THE REGISTRY

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CONTENTS

MISSION STATEMENT

The NIDCD National Temporal Bone, Hearing and Balance Pathology Resource Registry was established in 1992 by the National Institute on Deafness and Other Communication Disorders (NIDCD) of the National Institutes of Health (NIH) 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 scientific community about research on the pathology of the human auditory and vestibular systems.

Contemporary Interpretation of Harold Schuknecht's Feline Model of Labyrinthine Concussion

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Auditory symptoms, including hearing loss, tinnitus, and hyperacusis, resulting from head injury are a well-described clinical phenomenon.[1,2] In cases of head injury with a temporal bone (TB) fracture, auditory dysfunction is thought to be caused by direct anatomic disruption of the middle ear and/or inner ear sensory neuroepithelium.[3,4] However, in the absence of a TB fracture, it can be difficult to predict whether a patient will sustain auditory deficits after head injury.

A recent systematic review examining head injury-related hearing loss in the absence of a TB fracture identified hearing loss in as many as 58 percent of patients.[5] The term "labyrinthine concussion" or "inner ear concussion" has been used to describe sensorineural hearing loss following head trauma in the absence of TB fracture.[6,7] Labyrinthine concussion is generally defined as auditory and/or vestibular dysfunction resulting from head injury without physical exam or imaging findings to suggest an etiology. As such, it is commonly a diagnosis of exclusion.

Around the turn of the 20th century, otopathologists identified histologic changes in the inner ears of individuals who sustained head injury without temporal bone fractures. Early experiments investigating the pathophysiology of labyrinthine concussion were performed in animals through either the delivery of blows to the head or direct introduction of a pressure wave into the labyrinthine fluid.[8–10] Otopathologists

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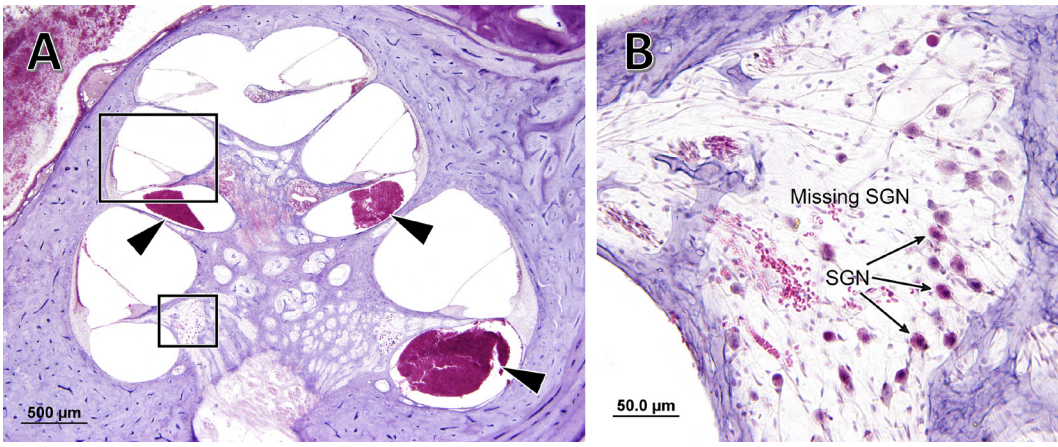


Figure 1. Low and high-power view of the cochlea following injury. (A) Low-power view of the cochlea, showing blood in the scala tympani of the basal and middle turns (arrowhead). **(B)** High-power view of Rosenthal's canal presenting reduced population of cochlear ganglion neurons. **(C)** High-power view of the middle turn of the cochlea showing flattening of the organ of Corti with complete degeneration of the outer and inner hair cells. Pathology most likely attributed to Cat 9; however, definitive records are limited. *(Schuknecht, et al. 1949, unpublished.)*

hypothesized that predominant mechanisms for labyrinthine concussion included inner ear hemorrhage, cochleovestibular nerve traction injury, direct damage from a labyrinthine fluid pressure wave, or vasomotor dysfunction.

Many of these studies are largely considered "historical;" however, they are gaining interest among contemporary investigators given increased recognition of auditory and vestibular symptoms following traumatic brain injury (TBI).

Studies by Harold F. Schuknecht, MD, former Chair of the Harvard Medical School Department of Otolaryngology and world-renowned otologist, in a feline head injury model remain the best evidence to date of potential etiologies of labyrinthine concussion. Histological slides dating back to 1949 that likely served as the foundation for a series of classic papers on the topic were recently rediscovered at Massachusetts Eye and Ear.[8,9]

In a feline head injury model, Schuknecht behaviorally conditioned 10 cats to respond to sounds at specific frequencies and then delivered one or more head blows using an interposed iron rod.[8,9] For one animal, direct impact without the interposed metal rod was performed with the animal in the lateral decubitus position, so that the head was allowed to accelerate freely. Hearing tests were performed once or twice weekly until euthanasia, which occurred two days to five months following the trauma. Feline TBs were harvested and prepared for histological analysis.

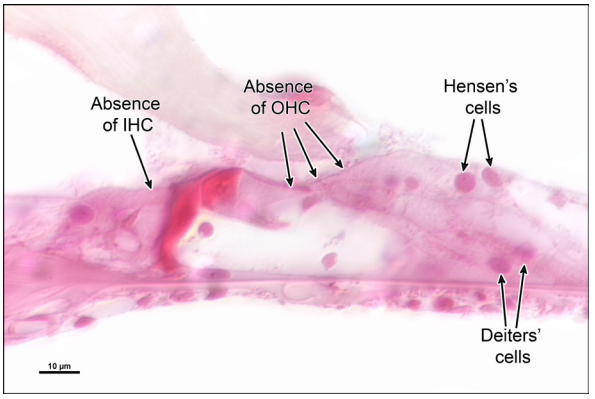
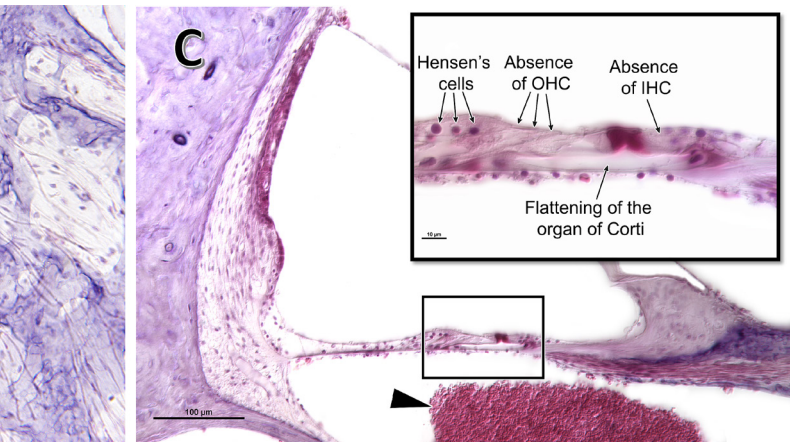


Figure 2. High-power view of the cochlear upper basal turn. Photomicrograph shows severe disruption of the organ of Corti, with loss of inner and outer hair cells. Blood in scala tympani (arrowhead). *(Schuknecht, et al. 1949, unpublished.)*

Schuknecht found that most of the head blows delivered over the temporal and parietal bones near the experimental ear resulted in hearing loss, whereas blows to the contralateral side of the skull failed to produce deafness in the studied ear in four experiments. Trauma to the vertex of the skull was found to result in mild deafness in two out of five animals. On audiometric evaluation, animals presented with 14–40 dB recovery in hearing



thresholds over the frequency range tested (125Hz–16kHz) in the first two weeks following the head blow. Hearing losses were greatest for high frequencies, particularly for the range from 3 to 8kHz, with maximum loss at 4kHz. Schuknecht posited that this audiometric pattern was very similar to noise and blast-induced hearing loss.

Histopathological analysis demonstrated that four out of the 10 animals had skull fractures, in which one involved the TB (Cat 7). Otopathological findings were variable, ranging from slight anatomical degeneration of the outer hair cells and supporting cells to extensive loss of hair cells to complete degeneration of the organ of Corti (Figure 1 and Figure 2). Blood in the scala tympani and vestibuli was found in five cats, with no evidence of local tissue reaction, and leukocytes were identified only in cats euthanized two days after injury. Additionally, only animals euthanized three weeks or longer after injury presented with cochlear nerve degeneration, although changes were less severe than what was found in the organ of Corti. In order to explain this finding, Schuknecht proposed that nerve degeneration might be secondary to a primary injury of the organ of Corti.

When relating hearing loss to otopathological findings, Schuknecht found the most severe damage to the organ of Corti was in the upper basal turn, specifically in the area corresponding to 4kHz, correlating with the aforementioned audiometric findings. In addition, there was a linear relationship between severity of hearing loss and extent of cochlear degeneration (Table 1, Figure 3). Interestingly, cats euthanized two days after trauma had less profound otopathological changes than what would be expected given their severe hearing loss on audiometric evaluation. Schuknecht conjectured that this might be caused by an insufficient time for auditory threshold recovery, since he only observed recovery after three weeks in the other cats.

From these observations, he concluded that the severe audiometric changes he measured were not reflected in his histopathological specimens. He surmised that other cellular changes caused by the injury were likely too subtle to be detected by conventional histopathological preparation.

Following this experiment, Schuknecht proposed that the mechanism of inner ear damage following head injury was very similar to intense noise and/or blast impulse trauma, in which a pressure wave or sound is transmitted through bone to the cochlea, resulting in a "shock pulse." This pressure pulse leads to violent displacement of the basilar membrane, causing injury of the organ of Corti. Schuknecht was also puzzled with high frequencies being the most commonly involved in his experiment, in particular the range from 3 to 8kHz. He considered some possible explanations for this finding, such as an inherent fragility in the upper region of the basal turn or physical properties of the impulse.

Although there has been additional experimentation since the mid-20th century[11–13], the precise pathophysiology of labyrinthine concussion remains unknown for several potential reasons and treatment options are largely nonexistent. Many of the historic clinical studies lacked rigorous methods for diagnosing TB fractures, such as high-resolution imaging, and were not able to provide pathologic correlation. Some animal studies have lacked consistent approaches to head trauma, utilized non-validated rodent models, or were not in line with contemporary definitions of TBI.

Furthermore, our understanding of inner ear pathologies has grown and now includes an enhanced understanding of several different pathologies, including neuropathies and synaptopathies.

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Table 1. Audiometric and histopathological findings

Cat	Behavioral Pure Threshold Audiometry	Histopathology
1 and 2	Mild threshold losses at 4000Hz	No cochlear changes
3, 4, 5, and 6	Mild to severe threshold losses from 2000 to 8000Hz	Cochlear injury restricted to the upper basal and lower middle cochlear turns
7† and 8	Severe to profound threshold losses in all frequencies	Widespread cochlear injury
9	Profound threshold losses in all frequencies	Complete loss of hair cells in all cochlear turns

*No post-concussion audiogram was obtained in Cat 10 due to partial loss of motor function after trauma.
†This animal presented a small linear fracture involving the bony wall of the posterior semicircular canal.

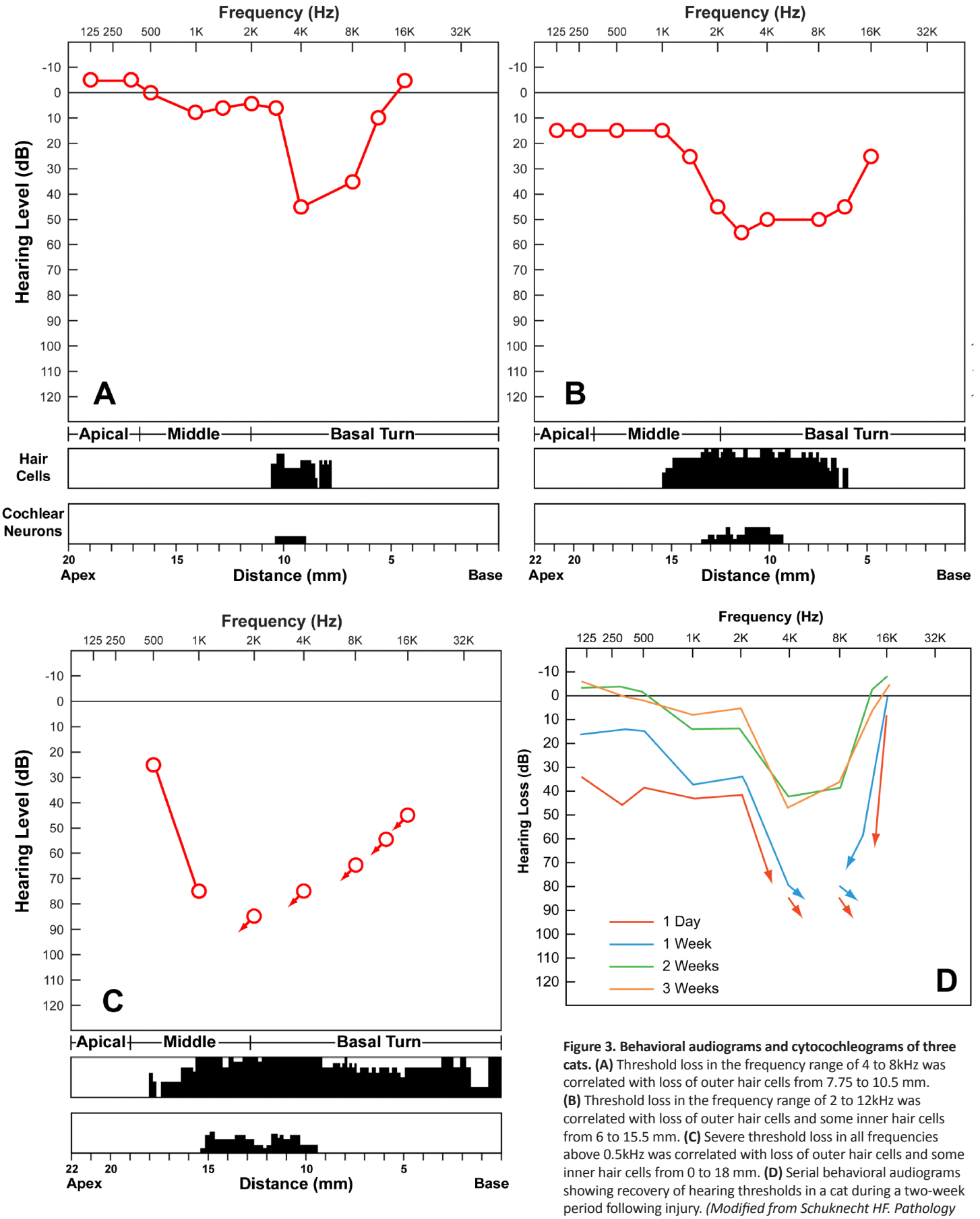

Figure 3. Behavioral audiograms and cytocochleograms of three cats. (A) Threshold loss in the frequency range of 4 to 8kHz was correlated with loss of outer hair cells from 7.75 to 10.5 mm. **(B)** Threshold loss in the frequency range of 2 to 12kHz was correlated with loss of outer hair cells and some inner hair cells from 6 to 15.5 mm. **(C)** Severe threshold loss in all frequencies above 0.5kHz was correlated with loss of outer hair cells and some inner hair cells from 0 to 18 mm. **(D)** Serial behavioral audiograms showing recovery of hearing thresholds in a cat during a two-week period following injury. *(Modified from Schuknecht HF. Pathology of the ear. PMPH-USA, 2010.)*

For example, the degeneration of synaptic connections has been demonstrated in numerous animal models and in post-mortem human samples and is correlated with noise-exposure that leads to tinnitus, hyperacusis, and varying levels of hearing loss. Interestingly, patients who have sustained mild head injuries also appear to present with similar complaints of tinnitus and hyperacusis.[14–18] Our evolving understanding of degenerative changes that occur in the auditory periphery may provide a new paradigm to study auditory dysfunction following TBI.

Finally, while the term "labyrinthine concussion" seems predominantly used in otolaryngology and audiology literature, other medical specialties, such as neurology, neurosurgery, and physical medicine and rehabilitation, have also identified this phenomenon[17–19] and there may be central auditory pathway etiologies that contribute to auditory symptomatology.[20–22] Indeed, literature on TBI[23–26], sports-related concussion[14–16], and emerging evidence on chronic traumatic encephalopathy (CTE)[27] highlight potential auditory symptoms without fracture of the temporal bone.

CTE was initially known as Punch Drunk Syndrome[28] and Dementia Pugilistica.[29] These diagnoses described a range of neurologic symptoms commonly seen in boxers, such as tremors, slowed movements and speech, confusion, memory loss, and psychiatric issues.[28,30,31]

Auditory and vestibular symptoms have been associated with Punch Drunk Syndrome, Dementia Pugilistica, and CTE since the earliest reports of these conditions by pathologists Dr. Harrison Martland and Dr. J.A Millspaugh.[28,29] To date, however, discrete pathologic changes that may occur to the auditory pathway in individuals with CTE[28] are unknown. There is no evidence of discourse among Martland, Millspaugh, and otopathologists of their era.

In summary, Schuknecht found the hearing losses in his feline labyrinthine concussion model to be similar to those occurring in human patients, with a characteristic feature of hearing loss at 4kHz. His study remains the best evidence to date to explain this phenomenon and few studies have been conducted on this topic since the 1950s. In the future, highly controlled and validated animal models of TBI are necessary to correlate mechanisms of auditory injury with pathologic findings in the acute and chronic settings. Additional research is also needed to better understand the pathophysiology and parse potentially overlapping diagnoses among various medical subspecialties. ●

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The Endolymphatic Sac and Ménière's Disease

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Ménière's disease (MD) constitutes one of the most vexing problems in the field of neurotology. Questions regarding the pathophysiology of its clinical symptoms and the underlying inner ear pathology are intricately linked, but remain unanswered. The episodic nature of its early-phase symptoms[1, 2] and post-mortem temporal bone histopathology correlated to this early disease phase suggest a primary inner ear pathology that is distinct from progressive neurosensory degeneration.[3, 4]

In fact, the first human temporal bone studies in MD already brought attention to the endolymphatic sac (ES) as a possible site of primary pathology.[5,6] These seminal studies, together with earlier studies on the cellular structure of the ES[7,8], the ES's role in inner ear fluid physiology[9] and clinical observation on MD patients[10,11] concordantly drafted the following disease concept: "A failure of secretory or resorptive functions in the ES causes disturbances in endolymph volume regulation, which lead to the formation of endolymphatic hydrops (EH), and the latter, in turn, elicits the fluctuating clinical symptoms of MD."

This disease concept became a generally accepted paradigm. It continues to influence research on the etiology of MD today. Numerous temporal bone studies have investigated the proposed underlying ES pathology in MD. Those studies reported alleged pathological changes in the ES epithelium[12,13], the perisaccular

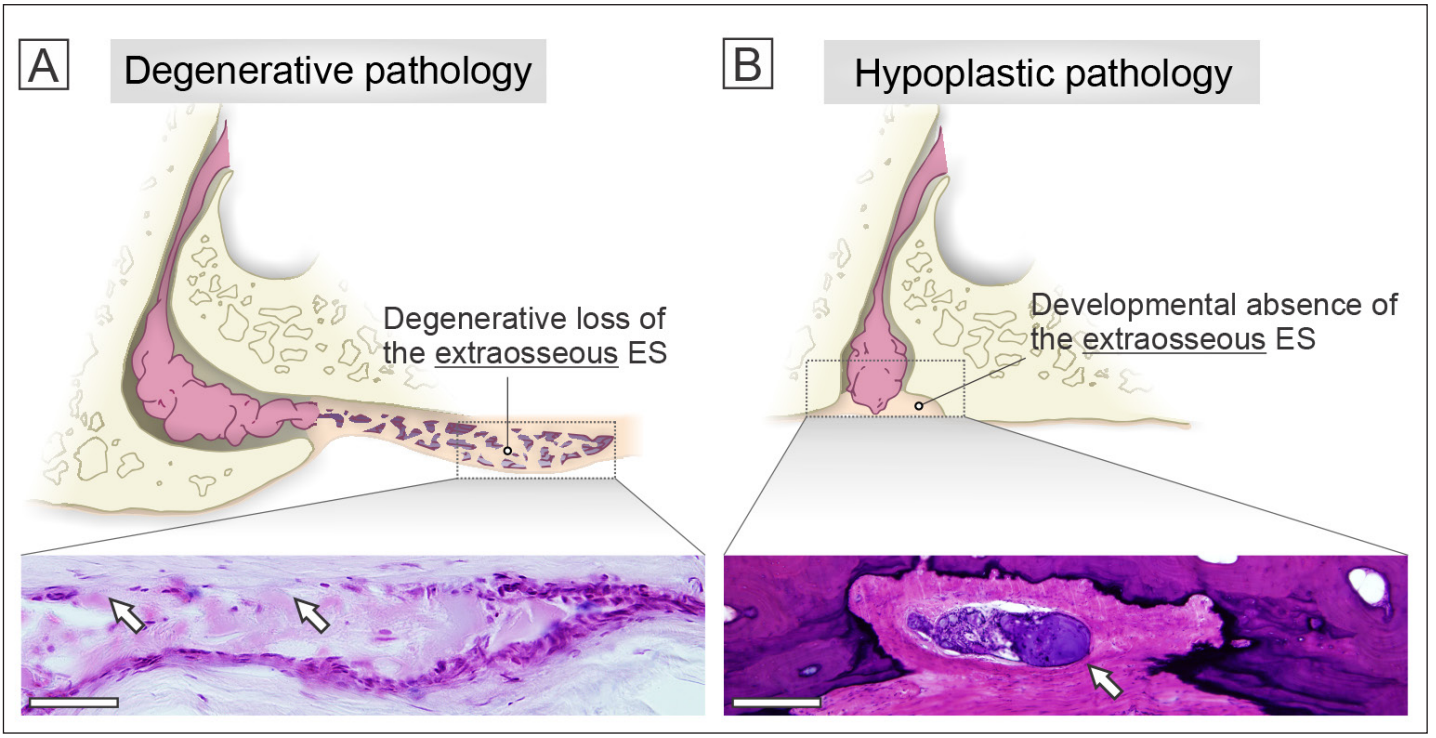

Figure 1. Schematic representation and histological examples (hematoxylin/eosin staining) of degenerative **(A)** and hypoplastic **(B)** ES pathologies, as present in cases with idiopathic endolymphatic hydrops. *Adapted from (37), according to the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), under which the original article is distributed.*

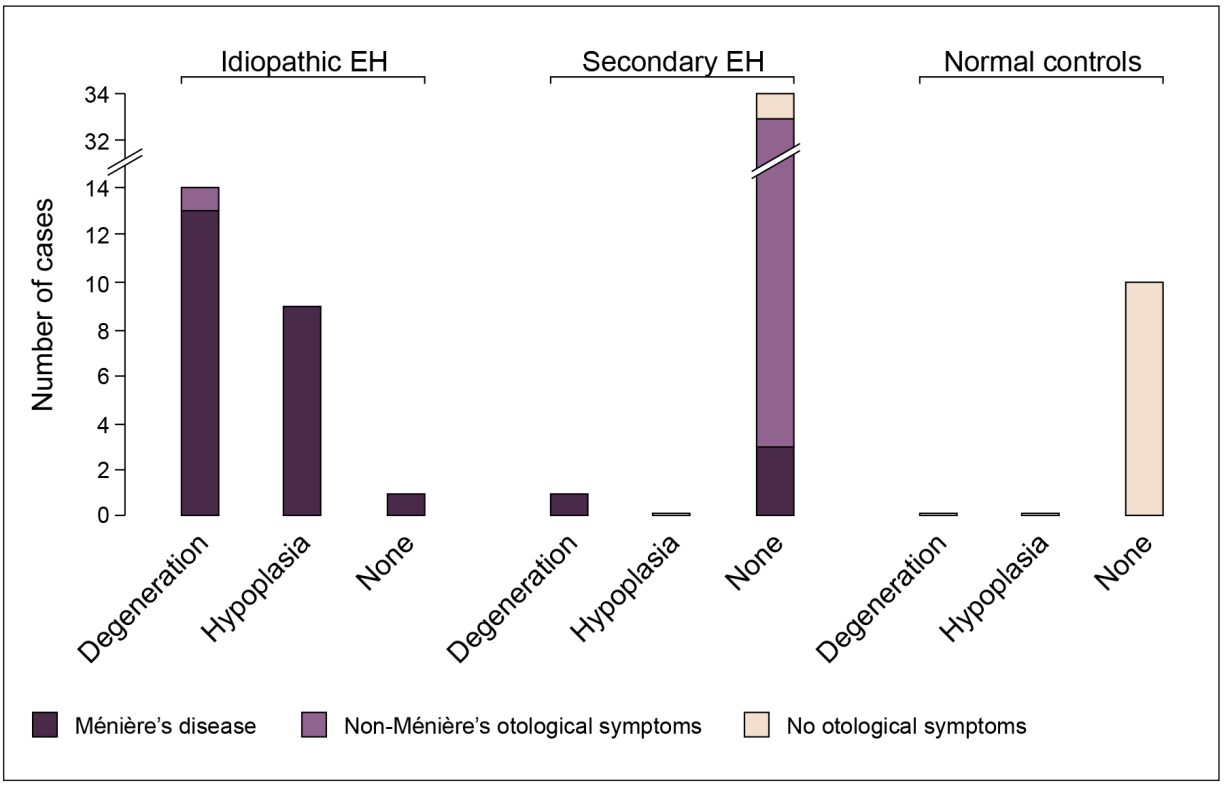

Figure 2. Prevalence of ES pathologies (degenerative, hypoplastic, none) and clinical symptomatologies (MD, non-Ménière's otologic symptoms, no symptoms) in groups with idiopathic EH, secondary EH (38), and control cases without EH and a clinical history of otologic disease. *Adapted from (37), according to the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), under which the original article is distributed.*

tissue[14], the blood and lymph supply of the ES[15], and in the bony structures surrounding the ES.[16] However, subsequently, more thoroughly controlled temporal bone studies did not confirm these findings as consistent and specific in MD.[17–20] Thus, no ES pathology has been conclusively and consistently linked to EH and MD.

More recently, the disease paradigm was challenged by studies that disproved "longitudinal endolymph flow" and bulk fluid siphoning by the ES as major fluid homeostatic mechanism in the inner ear[21,22] and by studies that casted reasonable doubt over the causal connection between EH and the fluctuating clinical symptoms in MD.[23–25] Furthermore, the advent of magnetic resonance imaging of the inner ear fluid spaces, which now enables the *in vivo* detection of EH in clinical patients[26,27], demonstrated that EH is associated with a broader range of (non-Ménière's) otologic symptoms and syndromes[24,25,28,29], and is even present in a considerable number of cases with no otologic symptoms at all.[30–32] This substantiates previous histopathological findings.[25]

Additionally, migraine-associated vertigo (vestibular migraine[33]) constitutes a newly recognized, non-otologic disease concept that shows considerable clinical overlap with MD. Some authors even propose a common etiopathology of the two syndromes.[34–36]

The initial disease concept of MD is now considered outdated. New, diverse concepts regarding the pathophysiology and the clinical phenotypes that are associated with EH are emerging instead. Whether ES pathologies play a role in the etiology of, or at least some of, these conditions remain to be explored.

We approached these questions in a comprehensive human temporal bone study.[37] We took into account (1) the different previously suspected etiologies of EH (idiopathic vs. secondary[38]), (2) the different clinical symptomatologies that are associated with EH (Ménière's vs. non-Ménière's or no otologic symptoms), and (3) the different anatomical portions of ES, including its intraosseous portion (iES, located within the vestibular aqueduct). Additionally, for the first time, we looked at its extraosseous portion (eES, located in the dura of the posterior temporal bone surface).

Differential evaluation of the structural integrity of the epithelium in all ES portions was of particular interest, since no previous histopathology study on MD had done so. The analysis showed that the epithelium in the eES portion exhibited degenerative changes in 54.2 percent of the cases with idiopathic EH (EH due to no known cause[38]) from which 95.8 percent had a clinical diagnosis of MD (Figure 1A and 2).

From the remaining cases with idiopathic EH, 37.5 percent exhibited a developmentally hypoplastic (underdeveloped) ES, all with a clinical diagnosis of MD (Figure 1B and 2). In contrast, overall cases with secondary EH (EH associated with a known otologic disease[38]) did not exhibit degenerative changes of the eES epithelium and had no clinical diagnosis of MD (Figure 2).

We concluded that both pathologies, degeneration and hypoplasia, lead to the structural loss or absence of the eES portion. They are also consistently associated with idiopathic EH and

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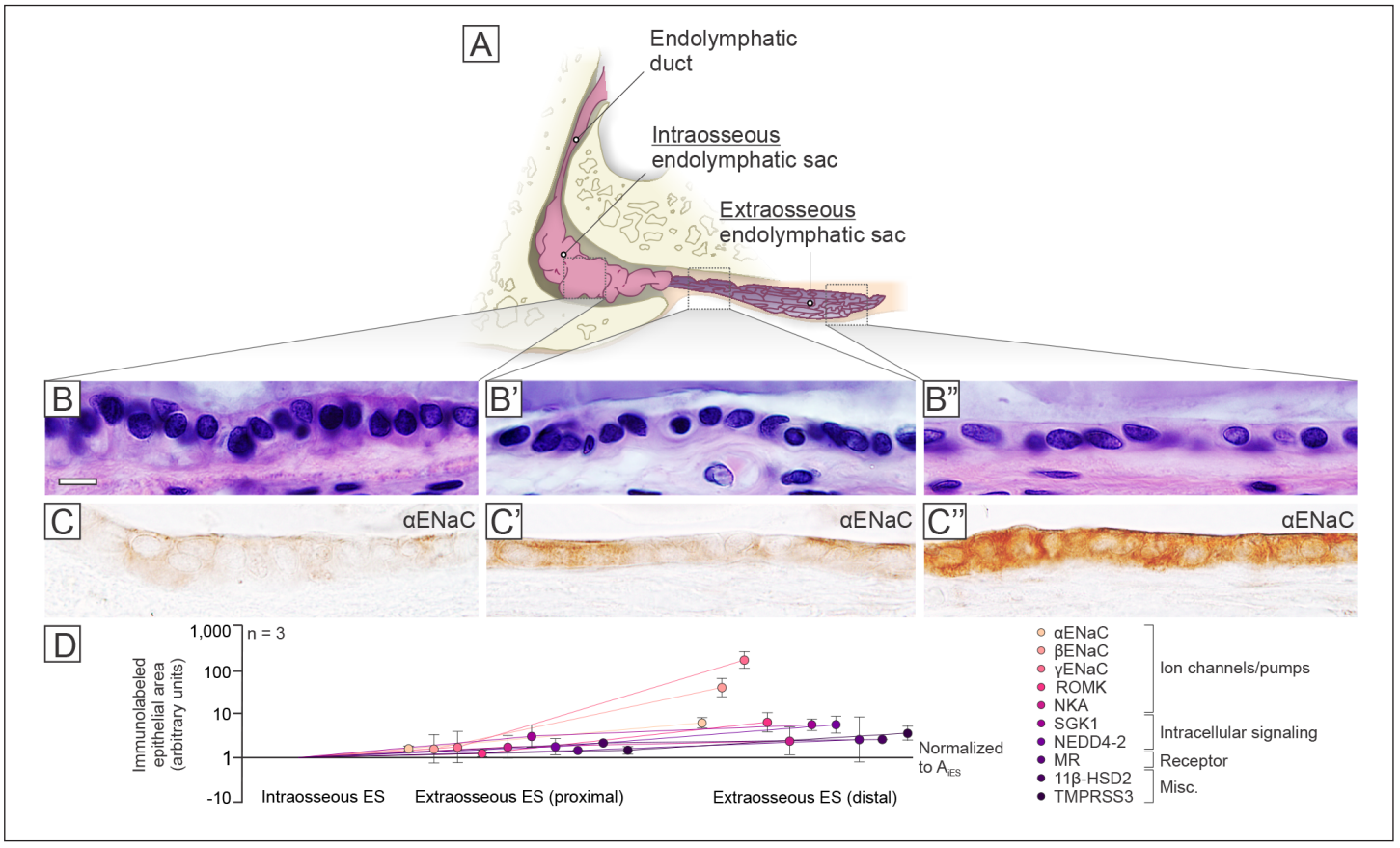

Figure 3. Proximal-to-distal immunolabeling gradients of proteins involved in aldosterone-regulated sodium transport in the normal human ES epithelium. Schematic representation of the normal human endolymphatic duct and ES **(A)**. Changing epithelial morphology (hematoxylin-eosin staining) and gradually increased immunolabeling for the alpha-subunit of the epithelium sodium channel (αENaC) from the intraosseous **(B, C)** to the extraosseous (proximal, **(B', C')**; distal (**B'', C''**)) ES portions. A gradually increasing proximal-to-distal immunolabeling in the ES epithelium was demonstrated for all molecular determinants involved in aldosterone-regulated sodium transport **(D)**. *Adapted from (37), according to the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), under which the original article is distributed.*

a clinical MD diagnosis, but were not found in the inner ears with secondary EH or no EH. We demonstrated that the ES pathologies that are consistently associated with idiopathic EH and had a clinical history of MD, despite being of different etiologies, affected the same anatomical site within the inner ear.

We then raised the question whether the eES epithelium has a distinct function in endolymphatic fluid regulation. Based on the close structural similarities between the ES and the renal nephron on the cellular[39–41] and molecular[42,43] level, we hypothesized spatial differences in ion transport functions along the ES epithelium, analogous to the functionally segmented nephron system.[44] In line with this hypothesis, using immunohistochemistry in the normal mouse and human ES, we identified molecular determinants of an aldosterone-regulated sodium transport mechanism in the eES epithelium (Figure 3). The same molecular mechanism is known to be localized in the distal collecting duct epithelium of the renal nephron, where it has critical functions for the fine-tuning of the whole body fluid homeostasis.[45]

Finally, in the temporal bone specimens from human cases with the ES pathologies mentioned above, we found the expression of those ion transport proteins in the eES epithelium to be strongly diminished or absent due to the degenerative (Figures 4A and B) and hypoplastic (Figures 4C and D) pathologies, respectively. From those findings, we concluded that the eES harbors distinct ion transport functions that are probably crucial for endolymphatic fluid homeostasis. We also found that these ion transport mechanisms are regulated on a systemic level via the mineralocorticoid axis (e.g., by changes in salt consumption) and that degenerative loss and hypoplastic underdevelopment lead to the loss of these eES-specific ion transport functions, and thereby precipitate the formation of EH—and possibly predispose for the clinical symptoms of MD.

These described findings raise further questions. In our ongoing work, we are using basic animal studies to investigate the etiology and pathophysiological implications of those ES pathologies on inner ear fluid homeostasis, as well as clinical temporal bone imaging studies to develop methods for the delineation and

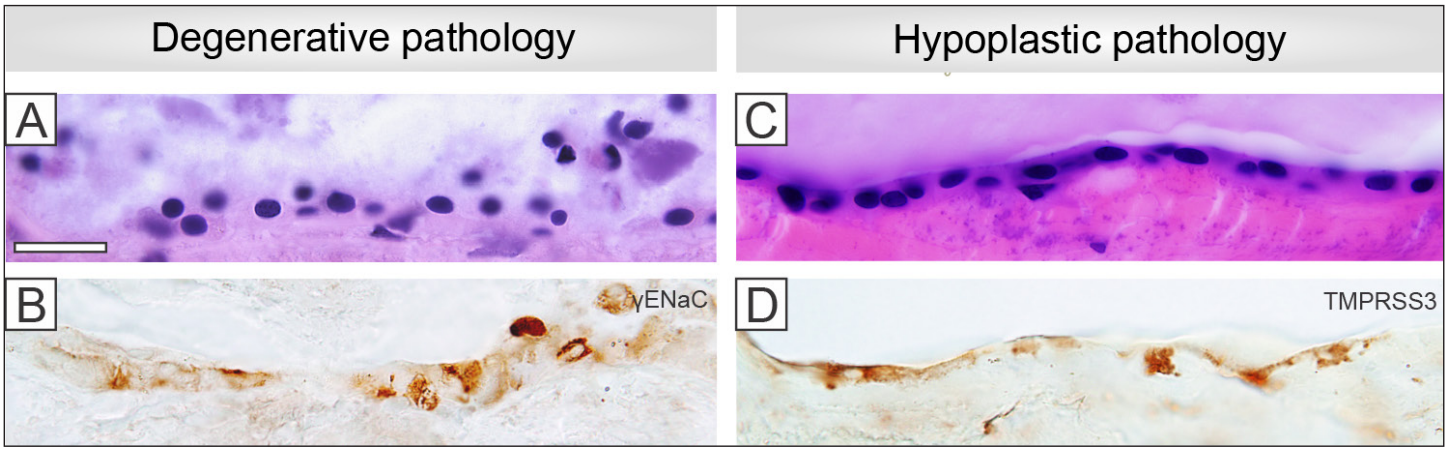

Figure 4. Loss/absence of proteins involved in aldosterone-regulated sodium transport in the degenerated **(A** and **B)** and hypoplastic **(C** and **D)** ES epithelium in patients with idiopathic endolymphatic hydrops and a history of MD. *Adapted from (37), according to the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), under which the original article is distributed.*

phenotypic characterization of those ES pathologies in clinical patients.[46] Our results, so far, indicate that the ES pathologies are associated with clinically distinct subgroups of MD patients, suggesting the existence of clinically definable and possible predictable "endotype-phenotype patterns."[47] Animal models will be helpful to pinpoint the molecular determinants in the eES epithelium, whose loss is most critical for endolymphatic fluid homeostasis, in order to direct future efforts to restore those functions in MD patients. ●

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UPCOMING EVENTS

ASHA
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