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No. 8

The Royal National Institute for the Deaf
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## HEREDITARY DEAFNESS NEWSLETTER

May 1992  
No. 8

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Editorial

The rate of localising and cloning genes for deafness in humans appears to be increasing, with several more localisations and a gene for Waardenburg syndrome type I (WSI) being reported since the last issue of the newsletter. The finding of mutations in the PAX3 gene of humans with WSI (Tassabehji et al. Nature 355:635-636, 1992; Baldwin et al. Nature 355:637-638, 1992; see also report on the Molecular Biology of Hearing and Deafness meeting in this newsletter) followed rapidly the report of a mutation in Pax-3 in the splotch mouse mutant (Sp²H, Epstein et al. Cell 67:767-774, 1991), which emphasises the usefulness of comparative mapping in identifying candidate genes. In the last few weeks, three new deafness genes have been localised: one gene for Usher syndrome type I (USHI) has been found on 11q, another gene for USHI is on 11p, and a gene causing branchio-oto-renal syndrome is linked to markers on 8q (see meeting report in this newsletter). Within the last few months, other genes causing deafness in humans that have been localised include: another gene for USHI on 14q (see Usher consortium report in this newsletter), dominant progressive hearing loss to 5q (Monge's deafness, see meeting report and laboratory report in this newsletter), Treacher Collins syndrome on 5q (see newsletter no. 6), and two pedigrees in which deafness is associated with mitochondrial inheritance (Jaber et al. J Med Genet 29:86-90, 1992; Ballinger et al. Nature Genetics 1:11-15, 1992).

This issue of the newsletter includes reports of three recent meetings - the Molecular Biology of Hearing and Deafness conference in San Diego organised by Allen Ryan, and the Waardenburg and Usher syndrome consortia reports. Several laboratory reports are included as usual.

The next issue of the newsletter is due out in the autumn, so please send your contributions - lab or clinic reports, details of new linkages, interesting families or animals with inherited deafness, meeting information and meeting reports, details of publications about hereditary deafness, and so forth - to me by the end of September.

Karen Steel, Editor
Report of the meeting on The Molecular Biology of Hearing and Deafness

This meeting was held on May 1st-4th 1992 in La Jolla, California, and was sponsored by the Deafness Research Foundation, the National Institute of Deafness and Other Communicative Disorders and the UCSD School of Medicine, Division of Otolaryngology.

The first session, on development, growth and regeneration, started with a review of growth factors (Baird) which emphasised the large numbers that have now been described, and the probable overlap in their distribution and function in the developing embryo. Two talks (Van De Water, Ylikoski) described the distribution of neurotrophic factors and their effects on auditory neuron development, and Fermin described changes in neurofilament NF200 and microtubule associated protein MAP5 in developing chick vestibular neurons. The kinocilium appears to be involved in recovery of hair cells following damage (Sobkowicz). Talks by Cotanche and Raphael suggested that supporting cells divide to provide new hair cells in damaged bird cochleas, while Salvi found that auditory neurons innervating regions of regenerating avian hair cells did not rapidly recover normal function.

The session on inner ear mutations in animals included a review of positional cloning of genes for deafness in mice, illustrated by progress in localising the shaker-1 mutation on chromosome 7 (Brown). Three insertional mutations in the mouse were described: the Wocko mutant, on chromosome 1 (Friedman), the head bobber mutant (Smith) and an insertion near the twirler locus on chromosome 18 which appears to mimic the twirler gene in its effects on the inner ear (Meisler). All three transgenics show morphogenetic defects including malformation of the vestibular part of the inner ear, and in each case the investigators have isolated a flanking clone on one side of the insertion. Morphogenetic inner ear defects were also reported in transgenic mice with the int-2 gene disrupted, but interestingly these effects were not fully penetrant and 12 out of 28 ears appeared normal with six mice showing asymmetry (Mansour). Cosgrove described his progress towards production of a transgenic mouse model of X-linked Alport syndrome by disrupting the collagen 4a5 gene. In the deaf mouse mutant kreisler, which has morphogenetic defects of the inner ear, the patterns of expression of int-2, krox-20 and Hox-1.5 in the adjacent hindbrain were described (Lewis). Finally, the deleterious effects of mutations at the W and Steel loci on melanocyte migration to the stria vascularis of the cochlea, the associated lack of an endocochlear potential, and consequent hearing impairment in the mutant mice were described (Steel).

Human genetics was the topic of the third session, and it was dominated by the very recent findings of mutations in the PAX3 gene in Waardenburg syndrome. The Manchester group described four such mutations, including an 18 bp deletion in exon 2 (Nature 355:635-636, 1992), a single base deletion in exon 2, a 2 bp deletion in exon 4, and a missense mutation in exon 2 (Read, Strachan). The last of these was found in a probable type II family, while the others are all in type I families. The East Lansing group described a 14 bp deletion in exon 2 in a large Indonesian family (Morell), and the Boston group (Baldwin) reported a missense mutation in exon 2 (Nature 355:637-638, 1992). Furthermore, PAX3 appears to be deleted along with other genes on chromosome 2q in a case of Waardenburg syndrome type III (Gorski). The inversion breakpoint presumed to cause WSI in the Japanese boy described by Ishikiriyama has not yet been identified, and neither has exon 5 of PAX3 although exon 1 has now been found (Fex). The first report of the Waardenburg Consortium was described, and this has recently been published (Farrer et al. Am. J. Hum. Genet. 50:902-913, 1992). Additional presentations describing work in progress on Waardenburg syndrome were given by Reynolds, X Z Liu, and A Liu.
Localisation of three further genes for deafness in humans were announced at the conference. A gene for BOR syndrome on 8q linked to PENK and D8S165 was reported (Kumar, Smith), and Kimberling and Smith reported two genes for Usher syndrome type I, one on 11q about 10cM from INT2 and the other on 11p linked to brain-derived growth factor. The Usher syndrome consortium presented its exclusion data for other genes for Usher type I, concluding that the disease was heterogeneous, as at least one other USHI gene has been located in a French population at 14q32. The gene causing dominant progressive deafness in the large Costa Rican kindred has been further localised to a 3cM interval between D5S89 and FGFA on 5q31 (Lynch). Other families with dominant progressive hearing loss do not map to 5q (Smith). A kindred with maternally-inherited deafness was described which was best explained as mitochondrial inheritance plus homozygosity for an autosomal recessive gene, and candidate mitochondrial genes are being investigated (Prezant). The range of inherited deafness in Southern Africa was described by Ramesar, including many families with piebaldism, and the molecular bases of some piebald families, involving several different mutations at the c-kit locus (W, dominant spotting in the mouse) were described (Spritz). The only apparent homozygote for piebaldism was deaf. Several genes causing deafness on the X chromosome were reviewed by Pembrey. Audiometric techniques were found to be unhelpful for identifying carriers of a gene for Norrie’s syndrome (Parving).

Sessions on neuronal receptors and molecular and cell biology studies of the auditory system were included on the second day of the meeting. The presentations included much basic information about the distribution of various types of receptors and other relevant molecules in the auditory system (many contributors), and structural details about some cochlea-specific elements such as tectorial membrane proteins (Richardson) and organ of Corti proteins (Thalmann). Two sites of physiologically-important molecules were proposed: the tip links between adjacent stereocilia (Corey), and the lateral plasma membrane of the outer hair cells (Kachar).

A later session on gene cloning in the normal labyrinth included three talks describing the production and screening of inner ear cDNA libraries. Morton described a human foetal cochlear library constructed from cochleas of second trimester foetuses, which has been subtracted from a brain cDNA library, and several cochlea-specific clones are being analysed. Wilcox has constructed a guinea pig organ of Corti cDNA library, and aims to use it to identify genes involved in non-syndromic deafness. A sequence from this library was identified and cloned using degenerate primers to highly conserved regions of zinc finger domains, and its expression pattern investigated. The third library to be described was an adult mouse inner ear cDNA library, which has been screened with human retina-specific cDNA sequences, and of the clones so far characterised, two show expression limited to the ear and eye and are thus candidates for Usher syndrome genes (Beisel).

Ion channels and transport systems was the topic of one of the sessions, and in addition to a number of excellent talks and posters about ion channels and their characteristics in the stria vascularis, hair cells, nerve terminals and vestibular dark cells, a presentation by Tempel described abnormal expression of a potassium channel gene in the deaf waddler mouse mutant. mRNA levels for the cloned gene were reduced in homozygous dfw/dfw mice, and also in the heterozygotes, and this was associated with raised thresholds for evoked cochlear responses but a normal endocochlear potential.

The last afternoon of the conference focussed upon the molecular biology of temporal bone disease and clinical applications of gene-related research. An association of measles and otosclerosis was suggested by the finding of measles virus sequences in material from active otosclerosis (McKenna). Molecular approaches to investigating hearing loss associated with autoimmunity were described by several participants (Harris, Jenkins, Yoo), and the variety of reasons for the association
discussed, including primary cochlear damage leading to autoimmunity and primary autoimmune disease causing hearing loss. The use of molecular techniques for identifying infectious agents in middle or inner ear infection was described (Lim, Bernstein, Post, Furuta, Takasu, Obermyer). The role of growth factors in response to middle ear infection (Ryan), tympanic membrane damage (Fina, Lee), and neuronal regeneration (Lefebvre) were described. Finally, the possibilities for gene therapy in the treatment of hearing impairment were discussed, and a surprisingly optimistic note was struck (Friedman).

An informal survey of the audience suggested that there was support for a second conference on the molecular biology of hearing and deafness, probably to be held in two years' time on the east coast of the USA. Watch this space for further details.

Report by Karen Steel
Members of the Waardenburg Consortium met on 30th April 1992 at La Jolla, California, as a satellite to the conference on Molecular Biology of Hearing and Deafness. The first report is about to appear in the American Journal of Human Genetics (50:902-913, May 92). The report proposes that criteria for diagnosis of Waardenburg syndrome should be the presence of two major, or one major and two minor, features as briefly listed below:

**Major features**
- Audiovestibular hearing deficit
- Iris pigmentary anomaly
- Hair hypopigmentation
- Dystopia canthorum (Type 1 WS only)
- Affected first-degree relative

**Minor features**
- Congenital leukoderma
- Synophyris or medial eyebrow flare
- Broad high nasal root
- Hypoplasia of alae nasi
- Premature greying of the hair

All these criteria are defined more fully in the report. The report also gives important evidence of locus heterogeneity, both within Type 1 Waardenburg Syndrome (WS1) and between WS1 and WS2. However, of the six genetic markers studied, only ALPP showed good linkage to WS, and this limited the power of the analysis.

Two new developments will greatly clarify the problem. First, of course, PAX3 (this is the official Database name of the Markus Noll's HuP2) has been identified as the seat of some WS mutations. Consortium members reported six fully characterised PAX3 mutation (five in exon 2, one in exon 4) and preliminary indications such as heteroduplexes for several others. Second, a highly informative microsatellite polymorphism has been discovered at the 5'end of PAX3. This will enable PAX3-linked and unlinked families to be distinguished much more clearly than before.

In the next round of collaborative studies, all families will be typed for this PAX3 microsatellite. Those showing recombinants will be typed for flanking markers (ALPP or SAG distally, FNI, TNPI or hopefully a new DES microsatellite proximally). Apparent double recombinants are a sensitive indicator of an unlinked disease locus. At the same time, more emphasis will be put on building up the standardised clinical database. This will take on a key role in defining differences between PAX3-linked and unlinked WS. In view of the unexpected finding of a PAX3 mutation in one probable WS2 family, an attempt will be made to increase the number of WS2 families in the Consortium collection. It is clear that this set of families constitute a unique resource for unravelling the molecular pathology of Waardenburg syndrome.

The Waardenburg Consortium gratefully acknowledge the role of N.I.D.C.D. in supporting its meetings.

*Report by Andrew Read and colleagues*
The Usher Syndrome Consortium, organized and chaired by Dr Kimberling, met February 1-2, 1992, at St Petersburg Beach, Florida. One purpose of the meeting was to formalize the Consortium's Terms of Agreement that were drafted by Dr Pelias; suggestions for revisions were discussed, decided, and incorporated into the document. A second purpose of the meeting was to discuss the current status of the search for the genes that cause Usher syndrome. Dr Keats compiled and analyzed the genetic marker data from participating laboratories and presented an up-to-date exclusion map for Usher Syndrome Type 1. These results, soon to be submitted for publication, exclude about 30% of the genome for USH1 and further genome searching is in progress. Dr Kaplan presented data about the linkage of a gene for a form of Usher Syndrome that occurs in a group of French families to the long arm of chromosome 14. Dr Smith presented a Data Sheet for clinical information on persons with Usher Syndrome; he is drafting the consensus of the Consortium for publication. The next meeting of the Consortium will be in San Francisco in conjunction with the meeting of the American Society of Human Genetics in November, 1992. This work is funded by the NIDCD and the National RP Foundation Inc. and were represented by Dr James Snow and Dr Jeanette Felix, respectively. Names and addresses of the members of the Consortium are listed below.

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Report by William Kimberling and colleagues
Histopathology associated with a circling mutation in transgenic mice

A line of transgenic mice which exhibits bidirectional circling and hyperactivity was generated by microinjection of fertilized mouse eggs with a 25 kb human genomic fragment containing a human salivary amylase gene. This line was maintained as heterozygotes by breeding with the inbred strain C57BL/6J. The circling behaviour co-segregated with the transgene through three generations. The pedigree is consistent with autosomal dominance with 80% penetrance of the circling phenotype. Circling mutants can be caused by abnormalities of the brain and/or ear. We therefore examined the inner ear of this line of mutant mice to assess the presence of any pathology. Seven transgenic mice and five normal C57BL/6J mice were perfused through the heart with 4% paraformaldehyde, followed by an intrascalar perfusion of the same fixative through the round window. Inner ears from four transgenic and two normal mice were dissected and drilled to expose the semicircular canals. All inner ears were then decalicifed with 2% EDTA, embedded in plastic (EMBED 812) and six micron sections were cut through the auditory and vestibular sensory epithelium.

Dissection of semicircular canals revealed an underdevelopment or absence of the horizontal canal in the circler transgenic mice. Crista normally have a convex shape, with sensory epithelium overlying an evagination. In the horizontal canals of the circler mice the crista was either flattened or invaginated into a concave shape. The crista of anterior and posterior canals was occasionally flattened but was normal in most transgenic animals. Hair cells, supporting cells and the overlying cupula of the crista of horizontal, anterior and posterior canals appeared normal. Utricle and sacculus and their maculae appeared normal, as did the cochlea and organ of Corti. Animals had normal hearing, as assessed by auditory brain stem responses. The non-transgenic C57BL/6J mice had normal appearing auditory and vestibular systems, including normal horizontal canals with convex cristae.

The transgene for the circler mutant is located on mouse chromosome 18 (unpublished observations), at or near the spontaneous Twirler mutation, which produces a similar behavioural and morphological pathology. Genetic and phenotypic similarities suggest that Twirler may be the mouse homolog of Treacher Collins Syndrome, an inherited craniofacial dysmorphology on human chromosome 5q3.
Audiometric detection of carriers of Usher's Syndrome Type II

Various researchers in the past have attempted to define an audiometric technique for the detection of carriers of autosomal recessive genetic deafness. The most promising work was with the detection of audiometric notches using sweep frequency Békésy audiometry, but results with this technique have not been universally encouraging. In the present study we have tested the hearing of carriers of Ushers syndrome Type II in three families using a new sweep frequency technique, the Audioscan. With this technique we found audiometric notches in the frequency range 500-3000 Hz in all obligate carriers tested and in the predicted proportion of non-obligate carriers. With Békésy testing only one notch was found in a possible carrier and none in the obligate carriers. We conclude from these initial results that the Audioscan technique may offer a sensitive technique for the detection of carriers in families having Ushers syndrome Type II.

Uvomorulin (E-Cadherin) in the cochlea of the developing mouse

Cadherins are a family of transmembrane glycoproteins that mediate calcium dependent cell-cell adhesion. It has been suggested [Takeichi, Development 102: 639-655 (1988)] that in development, the up- or down-regulation of cadherin expression might be involved in the association or disassociation of different cell layers. One cadherin, uvomorulin (also known as E-cadherin) has been implicated in mechanisms underlying the compaction of pre-implantation embryos and in other adhesive interactions in embryonic and adult tissues. The chick equivalent of uvomorulin, LCAM, is thought to play a role in feather morphogenesis and in in vitro cell-sorting out.

The distribution of uvomorulin was studied in the organ of Corti by immunocytochemistry in order to make predictions about the molecule's developmental role. Cochleas from ages E15, P1-3, P5-7, P11, and P20 HA/ICR mice were stained as whole mounts using a monoclonal antibody against uvomorulin (DECMA-1, Sigma). Over the time period studied, only pillar cells, outer hair cells and their adjacent Deiter cell processes were uvomorulin-positive. Inner hair cells were unstained. Nerve fibers were also negative. At E15, only cells in the outer hair cell region expressed uvomorulin. By P2, pillar cells were also positive. During the next few days, the hair cell region became less intensely stained as the pillar cells became more immunoreactive. By P11, no cells in the outer hair cell region were outlined by immunoreactivity. The tightly apposed heads of the pillar cells and the junctions at the tops of outer hair and Deiter cells were the only uvomorulin-positive structures in the organ.

In summary: In the E15-P20 mouse organ of Corti, only the cells destined to develop adjacent fluid spaces (hair cells, Deiter cells and pillar cells) express uvomorulin. Uvomorulin disappears on hair and Deiter cells at the time in development when fluid spaces between the cells are opening. Fluid spaces do not open around inner hair cells which are always uvomorulin-negative. These data suggest that uvomorulin may help mediate pillar cell-pillar cell and hair cell-Deiter cell adhesion and raise the possibility that the down regulation of uvomorulin may aid in the opening of fluid spaces in the organ of Corti. (Supported by NIDCD grant #DC00653).
The deaf kreisler mouse: a hindbrain segmentation mutant

Kreisler is a recessive mutation causing deafness and loss of vestibular function: affected mice have grossly malformed inner ears (P Hertwig, Z KonstLehr, 28: 327-354, 1944). The defects in the ear have been attributed to earlier abnormalities in the hindbrain of the embryo, adjacent to the ear rudiments: at E9.5, the neural tube posterior to the boundary between rhombomeres 3 and 4 appears unsegmented, and the region that would normally correspond to rhombomeres 4 and 5 is unusually thick-walled and contains many dying cells (M Deol, J Embryol Exp Morphol 12: 475-490, 1964). We find that the absence of anatomical segmentation in the hindbrain corresponds to an altered pattern of gene expression there. Normally, Krox-20 is expressed in rhombomeres 3 and 5. In kreisler, the rhombomere 5 domain is absent, although the rhombomere 3 domain is present. Thus loss of anatomical segment boundaries in the mutant correlates exactly with loss of boundaries defined by Krox-20 expression. In a normal embryo, Hox 1.5 also demarcates rhombomere 4 from rhombomere 5: the gene is expressed posterior to the 4/5 boundary. In kreisler, Hox 1.5 still has an expression boundary in approximately the position where the 4/5 segment boundary would normally be, correlated in the normal way with the antero-posterior position of the otocysts; there is also a weak ectopic Hox 1.5 domain in rhombomere 3. These findings strongly suggest that the mechanisms that form segments and those that define antero-posterior positional values through the expression of Hox genes are distinct and can operate independently. The antero-posterior location of the otocysts seems to be defined by the latter set of mechanisms.

It is possible that production of neural crest cells at the level of rhombomere 5 (which normally produces few or none) may contribute to the inner ear deformity in kreisler, since the otic capsule is normally formed from neural-crest-derived cells; but it is also possible that the kreisler gene may act directly in the otic epithelium or affect production by the hindbrain of an inductive signal (or signals) for ear development.

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Genetic investigation of families with non syndromic sensorineural deafness in Saudi Arabia

Several families with more than one deaf individual have been identified with non syndromal autosomal recessive hearing loss. A community survey had been conducted during the past 3 years to study the epidemiology of hearing impairment among Saudi children up to 12 years of age. The preliminary results showed that hereditary and consanguinity were predominantly prevalent.

We propose to investigate families in Saudi Arabia, who have no evidence of an infective or toxic cause and have no other clinical complaint apart from their deafness.

Information on many such families has already been collected and we propose to carry out investigation of those families. Initial results from the clinical data suggest that most non-syndromic
severe early deafness is inherited through recessive genes. Because of intermarriages, in the community, this inheritance due to recessive genes is exaggerated.

We plan to carry out cytogenetics investigation on families with affected children. We also propose to perform genetic linkage studies with the help of available mouse clones. This study would facilitate location of recessive gene for deafness on chromosomes. This study would be eventually beneficial for assessing the prognosis for the patient and for providing appropriate genetic counselling.

SAN DIEGO

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*Molecular studies of the Wocko insertional inner ear mutation*

We have previously described an insertional inner ear mutant in a transgenic mouse line, Wocko (Crenshaw et al, J Neurosci 11:1524-1430, 1991). The mutation is expressed as an autosomal dominant trait. Phenotypically the mice display waltzing behaviour consisting of bidirectional circling, head bobbing, and hyperactivity. Anatomical studies have revealed severe endolymphatic hydrops which develops soon after birth, followed by collapse and degeneration of the pars superior. These data suggest that the gene disrupted in Wocko may participate in cochlear fluid homeostasis.

Previously presented data have also demonstrated the transgene integration site to consist of a single copy insert of the transgene construct. Nine clones containing a portion of the integration site were isolated from a Wocko genomic DNA library. These clones taken together have provided a detailed map of the integration site including several kilobases of normal mouse DNA flanking the inserted transgene copy. Both flanking sequences contain regions of repetitive DNA which are not useful for localization studies. However, they also contain nonrepetitive (single-copy) sequences which have been identified and isolated.

These nonrepetitive flanking DNA sequences have been used to identify the region in the mouse genome at which the integration event occurred. Three non-mutant mouse genomic clones have been isolated from a normal mouse genomic DNA library, using a single copy probe from the normal mouse DNA flanking the transgene on the 5’ side. A detailed restriction map of two of these clones has identified approximately 15 kilobases of DNA further downstream, potentially spanning the integration site.

A one kilobase Pst I fragment located approximately 400 base pairs 5’ to the transgene reveals significant cross-species hybridization on a low stringency inter-species genomic Southern blot. This cross-hybridization suggests that the fragment may contain portions of an exon from the gene which was disrupted by the transgene insertion. This fragment has been localized to mouse chromosome 1, within one centiMorgan of the interleukin-1 receptor gene. These data represent
significant progress toward the molecular characterization of the Wocko mutation site and the isolation of the disrupted gene.
Monge's Deafness. Low Frequency Hearing Loss 1 (LFHL 1)

We are involved in a project to map the gene involved in Monge's Deafness, an autosomal dominant sensorineural hearing loss with complete penetrance. Low tone deafness generally begins by age ten and inevitably progresses by age 30 to a profound bilateral deafness for all frequencies. No associated abnormalities have been detected. All family members trace their ancestry to a common founder named Felix Monge of Spanish descent. At present, there are 53 nuclear families and more than a hundred affected members living near San Jose.

We have found linkage to eight markers on the long arm of chromosome 5: IL9, D5S70, GRL, D5S210, D5S207, D5S119, D5S209, D5S22. We would welcome information about families with similar hearing losses that would be available for study.


Distinguishing between two active processes in the cochlea of the waltzing guinea pig.

Mammalian hearing has the unique feature of possessing an active mechanism which amplifies acoustic stimuli over a range of frequencies whereby improving sensitivity and frequency selectivity. Since the outer hair cells show a motile response when stimulated electrically, chemically, or mechanically, as well as being involved in generating acoustic emissions from the cochlea, they are believed to be the structure responsible for the active mechanism. However, neither the underlying mechanism nor the subcellular structure within the outer hair cell responsible for these active mechanisms have been determined. One hypothesis is that the subsurface cisternae along the plasma membrane are involved in generating the slow length changes. In order to directly test the hypothesis that the subsurface cisternae are involved in these active mechanisms, we investigated the outer hair cells from the waltzing guinea pig. This strain of guinea pig has a genetically induced progressive deafness that begins postnatally and an actin-defect is involved. It has been found that the waltzing guinea pig develops abnormal subsurface cisternae along the lateral wall of the outer hair cell. Their subsurface cisternae are disorganized and the cisternae are often swollen. In the cells demonstrating abnormal subsurface cisternae, the adjacent mitochondria also exhibit alterations. As a result of these morphological abnormalities, we examined the motile behaviour of isolated outer hair cells from control and waltzing guinea pigs. Outer hair cells were stimulated electrically, chemically, and mechanically.

At a time when the waltzing guinea pigs have a moderate hearing loss (30-40 dB) the two different active processes were affected differently. Chemical (ionomycin, 10 uM; and osmolarity changes) and acoustic (200 Hz tone burst) stimulation was ineffective in causing outer hair cell length changes from the waltzing guinea pig whereas length changes were observed from control outer hair cells. On the other hand, isolated outer hair cells from both groups responded in a similar manner to electrical stimulation. Furthermore, the amplitudes of distortion product emissions were not different between the two groups, while the brainstem thresholds for the waltzing guinea pigs were elevated by at least 30 dB. On the basis of these findings, it is suggested that the lateral cisternae contribute to the slow motility whereas other structures contribute to the fast motility and the generation of distortion product emissions.
MEETINGS NOTICES

7TH INTERNATIONAL SYMPOSIUM IN AUDIOLOGICAL MEDICINE 1993

to be held at the University Hospital of Wales, Cardiff, Wales. 19-22 September 1993.

Themes: Genetic Hearing Loss

Training in Audiology for Primary Physicians

Investigation of vertigo - how and why?

Social Programme:

Civic Reception: National Museum of Wales

Banquet in City Hall

Visits to Welsh National Folk Museum, Big Pit, etc.

Cardiff is the capital of Wales and has a population of 300,000. It is reached by direct air flights from Amsterdam, Brussels, Dublin, Dusseldorf and Paris. For flights to Heathrow Airport there is an express coach service which takes 2\(\frac{3}{4}\) hours. It is 1\(\frac{3}{4}\) hours by high speed train from London and there are numerous motorway links to Dover and elsewhere.

For further details, please write to Dr D. Stephens, Welsh Hearing Institute, University Hospital of Wales, Cardiff, CF4 4XW, Wales.
THIRD INTERNATIONAL SYMPOSIUM ON MENIERE'S DISEASE,

Roma, Italy, October 20-23, 1993

President: R. Filip, M.D., Roma

This symposium highlights an otological disorder which attracts the interest of many researchers and clinicians throughout the world. The two previous symposia were held in Dusseldorf in 1981 and in Boston in 1988.

Recent advances in basic sciences and clinical aspects will be covered by overview lectures and round-table sessions presented by experts in the field.

Posters and selected free papers are also welcome.

Invited papers - Round-table sessions - Free Communications - Posters

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**General Information about the Newsletter**

The Hereditary Deafness Newsletter is distributed by the Royal National Institute for the Deaf (105, Gower Street, London, WC1E 6AH). The Honorary Editor is:

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The aim of the Newsletter is to stimulate interest in hereditary deafness research and to encourage communication between the various groups involved. Most issues will contain an updated list of both human and mouse mutations causing hearing impairment, with their chromosomal locations where known. The main part of the Newsletter will consist of informal laboratory or clinic reports describing current work. Contributions can be about any aspect of research in hereditary deafness, genetic or audiological, clinical or laboratory-based.

The Newsletter is not a publication, so information from it should be regarded as a "personal communication", and the author consulted if you wish to cite it. This is intended to encourage people to write about work in progress rather than work which is finished and published elsewhere.

The Newsletter will be circulated twice a year, and the first few issues will be distributed free by the RNID. Any correspondence about the Newsletter, including suggestions for changes to the mailing list, should be addressed to the Editor. Requests for back copies of the Newsletter should also be addressed to the Editor. Contributions may be sent by post or by FAX. The deadline for contributions to the next issue will be:

**30th September 1992**

**Notes for Contributors**

The Editor welcomes contributions for the Newsletter. Contributions will normally be:

- Informal laboratory or clinic reports, describing current work, or plans for future work. Include your full postal address and a list of people actively involved in research in hereditary deafness, underlining the name of the person who sends the report. Include also your telephone number, FAX number, and electronic mail address if you wish. You may use your report to ask for collaboration with other clinicians who may be in contact with families with specific disorders.

- Additions or corrections to the mouse and human gene lists. Any relevant references would be particularly useful.

- Letters to the Editor, particularly about any issues raised in articles.

- Viewpoint article. This will be an occasional invited contribution, but do let the Editor know if you have any particular suggestions or requests for topics to be discussed or people whose views you would like to hear. The viewpoint articles will normally concern broad issues, such as the organisation and long-term aims of research, the provision of services to those with hereditary deafness, and so forth.

- Meetings notices.