The Journal of Laryngology & Otology
March 2001, Vol. **115,** pp. 171–178

Review Article

Presbyacusis

C. R. Jennings, F.R.C.S., N. S. Jones, M.D., F.R.C.S.

Key words: Presbyacusis; Histology; Epidemiology; Genetics; Hearing Loss, Sensorineural

Introduction

Presbyacusis (spelt presbycusis in American texts) is defined as 'the natural failure of hearing with advancing years, caused by degenerative changes in the internal ear.[1] Presbyacusis is derived from presbyacusia the title Zwaardemaker gave to hearing loss in the elderly in 1894. He used a series of whistles called Galton's whistles that produce a series of notes that increase in octave increments. He compared children with the elderly and found that the 11th or highest octave could not be heard by the elderly. He concluded that high tone hearing selectively decreased with age.[2] The scientific study of hearing loss in the elderly started with Toynbee in the mid-19th century predating Zwaardemaker by about 50 years. Toynbee attempted to correlate pathological and clinical findings. He dissected 18 temporal bones on elderly patients who had pre-mortem hearing loss. Limited by technology he had to diagnose deafness by asking patients if they could hear his ticking watch, and did not have use of a microscope for histological examination. Toynbee focussed his attention on the middle ear concluding that thickening of the mucosa and the tympanic membrane was the cause of the hearing loss.[3]

Further advances had to wait until electrical audiometers were used to accurately measure thresholds at different tones.[4] Bunch noted a decrease in hearing at frequencies above 2 kHz in the elderly.[4] Histological evaluation of the inner ear in the elderly was first reported by Crowe[5] and then by Saxon.[6] They described degenerative changes in the organ of Corti and the spiral ganglion with ageing. It was first considered to be a process that originated in the spiral ganglion, but this was refuted by Saxen in 1952.[7] In observational studies that correlated audiological data with histological findings Schuknecht in 1955[8] further muddied the water by adding two further groups, metabolic and mechanical. In 1994 he reaffirmed his finding with a small study of 21 temporal bones, admitting himself that these groupings were 'somewhat arbitrary'.[10] The above work by Schuknecht has dominated thinking on presbyacusis for five decades.

The histological investigation of presbyacusis was advanced by the use of the electron microscope by Bredburg in 1965;[11] The physiological investigation was advanced by such tools as evoked response audiometry (ERA), electrocochleography (ECOG) and otoacoustic emissions (OAEs). The most recent advances have been in the fields of epidemiology, molecular biology and genetics.

Epidemiology of hearing loss

The UK National Study of Hearing Disorders in 1995[12] illustrated the epidemiology of sensorineural hearing loss in adults. This study involved 48 313 people contacted by postal questionnaire, 2 708 were invited to attend a research unit where the second stage was carried out. The findings were that 20 per cent of adults had a hearing impairment in the best hearing ear of >25 dB (mean 0.5, 1, 2, 4 kHz), this gives a hearing impaired population in the UK of 8.58 million, 75 per cent being over 60 years. In the same study 2.94 million adults were found to have a moderate hearing loss of >45 dB hearing level.[12] The over 60 age group represented 84 per cent and the over 80, 45 per cent of this group. The percentage with a sensorineural hearing loss >25 dB loss in the over 60s is 92 per cent and >45 dB is 31 per cent. This large cross-sectional study indicates that the majority of hearing loss occurs in the elderly, is sensorineural in character, and that it becomes more prevalent with age.

Davis in the UK and Ostri in Denmark[13] performed longitudinal studies of hearing loss and stratified subjects according to age, sex and reported noise exposure and found that 97 per cent of subjects experienced a decline in hearing over time. The rate

From the Department of Otorhinolaryngology, Queen's Medical Centre, University Hospital, Nottingham, UK.
Accepted for publication: 20 September 2000.

of decline was dependent on age, those under 55 years lost hearing at 3 dB decade and those over 55 at a rate of 9 dB decade. Therefore it appears that, with time, hearing declines gradually in the majority of the population, and that this accelerates with advancing age.

Is presbyacusis a central or peripheral phenomenon?

The functional evidence in support of a central cause for presbyacusis includes a hypothesis proposed by Hinchcliffe[14] who suggested that the main cause of hearing loss in the aged was degeneration of the brain concomitant with ageing. Maspetiol and Feldman found reaction times to visual, tactile and auditory stimuli when compared in the elderly were found to increase with age, although the response to auditory stimulation increased more than the competing senses.[15,16] A battery of tests of central processing by Welsh[17] on three groups of mean age 65.3, 75.2 and 85.3 found a progressive failure rate in the older group compared with the younger. Evidence against a central lesion being the main contributor to presbyacusis includes work by Soucek[18] who investigated both pure tone audiometry and speech audiometry and found the deficiency in the coding of phonemes was likely to be peripheral as it was related to abnormal pure tone thresholds. It has been suggested that as a result of a central disturbance the elderly are less able to discriminate speech. This phenomenon is known as phonemic regression.[19] In order to test this hypothesis Holmes[20] compared open and closed set type tests in the elderly and young controls with normal hearing. No significant difference between the two was found, suggesting that phonemic regression and hence a central disturbance is not the cause of age-related hearing loss. The elderly clearly have central impairment, but for this to be the only explanation of presbyacusis would appear untrue.

The histological support for the hypothesis that presbyacusis is a central phenomenon is weak. Hansen and Reske-Nielsen[21] performed a qualitative study and found central degeneration, and atherosclerotic changes were evenly spread and did not correlate with the degree of degeneration of the organ of Corti or the spiral ganglion.

Konigsmark[22] looked at the auditory tract in cadavers from the newborn to 90 years of age. He found no difference in the number of cells but had no audiological investigations with which to correlate his findings. It seems likely that whilst there can be a reduction in the number of cells in the cochlear nuclei, there is no evidence that this is the primary factor in reducing hearing thresholds.

Toynbee hypothesized that the middle ear was the site of dysfunction in presbyacusis.[3] Since then few papers have supported this view, although Nixon[23] did report fibrous and bony ankylosis in ossicles and measured a 12 dB hearing loss at 4 kHz in the elderly.

Using the short increment sensitivity index (SISI) devised by Beagley and Barnard, Lehnhardt found a higher degree of recruitment present in patients with presbyacusis than younger controls matched for hearing loss.[24] This suggests a cochlea lesion in presbyacusis. Lehnhardt also looked for tone decay and found none in patients with presbyacusis, making a retrocochlear lesion less likely. Soucek and Michaels[25] investigated auditory brainstem responses (ABR) and electrocochleography (ECochG) to localize the lesion. They found that there were significantly prolonged latencies from sound stimulus to generation of the peaks of the ABR. This indicates a lower level of activity within the aged cochea. The amplitude of the I, III and V peaks was reduced in the elderly, again suggesting less cochlear activity. However, they found that the interwave latency was the same as in the younger controls suggesting that the central conducting time was unaffected with advancing age. This supports the hypothesis that degeneration of the cochlea is the site of the lesion, however ABR evidence alone may also be explained by a loss of neurones in the auditory tract that may be the primary event. Soucek and Michaels[25] also investigated the extratympanic ECoG. The ECoG records the cochear microphonic, the summating potential and the N1 and N2 components of the action potential. The N1 results mainly from depolarization of the hair cells, and the N2 to the depolarization of the spiral ganglion and acoustic nerve. In the elderly the ECoG has a different pattern compared to the younger controls. In the elderly the N1 amplitude is less than the young controls, but the N2 component remains constant in both groups. This suggests a disturbance at hair cell level with the spiral ganglion and acoustic nerve being spared. Using the ECoG as an output measure Soucek and Michaels[25] looked at how the input/output function of the cochlea changed with age. Interestingly they found by increasing the intensity of stimulus the latency of the N1 component fell faster in the elderly. This is the electrophysiological correlate of recruitment and supports the cochlear hair cell as the locus for the disturbance in presbyacusis. When investigating the effect of repeated stimuli on the ABR and the ECoG measured simultaneously the investigators found no difference in the rate of adaptation in the elderly compared to the young controls.[25] Prijis has suggested that adaptation is a property of the hair cell – neurone synapse.[26] This suggests that presbyacusis does not involve the hair cell-first order neurone or any subsequent synapse but is a hair cell phenomenon. Electrophysiological evidence strongly supports the hypothesis that presbyacusis represents a lesion of the hair cells. Otoacoustic emissions (OAEs)[27] are energy generated by the cochlea and can be measured in the external auditory canal. The source of this energy is the motile activity of the outer hair cells.[28] Otoacoustic emissions have been found to be of most use when measured after the cochlea has been acoustically stimulated. This stimulation can be in the form of clicks or tone bursts giving transient evoked OAEs, or two pure tones of specific frequency and intensity ratios can be used, these are known as distortion product OAEs.

https://doi.org/10.1258/0022215011906984 Published online by Cambridge University Press

If the hypothesis is that the lesion in presbyacusis is at the site of the outer hair cell one would expect to find reduced OAEs in the elderly in proportion to, or greater than, the degree of a hair loss.[29] Bonfils[30] investigated OAEs from subjects aged two to 88 years. He found that OAEs were present in all subjects up to age 60, in the over 60 age group the prevalence of OAE absence significantly increased. From 40 years onwards the thresholds for OAEs increased. Bonfils interpreted this to mean the ageing process had a preferential effect on the outer hair cell.

It has been further shown that click evoked OAEs deteriorate with age.[31–33] This reduction in OAE magnitude is in proportion to pure tone thresholds. No further effect of age was noted when compared to a young control group of equal pure tone thresholds. A similar conclusion has been found when studying the elderly using distortion product OAE's.[34,35] Two studies have found distortion products of OAEs in the elderly to be of a reduced magnitude and that the magnitude of this reduction is greater than would be expected given the pure tone thresholds alone.[36,37] This would indicate a disruption of the outer hair cells that may predate the hearing loss and would reaffirm this as the site of the lesion.

A reliable method of histologically fixing the cochlea without post-mortem artefact has been lacking until relatively recently.[38] The main challenge facing investigators has been to correlate histological findings with the results of audiological-testing in the elderly population. The majority of the work looking for the lesion in presbyacusis relates to the inner ear. The middle ear has been investigated,[23] as has a hypothesis concerning bone overgrowth of the fundus of the internal auditory meatus,[39,40] though neither is convincing. Schuknecht[8] correlated pure tone audiometry and histological findings, and proposed two types of presbyacusis, sensory and neural. In 1964[9] he added metabolic (strial) and mechanical types of presbyacusis. Thirty years later Schuknecht[10] reaffirmed his findings. Despite only being observational studies in a small number of subjects Schuknecht's work is often quoted and forms the basis of much written on presbyacusis.

Sensory presbyacusis categorizes the patients with normal low frequency hearing, but a high tone loss, in line with a hair cell loss in the proximal 12 mm of the cochlea, deposition of lipofuscin in the hair cells and the loss of stereocilia on electron microscopy.[41] Schuknecht described neural presbyacusis as having a sloping audiogram with all frequencies reduced, an a reduction in spiral ganglion neurones,[42] and strial presbyacusis affecting a younger age group of 30–60 years with a flat audiogram affecting all frequencies. Microscopy can involve atrophy of all three layers of the stria vascularis although the marginal layer is most frequently affected. Pauler[43] found that increased thresholds were directly proportional to the quantified loss of the stria vascularis. He described cochlear-conductive presbyacusis as starting in the fifth decade and hypotheized that it consisted of a downward sloping pure tone audiogram without any histological correlate. This is thought to be due to a change in the resonant qualities in the cochlear duct, that resembles the cochlear histology found in otosclerosis. In 1919 Mayer hypothesized that old age deafness was due to an increase in basilar membrane stiffness.[44] Schuknecht described patients with more than one of the above as having mixed presbyacusis and those with a different audiogram than the cochlear conductive group, but no histological abnormality, as indeterminate presbyacusis. It is worth reiterating that the above classification is based on a small number of observations that are by Schuknecht's own admission[10] 'admittedly somewhat arbitray'. The question one asks is whether a lot of the changes he describes really translate into hearing loss or are epiphenomena of ageing.

Jorgensen[45] described a reduction in the thickness and number of blood vessels in both the organ of Corti and the stria vascularis. He agreed with the work of Saxen[7] who likened the ageing of the vascular elements of the inner ear to the ageing of the kidney. They both hypothesized that the function of the inner ear declined with age because of reduced endolymph production. The loss of hair cells and supporting cells was noted but not thought to be important.

Hansen[21] reviewed the literature and described changes in a group of 12 elderly patients, although he did not have a control group. He suggested that numerous sites were affected in the presbyacusis ear, with an equal emphasis on central and cochlea changes. Soucek and Michaels[25] demonstrated hair cell loss in the aged cochlea. They looked at the cochleas of elderly patients, all of whom had audiological investigation and most had an ABR before dying and they compared them to young controls. Using light microscopy they found outer hair cell loss in all coils of the cochlea supporting work by Bredburg in 1966 using the electron microscope.[11] The start of the basal coil of the cochlea consistently showed a complete loss of hair cells. Many of the surviving hair cells had undergone a process of giant stereociliary degeneration (GSD). This involves the adhesion of groups of stereocilia to form a thick structure that also elongates to a length of about 60 μm, about the same length of a hair cell. This gives the appearance to the light microscope[25] and electron microscope[46] of a giant stereocilium. GSD is thought to be a stage in the natural degeneration of the hair cells and has been noted in guinea pigs.[47]

Animal models for presbyacusis have also been used. In controlling the environment by 'quiet ageing' Bohne histologically examined 80 chinchilla cochleas ranging in age from premature to 19.2 years.[48] He found that inner hair cells degenerated at a rate of about 0.29 per cent per year and outer hair cells at one per cent per year. The chinchillas showed minor strial and spiral ganglion atrophy. The changes found in the chinchilla cochlea were

https://doi.org/10.1258/0022215011906984 Published online by Cambridge University Press

morphologically similar to humans and Bohne concluded that degeneration of the outer hair cell was responsible for presbyacusis. Animal studies by Gratton looking at the stria vascularis have found microvascular changes associated with ageing,[49] and evidence for a fall in the endocochlear potential has been associated with the changes of ageing, but interestingly this does not seem to significantly affect hearing thresholds.[50]

Animal studies allow for control of the genetic background as well as the environment. Adams studied quiet-aged Mongolian gerbils and found that the majority of the age-related changes occurred at the hair cell level, with the stria vascularis and the spiral ganglion being relatively spared.[51] Interestingly there was a huge variation amongst this relatively homologous group indicating that probably genetic factors were at play and these had not been controlled. The evidence would suggest that the cochlea is the site of age-related hearing loss. The location of the site within the cochlea responsible for presbyacusis is less clear. To a degree there is evidence for multiple site involvement, however the hair cells, particularly the outer hair cells seem most likely to be responsible.[52]

Aetiology of presbyacusis

Many systemic factors have been implicated as contributing to, if not being the cause of, presbyacusis. However, the majority of studies have been poorly controlled or have not accounted for important variables such as age and noise.

Cardiovascular disease and hypertension have been hypothesized to cause presbyacusis since 1902.[53] The Framingham Heart Study Cohort was used as a reference population by Moscicki who performed a cross-sectional study based on this population group. He found that 83 per cent had at least mild hearing loss. Multivariate analysis suggested that noise exposure, several medical illness, Menière's disease and family history were significant but minor risk factors, however age was by far the most significant.[54] Gates in 1993 used the same cohort but attempted to relate cardiovascular disease with presbyacusis.[55] He found that cardiovascular factors had no direct link to hearing loss, except for systolic (but not diastolic) blood pressure. Numerous studies have found no relationship between cardiovascular disease and presbyacusis. Parving in 1993 studied 5000 subjects for 10 years and could find no correlation.[56] An interesting relationship that may confound the above is that noise exposure itself can be related to hypertension.[57–59]

Blood hyperviscosity has also been considered in relation to presbyacusis. Browning[60] found a relationship between high shear blood viscosity and poorer thresholds although they were within the normal range. This typifies the results of other studies into hearing and blood viscosity that were inconclusive.

The association of noise and presbyacusis has been studied by comparing cross-sectional studies of noise-exposed and non-exposed populations. Non-exposed populations used include a tribe from the Sudan called Mabaan studied by Rosen,[61] the Todas who are an isolated hill-dwelling tribe in South India[62] and islanders in the Orkneys.[63] These populations have been compared with other populations from industrial centres, Glorig from the Wisconsin State Fair[64] and Hinchcliff from the United Kingdom.[65] Predictably the non-noise exposed populations had better preservation of hearing into old age. Interestingly the Mabaan differed from the Orkney islanders, in that up to 60 years the Mabaan had worse hearing but over 60 significantly better. This may indicate that genetic rather than environmental factors are the most significant.[66]

Del Guidice in 1960 hypothesized that atherosclerosis and hypercholesterolaemia are associated with presbyacusis.[67] Rosen compared a population with high blood cholesterol from Finland with a population from Yugoslavia with low cholesterol and low incidence of cardiovascular disease.[68] The Yugoslav group had a slower decline in hearing loss with age but there was no evidence that this was anything more than an association rather than a causal relationship.

The glutamate hypothesis has been proposed as a mechanism for presbyacusis by Pujol.[69] Glutamate is the neurotransmitter between the inner hair cells and the auditory nerve. The hypothesis suggests that excess release of glutamate due to excess auditory stimulation either by noise, or in hypoxia conditions that are thought to occur with age results in a large influx of calcium ions. As a result calcium homeostasis is compromised and calcium becomes toxic to the cells leading to cell death. Support for this theory comes from observations using kainic acid, a glutamate analogue. However its applicability to presbyacusis has to be questioned in the light of evidence that the majority of the disturbance appears to be at the outer hair cell, and glutamate is not a neurotransmitter at this site.

Calcium may have a role in presbyacusis other than through the glutamate mechanism. Small cross-sectional studies have suggested that patients taking calcium channel blocking medication had better pure tone thresholds than patients that were not.[70,71] This effect was only noticed in women and the possibility of a sampling error is high. An association between presbyacusis and metabolic bone disease has been hypothesized. A small study of 56 patients with metabolic bone disease[72] associated high serum calcium and high alkaline phosphatase with presbyacusis suggesting a possible protective effect of vitamin D. The deleterious effect of serum calcium on hearing was later disputed in a bigger study.[73]

An association between hyperlipidaemia and presbyacusis has been hypothesized. Rosen[61] suggested that the Mabaan's tribe's good hearing was due partly to diet and low lipid levels although they were not measured. Spencer in 1973[74] studied a large group of 444 cases with SNHL and found that 46 per cent had significant hyperlipoproteinaemia. However, there was no control group and no

https://doi.org/10.1258/0022215011906984 Published online by Cambridge University Press

publication of what was considered to be normal levels. In 1997 Jones[75] found no difference in the prevalence of SNHL in a population with hyperlipidaemia compared to a control population, he also found no significant difference in the prevalence of hyperlipidaemia in a population with SNHL compared to a control population. He concluded that hyperlipidaemia had no significant effect on hearing loss when age was controlled as a variable.

Parving hypothesized that diabetes and hypothyroidism have an effect on presbyacusis.[76] She investigated the effect of hypothyroidism and two groups of diabetic patients, one group was small vessel disease and the other without. She found no effect of presbyacusis causing hearing loss when compared to age and sex matched population. There were no differences between a diabetic and a matched population in the cochlea or retrocochlear function. However, other studies have shown abnormal ABR responses in 40 per cent of diabetics, but without any attenuation of pure tone thresholds possibly indicating a mild diabetic encephalopathy.[77]

The cochlea relies on about 100 genes for normal function,[78] and a genetic explanation for presbyacusis has been sought. As only the elderly are affected studying generations would take an impossibly large number of years. The modern small family size makes any linkage analysis difficult, as does controlling for environmental variables. A good animal model exist in the mouse, particularly a strain that 'ages' quickly, the senescence accelerated mouse (SAM). ABR and histopathological studies show this to be a useful model of human presbyacusis.[79] These mice show permanent and progressive degeneration of the organ of Corti.[79] Genetic homology between mouse deafness and human deafness has been demonstrated with other mouse strains. For example the Shaker 1 mouse has a defect in the gene for myosin VIIa, a protein essential for OHC function, the same defect has been found in Usher's syndrome USH 1B, and non-syndromic loss DFN B2.[80] Age-related hearing loss in mice has been found to have a powerful genetic basis. In 1996 the strain of mouse that developed deafness with age, the C57BL/6J strain was found to be particularly susceptible to noise damage.[81] In 1997 the allele responsible was mapped to the mouse Chromosome 10 and was found to produce α-1 gap junction protein.[80] This gene known originally as B6 codes for a 'special' family of short chain collagens that are found only in the cochlea. They are essential for the formation of inter-cellular junctions. Genetic mutations presents phenotypically with progressive sensorineural hearing loss analogous to prebyacusis. The B6 gene has since been named the adult hearing loss gene, or Ahl.

Further work was found three genes that lead to a progressive hearing loss in adult mice. They are Ahl, Ahl 2 and Ahl 3 and code for the 'special' collagens. Ahl and Ahl 2 have been mapped to Chromosome 10, Ahl 3 has as yet to be mapped to a chromosome. Interesting experiments have been performed crossing the strain of mouse with only the Ahl gene, denoted as the B strain, and the mouse with all the hearing loss genes Ahl, Ahl 2 and Ahl 3 known as the D strain.[82] The B mouse as expected has phenotypically better hearing than the D. However, when crossed the result is a range of hearing losses between B and D, but a number of mice with worse hearing than the D stain occur, other genes are probably involved.[82] This recent work does indicate that in the prebyacusis mouse model there is good evidence for the involvement of the Ahl genes, and possibly others.

Detailed genetic analysis in humans may have to await the 'gene chip' to help analyse data from large numbers of people. However, a Jewish family who suffered progressive age-related hearing loss over six generations traced back to 1843 have been analysed and this has revealed a defective gene on Chromosome 5. This gene is known as POU 4F3, and transcribes a transcription factor which is only expressed in the cochlea hair cell and which is necessary for their terminal differentiation and trophic support.[83] The eight base pair deletion gives th non-syndromic loss now known as DFNA 15. It may be this gene, or genes homologous to it from which it will be possible to extrapolate to the entire population. The Framingham Cohort has also been used to investigate the genetics of presbyacusis.[84] The age-related hearing thresholds of genetically unrelated spouse pairs were compared to genetically-related sibling and parent-child pairs. They found that clear familial aggregation existed. This was most notable in women, and was up to 55 per cent. In men the trend was less noticeable probably due to a higher incidence of noise exposure. Gates *et al*.[85] suggested a 'genetic effect on the inheritance of presbyacusis.'

A further set of genes that may be significant with respect to presbyacusis are the mitochondrial genes. The mitochondria, of which there may be thousands per cell, perform oxidative phosphorylation that generates the ATP for cellular activity. Mitochondrial DNA (mtDNA) is packed into two to 10 chromosomes each of which has 13 protein-coding genes, and for expression two mitochondrial rRNAs and 22 organelle specific tRNA's. all of which are necessary to assemble the functioning mitochondrial unit.[85,86] Mitochondrial mutations resulting in loss of ATP production will affect tissue that has a high-energy demand. In the cochlea the outer hair cells have the greatest energy requirement. Mitochondrial mutations are thought to have a role in general body ageing.[87] Mitochondrial DNA is more prone to mutation than other cellular DNA. The mt DNA is in close proximity to free radicals from the cell's oxidative process and it lacks the histone protection and repair mechanisms that serve cellular DNA.[88] The human mt DNA has a common deletion at nucleotide 4977. The frequency of this deletion is increased in the elderly when compared to controls.[89] The gene encoded by mt DNA cytochrome oxidase II has been found to have a significantly increased rate of mutation in the elderly. Fischel-Ghodsian[88] found that the site of such mutation in

https://doi.org/10.1258/0022215011906984 Published online by Cambridge University Press

the elderly was the spiral ganglion cells and the stria vascularis. This would suggest that the mt DNA has a minor effect on presbyacusis because it seems to spare the outer hair cells. However, Siedman[89] looked at mt DNA in an animal model. He used rats that like humans have a common deletion at base pair 4834. He studied stria and auditory nerve and brain in the rats on which he had performed ABR. He found that there was a positive correlation between the incidence of common deletion and hearing loss, and that this may play a part in presbyacusis.[90,91]

The relationship between the major histocompatibility complex (MHC) group of genes has been studied. The MHC group encode for three groups of proteins that are involved in the immune response. They are Group I, genes A, B and C, Group II DR, DP, DQ and Group III that include certain complement proteins, heat stable Protein 70 and TNF-α. The interest in the MHC genes is whether there may be linkage to a hearing loss gene. Bernstein[92] found that SNHL was 17 times more likely if the patient had the A1/B8/DR3 genotype, and 8.5 times more likely of 'strial' presbyacusis with the same genotype. It has also been hypothesied that presbyacusis could be caused by an immunological mechanism. Bernstein[92] hypothesized that erythrocytes with defective C3b complement attached would not mop up immune complexes to cochlea type II collagen protein, however, there is little evidence to support this as a cause for presbyacusis.

A further area of investigation into presbyacusis aetiology is that of apoptosis. Could programmed cell death be the cause? Using two strains of mouse, one senescence accelerated and one senescence prone, Usami compared the rates of apoptosis in different parts of the cochlea in each group. Usami used the Tunel technique to identify the fragmented DNA in the apoptotic cells.[93] The positively staining cells were found in the hair cells, supporting cells and the cells of the stria, but not the spiral ganglion. This is consistent with the histological findings in humans, although the cause of the trigger for apoptosis in the cochlea is not known.

Summary

Studies of presbyacusis, or the failure of hearing with age, need to ensure that other causes of sensorineural hearing loss have been excluded. The locus of the disturbance is within the cochlea and the evidence for this is strong, however multiple sites within the cochlea are affected by age. The site of most functional significance is an area of much controversy, however, we would suggest that the evidence points to it being the outer hair cells.

The aetiology is much less certain, however, it would appear that a complex genetic cause is most likely. The most exciting future work will be in this area.

References

1 Critchley M. *Butterworths Medical Dictionary*, 2nd edn. London: Butterworth and Co., 1990
2 Zwarardemaker H. Der Verlust au hohen Tonen mit zunehmendem Alter. Ein neues Gesetz. *Arch Ohr Nas und Kehlkopfheilkunde* 1874;**32**:53–6
3 Toynbee J. On the pathology and treatment of the deafness attendant upon old age. *Mon J Med Sci* 1849;**1**:1–12
4 Bunch CC. Age variations in auditory acuity. *Arch Otolaryngol Head Neck Surg* 1929;**9**:625–36
5 Crowe SJ, Guild SR, Polvought LM. Observations of the pathology of high tone deafness. *Bull Johns Hopkins Hosp* 1934;**54**:315–80
6 Saxen A. Pathologie und Klinik der Altersschwerhougkeit. *Acta Otolaryngol Suppl* 1937;**23**:1–85
7 Saxen A. Inner ear in presbycusis. *Acta Otolaryngol* 1952;**4**:213–27
8 Schuknecht HF. Presbycusis. *Laryngoscope* 1955;**65**:402–19
9 Schuknecht HF. Further observations of the pathology of presbycusis. *Arch Otolaryngol Head Neck Surg* 1964;**80**:368–82
10 Schuknecht HF, Gacek MR. Cochlear pathology in presbycusis. *Ann Otol Rhinol Laryngol* 1994;**102**:1–16
11 Bredburg C. Cellular pattern and nerve supply of the human organ of Corti. *Acta Otolaryngol Suppl* 1965;**236**:1–135
12 Davis A. *Hearing in Adults*. London: Whurr Publishers, 1995
13 Davis AC, Ostri B, Parving A. Longitudinal study of hearing. *Acta Otolaryngol Suppl* 1991;**476**:12–22
14 Hinchcliffe R. The anatomical locus of presbycusis. *J Speech Hear Disord* 1962;**27**:301–10
15 Maspetiol R, Semmette D. Les testes d'audiometric tonal dans les atteintes auditives corticales et centrales. *Int Audiol* 1968;**7**:66–76
16 Feldman RM, Reger SN. Relations between reaction time and ages. *J Speech Hearing Res* 1967;**10**:479–95
17 Welsh LW, Welsh JJ, Healy MP. Central presbycusis. *Laryngoscope* 1985;**95**:128–36
18 Soucek S, Michaels L. *Hearing Loss in the Elderly*, Loon: Springer-Verlag, 1990
19 Gaeth JH. *Study of Phonemic Regression in Relation to Hearing Loss* (Thesis). Chicago: Northwestern University, 1948
20 Holmes AE, Kricos PH, Kessler RA. A closed versus open set measure of speech discrimination in normally hearing young and elderly adults. *Br J Audiol* 1988;**22**:29–33
21 Hansen CC, Reske-Nielsen E. Pathological studies in presbycusis. Cochlear and central findings in 12 aged patients. *Arch Otolaryngol* 1965;**82**:115–32
22 Konigsmark BW, Murphy EA. Volume of the ventral cochlear nucleus in man: its relationship to neuronal poplation and age. *J Neuropathol* 1972;**31**:304–16
23 Nixon JC, Glorig A, High WS. Changes in air and bone conduction thresholds as a function of age. *J Laryngol Otol* 1962;**76**:288–99
24 Lehnhardt E. *Clinical Aspects of Inner Ear Deafness*. Berlin: Springer, 1984
25 Soucek S, Michaels L. *Hearing Loss in the Elderly*. London: Springer-Verlag, 1990
26 Prijis VF. On peripheral auditory adaptation II. Comparison of electrically and acoustically evoked action potential in the guinea pig. *Acoustica* 1980;**45**:35–47
27 Kemp DT. Stimulated acoustic emissions from within the human auditory system. *J Acoustic Soc Am* 1978;**64**:1386–91
28 Brownell WE, Bader CR, Bertrand D, Ribaupierre Y. Evoked mechanical responses of isolated cochlear outer hair cells. *Science* 1985;**227**:194–6
29 Zenner HP. Motile responses in outer hair cells. *Hearing Res* 1986;**22**:83–90
30 Bonfils P, Bertrand Y, Uziel A. Evoked otoacoustic emissions: Normative data and presbycusis. *Audiology* 1988;**27**:27–35
31 Avan P, Elbez M, Bonfils P. Click evoked otoacoustic emissions and the influence of high frequency hearing losses in humans. *J Acoust Soc Am* 1997;**101**:2771–7
32 Prieve R. COAEs and SSOAEs in adults with increasing age. *Ear Hear* 1995;**16**:521–9

33 Collet L, Moulin A, Gartner M, Morgon A. Age-related changes in otoacoustic emissions. *Ann Otol Rhinol Laryngol* 1990;**99**:993–7

34 Strouse AL, Ochs MT, Hall JW IIIrd. Evidence against the influence of ageing on distortion product otoacoustic emissions. *J Am Acad Audiol* 1996;**7**:339–45

35 Avan P, Bonfils P, Loth D, Elbes M, Erming M. Transient evoked otoacoustic emissions and high frequency acoustic trauma in the guinea pig. *J Acous Soc Am* 1995;**97**:3012–20

36 Takahashi S, Ikeda K, Kobayashi T, Takasaka T, Ohyama K, Wada H. Effect of age on distortion product otoacoustic emissions. *J Oto-Rhino-Laryngol Soc Jpn* 1996;**99**:978–84

37 Nieschalk M, Hustert B. Clinical application of distortion products of otoacoustic emissions in presbycusis. *Laryngo-Rhino-Otologie* 1996;**75**:129–34

38 Iurato S, Bredberg G, Bock G. Functional histopathology of the human audiovestibular organ. *Eurodata Hear Proj.* Commission of the European Communities, 1982

39 Sercer A, Krmpotic J, Uber die Urasche der proressiven Altersschwerhorigkeit, (Presbyacusis). *Acta Otolaryngol Suppl* 1958;**143**:5–36

40 Krmpotic-Nemanic J. A new concept of the pathogenesis of presbycusis. *Arch Otolaryngol Head Neck Surg* 1971;**93**:161–6

41 Nomura Y, Kawabata I. Loss of stereocilia in the human organ of Corti. *Arch Otolaryngol Head Neck Surg* 1979;**222**:181–5

42 Otte J, Schuknecht HF, Kerr AG. Ganglion cell population in normal and pathological human cochleae. Implications for cochlear implantation. *Laryngoscope* 1978;**88**:1231–46

43 Pauler M, Schuknecht HF, White JA. Atrophy of the stria vascularis as a cause of sensorineural hearing loss. *Laryngoscope* 1988;**98**:754–9

44 Mayer O. Das anatomische Substrat der Alterschwerhorigkeit. *Arch Ohr Nas und Kehlkopfheilkunde* 1919;**105**:1–12

45 Jorgensen MB. Changes in ageing in the inner ear. Histopathological studies. *Arch Otolaryngol Head Neck Surg* 1961;**74**:164–70

46 Wright A. Giant cilia in the human organ of Corti. *Clin Otolaryngol* 1982;**7**:193–9

47 Ernstson S. Cochlear morphology in a strain of waltzing guinea pig. *Acta Oto-Laryngol* 1971;**71**:469–82

48 Bohne BA, Gruner MM, Harding GW. Morphological correlates of ageing in the chinchilla cochlea. *Hearing Res* 1990;**48**:79–92

49 Gratton MA, Shulte BA. Alterations in microvasculature are associated with atrophy of the stria vascularis in quiet aged gerbils. *Hearing Res* 1995;**82**:44–52

50 Gratton MA, Schmeidt RA, Schulte BA. Age related decreases in endocochlea potential are associated with vascular abnormalities of the stria vascularis. *Hearing Res* 1996;**102**:181–90

51 Adams JC, Schulte BA. Histopathologic observations of the ageing gerbil cochlea. *Hearing Res* 1997;**104**:101–11

52 Wright A, Davis A, Bredburg G, Ulehlova L, Spencer H. Hair cell distributions in the normal human cochlea. A report on a European working group. *Acta Otolaryngol Suppl* 1987;**436**:15–24

53 Alexander G. Zur pathologischen Histologie des Ohrenlabyrinthes mit besonderer Berucksichtingung des Coortischenen Organes. *Arch Ohrenheilkd* 1902;**56**:1–23

54 Moscicki EK, Elkins EF, Baum HM, McNamara PM. Hearing loss in the elderly: An epidemiologic study of the Framingham Heart Study Cohort. *Ear Hear* 1985;**6**:184–90

55 Gates GA, Cobb JL, D'Agostino RB, Wolf PA. The relation of hearing in the elderly to the presence of cardiovascular disease and cardiovascular risk factors. *Arch Otolaryngol Head Neck Surg* 1993;**119**:156–61

56 Parving A, Hein HO, Suadicani P, Ostri B, Gyntelberg F. Epidemiology of hearing disorders. *Scand Audiol* 1993;**22**:101–7

57 Johnsson LG, Hawkins JE. Sensory and neural degeneration with ageing, as seen in microdissections of the human inner ear.*Ann Otol Rhinol Laryngol* 1972;**81**:179–93

58 Sanden A, Axelsson A. Comparison of cardiovascular responses in noise-resistant and noise-sensitive workers. *Acta Otolaryngol Suppl* 1981;**377**:75–100

59 Beli S, Sari L, Scarficcia G, Sorrentino R. Arterial hypertension and noise: a cross-sectional study. *Am J Ind Med* 1984;**6**:59–65

60 Brownig GG, Gatehouse S, Lowe GD. Blood viscosity as a factor in sensorineural hearing impairment. *Lancet* 1986;**1**:121–3

61 Rosen S, Bergman M, Plester D, El-Mofty A, Satti MH. Presbycusis study of a relatively noise free population in the Sudan. *Ann Otol Rhinol Laryngol* 1962;**71**:727–43

62 Kapur YP, Patt AJ. Hearing of Todas of South India. *Arch Otolaryngol Head Neck Surg* 1967;**85**:400–6

63 Kell RL, Pearson JCC, Taylor W. Hearing thresholds in an island population in North Scotland. *Int Audiol* 1970;**9**:334–9

64 Glorig A, Nixon J. Distribution of hearing loss in various populations. *Ann Otol Rhinol Laryngol* 1960;**69**:497–516

65 Hinchcliffe R. Population studies concerned with presbyacusis. *Indian J Otol* 1968;**20**:52–7

66 Bergman M. Hearing in the Mabaans. A critical review of related literature.*Arch Otolaryngol Head Neck Surg* 1966;**84**:411–5

67 Del Guidice M, Amorelli A. Cholesterolemia and presbyacusis. *Arch Ital Otolaryngol* 1960;**68**:175–9

68 Rosen S, Olin P. Hearing loss and coronary heart disease. *Arch Otolaryngol Head Neck Surg* 1965;**82**:236–43

69 Pujol R, Rebillard G, Puel J-L, Lenoir M, Eybalin M, Recasens M. Glutamate neurotoxicity in the cochlea: A possible consequence of ischaemic or anoxic conditions occuring in ageing. *Acta Otolaryngol Suppl* 1991;**476**:32–6

70 Mills JH, Matthews LJ, Lee F-S, Dubno JR, Schulte BA, Weber PC. Gender-specific effects of drugs on hearing levels of older persons. *Ann New York Acad Sci* 1999;**884**:381–8

71 Lee F-S, Matthews LJ, Mills JH, Dubno JR, Adkins WY. Gender-specific effects of drugs on hearing levels of older persons. *Otolaryngol Head Neck Surg* 1998;**118**:221–7

72 Yamazaki T, Ogwa K, Imoto T, Hayashi N, Kozaki H. Senile deafness and metabolic bone disease. *Am J Otol* 1988;**9**:376–82

73 Lee FS, Matthews LJ, Mills JH, Dubno JR, Adkins WY. Analysis of blood chemistry and hearing levels in a sample of older persons. *Ear Hear* 1998;**19**:180–90

74 Spencer JT. Hyperlipoproteinemia in the aetiology of inner ear disease. *Laryngoscope* 1973;**83**:639–78

75 Jones NS. *Hyperlipidaemia and Hearing Loss*. (MD Thesis) University of London, 1997

76 Parving A. Hearing problems and hormonal disturbance in the elderly. *Acta Otolaryngol Suppl* 1991;**476**:44–53

77 Parving A, Elberling C, Balle V, Parbo J, Dejgaard A, Parving HH. Hearing disorders in patients with insulin dependent diabetes mellitus. *Audiology* 1990;**29**:113–21

78 Morton NE. Genetic epidemiology of hearing impairment. *Ann New York Acad Sci* 1991;**630**:16–31

79 Saitoh Y, Hosokama M, Shimada A, Watanabe Y, Yasuda N, Takeda T, *et al*. Age related hearing impairment in the senescence accelerated mouse (SAM). *Hearing Res* 1994;**75**:27–37

80 Faddis BT Hughes RM, Miller JD. Quantitative measures reflect degeneration, but not regeneration in the deafness mouse organ of Corti. *Hearing Res* 1998;**115**:6–12

81 Johnson KR, Erway LC, Cook SA, Willott JF, Zheng QY. A major gene affecting age related hearing loss in C57BL/6J mice. *Hearing Res* 1997;**114**:83–92

82 Erway LL, Shiau Y-W, Davis RR, Krieg EF. Genetics of age related hearing loss in mice III. Susceptibility of inbred and F1 hybrid strains to noise induced hearing loss. *Hearing Res* 1996;**93**:181–7

83 Willot JF, Erway LC, Archer JR, Harrison DE. Genetics of age-related hearing loss in mice II. Strain differences and effects of caloric restriction on cochlear pathology and evoked response threshold. *Hearing Res* 1995;**88**:143–55

84 Willot JF, Erway LC. Genetics of age-related hearing loss in mice IV. Cochlear pathology and hearing loss in 25 BXD recombinant inbred mouse strains. *Hearing Res* 1998;**119**:27–36

85 Gates GA, Couropmitree MP, Myers RH. Genetic associations in age-related hearing thresholds. *Arch Otolaryngol Head Neck Surg* 1999;**125**:654–9
86 Vahava O, Morell R, Lynch ED, Weiss S, Kagan ME, Ahituv N, *et al*. Mutation in transcription factor POU4F3 associated with inherited progressive hearing loss in humans. *Science* 1998;**279**:1950–4
87 Attardi G, Schatz G. Biogenesis of mitochondria. *Ann Rev Cell Biol* 1988;**4**:289–333
88 Nagley P, Zhang C, Martinus RD, Vaillant F, Linnane AW. Mitochondrial DNA mutation and human ageing. Molecular biology, bioenergetics and redox therapy. In: DiMauro S, Wallace DC, eds., *Mitochondrial DNA in Human Pathology*. New York: Raven Press, 1993;54–72
89 Fischel-Ghodsian N, Bykhovskaya Y, Taylor K, Kahen T, Cantor R, Ehrenman K, *et al*. Temporal bone analysis of patients with presbyacusis reveals high frequency of mitochondrial mutations. *Hearing Res* 1997;**110**:147–54
90 Seidman MD, Bai U, Kahn MJ. The association of mitochondrial DNA deletions and cochlear pathology: a molecular biological tool. *Laryngoscope* 1996;**106**:777–83
91 Seidman MD, Bai U, Kahn MJ, Quirk WS. Mitochondrial DNA deletions associated with ageing and presbyacusis. *Arch Otolaryngol Head Neck Sur* 1997;**123**:1039–45
92 Bernstein JM, Shanahan TC, Schaffer FM. Further observations on the role of the MHC genes and certain hearing disorders. *Acta Otolaryngol Stockh* 1996;**116**:666–71
93 Usami S, Takumi Y, Fijita S, Shinkawa H, Hosokawa M. Cell death in the inner ear associated with ageing in apoptosis? *Brain Res* 1997;**747**:147–50

Address for correspondence:
Professor N. S. Jones,
Department of Otolaryngology,
Queens Medical Centre,
Nottingham NG2 7UH, UK.

Professor N. Jones takes responsibility for the integrity of the content of the paper.
Competing interests: None declared