This monograph presents an update to the strategic plan of the National Institute on Deafness and Other Communication Disorders (NIDCD), focusing on recent accomplishments, program goals, strategies, and priorities in research opportunities in the areas of hearing/hearing impairment and voice/voice disorders. Specifically considered for the hearing area are research needs in transduction and homeostasis, sound processing in the brain, auditory perception, and aging and regeneration of sensory cells. For hearing impairment, research plans are outlined in the areas of hereditary hearing impairment; acquired sensorineural hearing loss; otitis media, otosclerosis, and other middle-ear disorders; and assessment, diagnosis, treatment, and rehabilitation. For voice and voice disorders, research is suggested on: (1) normal structure and function (including laryngeal physiology, lifespan changes, exceptional behavior, and anatomy and physiology of swallowing); and (2) diagnosis and treatment of voice disorders (vocal fold neoplasms, vocal fold lesions and glottal insufficiencies, neurogenic disorders, gastroesophageal reflux, and technology). An executive summary is provided. Appended is the text of Public Law 100-553 which established the Institute. (DB)
National Institutes of Health
National Institute on Deafness and Other Communication Disorders

National Strategic Research Plan

for

Hearing and Hearing Impairment

and

Voice and Voice Disorders

1992
National Institute on Deafness and Other Communication Disorders

National Strategic Research Plan
for Hearing and Hearing Impairment and Voice and Voice Disorders
1992

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The National Deafness and Other Communication Disorders Act of 1988 became Public Law 100-553 (Appendix A) on October 28, 1988, establishing the National Institute on Deafness and Other Communication Disorders (NIDCD) within the National Institutes of Health (NIH). The law required that the Director, NIDCD, establish a National Deafness and Other Communication Disorders Program and prepare a plan to initiate, expand, intensify and coordinate Institute activities concerning disorders of hearing, balance, smell, taste, voice, speech and language.

In response to this mandate, a Task Force of scientific experts representing the seven program areas of the Institute prepared the first National Strategic Research Plan which has guided the Institute over the past three years. The National Strategic Research Plan is also intended to inform the Nation's scientists of areas of opportunity for research and to provide them with guidance as they formulate their own research plans. The Plan informs persons with communication disorders and their support organizations of past research accomplishments and potential future activities. In addition, the Plan is intended to inform members of Congress of research progress and future research opportunities in scientific areas within the purview of the NIDCD.

Public Law 100-553 requires the National Deafness and Other Communication Disorders Advisory Board to review, evaluate and update the plan periodically to assure its continuing relevance. To meet this legislative mandate, the National Advisory Board decided that it would update two of the six sections of the plan every year thus updating the entire plan within a three-year period. The two sections the National Advisory Board selected to be updated in 1992 were Hearing and Hearing Impairment and Voice and Voice Disorders. The National Advisory Board established subcommittees for these two areas which met and made recommendations for panel members to update the Hearing and Hearing Impairment and Voice and Voice Disorders sections of the Plan, compared the research portfolio of the Institute to the National Strategic Research Plan, identified changes in the field since the Plan was developed, recommended levels and areas of research activity and suggested potential initiatives.

Members of the expert panels are due special thanks for giving of their talents and time in seeing this document through to completion. Their meetings brought together representatives of a broad array of scientific disciplines within the areas of hearing and hearing impairment and voice and voice disorders. Members of the expert panels shared their diverse ideas and worked diligently to achieve consensus on a comprehensive view of each field and a vision for the future. Subsequently, expert panel members refined their efforts with numerous revised texts.

Dr. Jeffrey P. Harris and Dr. Mary Joe Osberger, Cochairpersons of the Hearing and Hearing Impairment Expert Panel, and Dr. Thomas J. Hixon and Dr. Gayle E. Woodson, Cochairpersons of the Voice and Voice Disorders Expert Panel, should be singled out for special appreciation. This update to the National Strategic Research Plan is very much a product of their experience, expertise and guidance. Along with their fellow expert panel members, they have formulated a plan for future research in two important scientific areas of the NIDCD.

James B. Snow, Jr., M.D.
Director
National Institute on Deafness and Other Communication Disorders
The National Strategic Research Plan of the National Institute on Deafness and Other Communication Disorders (NIDCD) was prepared in April 1989 and presented the research recommendations of more than 100 eminent scientists in the seven program areas of the NIDCD. These areas are hearing, balance, smell, taste, voice, speech and language. This report contains an update of the Hearing and Hearing Impairment and Voice and Voice Disorders sections of the 1989 plan.

Disorders of hearing and voice affect millions of people in this country. More than 28 million Americans are believed to have impaired hearing, and this number is expected to increase substantially in the next few decades. Hearing impairments may result from aging, genetic factors, infectious and inflammatory diseases, exposure to noise, or other causes. Whatever the basis, these impairments have serious and far-reaching implications for the quality of life of those affected and represent enormous economic costs for treatment. Pursuit of research on normal and disordered hearing will lead to a better understanding of normal hearing processes and to improvements in the prevention, diagnosis, treatment and rehabilitation of hearing impairments.

Voice production or phonation is the generation and modulation of sound and is a subset of the more global process of speech production. In the context of communication, voice is an acoustical representation of language. Disorders of voice involve difficulties with pitch, loudness and quality and can be distinguished from articulation disorders, which present difficulties of speech sound production. Although the economic impact of voice disorders cannot be accurately assessed, these disorders can have devastating effects on those who suffer from them, interfering with their ability to function in a work or social setting.
The updates of the Hearing and Hearing Impairment and Voice and Voice Disorders sections of the National Strategic Research Plan have provided an opportunity to evaluate the progress that has been made in these areas during the past years of the Institute and to assess future needs and opportunities. The recommendations presented here are expected to lead to exciting advances in scientific knowledge and improve the quality of life for many people.

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National Institute on Deafness and Other Communication Disorders
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Hearing and Hearing Impairment

More than 28 million Americans have impaired hearing, and this number is expected to increase substantially in the next few decades due to increasing longevity and the consequent overall aging of the population. Levels of hearing impairment vary from a mild but important loss of sensitivity to a total loss of hearing. The largest group of Americans suffering from hearing loss is the elderly. Age-related hearing loss affects 30 to 35 percent of the United States population between the ages 65 to 75 years and 40 percent of the population over the age of 75 years. Approximately one of every 1000 infants is born with a hearing impairment that is severe enough to prevent the spontaneous development of spoken language, and over 50 percent of these impairments are believed to be of genetic origin. The most common cause of hearing loss in children is otitis media. Otitis media is predominately a disease of infants and young children. This disease is estimated to account for over 10 million visits to the offices of physicians per year and to have a total annual cost of over $3.5 billion. A substantial number of hearing impairments are caused by environmental factors such as noise, drugs and toxins, and many acquired sensorineural hearing losses may result from a genetic predisposition to the development of hearing loss due to these factors. At least 15 percent of the population are affected by tinnitus, many so severely that it disrupts their lives.

Important progress has been made during the last decade in understanding the auditory system. Many insights into the function of the inner ear have been derived from in vivo and in vitro studies. Using in vitro biophysical approaches, characterization of the membrane properties of sensory and neuronal elements within the organ of Corti, the hearing organ, is beginning to provide us with an understanding of the molecular basis of auditory function. Sound energy is detected by inner hair cells, which are now understood as mechanoreceptors. It has been established that the transduction of stimuli by these cells is mediated by ion channels that are directly gated by mechanical forces. Progress has been made in understanding the motility of outer hair cells and how these mechanisms function in vivo. Changes in hearing have been shown to be the most closely associated with the loss of outer hair cells. The origin of the unique fluid movement within the cochlea and details of intracochlear blood flow have been established. In certain species, including the human, the hearing organ generates sound by spontaneous or evoked otoacoustic emissions.
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In humans, this phenomenon may be mediated by outer hair cells and has great promise for practical diagnostic use.

Major strides have been made in studying the regeneration of sensory cells in the ear. Sensory cells can be regenerated in the inner ear of cold-blooded animals, and in avian species in which the production of sensory cells normally ceases in early embryonic development, regeneration can also occur in young and adult birds. Regenerated hair cells originate from cells produced by the proliferation of supporting cells that survive at sites of damage in the inner ear. Since regeneration of sensory cells has not been demonstrated in mammals, sensory hearing impairment has been considered to be permanent and irreversible. Efforts are under way to stimulate regeneration of sensory cells in mammals. If these efforts are successful, they may provide a basis for the hope of stimulating regeneration of auditory hair cells in humans.

New information has been obtained concerning the encoding of complex signals transmitted from the auditory nerve to the brain. The relationship between the neural code for sound intensity, frequency and temporal characteristics and the perception of these stimulus variables has been further clarified. Molecular techniques have been used to identify many of the neurotransmitters and receptors involved at specific synapses throughout the auditory neural axis. Evidence suggests that efferent feedback pathways to the inner and middle ear may aid in the detection of signals in noisy environments and serve to protect the ear from acoustic injury. Neural plasticity or changes in the central nervous system have been described in response to enriched and deprived acoustic environments. New insights have been gained about the ways in which the brain creates maps of auditory space that interact with visual space.

Recent research in auditory psychophysics has produced a set of working models of auditory perception that have led to advances in the understanding of how human and nonhuman listeners assign identities and sources to the sounds that they perceive and how they recognize the communicatively important sounds of single and multiple speakers. There have been a number of important advances in the linking of psychoacoustic and physiologic research. Behavioral measures of frequency selectivity have been developed that allow comparison with electrophysiologic measures of auditory tuning which can now be used to characterize normal and impaired hearing. Increased understanding of the ability of the ear to distinguish changes in spectral shape from intensity changes has been achieved.
Studies on the role of across frequency-band enhancement and interference effects on the detection and location of sounds are providing improved understanding of complex "real-world" auditory perception. Many new approaches are being used to characterize the location of sounds by humans which may lead to new possibilities for presenting sounds through prosthetic devices. Increased study of the role of perceptual learning, selective attention, auditory memory and organization in the formation of auditory percepts has contributed to the understanding of how we attend to multiple sources in complex acoustic environments.

Major advances have been made in identifying the genes that cause hearing loss. Recent accomplishments include the mapping of an Usher syndrome type 2 gene to the long arm of chromosome 1 and a gene for Waardenburg syndrome to the long arm of chromosome 2. Also, a gene for a dominant nonsyndromic form of hearing impairment has been mapped to the long arm of chromosome 5. At least 28 X-linked disorders involve hearing loss. Recent accomplishments include precise location of the gene causing albinism-deafness and tentative evidence of more than one X-linked gene for clinically identical forms of progressive mixed deafness. A further advancement in the field of genetics is the ongoing use of powerful tools of molecular biology to clone the genes for inner-ear development and the assembly of human and animal cochlea-specific cDNA libraries.

The role of genetic factors in acquired sensorineural hearing loss has recently been underscored by the demonstration of a genetically controlled mitochondrial disorder which predisposes the host to aminoglycoside ototoxicity. Such models will enable researchers to understand how and which ototoxic metabolites cause damage to the cochlea. Similar factors may prove to be important in the development of presbycusis, and the identification of mouse models of this condition will also help elucidate potential new therapies for sensorineural hearing impairment.

Recent progress utilizing modern immunobiologic techniques has demonstrated that the inner ear is immunoresponsive and comes under the influence of the host's immune system. Furthermore, it has been shown that immune reactions within the inner ear occur as a result of both the host's normal defense mechanisms as well as an immune response gone awry in the form of autoimmunity. Recent evidence, in fact, has shown that some patients with rapidly progressive deafness have autoantibodies directed against their inner ear and if recognized and treated early, their
hearing can be restored. Applications of immunologic assays may become available to make this diagnosis and to open new avenues for treatment. The application of these techniques also may prove to be helpful in the diagnosis of perilymph fistulae.

Recent development of animal models of bacterial and viral infections of the labyrinth and meninges has led to a greater understanding of the development of sensorineural hearing impairment associated with these conditions. The time course, the role of immunity and inflammation, the routes of spread and therapeutic interventions are beginning to be understood for the first time. Newer forms of anti-inflammatory agents, antibiotics and antiviral drugs may find rapid application in the treatment for these conditions with the advent of suitable animal models in which to test their efficacy. Additionally, these models will allow a greater understanding of why and to what degree infants and children are susceptible to ototoxic drugs used in the treatment of infections.

Due to the prevalence, long-term sequelae and cost to our society, otitis media continues to be an important focus of research. Important progress in the understanding of the epidemiology and pathophysiology of otitis media has been made. Studies of the eustachian tube have provided new information on tubal compliance, surfactant-like substances, neural connections, mucociliary clearance and the effects of adenoidectomy and drugs on its function. Recent studies also have revealed the importance of cellular regulation, differentiation and receptor expression in the pathogenesis of otitis media. Application of immunocytochemistry has led to advances in our understanding of the filament proteins, neuropeptides, oxidative enzymes, immunocompetent cells and inflammatory mediators involved in otitis media. New evidence has surfaced which shows the importance of prior viral infection in the development of otitis media. Research at the cellular and molecular levels has begun to characterize the bacterial-cell genome to understand better adherence of bacteria to epithelial cells and antibiotic resistance, as well as cell-membrane receptors involved in bacterial invasion and how properties of the bacterial-cell wall and its breakdown products lead to middle-ear inflammation. The role of local and systemic immunity has also received recent attention by the demonstration that the middle-ear immune response may be manipulated by donor T-lymphocytes which are primed by oral antigen. Such studies might lead to newer methods of prevention by rendering the host immunologically tolerant to the antigens liberated during otitis media so that inflammation is abrogated.
Current research also suggests that impaired immunity or its delayed maturation may predispose certain children to otitis media.

Important research on developing new and more immunogenic vaccines for the prevention of otitis media caused by nontypable Haemophilus influenzae and Streptococcus pneumoniae (pneumococcus) are now under way. They have been encouraged by the success of vaccines with Haemophilus influenzae type b polysaccharide-protein conjugates in the prevention of meningitis in infants and young children, a major cause of profound hearing impairment. Clinical studies have also made strides in the diagnosis and antibiotic and surgical treatment for otitis media.

Recent advances in exploring the cause of otosclerosis, a disorder which affects one out of every 100 adults in this country, are promising. With the use of immunohistochemical techniques, viral antigens of rubella and rubeola have been found in the active lesions of this disease and newer ultrastructural studies are beginning to shed light on the mechanism of bone remodeling seen in this condition.

Studies of the host factors which lead to the development of cholesteatoma are emerging as well as the role of inflammation, enzymes and factors involved in bone resorption and remodeling. Despite extensive clinical efforts, chronic suppurative otitis media and cholesteatoma still account for the majority of conductive hearing loss cases in adults in the United States. The development of biocompatible, middle-ear implants for the correction of conductive hearing loss has resulted in great progress. Newer, prosthetic, ossicular and canal-wall implants are being developed and employed in clinical trials to establish their efficacy. Additionally, there has been important development of partially or fully implantable hearing aids for the correction of conductive hearing losses for which routine hearing aid applications have failed.

Considerable progress had been made in hearing aids and other auditory prostheses. Digital and programmable hearing aids with improved signal processing are being developed and fitted clinically. In addition, a variety of noise reduction schemes are being incorporated into hearing aids. The multichannel cochlear implant has become a widely accepted auditory prosthesis for children and adults who receive no benefit from conventional hearing aids. The vast majority of adult cochlear implant recipients derive substantial benefit in conjunction with speechreading, and many can communicate effectively without speechreading. Children, including the prelingually deafened, also
demonstrate substantial benefit from implants, particularly with continued use. New sound processing techniques based on high-rate, nonsimultaneous (interleaved), pulsatile stimulation have been shown to improve the effectiveness of cochlear implants. An important development is the application of neural prostheses to the auditory brain stem in individuals with destruction of the nerves of hearing due to bilateral acoustic neurinomas or head trauma. Studies of methods of tactual communication used by deaf and blind persons demonstrate the capacity of the skin and the proprioceptive system as a communication vehicle and provide a basis for the development of tactile aids as alternatives for powerful hearing aids and auditory prostheses.

Recent accomplishments in the area of auditory rehabilitation include the use of computer-controlled video and audio laser disc systems for fully or semi-automated instruction and the increased understanding of the contributions of context and prior knowledge to the perception of spoken language from impoverished sensory input.

The areas of assessment and diagnosis have benefited from the development of noninvasive methods for measurement of the acoustic properties of the external and middle ears (acoustic immittance), computer-based techniques for assessment of sound-evoked electrical activity in the cochlea (electrocochleography) and in the brain (auditory brain stem and cortical responses) and the discovery of spontaneous and evoked emission of sound from the inner ear (otoacoustic emissions). Otoacoustic emissions hold great promise for the precise evaluation of defects in the inner ear and for the early identification of hearing impairment in infants.

Research Opportunities in Hearing

**Transduction and Homeostasis**

- Measure the mechanical changes in hair bundles during transduction and adaptation and determine how these mechanical changes affect basilar-membrane motion.
- Elucidate the mechanism of outer-hair-cell motility and investigate the role of this process in frequency tuning on the basilar membrane.
- Relate the unique structure of the hair cell's afferent synapse to its role in sensitive, high-frequency synaptic transmission and identify the hair cell's neurotransmitter and its postsynaptic receptor and signaling mechanisms.
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- Identify and characterize the molecular substrate underlying transduction, motility and cellular homeostasis.
- Examine the homeostatic processes that regulate the cochlear environment, including the control of blood flow, ionic balance and intercellular communication.
- Construct cDNA libraries representing messages for proteins involved in transduction, motility and ionic regulation; probe the libraries in an effort to identify and sequence the proteins that are the transduction channel, the adaptation motor, the afferent transmitter receptor and growth-factor receptors.

**Sound Processing in the Brain**

- Study the functional connections of neurons and synaptic mechanisms at all levels of the auditory system.
- Relate neurophysiologic descriptions of the auditory system to animal and human psychophysical data.
- Characterize fully the afferent and efferent auditory systems.

- Study the potential for central reorganization subsequent to peripheral or central injury, determining the plasticity of the mature auditory system and the impact of modified auditory input upon its organization.
- Develop models to provide concise descriptions of normal and abnormal auditory function.

**Auditory Perception**

- Define the relations between complex acoustical signals and the resulting perceptual experiences of listeners.
- Elucidate the perceptual correlates of sound coding in the auditory nervous system.
- Enhance the understanding of sound location in animals and humans.
- Relate emerging knowledge about perceptual organization to the development of a comprehensive model for auditory perception of spoken language.
- Extend research conducted on listeners with normal hearing to study the consequences of sensorineural hearing loss on the perception of complex sounds and spoken language.
Development, Aging and Regeneration

- Assess the normal life cycle of the auditory system, including the definition of critical periods for the development of auditory processes.

- Evaluate the limits of neural plasticity in the auditory system.

- Define the influences of environmental, nutritional and pathologic factors that compromise the normal life cycle of the auditory system.

- Study the embryonic mechanisms for the formation of the normal ear and characterize the mechanisms underlying normal cell proliferation and differentiation.

- Study the developmental course of complex sound and speech perception in infants and young children.

- Elucidate the many aspects of age-related hearing loss in animals and humans.

- Isolate and identify molecular events that evoke proliferation leading to the replacement of lost sensory cells.

- Assess the roles of known and suspected growth factors that may influence the production and development of replacement sensory cells and the formation and maintenance of their contacts with neurons.

- Explore the molecular, morphologic, physiologic and behavioral consequences of sensory cell regeneration.

- Identify the mechanisms that determine neuronal survival and explore paradigms that may protect and maintain auditory neurons after trauma or deprivation.

- Characterize the morphogenetic processes of the embryonic ear.

- Identify the intercellular signals that regulate developmental specialization of cells that perform the sensory and supporting functions of the cochlea.

- Determine which growth factors mediate the trophic interdependence between sensory cells and neurons in the auditory system and assess the strength and the timing of those interactions in normal development and during regeneration.
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- Investigate the potential for sensory cell replacement and regeneration in mammals.
- Study the role of electrical stimulation in prolonging neuronal survival.

Research Opportunities in Hearing Impairment

**Hereditary Hearing Impairment**
- Map, isolate, clone, sequence and characterize genes responsible for hearing impairment in humans and animals.
- Solicit the participation of families in studies of hereditary hearing impairment. Educate professionals serving people with hearing impairment regarding selection criteria for these families.
- Develop clinical and physiological tests which identify carriers of recessive hearing loss genes.
- Develop comprehensive inner ear-specific cDNA libraries from humans and laboratory animals.

**Acquired Sensorineural Hearing Loss**
- Study the incidence, pathophysiology and treatment of hearing loss and ear disease associated with human immunodeficiency virus and the opportunistic infections it causes.
- Study the incidence, pathophysiology, diagnosis and treatment of hearing loss associated with viral and bacterial infections.
- Study the natural history, biology, treatment and rehabilitation following treatment of neoplasms which affect the temporal bone.
- Study the effects of trauma, environmental factors and ototoxic drugs on hearing; new means of establishing the causal relationship of the hearing impairment to the traumatic event or injurious agent; improved screening techniques for prevention; location of the insult within the auditory system; and identification of the molecular mechanisms underlying this damage so that strategies for treatment can be developed.
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- Study the possible causes of acquired sensorineural hearing loss of infancy to establish precise causes so that preventative interventions can be developed.

- Study the normal immune host responses involved in diseases of the middle and inner ear.

- Establish and investigate animal models of autoimmune sensorineural hearing loss, determine the inner-ear targets of autoimmunity, develop specific and sensitive diagnostic tests for this condition in humans and conduct controlled treatment trials to determine effective and safe therapeutic intervention.

- Study the idiopathic forms of hearing loss, such as otosclerosis and perilymphatic fistula, with attention toward establishing a cause, improving diagnosis and determining efficacy of treatment.

- Determine the natural history, pathogenesis and treatment of tinnitus.

- Perform clinical trials to determine the most efficacious treatment for the various causes of sensorineural hearing loss.

- Study the natural history, epidemiology, diagnosis, pathogenesis and treatment of Meniere’s disease.

- Establish more sensitive diagnostic tests for viral deafness, separation of peripheral from central causes of hearing loss, neurofibromatosis type 2 and those at increased risk for noise-induced hearing loss and ototoxicity.

- Apply newer research techniques involving molecular biology, immunohistochemistry, electron microscopy and computer-assisted reconstruction to the study of the temporal bone.

- Establish a national consortium to create cDNA libraries of the inner ear so that this technology can be made available to investigators in the field.

- Develop national registries to collect epidemiologic data on hearing loss and other diseases which affect the ear.

**Otitis Media, Otosclerosis and Other Middle-Ear Disorders**

- Study the epidemiology and incidence of otitis media among multicultural populations with attention to environmental versus genetic factors.
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o Study the anatomy, biochemistry and development of the eustachian tube and its role in otitis media and maintenance of middle-ear gas composition.

o Study the cellular elements and their function in the middle ear.

o Study the microbiology, immunology and biochemistry of the middle-ear inflammatory response.

o Study the role of local and systemic immune responses in the pathogenesis and recovery from otitis media.

o Develop vaccines for the prevention of otitis media and meningitis.

o Develop diagnostic measures for otitis media in infants under six months of age.

o Study existing and new treatment modalities in otitis media to establish their efficacy and safety.

o Study the long-term sequelae of otitis media on middle- and inner-ear function, middle-ear and mastoid pathology and speech, language, perceptual and cognitive development.

o Study the epidemiology and the molecular and cellular mechanisms involved in the pathogenesis of otosclerosis.

o Develop a precise diagnostic test or assay for perilymphatic fistula.

o Study the micromechanics of the conductive hearing apparatus and develop improved middle-ear implants and electromechanical or electromagnetic drivers of the ossicular chain.

Assessment, Diagnosis, Treatment and Rehabilitation

o Develop and validate new procedures to identify hearing loss and evaluate the perceptual consequences of hearing loss.

o Develop and evaluate new techniques for effective auditory rehabilitation of children and adults with hearing impairment.

o Continue the development and evaluation of sensory aids for persons with hearing impairment including hearing aids, cochlear implants, auditory brain stem implants, tactile aids and speechreading supplements.

o Continue the development and evaluation of visual technologies for individuals with hearing impairment.
Voice and Voice Disorders

The vocal folds in the larynx (voice box) separate during breathing so that air can enter the lungs. During swallowing, the vocal folds are forced tightly together to prevent food or liquid from entering the lungs. For coughing, which is a protective reflex action, the vocal folds seal tightly and then separate abruptly. Voice or phonation is produced when airflow from the lungs causes the vocal folds to vibrate. The vibration of the vocal folds is the sounding source, and the sound is further modified by actions of structures within the throat, nose and mouth. When vocal fold vibration is impaired, sound generation for voice, speech and singing is affected. A wide variety of voice disorders occur, some for structural, neural or behavioral reasons.

Voice science is a rapidly growing field. Within the last decade, the field has expanded in a variety of ways. A large, new knowledge base and clinical delivery system have developed, resulting in recognition, diagnosis and treatment of patients with voice impairments, laryngeal pathology and swallowing disorders.

New technologies for voice science have been developed. These technologies have enabled improved visualization of various components of the voice production mechanism, particularly the larynx. They have also opened new vistas on the functioning of the vocal folds and are leading to the development of new theoretical models of laryngeal behavior. Such technological improvements are also providing new databases of value in understanding, evaluating and treating individuals with voice or swallowing disorders.

Newly developed measures of voice can be used to evaluate the efficacy of existing therapy and suggest possibilities for future improvements. New surgical techniques called phonosurgery are being used to improve and restore voice by removing benign growths, correcting structural abnormalities and repairing trauma. Promising new treatments have emerged, including the use of botulinum toxin in spasmodic dysphonia.
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Major Basic and Clinical Research Opportunities

Normal Structure and Function

Respiratory, Laryngeal and Upper Aerodigestive Tract Physiology

- Study the nature of respiratory, laryngeal and upper aerodigestive tract actions and interactions in voice production and determine the principles that govern adaptive and maladaptive behaviors in response to laryngeal disorders or diseases.

- Gather data on voice production that encompass various domains, including neural, muscular, structural, aero-mechanical, acoustical and perceptual domains.

- Conduct research to delineate further the effects of bolus characteristics, respiratory parameters and voluntary control on timing and extent of laryngeal elevation and closure and pharyngeal contraction during swallowing.

- Conduct studies on the mechanisms involved in the control of vocal pitch, loudness, quality and register, including mechanisms associated with singing.

- Study the role of sensation, including hearing, vibrotactile sensation, proprioception and respiratory cues, in the development and use of voice in normal, impaired and exceptional subjects.

- Delineate the acoustic to perceptual transformation in voice-quality disorders, with special attention to those aspects of the voice signal that give rise to the perception of disorder and its quantities.

- Study the timing mechanisms of laryngeal behavior in coordination with respiratory and articulatory activity.

- Conduct studies on the exceptional (trained) singer to specify the limits of the human voice and its optimal efficiency.

- Determine the effects of lifestyle choices (diet, smoking, drug use, exercise and alcohol consumption) on the function of the larynx and upper aerodigestive tract.
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**Neural and Vascular Mechanisms**
- Conduct studies of neural control of the larynx for voice production, respiration and swallowing in humans and animals, including the elucidation of reflex mechanisms for each.
- Use transcranial magnetic stimulation and sensory evoked potentials to map cortical areas pertinent to laryngeal function.
- Determine the activity of the brain stem motoneuron pool during different phases of respiration, phonation and swallowing via the use of short- and long-latency reflexes elicited through electrical stimulation of the recurrent laryngeal nerves.
- Obtain information concerning the function of neural sensors in the control of voice production.
- Determine the similarities and differences in human laryngeal physiology to that of other species proposed as models for human voice production and swallowing.
- Use electrically or chemically elicited phonation from the periaqueductal gray area of the mid brain in anesthetized animals to study the behavior of laryngeal motoneurons, sensory afferents of the larynx and mechanisms of phonatory control.
- Conduct studies of blood circulation and its autonomic control to laryngeal tissues and the relations to biomechanical changes in the larynx, vocal fatigue and laryngeal lesions.

**Biomechanics**
- Develop common spatial and relational references for laryngeal function to make it possible to gather multivariate data to enhance the modeling of laryngeal function and dysfunction.
- Determine the importance of lubricating fluids on the vibratory function of the vocal folds and study the composition and aberrations in these fluids.
- Conduct studies of the material properties and biomechanical behaviors of laryngeal structures.
- Determine the physiologic consequences of muscular atrophy of the upper aerodigestive tract on vocalization, swallowing and respiratory function.
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**Development and Aging**

- Conduct studies of the mechanisms of epithelial-mesenchymal tissue interactions that are a driving force in the normal development of the larynx and its final form.
- Specify the nature of voice production as it relates to the developing structure of the entire respiratory system, upper aerodigestive tract and larynx in particular.
- Obtain data on laryngeal and upper aerodigestive function of normal octogenarians, nonagenarians and centenarians for voice production and swallowing.

**Cellular and Molecular Biology and Anatomy**

- Specify the sites of hormonal influence on the respiratory system, upper aerodigestive tract and larynx in particular, as well as hormonally affected changes in voice production.
- Determine the biochemical and structural specializations characteristic of laryngeal muscle fibers and their innervation.
- Define the distribution of extracellular matrix molecules, oncogene expression, growth factors and growth-factor receptors as they relate to normal structure of the aging larynx.
- Conduct studies of the cellular biology of cartilage and joint deterioration in the larynx as they affect voice production and swallowing in aging.

**Diseases and Disorders of the Larynx and Upper Aerodigestive Tract**

**Epidemiology and Prevention**

- Gather data on the incidence and prevalence of voice and swallowing disorders.
- Conduct epidemiological surveys of the influence of external environmental factors on voice production to identify important agents and clarify pathophysiology and develop strategies for prevention, diagnosis and management of the resultant voice disorders.
- Identify genetic and environmental causes of congenital disorders of the larynx and pharynx.
EXECUTIVE SUMMARY

- Develop strategies for prevention and early detection of cancer of the upper aerodigestive tract.

- Conduct epidemiologic and case-control studies to identify factors which may lead to focal dystonias of the head and neck.

Pathophysiology and Potential for Improved Therapy

- Improve the understanding of infectious and allergic disorders of the upper aerodigestive tract and develop better therapy.

- Identify and study genetic influences on laryngeal function and dysfunction.

- Obtain information on the effects of drugs (alone or in combination with other therapy) on the voice.

- Study the role of psychogenic factors in the pathogenesis of voice disorders and response to treatment and develop criteria for distinguishing psychogenic from organic voice disorders.

- Determine the role of extracellular matrix, growth factors and oncogenes in wound healing of the larynx and in the pathogenesis of laryngeal and tracheal stenosis.

- Determine reasons for gender differences in susceptibility to vocal disorders.

- Study the effects of aging on voice production to establish the true nature of age-related voice (not pathologic) changes and develop treatment to forestall or prevent such changes.

- Study the effects of respiratory disorders on the voice.

- Conduct studies of recurrent laryngeal nerve regeneration as well as denervated laryngeal muscles to improve the understanding of pathogenesis and treatment of laryngeal paralysis.

Evaluation of Current Therapy

- Conduct prospective, controlled trials to assess effectiveness of treatment for voice disorders, including phonosurgical procedures and voice therapy.

- Conduct long-term, large-scale studies of the management of laryngeal papillomata to address recurrence rates, effects of treatments, effects of cofactors and rates of association with carcinoma of the larynx.
EXECUTIVE SUMMARY

- Evaluate prospectively the effects of conservation surgery for upper aerodigestive tract malignancy on speech, swallowing and breathing.

- Determine the effects of irradiation and chemotherapy on laryngeal function.

- Conduct prospective trials to develop criteria to predict optimal dosage and placement of botulinum toxin injection in the management of focal dystonias and to determine the long-term effects of this therapy.

- Characterize the diffusion of botulinum toxin in tissues and determine whether retrograde transport to the brainstem accounts for some of the substance's therapeutic actions.

- Conduct studies of the effects of acid and alkaline gastroesophageal reflux on voice and swallowing and evaluate the efficacy of treatment for these disorders.

Technology

- Use simulation modeling to predict the effect of modifying individual elements controlling laryngeal function and account for the effects of surface tension, other tissue surface properties and the specific effects of muscle contractions, including non-linear phenomena.

- Use magnetic resonance imaging and positron emission tomography to seek structural lesions in the central nervous system in patients with voice and swallowing disorders and to improve understanding of the control of the upper aerodigestive tract.

Diagnosis

- Conduct studies on large populations of normal and disordered speakers to clarify the relations between quantitative measures and perceptual vocal characteristics to determine how to use quantitative measures in making treatment decisions.

- Determine the usefulness of aeromechanical measurements in the differential diagnosis and assessment of treatments for vocal disorders and evaluate the contribution of the respiratory system to aerodynamic measures.

- Develop meaningful parameters to evaluate quantitatively laryngeal visual images.
EXECUTIVE SUMMARY

- Study the impact on laryngeal electromyography of variations in electrode configuration, interaction of electrodes with muscles, techniques used to verify electrode placement and testing protocols.

- Develop techniques for nonvoluntary activation of laryngeal nerves as a means of verifying the integrity of laryngeal nerves in uncooperative or anesthetized patients.

Treatment

- Conduct studies of electrical pacing of the larynx to evaluate the procedure and determine its long term efficacy.

- Develop prosthetic speech instruments which mimic natural voice characteristics and express paralinguistic features of stress, intonation and juncture.

- Develop and determine the usefulness of techniques for intra-operative monitoring and assessment of vocal function in improving surgical results and preventing complications.
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Summary of Research Recommendations

Research Opportunities in Hearing

Transduction and Homeostasis
Sound Processing in the Brain
Auditory Perception
Development, Aging and Regeneration

Research Opportunities in Hearing Impairment

Hereditary Hearing Impairment
Acquired Sensorineural Hearing Loss
Otitis Media, Otosclerosis and Other Middle-Ear Disorders
Assessment, Diagnosis, Treatment and Rehabilitation
Overview

Prevalence, Incidence and Cost of Hearing Impairment

More than 28 million Americans are believed to have impaired hearing. Levels of hearing impairment vary from a mild but important loss of sensitivity to a total loss of hearing. Approximately one of every 1000 infants is born with a hearing impairment that is severe enough to prevent the spontaneous development of spoken language. Many more infants have a less severe but substantial impairment or will acquire one by age three or four. Over 50 percent of these impairments are believed to be of genetic origin. These impairments have serious and far-reaching implications for all aspects of development, and the costs of treatment and education for these children are enormous.

The most common cause of hearing loss in children is otitis media, an infection in the middle ear. Otitis media is predominantly a disease of infants and young children. Recent studies show that about 75 percent of all American children have an episode of otitis media by the time they are three years of age. This disease is estimated to account for over 10 million visits to the offices of physicians per year and to have a total annual cost of over $3.5 billion. The cost of managing otitis media is enormous, but it pales in comparison to the developmental and educational sequelae of otitis media.

The number of hearing-impaired people in the United States is expected to increase substantially in the next few decades due to increasing longevity and the consequent overall aging of the population. By far, the largest group of Americans suffering from hearing loss are the elderly. Thirty to 35 percent of the United States population between the ages 65 to 75 years have a hearing loss severe enough to require a hearing aid. The percentage increases with age, and 40 percent over the age of 75 years would benefit from amplification with a hearing aid. The costs of managing hearing impairments in the elderly are enormous and growing, but they are overshadowed by the costs in terms of quality of life. There are many and obvious benefits of eliminating or alleviating hearing impairments in the elderly. Recent advances in drug therapy suggest that it may be possible to replace neurotransmitters of the auditory system that are diminished in the aging process.

Hearing impairment includes auditory disorders that are not necessarily accompanied by a loss of sensitivity. Auditory processing disorders occur in learning disabled children.
A substantial number of hearing impairments are caused by exposure to noise, either in the workplace or as a result of leisure activities. Strategies need to be developed to educate the public on the importance of preventing noise-induced hearing impairment. The costs associated with prevention are minimal compared to the enormous costs of rehabilitating individuals once affected.

At least 15 percent of the population are affected by tinnitus, many so severely that it disrupts their lives. The socioeconomic impact of this form of hearing disorder is great but has not been fully quantified. 

**Historical Background**

Research on hearing impairment has not progressed as well as on other disorders. Research on the ear and the processes associated with hearing and its disorders was inhibited for many years by the fact that the tiny sensory organ for hearing, the organ of Corti, is encased by the bony cochlea (shaped like a snail shell) and was inaccessible to direct observation and experimental manipulation. The cochlea was, in fact, a “black box,” which could be investigated in the living state only by indirect methods. Studies of pathology were also difficult, since the preservation and histologic preparation of the delicate structures of the inner ear were complicated by the presence of the surrounding bone.

There is insufficient public appreciation of the vital importance of good hearing to overall health and employment opportunities. All societies depend upon the mutual abilities of their citizens to understand and produce speech and language. Hearing is essential to everyday human communication, and yet it is taken for granted much more than other areas of health. Furthermore, hearing is widely and thoughtlessly abused.

Some individuals who do not hear are members of a cultural community with its own language, American Sign Language. There is great interest about the nature and acquisition of signed language and about visual processing of language by deaf people within the 1991 update of the Language and Language Impairments section of the National Strategic Research Plan.

Recent research on deafness and hearing impairment has benefited greatly from major advances in biomedical research as a whole, such as molecular biology. Rapid advances in the molecular genetics of hereditary hearing impairment are at hand.
Hearing

Transduction and Homeostasis

The sensory cells of the auditory system are located in the organ of Corti (hearing organ) and are in contact with the fibers of the auditory nerve. The sensory cells in the organ of Corti consist of inner and outer hair cells. In the auditory system, transduction is the process in which acoustic energy is converted to electrical energy, resulting in the propagation of nerve impulses in the auditory nerve. Homeostasis is the process of maintaining a tendency of stability in the internal environment. Cochlear homeostasis is essential for the maintenance of normal hearing. Intracellular recordings from inner and outer hair cells have revealed important functional differences between the two hair cell populations. Sound energy is transduced by inner hair cells, which are now understood as mechanoreceptors. The transduction is mediated by ion channels that are directly gated by mechanical force. The hair cell's transduction channels thus differ importantly from previously characterized channels responsive to membrane potential or ligand binding.

The inner ear not only receives but also produces acoustic energy. The signals resulting from this energy are called otoacoustic emissions which can be detected with sensitive microphones in the external auditory canal. This finding has opened a new era of investigation. The source of the otoacoustic emissions is thought to be the outer hair cells. The isolation and maintenance of outer hair cells in vitro has led to the discovery that outer hair cells move in response to acoustical and electrical stimulation and changes in their chemical environment. Furthermore, the outer hair cell motility is influenced by nerves from the central nervous system to the inner ear. It is believed that the motility of the outer hair cells results in mechanical changes in the organ of Corti which make the inner hair cells more sensitive and capable of detecting fine frequency differences.

The origin of the unique fluid environment within the cochlea and details of intracochlear blood flow have been established, and the understanding of the biochemical mechanisms involved in transmembrane signaling is increasing.

Sound Processing in the Brain

When presented with the complex sounds of speech, the normally hearing listener is able to extract many different features of speech such as its frequencies, intensities, rhythm, location and identity of the speaker and the meaning of the words. The brain extracts these stimulus
features by processing patterns of neural activity along different pathways to different subregions of the brain. Each pathway may be specialized to analyze only certain aspects of the sound. These parallel pathways are constructed from a complex network of nerve cells interconnected by excitatory and inhibitory synapses.

At present, our understanding of the neuronal processes underlying sound analysis is incomplete. Nevertheless, important progress has been made in some areas, such as understanding how sources of sounds are located in space and how speech and other complex sounds are coded at lower levels of the auditory central nervous system.

To understand how complex sounds such as speech are processed, a variety of anatomic and physiologic techniques are being used to measure and analyze responses to sounds from neurons located in different subregions of the brain. Neuronal activity patterns are associated with different cell types within each region and with the chemicals (transmitters) they use for interneuronal communication.

The aim is to describe, for each subsystem, the chain of neurons involved in the analysis and how the relevant information is represented in patterns of neural activity. Knowledge of the subsystems' transmitters can be critical in selectively stimulating or blocking elements of the neural circuits and thereby dissecting their functional roles or treating their disorders. This knowledge also can be used in mapping the location of different cell types by the application of immunologic or molecular probes.

In view of the complexity of the inner ear and the brain, small disturbances in normal function can produce substantial hearing impairments. To provide successful treatment strategies for hearing disorders or to design neural prostheses and therapeutic agents, there must be an understanding of the normal anatomy, physiology and biochemistry of the auditory system. Progress already made in these areas is being applied to the periphery in the design of cochlear prostheses and hearing aids and has led to great improvements in the ability to overcome the disabling consequences of many types of hearing impairments. Identification of transmitters could ultimately lead to the development of drug therapies for a variety of auditory system disorders including hearing impairment and tinnitus.

Auditory Perception

The study of auditory perception is concerned with how sound patterns are converted by the auditory system to experiences by the listener.
Auditory perceptual research extends and relates work on physiologic aspects of sound coding to the resulting experience of sound.

Research on auditory perception also determines the relation between physical properties of complex sounds (such as environmental sounds and speech) and the experiences arising from them. Work on determining how listeners recognize the source of sounds or individual speakers and how they separate and locate inputs from several different sound sources is in progress. The benefits to be derived from increasing our understanding of how normal and impaired auditory systems mediate the perception of sound are many, and they include: (1) innovative designs for auditory prostheses, (2) greatly improved behavioral tests for diagnosis of specific auditory disorders and (3) improved methods for training and rehabilitation of hearing-impaired individuals.

**Regeneration of Sensory Cells**

Sensory cells in the ear of cold-blooded animals can be regenerated. Even in species such as birds, in which the production of sensory cells normally ceases in early embryonic development, regeneration can occur in young and adult birds. Furthermore, the regeneration of sensory cells has been shown to contribute to recovery of hearing. Recent investigations have shown that the regenerated hair cells originate from cells produced by the proliferation of supporting cells that survive at sites of damage in the inner ear. Efforts are now under way to identify the molecular events that stimulate the proliferation of those cells, so that those events or their analogs may be tested for their potential to induce sensory cell regeneration in mammalian ears where it does not appear to occur spontaneously. Investigations of sensory cell regeneration must utilize a combination of conventional methods and methods that originate from the cutting edge of biotechnology. The questions are formidable, but the potential payoff from this research may be the long-hoped for regeneration of auditory hair cells in humans.

**Hearing Impairment**

*Hereditary Hearing Impairment*

Hereditary hearing impairment accounts for at least 50 percent of congenital deafness. Syndromes in which there is some other finding associated with the hearing impairment account for 30 percent while nonsyndromic forms (hearing impairment alone) account for 70 percent of congenital hereditary hearing impairment. Of the nonsyndromic forms, 70 to 85 percent are transmitted as autosomal recessive, 12 to 27 percent are autosomal...
dominant and approximately three percent are sex-linked. A large percentage of hearing impairment with onset in childhood and adulthood also has a genetic basis, and an underlying genetic susceptibility probably contributes to many forms of hearing loss attributed to environmental factors such as noise-induced hearing loss and presbycusis.

The mapping of genes involved in hearing impairment will continue to provide important information and depends on the identification of families with the gene and their participation in molecular genetic studies. Location of the gene in a specific chromosomal region provides more precise information for genetic counseling and is an important first step towards isolating the gene, determining its protein product and understanding the cause of the hearing impairment.

Advances in comparative mapping of the human and mouse genomes promise to be valuable for identifying human genes responsible for hearing impairment. The insertion of genetic material into cells to prevent or ameliorate hereditary hearing impairment may soon become a possible treatment option.

**Acquired Sensorineural Hearing Loss**

There are a great variety of causes of acquired sensorineural hearing loss. These include: noise exposure, infections, neoplasms, trauma, degeneration and aging and immune-mediated disorders as well as unknown causes. Although the term "acquired" sensorineural hearing loss implies a nongenetic cause, there may be a genetic predisposition for the development of hearing loss from these causes.

It has been estimated that as many as 38,250 new cases of Meniere's disease are diagnosed each year in the United States. This condition results in hearing impairment and balance disturbances that wax and wane, yet continue in a progressive fashion. Despite the vexing nature of this illness, studies have led to a better understanding of the fluid homeostasis within the inner ear and the anatomical sites responsible for its maintenance. Studies of temporal bone pathology have suggested possible viral, immunologic, allergic, hormonal and environmental causes for this disease. While animal models have been developed which show some of the histologic features seen in the human condition,
no model has been found which simu-
lates recurrent attacks described in 
this patient population. A number of 
longitudinal, controlled studies on 
the medical and surgical treatment 
for this condition have been reported, 
however, no treatment has been shown 
to improve or stabilize the hearing in 
these patients. Furthermore, there is 
a disturbing tendency for this disease 
to become bilateral (20 to 40 percent). 
Therefore, there is a critical need to 
discover the cause of this condition 
and to develop treatment strategies 
to prevent the late sequelae of this 
relentless illness.

Bacterial, fungal or viral infec-
tions including acquired immuno-
deficiency syndrome (AIDS) can 
cause sensorineural hearing loss. 
Bacterial and viral infections may 
cause sensorineural hearing loss by 
spreading from the middle ear or 
mastoid cavity into the inner ear or 
may spread into the inner ear from the 
subarachnoid space as in meningitis.

Viruses have also been implicated 
in sudden deafness. Patients with 
AIDS may have hearing loss from the 
AIDS virus itself or from other patho-
gens, including viral and fungal agents 
that cause opportunistic infections.

The immune system is not only 
an important factor in the defense of 
the ear against infections, but it also 
may be involved in hearing loss in 
autoimmune diseases and other types 
of immune-mediated hearing loss. 
These include systemic diseases 
such as polyarteritis nodosa, Cogan’s 
syndrome and lupus erythematosus, 
in which the inner ear may become the 
target organ of antibodies or become 
damaged by the resultant inflammatory 
process. Research is needed in the 
diagnosis and the treatment of these 
disorders. Special opportunities exist 
to study these problems because of new 
technology derived from molecular 
biology and immunology. The role that 
allergic processes play in the cause of 
hearing impairment has been suggested 
but requires further study to establish 
its relationship.

A variety of tumors may result 
in a sensorineural hearing loss. One 
of the most frequent tumors is acoustic 
neurinoma (vestibular Schwannoma), 
the most common tumor in the poste-
rior cranial fossa. Both benign tumors 
and malignant tumors, such as squa-
mous cell carcinoma and chemoedect-
tomas, may affect the temporal bone. 
Further studies of the natural history, 
genetics, factors controlling growth 
and treatment, including chemo-
therapy, radiation therapy and 
surgery, are needed. For example, 
the recent application of the gamma 
knife and laser surgery to the removal 
of acoustic neurinomas should be 
studied to evaluate the efficacy of 
these new therapeutic approaches.
During the last decade, important progress has been made in understanding how hearing loss may be caused by environmental factors such as noise, drugs and toxins. For the first time, rational hypotheses have been advanced for the mechanisms underlying hearing loss induced by aminoglycoside antibiotics, leading the way to the design of protective measures and drug modification. The understanding of inner-ear damage by diuretics has allowed the development of preventive pharmacologic strategies to be successful in animal models.

The mechanisms by which intense noise affects the inner ear are better understood. Advances include novel and important information about the effects of noise on the cochlear microcirculation, fluid homeostasis and mechanical properties of the sensory cells. These advances provide an excellent basis for future research to elucidate the molecular mechanisms underlying environmentally induced hearing deficits and strengthen the hope of finding means to prevent or ameliorate these forms of hearing impairment.

Inner ear, auditory nerve and brain stem degeneration probably contribute to the hearing disorders seen in aging persons. In most cases, no discrete cause can be found.

In these instances, the term presbycusis is used. Noise exposure, both occupational and nonoccupational, is often partially responsible for the inner-ear damage observed. Some people are genetically predisposed to premature loss of hearing. Systemic illnesses such as atherosclerosis and diabetes are poorly assessed as risk factors for hearing loss in aging.

The prevalence of presbycusis has been reasonably well documented, but future population-based studies are needed to identify more clearly risk factors, including moderate (especially nonoccupational) noise exposure, smoking, diet and systemic disease. These studies should go beyond pure-tone audiometry to include measures of speech perception performance and other high-level auditory processes. Family studies can help elucidate the genetic component. Finally, epidemiologic studies should explore the impact of presbycusis on affected persons and on society.

Unfortunately, there are many disorders of the inner ear for which the cause is unknown. These include disorders as perilymphatic fistula, noises in the ear or head (tinnitus) and Meniere’s disease. There is a critical need to elucidate the pathogenesis and develop treatments for these puzzling disorders.
Otitis Media, Otosclerosis and Other Middle-Ear Disorders

Otitis Media

Otitis media is the most common treatable disease of infants and young children and the most frequent cause of fluctuating hearing loss. Three-fourths of the children born each year experience at least one episode of otitis media by their third birthday, and one-third have repeated bouts of otitis media. The disease necessitates frequent health care visits for the child and parents, with an enormous impact on family lifestyle and parent work productivity. The economic impact of this disorder for families with young children is extraordinary; estimated annual health care costs for otitis media in the United States are $3.5 billion. Furthermore, some of the children who experience frequent otitis media during early childhood experience difficulty in speech and language development and some have lifelong hearing impairment. These sequelae compound the economic and societal costs of otitis media.

Remarkable advances have occurred in improving the understanding of the epidemiology, natural history and pathophysiology of otitis media. This progress is being translated into improved methods of prevention, diagnosis and treatment. New techniques of molecular and cellular biology and genetics are being applied to elucidate underlying mechanisms that predispose children to the entire spectrum of middle-ear inflammatory disorders grouped within otitis media.

Otosclerosis and Other Middle-Ear Disorders

Otosclerosis is one of the most common causes of progressive, adult-onset hearing loss, affecting one in 100 persons. It is a localized disorder of bone remodeling within the middle and inner ears. Recent advances in genetics, molecular biology and ultrastructure have improved the understanding of this disease, however, its exact cause is still unknown.

Middle-ear structures collect environmental sound and transmit it to the inner ear. An understanding of middle-ear micromechanics is essential to the development of improved middle-ear implants and implantable hearing aids.

Assessment, Diagnosis, Treatment and Rehabilitation

The identification and assessment of hearing impairment and the diagnosis of specific disorders involve collaboration among primary care
HEARING AND HEARING IMPAIRMENT

physicians, otolaryngologists, audiologists and geneticists. The procedures in current use include measurement of auditory thresholds, determination of the acoustic properties of the external and middle ears, measurement of speech recognition thresholds, quantification of the acoustic reflex threshold, measurements of otoacoustic emissions and recording of the electrical activity of the brain in response to sound. Assessment and diagnosis are precursors to treatment and essential to the determination of treatment efficacy.

During the past decades, major progress has been made in the medical and surgical treatment of some hearing impairments. For the hearing impairments that cannot be alleviated by medical or surgical treatment, there is a rich array of rehabilitative intervention. This intervention has two basic components: prosthetic management and auditory rehabilitation. Prosthetic management seeks to provide access to sound patterns by means of hearing aids, cochlear implants, tactile aids, visual speech training aids and other sensory aids. Auditory rehabilitation involves training to accelerate adaptation to novel sensory inputs; develop auditory (and nonauditory) perceptual skills; enhance the integration of inputs from different modalities, such as vision and hearing; and create an emotional state that is optimally conducive for communicating.

For children with hearing impairment of sufficient severity to prevent or impair the spontaneous development of spoken language, intervention and management go well beyond prosthetics and auditory rehabilitation. The development of the basic cognitive and language skills on which subsequent development and education depend is addressed in depth in the 1991 update of the Language and Language Impairments section of the National Strategic Research Plan.

Recent Accomplishments

Basic and clinical investigators in hearing and hearing impairment are undertaking research in many new directions. They are exploiting past accomplishments and taking advantage of the tools and insights offered by recent progress in neuroscience, cellular biology, immunology, molecular biology, genetics and computer technology. Progress in understanding the mechanisms of normal hearing is accelerating. However, transferring new knowledge into clinical applications is not occurring at a comparable rate.

The relatively slow rate of applying new knowledge to the problems of patients is due to many factors:
the difficulty of the problems, the incomplete state of knowledge in the basic sciences, the lack of appropriate tools and models and the shortage of investigators bridging basic and applied areas. There is a severe shortage of clinical investigators who are conversant with the state-of-the-art research methods and their applicability to relevant clinical issues.

Hearing

Transduction and Homeostasis

Many insights into the function of the cochlea have been derived recently from in vivo and in vitro studies. Considerable progress is being reported in the measurement of cochlear blood flow and the study of its regulation. Studies of the composition, production, circulation and absorption of endolymph (the fluid in the membranous inner ear) are providing insights into the regulation of the properties of this unique fluid as well as the effects of these properties on transduction. Immunohistologic techniques have been employed and allow for an in-depth characterization of the inner ear. New research has shown that changes in hearing are associated with the loss of outer hair cells. Scientists have learned more about stereocilia and how they are physically linked at their tips and participate in frequency selectivity or tuning.

In vitro studies of isolated hair cells have led to a greater understanding of the biophysics of mechanoelectrical transduction and of ion channels in hair cell membranes. Progress has been made in the molecular and functional characterization of the structural and contractile proteins of stereocilia, hair cells and the cuticular plate. This knowledge contributes to a better understanding of how stereociliary stiffness and hair-cell micromechanics are modulated.

Important progress has been made in understanding fast and slow motility of the outer hair cell. Stimulus and response characteristics have been detailed and provide clues about the function of these mechanisms in vivo. Biochemical studies have revealed the presence of second messenger molecules in outer hair cells, which may play a role in their slow motile mechanisms. Modern immunohistochemical techniques have shown the presence of more than one neurotransmitter at hair-cell synapses and are being used to identify the proteins associated with ion channels. Characterization of the membrane properties of sensory and neuronal elements using in vitro biophysical approaches is beginning to provide an understanding of the molecular basis of auditory function. For example, the ion-channel basis of electrical resonance has been elucidated in hair-cell membranes of several species. Ultrastructural
HEARING AND HEARING IMPAIRMENT

studies have revealed details about the contact zones between outer hair cells and efferent nerve fibers. In addition, cells and tissues from the inner ear can be grown in tissue culture and hence are available for in vitro studies.

Recent studies of basilar-membrane motion and receptor potentials in the intact animal have led to a finer appreciation of the active process responsible for cochlear frequency selectivity. In certain species, including the human, the hearing organ generates sound spontaneously or in response to acoustic stimulation. In humans, these otoacoustic emissions are produced by outer hair cells and have great promise for practical diagnostic use to identify hearing loss.

**Sound Processing in the Brain**

Auditory nerve fibers connecting hair cells to the cochlear nucleus in the brain stem have been identified with intracellular marking techniques. New information is also available concerning the transformation of auditory nerve input in the cochlear nucleus. The membrane properties of some of these cochlear nucleus cells have been analyzed with in vitro techniques that allow the manipulation of the electrical and chemical environment and subsequent intracellular staining to elucidate cell morphology including the arborization of the entire axon. There has been substantial additional progress in understanding the encoding of complex signals transmitted from the auditory nerve to the cochlear nuclei. The relationship between the neural code for sound intensity, frequency and temporal characteristics and the perception of these stimulus variables has been further clarified. Chemical neuroanatomical studies have successfully used immunocytochemical, neurochemical, neuropharmacologic and molecular techniques to identify many of the neurotransmitters and receptors involved at specific synapses in structures throughout the auditory neural axis, especially with respect to the cochlear nuclei and the efferent feedback to the inner ear. The mapping of transmitter-receptor subtypes in the central auditory system has been initiated.

Research conducted in the central nervous system has produced exciting new findings. Progress has been made in understanding the structure and function of efferent feedback pathways to the inner and middle ears. There is now good evidence that both systems aid in the detection of signals in noisy environments, and there is the possibility that both may serve to protect the ear from acoustic injury.
Changes in the central nervous system have been described in response to enriched and deprived acoustic environments. New insights have been generated with respect to how the brain performs complex computations to create maps of auditory space and how these maps interact with visual space.

**Auditory Perception**

Recent research in auditory psychophysics has produced a set of working models of auditory perception that far exceed the bounds of the simple “energy detector” models of hearing in general use. Research under way in a variety of areas is providing remarkable advances in the understanding of how human and non-human listeners make sense of the auditory world around them, that is, how they assign identities and sources to the sounds they perceive and how they recognize the communication sounds of single and multiple speakers. This research provides the essential link that will enable the application of advances at the molecular, anatomic and physiologic levels to the design of improved auditory prosthetic devices.

There have been a number of exciting recent advances in the linking of psychoacoustical and physiological research. Behavioral measures of frequency selectivity have been developed that allow comparison with electrophysiologic measures of auditory tuning. These measures can now be used to characterize normal and impaired hearing, and the potential exists for the diagnostic application of such measures. Perceptual evidence of the role of various populations of auditory nerve fibers in coding sound intensity has recently been obtained. The influences of adaptation and active cochlear processes on perception have been elucidated in psychophysical tasks.

Increased understanding of the perception of spectral shapes and the ability of the ear to distinguish changes in shape from changes in intensity have been achieved. Spectral shape cues are used to distinguish many classes of speech sounds and contribute to auditory localization. Studies on the role of across frequency-band enhancement and interference effects on the detection and localization of sounds are providing improved understanding of complex “real-world” auditory perception.

New approaches are being used to characterize auditory localization by humans. Sounds presented over headphones can now provide the perceptions found in real auditory space, particularly when head movements
are accounted for. These results provide new possibilities for presenting sounds in simulated situations and through prosthetic devices.

Increased study of the role of perceptual learning, selective attention, auditory memory and streaming in the formation of auditory percepts has contributed to the understanding of how we attend to multiple sound sources in complex acoustic environments.

**Regeneration of Sensory Cells**

Decades ago, it was shown that production of sensory cells in the ears of mammals ceases before birth. This finding confirmed that sensory cells are produced only during embryonic development and meant that damage to sensory cells later in life was irreparable. This fact is the basis for considering sensory hearing impairment as a permanent and irreversible condition.

It is now known that sensory cells are continually being added to the functional populations of cells in the ears of cold-blooded animals. Even more recently, it was shown that sensory cells can be regenerated in damaged cochlear epithelia in juvenile birds in which the production of these cells normally ceases early in embryonic development. This regenerative potential has been confirmed in several species and is not limited to immature animals. The results have provided an opening to understanding and perhaps manipulating the growth of human sensory cells.

**Hearing Impairment**

**Hereditary Hearing Impairment**

The genes causing a number of syndromes that involve hearing impairment have now been mapped. Recent accomplishments include the mapping of an Usher syndrome (deafness, vestibular loss and blindness due to retinitis pigmentosa) type 2 gene to the long arm of chromosome 1 and a gene for Waardenburg syndrome (deafness and pigmentary and integumentary changes) type 1 (WS1) to the long arm of chromosome 2. More than one gene is involved in both of these syndromes. At the same time, considerable effort is being expended to isolate the two genes that have been mapped. Comparative mapping suggests that WS1 is homologous to the Splotch gene in the deaf mouse.

Analyses of a large Costa Rican family in which many members have progressive low frequency hearing loss recently allowed the mapping of a gene for an autosomal dominant nonsyndromic form of hearing impairment to the long arm of chromosome 5. Other families with similar audiometric
findings can now be tested to determine whether the same gene causes their impairment.

At least 28 X-linked (sex-linked) disorders involve hearing loss. Recent accomplishments include precise location of the gene causing albinism-deafness and tentative evidence of more than one X-linked gene for clinically identical forms of progressive mixed deafness. The gene for Alport syndrome has been located to the same region as one of the collagen genes (COL4A5). Further studies of several individuals with Alport syndrome suggest that mutations in the collagen gene cause this syndrome. It is of interest to note that hearing loss is associated with other syndromes caused by collagen defects, such as Stickler syndrome (COL2A1) and one form of osteogenesis imperfecta (COL1A1).

The development of human and animal cochlea-specific cDNA libraries is proceeding rapidly.

Acquired Sensorineural Hearing Loss

The role of genetic factors in disease processes that would otherwise be considered acquired has been underscored by the recent demonstration of a genetically controlled mitochondria defect which predisposes to aminoglycoside ototoxicity.

Similarly, mouse models of genetically induced sensorineural hearing loss of late onset may provide a better understanding of the genetic predisposition to presbycusis. The recent elucidation of the nature of a variety of afferent and efferent neurotransmitters will provide better understanding and possible therapy for sensorineural hearing loss. For example, the discovery of a variety of oncogenes associated with various tumors holds promise for better understanding of the development and growth of acoustic neurinomas and other tumors of the temporal bone. New insights into the prevention and treatment of ototoxicity may result from studies of pharmacologic blocking of ototoxic actions of various drugs. A better understanding of how ototoxic metabolites may cause damage to the cochlea may provide new insights into prevention and treatment of this problem.

Application of new immunobiologic techniques will provide an understanding to the normal and disrupted immune mechanisms responsible for damage to the inner ear in immune-mediated disorders. Recent evidence suggests that some individuals with progressive deafness have autoantibodies directed against inner-ear proteins. These studies open up avenues for the diagnosis of treatable forms of sensorineural hearing
loss. Better techniques to diagnose perilymphatic fistulae might emerge from the findings of recent studies, suggesting a specific inner-ear protein may be detectable in perilymph that is not found in serum, cerebrospinal fluid or middle-ear fluid.

Recent developments of animal models for bacterial and viral infections, such as bacterial labyrinthitis, congenital cytomegalovirus infection and other viral infections holds promise for the development of new diagnostic and treatment modalities for sensorineural hearing loss caused by infections. In particular, recent developments in antiviral therapy hold promise for the treatment of inner-ear viral infection. Studies of biochemical factors including enzymes and the susceptibility of developing animals to ototoxic drugs will help clarify the unique susceptibility of the immature human to ototoxic drugs.

During the past three years, there has been important progress in understanding the epidemiology and pathophysiology of otitis media, and this progress has led to advances in prevention and treatment. This research has led to new questions and has revealed pathways for more detailed investigation.

Research in epidemiology and natural history indicates that otitis media forms a continuum of clinical and pathologic entities from acute, self-limited disease to chronic forms with destruction of middle-ear structures. Many persons affected with otitis media do not display clinical symptoms and ordinarily would go undetected. Several risk factors for acute otitis media and otitis media with effusion have been identified using multivariate models, and a genetic basis for otitis media has been suggested.

Research on eustachian-tube and middle-ear physiology and pathophysiology has provided new information on a surfactant-like substance, mucociliary clearance, neural connections between the middle ear and brain stem, tubal muscles, tubal compliance and effects of pharmacologic agents and adenoidectomy on tubal function.

Otitis Media, Otosclerosis and Other Middle-Ear Disorders

Otitis Media

The most common cause of hearing loss in children is otitis media. Primarily a disease of infants and children, otitis media produces sequelae that may affect hearing later in life.
Anatomic, pathologic and cellular biologic research has revealed the importance of cellular regulation and differentiation and receptor expression in the pathogenesis of otitis media. Developmental changes in tubotympanic anatomy have been recorded, and ultrastructural changes of the tubotympanum have been studied in normal and several pathological conditions. The application of immunocytochemistry to the study of the pathogenesis of otitis media has led to characterization of filament proteins, neuropeptides, oxidative enzymes, immunocompetent cells and inflammatory mediators. In addition, cellular patterns of middle-ear alteration, including epithelial metaplasia and migration and bone-cell activation, have been identified.

Microbiological, immunological and biochemical research has yielded additional evidence that upper-respiratory viral infections contribute to a high proportion of acute episodes of otitis media. The importance of the interaction between respiratory viruses and bacterial infection in the pathogenesis of otitis media has been revealed by human and animal studies. Research at molecular and cellular levels has begun to characterize cell-membrane receptors for bacteria causing otitis media and to reveal the contribution of bacterial cell-envelope products in middle-ear inflammation. Evidence suggests that the middle-ear immune response can be manipulated by donor T-lymphocytes from animals presensitized by oral antigen. Research has suggested that the presence or absence of an impaired immune response to certain bacterial antigens may allow differentiation between otitis media-prone and normal children.

Improving the immunogenicity of pneumococcal polysaccharide antigens and identification of common nontypable *Haemophilus influenzae* antigens have been primary goals in vaccine development for prevention of otitis media. The development, licensing and widespread use of *Haemophilus influenzae* type b polysaccharide-protein conjugate vaccines beginning in infancy is causing a major reduction in bacterial meningitis, which is an important cause of acquired sensorineural deafness.

Important progress has been made in the biochemical and molecular characterization of middle-ear inflammation including the role of bacterial products and host responses. Molecular studies have explored the bacterial genome that is related to adherence and antibiotic resistance.

Clinical research has yielded important progress in the screening and diagnosis of otitis media and has improved the medical and surgical
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management of otitis media. Advances in tympanometry have resulted in improved terminology and objective parameters. Bacterial surveillance has revealed changing patterns of bacterial resistance among the microorganisms that cause otitis media. The pharmacology of antibiotics used in the treatment of otitis media and their distribution into and out of the middle ear have become the subjects of intense investigation. Surgical prophylaxis and chemoprophylaxis of recurrent acute otitis media have been explored in several recent studies.

Otosclerosis and Other Middle-Ear Disorders

The understanding of otosclerosis and other types of conductive hearing losses due to infection or trauma has advanced in recent years. Using immunohistochemical and ultrastructural techniques, viral antigens of rubella and rubella have been identified in otosclerotic tissues. These findings suggest that childhood viral infections may play a role in the genesis of otosclerosis. Recent ultrastructural studies have further elucidated this unique disorder of localized bone remodeling.

Advances have occurred in the development of biocompatible implants for the replacement of middle-ear ossicles. Additionally, there has been progress in the development of implantable or partially implantable hearing aids.

Assessment, Diagnosis, Treatment and Rehabilitation

Considerable progress has been made in the technology of hearing aids and auditory prostheses. Digital and programmable hearing aids with vastly increased potential for signal processing are being developed and fitted clinically. Programmable hearing aids permit much more precise fitting of hearing aid characteristics on the basis of individual needs than is possible with nonprogrammable hearing aids. In addition, a variety of noise-reduction schemes are being incorporated into hearing aids, ranging from those that vary the frequency response as the background noise spectrum and level change to those that process the outputs of arrays of microphones.

The multichannel cochlear implant has become a widely accepted auditory prosthesis for both adults and children. The vast majority of adult implant recipients derive substantial benefit in conjunction with speechreading, and many can communicate effectively without speechreading. Some implanted children, including the prelingually deaf, derive substantial benefit, particularly with continued use. New sound processing techniques based on high-rate, nonsimultaneous (interleaved), pulsatile stimulation have been shown to improve the effectiveness of cochlear implants.
A neural prosthesis for insertion into the cochlear nucleus of the brain stem has provided encouraging levels of speech reception in individuals who have had bilateral destruction of the nerves of hearing caused by bilateral acoustic neurinomas or head trauma.

Studies of methods of tactual communication used by deaf and blind persons demonstrate the capacity of the skin and the proprioceptive system to provide a secure basis for the development of tactile aids. Such aids could serve as effective alternatives to powerful hearing aids and auditory prostheses.

Recent accomplishments in the area of auditory rehabilitation include use of computer-controlled video and audio laser disc systems for fully or semi-automated instruction, development of connected discourse tracking procedures for speech reading instruction, efficient enhancement of speech perception and increased understanding of the contributions of context and prior knowledge to the perception of spoken language from impoverished sensory input.

The areas of assessment and diagnosis have benefited from numerous developments in recent years, including development of noninvasive methods for measurement of the acoustical properties of the external and middle ears (acoustic immittance), that permit precise assessment and diagnosis of middle-ear disorders and disorders of discrete portions of the central auditory pathways, computer-based techniques for assessment of sound-evoked electrical activity in the cochlea (electrocochleography) and in the brain (auditory brain stem and cortical responses) and discovery and exploitation of spontaneous and induced emissions of sound from the inner ear (otoacoustic emissions). Measurements of otoacoustic emissions holds great promise for precise evaluation of defects within the inner ear and early identification of hearing impairments in infants.

Program Goals

Research to alleviate hearing impairment has yielded impressive results and promises to provide greater insight into how hearing disorders may be treated more effectively.

The prevention, diagnosis, treatment and rehabilitation of hearing disorders depend on the identification of the disease process, an understanding of its underlying basic mechanism and the development of effective intervention and rehabilitation strategies. Success in these endeavors requires close integration of research on hearing and hearing impairment.
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An increasing number of new and evolving technologies will be applied to the elucidation of normal hearing processes, particularly those concerned with how speech and other biologically meaningful sounds are understood.

Further understanding of the mechanisms of normal hearing and hearing impairment rests on the synthesis of numerous factors: from understanding the physics of sound and the ear, through identifying molecular events at the cellular and subcellular levels, to analyzing the processing of sound information in the auditory nervous system and learning how these activities and interactions result in the perception of sound and the understanding of speech.

A multidisciplinary approach to the study of hearing is required to interpret these complex processes. In fact, improved understanding of hearing mechanisms have resulted from the integration of strategies and technologies from a wide variety of fields. As this research is validated by ongoing investigation, clinical applications are being developed to enhance patient care.

Progress in key areas offers special opportunities to enhance prevention, diagnosis and treatment of many of the disorders that cause hearing loss and deafness. Pursuit of these opportunities will reduce the incidence and prevalence of hearing impairment.

Research in hearing and hearing impairment requires a multidisciplinary base and accelerated integration of basic knowledge with clinical needs. The broad objectives of the hearing and hearing impairment research program include the study of normal mechanisms and disorders that disrupt auditory function.

Goals of research on hearing should include:

- Determination of how the ear processes and encodes sound.
- Determination of how the central nervous system processes the output from the ear.
- Determination of how central nervous system processing leads to perception and behavior.
- Characterization of the life cycle (development, maturation and aging) of the normal auditory system.
Goals of research on hearing impairment should include:

- Development of population studies to determine and track the incidence, prevalence and risk factors of hearing impairment and ear disease.

- Initiation of multidisciplinary studies to determine the pathogenesis of specific hearing disorders and ear diseases.

- Mapping, isolating, cloning, sequencing and characterizing the genes responsible for hearing impairment.

- Performance of clinical trials to establish the efficacy of existing and new treatments for hearing impairment and ear disease.

- Development and improvement of devices and rehabilitative strategies to assist people with hearing impairment and tinnitus.

- Development of professional and public educational strategies to prevent hearing impairment and ear disease.

Research with Multicultural Populations and Women

The range of scientific and clinical concerns encompasses the pluralistic character of society, as well as the demographic projections for the nation. Whereas minority groups suffer from the same types of hearing impairments as nonminority groups, there are some pertinent differences in prevalence, causes and manifestations of communication disorders that merit research. There is a need for epidemiologic information on the incidence, prevalence and risk factors of hearing impairments in multicultural populations. Otitis media has a higher incidence in American Indians and Alaskan Natives and a lower incidence in African Americans than in the population at large. Although various explanations have been offered, ranging from cross-racial differences in eustachian-tube structure and function to differences in general health status, there is no definitive evidence for these explanations. There is some evidence that African Americans may be less susceptible to hearing
loss from noise exposure than other racial groups, although additional research is needed to substantiate this observation. The elderly African-American population has a lower prevalence of tinnitus than the elderly population at large. The reasons for these differences are not known. There is a need for further research on the impact of socioeconomic, educational and cultural factors on hearing impairment.

Research is needed on multilingual factors that have an impact on speech perception. For example, the effect of hearing impairment on speech understanding may be greater for individuals who are raised in bilingual environments than in environments where only English is spoken. There are no known racial differences in terms of the basic mechanisms involved in encoding and processing of sound. Some diseases of the ear may vary between the sexes. Otosclerosis, for instance, has a greater prevalence in females, whereas some studies suggest that males are more likely to develop Meniere's disease. The reasons for these gender differences in susceptibility to certain ear diseases are not known.

**Research Opportunities, Strategies and Priorities**

The understanding of any disease or impairment requires basic knowledge about how the affected system functions in its normal state. In search for this knowledge, auditory scientists have recently made some fundamental discoveries. Exploitation of these discoveries during the next few years promises to provide essential new information about how the auditory system is organized and functions. Areas that offer particularly strong opportunities for progress are discussed below.

**Hearing**

**Transduction and Homeostasis**

**Mechanoelectrical Transduction Mechanism of Hair Cells**

The key step in the function of the ear is the transduction of
mechanical stimuli into electrical responses that can be synaptically forwarded as neural impulses to the brain. Several lines of experimental evidence indicate that inner hair cells effect this function by a unique transduction process in which stimuli directly gate the opening and closing of mechanically sensitive ion channels. This direct mechanism of transduction raises the possibility of reciprocal interactions between a hair cell's electrical response and the mechanical properties of the cochlea. The use of solid-state microfabrication techniques, lasers, optical methods and other technologies offers the possibility of constructing probes for direct examination of the mechanical changes in the hair bundle during transduction and during adaptation to protracted stimuli. Similar techniques may also be used to make accurate measurements of the basilar membrane's properties and of the possible influence of hair bundles on basilar-membrane mechanics.

Role of Outer Hair Cells in Amplification and Tuning

The mammalian auditory system is an exquisite discriminator of the qualities of sound. Over the past several years, a wealth of information has accumulated which indicates that the basis of such acute frequency selectivity resides in the outer hair cells. Outer hair cells appear to enhance the mechanical input to the inner hair cells, the cells mainly responsible for the transduction of acoustic stimuli. Three plausible underlying mechanisms of this enhancement have been identified in the activity of the outer hair cells. These include fast voltage-dependent motility, slow metabolically dependent motility and interactions between stereocilia and the tectorial membrane.

At the system level, the elucidation of the contributions of each mechanism to enhanced transduction is a fundamentally important goal. While much basic information has been gathered either through modeling or in vitro approaches, the significance of these mechanisms in the intact, in vivo system must be addressed. There is a need to determine whether these mechanisms are capable of influencing cochlear micromechanics in the high-frequency region, where enhancement of tuning is acknowledged to be substantial. Modern techniques capable of measuring alternating-current and direct-current basilar-membrane motion in the high-frequency region are particularly useful, as are measures of otoacoustic emissions. However,
strategies must be developed that transcend mere confirmation of the outer hair cells' importance in feedback schemes. There is a need to appraise contributions from each of the potential enhancement mechanisms of outer hair cells. In particular, the experimental exploitation of known temporal differences among the three mechanisms may be worthwhile.

On the cellular level, an understanding of the molecular mechanisms governing these outer-hair-cell mechanical phenomena is of special interest and will aid in the determination of microenvironmental factors which influence frequency discrimination. A notable example is the observation that cell turgor affects outer-hair-cell fast motility. There is little doubt that continued study of the outer hair cell's effector role, using both in vitro and in vivo approaches, will lead to a better understanding of normal and abnormal cochlear function.

**Afferent Synaptic Signaling by Hair Cells**

The ability to locate sounds in space relies on the precise encoding of responses to sounds arriving at both ears. To account for the observed ability to locate sounds, the afferent synapses that relay information from hair cells to auditory nerve fibers must operate with an unusually high temporal resolution. These synapses are morphologically unique, both in their presynaptic specializations and in their large number of postsynaptic elements. Appropriate physiologic experiments, especially those on new experimental preparations including pre- and postsynaptic elements, are needed to document and analyze the synapses' operation.

**Pharmacologic, physiologic and molecular studies are needed to elucidate the nature of the afferent transmitter, the enzymes of its synthesis and the mechanism of its release.** At the postsynaptic level, receptors and their subtypes should be identified as well as the ensuing physiological and biochemical processes. It is essential to focus on the characteristics of ion channels, G-proteins and second messengers associated with these receptors. Furthermore, biochemical modulation of pre- and postsynaptic processes need to be elucidated. The results will aid in the understanding of synaptic function and of coding in the eighth nerve.

**Molecular Structure of Auditory Receptor Organs**

The unique structure of the hearing organ is the basis for its function as a mechanotransducer. It encompasses elements that provide structural support for the receptor cells, the substrate for transduction and motility, and regulate the intra-
cellular milieu. The integrity of these structural elements is essential both in transduction proper in inner hair cells and in regulatory feedback in outer hair cells. Past research has delineated many of the cellular and subcellular components of the structure that are responsible for normal and abnormal auditory function. Permanent losses of hearing sensitivity can result from small fractures at the bases of the stereocilia caused by exposure to intense sound. Although several of the component molecules of the stereocilia have been identified, many other stereociliary constituents, which are essential for hearing and probably unique to the inner ear, are as yet unidentified.

The mechanoelectrical transduction channels, the afferent synaptic bodies and the components of the subsurface cisternae of hair cells are other examples of unique but biochemically unidentified structural elements of the hearing organ. If there is to be an understanding of the molecular substrate of hearing, constituents that have been isolated by immunologic and electrophoretic methods need to be identified and functionally characterized. That knowledge is fundamental to theoretical frameworks for the development of new drug therapies that could be applied to such conditions as tinnitus and Meniere's disease and in the protection of the auditory system from damage induced by intense sound, ototoxic antibiotics and anticancer, chemotherapeutic agents.

Homeostatic Mechanisms in the Cochlea

Homeostatic mechanisms in the cochlea are processes that generate and maintain the natural environment in which transduction takes place. Supporting tissues and structures, such as the stria vascularis, Reissner's membrane, the basilar membrane and supporting cells of the organ of Corti participate in the homeostatic processes. Included are the maintenance of the ionic composition and electric potential of the extracellular fluids (endolymph and perilymph), the internal milieu of hair cells and supporting cells, the communication between cells by means other than synaptic mechanisms, the local control of blood flow to provide oxygen and nutrients and the local control of immune responses. While some of these mechanisms may reflect general physiologic principles, others may be unique to the cochlea. Endolymph, for example, is the only extracellular fluid with its particular ionic composition and electric potential.

Recent years have brought new information and theories on regulation of fluid composition, autoregulation of cochlear blood flow and cellular communication. In addition, research has begun to characterize molecular and cellular regulatory processes such as those involving ion channels and...
second messenger systems. A comprehensive understanding of the means by which the cochlea maintains its environment has not been achieved, and research should focus on the underlying regulatory mechanisms. This understanding is essential for a full appreciation of auditory processing, understanding disease processes and designing therapeutic approaches. Disorders of cochlear homeostasis and regulation may underlie a variety of disorders including sudden hearing loss, Meniere's disease, tinnitus and presbycusis. On the other hand, specific cellular processes may be involved in protective phenomena in the cochlea. For example, pre-exposure to moderate-level sound will protect the ear from some of the effects of traumatic noise exposure. The mechanisms of such long-term modulation of responses to acoustic stimulation remain to be elucidated.

There is a need to pay particular attention to:

- Regulation of the ionic environment of the cochlea.
- Regulation of the intracellular milieu of hair cells.
- Regulation of cochlear metabolism including hormonal and local influences; receptor mechanisms and the role of second-messenger systems.
- Intercellular communication.
- Local regulation of blood flow.
- Regulation of local immune responses.
- Modulation of responses to traumatic acoustic stimulation.

Investigations into these topics require exploration of the system at all levels from molecular mechanisms to functional aspects.

Molecular Biology of the Cochlea

The recent advances in molecular biology afford powerful new techniques for investigation of the molecular bases of the various phenomena discussed above. Many of the important proteins of the cochlea may be identified and sequenced more efficiently by molecular cloning than through biochemical techniques. The identification of promoter and enhancer sequences for genes expressed in the cochlea should be valuable in elucidating the processes that regulate the development and perhaps the regeneration of cochlear cells.

At the same time, however, there are exceptional difficulties associated with molecular-biologic analysis of the inner ear. In particular, the small amount of cellular material in the ear severely restricts our ability to construct a complex, complete and specific cDNA library representing mRNAs for proteins important in
mechanoelectrical transduction, synaptic transmission, ionic homeostasis and the other functions of cochlear cells. From the animals on which auditory experimentation is done, it would be useful to select a few species for which cDNA libraries can be made efficiently. In view of the laborious nature of library construction, it may be desirable to promote collaborative construction of libraries that will be accessible to investigators from numerous laboratory groups.

Beyond its utility in defining the proteins of the inner ear, molecular genetics offers the long-term prospect of gene therapy. Which genetic lesions of hearing can be meaningfully attacked by this means remains uncertain; it will first be necessary to isolate and characterize various genetic lesions and to ascertain in which cells mutant genes are expressed. Despite the long-term nature of this objective, it holds great promise that will steadily increase as new techniques for genetic therapy emerge throughout medicine.

**Sound Processing in the Brain**

**Cellular Basis of Signal Processing in the Central Auditory System**

Understanding the neural basis of hearing disorders requires an understanding of the cellular mechanisms involved in normal hearing. Neural impulses generated in the auditory nerve are processed by neuronal networks connected by synapses. Thus, the synapse forms the basis for mechanisms underlying acoustic information processing, the formation of neuronal circuits and response plasticity. Using a variety of chemical neurotransmitters and specialized receptors, synapses can transmit excitatory or inhibitory influences from one neuron to another. At synaptic junctions, pathologic and age-related changes may produce hearing impairment by alterations in the receptor sensitivity to and synthesis, degradation, uptake and release of neurotransmitters, as has been demonstrated in other regions of the brain. Understanding these changes may lead to the development of specific chemical blockers which can be of great practical value in basic research and ultimately lead to drug therapy to ameliorate certain kinds of hearing impairment.

At all levels of the auditory system, high priority should be given to studies of functional connections of neurons and synaptic mechanisms. Whenever possible, these studies should include:

- Identification and location of specific neurotransmitters and neuromodulators.
- Definition of receptor type.
- Understanding of transmitter-receptor interactions including ion channels and second messengers.
Characterization of electrical properties of the cell membrane.

Description of the size, source and distribution of different terminal types on the target cell's soma and dendrites.

These studies should exploit the wide range of existing and emerging methods of modern neuroscience using intact animals, tissue slices and isolated-cell preparations. A variety of approaches should be pursued, such as pathway-tracing techniques and promising new methods for trans-synaptic labelling. Other valuable approaches utilize intracellular staining to identify precisely the neurons under study and the use of genetic, molecular, immunocytochemical and pharmacologic probes. Application of these technologies to human material should be pursued wherever possible.

During the past decade, enormous technological advances have been made which permit high-resolution studies of neural circuits, subcellular components and even single molecules. Despite these advances, many basic questions remain to be answered. Long-term systematic studies addressing these questions will ultimately lead investigators toward an understanding of the mechanisms involved in normal auditory function and toward the successful treatment of hearing impairment.

Neural Basis of Auditory Perception

All acoustic information enters the brain as discharge patterns in the fibers of the auditory nerve. This incoming neural input is reprocessed in the brain stem into multiple parallel pathways, each of which may be specialized to extract different features of the acoustic stimulus, such as frequency content, temporal pattern, intensity, location in space, phonetic identity, etc. Each of the ascending pathways, in turn, may be controlled by descending pathways from higher centers, some of which may enable us to attend to certain features of a stimulus while ignoring others or help discern signals embedded in background noise.

In recent years, tremendous progress has been made in understanding the neural basis for auditory perception, especially location of sound, through a variety of classic and novel neuroanatomic, neurophysiologic and mathematical modeling techniques. Such knowledge is necessary if there is to be understanding and effective treatment for complex, sensorineural hearing impairments. As knowledge of these phenomena increases, it should be possible to improve the ability of people with
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hearing impairment to hear in noisy environments, to improve the naturalness of sounds reproduced by earphones, hearing aids and cochlear prostheses and to create better interfaces between humans and computers in robotics and other sensing applications.

Although important progress has been made, the current level of understanding is very limited compared with what remains unknown. High priority should be given to the following areas of research:

- Studies of all levels of the auditory pathway to relate neuroanatomic and neurophysiologic findings to animal and human psychophysical observations, using similar paradigms and stimuli whenever possible.

- Complete anatomic and physiologic characterization of both afferent and efferent systems and description of the differences in response processing between anesthetized and unanesthetized, behaving subjects.

- Definition of the effects of aging on neuronal processing in those areas in which the normal system is well understood.

- Study of the potential for central reorganization subsequent to peripheral injury such as noise-induced hearing loss or central injury such as stroke.

- Investigation of the plasticity of the mature auditory system and the impact of modified input or experience on its organization. Ultimately, research in plasticity must be tied to human studies. This link may now be possible given the recent improvement in imaging techniques permitting the correlation of specific psychophysical deficits with well-defined anatomic defects in humans with lesions in the central auditory pathways.

The use of animal models will continue to be an important approach to understanding hearing and hearing impairment. In particular, a comparative approach that includes different animal models and the study of different hair cell systems (auditory, vestibular, lateral line and electro-reception) should be employed. Information from studies of this nature will add to the wealth of data that has been obtained during the past few years from animal models.
Mathematical Modeling of Auditory Function

Rapid advances in understanding the auditory mechanisms in the middle ear, inner ear and central nervous system permit the development of quantitative models for auditory function that are based on anatomical, physiological and psychophysical data. Many of these models have become feasible only with the advent of large-scale computer facilities. Specific examples of functions to be modeled include sound transmission in the middle ear; macro- and micromechanics of the inner ear; mechanical, electrical and electromechanical transduction by hair cells; active processes of neural control of transduction events; representation of speech-like stimuli in terms of auditory nerve discharges; distributed neural processing of auditory nerve discharges by cell groups in the central nervous system; sound location; and relationships between auditory neural responses and human auditory perception. These models are essential; they will provide concise descriptions of normal auditory function of groups of neurons that can be tested experimentally to relate to psychophysical and perceptual function and used to study abnormal systems. At the middle-ear level, this modeling can be used to predict outcomes of different approaches to surgical reconstructions of the middle ear. Neural models are also applicable to the design of coding strategies for inner-ear and more central prosthetic devices, and they could contribute to the development of computer neural networks simulating and perhaps augmenting brain function.

Auditory Perception

An essential component of understanding auditory function is the study of the process by which sound patterns are perceived. An overriding question is: "How are acoustic inputs to the ear converted into meaningful percepts in the mind of the listener?" To answer this question requires continued and expanded research efforts in three principal areas: (a) the psychophysics of sensory coding, that is, studies in both human and nonhuman subjects of the psychophysical manifestations of normal and impaired cochlear and neural processes; (b) the psychophysics of complex sound perception, that is, studies of the relationships between the physical properties of sound patterns and the perceptual properties of the resulting sensations; and (c) perceptual organization and cognition, that is, studies of the processes by which acoustic patterns are interpreted in terms of the location, identity and significance of the objects and events that produce them.
Psychophysics of Sensory Coding

As new discoveries are made about the structure and function of the auditory system, it will be essential to establish their relation to auditory perception. For example, a large body of data currently exists on frequency selectivity in human and animal subjects, yet little is known about how psychophysical measures of frequency selectivity reflect what is currently thought to be the underlying mechanism, such as outer hair cell function and the active processes in the cochlea. Definition of the auditory perceptual correlates of peripheral auditory function should lead to behavioral measures that go far beyond audiometry in characterizing the perceptual aspects of auditory function, as well as the intactness of the underlying auditory structures.

Opportunities for research in this area will include:

- Psychophysical studies aimed at defining perceptual correlates of peripheral and central auditory function, as well as the inverse (physiologic studies guided by psychophysical data and models, utilizing similarly complex signals).

- Psychophysical studies of the perceptual consequences of damage to the auditory system.

Psychophysics of Complex Sound Perception

Considerable progress has been made in understanding perception under conditions in which acoustic information is combined across several adjacent or remote spectral regions and over time. Beyond demonstrating that simple “within-critical-band” models of auditory function are inadequate, these studies provide a basis for understanding the perception of spectral shapes and will contribute to an understanding of complex “real-world” processes such as those involved in the perception of speech. Examples of this work come under such headings as “spectral profile analysis,” “comodulation masking release,” “dynamic properties of hearing” and “informational masking.” Specific research opportunities include:

- Expanding our understanding of the ways in which acoustic information, from several spectral or temporal regions or from the two ears, combines to enhance or mask the perception of target sounds.

- Increasing understanding of dynamic and adaptive processes in auditory perception.
Expanding our understanding of the ways in which the information content of complex sound patterns can enhance or interfere with detection and identification.

Elucidating the connections between psychophysical performance and the perception of speech sounds, both in quiet and in the presence of competing signals.

Developing descriptive and quantitative models to account for the perception of complex sound patterns.

Increasing understanding of the ways in which sensorineural hearing loss affects these functions.

Perceptual Organization and Cognition

In recent years, there has been increased effort aimed at understanding how acoustic inputs are combined with prior knowledge and contextual information to result in the generation of meaningful percepts. This work has proceeded under such headings as "auditory streaming," "auditory scene analysis," "auditory object perception," "auditory perceptual learning," "selective and divided attention," "auditory memory," "auditory space perception" and "acoustic versus phonetic coding." This work has provided valuable insights into the separation of signals from noise, the perception of multiple inputs and the perception of speech. Its continuation and expansion are strongly encouraged. Specific research opportunities include:

Expanding understanding of the acoustic properties of signals that allow them to contribute to unitary or multiple percepts.

Expanding understanding of the ways in which both monaural and binaural inputs contribute to decisions about the direction and location of a sound source in both humans and animals.

Experimenting on the integration and separation of several sources of information, both intramodally and cross-modally.

Developing descriptive and quantitative models of perceptual organization.

Relating emerging knowledge about perceptual organization to the development of a comprehensive model for perception of acoustic communication signals.

Extending perceptual organization and modeling by including animal models to provide an understanding of the perceptual
consequences of sensorineural hearing impairments and auditory perceptual disorders.

- Integrating an understanding of perceptual consequences of sensorineural hearing impairments and auditory perceptual disorders with emerging physiologic understanding of central auditory processing.

**Development, Aging and Regeneration**

**Development of the Auditory System**

The development and maturation of normal hearing and the auditory problems of children are now appropriate subjects for systematic and comprehensive investigation. The molecular genetic basis of normal and abnormal auditory structure and function should be studied in animal models and humans:

- Research on embryonic mechanisms for the formation of the normal ear and the auditory pathways of the brain will lead to an understanding of mechanisms that produce congenital defects and approaches toward correction.

- The importance of critical periods for functional development and changes in the strength of interactions and interdependencies in the auditory system are likely to be related to changes in susceptibility to hearing loss.

- Influences of environmental factors through several stages of auditory development should be evaluated. Metabolic, biochemical and immunological changes in the middle ear, the inner ear and the brain that occur over the life span should be investigated.

Although there is adequate information on developmental aspects of sensitivity within the auditory system, understanding of other perceptual attributes is not well documented. Insights into the auditory abilities of infants and young children are needed. It is vital to appreciate the other complex developmental processes that underlie speech perception so the growing potential for early diagnosis and treatment of all auditory disorders can be made.

This research should be integrated with studies characterizing the mechanisms that are responsible for cell proliferation and differentiation in the cochlea. It is likely that similar mechanisms are responsible for the induction of sensory cell regeneration and recovery of hearing found after trauma in nonmammalian auditory systems.
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The survival of neurons is dependent upon their connections with sensory cells, so the loss of receptors can result in the loss of auditory neurons. Cochlear implants depend upon surviving neurons for their prosthetic efficacy. Recent studies suggest that electrical stimulation may prevent progressive neural degeneration in congenital or early acquired profound hearing loss and that nerve terminal regeneration can occur under certain conditions. The mechanisms underlying these processes should be defined through further research and applied to enhance the efficacy of cochlear prostheses.

Age-Related Changes in Hearing

Age-related hearing loss is a complex state which reflects, to a large extent, changes throughout the entire auditory system. All mechanisms for acoustic transduction, transmission and perception must be considered in light of the aging process. One hallmark of age-related hearing impairment is an unexplained loss in speech understanding without a concomitant loss in sensitivity. Progress in elucidating all of the aspects of age-related hearing loss will result from our ability to study peripheral and central components in humans while developing appropriate animal models. Studies in humans should include behavioral, electrophysiologic, neuropathologic and molecular measures of aging. Animal models will be particularly useful in elucidating genetic controls of age-related hearing loss. Moreover, animal models can be correlated with human results to provide a framework for the changes observed with age.

Since many factors contribute to age-related hearing loss, studies in structural changes in the cochlea and central auditory pathways, homeostatic mechanisms of the inner ear, environmental and genetic effects on hearing, and psychologic bases of perception and recognition will contribute greatly to understanding and prevention.

Regeneration of Sensorineural Elements and Accessory Structures

Sensorineural hearing loss has long been considered irreversible because the production of the permanent sensory and nerve cells in the inner ear normally ceases before birth. However, recent animal research has shown that under certain conditions, sensory cell production can be reactivated in mature damaged ears. It is also known that these regenerated cells contribute to a recovery of hearing. Study of the molecular control and the cellular mechanisms of this self-repair process is possible with the methods of modern biotechnology. Elucidation of the basic processes should lead to therapeutic advances.
It is reasonable to expect that the molecular events that stimulate progenitors cells to regenerate will be identified within the foreseeable future. This identification will allow the development of pharmacologic agents for controlling cell replacement and auditory recovery. Research in this area should:

- Identify molecular events that evoke proliferation leading to the replacement of lost sensory cells.
- Assess the roles of known and suspected growth factors that may influence both the production and development of replacement sensory cells and the formation and maintenance of their contacts with neurons.
- Explore the underlying mechanisms for the induction and regulation of postnatal sensory cell regeneration and differentiation. Encourage the application of this knowledge so that the mammalian cochlea and vestibular system could be artificially induced to undergo regeneration or self repair.
- Investigate the basis for the recent discovery of additional sensory cell production evoked in the embryonic mammalian cochlea and explore the potential for spontaneous sensory cell regeneration in the auditory and vestibular systems of postnatal mammals.
- Assess the contributions of various other potential repair processes in the ear, including repair of damaged subcellular components of hair cells and repair of damaged links between sensory cells and the overlying tectorial membrane.
- Evaluate mechanisms leading to the reformation of neuronal connections in the hearing organ and their functional recovery.

A multifaceted approach, which includes biochemical, cellular, physiological and behavioral investigations, is necessary to understand fully the complex processes that underlie restoration of auditory function. The realization of clinical gains from this research is likely to require years of sustained investigation, but the potential benefits are great. For 80 percent of the more than 28 million Americans affected by hearing impairment, their loss is currently irreversible due to inner-ear hearing impairment. The studies proposed here suggest that this type of hearing impairment may not have to be considered permanent.
Hearing Impairment

Hereditary Hearing Impairment

More than 300 hereditary disorders cause hearing impairment. Many forms of hereditary hearing impairment result from the actions of more than one gene.

The rapid identification over the past few years of large numbers of DNA markers showing considerable variation among individuals and spanning most of the human genome has provided the framework for locating genes whose protein products are unknown. The discovery of the polymerase chain reaction (PCR) for amplifying DNA segments has played a major role in the rapid accumulation of these informative markers. The potential to map genes involved in hearing impairment now depends on obtaining sets of families in which the same mutation causes the disorder in affected members. However, clinically identical disorders are not necessarily due to the same gene. In fact, more than 40 genes are estimated to cause autosomal recessive early-onset deafness.

High priority should be given to the identification of families suitable for mapping genes that cause hearing impairment. International collaborations and the establishment of consortia for studying specific disorders are essential for this effort. The establishment of a database of families with probable hereditary hearing impairment, willing to participate in genetic studies, will require the active participation of clinicians who can provide complete and accurate diagnostic information. Gene mapping is most likely to result from the analysis of data collected from a large pedigree in which there are many family members with autosomal dominant patterns of hearing impairment transmission and from sets of related families (such as those in isolated populations) with autosomal recessive forms of hearing impairment transmission. In these sets of data the problem of genetic heterogeneity is minimized as the same gene is likely to cause the disease in all affected family members. Both syndromic and nonsyndromic forms of hearing loss should be studied.

Advances in comparative mapping of the human and mouse genomes promise to be valuable in identifying human genes. Since there are extensive regions of homology, locating genes for hearing impairment in the mouse indicates a likely chromosomal location for similar genes in humans and suggests candidate genes. DNA markers spanning the mouse genome are being developed, and the use of different species and subspecies to map mouse genes is proving fruitful. Many mouse strains with hearing loss...
are available through federally supported laboratories. Several deafness genes have been located in humans and mice, and progress toward isolating and chemically characterizing these genes should be rapid.

Auditory assessments that differentiate carriers of recessive genes for hearing impairment from noncarriers would be most useful. Parents of affected individuals are obligate carriers; and, as an adjunct to the gene mapping studies in humans and mice, the hearing of obligate carriers and normal controls should be measured.

The successful mapping of a hearing impairment gene provides useful information for early detection of affected individuals and for identifying carriers of the gene. Locating the gene on a chromosome allows isolation, cloning, sequencing and determining the mutation and its protein product. The way in which the protein product produces the hearing impairment in the inner ear can be determined, and the counterpart gene and its protein product can be determined. The role of its product in development or maintenance of the inner ear can be determined. New technology, including the development and screening of inner ear-specific cDNA libraries, will facilitate the breakthroughs in defining the genetic basis of hearing impairment. Successful treatment and prevention of genetic hearing impairment may eventually be achieved by introducing normal genetic material into affected cells. The technique of gene therapy, which is already being applied to other genetic disorders, is likely to become an option for the prevention or amelioration of hereditary hearing impairment.

Studies of hearing impairment in which a genetic and an environmental component are suspected, should be carried out. Epidemiologic studies on hearing disorders are needed to augment available data on incidence, prevalence and risk factors. Data on multiple variables, including age, gender, ethnicity, trauma, drugs, toxins, infections, smoking, diet, genetic markers (particularly those involved in the immune system), autoimmune diseases and congenital malformations, should be analyzed for etiologic clues. In some instances, an environmental cause will be more likely. When there is evidence of a familial component to the hearing impairment, extensive and detailed family history information should be obtained on first and second degree relatives. Many different measures of auditory function should also be obtained on family members, including pure-tone audiometry, spondee threshold, speech recognition thresholds, tympanometry, measurement of acoustic reflexes, electrocochleography,
auditory brain stem response and otoacoustic emissions, as well as imaging studies. These data may contribute to the genetic analysis of the hearing disorder. Hypotheses of dominant, recessive, sex-linked, polygenic and mitochondrial inheritance should be examined.

In summary, research priorities to better understand the genetic basis of hearing impairment include:

- Map, isolate, clone, sequence and characterize genes responsible for hearing impairment in humans and animals.
- Solicit the participation of families in studies of hereditary hearing impairment. Educate professionals serving people with hearing impairment regarding selection criteria for such families.
- Develop clinical and physiological tests which identify individuals with hereditary hearing impairment and carriers of recessive genes for hearing impairment.
- Develop comprehensive inner ear-specific cDNA libraries in humans and laboratory animals.

**Acquired Sensorineural Hearing Loss and Environmental Influences**

**Role of Genetics in Acquired Hearing Loss**

A number of disorders which result in acquired sensorineural hearing loss may have a genetic basis which predisposes the individual to the deleterious effects of environmental factors. These include susceptibility to noise-induced hearing loss and drug ototoxicity. Degenerative disorders such as presbycusis may also have a genetic basis. Studies using molecular genetics and related techniques should define these disorders better.

**Infectious Diseases Affecting Cochlear Function**

**Maternal Cytomegalovirus Infection and Hearing Loss in Children**

It is estimated that one percent of all children born in the United States contract maternal cytomegalovirus (CMV). Ten percent of these children are born with mental retardation and hearing loss. Fourteen percent develop hearing loss alone, which may not become apparent until years later. It is possible that CMV-related hearing loss in children may have a greater
incidence than suspected. Research is needed to devise effective screening techniques to detect CMV infection in the newborn. Studies are needed to investigate the pathophysiology of CMV infection in the developing inner ear of the fetus in comparison to CMV infection in the adult inner ear. Research on genetic or environmental factors that may predispose a developing fetus to CMV infection are needed. Since not all newborns exposed to CMV develop hearing loss, there is a need to determine if certain factors predispose the inner ear to damage as a result of CMV infection. High priority should be assigned to the development of strategies to prevent CMV-induced congenital deafness.

**Postnatal Infections**

Sudden sensorineural hearing loss may be caused by a viral infection. Further study is needed of putative viral pathogenesis of this and other inner-ear disorders. Diagnostic techniques, such as serology, immunohistochemistry, microbiology and molecular biology, should be explored in greater detail. Bacterial meningitis, such as that caused by the pneumococcus, results in a high incidence of acquired sensorineural hearing loss. Additional research is needed to determine the mechanism and the locus of the auditory pathway damaged by meningitis. The development of vaccines and the evaluation of their efficacy are essential.

Treatment with corticosteroids and antibiotics may reduce the incidence of sensorineural hearing loss in patients with bacterial meningitis. The role of the inflammatory and immune process in meningitis may therefore have a major impact on the outcome of hearing in these patients. Animal models of meningitis are needed, and new treatment modalities should be tested. Clinical trials of the treatment of patients with meningitis are needed.

The effect of viral meningitis on the auditory system should be studied. Delayed sequelae from viruses are known to occur in infections of the central nervous system, and their role in auditory system dysfunction can be presumed but should be substantiated. Particular attention should be focused on latent viruses of the Herpes group, which have been implicated in several inner-ear and eighth cranial nerve disorders, such as Meniere's disease, vestibular neuronitis and Ramsay Hunt syndrome.

Fungal meningitis may produce sensorineural hearing loss, particularly in patients who are immunosuppressed, including patients with acquired
immunodeficiency syndrome (AIDS) and transplant patients. The mechanisms of damage to the auditory system should be further delineated.

**Auditory Consequences of Acquired Immunodeficiency Syndrome**

Infection with human immunodeficiency virus (HIV) can result in AIDS, characterized by immunosuppression, the presence of Kaposi’s sarcoma and a high level of opportunistic infections. HIV infection can also lead to AIDS-related complex (ARC), which is part of the clinical spectrum of this disease but has a lower incidence of opportunistic infections. Both AIDS and ARC are associated with sensory and neural complications that include hearing impairment. It is estimated that 75 percent of adult AIDS patients and 50 percent of ARC patients develop hearing loss.

The cause of auditory system changes in HIV-positive patients is unknown. Direct infection of the central nervous system by HIV is well documented, and strains of the virus are known to infect selectively specific neural populations. Hearing disorders in AIDS patients could be caused by HIV infection of the inner ear or the central auditory system. Many of the complications of AIDS, however, are the result of opportunistic infections rather than of HIV itself. By far the most prevalent co-pathogen is CMV, with more than 90 percent of AIDS patients having CMV infections. Since CMV is known to damage the auditory system preferentially in congenital infections, it seems likely that CMV is involved in HIV-related auditory lesions as well. Research to clarify the role of HIV and CMV infection in the auditory systems of AIDS patients should lead to improved strategies for treatment of hearing impairment in AIDS.

Some drugs that have been used to treat AIDS or infections which occur in AIDS have caused temporary or permanent hearing loss. Research needs to be done to investigate the mechanism underlying this hearing loss and the ototoxic potential of drugs being developed in the future to treat AIDS patients.

The use of new antiviral agents in AIDS patients with sensorineural hearing loss will be an area of high interest. Studies of the mechanisms of action of these antiviral agents in preventing or reversing hearing loss in AIDS will be important and have far-reaching implications for treating viral infections of the inner ear in the general population.
Neoplasia

The natural history, genetics, presence of hormone receptors and factors controlling growth should be studied further in neoplastic disorders, such as acoustic neurinoma (vestibular Schwannoma) and chemodectoma (glomus tumors). The incidence of acoustic neurinomas is higher at autopsy than in patient populations implying that the growth rate of these tumors may be extremely slow in some patients. Methods of treatment are controversial, and multi-institutional trials are needed to address questions about radiation, medical and surgical treatments.

Squamous cell carcinoma of the external ear appears to be related to exposure to the sun. The role of environmental factors, including depletion of the ozone layer, should be investigated. The etiologic factors underlying squamous cell carcinoma of the middle ear and mastoid should be elucidated. Multi-institutional, well-controlled trials of surgical, radiation and medical therapy need to be carried out to improve survival. Improvement in survival of patients with rhabdomyosarcoma who receive multimodality therapy has been achieved.

Age-Related Changes in the Cochlea

Presbycusis or age-related hearing loss is the most prevalent and least studied disabling condition. Although long life is associated with loss of hearing, there is relatively little information about the internal controls over aging within the auditory system. For example, what is the influence of long-term homeostatic regulation on cochlear integrity? What are the genetic factors associated with aging and hearing loss? Controlled systematic genetic recordkeeping in humans will be particularly useful in elucidating genetic controls of presbycusis.

Studies in homeostatic mechanisms of the inner ear, environmental effects on hearing, epidemiology of hearing loss, human genetics and otopathology will contribute greatly to understanding and preventing presbycusis. Specific research opportunities include:

- Epidemiologic studies.
- Studies of risk factors for apparent age-related hearing loss (diet, medications, heart disease, smoking or non-occupational-noise exposure).
Studies of potential treatment, such as regeneration of sensoryneural components within the cochlea and drug replacement therapy for specific peripheral and central deficits due to aging.

Studies directed at development and implementation of new signal processing strategies for auditory rehabilitation.

Animal models can be particularly helpful in clarifying the overlapping contributions of genetic predisposition, systemic disease and exposure to moderate noise levels in age-related hearing loss. These models can also identify different morphologic subtypes characterized by degeneration of hair cells and by structural changes in the stria vascularis (part of the inner-ear blood circulation), auditory nerve and brain. Interventions can also be studied in animal models. For example, does dietary change in animals with vascular disease reduce hearing loss while concomitantly reducing morbidity and mortality from involvement of other organ systems?

Clinical studies of presbycusis should attempt to delineate the separate effects of loss of sensitivity and aging on real-world speech recognition tests. To the extent that apparent central processing deficits are present, these deficits should be correlated with other measures of central nervous system structure and function such as magnetic resonance imaging, positron emission tomography and evoked potentials. Blood and tissue should be analyzed as well as retained for future studies, and the study of temporal bone and brain tissue post mortem should be a continuing research priority.

Clinical intervention in presbycusis at present includes detection, measurement and rehabilitation principally through amplification with hearing aids. As presently practiced, these methods are effective, but their benefits in communicative skills and psychosocial well-being should be better documented. Methods of intervention can and should be improved. Better hearing aids are being developed, and their efficacy and acceptability with older persons will require specific attention. Early intervention, when hearing loss is milder, may improve later function as the loss progresses. New psychoacoustic and audiologic diagnostic methods may permit identification of patients who have a poor prognosis for successful use of hearing aids and lead to an appropriate modification of rehabilitative strategies.

Trauma and Environmental Effects

Detrimental influences from the environment have long been recognized as a major contributing factor to hearing loss in the general population.
A number of factors have been identified. Others have been tentatively implicated. These factors can be classified into four broad categories:

- Exposure to noise, including steady, intermittent and impulse noise of various levels and durations. It may be associated with occupational activities (industrial plants, aircraft engines) or recreation (gunfire, rock music).

- Exposure to industrial by-products and pollutants such as the solvents toluene, xylene and styrene.

- Administration of clinically important and potentially lifesaving therapeutics such as aminoglycoside antibiotics, diuretics, antitumor agents (cisplatin) and salicylates (including aspirin).

- Results of trauma or accidents. These may be consequences of head injuries, intracranial surgery or barotrauma.

Depending on the type and severity of the insult, the resulting hearing loss may be partial or complete and reversible or permanent, or the disorder may manifest itself as tinnitus. In addition, hearing loss can be exacerbated by a combination of these insults or their interaction with other factors. A genetic predisposition for individual susceptibility may also exist.

While major inroads have been made in understanding the conditions under which these agents cause hearing loss, important questions remain unresolved. Moreover, the study of many of these problems still awaits the application of modern research techniques to elucidate the molecular mechanisms leading to the impairment of auditory function. Knowledge of these mechanisms will enable the design of rational approaches to prevention, amelioration and treatment, which are the major concerns in research on these auditory disorders.

Specifically, investigations are needed in epidemiology, pathogenesis and pathophysiology of hearing loss from environmental insults as well as into their prevention and management.

- For any suspected traumatic agent, the causal relationship to the observed hearing loss should be established.

- Electrophysiologic and histopathologic investigations may be helpful in determining the site of the insult within the auditory system.
Investigations into the molecular mechanisms elicited by these insults and leading up to the hearing loss are fundamental to understanding, preventing and treating these forms of hearing loss. These studies require the entire repertoire of modern analytical techniques of biochemistry, pharmacology, physiology, electrophysiology and molecular and cellular biology.

In prevention and management, advances can be achieved through focus on the following strategies:

- Improved methods for screening hearing impairment in populations that are at risk (for example, certain industrial workers).
- Use of high-frequency audiometry for early detection of hearing impairment due to pharmacologic agents.
- Investigations into the predictability of permanent hearing loss, based on temporary shifts in hearing threshold.
- Determination of safe levels for occupational-noise exposure.
- Development and evaluation of more effective devices for ear protection and establishment of better methods for public awareness of this important health issue.
- Determination of the extent to which hearing impairment can be alleviated or reversed, based on early detection and removal of the insulting agents.
- Development of methods for protecting the inner ear from damage by drugs administered as pharmacologic agents. These methods, while preventing inner-ear damage, should not adversely affect the efficacy of the drugs.
- Investigations into the relationship between the structure of drugs and their ototoxicity. This research is directed to the design of new products or the modification of existing ones so that their ototoxicity is attenuated while their therapeutic efficacy is maintained.
- Development of procedures to test deleterious effects of drugs in models other than animals. Artificial membranes or cultures of sensory cells offer promising alternatives that should be developed further.

This multifaceted approach, ranging from the elucidation of molecular mechanisms through improved
diagnostic and protective measures to pharmacologic prevention and new drug design, is essential. It has the potential of providing tangible benefits to the millions of Americans now at risk of environmental harm to their hearing.

The combination of noise exposure and organic solvents, which can be present in the workplace or as environmental pollutants, can potentiate hearing loss. A great deal of research is needed on the mechanisms of these interactions.

Research into the efficacy of possible therapeutic agents to reduce temporary or permanent hearing loss from noise exposure should be performed.

Experiments on the mechanisms of central and peripheral auditory injury resulting from various types of head or neck trauma should be carried out.

Acquired Sensorineural Hearing Loss in Infancy

Research is needed to study the susceptibility of the developing inner ear to such factors as maternal illness, substance use and abuse, and noise and trauma. The effects of the intrauterine environment require analysis. Studies should examine the individual differences in fetal susceptibility to hearing loss. The roles of prematurity, low birth weight and neonatal jaundice require continued investigation. Research is needed to study the effects of the environment of the newborn nursery, including the neonatal intensive care unit that admits newborns who are already at risk for hearing loss. The interaction of genetics, infections and various environmental factors in children born with a sensorineural hearing loss who subsequently develop a progressive and fluctuating hearing loss requires investigation.

Immune-Mediated Disorders

The immune system is crucial to the defense of the middle and inner ears against infection. In recent years, the role of immune mechanisms in many disorders of hearing has been recognized. Inflammation generated by the immune response undoubtedly contributes to tissue damage associated with infection. Evidence suggests that immune mechanisms induce hearing loss and are responsible for the progression of chronic otitis media. Immune mechanisms may also contribute to the pathogenesis of other disorders for which no cause has been established, such as Meniere's disease.

Research is needed on normal immune processes in the middle and inner ears as well as on the immune response to infecting microorganisms. Animal models of autoimmune sensorineural hearing loss should be
developed, if possible, for research on the pathogenesis of this phenomenon. Application of research techniques of neuroimmunology to the auditory system should contribute to a rapid expansion of knowledge in this evolving field.

Problems exist in the diagnosis of autoimmune sensorineural hearing loss, and new diagnostic tests should be developed so patients with this treatable form of sensorineural deafness can be identified early in their course.

Multi-institutional controlled treatment protocols for autoimmune sensorineural hearing loss using corticosteroids, cytotoxic agents, plasmapheresis and related therapeutic modalities should be carried out.

**Idiopathic Disorders**

The middle and inner ear are subject to a variety of idiopathic processes, such as otosclerosis and perilymphatic fistula. Otosclerosis may have a genetic or viral cause, but more research is needed in determining the cause and effective medical treatment for otosclerosis. Perilymphatic fistula is a disorder which requires continued research into the cause, diagnosis and efficacy of treatment.

**Meniere's Disease**

Meniere's disease is an idiopathic disorder resulting in prostrating vertigo, fluctuating sensorineural hearing loss, tinnitus and the sensation of fullness of the ear. Diagnosis of Meniere's disease is difficult in patients in whom the disease is quiescent. New diagnostic methods utilizing electrocochleography, otoacoustic emissions and related tests should be developed.

The natural history of Meniere's disease should be thoroughly investigated. Studies are needed to determine the incidence of bilateral involvement. New animal models of Meniere's disease which more closely mimic the human disease should be developed. Genetic studies are needed to determine whether Meniere's disease has a hereditary basis. The effects of disruption of inner-ear homeostasis and fluid regulation of endolymph and perilymph by manipulation of hormonal and systemic factors should be thoroughly studied. A possible autoimmune basis for Meniere's disease should be thoroughly examined in humans and animals. The efficacy of medical or surgical treatment should be carefully studied with controlled clinical trials. The psychosocial effects of Meniere's disease should be studied. The consequences of untreated Meniere's disease should be elucidated.
Pathogenesis and Treatment of Tinnitus

Many persons with ear disorders hear noises (ringing, buzzing or roaring) when no external acoustic stimulus is present. This disorder is called tinnitus. At least 15 percent of the American population have frequent or constant tinnitus. Persons over 50 years of age are twice as likely to have tinnitus. Research on tinnitus is in its infancy and should be greatly expanded.

The natural history of tinnitus resulting from trauma or disease is incompletely defined. While some data on the prevalence of tinnitus in adult populations are available, the types and degrees of disability caused by tinnitus should be characterized and measured in population surveys.

Aspirin toxicity causes tinnitus, while simultaneously affecting inner-ear hair cell motility in a way that can be measured noninvasively. A possible relationship between otoacoustic emissions and some forms of tinnitus deserves additional study. The use of animal models can help elucidate mechanisms and sites of origin of tinnitus and test treatment such as acoustic masking and electrical suppression. These models should be developed because they promise new insights into tinnitus and normal inner-ear function.

Reliable and valid measures of tinnitus sensation and disability must be developed for use as outcome measures in studies of existing and new treatments.

Clinical Trials in Sensorineural Hearing Loss

For sensorineural hearing losses that are sudden, fluctuant or rapidly progressive, a variety of empirical therapies are currently used. Often these therapies are based on assumptions about the pathogenesis of the hearing loss. Fluctuating losses, for example, are often believed to be caused by endolymphatic hydrops and are treated with diuretics and salt restriction, while losses believed to be caused by inflammation or ischemia may be treated with corticosteroids or vasodilating agents, respectively. There is some evidence supporting the therapeutic efficacy of corticosteroids in certain patients with sudden hearing losses; in general, however, medical therapy for sensorineural hearing loss has not been shown to be efficacious.
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There is a pressing need for properly controlled therapeutic trials in these areas. The use of agents affecting cochlear blood flow, for example, should be studied both in sudden and in rapidly progressive sensorineural hearing loss as well as in fluctuant hearing loss. The outcomes from various treatment strategies should be compared to the outcome of the natural history of the disease under study.

Some of the treatments now being used empirically may be effective only in certain subsets of patients. If better diagnostic tests were available for these patients, more rational and effective treatments could be readily determined. Further studies with animal models of sensorineural hearing loss are essential to provide insights into pathogenesis and to suggest to clinicians possible pathogenic factors in their patients.

Diagnostic Challenges

- The role of a viral infection in sensorineural hearing loss requires better diagnostic techniques.
- A diagnostic test for autoimmune hearing loss is urgently needed.
- A test to determine if the other ear of a person with Meniere's disease is at risk for development of the disease is needed.
- Diagnosis of perilymphatic fistula is difficult, and new objective diagnostic techniques are needed.
- Better diagnostic tools are needed to distinguish peripheral from central causes of hearing impairment, especially in patients with age-related hearing loss. The results should be validated with histopathologic studies of the peripheral and central auditory structures.
- Techniques for earlier identification of patients affected by neurofibromatosis type 2 are needed.
- Methods to identify patients at increased risk for noise-induced hearing loss and ototoxicity are needed.

Research Techniques

Although a variety of research techniques may be applicable, it is anticipated that epidemiology, molecular genetics, multicultural studies, and histopathology and pathophysiology of the damaged ear will be particularly useful in studying these hearing disorders.

Otopathology, particularly with newer techniques such as immunohistochemistry, three-dimensional reconstruction, electron microscopy
and in situ hybridization, can be expected to add insights into the mechanisms of sensorineural hearing loss. The development of a national temporal bone pathology database will provide a valuable resource for studies of sensorineural hearing loss.

A national effort to collect and share cDNA libraries should be encouraged so that this technology can be applied to the study of causes of acquired sensorineural hearing loss. National registries and demographic studies will help provide much needed epidemiologic data on hearing loss of this nature.

Otitis Media, Otosclerosis and Other Middle-Ear Disorders

Otitis Media

Epidemiologic studies should be designed to reveal immune and genetic markers of otitis media-prone children. Study of environmental factors should identify prenatal, perinatal and postnatal conditions, as well as environmental pollutants, that affect the incidence of otitis media.

Anatomical, biochemical, neural, circulatory and developmental factors that affect the eustachian tube and middle-ear gas composition and pressure should be defined and correlated with the incidence, prevalence and pathogenesis of otitis media. Noninvasive tests of eustachian-tube function should be further developed.

The anatomic characteristics of the middle ear and related structures should be studied in various patient populations, including patients with asymptomatic middle-ear disease, employing the methods of systematic and quantitative human temporal bone pathology research. Methods of establishing cellular lineage and differentiation and investigating cellular regulatory mechanisms, including the molecular biology of secretory products in normal and pathologic conditions, should be emphasized in future research. The role of the round window membrane in possible inner-ear sequelae of otitis media should be a continued focus of research.

Microbiological, immunological and biochemical research opportunities include further elucidation of the mechanisms by which viral infections enhance or predispose to bacterial infections of the middle-ear space. Study of the role of bacterial-cell products in the inflammatory response and the genetic diversity and molecular features of bacteria involved in otitis media should be emphasized. Study of relevant adherence factors for each of the common middle-ear pathogens, characterization of genes
encoding adherence factors and identification of the corresponding cell-surface receptors should be carried out to understand host and environmental factors that impact the microbial ecology in the nasopharynx. Future investigation should explore the role in homeostasis of secretion products and continue characterization of middle-ear inflammatory mediators.

Research to date has revealed important contributions of local and systemic immunity to middle-ear protection and inflammatory responses. Future research should determine the relative roles of systemic and local immune responses in the pathogenesis and mechanism of recovery from otitis media. This research may delineate the role of specific lymphocyte receptors and growth, proliferation and transcription factors in lymphocyte recruitment to and function in the middle ear.

High priority should be given to the development of vaccines that would reduce the incidence of viral and bacterial infections that cause otitis media and bacterial infections that cause meningitis. Priority should be given to further development and testing of pneumococcal capsular polysaccharide-protein conjugate vaccines for prevention of otitis media and meningitis. Protective mechanisms for nontypable *Haemophilus influenzae* and *Moraxella catarrhalis* should be further defined, and new genes for which expression products might be vaccine candidates should be identified.

Research should identify measures to detect otitis media and hearing loss in infants less than six-months of age, and improved methods of tympanometry and quantitative pneumotoscopy should be developed.

Study of treatments for otitis media should identify demographical, clinical, biochemical, microbiological and immunological factors that predict antimicrobial efficacy, complications and sequelae. Future research should emphasize antimicrobial and anti-inflammatory drug pharmacokinetic studies in the middle ear and safety profiles of existing and new antimicrobial and anti-inflammatory drugs. More effective pressure equalization of the tymanostomaid cavity should be a goal of therapeutic research. Multicenter, cooperative clinical trials should be explored to accelerate the testing of new treatment modalities on large, broadly representative population samples.

Since otitis media can have long-term effects on health and development, future research should measure the incidence of long-term otitis media sequelae including middle-ear and mastoid pathology and functional disability. These studies need to determine the effect of otitis
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media and hearing loss on speech, language, perceptual and cognitive development. Long-term sequelae of surgical and pharmacological interventions for otitis media are necessary including timing of antibiotic treatment. The pathogenesis and molecular and cellular mechanisms of the development of tympanosclerosis, chronic otitis media with and without perforation and cholesteatoma should be investigated further.

Otosclerosis and Other Ear Disorders

Understanding molecular and cellular mechanisms of otosclerosis should be a research priority. These mechanisms should include identification of specific viral antigens and identification of RNA or DNA in otosclerotic bone. Epidemiologic studies to search for genetic factors and preceding viral infections in otosclerotic patients should be performed.

The prevalence of perilymph fistulae should be determined, and tests for middle-ear perilymph should be developed.

Continuing studies of middle-ear micromechanics and development of middle-ear implant materials including ceramics, hydroxyapatite, plastics and banked middle-ear homografts should be pursued. Research should include determination of long-term results of middle-ear grafts and prostheses. Further study of the feasibility of partially or totally implantable electromechanical or electromagnetic drivers of the ossicular chain and temporal bone should be conducted. These studies should be done in light of increasing use of intense magnetic fields in medical diagnosis.

Assessment, Diagnosis, Treatment and Rehabilitation

The consequences of impaired hearing on speech perception are currently addressed by two approaches: prosthetic management and auditory rehabilitation. (Refer to the 1991 update of the Language and Language Impairments section of the National Strategic Research Plan for research opportunities involving the linguistic, educational and cultural concomitants of hearing impairment.) Prosthetic management includes both the fitting of hearing aids, auditory prostheses and tactile aids, and in the case of children, the use of other technological aids to facilitate speech training and language development. Auditory rehabilitation attempts to remedy problems arising from hearing impairment by providing instruction in speechreading, communication therapy and training for children and adults who have difficulty with the interpretation of sound.
Assessment and diagnosis are prerequisites for treatment and remain essential components of rehabilitative management.

**Assessment and Diagnosis**

Quantum leaps have been made in the development and use of noninvasive diagnostic procedures to identify hearing impairment. An urgent research goal continues to be the early identification of hearing impairment in infants. The average age at which profound hearing impairment is first detected in this country is nearly three years, with less severe losses detected even later. Detection of hearing impairment during late stages of language development has a negative impact on the acquisition of communicative, academic and social skills in children. There are powerful strategies for early identification of hearing impairment in newborns and infants. Research is needed to study these strategies to determine their effectiveness in screening for hearing impairment and to determine the best method for implementation in various settings.

Advances in technology hold promise for the development of improved assessment and diagnostic procedures for adults, as well as for infants and children. Research opportunities in the area of assessment and diagnosis include:

- Establishment of validity, reliability and efficiency of new and existing audiologic test procedures.
- Application of new and emerging information about normal and pathological processes to improve diagnostic and evaluative techniques.
- Application of new and emerging technologies to improve diagnostic and evaluative techniques.

**Treatment and Rehabilitation**

**Prosthetic Management**

**Fundamental Understanding**

While much remains to be learned about the characteristics of normal auditory function, a major lack of knowledge exists in the current understanding of how impaired auditory systems encode the cues salient for communication, of how auditory perceptions are distorted by hearing impairment and of the mechanisms of the ear and central auditory system that underlie these changes. Such an understanding is basic to the development of prosthetic devices and rehabilitative strategies.
This area of research should include physiologic and perceptual studies of impaired auditory function, including the effects of aging and electrical stimulation; studies of speech perception by hearing-impaired persons; studies of the linguistic, social, emotional and vocational consequences of hearing impairment; and studies of nonauditory processing disorders associated with hearing impairment.

**Hearing Aids**

Continued research on hearing aids is important and timely. The population who can benefit from hearing aids is likely to grow as the population ages. In addition, progress in the miniaturization of electronic devices and transducers as well as the technology of digital signal processing may far outstrip the basic understanding required to apply these advances successfully. Specific research opportunities include:

- Research on the design and optimization of hearing aids consistent with emerging knowledge of impaired auditory function.

- Application of promising technologies and concepts to the design of improved hearing aids, including increased directionality and noise suppression, higher functional gain and output levels, reduced acoustic feedback, adaptation to variation in input level and improved signal processing in reverberation.

The potential for functional benefits associated with implanted hearing aids that drive inner-ear structures directly should be investigated.

- Development of improved techniques for the fitting, selection and validation of hearing aids for both children and adults.

- Refinement of the theoretical basis, including standardized materials and methods, for evaluating hearing aid efficacy.

- Evaluation of the efficacy of new and existing hearing aids, so that appropriate devices can be recommended to impaired listeners.

- Evaluation of the efficacy of new hearing aid technology for specific subpopulations of individuals with hearing impairments, based on age, etiology, degree of hearing impairment and site of lesion (sensory versus neural versus central).

**Neural Prostheses**

Implantable neural prostheses are increasingly used to treat profound sensorineural hearing impairment.
One type of prosthesis is placed directly in the cochlea; another is introduced within the auditory pathway of the central nervous system.

The peripherally placed cochlear implant has become an accepted prosthesis for both adults and children. More than 80 percent of adult recipients of cochlear implants receive substantial benefit in communication when speechreading is possible and about one-half of these individuals are able to understand some speech without speechreading. Of those people who can understand speech without speechreading, about one-half are able to communicate by telephone. Substantial benefits have also been observed for children, including those deafened prelingually; moreover, there is evidence that the benefits derived improve with continued use of the prosthesis. New sound processing schemes based on high-rate, pulsatile stimulation have been shown to provide even greater levels of speech perception.

Improved prostheses suitable for placement within the central auditory pathways have been developed. Initial studies of selected patients with auditory brain stem implants have produced encouraging levels of speech segment and word reception, and the potential of this approach for aiding deaf persons is great. Future refinement of this approach should be pursued using strategies in which basic research results (e.g., on the tonotopic organization of central structures) are interfaced with technical and clinical research on electrode design and coding strategies.

Research on neural prostheses, in addition to providing amelioration of hearing impairment, provides an important opportunity for examining auditory function as well as for studying maturation and plasticity within the auditory system. Research opportunities in neural prostheses include:

- Developing improved speech coding schemes capable of providing enhanced perception to more implant recipients.
- Understanding the factors that determine the degree of benefit provided to a specific patient by a specific prosthesis and thereby facilitating the prediction of the potential for success before implantation.
- Developing longitudinal studies of the development of auditory, speech perception and production and language skills in hearing-impaired children fitted with cochlear implants, hearing aids or tactile aids.
- Investigating the potential role of nerve growth factor and other growth factors in stimulating
the regrowth and the maintenance of nerve terminals in the cochlea.

- Studying the role of electrical stimulation in prolonging the survival of neural elements.

- Developing improved electrode systems that will allow for a greater number of perceptual channels and increased channel selectivity, yet will be suitable for replacement as required.

- Developing and studying electrode systems and coding techniques appropriate for central auditory system prostheses.

- Developing and validating models of the factors that affect electric-current spread in auditory structures.

- Developing models of the ways in which electrical stimuli elicit distributed patterns of neural activity at various levels in the auditory system to achieve a full understanding of prosthetic function.

Tactile Aids

Studies of natural methods of tactile communication employed by the deaf and blind (e.g., the Tadoma method of speechreading and the tactile reception of sign language and finger spelling) provide evidence that the skin and proprioception can serve as useful communication channels. Thus, there is strong evidence that successful prosthetic devices can be developed based on coding acoustic signals for the tactile and kinesthetic senses. Several multichannel tactile aids have been developed and are currently being used by deaf people.

- Coding techniques capable of extracting the necessary information-bearing cues from the acoustic speech signal and encoding the required tactile sensations should be developed.

- The efficacy of existing tactile aids, particularly in children after extended periods of use, should be studied.

Supplements for Speechreading

Recent advances in speech processing and automatic speech recognition technologies may provide substantial benefits to hearing-impaired individuals who rely on speechreading for communication. The visual signal is impoverished so that, for example, distinctions between consonants based on voicing are not easily made. When the resulting confusions are resolved, as in the case of manually cued speech, near normal communication is possible using vision...
HEARING AND HEARING IMPAIRMENT

alone. Even simple auditory and tactile signals can improve speechreading substantially. Recent research greatly increases our understanding of the benefits to be expected from these supplements and may permit analysis in clinically useful terms.

- Additional research on auditory supplements is required to establish how to select and match the supplementary signal to the characteristics of the impaired auditory system.

- The application of speech recognition technology to the automatic generation of cued speech also warrants study. Research is needed to develop recognition and display techniques appropriate for speechreading supplementation and also to establish the levels of performance that must be achieved if useful benefits are to be provided.

Telecommunication Devices

Research is needed to develop and evaluate visual technologies for hearing-impaired individuals such as visual telephone communication, electronic mail, video conferencing, Videotex and real-time captioning.

Application of these technologies has important implications for maximizing rehabilitative opportunities for individuals with hearing impairment.

Auditory Rehabilitation

Adults and children with acquired sensorineural hearing loss require rehabilitative intervention, including opportunities to adjust to diminished hearing, to adapt to sensory prostheses and to develop improved speech perception skills in visual, auditory and auditory-visual modes. Much of the applied work in this area has developed with minimal guidance from research. The establishment of a scientific basis for continuation and expansion of this work is a high priority. Specific research opportunities include:

- Establishment of the prerequisites and essential components of effective rehabilitation.

- Establishment of appropriate and realistic expectations for the outcome of rehabilitative strategies.

- Establishment of the need for and efficacy of rehabilitative intervention in various populations with acquired sensorineural hearing loss.
Summary of Research Recommendations

Research Opportunities in Hearing

Transduction and Homeostasis

- Measure the mechanical changes in hair bundles during transduction and adaptation and determine how these mechanical changes affect basilar-membrane motion.

- Elucidate the mechanism of outer-hair-cell motility and investigate the role of this process in frequency tuning on the basilar membrane.

- Relate the unique structure of the hair cell's afferent synapse to its role in sensitive, high-frequency synaptic transmission and identify the hair cell's neurotransmitter and its postsynaptic receptor and signaling mechanisms.

- Identify and characterize the molecular substrates underlying transduction, motility and cellular homeostasis.

- Examine the homeostatic processes that regulate the cochlear environment, including the control of blood flow, ionic balance and intercellular communication.

- Construct cDNA libraries representing messages for proteins involved in transduction, motility and ionic regulation; probe the libraries in an effort to identify and sequence the proteins that are the transduction channel, the adaptation motor, the afferent transmitter receptor and growth-factor receptors.

Sound Processing in the Brain

- Study the functional connections of neurons and synaptic mechanisms at all levels of the auditory system.

- Relate neurophysiologic descriptions of the auditory system to animal and human psychophysical data.
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Characterize fully the afferent and efferent auditory systems.

Study the potential for central reorganization subsequent to peripheral or central injury, determining the plasticity of the mature auditory system and the impact of modified auditory input upon its organization.

Develop models to provide concise descriptions of normal and abnormal auditory function.

**Auditory Perception**

Define the relations between complex acoustical signals and the resulting perceptual experiences of listeners.

Elucidate the perceptual correlates of sound coding in the auditory nervous system.

Enhance the understanding of sound location in animals and humans.

Relate emerging knowledge about perceptual organization to the development of a comprehensive model for auditory perception of spoken language.

Extend research conducted on listeners with normal hearing to study the consequences of sensorineural hearing loss on the perception of complex sounds and spoken language.

**Development, Aging and Regeneration**

Assess the normal life cycle of the auditory system, including the definition of critical periods for the development of auditory processes.

Evaluate the limits of neural plasticity in the auditory system.

Define the influences of environmental, nutritional and pathologic factors that compromise the normal life cycle of the auditory system.

Study the embryonic mechanisms for the formation of the normal ear and characterize the mechanisms underlying normal cell proliferation and differentiation.

Study the developmental course of complex sound and speech perception in infants and young children.

Elucidate the many aspects of age-related hearing loss in animals and humans.

Isolate and identify molecular events that evoke proliferation leading to the replacement of lost sensory cells.
Assess the roles of known and suspected growth factors that may influence the production and development of replacement sensory cells and the formation and maintenance of their contacts with neurons.

Explore the molecular, morphologic, physiologic and behavioral consequences of sensory cell regeneration.

Identify the mechanisms that determine neuronal survival and explore paradigms that may protect and maintain auditory neurons after trauma or deprivation.

Characterize the morphogenetic processes of the embryonic ear.

Identify the intercellular signals that regulate developmental specialization of cells that perform the sensory and supporting functions of the cochlea.

Determine which growth factors mediate the trophic interdependence of sensory cells and neurons in the auditory system and assess the strength and the timing of those interactions in normal development and during regeneration.

Investigate the potential for sensory cell replacement and regeneration in mammals.

Study the role of electrical stimulation in prolonging neuronal survival.

Research Opportunities in Hearing Impairment

**Hereditary Hearing Impairment**

- Map, isolate, clone, sequence and characterize genes responsible for hearing impairment in humans and animals.

- Solicit the participation of families in studies of hereditary hearing impairment. Educate professionals serving people with hearing impairment regarding selection criteria for these families.

- Develop clinical and physiological tests which identify carriers of recessive hearing loss genes.

- Develop comprehensive inner ear-specific cDNA libraries from humans and laboratory animals.

**Acquired Sensorineural Hearing Loss**

- Study the incidence, pathophysiology and treatment of hearing loss and ear disease associated with human immunodeficiency virus and the opportunistic infections it causes.
Study the incidence, pathophysiology, diagnosis and treatment of hearing loss associated with viral and bacterial infections.

Study the natural history, biology, treatment and rehabilitation following treatment of neoplasms which affect the temporal bone.

Study the effects of trauma, environmental factors and ototoxic drugs on hearing; new means of establishing the causal relationship of the hearing impairment to the traumatic event or injurious agent; improved screening techniques for prevention; location of the insult within the auditory system; and identification of the molecular mechanisms underlying this damage so that strategies for treatment can be developed.

Study the possible causes of acquired sensorineural hearing loss of infancy to establish precise causes so that preventative interventions can be developed.

Study the normal immune host responses involved in diseases of the middle and inner ears.

Establish and investigate animal models of autoimmune sensorineural hearing loss, determine the inner-ear targets of autoimmunity, develop specific and sensitive diagnostic tests for this condition in humans and conduct controlled treatment trials to determine safe and effective therapeutic intervention.

Study the idiopathic forms of hearing loss, such as otosclerosis and perilymphatic fistula, with attention toward establishing a cause, improving diagnosis and determining efficacy of treatment.

Determine the natural history, pathogenesis and treatment of tinnitus.

Perform clinical trials to determine the most efficacious treatments for the various causes of sensorineural hearing losses.

Study the natural history, epidemiology, diagnosis, pathogenesis and treatment of Meniere's disease.

Establish more sensitive diagnostic tests for viral deafness, separation of peripheral from central causes of hearing loss, neurofibromatosis type 2 and those at increased risk for noise-induced hearing loss and ototoxicity.
HEARING AND HEARING IMPAIRMENT

- Apply newer research techniques involving molecular biology, immunohistochemistry, electron microscopy and computer-assisted reconstruction to the study of the temporal bone.

- Establish a national consortium to create cDNA libraries of the inner ear so that this technology can be made available to investigators in the field.

- Develop national registries to collect epidemiologic data on hearing impairment as well as diseases which affect the ear.

**Otitis Media, Otosclerosis and Other Middle-Ear Disorders**

- Study the epidemiology and incidence of otitis media among multicultural populations with attention to environmental versus genetic factors.

- Study the anatomy, biochemistry and development of the eustachian tube and its role in otitis media and maintenance of middle-ear gas composition.

- Study the cellular elements and their function in the middle ear.

- Study the microbiology, immunology and biochemistry of the middle-ear inflammatory response.

- Study the role of local and systemic immune responses in the pathogenesis and recovery from otitis media.

- Develop vaccines for the prevention of otitis media and meningitis.

- Develop diagnostic measures for otitis media in infants under six months of age.

- Study existing and new treatment modalities for otitis media to establish their efficacy and safety.

- Study the long-term sequela of otitis media on middle- and inner-ear function, middle-ear and mastoid pathology and speech, language, perceptual and cognitive development.

- Study the epidemiology and the molecular and cellular mechanisms involved in the pathogenesis of otosclerosis.

- Develop a precise diagnostic test or assay for perilymphatic fistula.

- Study the micromechanics of the conductive hearing apparatus and develop improved middle-ear implants and electro-mechanical or electromagnetic drivers of the ossicular chain.
Assessment, Diagnosis, Treatment and Rehabilitation

- Develop and validate new procedures to identify hearing loss and evaluate the perceptual consequences of hearing loss.

- Develop and evaluate new techniques for effective auditory rehabilitation of children and adults with hearing impairment.

- Continue the development and evaluation of sensory aids for persons with hearing impairment including hearing aids, cochlear implants, auditory brain stem implants, tactile aids and speechreading supplements.

- Continue the development and evaluation of visual technologies for individuals with hearing impairment.
VOICE AND
VOICE DISORDERS
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Overview

Emergence of Voice Science and the Science of Voice Disorders

Voice production (phonation) is the generation and modulation of sound and is a subset of the more global process of speech production. Disorders of voice involve difficulties with pitch, loudness and quality. Voice disorders can be distinguished from articulation disorders, which present difficulties of speech sound production. Many people who have acquired normal speaking skills become communicatively impaired when their vocal apparatus fails. This impairment is important in modern society because there is much demand for effective speech and oral communication.

Additional demands on the voice are made because of negative influences from noise and pollutants in the environment. There are also increasingly larger populations of the aged and hearing-impaired persons and people under psychological and physical stress. Voice production is not the only function of the larynx (voice box). This organ plays a vital role in protecting the tracheobronchial tree, particularly during swallowing.

Within the last decade, the field of voice science has expanded in several ways. A large new knowledge base has been developed on the mechanisms of phonation. Awareness of voice disorders has increased. A clinical delivery system has emerged with improved diagnosis and treatment of individuals with voice impairment, laryngeal pathology and swallowing disorders. These developments have resulted in the need to address research strategies in the voice and speech systems separately.

Interaction of the Voice and Speech Systems and Their Disorders

In the context of communication, voice is an acoustical representation of language. It is a product of laryngeal and upper aerodigestive tract adjustments that act upon and interact with the respiratory airstream to create the physical disturbances we perceive as sounds. The respiratory system, which is an integral part of the voice production system, provides the energy source and must be coordinated with laryngeal valving and upper aerodigestive tract modulation of the respiratory airflow. Vocal tract shaping above the larynx in the hypopharynx, pharynx, nasopharynx, oral cavity and nasal cavities affects the quality of the voice and is also part of the voice-production system.
Speech involves adjustments of the pharynx, tongue, velum (palate), lips and jaw, which modify and enhance the sound source. Articulatory valving and obstructions of the airflow can produce major downward modulations on glottal function. This is only one example of the close interaction between the voice and speech systems. Other significant interactions result from the effects of tongue position on the height of the hyoid bone and larynx during speech.

The same upper aerodigestive tract structures involved in voice and speech production are also required to coordinate the activity of swallowing. Therefore, although normal structure and function and diseases and disorders of the voice, speech systems and swallowing can be studied independently, their interrelations also need to be studied.

**Background**

The larynx is a valve structure between the trachea (wind pipe) and the pharynx. It has a skeleton consisting of several cartilages, the largest of which is attached to the hyoid bone in the upper part of the neck. Muscles covered with mucous membrane form the vocal folds, which are moved apart to open the larynx or are pulled together for closure.

An important role of the larynx is protection and maintenance of the airway. The vocal folds are separated during inspiration, and air passes into the trachea to the lungs. During expiration, movements of the vocal folds participate in the control of the rate of airflow out of the lungs. During swallowing, the larynx is elevated, moves anteriorly and is closed tightly, while the tongue and pharyngeal muscles move food or fluid into the esophagus. During a cough, the vocal folds close while expiratory muscles contract to increase pressure in the lungs. The larynx opens abruptly, air rushes out and mucus or foreign matter is ejected from the tracheobronchial tree. If the larynx is irritated by particulate matter, reflex closure of the vocal folds and coughing occur. These actions prevent life-threatening aspiration pneumonia.

Voice or phonation is generated by airflow from the lungs as the vocal folds are brought close together. The vocal folds vibrate when air is pushed past them with sufficient pressure. The vibration of the folds causes the airflow to become pulsed. This pulsed airflow is then modulated by aerodigestive tract structures (the pharynx, oral cavity and nasal cavities) to produce the sound that is perceived as voice during speech. Without normal vibration of the vocal folds in the larynx, the sound of speech is absent and words can only be mouthed. They cannot be heard or understood by others, either in face-to-face conversation or over the telephone.
To produce a whisper, the vocal folds need to be partially separated, and speech can only be understood by persons very close by.

When vocal fold vibration is impaired, sound generation for speech is affected. An absence of one vocal fold may result in voice loss or impairment. Absence of both vocal folds results in a loss of voice or aphonia. This happens when the larynx is removed, as may be required in laryngeal cancer. Growths on one or both of the vocal folds can change the mechanical properties of the tissue, which affect its vibration. Lesions, such as polyps, result in a hoarse voice caused by irregular vocal fold vibration. Other tissue changes, such as nodules, edema or contact ulcers, can also cause a hoarse voice. Papillomatosis, a spreading of wart-like growths on the vocal folds, also interferes with voice production by limiting vocal fold vibration and the intake of air through the larynx to the lungs.

The nerves controlling the functions of the larynx can be impaired as a result of accidents, surgical procedures or viral infections. When the motor nerves on one side are affected, the muscles moving the vocal fold are paralyzed and the vocal folds cannot come close enough to the center of the larynx. In such individuals, there is excessive air loss between the vocal folds during phonation, which results in a breathy voice. When the nerves on both sides of the larynx are affected, the muscles may not separate the vocal folds properly for breathing. This situation may occur in some motor neuron diseases or following operations on or trauma to the neck.

Both unilateral and bilateral laryngeal nerve paralysis can result in aspiration during swallowing, because laryngeal movement is reduced and the larynx does not close.

Loss of laryngeal sensation can also be a problem. A sensory loss alone can result in food or liquid entering the trachea, and aspiration can cause pneumonia.

The complex functions of the upper aerodigestive tract can be severely impaired by diseases of the central nervous system. Both sensory and motor lesions can significantly impair reflex control as well as voluntary control. Brain stem damage is particularly devastating to swallowing function.

Laryngeal movement disorders have only recently been studied systematically. In spasmodic dysphonia, the muscles of the larynx contract abnormally during speech, causing uncontrolled pitch and voice breaks and sometimes affecting swallowing and breathing. Vocal fold tremor, a disorder attributed to rhythmic contractions of the muscles of the larynx, causes the voice to quaver with frequent pitch and voice breaks.
Another disorder, laryngospasm, is an uncontrolled closing of the vocal folds, which interferes with breathing.

Interpersonal stress and psychological factors can have a profound impact on the upper aerodigestive tract. This is not surprising, as the voice directly expresses emotion, and eating is a frequent focus of psychogenic disorders.

Incidence, Prevalence and Impact on Society

Most of the statistics regarding voice disorders are from studies of school-age children. In these populations, estimates of the incidence of voice disorders range from six to 23 percent. The majority of these children have hoarseness, which has resulted from vocal abuse.

There are no data available on the incidence of voice disorders in the general adult population. However, voice disorders are believed to be more common in older adults. Voice and swallowing problems are very frequent in patients with acquired neurogenic diseases.

The economic impact of voice disorders on our society cannot be accurately assessed. However, voice disorders can have devastating effects on individuals, interfering with speech. Often, individuals are unable to function in work situations. Use of the telephone may be impossible without utilizing a telecommunication device for the deaf (TDD) and some individuals are forced to rely on writing for communication. Careers can be lost or limited because of the onset of a voice disorder.

Impairment of respiration or swallowing can be life threatening. Often, the only available treatment results in a loss of voice. When swallowing is severely affected, nonoral feeding is required and the quality of life is diminished.

Recent Accomplishments and the Current State of Research

Normal Structure and Function

Laryngeal Physiology

The biomechanics of laryngeal behaviors that produce different movement trajectories during respiration, airway closure, swallowing, coughing, singing and speech have been studied.
Recently, properties of laryngeal muscles have been found to differ from properties of other muscles. Laryngeal muscles are resistant to fatigue, are able to contract rapidly and are less susceptible to injury. Experimental studies have demonstrated the possibility of reinnervation of the laryngeal muscles after neural injury with and without surgical intervention.

Lifespan Changes

Research has revealed specific anatomical, physiological and biochemical alterations with maturation of the upper aerodigestive system. Laryngeal position and configuration change during development and with aging. Swallowing is also affected by aging. Prolongation in oral transit times and delay in initiating the pharyngeal phase of swallowing have been defined in the elderly. Changes in laryngeal muscle contraction behaviors with maturation have also been reported. As well, the cellular biology of the upper aerodigestive system has been found to change with age.

A series of histochemical, ultrastructural and stereological investigations have been initiated on the aging human larynx and its innervation. Studies on animal models have demonstrated a number of changes in morphologic parameters that are likely to play key roles in the mechanisms underlying age-related laryngeal dysfunction. In addition, studies on the human superior laryngeal nerve have shown a large, selective loss of the smallest nerve fibers. This finding may help to explain the age-related dysfunction of the laryngeal protective mechanism.

The use of organotypic cultures to study epithelial-mesenchymal interactions and enhance epithelial differentiation in vitro has been stimulated by advances in dermatology. Application of these techniques to the larynx has provided insight into the plasticity of the adult human laryngeal epithelium. The differentiation pathway into either stratified squamous or ciliated columnar epithelium can be modulated by changing the concentration of retinoic acid in the medium. This understanding raises questions regarding the use of retinoids in chemoprevention of cancer, and it opens potential avenues of research.

Exceptional Behavior

Training of the voice leads to morphological and behavioral changes in the quality and health of the laryngeal tissues. An understanding of these changes can improve the quality and health of the voices of nonprofessionals as well.
Voice training has an important impact on vocal function. Singers have greater frequency and intensity ranges and lower airflows. One consequence of these advances in knowledge is to include singers as a special population in descriptive databases.

There is growing evidence that the voices of trained vocalists change less rapidly with age than those of their nonsinging counterparts. Further study may help develop preventive programs for presbylarynx. In addition, singers appear to be better able to compensate for laryngeal deficits. This finding has implications in voice training for patients with vocal disorders.

Animal Models

Studies are under way to document the role of the central nervous system in the control of laryngeal behavior, vocalization and swallowing. Through the recording of electrical potentials from single neurons in awake, vocalizing animals, the function of various structures is now being understood in the context of the behavior of a normal, healthy animal.

Neural activity has been recorded concomitantly with electromyograms of the upper aerodigestive tract to investigate the integrative actions of the larynx and the rest of the respiratory system in behaviors such as vocalization and swallowing.

Sets of neurons in the periaqueductal gray area of the midbrain have been documented to influence the activity of coordinated groups of neurons to the larynx and the rest of the respiratory system during vocalization. Neurons in the nucleus ambiguus are strongly influenced by cells of the midbrain periaqueductal gray area during vocalization and by cells of the nucleus tractus solitarius and reticular formation during swallowing.

Techniques using multiple arrays of neural recording electrodes have been developed for the study of other systems in awake or anesthetized animals. As the software supporting technology develops, these techniques should yield data on large samples of simultaneously recorded cells and lead to an improved understanding of the functions of specific structures.

Knowledge of the interactions between laryngeal sensory and motor systems has recently been advanced by the development of an animal model that can produce phonation even though the animal is completely anesthetized. This preparation affords
researchers the opportunity to study
the behavior of laryngeal motor neu-
rans, sensory afferents of the larynx
and the mechanisms of how phonatory
control interacts with protective
reflexes and swallowing.

Anatomy and Physiology
of Swallowing

The application of electro-
myography, endoscopy, manometry
and combined techniques (such as
videofluoroscopy and manometry
combined with computer image
analysis) has offered new insights into
normal and disordered swallowing.
In the past five years, there has been
recognition that swallowing is not one
behavior but a set of behaviors that
vary in their temporal and kinematic
characteristics. Some of the factors
responsible for systematic variation
in swallowing have been identified.
These include bolus volume, viscosity
and voluntary maneuvers. In particu-
lar, the potential for volitional control
over laryngeal movement, cricophar-
yngeal opening and airway closure
has been delineated.

The physiology of the upper
esophageal sphincter has received
special attention relative to the
mechanisms of opening and variations
with bolus volume. The major elements
responsible for opening of the upper
esophageal sphincter have been
defined as: (1) relaxation of the
cricopharyngeal muscle; (2) anterior
and vertical laryngeal movement,
which opens the sphincter; and
(3) bolus pressure, which modulates
the width of the opening.

Advances in the
Diagnosis and Treatment
of Voice Disorders

Vocal Fold Neoplasms

The development of improved
visualization of the larynx along
with video recordings should lead
to improved accuracy in the early
diagnosis of laryngeal cancer.
When such disorders are detected
early, the prognosis for cure while
maintaining voice function is good.

Patients can now be fitted
with prosthetic devices to redirect
airflow and allow voice production
soon after surgical removal of the
larynx for treatment of laryngeal
cancer. Previously, such patients
had only two alternatives: to learn
esophageal speech or to use a mechanici-
cal larynx or electrolarynx. Prostheses
provide voice for speech with less
training and without an external
device. Refinements in design of
these prostheses should make speech sound more natural.

Recent advances in the understanding of recurrent respiratory papillomatosis should improve management of this disease and hopefully prevention. The viral cause and latency of the infection are better understood. Quite recently, it was shown that a major contribution to the mass of these tumors is derived from a failure of differentiation rather than increased proliferation. Organotypic tissue cultures mirror this abnormality, thus providing a good model for studying potential modulations of the differentiation process. Interferon cannot eliminate the papilloma virus infection, but it may have a potential adjuvant role in managing patients with severe disease.

Photodynamic therapy using agents that are absorbed by the tumor is currently being evaluated for respiratory papillomas and superficial malignancies.

**Vocal Fold Lesions and Glottal Insufficiencies**

Phonosurgery is a relatively new specialty that requires skill and new instruments for delicate operations on the vocal folds. Surgical techniques are being designed to improve and restore voice by removing benign growths, correcting structural abnormalities and repairing trauma.

Previous common practices such as vocal fold stripping have been found injurious to the voice. Improvements in technique make it easier to restore normal vocal function.

**Neurogenic Disorders**

**Neurogenic Disease**

Neurally based laryngeal problems account for a substantial portion of all voice disorders and such disorders are frequently the first signs of neurogenic disease. Recent technological advances have made it possible to view the laryngeal structure and its gross movement patterns, as well as to make fine measurements of moment-to-moment changes in the cycles of vibration. Voice measurement techniques and computational analysis have yielded information delineating voice changes related to the early course of neurogenic diseases. This information may now be used to make earlier identification of some diseases and to allow investigators to have a measure against which to determine the efficacy of treatment.

**Laryngeal Paralysis**

Unilateral laryngeal paralysis can result in hoarseness and aspiration due to incomplete closure of the glottis. Vocal fold paralysis abolishes abduction and adduction of the vocal folds and alters the configuration of the
glottis. The paralyzed vocal fold is shorter than the normal vocal fold and frequently lies at a different level. Compensatory behavior includes hyperadduction of the mobile vocal fold and anterior-posterior compression of the glottis.

Bilateral paralysis is potentially life threatening, because the airway is severely reduced. Established therapy is to perform a tracheotomy, move one vocal fold laterally or excise an arytenoid. Research is being conducted on alternative therapies, such as reinnervation of laryngeal muscles or artificially stimulated laryngeal movement synchronous with breathing.

Many individuals with clinically apparent laryngeal paralysis do not have muscle denervation that can be demonstrated by electromyography. These individuals seem to have partial neural lesions or ineffective neural regeneration. It is now known that recovery from paralysis requires not only regeneration of a sufficient number of motor nerve fibers but also the connection of nerve fibers to appropriate muscle fibers. Synkinesis is the simultaneous contraction of opposing muscles and results from the innervation of muscles by inappropriate nerves. Research into nerve regeneration may elucidate factors that could prevent synkinesis.

Spasmodic Dysphonia

Spasmodic dysphonia is a voice disorder characterized by frequent voice and pitch breaks or a breathy voice. It is a focal dystonia of the larynx. Dysfunction results from involuntary contractions of laryngeal muscles during speech. Surgical division of the nerve to one side of the larynx can diminish the signs and symptoms of adductor spasmodic dysphonia, but the voice is frequently breathy and the long-term results are often not satisfactory.

Several years ago, botulinum toxin was introduced as an experimental treatment. Minute quantities of the toxin are injected into the affected muscles to produce temporary weakness. Recently, a National Institutes of Health consensus development conference judged this approach to be a safe and effective treatment for patients with adductor spasmodic dysphonia. Although it does not cure the disorder, it significantly reduces signs and symptoms, usually for periods of four to six months.

Other Movement Disorders

Movement disorders affecting the larynx, such as false laryngeal asthma or paradoxical movements, have been recognized. Information
concerning the effects of these movement disorders on voice and breathing and their remediation is emerging.

**Population Considerations**

Advances have been made in recognizing that the impact of vocal lesions is population-specific. For example, singers with vocal nodules may compensate sufficiently to mask vocal signs during speech but have difficulties singing. These population differences help explain some discrepancies in the existing literature and underscore the need to look at singers as a special population even when testing for voice disorders.

**Gastroesophageal Reflux**

Recent studies have elucidated a variety of disorders caused or aggravated by gastroesophageal reflux to the larynx and pharynx. These disorders include contact ulcers, subglottal stenosis, hoarseness, chronic cough, throat clearing and cancer. There is a need to understand more fully the role of acid and alkaline materials in the causes of these disorders.

**Technology**

There have been advances in computational tools, both hardware and software. Speed, memory, ease of use, cost and compactness have been improved. These developments have affected virtually all aspects of research in the larynx and upper aerodigestive tract.

Analysis and interpretation of signals from electromyographic, electroglottographic, photoglottographic, accelerometric and aerodynamic transducers can now be accomplished with greater accuracy and ease. The use of microprocessors now permits multichannel data acquisition, near real-time quantification and graphic display of complex data. Furthermore, advanced signal processing techniques, in combination with the general availability of digital signal processing boards, have also made it possible to extract interpretative data for scientific and diagnostic purposes in near real time. Improvements in performance and reductions in size and cost have also increased widespread clinical access to the new technologies.

In conjunction with increasing computational capability and transducer design, important progress has been made in imaging and the interactive display of three-dimensional laryngopharyngeal structures. There have been technological advances in videoendoscopy and related digital imaging, magnetic resonance imaging, computed tomography and ultrasound. Advances in available software make it possible to achieve quantitative evaluation of the images.
These developments have led to intraoperative applications that improve surgical results. Currently, intraoperative monitoring of vocal fold kinematics, electrical stimulation and acoustic output are being used. Further advances in surgical technologies have included the use of endoscopic, fiberoptic, tunable lasers for treatment of disease of the airway.

Augmentative and alternative communication devices and aids are beginning to include an increased variety of synthesized voices with better voice quality. These improvements include the choice of a more natural female or male voice. Further computational analyses and modeling of the human vocal tract should lead to the development of prosthetic devices with even more natural sounding voices.

Program Goals

The program goals for voice and voice disorders are to support research that will enable the acquisition of new knowledge of a fundamental and applied nature that will enhance our understanding of: (1) normal voice and swallowing mechanisms; (2) disordered voice and swallowing mechanisms; (3) evaluation processes for disordered voice and swallowing; and (4) therapeutic interventions for disorders of voice and swallowing.

Broad goals include:

- Support epidemiologic studies of the incidence, prevalence and impact of voice disorders, as well as the factors that cause or contribute to vocal dysfunction.
- Foster research that examines the multiple functions of the larynx and upper aerodigestive tract in an integrated manner.
- Encourage multidisciplinary research that studies interactions of molecular, cellular and organ systems within whole organisms.
- Encourage studies of the efficacy and relevance of new technologies, procedures and treatments.
- Support acquisition of a database that permits the evolution of standards for documentation of vocal function.
- Facilitate training of scientists to study voice, voice disorders, swallowing and swallowing disorders.
Normal Structure and Function

Knowledge of normal structure and function is an important basis for understanding the voice and its disorders. Voice is produced by a unitary system consisting of functional subsystems—respiratory, laryngeal and upper aerodigestive. It is important to understand how these subsystems act and interact with one another and to know the principles that govern the overall system's potential to reorganize and adjust its behavior. Such information is also relevant to understanding both the adaptive and maladaptive behaviors of the voice-producing mechanism in response to laryngeal disorders or diseases.

To be relatively comprehensive, the knowledge base about voice and its disorders should include data from several domains, such as the neural, muscular, structural, aeromechanical, acoustical and perceptual domains. It is also important to relate such knowledge to specific functions and forms of expression, including those that are psycholinguistic and artistic.

Laryngeal Function in Vocalization, Respiration and Swallowing

The use of common spatial and relational references should make it possible to use multivariate data to support the comprehensive modeling of laryngeal function and dysfunction. Studies are needed on a wide range of parameters to facilitate the integration of multivariate data from various research groups using different techniques. Contributions to this database should include information on morphology, physiology, molecular biology, cellular biology, biochemistry, histochemistry, immunocytochemistry, biomechanics, age, gender, cultural background and lifestyle.

Emerging techniques make it possible to study the neural control of the larynx in vocalization, respiration and swallowing in humans and animals. Such studies should address the ways in which the nervous system integrates the control of these behaviors autonomously and in response to changes in sensory inputs to the nervous system. Additional work needs to be done on defining mechanisms in terms of receptor type and pathways for the cough, gag and swallow reflexes.

There is a need to delineate the effects of sensory input from bolus characteristics, respiratory parameters and voluntary control on
timing, the extent of laryngeal elevation and closure and pharyngeal contraction during swallowing.

Recently developed noninvasive techniques, such as transcranial magnetic stimulation and sensory evoked potentials, offer new opportunities for research on humans. These techniques can be used for mapping the cortical control of the larynx.

Electrical stimulation of the recurrent nerve can elicit short- and long-latency reflexes and provide new insights into the on-line modifications of activity of the brain stem motor neuron pool during different phases of respiration, phonation and swallowing.

**Biomechanics of the Larynx**

To understand how vocal pitch and loudness and voice quality are controlled, it is important to study the mechanism by which the laryngeal and respiratory muscles move tissue and air. Study of the effectiveness of muscle groups working in concert is needed. The importance of the lubricating fluids on the vibratory behavior of the vocal folds is recognized, and further study is needed of the composition and aberrations of this fluid layer.

The biomechanics of complex laryngeal structures and material properties, which formerly posed many problems for quantitative analysis, can now be addressed by finite element and other computational means. In other fields of biomechanics, the mechanical properties of skin, cartilage, fat, ligament, tendon and muscle have been studied extensively. The results give voice scientists a rich database for comparisons. The combination of new analytic tools and new databases makes the biomechanics of the larynx an attractive area of investigation. Progress in this area should lay the groundwork for simulation of reconstructive and augmentative clinical procedures.

Studies of laryngeal movement and closure in relation to movements of the hyoid bone, pharyngeal wall and tongue base during swallowing in healthy adults of various ages can contribute to our understanding of normal bolus propulsion and airway closure mechanisms.

**Cellular and Molecular Biology and Anatomy**

Normal laryngeal anatomical studies are needed in many species, including human postmortem specimens, on light microscopic and ultrastructural levels. These studies would provide an opportunity to define the distribution of extracellular matrix molecules, oncogene expression, growth factors (for example, epithelial growth factor) and growth-factor receptors as they relate to normal structure of the larynx. Organotypic cultures would permit the study of the effects of modulating these components. This research could be done
through changes in culture conditions, such as hormone additions and altered matrix components or through insertion of genes into cells that would express growth-factor receptors, etc.

Animal models should be studied to determine their similarities to and differences from the cellular structure of the human larynx. Transgenic animals could be used to define and dissect interactions of multiple components at molecular function and anatomic levels. Shifts in the relation of these components have been implicated both in disease processes and in wound healing.

There have been few studies addressing the cellular and molecular mechanisms of the central nervous system in the control of the larynx for vocalization and swallowing. Descriptive studies are needed to establish the baselines from which various neurogenic disorders affecting laryngeal function can be understood. Studies are needed on the biochemical and structural specializations characteristic of laryngeal muscle fibers and their innervation.

Quantitative, three-dimensional, geometrically referenced anatomical, cellular and biochemical studies are needed in all of the above areas.

Control of Pitch, Loudness, Register and Vocal Quality

Over the past decade, functional models have enhanced the available knowledge of the dynamic behavior of the vocal folds. Electromyographic studies have increased understanding of the role of the extrinsic and intrinsic laryngeal muscles in the control of pitch. The results of these studies have suffered, however, from the small populations sampled and from individual variations. Systematic work on the control of pitch, loudness, register and quality should be continued.

Concentrated work is needed on the role and interactions of specific muscles and of their aerodynamic effects in relation to changes in the length, shape, configuration and forces of the vibrating structures. Studies should consider laryngeal function and the interaction of the larynx with the dynamics of the entire upper aerodigestive tract. In addition, work in this area should be extended to include subject populations other than those studied to this point. Attention should also be devoted to control mechanisms in the singing voice. There is a need to delineate the acoustic to perceptual transform in voice-quality disorders. Advances in signal analysis, control and synthesis, combined with psychophysical procedures, make the time ripe to gather
information that would be of use in determining those aspects of the voice signal that give rise to the perception of disorder and its quantities. Age, gender and cultural variables warrant attention.

**Vocal Tract Component Interactions**

The interactions among phonation, respiration, swallowing and articulation are important. Research should stress the role of the respiratory system as an energy source for the voice. Further study should be given to acoustics and biomechanical interactions, particularly the effects of vertical movements of the larynx and source-filter effects related to adjustments in the pharynx. Additional demands such as increased loudness may bring additional loads to the system. Although such demands have been studied, they must be more clearly defined for different types of vocalization as in whispering, breathy phonation or as a coping strategy accompanying a disease state. In addition, the role of changes of supraglottic and subglottic acoustic and aerodynamic pressures in vocal function and training could be better understood if the neural sensors that help control the process were more clearly defined.

The dynamic behavior of the larynx and its role as an articulator in speech need further attention. Studies focused on the control of timing of laryngeal behavior in coordination with respiratory and articulatory activity may shed considerable light on communication disorders. Interactions between timing and pattern of laryngeal movements during swallowing, as a result of oral sensory input and depending on the respiratory status, are important but poorly understood and deserve further study.

**Role of the Larynx and Pharynx in Swallowing**

The control of the larynx and pharynx in the swallowing process deserves further study. The systematic effects of sensory input from bolus variables are beginning to be understood. More research is needed on the effects of systematic changes in laryngeal and pharyngeal function during swallowing on various bolus types and on using various voluntary controls. This research has implications for the evaluation and treatment of individuals with dysphagia. Studies of peripheral and central mechanisms controlling laryngeal and pharyngeal transitions among respiration, swallowing and phonation are also relevant to the management of dysphagia.
The Use of Animal Models

Much of the information currently available on the neural control of the larynx has come from animal studies. Attention should be given to the similarities and possible differences in human laryngeal physiology to that of other species proposed as models for human voice production and swallowing. This research is fundamental to an understanding of developmental structure and function.

The use of multiple electrode arrays for the recording of small populations of neurons in the brains of animals should be used to define neural mechanisms of laryngeal control. This technique should lead to more rapid development of models of the neural control of specific behaviors.

Electrically or chemically elicited phonation from the periaque ductal gray area of the midbrain or its immediate surroundings in anesthetized animals should be used to study the function of laryngeal motoneurons, sensory afferents of the larynx and the mechanisms of how phonatory control interacts with protective reflexes and swallowing. This animal model may also be used for experimental manipulation of laryngeal biomechanics and studies of the effects of tissue alterations.

Information gained from the anesthetized animal needs to be tested in the awake, vocalizing or swallowing animal. Only in the awake animal can the interactions among all structures of the upper aerodigestive tract be studied during normal vocalization, swallowing and respiration. The use of chronic single or multiple neuronal recordings combined with voice, electromyography and pressure recordings should be expanded to learn how the central nervous system controls the complex interactions of the larynx during vocalization and swallowing.

Development

The development of vocalization and swallowing, gender differences in these functions and their aging are fertile areas of study. Detailed comparative descriptions are needed that could be used to facilitate the selection of models appropriate to human function.

Embryology

Current knowledge consists of a series of well-defined, descriptive reports of different stages of laryngeal development in several species, including humans. Precursors of the larynx consist of two cell populations, epithelial and mesenchymal elements that interact continuously during development. The mechanisms of epithelial-mesenchymal tissue interactions that are driving forces in the normal development of the larynx and the way that these interactions affect cell differentiation and final organotypic form require study. The
understanding of the embryology of this unique organ, therefore, is still quite limited as is the understanding of the repair processes in the injured larynx. Attention should be directed to the study of the anatomic and physiologic effects of operations on the infantile larynx.

Critical Periods

Critical periods for optimum development of vocal control, as well as periods when a speaker may be at risk for developing dysphonia, have been recognized, but they have not been adequately studied. The critical periods that are particularly important for the prevention and treatment of voice disorders include infancy, childhood, puberty and other life cycle stages characterized by hormonal changes. The development of hearing impairment or subjection to a noisy environment at any time may produce critical periods for the development of voice disorders.

- **Infancy:** A time when there are many unique structural and functional changes occurring in this highly specialized system, and the infant is experimenting with vocal controls during playful or demanding vocalization, often at loud levels for long durations.

- **Puberty:** A time when there is rapid growth in the larynx resulting in vocal fold lengthening with perhaps insufficient time to allow for proper mechanism adaptation. That this adaptation is not always done readily results in abnormal attempts to maintain the higher childlike voice at the expense of vocal strain and poor vocal quality. These vocal characteristics may result in unwanted attention and have a major effect on the psychosocial development of the speaker.

- **Hormonal changes:** Times when masculinizing tumors or male hormone therapy, pregnancy or menopause result in edematous changes in the larynx. Studies are needed to determine the time periods during which the problem is reversible. Research is needed to understand the role of androgenic hormones and how their effects can be prevented or ameliorated.

- **Children:** A time when communicating out of doors over large distances and athletic competition place demands on the voice that may result in misuse and abuse. Alteration of pitch, particularly by boys, increases the chance of voice disorders.

Vocal Control

Research studies are needed to characterize voice production as it relates to the developing structure. A major concern is the control of pitch, loudness, register and voice quality...
with changes in structure of the larynx. Knowledge of normal structure and function in relation to age is requisite for understanding voice production, for developing standards of tests for the early detection of disorders and for determining the efficacy of various forms of treatment. This information is also valuable in developing theoretical models of the cause of voice disorders.

**Effects of Hearing Impairment on Developmental Vocal Control**

Individuals with congenital and later-onset hearing impairment may have disorders of pitch and loudness control, as well as distinctive abnormalities in voice quality. Only limited attention has been given to the critical periods for the habilitation and rehabilitation of vocal control in these populations. Attention needs to be given to the use of biofeedback and motor learning in training vocal control in hearing-impaired persons.

The effect of cochlear implantation on voice quality in the prelingually and postlingually deaf persons should also be studied further.

**Vascular Function**

The circulation of blood and its autonomic control in the larynx and the possible relationships to biomechanical changes, vocal fatigue and laryngeal lesions require study. Further research is needed on the relation between circulatory changes and the function of the upper aerodigestive tract.

**Aging**

Preliminary observations indicate that some of the vocal alterations that have been ascribed to aging are perhaps not attributable to irreversible physiologic or anatomic changes. More research is needed to establish the true nature of aging voice and swallowing changes and to develop techniques to forestall or prevent these changes when they may interfere with a person’s life or livelihood. In addition, irreversible changes need to be understood in depth. Study populations should include normal speakers, octogenarians, nonagenarians, centenarians and special populations of voice users, such as singers.

**Cell Death**

The selective neuronal death in the brain stem as a consequence of aging should be studied. Study of this problem may provide important insights into understanding changes in voice control, respiratory function, reduced airway protection and bolus propulsion in older persons. In some neurogenic diseases, selective reduction in motoneuron pools that
modulate speech and breathing have recently been found. Research is needed to determine the degree to which selective cell death due to aging adversely affects voice, swallowing and respiration.

**Anatomy and Cellular and Molecular Biology**

The anatomy of the aging larynx has been described in human specimens obtained primarily from cadavers. There has been no detailed study of the aging process in other species in which a more uniform genetic background is possible. It would be very useful to collect molecular, cellular and anatomic information from aged larynges of genetically defined species. Information is needed on the localization of extracellular matrix components, growth factors, oncogene expression and growth-factor receptors. This information should be compared with the data collected from normal young adult larynges and related to the reduced ability of the larynx and pharynx to recover from injury with aging and the increased susceptibility of the pharynx and larynx to general weakness and dysfunction when an elderly individual becomes debilitated.

**Muscle Atrophy**

It is known that muscle tissue gradually degenerates with age. This process involves an age-related cell death of motoneurons with subsequent reinnervation of denervated muscle fibers by the surviving motoneurons. Because this mechanism can alter the number of muscle fibers innervated by each of the surviving motoneurons, this remodeling process can contribute to age-related changes in motor control. In addition, the muscle fibers may undergo age-related atrophy, hypertrophy or cell death, which may be specific to the muscle fiber type. These changes can differ among types of skeletal muscles and should be important in determining the basic pathogenic mechanisms underlying age-related degenerative processes in the highly-specialized muscles of the larynx and upper aerodigestive systems. Because such changes are likely to be reflected in diminished capacities for vocalization, swallowing and respiratory function of the upper aerodigestive systems, the functional consequences of muscle atrophy should be an area of investigation.

**Deterioration of Joints, Ligaments, Membranes and Other Tissues of the Laryngeal, Pulmonary and Secretory Systems**

Vocal deterioration or swallowing disorders may result from restrictions in the movement of the glottal structures, as well as from reductions in lubrication. Specifically, the cricoarytenoid joint, which subserves vocal
fold abduction and adduction capabilities, tends to lose the freedom of movement because the capsule of the joint deteriorates. Changes in articular cartilage with thinning and irregularities of the articular surface have been noted with age. Further arthritic changes can result in a joint that is fixed. Little is known about the biology of this process. To correct these changes by means other than surgery, more information is needed on the cellular biology of cartilage and joint deterioration as it affects voice production and swallowing in the aging larynx. This knowledge might lead to medical or exercise therapy to help arrest or reverse the process.

Stiffness and lack of elasticity limit the pliability of the aging larynx. This state affects the membranous cover, which results in less motion of the mucosal wave. With vocal stress, the vocal mechanism is less resilient. The mechanisms involved warrant further research.

Atrophy of mucus-producing glands with aging can lead to changes in the fluid layer of the vocal folds, making clear phonation more difficult. Research is needed to determine how to improve the secretory process leading to increased laryngeal efficiency.

Exceptional (Trained) Vocal Behavior

The larynx is an inefficient sound source in normal conversational speech. Typically, less than one percent of the aerodynamic power of the lungs is converted to acoustic power in speech. As a result, the system might optimize itself for criteria other than efficient phonation. Undesirable vocal habits may be formed in various developmental stages.

When people with poor vocal habits are thrust into situations that require prolonged periods of vocalization, especially with high intensity under high psychological or physical stress, the loss of efficiency takes its toll. Vocally trained people (singers, actors and public speakers) have learned to overcome some of these problems.

The gifted or exceptional vocalist, either in speaking or singing, offers a very important model for the vocal evaluation of all voice users. The model establishes the limits of capability. In pitch control especially, it allows one to see what can be done with respect to range. This information can be used in the average-voice evaluation as a criterion. The same approach is applicable with respect to loudness. Questions of interest are:
VOICE AND VOICE DISORDERS

How far can the human voice be pushed without strain? What are its limits?

Answers to these questions could lead to better care of people who have deficient usage.

What is the basis for limited efficiency? Is it genetic? How is optimal efficiency achieved?

How does the optimal user gain a greater range of pitch or loudness?

The answers to these questions could lead to better care of a person with a narrow vocal range and low power. The results of the study of pitch, loudness and vocal quality control of this population should help to remediate vocal disorders, particularly in the direction of modifying behavior.

Gender

Gender differences in vocal production are currently under investigation. Research has shown that alterations in estrogen and progesterone levels cause cytologic and physiologic changes in the vocal folds. Reinke's edema has been shown to have an increased incidence in post menopausal women. There is a need for research into the sites of hormonal influence, as well as hormonally affected changes in voice production.

Glottal configuration differences have been noted between males and females and deserve further investigation.

Lifestyle

Little is known about the effects of lifestyle (diet, smoking, drug use, exercise and alcohol consumption) on function of the larynx and upper aerodigestive tract. Study of these variables would enhance knowledge of fundamental mechanisms, including maladaptive behaviors that contribute to the development of disorders. Resulting data would also facilitate the design of prevention programs and early identification of dysfunction.

Diseases and Disorders of the Larynx and Upper Aerodigestive Tract

Diseases and disorders of the larynx and upper aerodigestive tract involve a complex physiologic system and affect functions of voice, respiration and swallowing. Although these problems are often grouped according to etiology, many are multifactorial in origin. For example, vocal fatigue may result from stress, structural abnormalities, neuromuscular dysfunction and environmental factors. Hoarseness
may result from the combined effects of allergy and vocal abuse. Dysphagia may also result from multiple causes.

Research into the problems listed below should include both focused studies of specific factors, as well as multidisciplinary investigations. Understanding may be enhanced by the synthesis of knowledge in two conceptual dimensions. A disorder may have an impact on multiple levels in the cell-tissue-organ system, and a single problem may be the result of multiple causes.

Studies should not necessarily be limited to the analysis of specific anatomic or physiologic disorders. When appropriate, issues relating to gender, race and cultural differences should be considered. Outcome studies may shed light on causes, as well as strategies of prevention.

**Epidemiology**

Disorders of voice are increasingly recognized as a major health problem among persons of all ages and in all walks of life. The causes of voice problems are diverse and, in many instances, unknown. Despite recognition of the devastating effects of voice problems, there are no reliable data on the prevalence of voice disorders among any postpubescent population. Prevalence data are necessary for the adequate planning of health services.

**Structural Lesions**

**Congenital and Acquired Diseases of the Larynx and Upper Aerodigestive Tract**

Congenital and acquired lesions result in dysfunction in thousands of infants and children each year. These disorders include cysts, webs or scar tissue or they may result from failure of normal development. Developmental failure can result from interruption of epithelial-mesenchymal tissue interactions during organogenesis. Presently no animal models exist to aid investigators in the study of these problems. The differentiation of genetic and environmentally induced laryngeal and pharyngeal anomalies is important. Understanding the mechanisms of these disorders should lead to improved treatment and perhaps prevention.

**Inflammatory and Infectious Diseases of the Larynx and Upper Aerodigestive Tract**

Research is needed to improve the understanding of inflammatory diseases of the larynx and upper
aerodigestive tract. Rhinitis, sinusitis and laryngitis affect a high percentage of the population, and they cause hoarseness and dysphagia and range in severity from local irritation to irreversible tissue damage. The results of research on prevention, early detection and intervention should help to limit the effects of these diseases. Newer endoscopic sinus surgical techniques appear to represent an important technical advance, but studies are needed to reduce the associated complication rates and enhance long-term therapeutic benefits. Research designed to produce new medical treatments for infectious and allergic disorders is also needed.

Laryngeal papillomas are caused by an infectious virus. A clearer understanding of the biology of the disease would help to determine the therapeutic approach. Long-term research should assess the recurrence rate, the effects of treatment, the effects of cofactors such as smoking and voice abuse and the rates of association with carcinoma of the larynx.

Tumors of the Larynx and Upper Aerodigestive Tract

Neoplasms (new growths or tumors) of the larynx, pharynx, oral cavity and neck may result in loss or serious impairment of the ability to communicate with others. Benign tumors such as recurrent laryngeal papillomatosis may require multiple surgical (usually laser) excisions from the vocal fold region. Postoperative scarring may lead to permanent hoarseness, and failure to control the papillomas may result in death. Studies are needed on prevention, early detection methods and improved medical, immunological and surgical treatments.

Malignant neoplasms involving the larynx and other head and neck structures affect more than 50,000 Americans each year. Cancer in these structures is usually related to the use of tobacco and alcohol, and research is needed into more effective cessation strategies. Early diagnosis often permits the use of radiation therapy or limited surgical excision, such as partial laryngectomy or partial glossectomy. Although the conservative operations maintain most of the functions of speech, respiration and swallowing, more precise data are needed on the long-term deficits that are produced and on strategies to rehabilitate patients. Standardized, prospective clinical investigation and the collaboration of surgeons and speech scientists should be expanded in this area.

Laryngeal transplantation in patients requiring total laryngectomy remains an intriguing rehabilitation
that increasing numbers of patients will be maintaining organs such as the larynx following curative cancer therapy. Thus, increased efforts directed toward understanding the tumor-induced and treatment-induced abnormalities produced in organs such as the larynx should become as important as rehabilitating the postlaryngectomy patient. The impact on vocal function of endoscopic excision or irradiation of early vocal fold cancer should be systematically compared, as this information should be a major factor in selecting treatment.

Screening of High-Risk Patients for Laryngeal Cancer

High-risk patients, that is, those over the age of 50 years with a history of smoking more than 30 packs of cigarettes per year, may represent a select population for laryngeal cancer screening. The combination of indirect examination and videostroboscopic or acoustic analysis may provide a route for identifying cancers at an earlier clinical state. A screening process requires careful design so that it has relatively high sensitivity and specificity and moderate cost.

Effects of Chemopreventative Agents on Laryngeal Function

The era of chemoprevention for head and neck malignancies is well under way. Thousands of patients...
are now being entered on chemoprevention protocols following curative therapy for a primary head and neck cancer in an attempt to diminish the likelihood of their developing a second one. The effects of these chemopreventative agents on laryngeal function is unknown. Since head and neck cancer is a select site for chemoprevention studies at this time, the effects of these agents on laryngeal function is deserving of study.

Trauma

Injury to the larynx, trachea and upper aerodigestive tract is an increasing and difficult management problem. Both blunt and penetrating injuries can result in serious functional disorders. Further studies are needed to determine the structural and functional sequelae requiring repair and rehabilitation.

Neural Lesions

Central

Control of laryngeal functions for breathing, voice and swallowing is impaired in many neurogenic disorders such as Parkinson's disease, amyotrophic lateral sclerosis, multiple systems disease (Shy-Drager syndrome), Huntington's chorea and stroke. A better understanding of the pathophysiology of these motor control disorders would lead to more effective management (medical, surgical, behavioral or prosthetic) to support speech, respiration and swallowing. Studies are needed to provide information about neuropharmacological and behavioral management of disorders of laryngeal motor control.

Research is needed to clarify the relation between neuropathology and pharyngeal disorders. Information about characteristics of different neurogenic disorders and disease progression is lacking.

Focal dystonias of the head and neck cause disruption of speaking and swallowing and impair the quality of life. Recent advances have been made in understanding dystonias, such as spasmodic dysphonia. Evidence from brain imaging and autopsy studies suggests that dystonias are due to brain lesions or biochemical changes in the basal ganglia. Epidemiologic and case-control studies are needed to identify possible causative factors leading to the onset of this disorder.

New treatment has been developed that uses botulinum toxin injections into the laryngeal muscles to reduce abnormal patterns of laryngeal muscle activation. The optimal dose and placement of injection vary greatly among patients. Research is needed to predict optimal dose magnitude and placement. Preliminary data suggest that the injection
of succinylcholine or other agents may be of predictive value. Long-term evaluation of this treatment is needed to determine whether the toxin continues to be effective with repeated injections over several years. Information is needed on the diffusion of the toxin in tissue, distant effects and possible retrograde transport to the brain stem. There is a need to investigate alternative toxins and to learn what the response of spasmodic dysphonia to botulinum toxin tells us about the pathophysiology of dystonias.

Respiratory dyskinesia is a problem that has recently been identified as a separate entity, sometimes associated with asthma. It presents an interesting opportunity for investigation because some patients can be successfully managed using anticholinergic drugs.

Peripheral

Peripheral nerve injuries may affect the larynx and upper aerodigestive tract. One of the most common injuries is to the recurrent laryngeal nerve which results in vocal fold paralysis. This injury occurs most frequently during operations on the skull base, neck or mediastinum. Tumors or infections along the path of the vagus nerve can also interrupt laryngeal function, producing alterations of phonation, airway protection and respiration. In bilateral paralysis, the consequences are often devastating. To date, observations about the effects of laryngeal reinervation remain controversial. Accumulation of a database will improve the ability to diagnose accurately and treat effectively these life-threatening conditions. Clinical trials are required to assess existing and new surgical procedures, including vocal fold augmentation, thyroplasty, arytenoidectomy, cordectomy, selective reinnervation and electrical pacing. Nerve regeneration studies are needed to understand the pathogenesis and to develop new forms of treatment.

Systemic Disorders Affecting the Larynx and Upper Aerodigestive Tract

Endocrine

There has been considerable interest in the effect of hormones on the voice. Imbalances of these biochemicals have a potent impact upon the distribution of electrolytes and water within the extracellular compartments of the vocal folds, causing them to become edematous or swollen and changing the characteristics of their vibrations. These changes occur during hypothyroidism, premenstrual syndrome, androgenic hormone-producing ovarian tumors, pregnancy, and puberty in boys. They may follow the administration of birth control pills and postmenopausal hormone therapy in women. Studies are needed to clarify the best strategies for evaluating and
treating these patients and to find new strategies for prevention. In addition, epidemiologic studies, standardization of clinical assessment and a coordinated effort to establish and define clearly a database in this area are needed.

Pharmacologic

Pharmacologic agents can have important effects on the voice. For example, some blood pressure medications cause severe coughing. Other agents that decrease secretions can impair the voice. Anecdotal evidence implicates anti-inflammatory agents or topical corticosteroid sprays in the pathogenesis of vocal fold polyps. There is little research on the effects of drugs on the voice or on the interaction of drugs with other vocal therapy, such as surgery or behavioral management. With an aging population taking increasing quantities of medication, further research is needed.

Psychogenic Disorders of the Larynx and Upper Aerodigestive Tract

Psychogenic disorders of the larynx and upper aerodigestive tract occur frequently but are not well understood. They may be a primary disorder or secondary to a loss of communication skills. It is often difficult to distinguish a psychogenic problem from an idiopathic organic disorder. Research is needed to permit clinical identification of the psychogenic component and to determine how psychologic factors influence treatment outcome.

Wound Healing

Wound healing after injury of or operation on the larynx can have a profound effect on the functional recovery of this generator of sound. New research advances demonstrate the role that some extracellular matrix proteins, for instance, fibronectin and its integrin receptor molecule, play in the improvement of the quality of wound healing. Myofibroblasts have been implicated in scarring and contracture of healing wounds.

At present, knowledge is limited on the role of extracellular matrix, growth factors and oncogenes in wound healing in the larynx. Studies of these factors in wound healing in the injured larynx of animal models are essential to the design of future experiments, in which specific treatments may be assessed that could reduce the negative effect that wound healing has on functional recovery.

The various strategies used in clinical practice to control or influence wound healing should be defined more clearly. There is lack of standardization in dilatation techniques, the timing of procedures and the use of stents to support the airway during healing. Basic information is needed on the pathophysiology, prevention,
assessment and treatment of problems associated with laryngeal surgery and injury.

**Misuse and Abuse Disorders**

Many people have voice misuse and abuse disorders that are attributed to abnormal patterns of phonation. These problems include vocal nodules, chronic laryngitis, hemorrhage into and polypoid degeneration of the vocal fold and vocal fatigue. Suspected contributing factors include excessive loudness and duration, inappropriate pitch, faulty patterns of muscle activation, speaking in noisy or dry environments, chronic coughs and throat clearing. Additional studies are needed to identify epidemiologic factors including prevalence and establish efficacy of treatment. This knowledge should help in the development of preventive measures.

**Influencing Variables**

**Gender**

Male and female voices differ acoustically, and there are clear gender differences in laryngeal anatomy. The male larynx is larger than the female larynx, and the configuration is different.

The menstrual cycle and pregnancy affect the nose and larynx and possibly the neural control of phonation. Therefore, it is not surprising that women are more susceptible than men to many voice disorders, including vocal nodules, spasmodic dysphonia and edema of Reinke's space. Vocal fold edema and increased risk of hemorrhage have been observed during menses. On the other hand, contact granuloma is more often observed in men. Research is needed to determine reasons for gender differences in susceptibility to improve prevention and treatment.

Vocal health is also affected by social and cultural factors that affect men and women differently. Bulimia, which is chiefly a disease of young women, may damage the larynx. Many jobs typically associated with women, such as teaching and aerobics instruction, result in vocal stress. Society places vocal role expectations on both genders, that can result in the affectation of inappropriate pitch or vocal quality.

**Aging**

There is a continued need to study the effects of aging on voice production. Research is needed to understand the mechanism of change and how its effects can be prevented and treated. Preliminary observations indicate that some of the vocal alterations, such as diminution of power and endurance, that have been ascribed to aging may be delayed or reversed through physical or singing exercises. Some alterations may also
be attributed to diseases of other systems. Additional research is needed to establish the true nature of age-related voice changes and to develop techniques to forestall or prevent them. There is a need to study such factors as physical health, mental health, nutrition, muscle atrophy, long-term vocal abuse, deterioration of the respiratory system and vocal hygiene and exercises.

Respiratory Tract Factors

The lower respiratory tract is an important, integral element in the production of the acoustical basis for speech. Although a variety of diseases and disorders of the lower respiratory tract affect the voice, detailed analyses of their effects on the voice are needed.

Influence of Environmental Factors on Voice Production

Environmental factors are thought to cause or perpetuate voice disorders. Noise, air pollution and relative humidity are factors that singularly or in combination may cause or maintain a particular disorder. Aspects of voice production that are improved or deteriorate with environmental changes warrant investigation. Understanding these relationships may help in the development of voice treatment and prevention programs.

Racial Factors

Studies have demonstrated clear anatomic differences among races in the size and shape of the skull and facial bones, which influence vocal resonance. Currently, there are no data on whether there are racial differences in laryngeal structure which could predispose different incidences of diseases or disorders. Research is needed to explore these possibilities.

Cultural Factors

Different languages and dialects, as well as social strata, place different demands on the vocal apparatus. Comparative studies may illuminate the incidence and prevalence as well as occupational factors in the pathogenesis of some disorders.

Gastroesophageal Reflux

Gastroesophageal reflux commonly affects the larynx and upper aerodigestive tract. Signs of gastroesophageal reflux include hoarseness, chronic cough, throat clearing and contact ulcers. Further studies are needed to elucidate the relative importance of the acid and alkaline components of gastroesophageal reflux.

Other Disorders

Recent advances in medical technology have produced a growing population of children with chronic
illness who require prolonged airway management. Long-term tracheostomies have been shown in the canine model to produce anatomic and physiologic alterations of the airway. Further research should be undertaken to investigate voice disorders in children who have had long-term tracheostomies.

Little is known about genetic influences on laryngeal function and dysfunction. Studies in this area are essential.

Technology

Diagnostic and Treatment Aids

Progress has been made in the development of new research tools for the observation and measurement of voice production. Systematic investigation of electromyographic, kinematic, acoustic, aeromechanical and imaging diagnostic aids should be continued to determine which technique or combination of techniques is most useful for detecting disorders, documenting changes resulting from treatment, identifying persons at risk for developing voice disorders, setting standards for routine assessment and improving the understanding of the process of voice production.

Definition of testing procedures varies from center to center and standards need to be established for voice assessment. It is essential for research and clinical purposes to establish valid, reliable and standardized methods for objective voice assessment, including at a minimum vibratory, acoustic, aeromechanical, electroglottographic and psychoacoustic measures.

More extensive normative studies are needed for the general population, including its cultural diversity, and for professional speakers and professional singers. Age and gender variables should be considered in all groups. In addition, data from the entire range of human vocal responses should be studied in communicative context. Finally, technology from allied fields should continue to be integrated into emerging voice technologies.

Electromyography

The observation of electrical activity in intrinsic and extrinsic laryngeal muscles of normal volunteers and patients with voice disorders is being performed in numerous laboratories. The results have been used in an attempt to understand the basis of normal speech processes, as well as to help in the diagnosis of voice disorders. Although it seems clear that electromyographic recording has great potential for contributing to the understanding and treatment of voice disorders, several issues require attention. Currently, there is neither uniformity among the
techniques that are used nor consensus on voice disorders in which these techniques have a high probability of being useful diagnostic procedures. Further research is needed to address variations in electrode configuration, interaction of the electrode with the muscle, verification of electrode placement and testing procedures.

Collaboration among experienced electromyographers, voice scientists and physicians with specific knowledge of laryngeal anatomy and diseases is important. Reporting of electric potentials in standardized units and methods should enable comparison of observations from different laboratories. Nonvoluntary activation of laryngeal nerves, by electrodes or magnetic stimulation, offers opportunities to verify the integrity of laryngeal nerves in infants or anesthetized patients.

**Acoustic Signal Analysis**

Recently, manufacturers have begun to offer a wide variety of relatively low-cost, acoustic analysis devices designed to provide quantitative information on voice production. There are large existing databases of acoustic signals of speech that should be exploited. Parallel studies of major categories of voice disorders are also needed to determine if sufficiently distinctive profiles make it possible to use this tool for the detection and characterization of specific disorders.

Attention to longer-epoch variability in sustained vowel signals is needed, as well as investigations using protocols containing words and sentences.

**Aeromechanical and Respiratory Measures**

Laryngeal lesions can disrupt the normal pattern of valving during speech. These lesions affect vocal tone and result in intentional and unintentional alterations in breathing and temporal patterning of continuous speech. There is a lack of aeromechanical data on continuous speech, voice-to-voiceless transitions and altered speech breathing parameters.

Inverse filtering has made it possible to study the alternating current and direct current components of the airflow signal. There is a need for additional information regarding the ultimate usefulness of airflow and air pressure signals in differential diagnosis and for quantifying the effects of various phonatory therapies.

**Imaging**

There have been technological advances in the imaging of the larynx and pharynx. Magnetic resonance imaging provides near real-time visualization of the vocal tract in reconstructed three dimensions. These images will improve the understanding of laryngeal adjustments and
the role of the vocal tract in shaping acoustic signals. Currently, ultrasound has limited application for laryngeal viewing, given the poor resolution of the images. The usefulness of the technology remains to be determined, with the potential application awaiting improvement of image quality.

Imaging of the entire upper aerodigestive tract is currently most often performed with video-fluoroscopic techniques. These techniques are undergoing precise quantification that will provide a database for normal and disordered function, particularly for evaluation of dysphagia. Advances in signal acquisition and computer enhancement will likely reduce radiation dosage. Magnetic resonance imaging should eventually provide similar information regarding swallowing. Additional information on swallowing is emerging from scintigraphic investigations of normal and impaired populations. Research should continue in all of these technologies to promote a greater understanding of the complex interactions of the upper aerodigestive tract.

Direct visualization of the laryngopharyngeal region continues to improve with advances in fiberoptic endoscopy. The widespread application of fiberoptic endoscopes has improved patient care and provided the means for direct observation of those sites. Further improvements should be pursued in this technology in the areas of image quality and analysis. Quantification of laryngeal images must be strengthened, and meaningful parameters should be developed for application of these images in research and clinical settings.

Videostroboscopy of the larynx through the use of fiberoptic endoscopes remains the best available technology to acquire laryngeal images in view of the inherent technological limitations of high-speed laryngeal photography. However, both technologies require further use with other measures to help relate structure to dynamic voice production. Recent technical developments using semiconductor sensor arrays promise direct digital storage of endoscopic images to provide sufficiently high frame rates to evaluate aperiodic movement of the vocal folds.

Structural and dynamic imaging of the brain have rapidly advanced to provide new insights in the organic basis of voice and swallowing disorders. Magnetic resonance imaging should be further used to investigate potential structural lesions in the central nervous system in various populations. Functional or dynamic imaging through the use of positron emission tomography and signal photon emission computed...
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tomography should be applied to improve the understanding of control of the upper aerodigestive tract in normal and disordered populations.

Observations obtained by using a combination of these technologies should be related to each other and to measures from nonimaging techniques to develop appropriate models for understanding voice production.

Augmentative and Alternative Voice Sources

Paralysis due to stroke, tumor or infection greatly alters the ability of the larynx to perform its vital functions of airway protection, respiration and phonation.

Advances have been made in the development of electronic, artificial larynges (external, internal and implantable) and in tracheoesophageal shunts (with and without alloplastic voice prostheses). Further study in this area is needed. Also important are efficacy studies to evaluate the relative benefits of these prostheses and to predict which prostheses are appropriate for various populations.

New technologies in signal processing now make it possible to activate individual laryngeal muscles at the precise moment that they are needed for subserving the diverse requirements in speaking, swallowing and breathing. Several laboratories now have the capability to pace electrically the paralyzed vocal fold to reestablish its abduction. Additional studies should enable investigators to evaluate this procedure.

If scientists are to extend electric pacing to a greater complement of individual muscles in the larynx, they must systematically define the best electrode configurations to give consistent and optimal stimulation strategies. Basic knowledge of muscle denervation is limited. Little is known, for example, about the effects of electric stimulation on the preservation of muscle integrity, which is known to degenerate when the muscle is separated from its nerve. In many respects, laryngeal investigation could serve as a model for other medical scientists involved in electric pacing.

Although a variety of communication devices and aids has been developed, individuals utilizing a voice source are limited in the number of voices available and the naturalness of the vocal quality. Research is needed to develop and make accessible an unlimited repertoire of voices to allow each individual the choice of a unique and acceptable voice. Furthermore, dynamic control of vocal quality, if possible, will enhance communication
functions greatly. Research should be undertaken to develop instruments with a wider range of frequency, intensity and timing characteristics that will closely mimic natural vocal characteristics. The end result should be access to affordable technology.

One of the major purposes of communication is to express affect or emotion. Control of voice source characteristics, including appropriate aperiodicity and spectral envelope, is vital for these purposes. In the development of augmentative and alternative communication devices and aids, research is needed to develop the paralinguistic features of stress, intonation and juncture that are important in deriving the full meaning of vocal behavior.

**Surgical Tools**

Recent developments in surgery related to new methodologies such as the intraoperative monitoring of laryngeal kinematics and viscoelasticity have given the surgeon the potential to alter reliably the structure and improve the function of the larynx. Phonosurgery, designed to alter vocal output, focuses on the modification of laryngeal biomechanics to increase or decrease vocal fold stiffness or closure to improve the acoustic source characteristics of the larynx. These operations are undergoing further refinement. As familiarity with existing and new surgical approaches increases, several research areas should be addressed:

- Encourage simulation modeling to predict the effect of modifying the individual elements controlling laryngeal function to tailor specific procedures to specific disorders.
- Compare the efficacy of existing and new procedures using longitudinal outcome studies.
- Conduct intraoperative assessment of vocal function by selecting parameters.
- Conduct intraoperative monitoring to prevent injury to laryngeal structures or nerves during surgery.
- Develop new alloplastic and use autogenous augmentative materials, based on the molecular and cellular structure of the tissues.

**Medical and Behavioral Treatment**

There is a critical and continuous need for research to develop and evaluate the efficacy of medical, surgical and behavioral treatment for voice disorders. With the rapid evolution of treatment, concern exists regarding the development and standardization of measures for assessing the results. Despite recent advances in knowledge
concerning which diagnostic techniques are likely to produce the highest yield for specific disorders, there is limited information on reported measures as they relate to the underlying pathophysiology. There is no clear understanding of how to use these results in making treatment decisions. With the emerging era of quantification of voice production, objective techniques should be applied to assessment of treatment.

In addition, behavioral studies are needed to determine which treatments are effective. Such quantification should enhance decisions as to the timing, selection, contraindications and outcomes of treatment options. Studies of large populations of normal and disordered speakers are needed to clarify the relation between quantitative measures and vocal characteristics accompanying different treatment alterations of laryngeal configuration and behavior.

Computational Analysis, Modeling and Speech Synthesis

Methods of computer simulation of vocal fold vibration have been effectively used to compare physiologic mechanisms and their control to acoustic signal characteristics in speech production. Past contributions have concerned voice fundamental frequency and intensity control. Recent progress has been made in understanding physical principles that determine the acoustic power generated or efficiency of producing voice power as the output for a given input of respiratory power. Additional research is needed. Understanding the mechanical cause of damage to the tissues is an example of the clinical implications of such research.

Voice-quality control is one of the major areas of voice science in the coming years, with important applications in areas ranging from speech development and voice disorders to speech technology such as text-to-speech synthesis and automatic recognition, as well as automatic speaker identification. To address these advanced areas of speech research, it is necessary to use fully emerging, computational tools, both hardware including high-speed digital signal processing boards and software including high-level computer languages and graphics tools. It is also essential to develop more detailed models that relate controlling muscle contractions to vocal fold configuration and properties including nonlinear phenomena. Also critical is the modeling of the surrounding structures related to the larynx as well as pharyngeal gestures, in part in relation to articulatory gestures involving the tongue and the mandible.

To be able to specify voice characteristics from a communicative functional point of view, there need
to be effective descriptive systems for representing extralinguistic specifications of utterances including, in particular, emotional elements, as well as linguistic specifications including prosodic information. It is important to understand and specify quantitatively temporal properties such as exact characterization of aperiodicity, as well as spectral characteristics, not only for describing the abnormal voice and idiosyncrasies of speakers, but also for prosodic and affective uses of voice.

As a physical phenomenon, vocal fold vibration has received some new attention in connection with the emerging concept of physical chaos, a deterministic but apparently random process. This point of view has not produced immediately useful results, but it holds promise for understanding the basic nature of voice production and, quite plausibly, may also provide new insights into vocal quality issues.

At the same time, new ideas need to be implemented in more realistic and effective computational modeling of the vocal fold vibration processes, such as the role of surface tension and other tissue surface properties that have been largely neglected. Such new modeling work may be expected to provide not only new understanding, expanding the coverage of phenomena explained, but also evaluation and correction of previous modeling work that was constrained in terms of computational feasibility.

Modeling work is sometimes difficult to evaluate; however detailed the model is intended to be, simplifications, and quite often oversimplifications, are inevitable. One general methodology to use to solve this problem is to synthesize speech signals according to the conclusions about critical elements of control in the given model and to evaluate the signal characteristics by human perception when control is altered factor by factor. Also, by comparing generated signal characteristics with analyzed natural speech signals, a precise, parametric description of observed speech phenomena can be obtained through analysis by synthesis.

Psychophysical and Perceptual Measures

Voice characteristics constitute an important aspect of speech perception. Perception is the ultimate process of evaluating the relevance of voice characteristics to communicative functions, and all findings and hypotheses eventually must be evaluated with respect to their perceptual effects.

Most psychophysical experiments in the past had to deal with either simple phonetic samples (such as consonant-vowel syllable for consonant identification) or
subjective labeling of complex stimuli (as in emotional states). Statistical assessment of a large number of comparisons between physically similar and dissimilar samples also provides objective and quantitative decomposition of psychophysical properties.

A new method is emerging to help determine objectively the auditory perceptual properties of voice. Auditory images can be computed by simulation according to specific models and presented visually for another type of subjective judgment. The difference from a listening evaluation of the acoustic signal is that one can point to a particular pattern or characteristic of the displayed image and discuss it. Also, as soon as pattern characteristics are explicitly identified, measures or criteria can be implemented as computational algorithms to have a machine perform the same judgment tasks more rigorously according to given criteria and more extensively, covering a larger amount of data.

There are a number of artificial intelligence techniques, such as expert systems and neuronetworks, that can be useful for such combinations of human evaluation and formal algorithmic procedure. In a sense, this is a new research methodology that can supplement or in some cases replace straightforward statistical inference in data analysis. This methodology can be particularly effective for quantitatively describing and characterizing complex phenomena such as vocal quality in conversational speech. Although statistical data reduction should be encouraged for quantifying research findings, innovative quantitative methods of data interpretation also should be studied.

Measurement of Laryngopharyngeal Gestures

Voice quality is controlled by subtle alterations in the setting or resetting of laryngeal and pharyngeal postures, such as laryngeal height, supraglottic constrictions and agonistic or antagonistic interaction of the intrinsic and extrinsic musculature. Measurement of these gestures can be directly or implicitly obtained with a variety of techniques. These include electromyography, electroglotto- graphy, photoglottography, high resolution magnetic resonance imaging, inverse filtering, stroboscopic imaging, direct fibroscopic imaging and digital storage.

Limitations exist in each technique. For example, glottography signals are the sum of vibrations occurring from each vocal fold; thus, in isolation, they seldom are diagnostic. Stroboscopy creates a montage by averaging images over many cycles; its analysis is often subjective and it cannot be used to describe highly chaotic vibration.
Inverse filtering relies on assumptions regarding linear, nonturbulent source tract interaction.

Multidimensional simultaneous approaches are advantageous in that the deficiencies of a particular measure may be counterbalanced by the advantages of other techniques.

Areas for investigation include the functional relevance of objective evaluation of kinematic and oscillatory signals or images during normal voicing and under conditions of compensation and adaptation in pathologic states.

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Summary of Research Recommendations

Major Basic and Clinical Research Opportunities

Normal Structure and Function

Respiratory, Laryngeal and Upper Aerodigestive Tract Physiology

- Study the nature of respiratory, laryngeal and upper aerodigestive tract actions and interactions in voice production and determine the principles that govern adaptive and maladaptive behaviors in response to laryngeal disorders or diseases.

- Gather data on voice production that encompass various domains, including neural, muscular, structural, aeromechanical, acoustical and perceptual domains.

- Conduct research to delineate further the effects of bolus characteristics, respiratory parameters and voluntary control on timing and extent of laryngeal elevation and closure and pharyngeal contraction during swallowing.

- Conduct studies on the mechanisms involved in the control of vocal pitch, loudness, quality and register, including mechanisms associated with singing.

- Study the role of sensation, including hearing, vibrotactile sensation, proprioception and respiratory cues, in the development and use of voice in normal, impaired and exceptional subjects.

- Delineate the acoustic to perceptual transformation in voice-quality disorders, with special attention to those
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aspects of the voice signal that give rise to the perception of disorder and its quantities.

- Study the timing mechanisms of laryngeal behavior in coordination with respiratory and articulatory activity.

- Conduct studies on the exceptional (trained) singer to specify the limits of the human voice and its optimal efficiency.

- Determine the effects of lifestyle choices (diet, smoking, drug use, exercise and alcohol consumption) on the function of the larynx and upper aerodigestive tract.

**Neural and Vascular Mechanisms**

- Conduct studies of neural control of the larynx for voice production, respiration and swallowing in humans and animals, including the elucidation of reflex mechanisms for each.

- Use transcranial magnetic stimulation and sensory evoked potentials to map cortical areas pertinent to laryngeal function.

- Determine the activity of the brain stem motoneuron pool during different phases of respiration, phonation and swallowing via the use of short- and long-latency reflexes elicited through electrical stimulation of the recurrent laryngeal nerves.

- Obtain information concerning the function of neural sensors in the control of voice production.

- Determine the similarities and differences in human laryngeal physiology to that of other species proposed as models for human voice production and swallowing.

- Use electrically or chemically elicited phonation from the periaqueductal gray area of the midbrain in anesthetized animals to study the behavior of laryngeal motoneurons, sensory afferents of the larynx and mechanisms of phonatory control.

- Conduct studies of blood circulation and its autonomic control in laryngeal tissues and the relations to biomechanical changes in the larynx, vocal fatigue and laryngeal lesions.

**Biomechanics**

- Develop common spatial and relational references for laryngeal function to make it possible to gather multivariate data to
enhance the modeling of laryngeal function and dysfunction.

Obtain data on laryngeal and upper aerodigestive function of normal octogenarians, nonagenarian and centenarians for voice production and swallowing.

**Cellular and Molecular Biology and Anatomy**

- Specify the sites of hormonal influence on the respiratory system and upper aerodigestive tract and larynx in particular, as well as hormonally affected changes in voice production.

- Determine the biochemical and structural specializations characteristic of laryngeal muscle fibers and their innervation.

- Define the distribution of extracellular matrix molecules, oncogene expression, growth factors and growth-factor receptors as they relate to normal structure of the aging larynx.

- Conduct studies of the cellular biology of cartilage and joint deterioration in the larynx as they affect voice production and swallowing in aging.

**Development and Aging**

- Conduct studies of the mechanisms of epithelial-mesenchymal tissue interactions that are a driving force in the normal development of the larynx and its final form.

- Specify the nature of voice production as it relates to the developing structure of the entire respiratory system and upper aerodigestive tract and larynx in particular.

- Conduct studies of the cellular biology of cartilage and joint deterioration in the larynx as they affect voice production and swallowing in aging.
Diseases and Disorders of the Larynx and Upper Aerodigestive Tract

Epidemiology and Prevention

- Gather data on the incidence and prevalence of voice and swallowing disorders.
- Conduct epidemiological surveys of the influence of external environmental factors on voice production to identify important agents and clarify pathophysiology and develop strategies for prevention, diagnosis and management of the resultant voice disorders.
- Identify genetic and environmental causes of congenital disorders of the larynx and pharynx.
- Develop strategies for prevention and early detection of cancer of the upper aerodigestive tract.
- Conduct epidemiological and case-control studies to identify factors which may lead to focal dystonias of the head and neck.

Pathophysiology and Potential for Improved Therapy

- Improve the understanding of infectious and allergic disorders of the upper aerodigestive tract and develop better therapy.
- Identify and study genetic influences on laryngeal function and dysfunction.
- Obtain information on the effects of drugs (alone or in combination with other therapy) on the voice.
- Study the role of psychogenic factors in the pathogenesis of voice disorders and response to treatment and develop criteria for distinguishing psychogenic from organic voice disorders.
- Determine the role of extracellular matrix, growth factors and oncogenes in wound healing of the larynx and in the pathogenesis of laryngeal and tracheal stenosis.
- Determine reasons for gender differences in susceptibility to vocal disorders.
- Study the effects of aging on voice production to establish the true nature of age-related...
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voice (not pathologic) changes and develop treatment to forestall or prevent such changes.

- Study the effects of respiratory disorders on the voice.
- Conduct studies of recurrent laryngeal nerve regeneration as well as denervated laryngeal muscles to improve the understanding of pathogenesis and treatment of laryngeal paralysis.

Evaluation of Current Therapy

- Conduct prospective, controlled trials to assess effectiveness of treatment for voice disorders, including phonosurgical procedures and voice therapy.
- Conduct long-term, large-scale studies of the management of laryngeal papillomata to address recurrence rates, effects of treatments, effects of cofactors and rates of association with carcinoma of the larynx.
- Evaluate prospectively the effects of conservation surgery for upper aerodigestive tract malignancy on speech, swallowing and breathing.
- Determine the effects of irradiation and chemotherapy on laryngeal function.
- Conduct prospective trials to develop criteria to predict optimal dosage and placement of botulinum toxin injection in the management of focal dystonias and to determine the long-term effects of this therapy.
- Characterize the diffusion of botulinum toxin in tissues and determine whether retrograde transport to the brain stem accounts for some of the substance’s therapeutic actions.
- Conduct studies of the effects of acid and alkaline gastroesophageal reflux on voice and swallowing and evaluate the efficacy of treatment for these disorders.

Technology

- Use simulation modeling to predict the effect of modifying individual elements controlling laryngeal function and account for the effects of surface tension, other tissue surface properties and the specific effects of muscle contractions, including nonlinear phenomena.
- Use magnetic resonance imaging and positron emission tomography to seek structural lesions in the central nervous system in patients with voice...
and swallowing disorders and to improve understanding of the control of the upper aerodigestive tract.

**Diagnosis**

- Conduct studies on large populations of normal and disordered speakers to clarify the relations between quantitative measures and perceptual vocal characteristics to determine how to use quantitative measures in making treatment decisions.

- Determine the usefulness of aeromechanical measurements in the differential diagnosis and assessment of treatments for vocal disorders and evaluate the contribution of the respiratory system to aerodynamic measures.

- Develop meaningful parameters to evaluate quantitatively laryngeal visual images.

- Study the impact on laryngeal electromyography of variations in electrode configuration, interaction of electrodes with muscles, techniques used to verify electrode placement and testing protocols.

- Develop techniques for nonvoluntary activation of laryngeal nerves as a means of verifying the integrity of laryngeal nerves in uncooperative or anesthetized patients.

**Treatment**

- Conduct studies of electrical pacing of the larynx to evaluate the procedure and determine its long-term efficacy.

- Develop prosthetic speech instruments which mimic natural voice characteristics and express paralinguistic features of stress, intonation and juncture.

- Develop and determine the usefulness of techniques for intraoperative monitoring and assessment of vocal function in improving surgical results and preventing complications.
APPENDIX A

Public Law 100-553
Public Law 100-553
100th Congress

An Act

To amend the Public Health Service Act to establish within the National Institutes of Health a National Institute on Deafness and Other Communication Disorders.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.
This Act shall be cited as the "National Deafness and Other Communication Disorders Act of 1988".

SEC. 2. ESTABLISHMENT AND TRANSFER OF FUNCTIONS.
Title IV of the Public Health Service Act (42 U.S.C. 281 et seq.) is amended—
(1) in section 401(b)(1)—
   (A) by striking "and Communicative" in subparagraph (J); and
   (B) by adding at the end the following new subparagraph:
      "(M) The National Institute on Deafness and Other Communication Disorders;"
(2) in the heading for subpart 10 of part C, by striking "and Communicative";
(3) in section 457
   (A) by striking "and Communicative"; and
   (B) by striking "disorder, stroke," and all that follows and inserting "and disorder and stroke."; and
(4) in Part C, by adding at the end the following new subpart:

"Subpart 13—National Institute on Deafness and Other Communication Disorders"

"PURPOSE OF THE INSTITUTE"

"Sec. 464. The general purpose of the National Institute on Deafness and Other Communication Disorders (hereafter referred to in this subpart as the 'Institute') is the conduct and support of research and training, the dissemination of health information, and other programs with respect to disorders of hearing and other communication processes, including diseases affecting hearing, balance, voice, speech, language, taste, and smell.

"NATIONAL DEAFNESS AND OTHER COMMUNICATION DISORDERS PROGRAM"

"Sec. 464A. (a) The Director of the Institute, with the advice of the Institute's advisory council, shall establish a National Deafness and Other Communication Disorders Program (hereafter in this section referred to as the 'Program'). The Director or the Institute shall, with respect to the Program, prepare and transmit to the Director of NIH a plan to initiate, expand, intensify and coordinate activities of the Institute respecting disorders of hearing (including tinnitus) and..."
other communication processes, including diseases affecting hearing, balance, voice, speech, language, taste, and smell. The plan shall include such comments and recommendations as the Director of the Institute determines appropriate. The Director of the Institute shall periodically review and revise the plan and shall transmit any revisions of the plan to the Director of NIH.

"(b) Activities under the Program shall include—

"(1) investigation into the etiology, pathology, detection, treatment, and prevention of all forms of disorders of hearing and other communication processes, primarily through the support of basic research in such areas as anatomy, audiology, biochemistry, bioengineering, epidemiology, genetics, immunology, microbiology, molecular biology, the neurosciences, otolaryngology, psychology, pharmacology, physiology, speech and language pathology, and any other scientific disciplines that can contribute important knowledge to the understanding and elimination of disorders of hearing and other communication processes;

"(2) research into the evaluation of techniques (including surgical, medical, and behavioral approaches) and devices (including hearing aids, implanted auditory and nonauditory prosthetic devices and other communication aids) used in diagnosis, treatment, rehabilitation, and prevention of disorders of hearing and other communication processes;

"(3) research into prevention, and early detection and diagnosis, of hearing loss and speech and language disturbances (including stuttering) and research into preventing the effects of such disorders on learning and learning disabilities with extension of programs for appropriate referral and rehabilitation;

"(4) research into the detection, treatment, and prevention of disorders of hearing and other communication processes in the growing elderly population with extension of rehabilitative programs to ensure continued effective communication skills in such population;

"(5) research to expand knowledge of the effects of environmental agents that influence hearing or other communication processes; and

"(6) developing and facilitating intramural programs on clinical and fundamental aspects of disorders of hearing and all other communication processes.

"DATA SYSTEM AND INFORMATION CLEARINGHOUSE

SEC. 464B. (a) The Director of the Institute shall establish a National Deafness and Other Communication Disorders Data System for the collection, storage, analysis, retrieval, and dissemination of data derived from patient populations with disorders of hearing or other communication processes, including where possible, data involving general populations for the purpose of identifying individuals at risk of developing such disorders.

"(b) The Director of the Institute shall establish a National Deafness and Other Communication Disorders Information Clearinghouse to facilitate and enhance, through the effective dissemination of information, knowledge and understanding of disorders of hearing and other communication processes by health professionals, patients, industry, and the public.
MULTIPURPOSE DEAFNESS AND OTHER COMMUNICATION DISORDERS CENTER

Sec. 464C. (a) The Director of the Institute shall, after consultation with the advisory council for the Institute, provide for the development, modernization, and operation (including care required for research) of new and existing centers for studies of disorders of hearing and other communication processes. For purposes of this section, the term 'modernization' means the alteration, remodeling, improvement, expansion, and repair of existing buildings and the provision of equipment for such buildings to the extent necessary to make them suitable for use as centers described in the preceding sentence.

(b) Each center assisted under this section shall—

(1) use the facilities of a single institution or a consortium of cooperating institutions; and

(2) meet such qualifications as may be prescribed by the Secretary.

(c) Each center assisted under this section shall, at least, conduct—

(1) basic and clinical research into the cause, diagnosis, early detection, prevention, control, and treatment of disorders of hearing and other communication processes and complications resulting from such disorders, including research into rehabilitative aids, implantable biomaterials, auditory speech processors, speech production devices, and other otolaryngologic procedures;

(2) training programs for physicians, scientists, and other health and allied health professionals;

(3) information and continuing education programs for physicians and other health and allied health professionals who will provide care for patients with disorders of hearing or other communication processes; and

(4) programs for the dissemination to the general public of information—

(A) on the importance of early detection of disorders of hearing and other communication processes, of seeking prompt treatment, rehabilitation, and of following an appropriate regimen; and

(B) on the importance of avoiding exposure to noise and other environmental toxic agents that may affect disorders of hearing or other communication processes.

(d) A center may use funds provided under subsection (a) to provide stipends for health professionals enrolled in training programs described in subsection (c)(2).

(e) Each center assisted under this section may conduct programs—

(1) to establish the effectiveness of new and improved methods of detection, referral, and diagnosis of individuals at risk of developing disorders of hearing or other communication processes; and

(2) to disseminate the results of research, screening, and other activities, and develop means of standardizing patient data and recordkeeping.

(f) The Director of the Institute shall, to the extent practicable, provide for an equitable geographical distribution of centers assisted under this section. The Director shall give appropriate consideration...
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to the need for centers especially suited to meeting the needs of the elderly, and of children (particularly with respect to their education and training), affected by disorders of hearing or other communication processes.

“(g) Support of a center under this section may be for a period not to exceed seven years. Such period may be extended by the Director of the Institute for one or more additional periods of not more than five years if the operations of such center have been reviewed by an appropriate technical and scientific peer review group established by the Director, with the advice of the Institute’s advisory council, if such group has recommended to the Director that such period should be extended.

“NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS ADVISORY BOARD

42 USC 285m–4.

“Sec. 464D. (a) The Secretary shall establish in the Institute the National Deafness and Other Communication Disorders Advisory Board (hereafter in this section referred to as the 'Advisory Board').

“(b) The Advisory Board shall be composed of eighteen appointed members and nonvoting ex officio members as follows:

“(1) The Secretary shall appoint—

“(A) twelve members from individuals who are scientists, physicians, and other health and rehabilitation professionals, who are not officers or employees of the United States, and who represent the specialties and disciplines relevant to deafness and other communication disorders, including not less than two persons with a communication disorder; and

“(B) six members from the general public who are knowledgeable with respect to such disorders, including not less than one person with a communication disorder and not less than one person who is a parent of an individual with such a disorder.

Of the appointed members, not less than five shall by virtue of training or experience be knowledgeable in diagnoses and rehabilitation of communication disorders, education of the hearing, speech, or language impaired, public health, public information, community program development, occupational hazards to communications senses, or the aging process.

“(2) The following shall be ex officio members of each Advisory Board:

“(A) The Assistant Secretary for Health, the Director of NIH, the Director of the National Institute on Deafness and Other Communication Disorders, the Director of the Centers for Disease Control, the Chief Medical Director of the Veterans' Administration, and the Assistant Secretary of Defense for Health Affairs (or the designee of such officers).

“(B) Such other officers and employees of the United States as the Secretary determines necessary for the Advisory Board to carry out its functions.

“(c) Members of an Advisory Board who are officers or employees of the Federal Government shall serve as members of the Advisory Board without compensation in addition to that received in their regular public employment. Other members of the Board shall receive compensation at rates not to exceed the daily equivalent of...
the annual rate in effect for grade GS-18 of the General Schedule for each day (including traveltime) they are engaged in the performance of their duties as members of the Board.

"(d) The term of office of an appointed member of the Advisory Board is four years, except that no term of office may extend beyond the expiration of the Advisory Board. Any member appointed to fill a vacancy for an unexpired term shall be appointed for the remainder of such term. A member may serve after the expiration of the member's term until a successor has taken office. If a vacancy occurs in the Advisory Board, the Secretary shall make an appointment to fill the vacancy not later than 90 days from the date the vacancy occurred.

"(e) The members of the Advisory Board shall select a chairman from among the appointed members.

"(f) The Secretary shall, after consultation with and consideration of the recommendations of the Advisory Board, provide the Advisory Board with an executive director and one other professional staff member. In addition, the Secretary shall, after consultation with and consideration of the recommendations of the Advisory Board, provide the Advisory Board with such additional professional staff members, such clerical staff members, such services of consultants, such information, and (through contracts or other arrangements) such administrative support services and facilities, as the Secretary determines are necessary for the Advisory Board to carry out its functions.

"(g) The Advisory Board shall meet at the call of the chairman or upon request of the Director of the Institute, but not less often than four times a year.

"(h) The Advisory Board shall—
"(1) review and evaluate the implementation of the plan prepared under section 464A(a) and periodically update the plan to ensure its continuing relevance;

"(2) for the purpose of assuring the most effective use and organization of resources respecting deafness and other communication disorders, advise and make recommendations to the Congress, the Secretary, the Director of NIH, the Director of the Institute, and the heads of other appropriate Federal agencies for the implementation and revision of such plan; and

"(3) maintain liaison with other advisory bodies related to Federal agencies involved in the implementation of such plan and with key non-Federal entities involved in activities affecting the control of such disorders.

"(i) In carrying out its functions, the Advisory Board may establish subcommittees, convene workshops and conferences, and collect data. Such subcommittees may be composed of Advisory Board members and nonmember consultants with expertise in the particular area addressed by such subcommittees. The subcommittees may hold such meetings as are necessary to enable them to carry out their activities.

"(j) The Advisory Board shall prepare an annual report for the Secretary which—
"(1) describes the Advisory Board's activities in the fiscal year for which the report is made;

"(2) describes and evaluates the progress made in such fiscal year in research, treatment, education, and training with respect to the deafness and other communication disorders;
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“(3) summarizes and analyzes expenditures made by the Federal Government for activities respecting such disorders in such fiscal year; and

“(4) contains the Advisory Board's recommendations (if any) for changes in the plan prepared under section 464A(a).

“(k) The National Deafness and Other Communication Disorders Advisory Board shall be established not later than 90 days after the date of the enactment of the National Institute on Deafness and Other Communication Disorders Act.

"INTERAGENCY COORDINATING COMMITTEE"

42 USC 285m-5. "SEC. 464E. (a) The Secretary may establish a committee to be known as the Deafness and Other Communication Disorders Interagency Coordinating Committee (hereafter in this section referred to as the 'Coordinating Committee').

"(b) The Coordinating Committee shall, with respect to deafness and other communication disorders—

"(1) provide for the coordination of the activities of the national research institutes; and

"(2) coordinate the aspects of all Federal health programs and activities relating to deafness and other communication disorders in order to assure the adequacy and technical soundness of such programs and activities and in order to provide for the full communication and exchange of information necessary to maintain adequate coordination of such programs and activities.

"(c) The Coordinating Committee shall be composed of the directors of each of the national research institutes and divisions involved in research with respect to deafness and other communication disorders and representatives of all other Federal departments and agencies whose programs involve health functions or responsibilities relevant to deafness and other communication disorders.

"(d) The Committee shall be chaired by the Director of NIH (or the designee of the Director). The Committee shall meet at the call of the chair, but not less often than four times a year.

"(e) Not later than 120 days after the end of each fiscal year, the Committee shall prepare and transmit to the Secretary, the Director of NIH, the Director of the Institute, and the advisory council for the Institute a report detailing the activities of the Committee in such fiscal year in carrying out subsection (b).

"LIMITATION ON ADMINISTRATIVE EXPENSES"

42 USC 285m-6. "Sec. 464F. With respect to amounts appropriated for a fiscal year for the National Institutes of Health, the limitation established in section 408(b)(1) on the expenditure of such amounts for administrative expenses shall apply to administrative expenses of the National Institute on Deafness and Other Communication Disorders."

SEC. 3. TRANSITIONAL AND SAVINGS PROVISIONS.

(a) TRANSFER OF PERSONNEL, ASSETS, AND LIABILITIES.—Personnel employed by the National Institutes of Health in connection with the functions vested under section 2 in the Director of the National Institute on Deafness and Other Communication Disorders, and assets, property, contracts, liabilities, records, unexpended balances of appropriations, authorizations, allocations, and other funds of the National Institutes of Health, arising from or employed, held, used,
available to, or to be made available, in connection with such functions shall be transferred to the Director for appropriate allocation. Unexpended funds transferred under this subsection shall be used only for the purposes for which the funds were originally authorized and appropriated.

(b) SAVINGS PROVISIONS.—With respect to functions vested under section 1 in the Director of the National Institute on Deafness and Other Communication Disorders, all orders, rules, regulations, grants, contracts, certificates, licenses, privileges, and other determinations, actions, or official documents, that have been issued, made, granted, or allowed to become effective, and that are effective on the date of the enactment of this Act, shall continue in effect according to their terms unless changed pursuant to law.


LEGISLATIVE HISTORY—S. 1727 (H.R. 3361):

HOUSE REPORTS: No. 100-761 accompanying H.R. 3361 (Comm. on Energy and Commerce).


Oct. 7, considered and passed Senate.
Oct. 13, considered and passed House.
APPENDIX B

Hearing and
Hearing Impairment

and

Voice and
Voice Disorders

Panel Members
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