



the REGISTRY

Newsletter of the NIDCD National Temporal Bone, Hearing and Balance Pathology Resource Registry

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HUMAN TEMPORAL BONE CONSORTIUM FOR RESEARCH RESOURCE ENHANCEMENT

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Why study human temporal bones?

Knowledge of the pathologic basis of disease is central to the study of medicine. Otolaryngology is unique because the inner ear is inaccessible during life, so that conventional techniques of pathologic study such as biopsy and surgical excision are not feasible. Hence, insight into the pathologic basis of ear disease within the three-dimensional framework of the inner ear and its surroundings can be obtained only by postmortem study of temporal bones and by developing better animal models. Improved understanding of the pathology and pathogenesis of auditory and vestibular system disorders will lead to more rational diagnosis and management of these disorders. The procurement, processing, and study of human temporal bones is time consuming and costly, and is a research endeavor performed in the few existing temporal bone laboratories.

There are several reasons why continued study of human temporal bones is warranted:

- 1) To determine the still unknown pathologic bases of a large number of auditory and vestibular disorders, including genetic defects;
- 2) To compare human otopathology with animal models to determine which models provide valid information on the cellular and molecular bases of human inner ear disorders;
- 3) To benefit the practice of otologic surgery by providing postoperative information otherwise unobtainable; and
- 4) To obtain and study specimens from individuals across the human lifespan, with well-documented normal or age-appropriate levels of hearing and balance function.



The REGISTRY is published semiannually by the NIDCD National Temporal Bone, Hearing and Balance Pathology Resource Registry. The Registry was established in 1992 by the National Institute on Deafness and Other Communication Disorders (NIDCD) of the National Institutes of Health to continue and expand upon the former National Temporal Bone Banks (NTBB) Program. The Registry promotes research on hearing and balance disorders and serves as a resource for the public and the scientific community about research on the pathology of the human auditory and vestibular systems.

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ALL ABOUT BALANCE: SCIENTISTS IDENTIFY BUILDING BLOCKS OF INNER EAR STRUCTURE

Watch a bird overhead, turn toward a friend at your side, or exult in a cartwheel, and without knowing it, you are taking advantage of the vestibular portion of your inner ear. Combined with visual cues and information from muscles and joints, our inner ears allow us to maintain balance and a steady field of vision during movements.

A specific part of the inner ear contributes to good balance and steady vision by detecting angular head motions—such as nodding forward, tilting sideways, or looking over your shoulder. It also signals the brain about changes in head position so that simple movements do not leave us feeling imbalanced or give us vertigo.

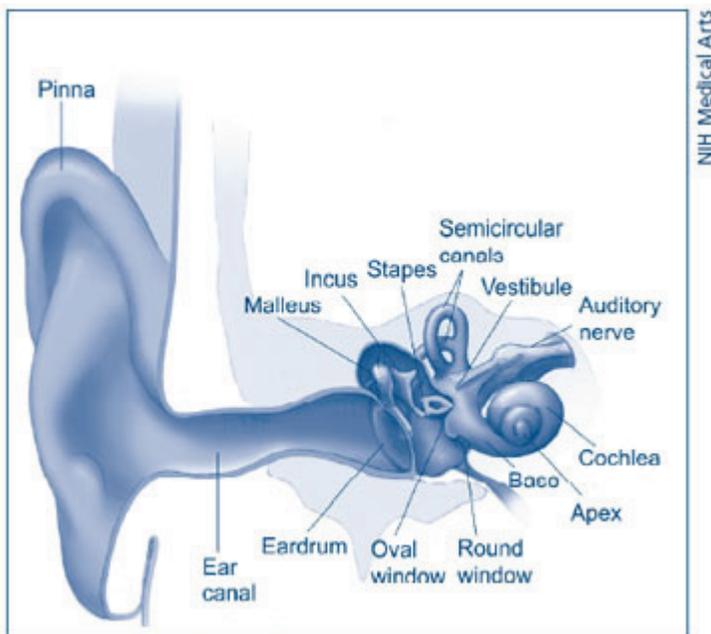
Scientists are seeking to better understand how our genes direct the development of this portion of the inner ear. Specifically responsible for detecting angular head movements, it is made up of three semicircular canals and their associated sensory tissues, called cristae. The cristae contain sensory cells that detect movement of fluid within the semicircular canals during head movements. The three precisely positioned semicircular canals, which are composed of nonsensory tissue, must develop in an exact geometry—approximately perpendicular to each other and connected to the inner ear's vestibule.

A research team led by Doris Wu, Ph.D., of the National Institute on Deafness and Other Communication Disorders (NIDCD), recently discovered that a gene encoding a particular growth factor protein is essential to the formation of the semicircular canals and the cristae. Dr. Wu and colleagues' earlier research has also identified other genes involved in the well-choreographed cascade of molecular events that form the inner ear.

Working with scientists at NIDCD, Duke University, and the Albert Einstein College of Medicine, Dr. Wu found that bone morphogenetic protein 4, or Bmp4, is required for formation of the semicircular canals and their cristae in mice. When she and her team inactivated or deleted the gene for Bmp4 in the inner ear, the semicircular canals did not develop. Bmp4 has long been known to play an important role in the formation of connective tissues and other organs such as eyes, limbs, and cartilage.

The researchers found that during inner ear development, Bmp4 is secreted by sensory tissue of the cristae in the base of each canal. Based on their new research, they hypothesize that sensory patches in the cristae regulate formation of the nonsensory tissue in the canals. Dr. Wu and her team are seeking a full understanding of the chain of events that give rise to the inner ear.

Dr. Wu and her team's work is published in the April 2008 issue of the journal PLoS Genetics. The paper is available online.



What methods have been used to study human temporal bones?

Historically, methods for temporal bone study can be viewed as having passed through several technologic periods (1). The period of light microscopic study began at the turn of the last century and encompassed the celloidin embedding and serial sectioning method. Autopsy specimens were often flawed by postmortem autolysis and preparation artifact, and these early studies concentrated on gross correlations of pathologic change with clinical manifestations of disease. The period of cytologic description began when Guild (2) initiated the method of graphic reconstruction of the cochlea and placed more emphasis on technical quality and specific disordered cytology. Meanwhile, standard audiometric tests became available, and more meaningful correlations of morphologic change with functional disorders could be made. The period of cytologic quantification began in the 1950s and 1960s with Schuknecht's (3,4) descriptions of correlations of hearing loss with losses of various cytologic elements in the sensory and neural systems of the cochlea. Such cytologic quantification was possible because the histologic preparations were technically excellent, and temporal bones were acquired soon after death to minimize postmortem autolysis. We are now entering another period that might be characterized as methodological integration whereby the same temporal bone can be used for light microscopic study and for electron microscopy, immunostaining, and molecular studies involving genomic and proteomic assays. The use of such technologies in combination may provide new information that could revolutionize our understanding of otologic disorders.

What is the National Temporal Bone Registry and its role?

In 1992, the *National Temporal Bone Hearing and Balance Pathology Resource Registry* (the "Registry"; <http://www.tbregistry.org>) was established by the National Institute on Deafness and Other Communication Disorders (NIDCD) of the National Institutes of Health (NIH). The Registry promotes research on otopathology by serving as a resource for the public and scientific community (5). It continues and expands the former National Temporal Bone Banks program created in 1960 to encourage temporal bone donation

and works closely with all temporal bone collections and laboratories in the United States. The Registry does not itself collect specimens or do research but serves many functions including enrolling temporal bone donors on a prospective basis, maintaining a 24-hour nationwide network to coordinate collection of temporal bones after a donor's death, maintaining a computerized database of all human temporal bone collections nationwide, conserving existing collections that may be at risk of being disbanded, disseminating information on the importance of temporal bone donation and research, and sponsoring professional educational activities in otopathology. Of note, more than 5,000 individuals have been recruited as temporal bone donors, and since its inception, the Registry has coordinated the retrieval of more than 700 temporal bone specimens, the vast majority from donors with well-documented otologic disorders. These specimens have been distributed to various U.S. laboratories for histopathologic processing and study. Registry activities have directly or indirectly supported more than 350 peer-reviewed articles or book chapters on human otopathology by various U.S. laboratories. The Registry is supported by a contract from the NIDCD that provides the infrastructure necessary for timely procurement of high-quality temporal bone specimens and a centralized national information source. Laboratories obtaining specimens must find their own funds and personnel to process and study the temporal bones. Despite the success of the Registry, the numbers of laboratories and investigators engaged in human temporal bone research have declined from 28 active laboratories in the United States in 1976 to fewer than 10 now. The reasons for this decline include difficulty competing for funding, escalating costs of tissue procurement, and a shortage of trained and committed physician-scientists in the field of otopathology.

How can temporal bone research impact both clinical and basic science?

Temporal bone research has played a major and significant role in enhancing the diagnosis and therapy of numerous otologic disorders, examples of which abound in standard otopathologic texts (1,6,7). A few recent examples are presented to illustrate the power of otopathologic studies in impacting both basic and clinical science:

1. *DFNA9*. A unique constellation of histopathologic findings of degeneration of the spiral ligament with eosinophilic deposits led to the discovery of DFNA9 (8), one of the few genetic nonsyndromic disorders involving both the auditory and vestibular systems. These initial histopathologic studies ultimately led to identification of its cause, namely, mutations in the COCH gene (9). Affected individuals exhibit significant sensorineural hearing loss despite having an intact organ of Corti (10). The histopathologic studies have supported basic science observations of the importance of the spiral ligament in inner ear physiology (11,12). Cochlin, the gene product of the COCH gene, is highly expressed within the inner ear, but its precise function and role in DFNA9 is not known. Temporal bone studies using techniques of immunostaining and proteomic analysis of archival sections have provided insight into the pathophysiology of the hearing loss (13).

2. *Facial nerve paralysis*. Although viruses have been implicated as etiologic agents in Bell palsy and Ramsay-Hunt syndrome, the evidence to support a viral etiology was circumstantial. Application of polymerase chain reaction amplification to archival temporal bone sections has shown varicella-zoster viral deoxyribonucleic acid (DNA) in Ramsay-Hunt syndrome (14) and herpes simplex viral DNA in Bell palsy (15). Thus, temporal bone studies have provided support for treating these disorders with antiviral therapy.

3. *Cochlear implantation*. Otopathologic studies of temporal bones from individuals that received cochlear implants during life have shown no correlation between the number of surviving cochlear neuronal cells and implant performance during life (16,17). This surprising and unexpected finding refutes a long-standing assumption that cochlear implant performance would be directly correlated with the number of cochlear neurons. This finding has significant implications for design and development of cochlear implant electrode arrays.

4. *Vestibular disorders*. There is a paucity of knowledge regarding the pathologic basis for many forms of dizziness and vertigo. Recent studies have provided evidence of lesions at the level of vestibular hair cells and the vestibular nerve, with implications for diagnosis and therapy (18-20). The demonstration of aquaporins in the human inner ear (21) may also lead to new in-

sights into the pathophysiology of labyrinthine disease such as Meniere's syndrome.

5. *Temporal bone models*. The human temporal bone contains a large number of complex structures within a small space. It can be challenging for students in the basic sciences or medical disciplines to learn this complex anatomy. Virtual models of the human temporal bone have been created from histologic sections and are available as downloadable freeware for teaching and educational purposes (22,23). These models serve as teaching tools by providing realistic, interactive, and anatomically accurate information with 3-dimensional visualization. More than 5,500 downloads (each download comprising a model plus interactive software) have occurred within the span of about a year.

How was the Consortium established?

The NIDCD sponsored a *workshop*, "Temporal Bone Histopathology Research: Laboratories and Research Training," in 2003 to assess the need to maintain active laboratories and encourage new researchers in the field. The workshop participants recognized the potential for modern molecular, genetic and imaging technologies to help human temporal bone research make discoveries that can translate into valuable clinical advances. They also noted that individuals considering a career in human otopathology research are dissuaded by a number of misconceptions (e.g., that otopathology is a field of historic interest only, with little relevance to modern otology, and that federal funding agencies have little interest in supporting otopathologic studies). Workshop participants concluded that it is critically important to support basic processing and study of human temporal bones and training of future generations of otopathologists. It was felt that protocol-driven acquisition and processing of specimens by a consortium of laboratories would promote methodological improvements, data sharing, and recruitment and training of future researchers. To this end, NIDCD announced a funding opportunity for a *Human Temporal Bone Consortium for Research Resource Enhancement* (the "Consortium"), and after peer review, the Consortium was established in late 2006 with 3 member laboratories: the Massachusetts Eye and Ear Infirmary (Boston, MA), the House Ear Institute (Los Angeles, CA), and the University of California at Los Angeles (Los Angeles, CA).

What is the Consortium and what are its goals?

The Consortium is supported as a cooperative agreement from NIDCD using the U24 funding mechanism and, in consultation with the NIDCD Program Officer, is governed by an internal Steering Committee and an external Advisory Committee. The goals of the Consortium are to improve and enhance methodologies for processing human temporal bones, to promote sharing of tissues and technologies, and to promote the recruitment and training of new investigators. The U24 mechanism includes funding of the member laboratories for processing and study of temporal bones. The Consortium promotes multidisciplinary collaborations between laboratories to address research questions that are too difficult for single laboratories to solve and maximizes the use of specimens that are difficult to obtain. The Consortium will optimize protocols for assessing prospectively acquired temporal bones using decision trees that allow processing methods to differ depending on the donor's medical history, pre-mortem auditory and vestibular test data, and results of imaging studies. The Consortium also will develop protocols for analysis that apply modern molecular biological techniques such as the use of immunoassays, DNA and ribonucleic acid assays, and mass spectrometry-based proteomic analysis, including techniques that may be possible on archival temporal bones. Sharing of tissues, data, and technologies will be promoted among the member laboratories and the wider scientific and research communities. Another goal is to archive information in digital format from temporal bones that have been studied and to make the information available to clinicians and researchers in the form of web-based freeware for teaching purposes.

The activities of the Consortium and the Registry are different in focus and funding, but they are complementary. The Registry is an administrative organization that provides the infrastructure for the acquisition of high-quality temporal bone specimens, whereas the Consortium concentrates on research in human otopathology and training the next generation of temporal bone researchers. The activities of the Consortium should lead to technical innovations in the study of temporal bones, sustain existing temporal bone laboratories, and become a resource for sharing specimens and data with the wider scientific and clinical communities.

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Visit the Consortium's web site at www.temporalboneconsortium.org. The web site describes the establishment of the Consortium and its laboratories. It also contains a wealth of resources on anatomy and pathology of the human temporal bone in an interactive and downloadable format.



HUMAN TEMPORAL BONE CONSORTIUM FOR RESEARCH RESOURCE ENHANCEMENT



ABOUT THE CONSORTIUM

The Consortium is a cooperative agreement between the National Institutes of Health and three Otopathology laboratories in the US. It seeks to enhance study of human temporal bones, promote sharing of tissues and technologies, and training of new investigators.

[Learn more...](#)



INTERACTIVE IMAGE LIBRARY

This atlas contains about 40 serial sections from a normal human temporal bone. The interactive program allows the viewer to examine each section at various magnifications. A great tool for learning the histologic anatomy of the temporal bone.

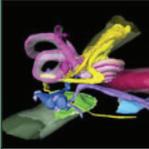
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TECHNICAL RESOURCES

The procurement, process and study of human temporal bones is a time-consuming and costly research endeavor. This section describes how to remove temporal bones and process them for standard light microscopy as well as other methods of study.

[Learn more...](#)



EDUCATIONAL RESOURCES

This section will be of interest to trainees, clinicians and researchers. Resources include an Atlas of the normal temporal bone, Downloadable 3-D models, a Library of over 1,500 images from pathologic specimens and Webcasts of clinico-pathologic conferences.

[Learn more...](#)

LABS OF THE CONSORTIUM

PUBLICATIONS

RESEARCH FELLOWSHIPS

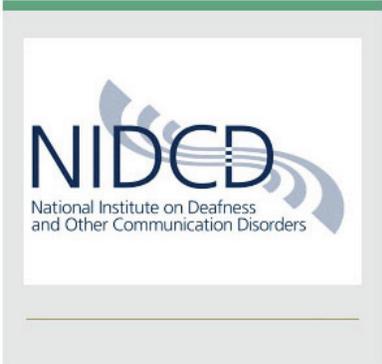
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"... if we carefully survey the history of the rise and progress of aural [surgery], as a distinct branch of scientific surgery, one main cause of the disrepute into which it has fallen may be traced to the neglect of the pathology of the organ of hearing"

Joseph Toynbee, 1868
From Schuknecht HF, Pathology of the Ear, 2nd Ed, Lea & Febiger, Philadelphia, 1993







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NEWS AND ANNOUNCEMENTS



50th
ANNIVERSARY
1958 - 2008

This year marks the 50th Anniversary of the Deafness Research Foundation. To recognize its achievements and to re-commit itself to the future, the Deafness Research Foundation hosted a special 50th Anniversary Celebration on May 14, 2008 at The Hudson Theatre in New York City. The event was held in honor of their founder, Mrs. Collette Ramsey Baker. The Deafness Research Foundation is one of the largest and oldest hearing research organization in the US, and is dedicated to making a lifetime of hearing health possible for all people through quality research and education.

The Registry is planning to exhibit at these up coming meetings:

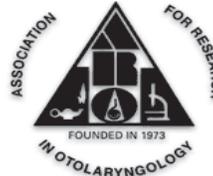


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OTOPATHOLOGY MINI-TRAVEL FELLOWSHIP PROGRAM

The NIDCD National Temporal Bone Registry is pleased to announce the availability of mini-travel fellowships. The fellowships provide travel funds for research technicians and young investigators to visit a temporal bone laboratory for a brief educational visit, lasting approximately one week. *The emphasis is on the training of research assistants, technicians and junior faculty.* The fellowships are available to:

- 1) U.S. hospital departments who aspire to start a new temporal bone laboratory
- 2) Inactive U.S. temporal bone laboratories that wish to reactivate their collections or
- 3) Active U.S. temporal bone laboratories that wish to learn new research techniques

Up to two fellowship awards will be made each year (\$1,000 per fellowship). The funds may be used to defray travel and lodging expenses. Applications will be decided on merit. Interested applicants should submit the following:

- 1) A 1-2 page outline of the educational or training aspect of the proposed fellowship
- 2) Applicant's curriculum vitae
- 3) Letter of support from temporal bone laboratory director or department chairman
- 4) Letter from the host temporal bone laboratory, indicating willingness to receive the traveling fellow

Applications should be sent to:

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Thank you!

FREE BROCHURES FOR YOUR OFFICE OR CLINIC ABOUT TEMPORAL BONE RESEARCH AND DONATION

That Others May Hear is a short brochure that briefly describes the functions of the Registry, and answers commonly asked questions regarding the temporal bone donation process. (Dimensions: 9" x 4")

The Gift of Hearing and Balance: Learning about Temporal Bone Donation is a 16-page, full-color booklet which describes in more detail the benefits of temporal bone research. It also answers commonly asked questions regarding the temporal bone donation process. (Dimensions: 7" x 10")

If you are willing to display either or both of these brochures, please complete the form below and return it to the Registry by mail or fax. The brochures will be sent to you **free of charge**. Please circle the amount requested for each brochure or write in amount not listed.

That Others May Hear _____ **25 50 100**

The Gift of Hearing and Balance _____ **25 50 100**

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