearing difficulty or presbycusis: 18 percent of American adults age 45-64 years, 30 percent of adults age 65-74 years, and 47 percent of adults age 75 years or older. The age-adjusted prevalence of reported hearing difficulty is higher for men (18.6 percent) than for women (12.6 percent). A less common form of presbycusis occurs in the stria or metabolic structure, which affects both the high and low frequencies of hearing, and usually occurs in families.

The sense of hearing depends on receiving and converting sound energy into nerve impulses that can be transmitted to the brain. The inner ear converts sound into nerve impulses through a system of sensory and motor cells known as the inner and outer hair cells. This nerve transduction requires a high amount of energy, which is supplied by the layer of cells on the lateral wall of the cochlea known as the stria vascularis (SV). The SV has an extremely high metabolism fueled by enzymes that release energy from biochemical compounds to “pump” the flow of potassium ions that form the electrical current within the cochlea. As we age, the function of these energy producing enzymes declines. The result is a decrease in power in the cochlear current, which makes hearing not possible even though the sensory hair cells are intact. Moreover, the loss of the SV is common in presbycusis.

In the aging auditory system, NIDCD continues to make research discoveries toward understanding the loss of SV cells and central neurons in presbycusis seen in animal studies as well as temporal bone studies of individuals with presbycusis. Ongoing NIDCD-supported studies have examined the possibility of the problems with maintaining the appropriate amount of current needed to maintain cochlear health and hearing, which leads to the eventual loss of auditory neurons. Moreover, it is likely that mutation of certain genes known to cause profound hereditary hearing impairment also cause presbycusis. NIDCD-supported studies demonstrate a clear genetic influence in presbycusis. NIDCD is supporting further research in order to formulate innovative strategies to minimize or delay hearing loss in presbycusis.

Item

Translational Research.--The Committee encourages NIDCD to establish a Translational Research Branch to support research activities aimed at accelerating the translations of new findings in the molecular and basic sciences into new interventions and technologies clinicians can use to treat individuals with communication disorders (p. 137).

Action taken or to be taken

NIDCD has created a new Translational Research Branch (TRB) to facilitate the translation of basic biomedical or behavioral research discoveries in the field of deafness and other communication disorders into new clinical and research tools, prostheses and assistive devices, behavioral, pharmacotherapeutic, and surgical therapies. This branch will also expand the existing clinical trials program, and grow a strong cadre of investigators who can lead and implement multisite clinical trials. A new branch chief has been in place since May 2005.

**NATIONAL INSTITUTES OF HEALTH
National Institute on Deafness and Other Communication Disorders**

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2006 Amount Authorized	FY 2006 Appropriation	2007 Amount Authorized	FY 2007 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
Other Communication Disorders	Section 41B	42§285b	Indefinite	\$380,428,000	Indefinite	\$378,591,000
National Research Service Awards	Section 487(d)	42§288	a/	13,030,000		12,965,000
Total, Budget Authority				393,458,000		391,556,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.

NATIONAL INSTITUTES OF HEALTH
National Institute on Deafness and Other Communication Disorders

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation <u>1/</u>
1998	192,477,000 <u>2/</u>	198,373,000	198,583,000	198,857,000
1999	213,184,000 <u>2/ 3/</u>	216,995,000	229,887,000	229,887,000
Rescission				(152,000)
2000	235,297,000 <u>2/</u>	251,218,000	261,962,000	265,185,000
Rescission				(1,414,000)
2001	276,418,000 <u>2/</u>	301,787,000	303,541,000	300,581,000
Rescission				(100,000)
2002	336,757,000	334,161,000	349,983,000	342,072,000
Rescission				(397,000)
2003	365,929,000	351,376,000	372,805,000	372,805,000
Rescission				(2,423,000)
2004	380,377,000	380,377,000	384,577,000	384,477,000
Rescission				(2,424,000)
2005	393,507,000	393,507,000	399,000,000	397,507,000
Rescission				(3,247,000)
2006	397,432,000	397,432,000	418,357,000	397,432,000
Rescission				(3,974,320)
2007	391,556,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research

3/ Reflects a decrease of \$650,000 for the budget amendment for Bioterrorism

NATIONAL INSTITUTES OF HEALTH
National Institute on Deafness and Other Communication Disorders

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Office of the Director	4	4	4
Office of Administration	35	35	35
Division of Extramural Activities	15	15	15
Division of Scientific Programs	14	14	14
Division of Intramural Research	72	72	73
Total	140	140	141
Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research FTEs supported by funds from Cooperative Research and Development Agreements			
	(0)	(0)	(0)
FISCAL YEAR	Average GM/GS Grade		
2003	11.2		
2004	12.2		
2005	12.4		
2006	12.4		
2007	12.4		

NATIONAL INSTITUTES OF HEALTH
National Institute on Deafness and Other Communication Disorders

Detail of Positions

GRADE	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Total - ES Positions	1	1	1
Total - ES Salary	\$149,200	\$152,200	\$155,200
GM/GS-15	22	21	21
GM/GS-14	10	10	10
GM/GS-13	18	17	17
GS-12	20	21	22
GS-11	12	12	12
GS-10	2	2	2
GS-9	8	9	9
GS-8	3	3	3
GS-7	1	1	1
GS-6	0	0	0
GS-5	0	0	0
GS-4	0	0	0
GS-3	0	0	0
GS-2	0	0	0
GS-1	0	0	0
Subtotal	96	96	97
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General Director Grade	1	1	1
Senior Grade Full Grade Senior Assistant Grade Assistant Grade			
Subtotal	1	1	1
Ungraded	47	47	47
Total permanent positions	97	97	98
Total positions, end of year	145	145	146
Total full-time equivalent (FTE) employment, end of year	140	140	141
Average ES salary	\$149,200	\$152,200	\$155,200
Average GM/GS grade	12.4	12.4	12.4
Average GM/GS salary	\$86,039	\$88,706	\$90,658