

Sketches of Otohistory

Part 9: Presby[a]cusis

Jochen Schacht Joseph E. Hawkins

Kresge Hearing Research Institute, University of Michigan, Ann Arbor, Mich., USA

Impaired hearing in old age probably afflicted our earliest ancestors – or at least those few who lived long enough to experience it. Ancient writers seem to have accepted it as one of the normal ‘woes that wait on age’, but somehow celebrated characters like the Bible’s Methuselah and Homer’s Nestor seem never to have complained of deafness, nor were they even described as hard of hearing. Hippocrates found deafness more frequently among his elderly patients, in contrast to effusion which he found more commonly among children. Cicero, in his essay *De Senectute* (‘On Old Age’), mentioned loss of the senses but did not specify diminished hearing as one of the possible excuses for a Roman’s withdrawal from an active civic, military, or literary career. Celsus had much to say about the diagnosis, treatment, and effects of otitis media on hearing, but he apparently did not conceive of aging as another potential cause of injury to the ears. In *The Comedy of Errors*, Shakespeare’s elderly merchant Aegeon complains of his own ‘dull deaf ears a little use to hear’. Thus, for centuries, diminished hearing has been accepted as an inevitable accompaniment of old age, as indeed it still appears to be. Some medical mysteries show little change over time.

A or No A?

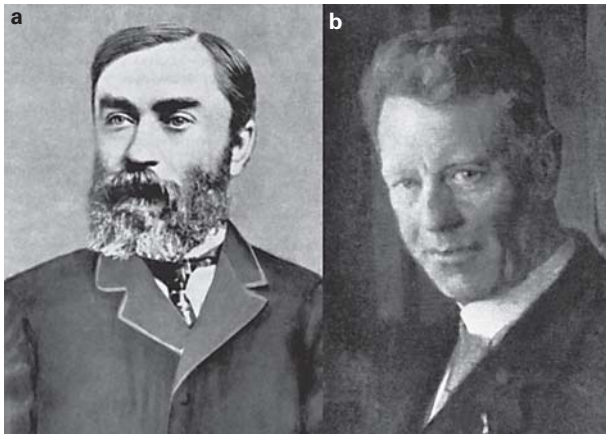
It was the New York otologist St. John Roosa (fig. 1) who first pointed out the diminished hearing of the elderly as a condition worthy of medical attention. In the

brief paper he presented at the meeting of the American Otological Society [St. John Roosa, 1885], he cited a case from his own practice, and proposed the name *presbykousis*, coined from the Greek *πρέσβυς*, ‘old man’, and *ἀκούειν*, ‘to hear’. He explained that for the sake of euphony, he had dropped the letter ‘a’ from his new addition to the medical vocabulary. That curious, arbitrary choice has caused minor transatlantic disagreements among authors and editors ever since. (We favor restoration of the missing letter.) The derivation from the masculine *πρέσβυς* may not be politically correct but it has found some belated justification in the fact that women are less prone to suffer from age-related hearing loss.

Early Attempts to Understand the Aging Ear

Zwaardemaker [1891] (fig. 1) of Utrecht reported the first systematic study of the ability of children and adults of various ages to hear the high-frequency sounds of the Galton whistle. He showed that as age increased that ability was gradually lost, and he even claimed that armed with the Galton whistle he could easily determine a person’s age. Later, audiometric studies fully confirmed what Zwaardemaker called the ‘presbycusis law’.

Like St. John Roosa [1885], Zwaardemaker [1891] was inclined to attribute the loss either to changes in the labyrinth or to a reduced bone conduction of sound. Otopathological investigations on the other hand have given a less clear picture of the anatomical changes that are re-



PRESBYACOUSIE (du gr. *presbus*, vieillard, et *acouein*, entendre). — Lésion sénile de l'ouïe, caractérisée par une meilleure audition des paroles dites de loin et de la voix chuchotée que des paroles dites de près et de la voix haute. Elle est due à un affaiblissement des muscles accommodateurs du tympan pour les sons.

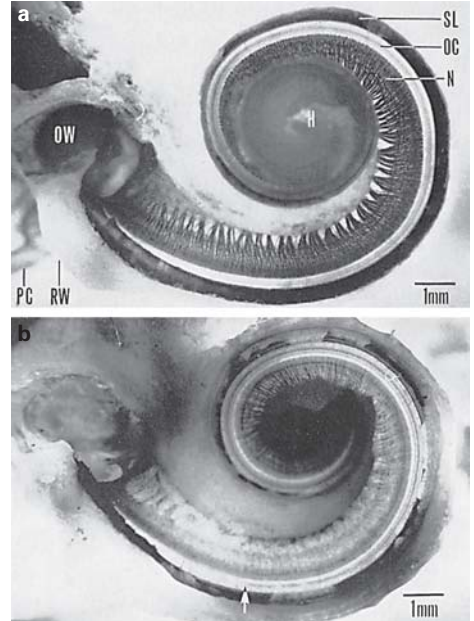
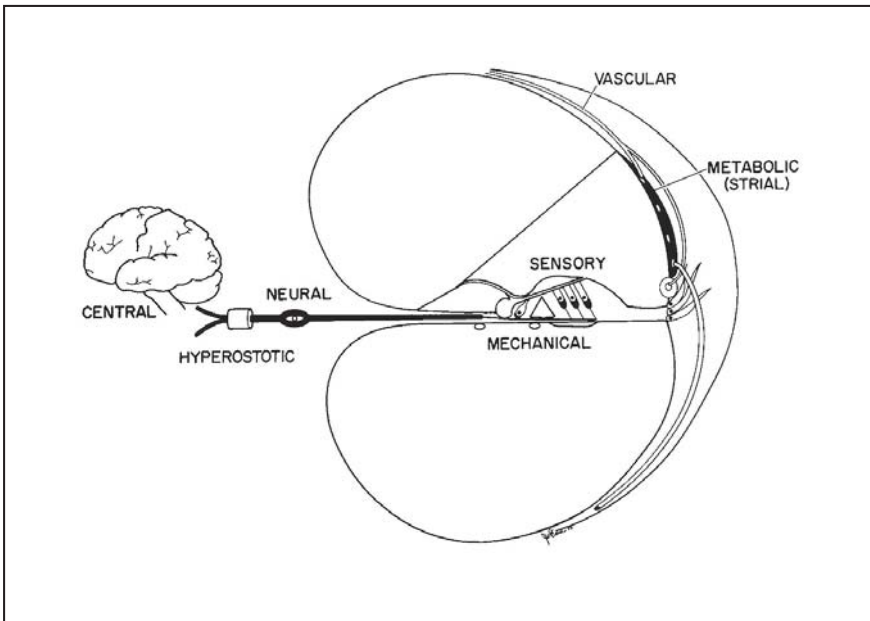


Fig. 1. The fathers of presbycusis. **a** The New York otologist St. John Roosa. From Politzer [1913]. **b** The Utrecht physiologist H. Zwaardemaker. From Murchison [1930].

Fig. 2. This entry from an old French encyclopedia plainly places the blame for presbycusis on the middle ear muscle.

Fig. 3. Schuknecht's [1964] classification of presbycusis. Reprinted with permission.

Fig. 4. Degeneration in the aging cochlea. **a** Normal-appearing cochlea from a 25-year-old female. OW = Oval window; RW = round window; PC = posterior canal; SL = spiral ligament, mostly dissected away; OC = organ of Corti seen as a dark band; N = myelinated radial and intralaminar spiral fibers; H = helicotrema. **b** The cochlea from a 72-year-old male. The apical turn and a part of the middle turn have been removed. There is loss of nerve fibers and hair cells throughout the cochlea. From Johnsson and Hawkins [1972]. Reprinted with permission.

responsible for the hearing loss. An investigation by Crowe et al. [1934] revealed atrophy of the organ of Corti and the auditory nerve in the basal cochlear turn and Guild [1932] showed the relation between histopathological changes in the inner ear and the acuity and range of human hearing as measured with the audiometer. In such studies, however, it is generally difficult or impossible to distinguish the changes caused by aging from those asso-

ciated with genetic defects, noise exposure, drug ototoxicity, or infectious disease. On the basis of very few cases, Mayer [1920] attributed 'presbycusis proper' to rigidity of the basilar membrane caused by its calcification, but he also recognized 'degenerative changes associated with the diseases of old age'. Von Fieandt and Saxen [1937]

wrote of two forms of cochlear changes, 'senile atrophy' of the spiral ganglion cells and 'angiosclerotic degeneration of the inner ear', with changes in its capillaries and degeneration of its hair cells and cochlear nerve fibers. Reflecting the uncertainty of the origins of presbycusis, weakened middle ear muscles were also invoked (fig. 2).

Schuknecht [1964], on the basis of his studies of histopathological changes in the temporal bones of aged cats as well as humans, postulated four distinct types of presbycusis: (1) sensory, with hair cell loss and secondary neural degeneration; (2) neural, with primary degeneration of cochlear neurons; (3) metabolic, or stria, with atrophy of the stria vascularis and a flat audiogram of hearing loss, and (4) mechanical, or inner ear conductive, with changes in the basilar membrane affecting its mechanical properties (fig. 3). His system of classification proved useful as a basis for discussion, and has since been modified and expanded [Ohlemiller, 2004].

Nerves or Cells: Which Come First?

One of the controversial issues in early discussions of presbycusis was the primary site of cochlear degeneration. Fleischer [1956] concluded that only the loss of cells from the spiral ganglion was characteristic of aging, while others blamed the cochlear blood supply to cause neural degeneration. Some clarification came from histopathological studies of whole-mount ('surface') preparations of cochlear tissues from microdissected human temporal bones [Bredberg, 1968; Johnsson and Hawkins, 1972] and electron or scanning microscopic investigations [e.g., Wright et al., 1987]. Most of the specimens showed a sensorineural degeneration that was most severe in the lower basal turn. The degeneration of nerve fibers seemed secondary to hair cell loss (fig. 4). In many specimens, there was devascularization and atrophy of the stria and the spiral ligament, especially in the upper turns. Not infrequently, capillaries supplying the basilar membrane had disappeared, leaving avascular channels. Because of these findings, Johnsson and Hawkins [1972] postulated the occurrence of an avascular type of presbycusis, affecting the stria and spiral ligament but not necessarily correlated with hair cell loss. There were no instances of exclusively neural degeneration, and no thickening or other change in the basilar membrane. If inner ear conductive ('mechanical') presbycusis exists, it must be extremely rare.

The existence of a central type of presbycusis, with neural changes at various levels of the ascending auditory

system, was first supported by studies using binaural speech audiometry [Matzker, 1958], and by neuropathological examination of the auditory pathways in the brains of elderly patients [Hansen and Reske-Nielsen, 1965].

From Men to Mice: Animal Models of Presbycusis

In the course of a lifetime of 60 years or more, the human ear is exposed to such a variety of insults by noise, ototoxic agents, genetic, dietary, cardiovascular or other disease conditions that 'pure' presbycusis may be merely a hypothetical concept, never to be found in the real world of human otology. The studies of Rosen et al. [1962] in remote areas of Sudan where detrimental environmental influences should have been minimal perhaps came closest to this ideal. Even there, they found signs of age-related loss of hearing acuity. Such changes, however, were vastly accelerated in a 'modern' environment of noise and diet.

It should be possible to observe an unadulterated presbycusis in noise-protected laboratory animals, but their pattern of presbycusis seems never to be identical to the human variety. In aged macaques that had lived their entire lives in strictly controlled laboratory conditions, the only presbycusis changes seen were of the sensorineural type, and they were confined to the extreme basal and apical ends of Corti's organ [Hawkins and Johnsson, 1985]. Aging mice, rats and gerbils are other models that reflect various aspects of human presbycusis changes. Mice are holding an advantage over other species because of the availability of genetic information, tools for molecular biology and transgenic and knockout animals [for reviews, see Willot et al., 2001; Gratton and Vazquez, 2003].

How Cells Age: A Radical View

Today, we are still far from having established an all-encompassing hypothesis of how our ears age and lose their function. Such a hypothesis, in fact, may not ever be found because of the multifaceted nature of presbycusis that may include genetic predisposition, environmental influences, in addition to cellular aging processes. Recent studies on the molecular level have focused on presbycusis as one manifestation of general aging processes. Studies in the nematode *Caenorhabditis elegans* and in other animal models have established a clear con-

tribution of reactive oxygen species to the demise of cells and tissues. Concentrations of free radicals increase in essentially all tissues during the lifetime of an organism, and mutations leading to life span extension typically led to resistance to multiple forms of stress including oxidant stress. Such findings gave considerable boost to the free radical theory of aging [Harman, 1956], which has now become one of the best-accepted theories.

Free radicals are nature's equivalent of wear and tear at a cellular level. As we breathe, we produce reactive oxygen species partly as byproducts of metabolism, and partly as direct participants in biological reactions. Without such reactive oxygen species, homeostatic mechanisms in our bodies would not be possible, because these agents fulfill a crucial role in signaling pathways and biosynthetic and degradative reactions. On the other hand, not all is well with free radicals since they are a chemically highly aggressive species that can adversely react with just about any constituents of our cells. Life of a cell is then a balancing act between producing these free radicals and keeping them in check by endogenous antioxidant systems. If this process gets out of kilter by external influences, such as noise trauma or drug exposure, cell damage and eventual cell death may ensue. The lifelong insult of free radicals may just be all that is needed to tip the balance in old age.

But, is there evidence that the cells in our inner ear age by a similar mechanism? Certain deletions in mitochondrial genetic materials are a telltale sign of free radical attack, and they indeed increase with age in the cochlea of aging animals [for recent reviews on this topic, see Willott et al., 2001; Seidman et al., 2002; Pickles, 2004].

Green Tea and Red Wine: Can We Slow Down Nature?

Fortunately, the balance between free radicals and our bodies' defenses can be manipulated. These manipulations do not have to occur at the level of our genes but, quite simply, in our diet. Both a caloric reduction (which decreases the metabolic rate and free radical formation) and the nutritional intake of natural antioxidant-rich foods (or, perhaps more conveniently, antioxidant supplements) strengthen cellular resistance and survival.

Indeed, miracle cures for presbycusis do exist – if we wish to believe the claims that abound on the Internet and in popular publications. The so-inclined presbycusis gardener may want to plant Saint John's wort, *Ginkgo biloba*, garlic, rosemary or periwinkle, while the urban

sufferer could resort to a wide variety of hearing pill concoctions, some of which may represent modern examples of otoquackery. Nevertheless, many pathologies have a free radical component, and antioxidant therapy is part of the clinical regimen in such cases of ischemic attacks, some neurodegenerative disorders or radiation damage. In the inner ear, the actions of noise and drugs can be efficiently attenuated in animal models by supplementation with antioxidants. This evidence, together with our general knowledge of the aging process, would suggest that a Spartan diet with a generous intake of green tea and red wine should protect not only from an early death, but also from presbycusis. While more appealing than many other dietary regimens, such a lifestyle, unfortunately, may not guarantee an auditory well-being in old age. Mitochondrial lesions in the ear can indeed be held at bay in a diet of caloric restriction, but supplementation with individual antioxidants provided some, but not a striking protection from age-induced threshold shifts [Seidman et al., 2002].

The sum of our knowledge emphasizes two points. On the one hand, there may be reason to look closely at free radicals and antioxidants in aging-induced hearing loss. On the other hand, the limited success of any therapy to date reminds us that presbycusis is not a simple condition that can be explained by a single mechanism.

References

Citations in this article emphasize the earlier literature and we apologize for having to neglect many of our colleagues' contributions. Several articles reviewing the past literature can be found in Han and Coons [1979]. Recent reviews include Willott et al., [2001], Jennings and Jones [2001], Gratton and Vazquez [2003], Ohlemiller [2004], and Pickles [2004].

References

- Bredberg G: Cellular pattern and nerve supply of the human organ of Corti. *Acta Otolaryngol* 1968;Suppl 236:1.
- Crowe S, Guild S, Polvogt L: Observations on pathology of high-tone deafness. *Bull Johns Hopkins Hosp* 1934;54:315.
- Fleischer K: Histologische und audiometrische Studie über altersbedingten Struktur- und Funktionswandel des Innenohres. *Arch Ohrenheilkd* 1956;170:142–167.
- Gratton MA, Vazquez AE: Age-related hearing loss: current research. *Curr Opin Otolaryngol Head Neck Surg* 2003;11:367–371.
- Guild SR: Correlations of histologic observations and the acuity of hearing. *Acta Otolaryngol* 1932;17:207–249.
- Han SS, Coons DH: Special Senses in Aging: A Current Biological Assessment. Ann Arbor, Institute of Gerontology, University of Michigan, 1979.
- Hansen CC, Reske-Nielsen E: Pathological studies in presbycusis. Cochlear and central findings in 12 aged patients. *Arch Otolaryngol* 1965;82:115–132.
- Harman D: Aging: a theory based on free radical and radiation biology. *J Gerontol* 1956;11:296–300.
- Hawkins JE Jr, Johnsson LG: Otopathological changes associated with presbycusis. *Semin Hear* 1985;6:115–133.
- Jennings CR, Jones NS: Presbycusis. *J Laryngol Otol* 2001;115:171–178.
- Johnsson LG, Hawkins JE: Sensory and neural degeneration with aging, as seen in microdissections of the human inner ear. *Ann Otol Rhinol Laryngol* 1972;81:179–192.
- Matzker J: Ein binauraler Hörsynthese-Test zum Nachweis zerebraler Hörstörungen. Stuttgart, Thieme, 1958.
- Mayer O: Das anatomische Substrat der Altersschwerhörigkeit. *Arch Ohrenheilkd* 1920;105:1–13.
- Murchison C (ed): *The History of Psychology in Autobiography*. Worcester, Clark University Press, 1930, vol 1, p xvii.
- Ohlemiller KK: Age-related hearing loss: the status of Schuknecht's typology. *Curr Opin Otolaryngol Head Neck Surg* 2004;12:439–443.
- Pickles JO: Mutation in mitochondrial DNA as a cause of presbycusis. *Audiol Neurootol* 2004;9:23–33.
- Politzer A: *Geschichte der Ohrenheilkunde*. Stuttgart, Enke, 1913, vol 2, Tafel XXIX.
- Rosen R, Bergman M, Plester D, El-Mofty A, Satti MH: Presbycusis study of relatively noise-free population in the Sudan. *Ann Otol* 1962;71:727–743.
- Schuknecht H: Further observations on the pathology of presbycusis. *Arch Otolaryngol* 1964;80:369.
- Seidman MD, Ahmad N, Bai U: Molecular mechanisms of age-related hearing loss. *Ageing Res Rev* 2002;1:331–343.
- St John Roosa DB: Presbycusis. *Trans Am Otol Soc* 1885;3:449–460.
- Von Fieandt H, Saxen A: Beiträge zur Histologie der stria vascularis und der prominentia spiralis bei Säugern (Hund und Mensch). *Z Anat Entwicklungsgesch* 1937;106:424.
- Willott JF, Hnath Chisolm T, Lister JL: Modulation of presbycusis: current status and future directions. *Audiol Neurootol* 2001;6:231–249.
- Wright A, Davis A, Bredberg G, Ulehlova L, Spencer H, Bock G, Felix H, Iurato S, Johnsson LG, Pauler M: Hair cell distributions in the normal human cochlea. *Acta Otolaryngol* 1987;Suppl 444:1–48.
- Zwaardemaker H: Der Verlust an hohen Tönen mit zunehmendem Alter. *Arch Ohrenheilkd* 1891;32:53–56.