Sound Wave Symposium, San Diego, 2018

SNHL- Understanding the Cause Is Important for Treatment

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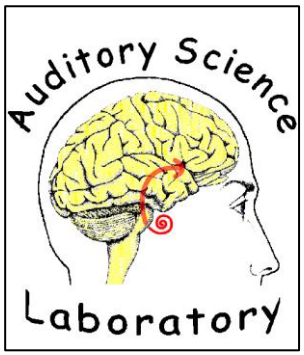

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An evolution of thought?

University of Toronto, Otolaryngology – HNS, Grand Rounds March 2018

Making Clinical Sense of New Knowledge on Inner Ear Pathology

Mediterranean Society for Otology and Audiology, Jerusalem May 2018

The pathogenesis of hearing loss; things we can learn from animal models

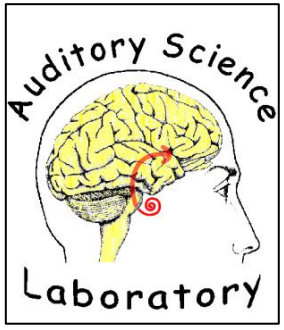
Sound Wave Symposium, San Diego, October 2018

SNHL- Understanding the cause is important for treatment

Annual meeting CAA 2018, Niagara Falls, October 2018

Towards an Improved Sub-Classification of SNHL Spectrum Disorder

SNHL- Understanding the Cause is Important for Treatment



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Learning Objectives:

To explore the anatomical damage to the cochlea and associated functional deficits in a range of animal models of sensorineural hearing loss (SNHL).

To provide a greater understanding of different sub-types of SNHL based on structural deficits and on etiology.

To encourage the development and clinical use of a sub-classification scheme for SNHL

My own studies of animal models of hearing loss include:

- Drug ototoxicity
- Acoustic Trauma
- Endolymphatic hydrops
- Cochlear hypoxia
- Autoimmune disease
- Cochlear ablation
- Genetic mutations
- Auditory deprivation
- Ageing
- Infection

These all result in what we call "sensorineural hearing loss" but are very different in terms of anatomical lesions and functional impairment. These differences are largely depending on ETIOLOGY

OVERALL THESIS: If we pay more attention to etiology we can distinguish classes or types of SNHL. This in turn will narrow our focus on treatment and rehabilitation strategy and provide more accurate prognosis

Cochlear areas of maximum vulnerability

Stria vascularis
hypoxia, ischemia
loop diuretics (Lasix)
metabolic inhibitors
old age
viral infection
genetic mutation
(sometimes reversible)

Haircells
ototoxic drugs
e.g. aminoglycosides
old age
acoustic trauma
genetic mutation
(not reversible)

Inner haircell synapse
some drugs e.g. aspirin
chronic hypoxia
anti cancer drugs – carboplatin
noise exposure
(sometimes there is recovery)

Spiral ganglion cells
loss of inner haircells
Glutamate excitotoxicity
Sensorimotor neuropathy
Hidden hearing loss?

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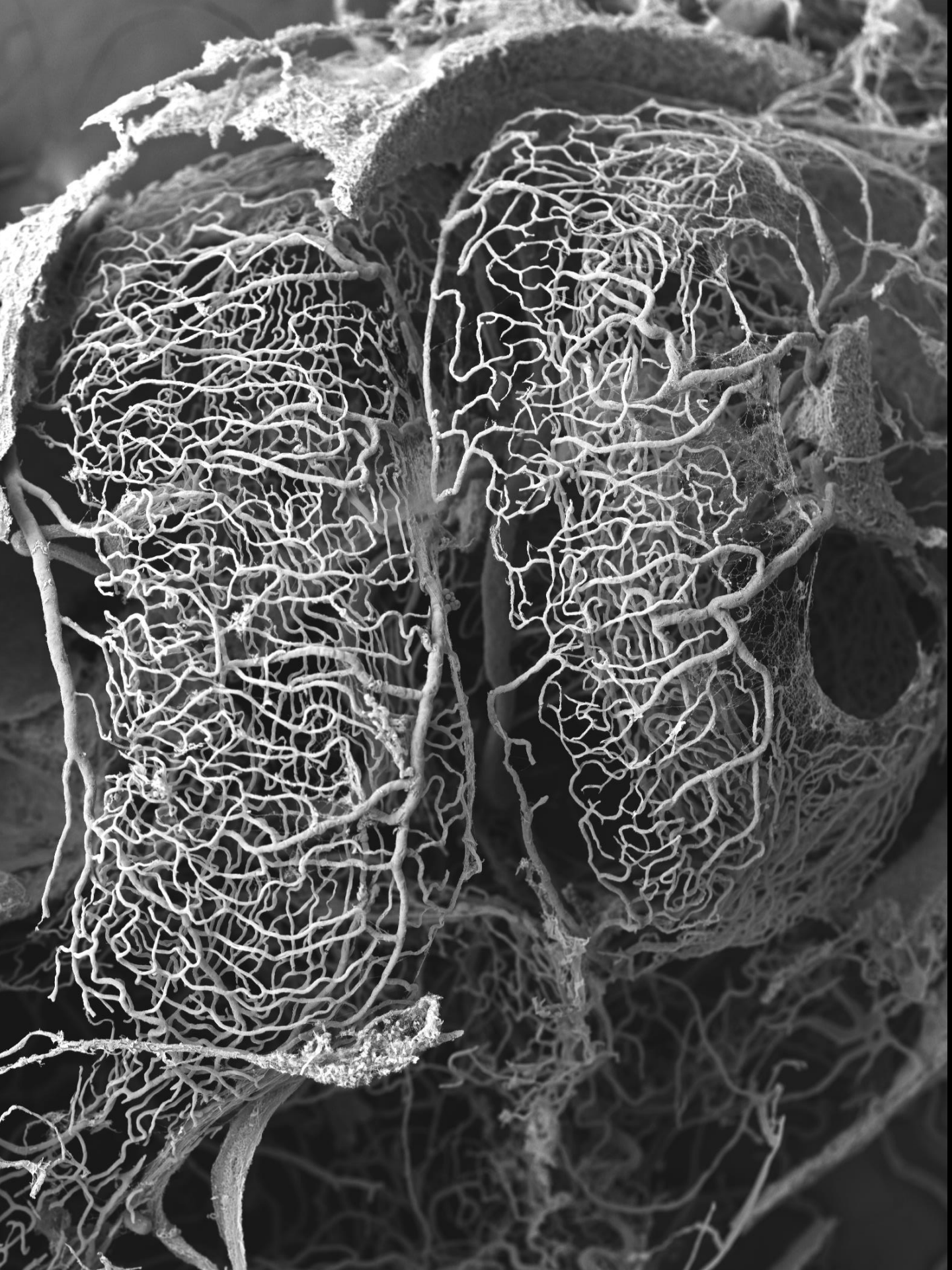
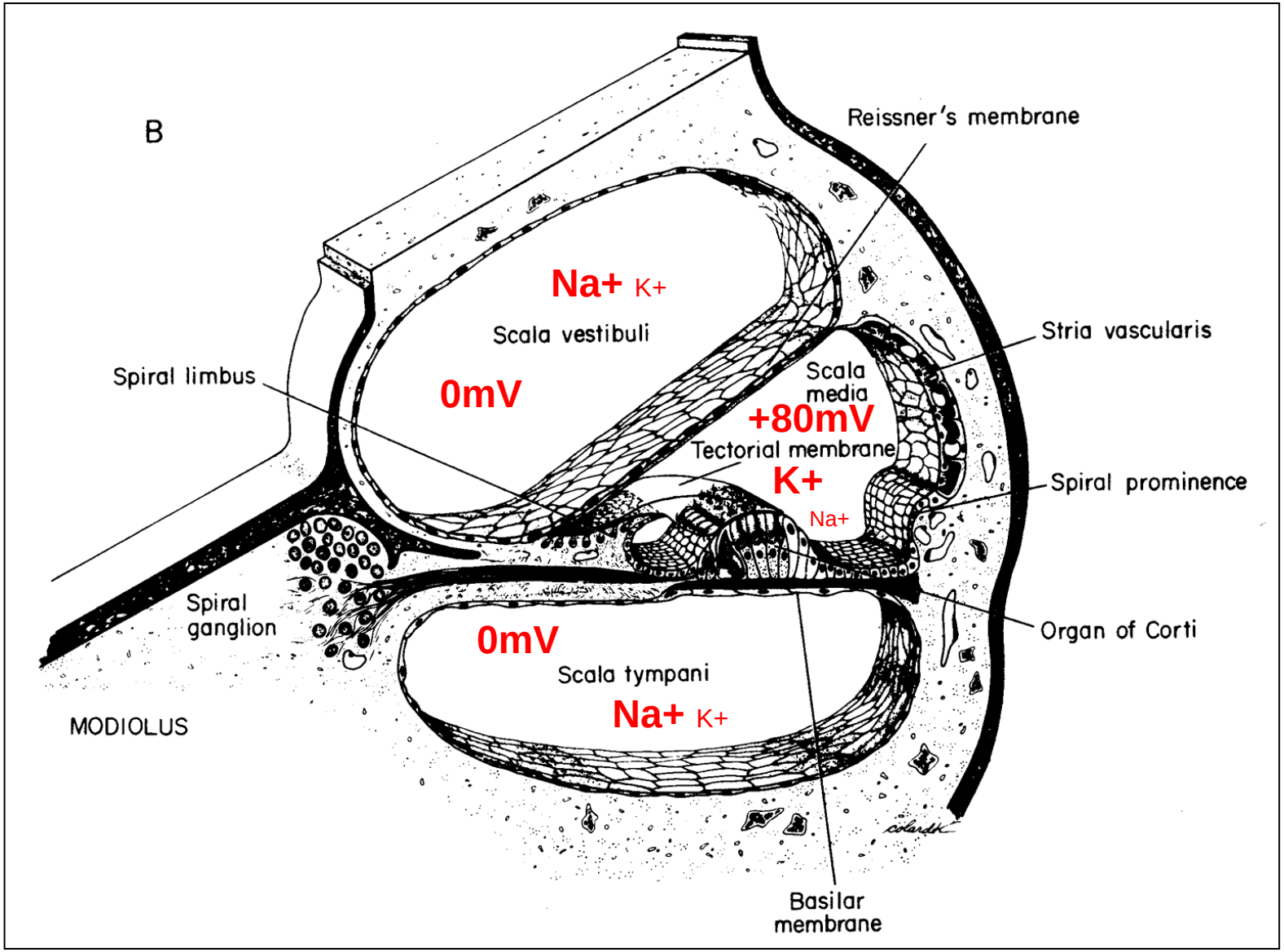
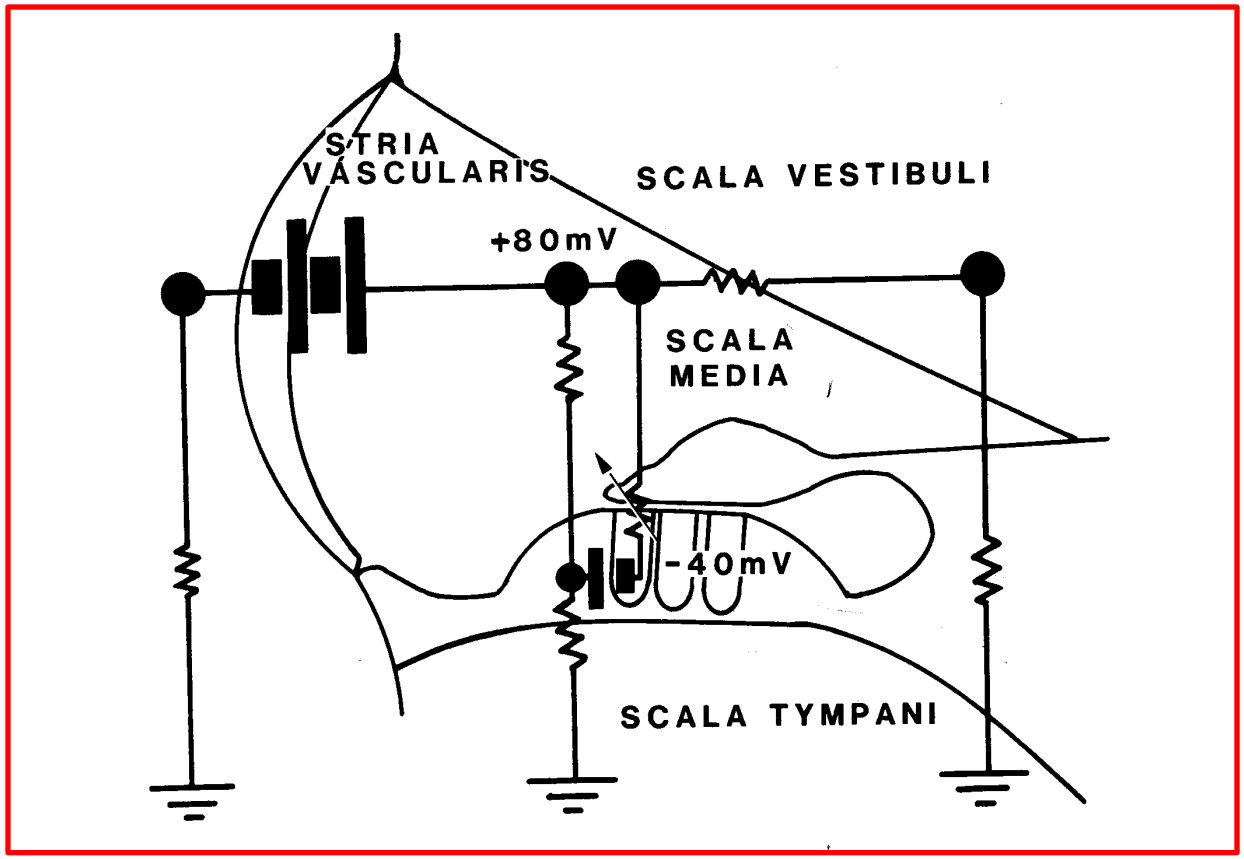


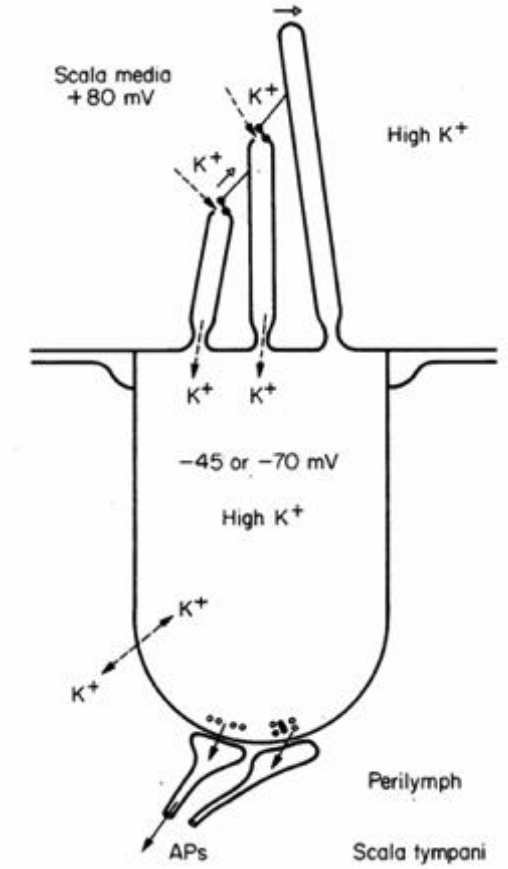
CARRARO M, PARK A, **HARRISON RV**. (2016) Partial corrosion casting to assess cochlear vasculature in mouse models of presbycusis and CMV infection. Hearing Research. 332 95-103.

The stria vascularis is the power-house of the cochlea



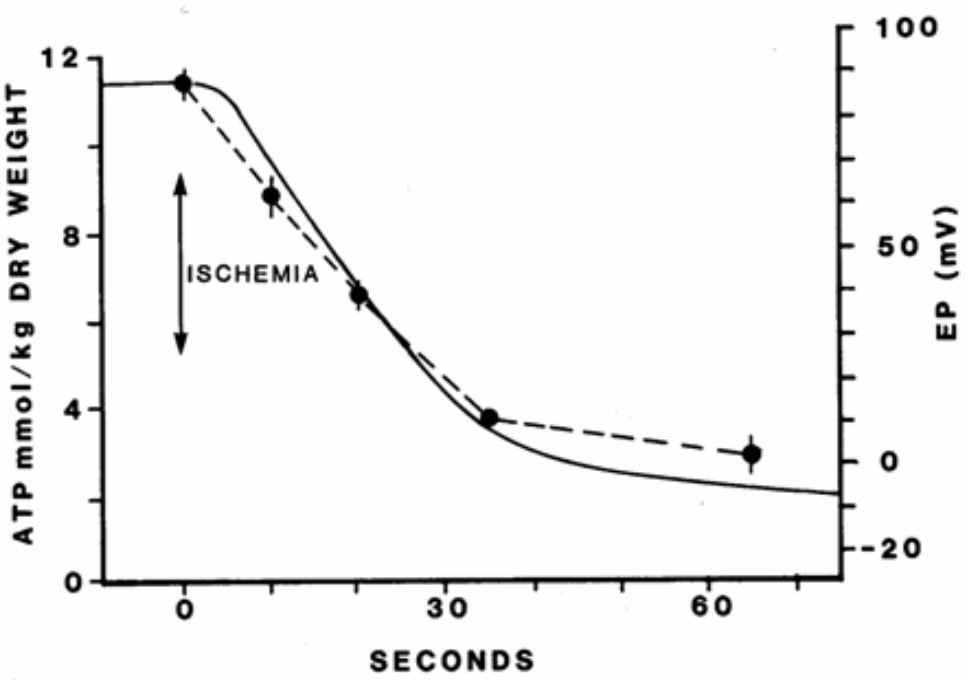
Impairment of strial function reduces electrical driving force for haircell activation



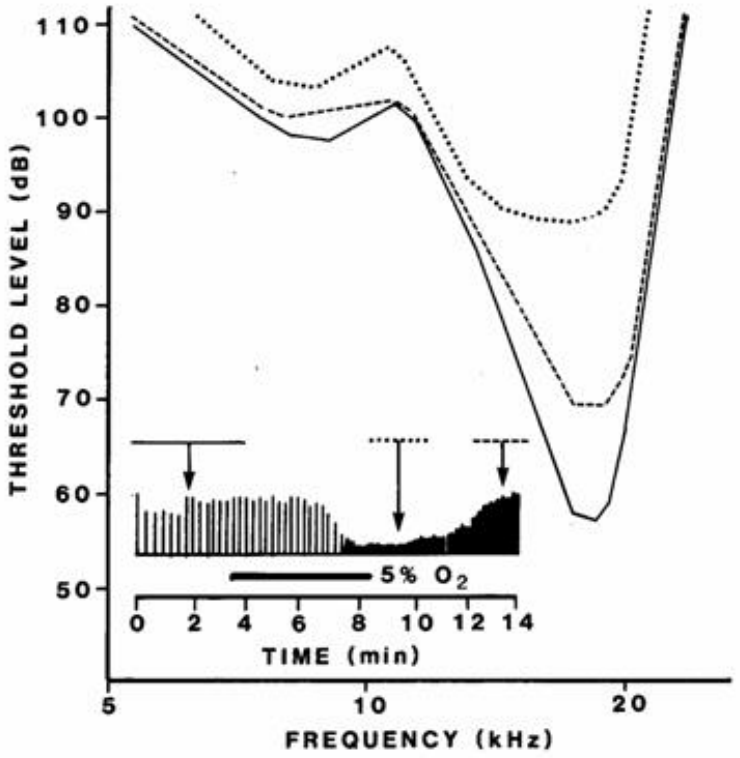


Standing cochlear potentials Davis' battery theory

Effects of hypoxia or ischemia on the strial function and the consequences on cochlear function

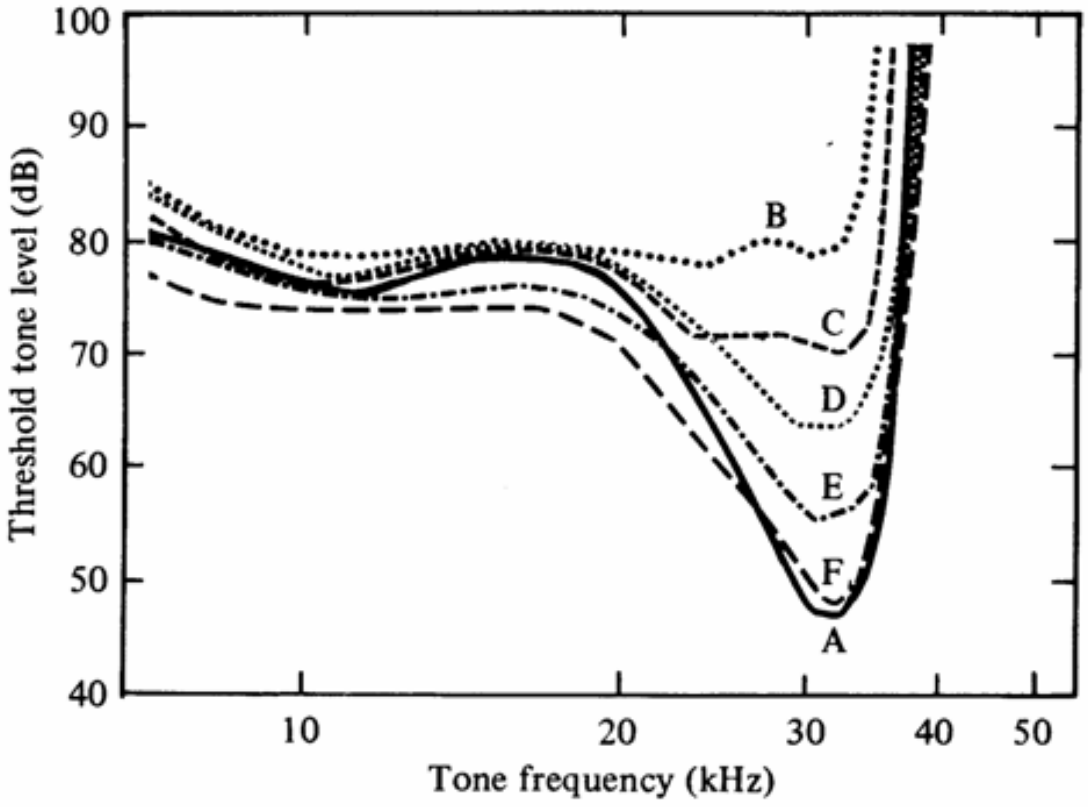


Thalmann et al. (1977) Noxious effects upon cochlear metabolism. Laryngoscope 87:699



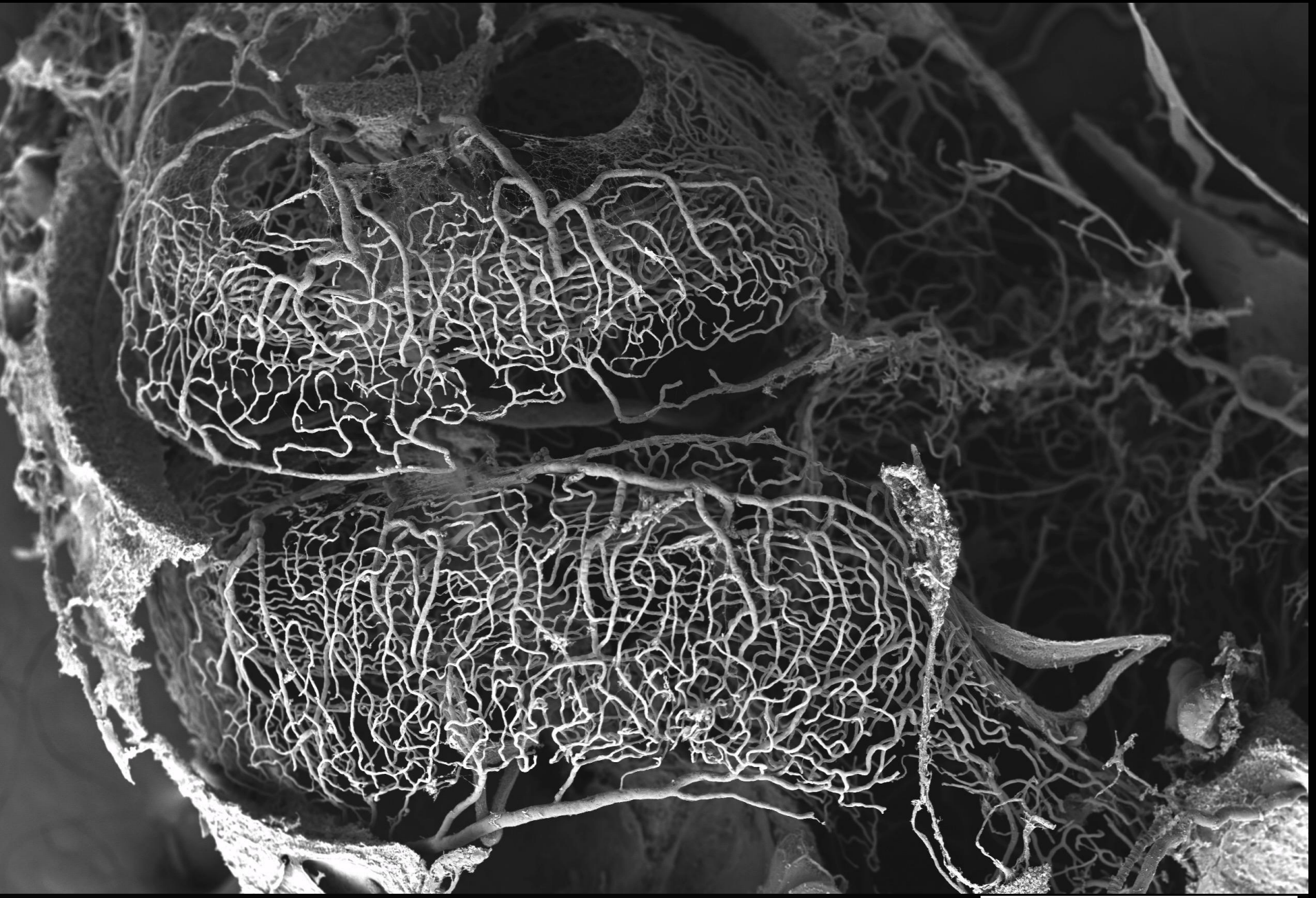
Evans (1974) The effects of hypoxia on the tuning of single nerve fibers. J Physiol. 238:65

Reversible effects of furosemide (lasix) on strial function

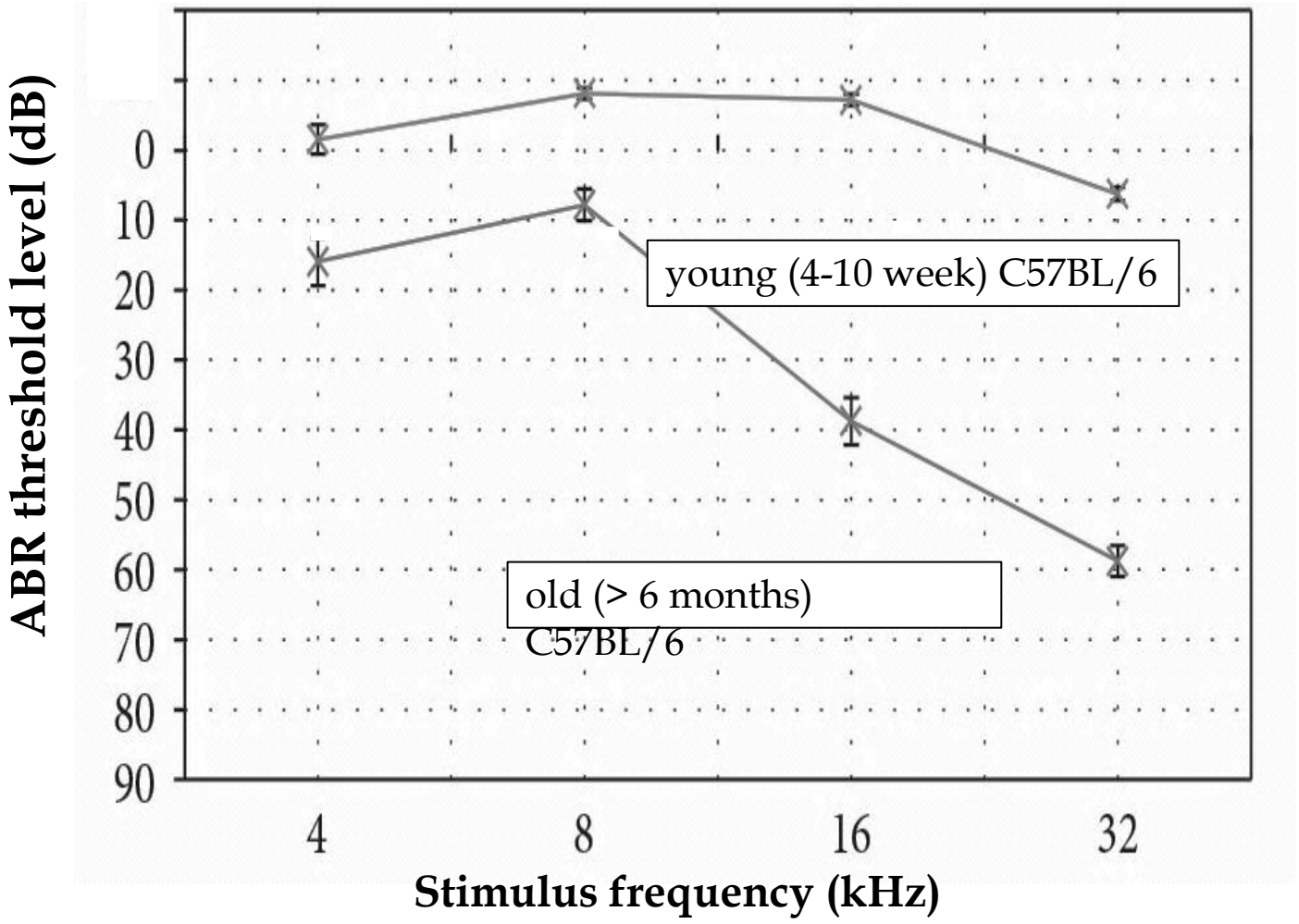


Threshold elevation (B) and subsequent recovery (C-F) of cochlear fibre responses

Evans and Klinke (1982) The effects of intracochlear and systemic furosemide on the properties of single cochlear nerve fibres in the cat. J Physiol 331:409

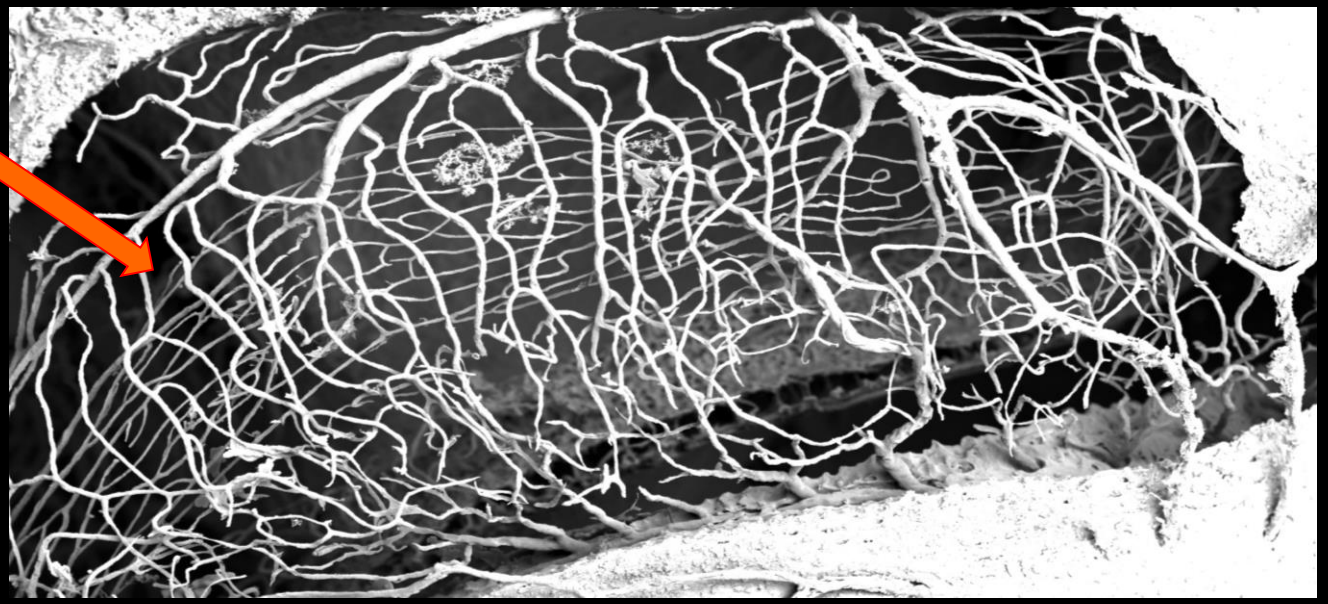

500um

ABR audiograms in a mouse model of presbycusis

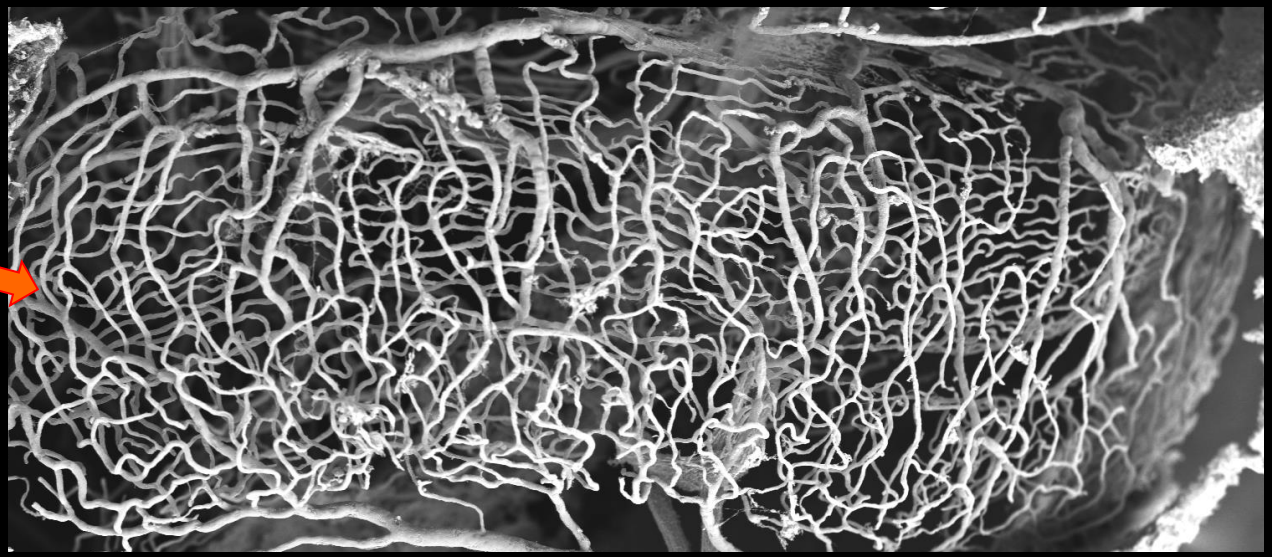


CLINKARD D, AMOODI H, KANDASAMY T, GREWAL AS, CHEN S, QIAN W, CHEN JM, HARRISON RV, LIN VY. (2013) Changes in the cochlear vasculature and vascular endothelial growth factor and its receptors in the aging C57 mouse cochlea. ISRN Otolaryngol. 2013 Jun 27;2013:430625.

Basal turn stria vascularis in age related hearing loss (mouse C57BL/6)



Basal turn of control (young) mouse



CARRARO M, **HARRISON RV**. (2016) Degeneration of stria vascularis in age-related hearing loss; a corrosion cast study in a mouse model. Acta Otolaryngol. 136(4):385-390

Basal turn stria in animal model of age related hearing loss (mouse C57BL/6)

Basal Turn

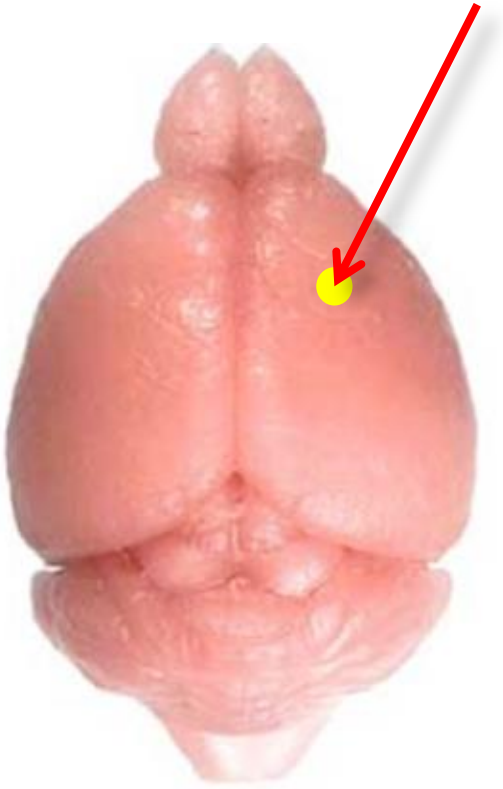
Stria vascularis in an animal model of cytomegalovirus (CMV) infection

Balb/C mice inoculated, postnatal day 3 with murine cytomegalovirus

(right) intra-cerebral injection (2000 pfu in 1 ul)

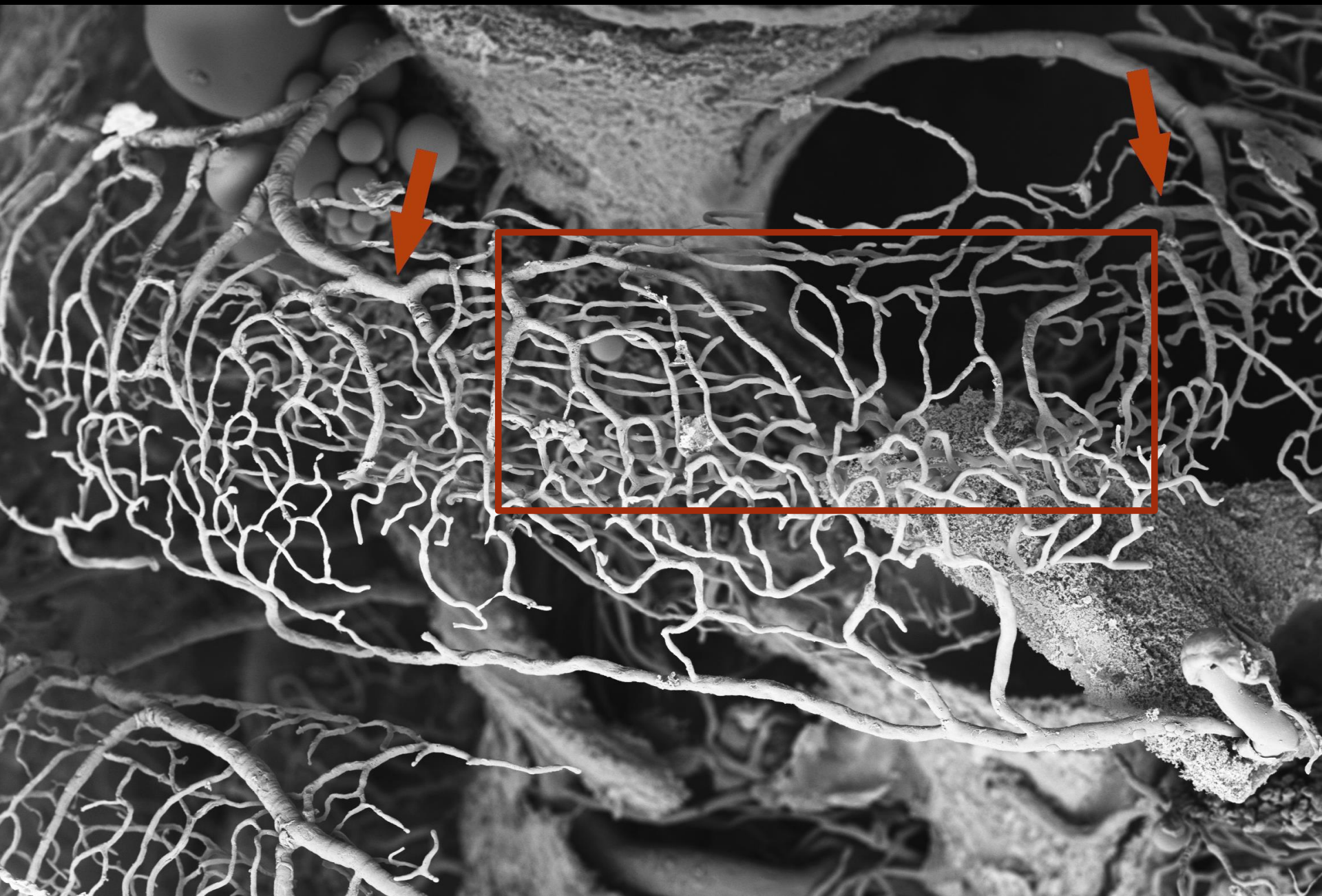
At 4 weeks, auditory function tested with ABR and OAE measurements

At 8 weeks, vascular damage evaluated using corrosion cast and SEM microscopy



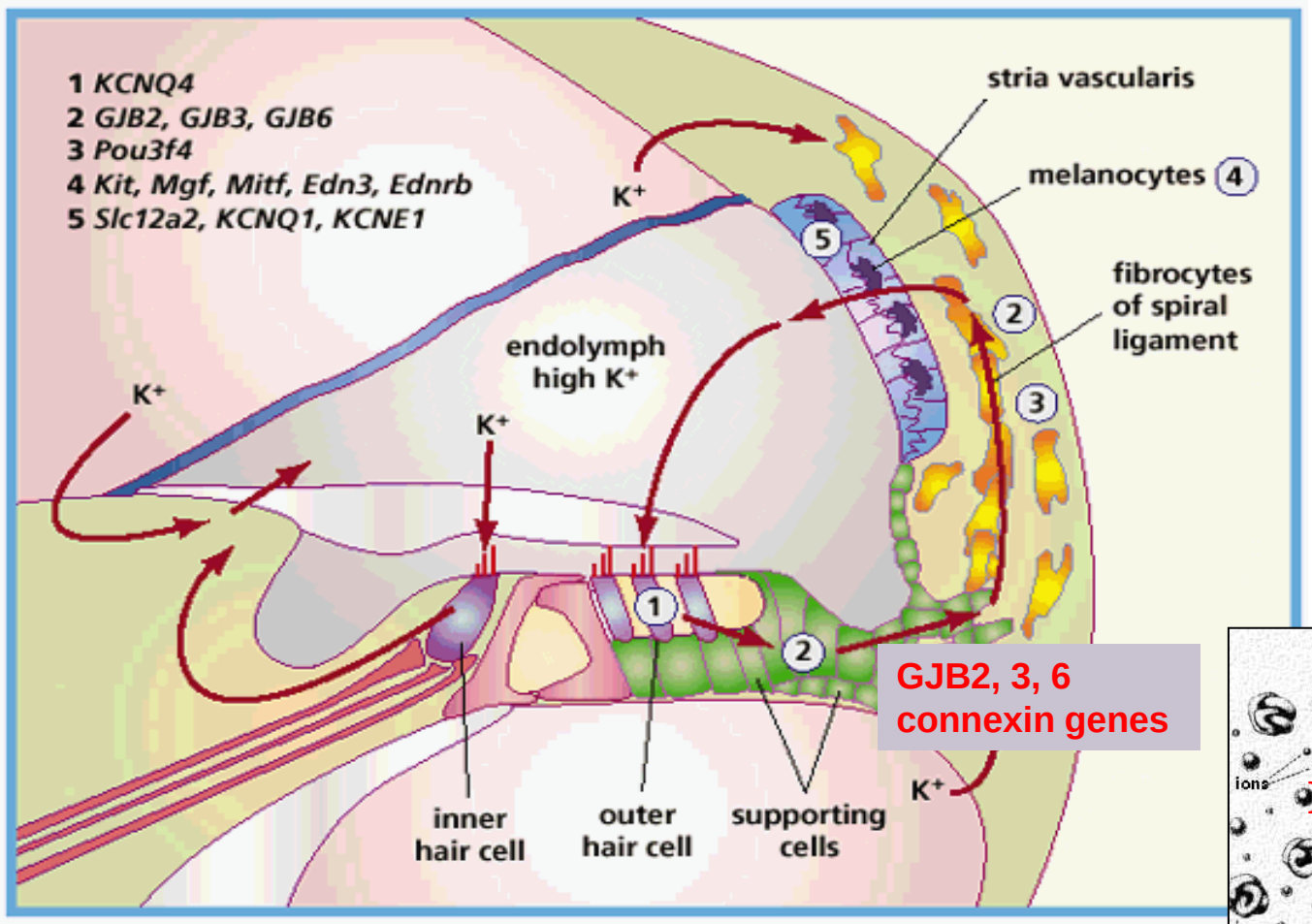
CARRARO M, ALMISHAAL A, HILLAS E, FIRPO M, PARK A, HARRISON RV. (2016) Cytomegalovirus (CMV) infection causes degeneration of cochlear vasculature and hearing loss in a mouse model. Journal of the Association for Research in Otolaryngology (JARO) 2016 Dec 19.

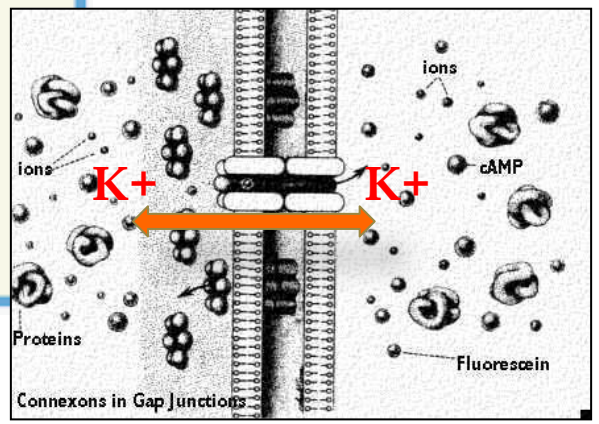
In CMV infection, first affected structure is stria vascularis in cochlear apex



In some subjects CMV infection causes total loss of apical vasculature

The role of the stria vascularis in connexin gene related hearing loss.





Karen P. Steel, Corné J. Kros 2001. A genetic approach to understanding auditory function. Nature Genetics volume 27, pages 143–149 (2001)

Cochlear areas of maximum vulnerability

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hypoxia, ischemia
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(sometimes reversible)

Haircells
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Spiral ganglion cells
loss of inner haircells
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Inner haircell synapse
some drugs e.g. aspirin
chronic hypoxia
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noise exposure
(sometimes there is recovery)

Take home message #1

In many forms of sensorineural hearing loss the stria vascularis is the initial/primary site of lesion. (e.g. loop diuretics, hypoxia/anoxia, presbyacusis, CMV infection, connexin gene mutation)

Patterns and site of vascular damage can differ.

(e.g. compare presbyacusis with connexin gene mutation, and with CMV induced damage)

Why not define a sub-class of "strial SNHL"?

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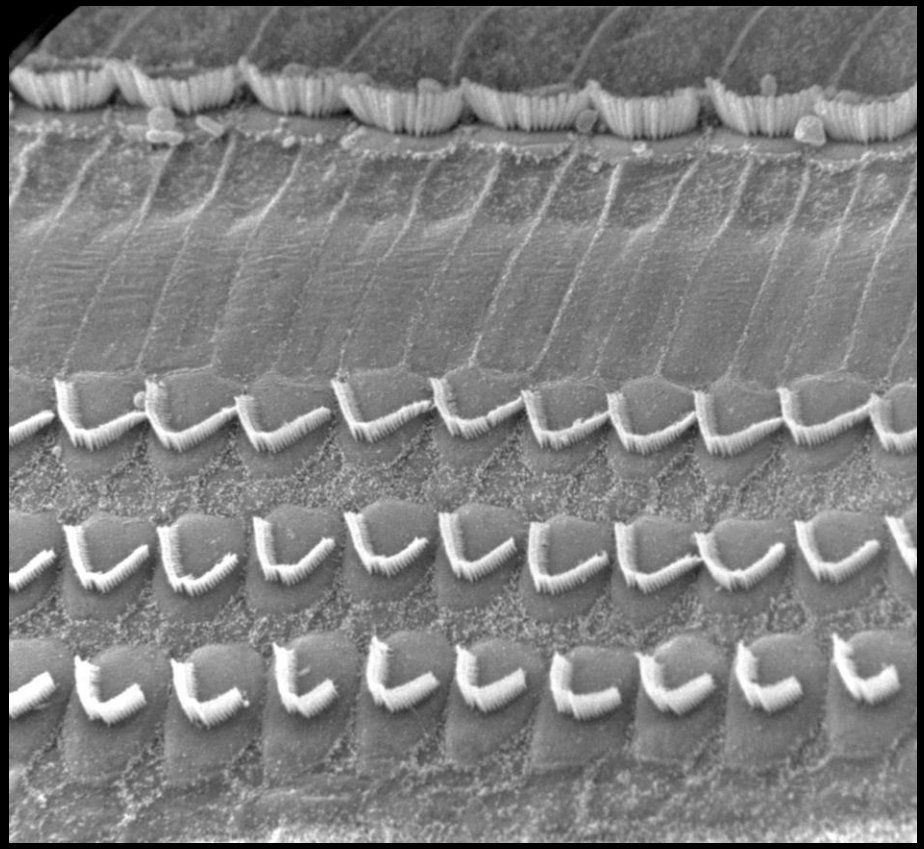
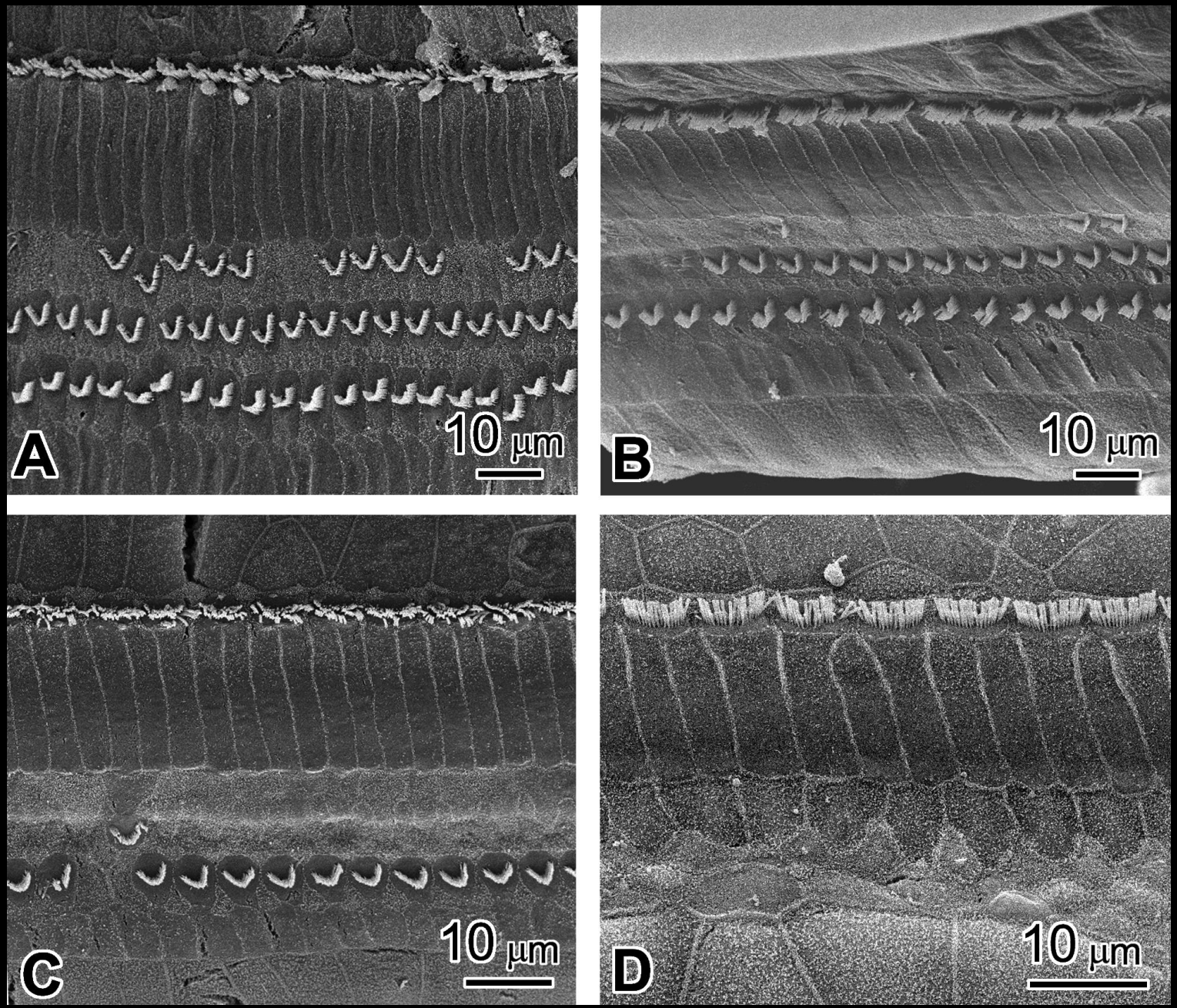
There are many “patterns” of haircell damage



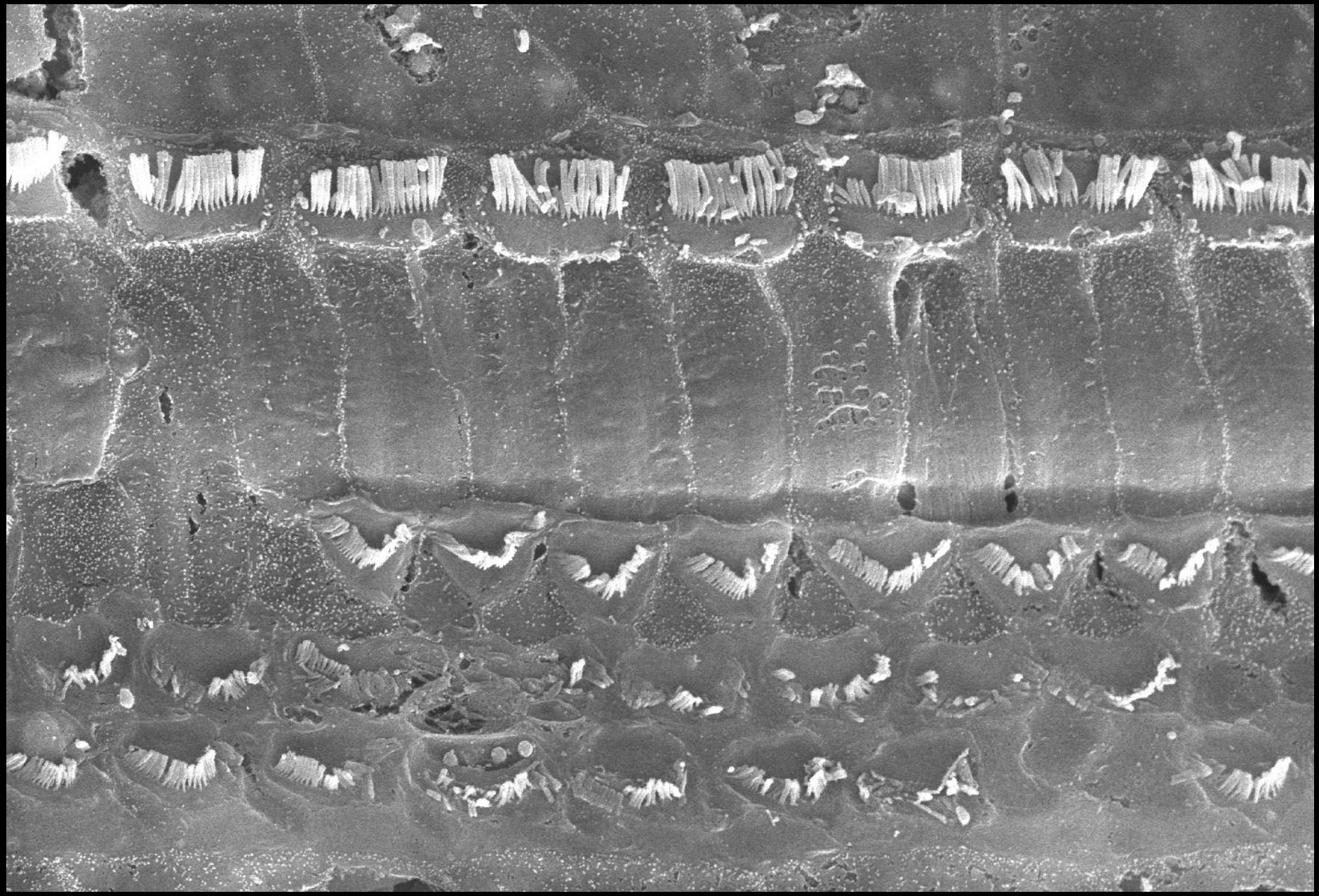
No damage

Total loss of haircells

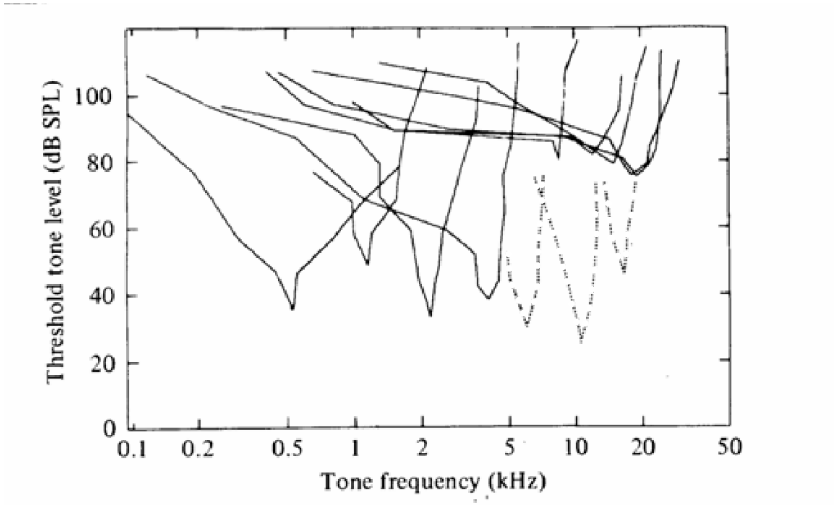
Outer haircell loss caused by aminoglycosides (amikacin; chinchilla model)

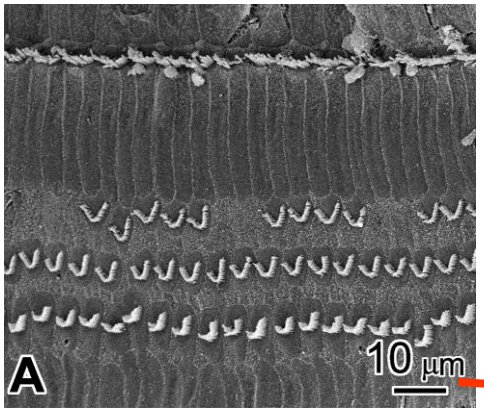


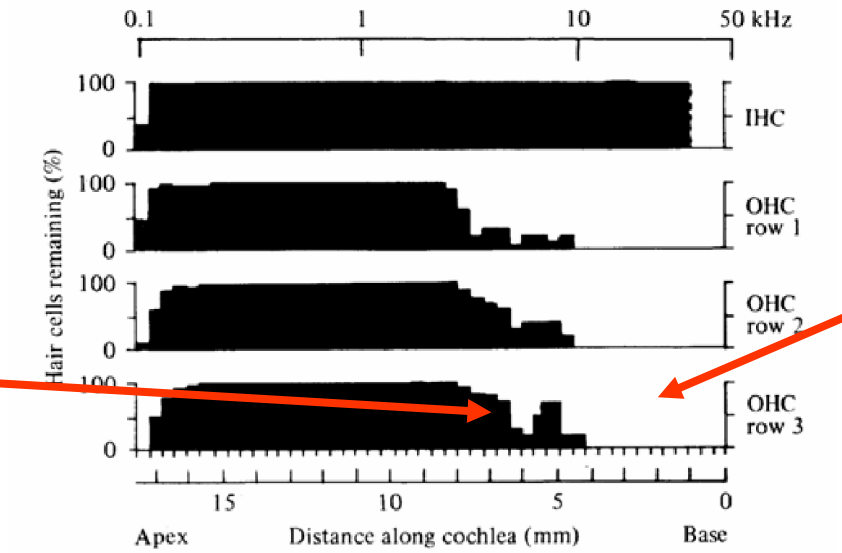
Outer haircells degenerating soon after gentamicin treatment (chinchilla model)

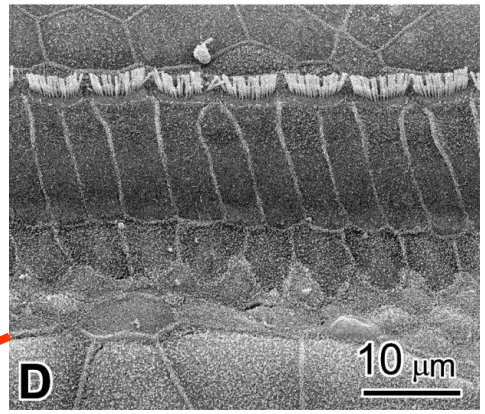


The effects of outer haircell loss on threshold and frequency tuning of cochlear nerve fibres









Evans and Harrison (1976) Correlation between outer hair cell damage and deterioration of cochlear nerve tuning properties in the guinea pig. J Physiol. 256:43

Frequency selectivity in HUMAN sensorineural hearing loss

Data derived with trans-tympanic Electro-cochleography

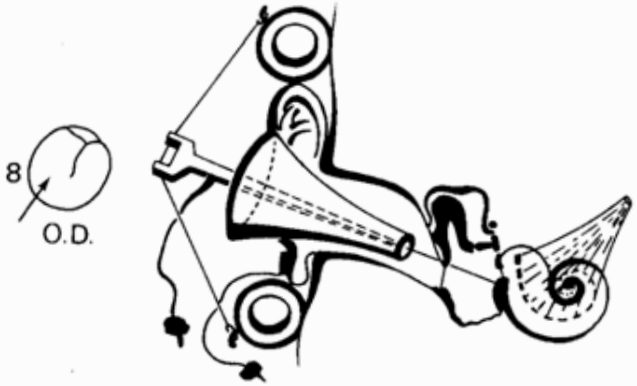
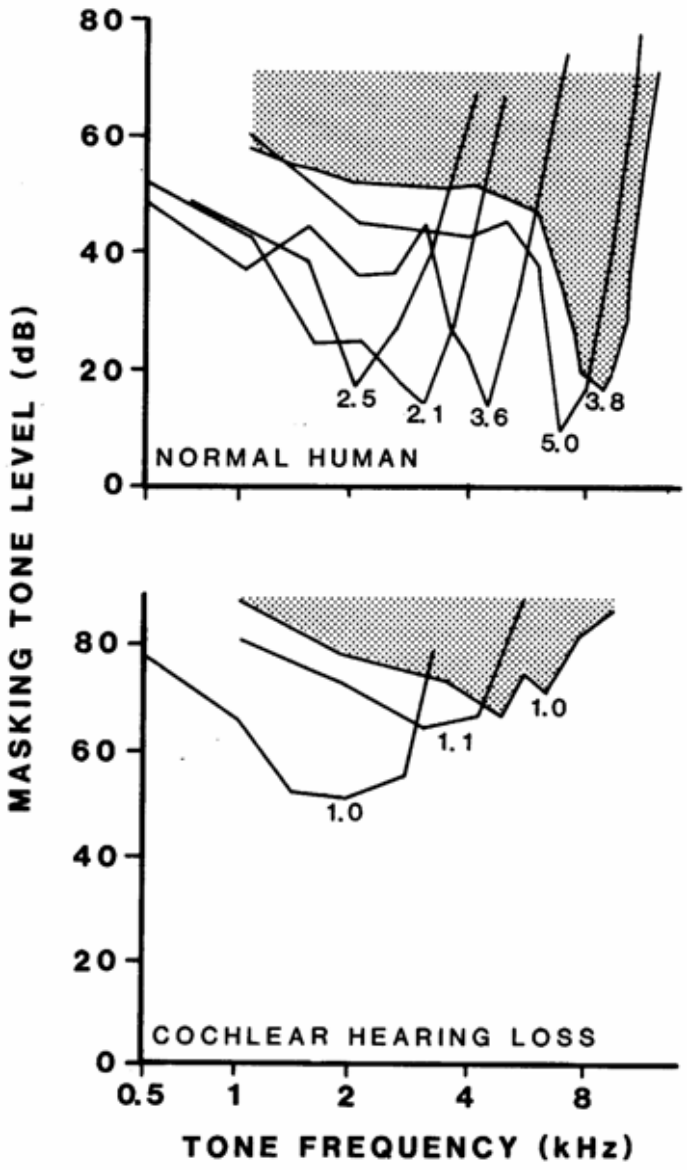


FIG. 90. – *Mise en place des électrodes active et indifférente pour l'électrocochléographie et indication (flèche) de l'endroit où l'électrode traverse le tympan pour une oreille droite* (d'après Aran, 1971).



Harrison, Aran and Erre (1981) AP tuning curves from normal and pathological human and guinea pig cochleas. JASA 69: 1374

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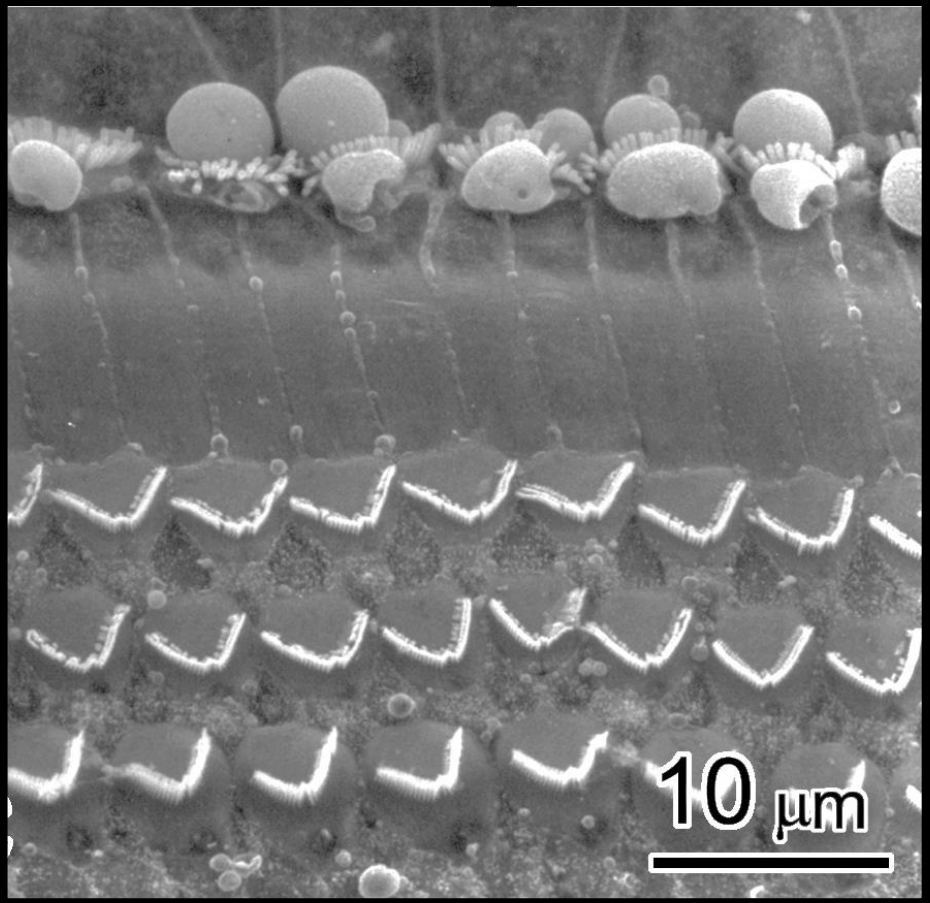
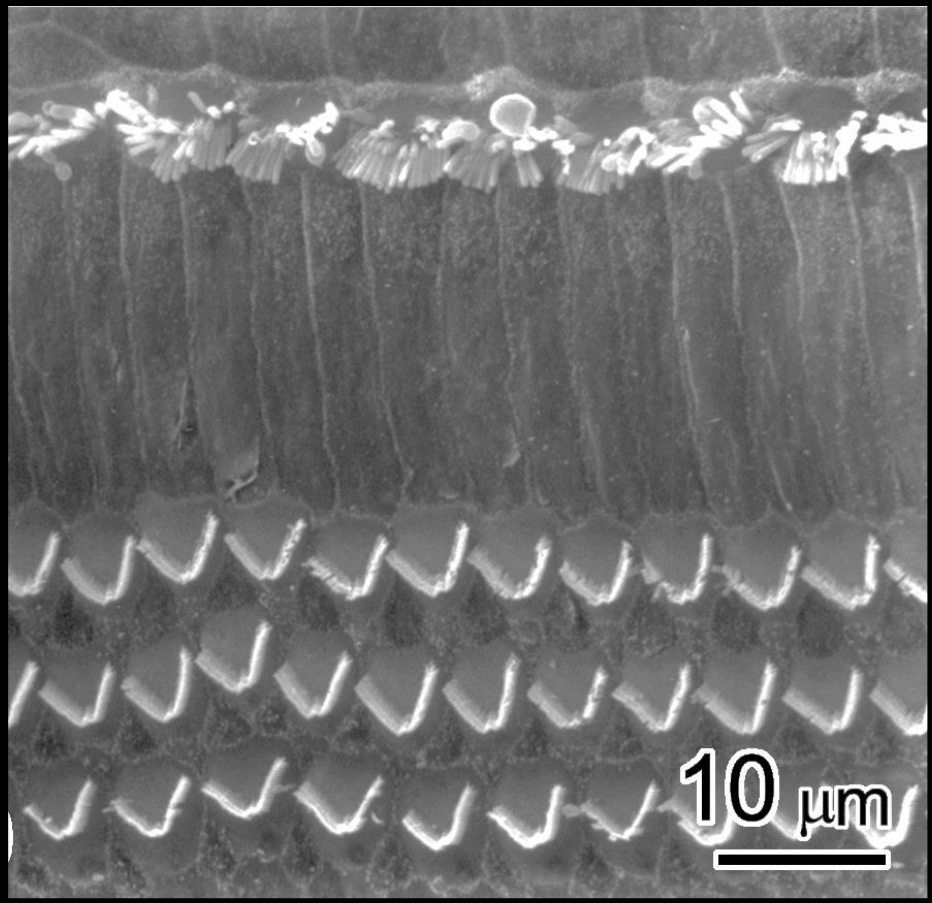
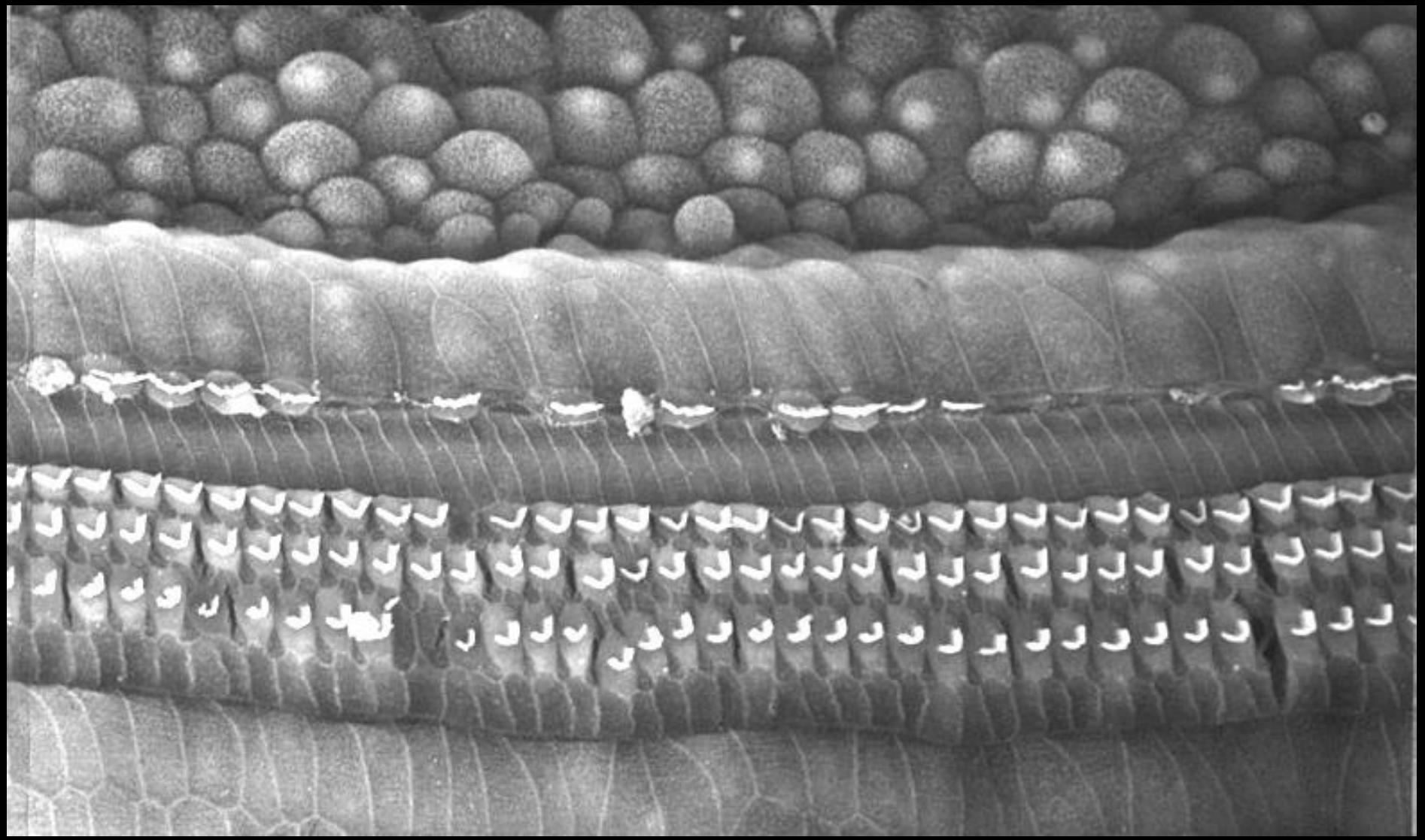
Ototoxicity of deferoxamine (chinchilla model)





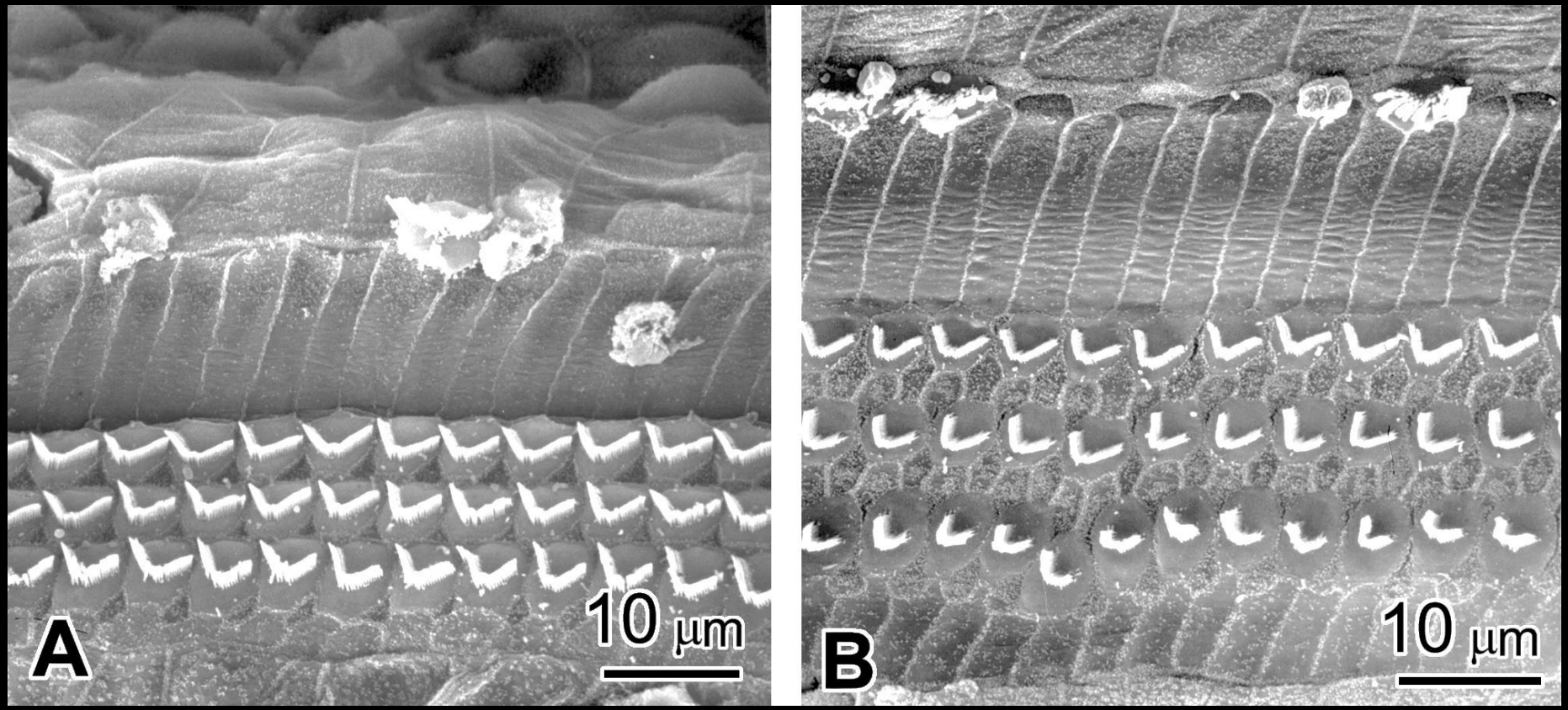
OLIVIERI N. F., BUNCIC, R., CHEW, E., GALLANT, T., **HARRISON, R.V.**, KEENAN, N., LOGAN, W., MITCHELL, D., RICCI, G., SKARF, B., TAYLOR, M., & FREEDMAN, M.H. (1985): Visual and auditory neurotoxicity in patients receiving subcutaneous deferoxamine infusions. New England J. of Med., Vol. 314, 869-873

Inner haircell lesions after carboplatin treatment (chinchilla)



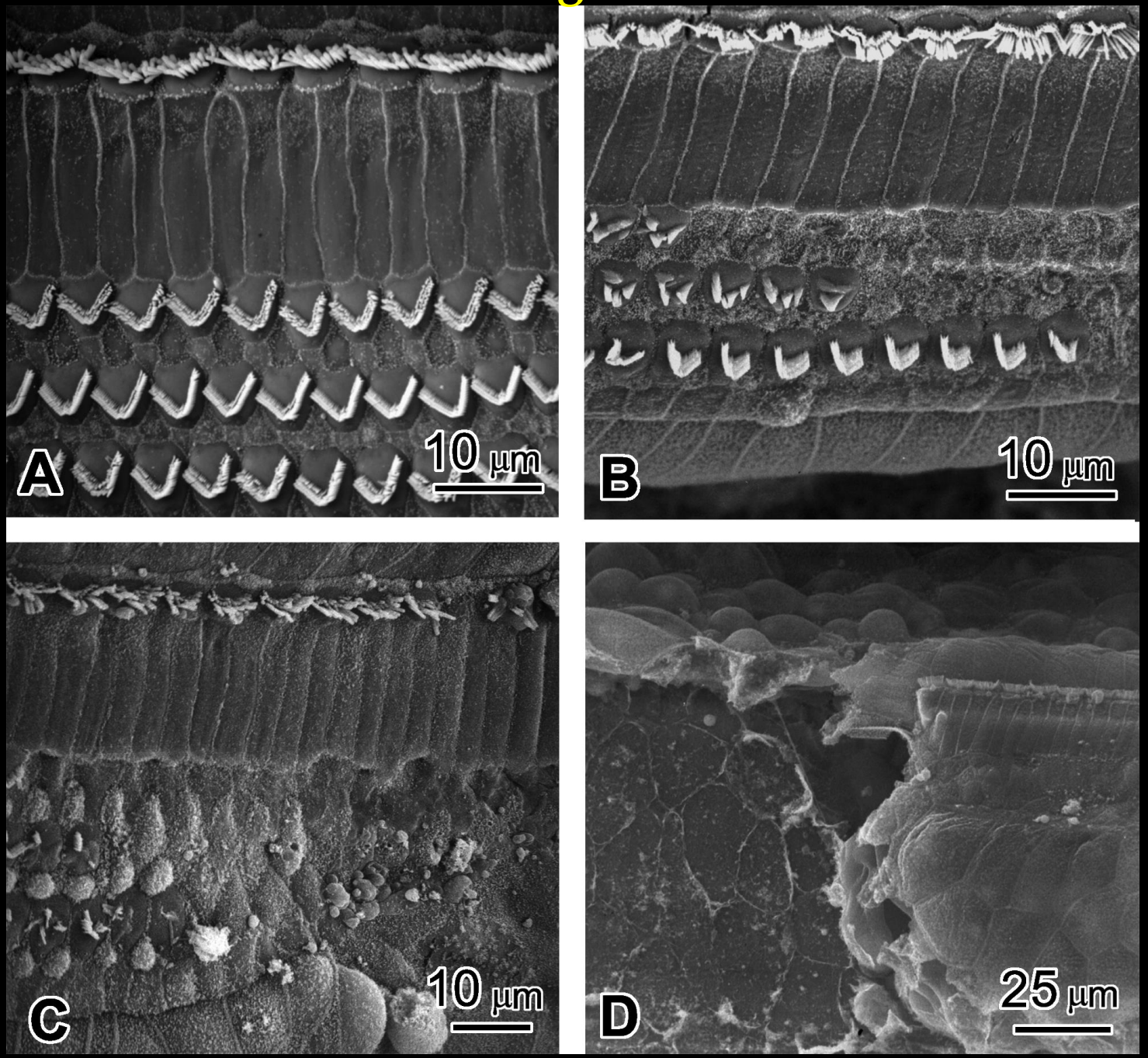
Cochlear inner haircell damage resulting from long term hypoxia

A causal factor in Auditory Neuropathy Spectrum Disorder (ANSD)

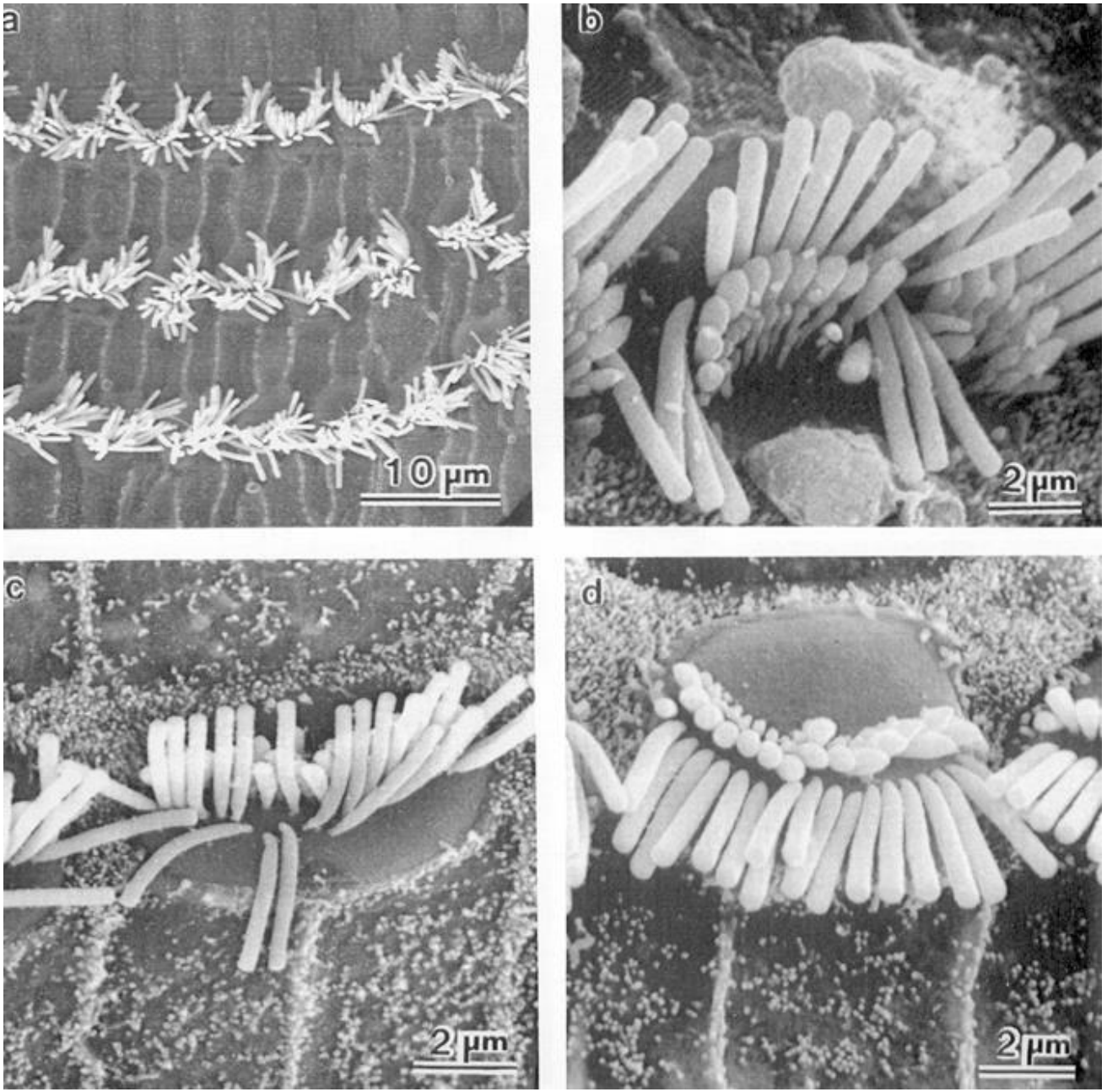


Harrison RV (1998) An animal model of auditory neuropathy. Ear and Hearing 19: 355-361

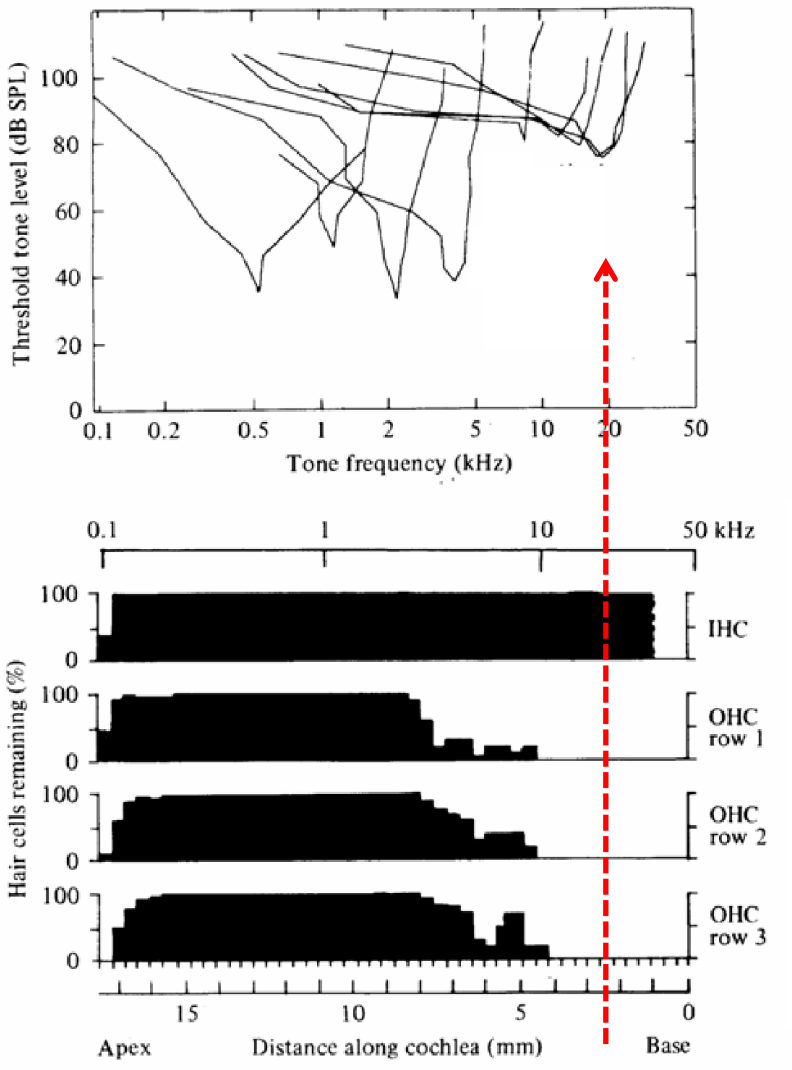
Acoustic trauma can damage outer and inner haircells



Effects of noise exposure on cochlear inner and outer haircells

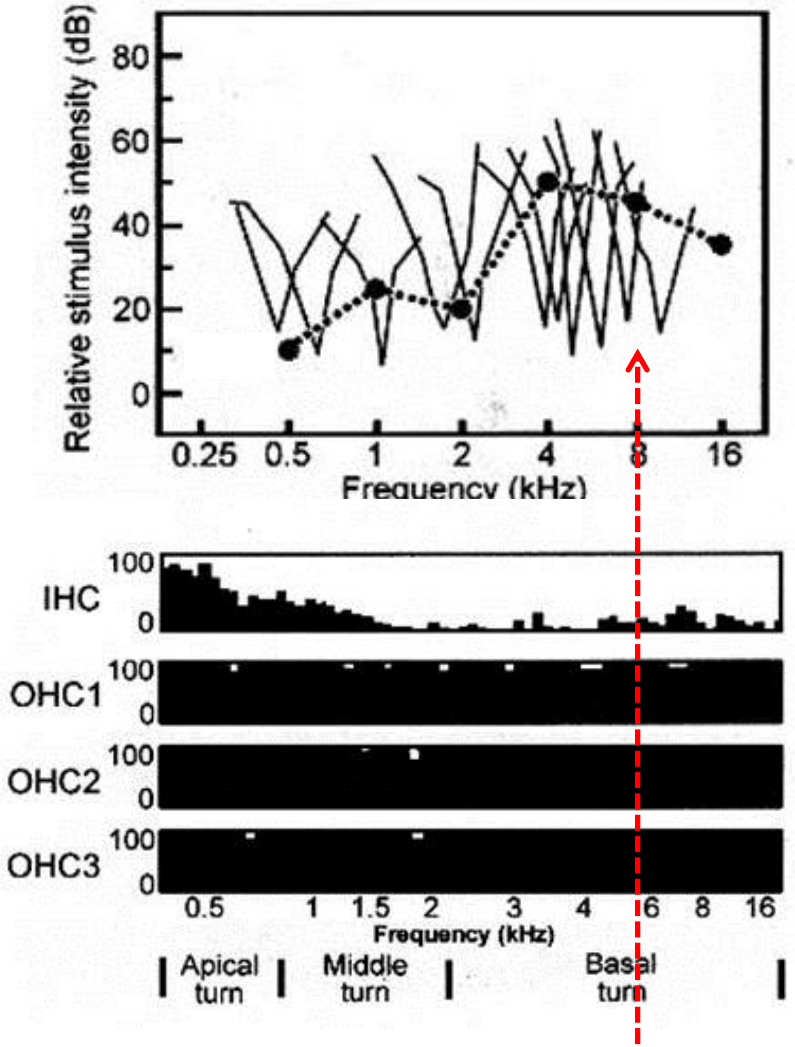


Central neurons have elevated thresholds, poor frequency tuning



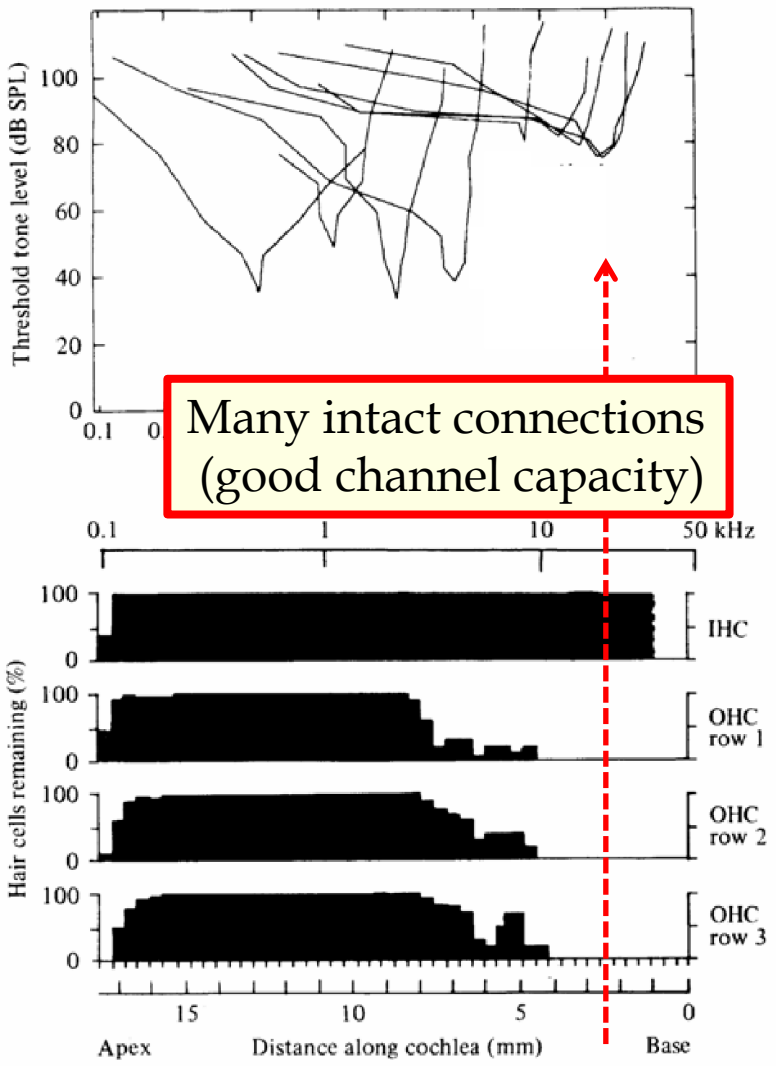
outer haircell loss.
inner haircells intact

Central neurons have low thresholds and sharp tuning



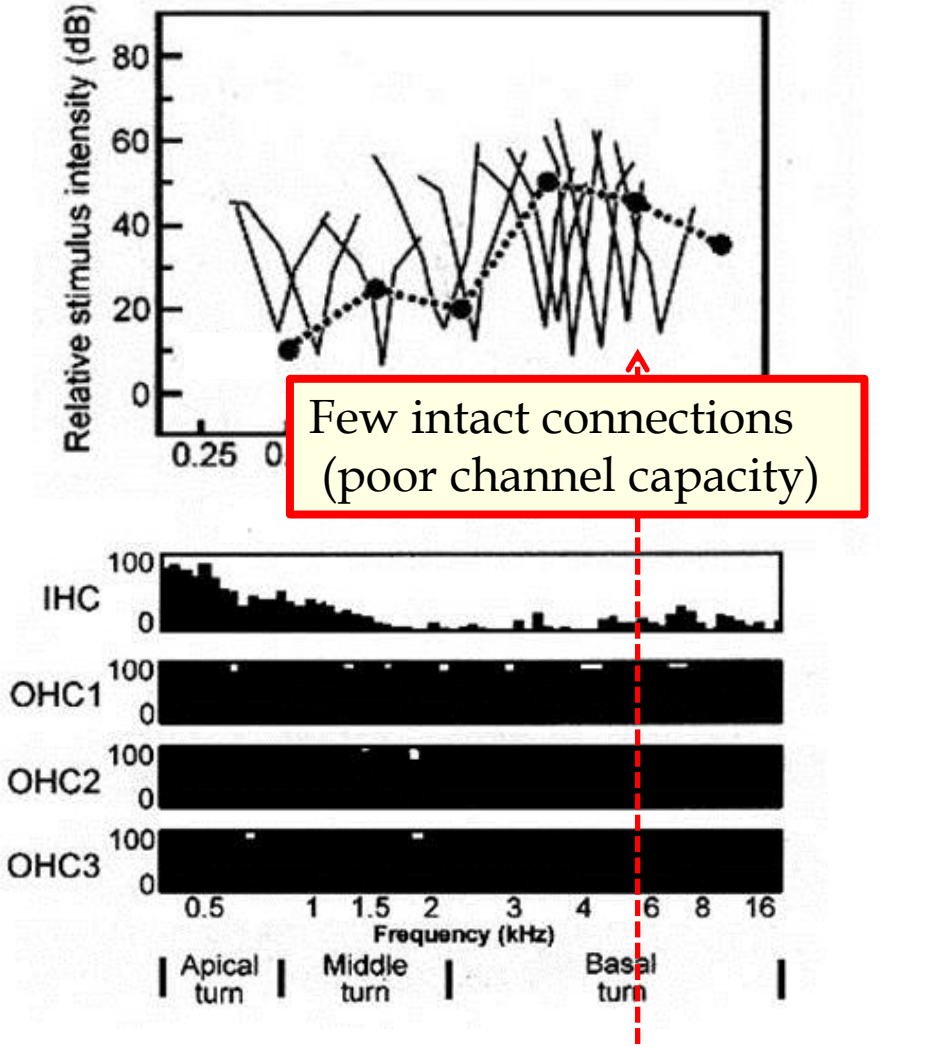
inner haircell loss (partial)
outer haircells intact

Central neurons have elevated thresholds, poor frequency tuning



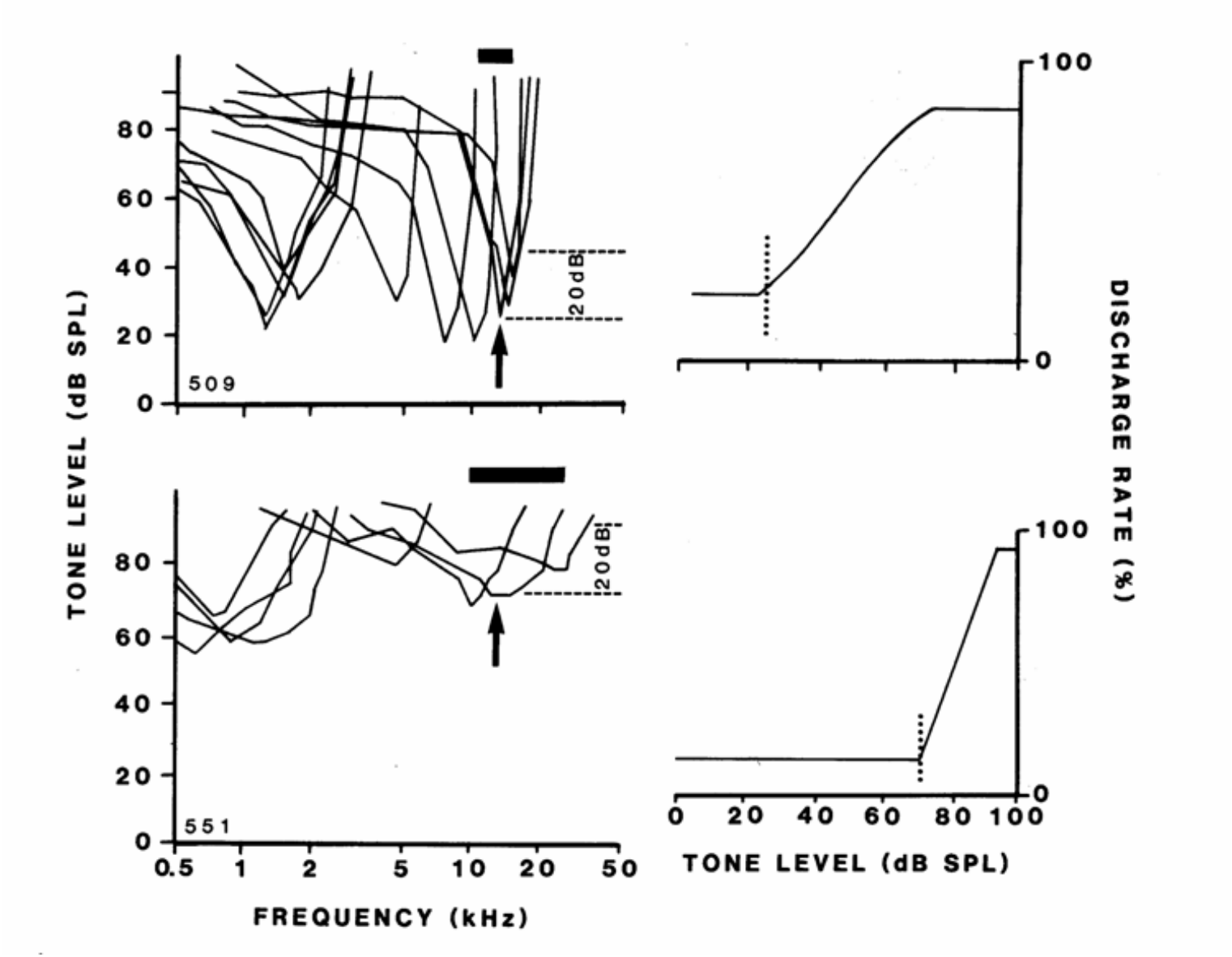
outer haircell loss.
inner haircells intact

Central neurons have low thresholds and sharp tuning

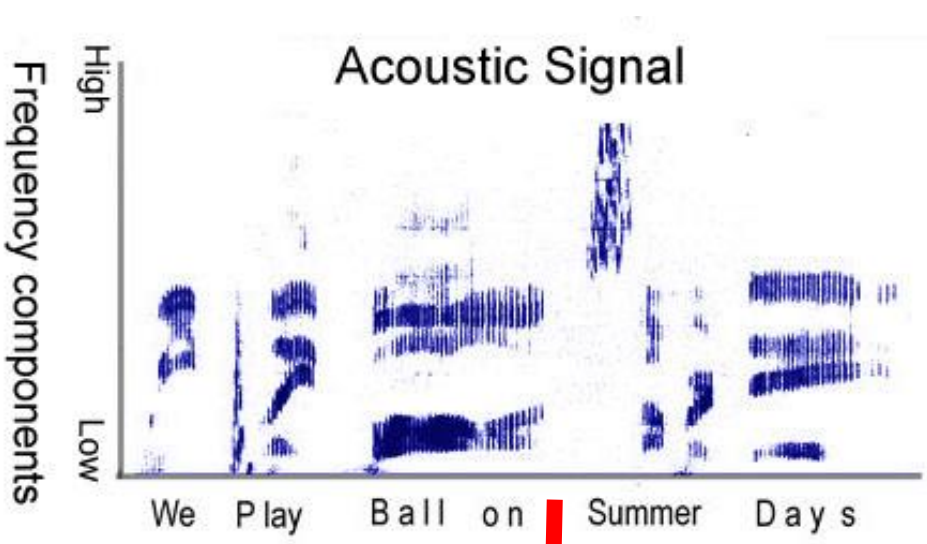


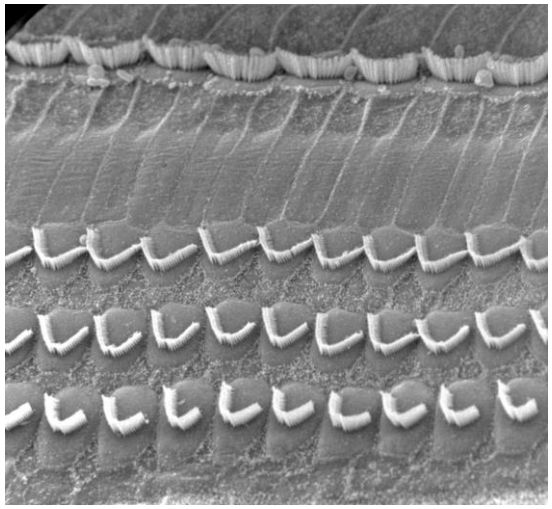
inner haircell loss (partial)
outer haircells intact

Loudness recruitment is a consequence of outer haircell loss

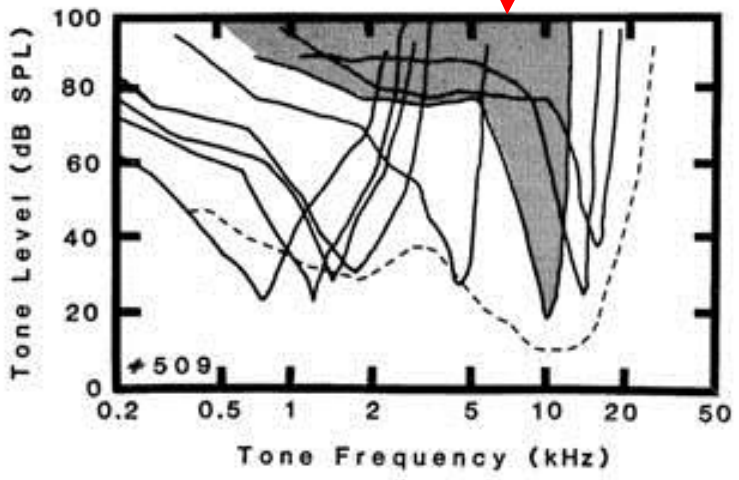


Coding of speech signals by the normal cochlea

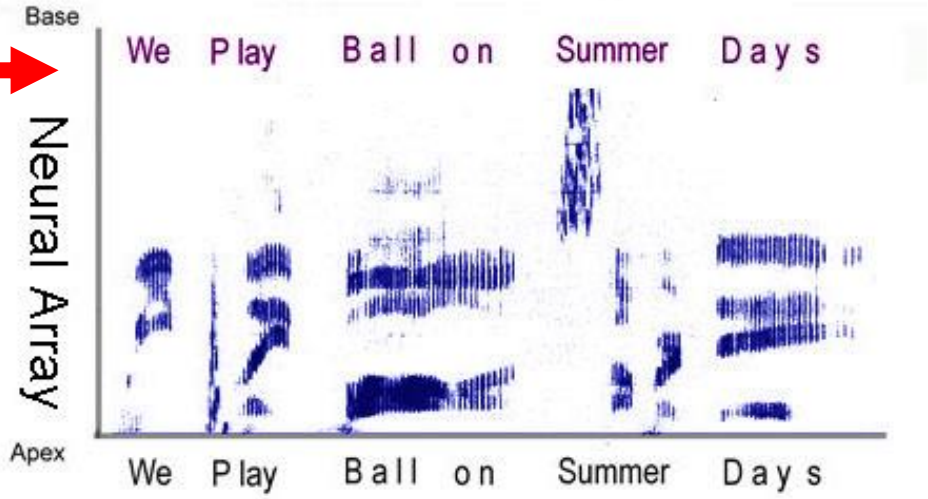




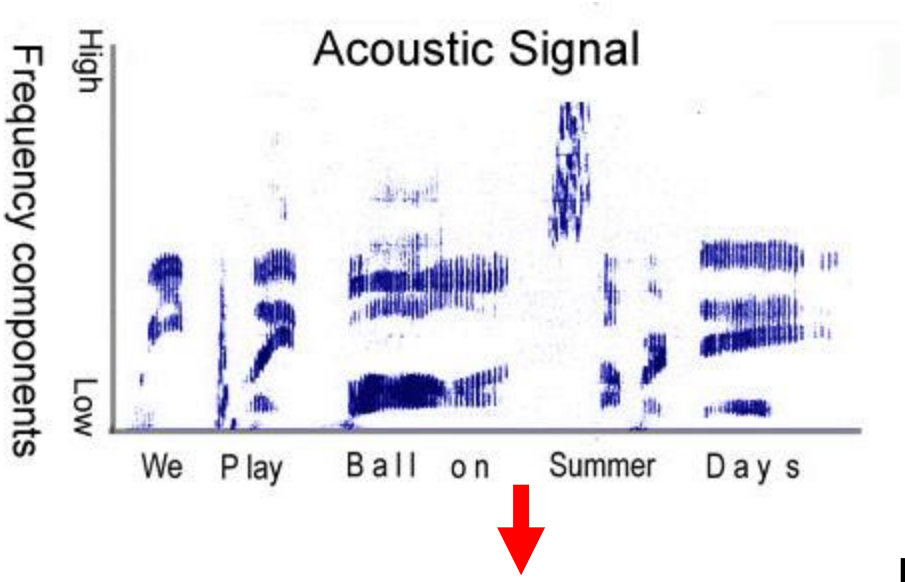
Good neural Representation

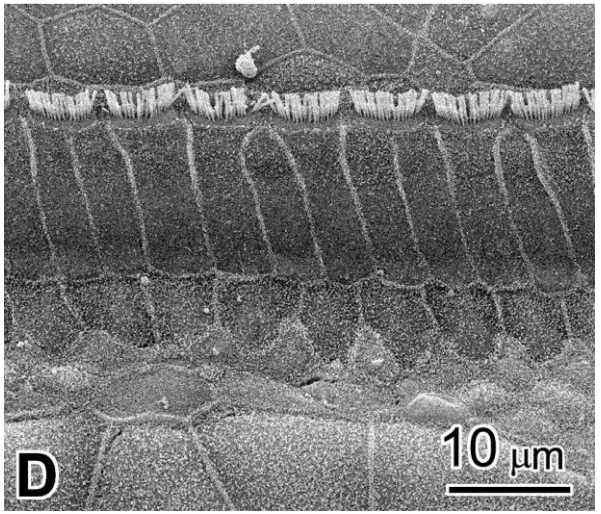


Cochlear Analysis Filters

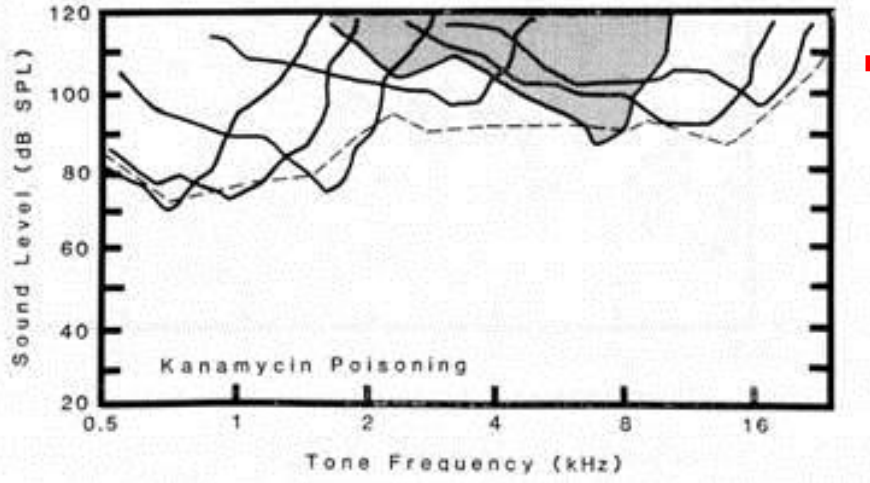


Coding of Speech Signal in Cochlea with OHC degeneration

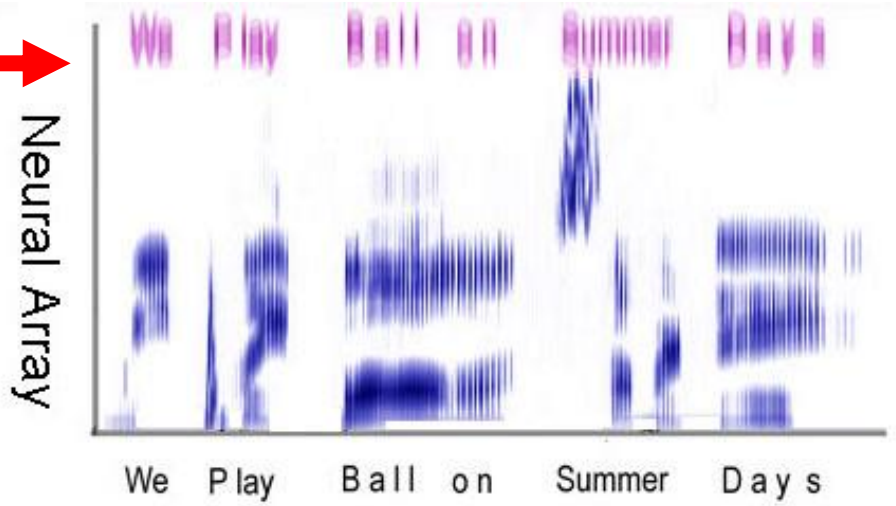




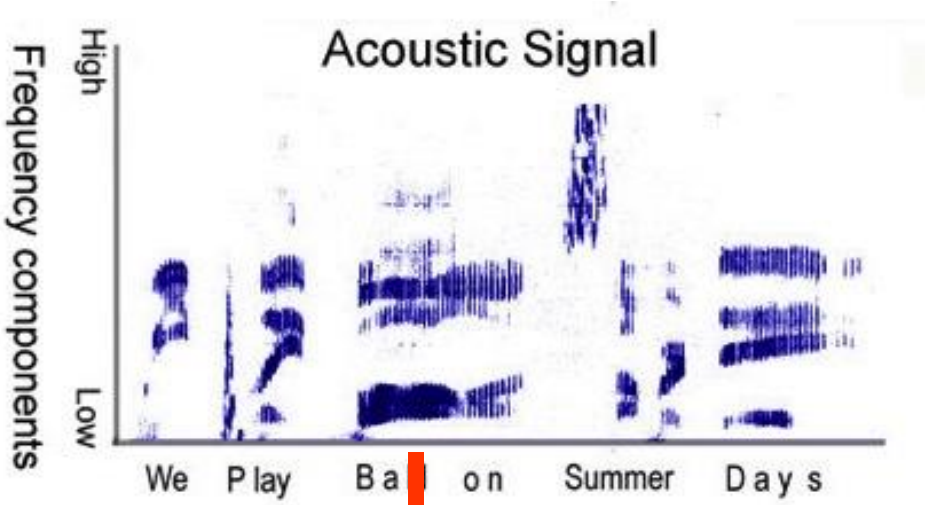
Degraded neural representation

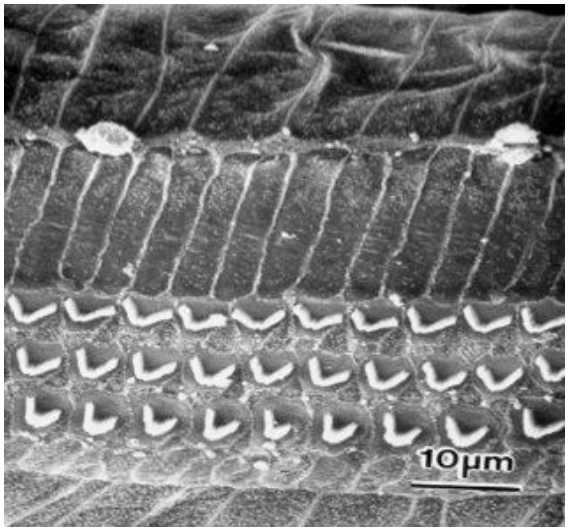


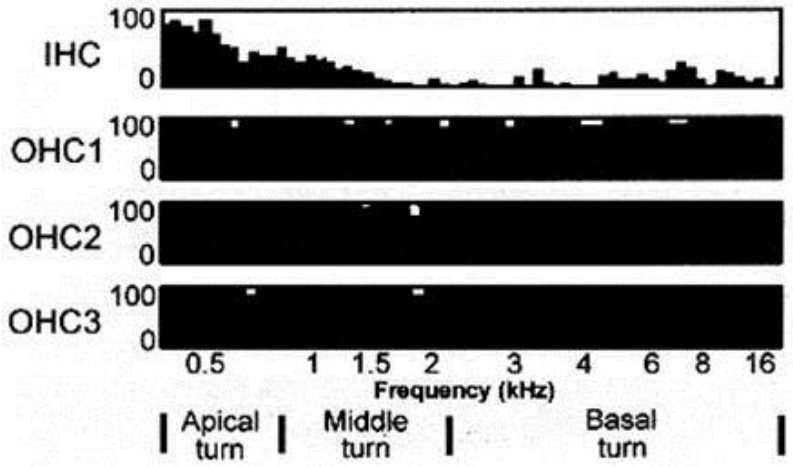
Cochlear Analysis Filters



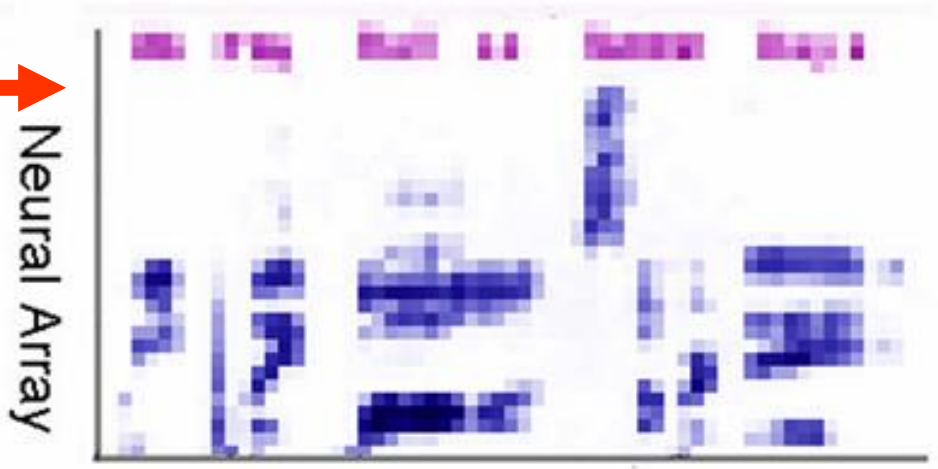
Coding of speech signals with (sub-total) IHC degeneration (as in auditory neuropathy)







poor neural representation because of reduction in channel capacity



Cochlear areas of maximum vulnerability

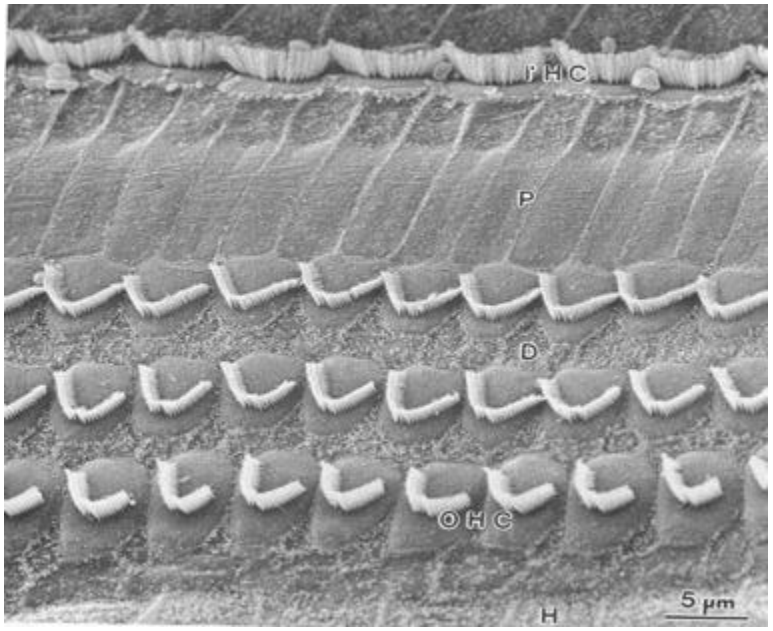
Stria vascularis
hypoxia, ischemia
loop diuretics (Lasix)
metabolic inhibitors
old age
viral infection
genetic mutation
(sometimes reversible)

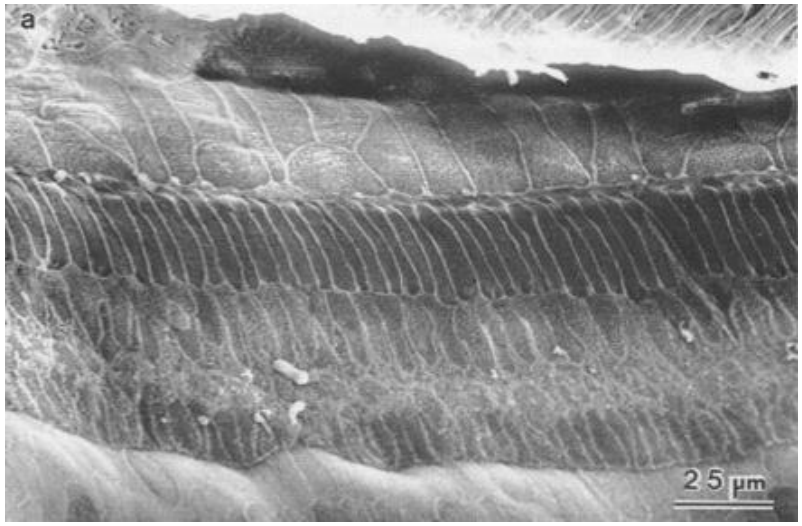
Haircells
ototoxic drugs
e.g. aminoglycosides
old age
acoustic trauma
genetic mutation
(not reversible)

Inner haircell synapse
some drugs e.g. aspirin
chronic hypoxia
anti cancer drugs – carboplatin
noise exposure
(sometimes there is recovery)

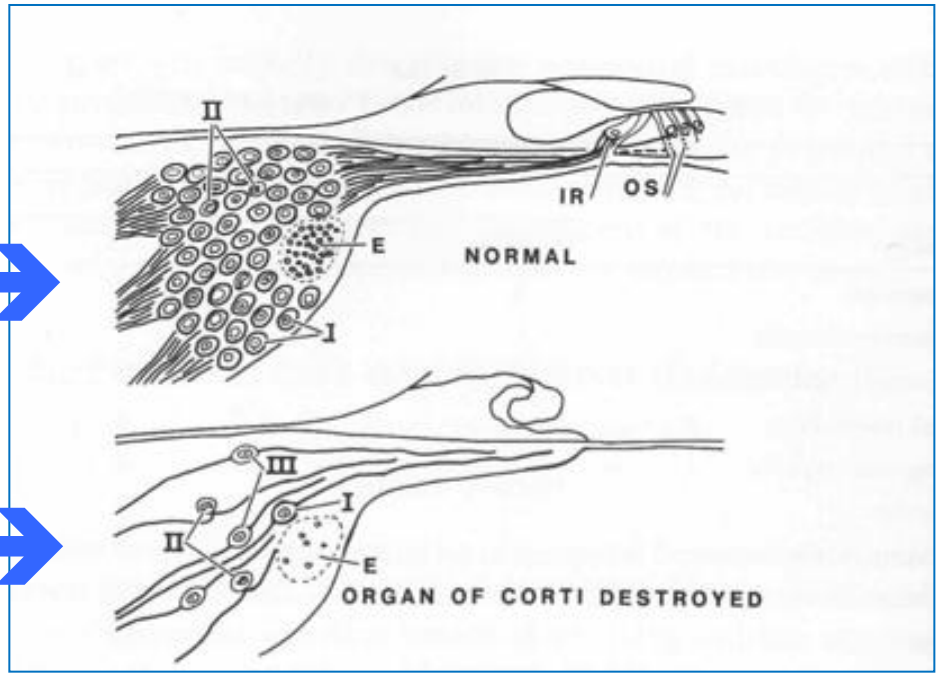
Spiral ganglion cells
loss of inner haircells
Glutamate excitotoxicity
Sensorimotor neuropathy
Hidden hearing loss?

When inner hair cells are damaged, spiral ganglion cells degenerate





From studies by Dr. H. Spoendlin



Inner haircell loss causes spiral ganglion cell degeneration AND degenerative change in second and third order central auditory neurons

THIS IS, OF COURSE, A MAJOR ISSUE IN COCHLEAR IMPLANTATION

Cascading progression of cochlear degeneration

Stria vascularis

hypoxia, ischemia
loop diuretics (Lasix)
metabolic inhibitors
old age
viral infection
genetic mutation
(sometimes reversible)

Haircells

ototoxic drugs
e.g. aminoglycosides
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Spiral ganglion cells

loss of inner haircells
Glutamate excitotoxicity
Sensorimotor neuropathy
Hidden hearing loss?

Take home message #2

Many ototoxic insults can cause haircell degeneration.

The pattern of haircell damage can take many forms depending on etiology.

Some ototoxic agents cause most damage to OHC, other agents appear to cause mainly IHC degeneration.

Functional deficits depend on type and pattern of haircell loss.

Perhaps we could define some distinct sub-classes:

"outer haircell SNHL"; "inner haircell SNHL"

"inner haircell synaptopathy" (Liberman and Kujawa)

Towards an improved classification of SNHL

We have studied the pathogenesis of sensorineural hearing loss In a range of animal models. Some of my own work presented today.

SNHL has many different causes, many sites, patterns and sequences of cochlear damage, resulting in many forms of hearing dysfunction

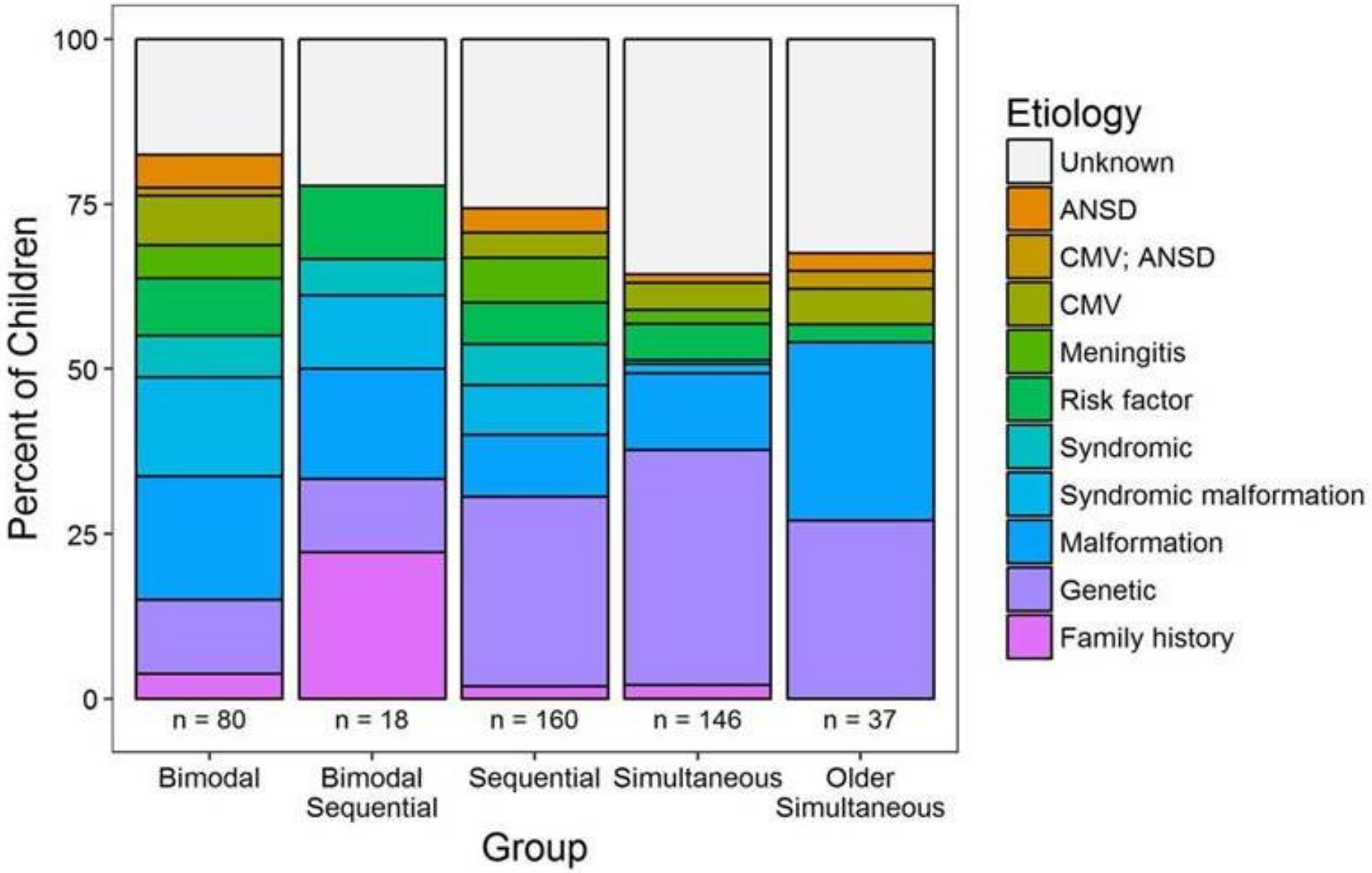
Sensorineural hearing loss is a SPECTUM DISORDER!

We need to pay more attention to etiology, and from there understand the pattern or sequence of cochlear damage. Then we can consider the very DIFFERENT functional consequences of each lesion type.

OVERALL THESIS:

If we pay more attention to etiology we can distinguish classes or types of SNHL. This in turn will narrow our focus on treatment and rehabilitation strategy and provide more accurate prognosis.

Classification of children with cochlear implants at the Hospital for Sick Children, Toronto



A Comprehensive Study on the Etiology of Patients Receiving Cochlear Implantation With Special Emphasis on Genetic Epidemiology

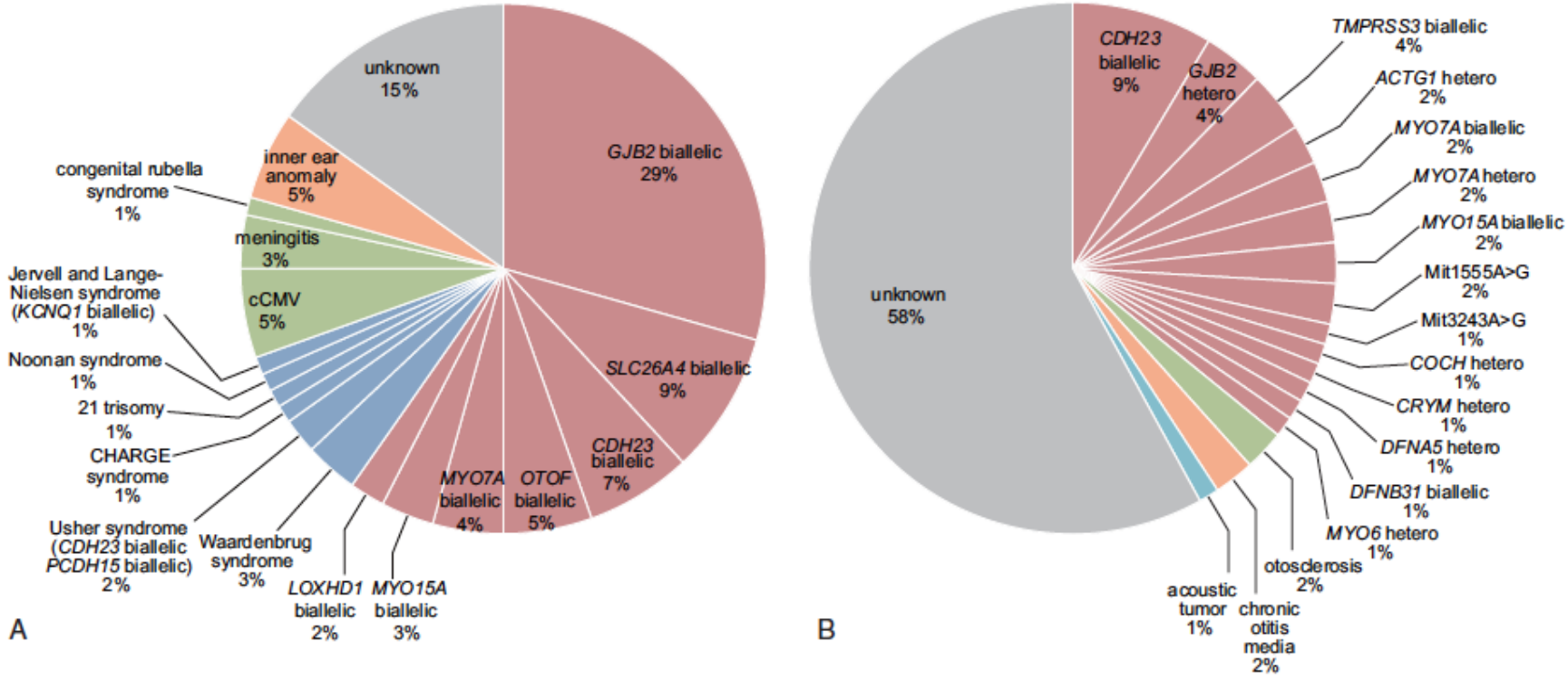


FIG. 1. Etiology of CI/EAS patients. (*A*) Prelingual CI/EAS patients (n = 88). Blue indicates syndromic hearing loss; gray, unkown; green, infection-induced hearing loss; orange, inner ear anomaly; pink, nonsyndromic hearing loss associated with specific gene mutations. (*B*) Postlingual CI/EAS patients (n = 77). Blue indicates acoustic tumor; gray, unkown; green, otosclerosis; orange, otitis media; pink, nonsyndromic hearing loss associated with specific gene mutations.

Maiko Miyagawa, Shin-Ya Nishio, and Shin-Ichi Usami (Matsumoto Japan)
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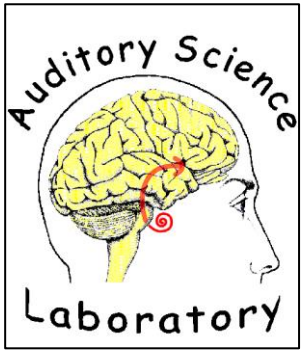
THE HOSPITAL FOR SICK CHILDREN

SNHL- Understanding the Cause Is Important for Treatment

END



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