Collective Expert Report

Hearing deficits

Emerging research and applications to children

Synthesis

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This document presents the synthesis and recommendations of the expert group designated by Inserm at the request of the CANAM[1] as part of a collective expert report about emerging research on hearing deficits and its applications to children.

This report is based on scientific data available in the first semester of 2005 and involved consultation of approximately 450 articles.

Inserm's collective expertise center ensured coordination of this collective expert report.

[1] Caisse nationale d'assurance maladie des professions indépendantes (French health insurance fund for independent professions)

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Foreword

In France, hearing impairment affects almost eight hundred newborn infants every year. This has consequences on the child's language acquisition and affects his/her intellectual, socioaffective and professional development. Neonatal hearing impairment is severe or profound in 25% of cases and around 75% of hearing disabilities in children are due to genetic defects. Public authorities are particularly attentive to any research work that might have an impact on the management of this public health problem.

The CANAM called upon Inserm to carry out a collective expert assessment on recent scientific advances likely to have an impact on screening, diagnosis and management of hearing disorders in children.

In order to meet this request, Inserm gathered a group of experts of medical and scientific background, with an array of skills in genetics, sensory biophysics, auditory physiology, audiology and pediatrics.

The international literature analysis performed by the group of experts hinges around the following questions:

- What is the prevalence of hearing impairment in children and what are the factors that may cause it to vary? What research is being carried out to assess the management of hearing-impaired children in France?
- What are the recent data on acoustic and physical mechanisms involved in auditory perception that might allow perfecting diagnostic tools for early hearing impairment, prosthetic devices and cochlear implants?
- What progress has been made in auditory pathologic physiology? What recent data are there on complex perception and cognitive mechanisms involved in listening to sounds and to what extent are these mechanisms taken into account for the development of hearing devices?
- Which advances in research on genetically determined deafness are likely to have an impact on the development of tests for genetic screening?
- What recent research data is likely to help develop better screening?
- How efficient are the various methods for diagnosing auditory deficits and what is being done to improve the assessment of auditory thresholds in each ear?
- What are the indications for fitting cochlear implants or hearing devices in relation to the plasticity of the central and peripheral auditory systems in children?

Following the seven work sessions that took place between June 2005 and January 2006, the experts presented a critical analysis and a summary of the work published on these issues worldwide. Based on this analysis, the experts made a set of broad recommendations for the years to come, which will require testing by complementary work in the relevant context.

Synthesis

Auditory deficit is the most common deficit in children and has major consequences on language and communication skills development.

Hearing impairment can be classified according to the degree of hearing loss (mean loss at 0.5, 1, 2 and 4 kHz frequencies for the better ear) as mild, moderate, severe or profound. Severe and profound hearing impairment correspond to an auditory deficit that impedes oral language acquisition if no rehabilitation is provided. Even moderate hearing impairment, which represents 50% of cases, has an impact on learning at school, cognitive development and social adaptation that should not be underestimated.

Hearing impairment can also be classified according to the place of the primary defect (outer, middle or inner ear). Based on the child's audiogram (comparison of air and bone conduction curves), the hearing impairment is found to be sensorineural (affecting the inner ear, auditory nerve, central auditory pathway) or conductive (essentially affecting the middle ear).

Child hearing impairment may be isolated (non-syndromic) or syndromic (i.e. associated with anomalies in other organs). The prevalence of hearing impairment rises with age. Certain types of hearing impairment, particularly of genetic origin, appear during childhood or even in adulthood. The distribution of prelingual hearing impairment (i.e. occurring before the age at which language develops) in developed countries is today estimated at 10-15 % for syndromic hereditary hearing impairment, 60-65% for isolated hereditary hearing impairment and 20-25% for hearing impairment of other origins (infections, drugs, complications of prematurity, etc.).

The identification of genes responsible for deafness constitutes a recent field of research on the origin of auditory deficits. These genes code for proteins involved in cellular processes responsible for the functioning of the cochlea, the auditory organ of the inner ear. Identifying such genes is important for daily clinical practice as it allows targeting of molecular diagnosis for prognosis and genetic counseling.

In France, there is to date no general organization for systematic screening at birth. The heading "neonatal screening for hearing impairment" nonetheless appears in every child's health notebook since 1970. Non-invasive tools for neonate screening have been available for a few years (otoacoustic emissions, automated analysis of auditory evoked potentials). Should an abnormality be detected by screening in a maternity setting, more complex diagnostic tests must be performed in a specialized environment in order to evaluate the precise level of hearing ability.

In any case, management should begin early in order to keep within the critical time frame (linked to brain plasticity) when oral language is being organized around the sounds that are being heard. Management possibilities are evolving significantly, particularly for rehabilitation of profound deafness using cochlear implants. These advances can contribute to a drastic reduction in the handicap linked to deficiency.

The old discipline of acoustics now faces new challenges to improve screening, diagnosis and management, whether it be through the use of prosthetic devices or cochlear implants, which still present multiple drawbacks in a noisy environment.

Hearing impairment affects one to two children among every thousand

Knowing the prevalence of congenital hearing impairment in a living area is useful in order for health authorities to judge the efficiency of neonatal screening programs and adjust their prevention and educational management policies to the needs of the population.

Thanks to automated recording of otoacoustic emissions (OAEs) and auditory evoked potentials (AEPs), it has become possible to study the prevalence of hearing impairment from birth. However, the possible progression of hearing impairment in the first year of life and the legitimate desire to corroborate early epidemiological data with large-scale reliable audiometric examinations motivates epidemiologists to define prevalence at the age of 2.5 to 3 years in order to obtain more precise figures.

The analysis of some twenty international studies published between 1995 and 2005 has revealed a variability in the levels of prevalence, as evidenced by the large difference observed between minimum and maximum values (0.9 to 2.2/1,000), and a relative lack of precision for certain estimates. In France, the prevalence for auditory deficits varies between 0.49 and 0.8/1,000. These prevalence levels correspond to populations of 7 to 16 year-old children over the period 1972-1996. Apart from age, which has already been mentioned, other factors may influence prevalence variability, such as the choice of auditory loss threshold or the technique used to identify deficits.

Having validated the method used for gathering data, one may then go on to invoke the possible influence of true epidemiological factors such as the socioeconomic (e.g. family vulnerability) or cultural environment (culturally determined inbreeding, which increases the occurrence of autosomal recessive diseases).

The notion of risk factor is more complex than it appears. It has been known for over ten years that a postnatal stay in an intensive care unit is associated with a higher risk of auditory deficit. In addition to pathological situations that may have led to the need for intensive care (severe prematurity, respiratory distress, hypoxia, etc.), potentially ototoxic health care may be involved (such as aminoglycoside administration for a severe infection).

Identifying children at risk in intensive care units should normally be easy in view of the severity of their condition and the specialized hospital setting (level III or even II). The context is quite different for the other great source of increased auditory risk, namely families where siblings or older relatives have a previous history of deafness: the child, born in one of the numerous level-I maternity services across the country, appears to be healthy, and the parents are often unaware of any genetic family predisposition. Maternity hospital personnel should therefore use rigorous methods for collecting genetic risk indicators in order to screen for risk of hereditary deafness. Indeed, one is struck by the absence of publications on the identification of hereditary hearing impairment in the first few months of life when there is no systematic neonatal auditory screening.

Profound deafness represents approximately 25% of all cases of hearing impairments at birth

Profound deafness (defined as an average hearing threshold greater than 90 dB[2] for the better ear) represents around 25% of hearing impairment cases identified in the first months of life, well behind moderate hearing impairment (in the 40–70 dB range for the better ear). These objective data, which are too often overlooked, show that the educational management

[2] decibel

of hearing-impaired children identified at birth should not only involve cochlear implant fitting but also more comprehensive early management allowing such children to draw real benefit from neonatal screening.

Hearing impairment distribution according to degree of auditory loss

Degree of hearing impairment	Level of hearing loss (dB)*	Level of hearing loss (dB) according to Fortnum et al., 2002**	Distribution (%)
Mild	20-40	-	-
Moderate	40-70	41-70	53
Severe	70-90	71-95	21
Profound	>90	>95	25

* Commonly used intervals for defining the degree of hearing impairment

** The most complete study available using the criteria of the British Society of Audiology (1988)

In spite of the high prevalence of hearing impairment, probably around 1.5/1,000, and the chronic nature of the care these children need, no health insurance fund (whether local or regional) has so far rigorously estimated the cost of auditory handicap and its management during childhood.

The national registers for child hearing impairment that exist in some countries (Australia, Canada, Sweden and Great Britain) provide basic data on the prevalence of hearing impairment and related care.

Child hearing impairment is genetically determined in approximately 75% of cases

The genetics of isolated (i.e. non-syndromic) hearing impairment in children is a recent discipline, both in terms of clinical research (etiological diagnosis, genetic counseling) and basic research, identification of the genes involved having only truly started around 1990. The reason for this delay is in part due to the great genetic heterogeneity of this sensory handicap (around a hundred genes are thought to be involved in non-syndromic hearing impairment) and the particular make-up of families with hearing-impaired individuals, which renders family genetic analysis (genetic linkage studies, a prerequisite to gene identification) particularly difficult. Indeed, for cultural reasons, marriages between deaf individuals or children of deaf individuals are frequent, which, given the stereotyped clinical picture, does not allow the genetician to follow the transmission of one or more (simultaneously segregating) deafness genes in such families. However, this obstacle was overcome, mainly through the study of large geographically isolated inbred families (where deafness is due to a single gene abnormality, for example).

Genetic deafness is due in most cases to a monogenic abnormality. Autosomal recessive transmission is the most common (around 80% of prelingual cases of deafness). To date, 93 chromosomal loci have been identified for deafness. These correspond to 50 forms of autosomal recessive (DFNB), 45 forms of autosomal dominant (DFNA), 3 forms of X chromosome-linked (DFN), 1 form of Y chromosome-linked, and 2 forms of mitochondrial transmission. It is worth noting that some of these loci are involved in both recessive and dominant forms of deafness. The 39 deafness-related genes that have been identified so far encode molecules involved in highly varied cellular functions.

In spite of the large genetic heterogeneity, one of the genes identified, which codes for connexin-26 (a constitutive protein of the gap junction intercellular network), is alone responsible for about 30% of isolated cases of deafness without a known extrinsic cause (form DFNB1) in France and many other countries (25-50%).

Studying the expression profile of these genes in the cochlea (the auditory organ) has often led to identify the primary cellular target of the genetic defect responsible for deafness. Given the particular frequency of the DFNB1 genetic form of deafness, which primarily involves the non-sensory cells of the cochlea, sensory cells (hair cells) are far from being the most frequent place of primary lesion in child deafness even if secondary lesion of theses cells is quite frequent. It is interesting to note that in the case of perception deafness, the type of cell affected by the underlying genetic defect in a given individual cannot be deduced from the clinical picture alone. This observation points to the need for using systematic molecular diagnosis if and when specific treatments for defects in the various cell types of the cochlea become available. For quite a number of genetic forms, however, the defect, whether primary or secondary, involves several cell types, which will no doubt make future therapeutic approaches more complicated.

In this respect, it is worth insisting on the importance of producing and studying mouse models for the different genetic forms of human deafness. These models allow histopathological analysis, which is impossible in man. They also allow precise functional analysis of the cochlea (measurement of endocochlear potential and endolymph ion levels, direct study of the electromechanical transduction in sensory cells, etc.). Such models should eventually help understand the molecular and cellular pathology of the various genetic forms of deafness, a prerequisite for a specific therapeutic approach. Murine models have already revealed pathogenic processes common to several genetic forms of deafness (such as the loss of endocochlear potential in DFNB1 and DFNB4 deafness, due to a defect in the gene coding for pendrin). In the case of developmental genes, such models would also allow analysis of the possible effect of a mutation in these genes on the mature organ using inducible or late conditional inactivation techniques. This is clearly important in order to guide the development of future therapeutic strategies. Murine models will also be very useful for testing the efficiency and innocuousness of such therapeutic approaches. In addition, mice can be very useful for identifying possible modifier genes in deafness phenotypes due to given monogenic defects, and these genes could open interesting therapeutic approach. Finally, the *Ahl* (*Age related hearing loss*) gene, which has been found to be involved in deafness linked to ageing in laboratory mice, also happens to code for cadherin 23, known to be responsible for a murine and human congenital form of deafness, suggesting that certain genes responsible for child deafness might also play a part in predisposition to presbyacusis. Other studies on murine models suggest that such a hypothesis might well be extended to genes involved in susceptibility to sound trauma.

Molecular diagnosis is proposed as part of genetic counseling to parents of deaf children

Today, molecular diagnosis of deafness may present a number of advantages for deaf people:

- understanding the origin of their handicap;
- preventing deafness: prevention is still rare given the current state of knowledge except for mitochondrial genome abnormalities, which are responsible for deafness

resulting from aminoglycoside antibiotic administration (the prevalence of such mutations remains to be determined for the French population);

- evaluating the risk of progression (stability or aggravation) in cases of moderate deafness: such assessment requires prior study of the natural history of the different forms of deafness;
- evaluating the risk that abnormalities are also present in other organs in cases of seemingly isolated deafness such as Pendred syndrome (goiter and thyroid dysfunction, often with belated onset);
- measuring the risk of recurrence in future generations, with the possibility in some cases (DFNB1) of predicting the extent of the deficit depending on the type of mutation (genetic counseling).

However, the molecular diagnosis currently available in hospitals only concerns a fraction of the 39 identified genes involved in isolated deafness: the genes coding for connexins 26 and 30 (DFNB1), the pendrin gene (DFNB4), the otoferlin gene (DFNB9), and the mitochondrial gene of the 12S rRNA conferring sensitivity to aminoglycosides. The genes studied correspond to the two most common genetic forms of deafness (DFNB1, DFNB4). The latter (DFNB4), can be detected by X-Ray, which reveals the presence of inner ear morphological abnormalities upon tomodensitometric examination of the temporal bone (dilation of the vestibular aqueduct). Molecular diagnosis also concerns DFNB9, a genetic form that is often detectable by audiological exam (conservation of otoacoustic emissions), and one form that is preventable (12S rRNA).

There are no European studies comparing the efficiency and cost of diagnostic strategies, including molecular diagnosis. However, a recent American study on 150 children, which only took into account molecular diagnosis for DFNB1 (also the most common form in the United States) as well as temporal bone scanner imaging, concludes that in cases of severe or profound hearing impairment, it is important to start with the molecular diagnosis and only perform a radiological exam when this turns out to be negative because temporal bone abnormalities (around 30 % in this series) are never found in the DFNB1 form. The study recommends the opposite approach for cases of mild or moderate deafness because the DFNB1 form is less prevalent (around 10 %) in this sub-population.

It is interesting to consider the special case of type-I Usher syndrome (deafness associated with vestibular disorders and blindness of post-childhood onset). The molecular diagnosis of this genetically heterogeneous syndrome is still difficult and costly (the various genes, which are very large, have not all been identified and display many different mutations). It should nonetheless be developed given the importance of genetic counseling and perhaps prenatal molecular diagnosis in this case given the double sensory handicap involved. Aside from the rather simple situation where other family cases exist, this diagnosis is indicated in the event of severe or profound hearing impairment associated with late walking and posture acquisition, which reflects an underlying vestibular defect. Identification of preclinical electroretinogram anomalies is very useful for diagnosis but may be difficult to interpret. Molecular identification of the defective gene would no doubt allow an even earlier diagnosis. Given the difficulty of performing systematic sequencing of all the genes involved for each patient, one of the solutions being considered is to develop a diagnosis technique based on DNA chips. However, in order to be efficient, this approach requires the prior identification of the great majority of the mutations encountered in the population concerned.

It is obvious that given the methods currently available for identifying mutations, and while waiting for more simple methods such as DNA chips to be used routinely, molecular

diagnosis of child deafness covering the whole set of genes identified to date cannot be reasonably considered, at least in the short term. Furthermore, it is understandable that the choice of "priority" genes is going to be based, in the absence of any clinical orientation criteria (which is generally the case for child deafness), on the prevalence of the various genetic forms in the population of hearing-impaired children, hence the need to perform large-scale genetic epidemiology studies.

Finally, two ethical questions must be considered. If it is already technically possible to perform a prenatal molecular diagnosis of deafness for a family identified as being genetically at risk, is such a diagnosis ethically justified in the case of non-syndromic deafness? Furthermore, the probably not far off identification of genes predisposing to presbyacusis, a perception deafness that affects a large percentage of the elderly population, will allow considering a presymptomatic molecular diagnosis, which raises the question whether this can afford any benefit.

Neonatal screening allows initiating management of deaf children in the first few months of life

Deploring late diagnosis for the majority of children whose deafness was not detected at birth, the need to clarify parents' doubts early on following a positive screening result at birth, and the development of reliable automated techniques (otoacoustic emissions, brainstem auditory evoked potentials) applicable in the first few days of life have all contributed in the last few years to giving new impetus for exploring auditory functions during the neonatal period (0-2 months).

Because screening tests and diagnostic tests are fundamentally distinct in their objective and modalities, and the environment in which they are performed, they should be analyzed separately.

The aim of the great majority of neonatal screening programs is to identify the children that present perception (or mixed) hearing impairment with a threshold level of at least 40 dB HL[3] in the better ear (the prevalence in neonates is generally around 1.5/1,000).

As with any type of screening, there are four types of results: true positives (the target population, characterized by ≥40 dB HL sensorineural hearing loss), false positives (results indicative of hearing impairment in the neonatal test but later contradicted by further examination), false negatives (negative neonatal screening results with the child later turning out to have ≥40 dB HL sensorineural hearing loss) and true negatives (negative neonatal screening results with the children later confirmed as indeed not having ≥40 dB HL sensorineural hearing loss). The level of false positives in a screening program is obtained by dividing the number of children turning out not to have a hearing impairment (i.e. who do not correspond to the target population) by the overall number of tested children. The positive predictive value (PPV) is obtained by dividing the number of hearing-impaired children by the number of children whose screening results were positive.

Two types of screening tests are used: otoacoustic emissions (OAEs) and automated testing of auditory evoked potentials (AEPs).

OAEs designate low-level sounds generated by the inner ear. These can be detected in the external auditory canal if the middle ear is working normally. The technical conditions in which signals are collected and their pathophysiological significance in terms of outer hair cell function in the cochlea make it a very good neonatal screening tool. The absence of OAEs

[3] Hearing Level

in the newborn can however result from two very different mechanisms. It can be due to even slight middle ear pathology since a conductive hearing impairment of 15-20 dB HL is generally sufficient to make OAEs disappear. It can also be due to a defect in outer hair cells leading to sensorineural hearing impairment of ≥25-30 dB HL (average of audiometric thresholds at 0.5, 1 and 2 kHz). This double involvement of the middle and inner ear explains why OAE specificity[4] (77 to 96% depending on the study) is not quite as good as OAE sensitivity (between 96 and 100% depending on the study)[5]. In order to maximize specificity, neonatal screening programs based on OAEs are therefore performed by a two-step process: children suspected of having a hearing impairment after the first test are tested a second time, usually in the maternity setting.

Automated testing of auditory evoked potentials (AEPs) is the other screening tool and involves recording signals on the skin surface after stimulating the ear with a single-intensity sound. This test explores the physiological activity of the cochlea, the auditory nerve and the brainstem hearing pathways. In this respect, it is quite different from OAE testing. Even though AEP specificity is superior to that of OAEs, neonatal screening programs are also performed in two steps (children initially giving a positive result being systematically tested again) in order to reduce the level of false positives and reinforce the positive predictive value (PPV).

OAE and AEP testing can be compared from a scientific point of view on the one hand, and from a technical and economical point of view on the other hand.

A first comparison of the two tests from a scientific standpoint involved analyzing the PPVs reported in about ten programs. Weighted PPVs, which allow taking into account the number of children included in the various studies, are higher in screening programs based on AEP rather than OAE testing (27.3% *versus* 8.2%).

Two-step programs should be the method of choice as they significantly reduce the number of false positives and above all reinforce the PPV.

The second scientific criterion that can be used to evaluate the efficiency of a newborn hearing screening program (NHSP) is the level of false negatives. Neonatal OAE screening does not allow detection of a particular category of hearing impairment in children. Children diagnosed as having an auditory neuropathy characteristically conserve OAEs but fail to exhibit brainstem AEPs. It is now known that cochlear implants can be successfully fitted in these children with profound hearing impairment.

Regarding practical aspects, AEP screening allows testing both ears at the same time. However, OAE testing is advantageous in requiring less costly apparatus and consumables, and involving a shorter examination.

Several NHSPs have been set up in France. The CNAMTS[6] and the AFDPHE[7] are developing a neonatal screening program based on AEP testing in six French cities. Other programs based on OAEs are being tested at local or regional level.

Automated AEP testing should be the standard technique of choice for screening in neonatal intensive care units where the proportion of infants presenting an auditory neuropathy is higher than in the general population. Whatever the decisions taken in France in the next few years, the impact of neonatal screening will have to be evaluated in terms of the efficiency

[4] Specificity: capacity to give a negative result when there is no sensorineural hearing impairment ≥40 dB HL

[5] Sensitivity: capacity to give a positive result when there is a sensorineural hearing impairment ≥40 dB HL

[6] *Caisse nationale d'assurance maladie des travailleurs salariés* - French health insurance fund for salaried employees

[7] *Association française de dépistage et de prévention des handicaps de l'enfant* – French association for the screening and prevention of handicap in children

indicators (PPV, proportion of children diagnosed before the age of 6 months, proportion of children fitted with hearing devices before the age of 12 months, false negatives) currently recommended in modelized projections.

Precise diagnosis is an essential complement to neonatal screening programs

Aside from meeting parental expectations and respecting their cultural values, early hearing and communication development programs must take into account the nature and degree of hearing impairment. It is therefore necessary to:

- confirm any hearing disability and evaluate the extent of impairment;
- identifying more precisely the origin of the hearing impairment.

Different tools are used in order to distinguish sensorineural from conductive hearing impairment. While a precise diagnosis should be performed before considering any prosthetic amplification, this is not easily put into practice during the first few months of life. Indeed, there are certain difficulties inherent to all auditory exploration techniques at this age, whether they be AEP, OAE, impedance measurement or behavioral audiometry.

Diagnosis by brainstem AEP (BAEP) is justifiably used in all screening programs to distinguish children with a hearing impairment (target population) from those with normal hearing (false positive screening results) and to measure their hearing threshold. Conditions under which AEP signals are to be collected and interpreted in the first months of life are quite strict: testing should be performed while the child is asleep, only thresholds ≥40 dB should be taken into account, keeping in mind that the measured threshold depends essentially on auditory sensitivity at frequencies of 2-4 kHz. Validation of thresholds is one of the difficulties encountered with all techniques for estimating hearing sensitivity in the first few months. Comparison of thresholds obtained by AEP and those recorded by a "gold standard" technique, behavioral audiometry, performed at an age when its reliability is guaranteed, shows that AEP is the method of choice. A study from 10 years ago finds a good correlation between thresholds derived from one or the other method (deviation ≤15 dB and ≤20 dB in 86% and 93% of cases respectively) if electrophysiological measurements are carried out by a sophisticated stimulation procedure. However, this study is more predictive than comparative since the two examinations were separated in time by an average of 7 months (median age of 21 months for AEP testing and 28 months for behavioral audiometry). A good correlation was also found more recently between electrophysiology measurements and behavioral audiometry on a population of 78 younger hearing-impaired children (median age of 11 months for AEP testing and 12 months for behavioral audiometry) suffering from sensorineural (71%) or mixed (29%) hearing impairment. Indeed, no audiometric response was found at 100 dB HL in 84% of the 57 children reproducibly found to have no AEPs at 100 dB (correlation coefficient ≥0.9 for the other 21 children).

Diagnosis by auditory steady-state responses (ASSR), which depends on the state of vigilance, is based on analyzing the electrophysiological responses obtained by stimulating the ear with pure sounds modulated in amplitude and/or frequency. Three systems are currently available clinically, MASTER® (developed in Canada), AUDERA® (developed in Australia) and Vivosonic[8]. A Belgium study on a small number (n=10) of young hearing-impaired infants (average age of 7 months) screened at 4 weeks by automated AEP testing, showed good feasability (95% at 0.1, 2 and 4 kHz, 50% at 0.5 kHz) and a good correlation

[8] www.vivosonic.com

with behavioral audiometry performed an average of 5.5 months later (threshold deviation ≤10 dB and ≤20 dB in 68 % and 94 % of cases respectively). The reliability of this technique, at the age when the children previously screened at birth must be diagnosed (first 3 months) nevertheless requires to be corroborated by larger-scale studies.

Diagnosis by impedance measurement is used to look for the origin of a hearing impairment. It gives no information on the threshold of hearing but helps understand why a child does not respond to a sound stimulus, whether in an electrophysiological (AEP), acoustic (OAE), or behavioral test. Indeed, the primary component in this examination, tympanometry, tells us something about the functional capacity of the middle ear. While the very high frequency of ear infections in the first 6 months is well known, research studies on impedance measurement at this age is scarce. However, a study led on more than 3,000 8 to 12-month infants with and without hearing impairment reports a 30% incidence of otitis media with effusion. In another American study on more than 650 young children aged 0 to 5 years, including no more than 5% of infants under 6 months, screening is positive in 35% of cases with tympanometry and 25% of cases with OAEs.

The other component of impedance measurement, the study of the stapedian reflex, has no predictive value for hearing thresholds since a child with a hearing impairment can have perfectly normal stapedian thresholds.

The use of OAEs in diagnosis is always very helpful for determining the nature of a sensorineural hearing impairment in newborn infants. Indeed, the presence of otoemissions in a child presenting flat (or high-threshold) AEP signals is strongly indicative of auditory neuropathy. However, OAEs must always be interpreted in the light of other exams such as tympanometry and AEP testing, in the first instance. If the tympanogram is flat, the absence of OAEs has no value whatsoever for determining whether the outer hair cells are functional. With respect to AEPs, the presence of OAEs at the diagnostic stage only guarantees proper hearing function if AEP thresholds are close to normal (<40dB HL). Relying solely only on OAEs to check a child's hearing rapidly after positive neonatal diagnosis could lead to a failure to recognize an auditory neuropathy. It is crucial to respect this rule, whatever the technique employed for screening. Indeed, a child testing positive by automated AEP screening can very well exhibit an auditory neuropathy, which will be missed if OAE and AEP examinations are not performed at the diagnostic stage.

Diagnosis by behavioral audiometry is very difficult in the first two months since the child has not yet gone through a key stage in psychomotor development, and in particular the ability to hold up its head, usually acquired by the third month. After this point, this test can be extremely valuable for analyzing air and bone conduction and measuring hearing over the spectrum of frequencies. The use of headphones, very well tolerated by infants, allows testing both ears at the same time, and very early on, each ear separately. Hearing thresholds measured in this way have recently been validated, on the one hand with AEP tests performed shortly before audiometry (at an interval of less than 3 months in almost 90% of cases), and on the other hand by a longitudinal study demonstrating excellent correlation with the gold standard at 3 to 4 years.

One of the major advantages of behavioral audiometry is to provide precise information for the audioprosthesist responsible for fitting the child with a hearing device, thus allowing appropriate management of the child's handicap.

In conclusion, BAEP testing remains the key diagnostic technique following neonatal screening. It helps reassure parents in many cases and serves to point the way for further diagnosis in other instances. However, performing this test at a very early age demands that very strict rules be respected. In the great majority of cases, the test will need to be repeated a

second time before confirming the diagnosis. Such caution can very well be reconciled with the legitimate demand to have a diagnosis before the age of 3 months.

Beyond locating the lesion, it is important to identify frequent syndromic deafness or cases requiring specific management. Some of these syndromes are identified by clinical examination and questioning (branchio-oto-renal syndrome and Waardenburg syndrome, for instance) but several common syndromes can present over a long period of time as isolated deafness, which justifies carrying out systematic complementary exams in deaf children in order to diagnose such syndromes. This includes fundoscopic examination (Usher's syndrome), temporal bone imaging (syndromes involving inner ear malformations such as Pendred syndrome), electrocardiogram (Jervell and Lange-Nielsen syndrome), and looking for hematuria/proteinuria (Alport's syndrome). Clinical genetics consultation must also be made available to families.

Early hearing rehabilitation is one of the major factors determining the quality of oral language development in deaf children

Early rehabilitation has been recognized for many years as one of the major factors determining the quality of oral language development in deaf children. However, because of the development of cochlear implantation in deaf children over the past 15 years and the lack of rigorous studies published before this period, methodologically sound studies (prospective or controlled studies with appropriate statistical analysis) on auditory rehabilitation and language development or auditory rehabilitation and function of central auditory pathways have been mostly carried out on cohorts of children with cochlear implants and very rarely on children fitted with conventional prosthetic devices, who nonetheless represent the majority.

Rare are the studies that focus on evaluating the benefit of prosthetic amplification in hearing-impaired children as a function of the age at which the device was fitted. There are many reasons for the lack of studies aiming to reproduce these results: on the one hand there are less children being belatedly fitted with devices (after the age of 2) thanks to the prevention and screening policies set up in most industrialized countries, and on the other hand cochlear implant technology began to be used at the end of the 1980's and beginning of the 90's for profound congenital child deafness, and the scientific community seems to display a lack of enthusiasm for evaluating with equal methodological rigor a technology seemingly less sophisticated than cochlear implants. One can identify four studies that are satisfying on methodological grounds: three of them argue there is a benefit to be drawn from early device fitting in terms of oral language comprehension and speaking intelligibility. The fourth study, which was led in Australia and is the most recent, disagrees with the preceding studies and correlates language quality at 7-8 years with the degree of hearing loss rather than the age at which the children were fitted with prosthetic devices. The important difference between this study and the preceding three is that degrees of hearing impairment are distributed differently, the Australian study has a higher proportion of mild hearing loss and a smaller number of children presenting severe and profound hearing impairment that was diagnosed early. It is possible that the correlation between early management and quality of language, shown by other teams, does not apply to all degrees of deafness, particularly for mild and moderate deafness. The contradictory results of the last study demonstrate the need for further studies in order to evaluate rigorously the long-term effects of fitting hearing devices and the relevance of fitting devices early for the various degrees of impairment.

Numerous studies have analyzed the relationship between comprehension/development of language and age of implantation. To date, over 60,000 people (approximately half of whom are children) are fitted with cochlear implants worldwide. However, when the cochlear implants are fitted in adolescents or adults with prelingual deafness, implantation usually only brings a very weak recognition of words or sentences in an open list, and a limited recognition (around 40%) of common words in a closed list (known by the patient before the test). The first pediatric cochlear implantations were performed about twenty years ago but the technique was only developed in children from the 1990's onwards. In France, the number of implants financed by the Ministry of health increased very significantly in 2000, with at present 250 pediatric implants financed each year for 600 to 700 births of infants with severe and profound deafness every year. The age of implantation, which long remained between 2 and 4 years, has been progressively lowered as the various studies showed younger children did not develop more complications and efficiency was increased. In 2000, the Food and Drug Administration recommended implantation from the age of 1 year.

Results of very early (age 1-2 years) cochlear implantation only began to be published at the end of 2001, initially with small-size cohorts. Several recent series of 20 to 80 children implanted before the age of 2 years have shown early cochlear implantation helps oral language comprehension and development, and increases the possibility for children with profound deafness to adapt to an ordinary school environment. In this particularly homogeneous context, and using standardized evaluations of implanted children, it clearly appears that age of implantation is a determining factor in the results obtained and that children fitted with implants before the age of 2 years show perception (under testing conditions in a non-noisy environment) and language development performances close to those of non-hearing-impaired children. There are nevertheless certain reservations for very early cochlear implantation since many factors or risks have not yet been evaluated, such as the risk of not having properly evaluated the level of deafness in a very young child (in the absence of objective testing for hearing at conversational frequencies).

Studies on the plasticity of central and peripheral hearing pathways in children are becoming important in order to corroborate physiologically the impressions gathered from subjective cognitive and educational evaluation. These studies can further our knowledge on critical periods beyond which fitting certain devices is no longer beneficial, and therefore help attain a more solid consensus concerning very early implantation, i.e. before the age of 1 year, recommended by certain implantation teams. This remark goes for other new indications such as implantation in both ears for which there are currently no studies to show that this can bring real benefit in terms of communication.

Currently available plasticity studies have been led by comparing children with normal hearing and children with implants, or by longitudinal follow-up of children with implants. Maturation of upper central hearing pathways was evaluated by studying P1 and N1 waves from cortical evoked potentials whereas maturation of the auditory nerve and the brainstem cochlear nucleus was evaluated by studying wave latency in electrically evoked potential. The conclusions of the studies led in the last five years may be summarized as follows: periods of prolonged auditory deprivation do not hamper the response capacity of the auditory nerve and brainstem to the initial stimulus delivered by the cochlear implant, and auditory brainstem plasticity persists whatever the age of implantation. Conversely, the plasticity of upper central auditory pathways decreases as the length of deprivation increases; for the P1 wave, it has been observed that there is a maximal period of plasticity before the age of three and a half and that the earlier implantation is performed, the more rapid the normalization. In the case of the N1 wave, which appears after the age of 5 and matures until adolescence, there is probably a critical period beyond which this wave will no longer appear. Indeed, the prolonged longitudinal follow-up of 2 children fitted with

implants at the age of 6 – with two and a half years of auditory deprivation in one case and four and a half years of being fitted with a super powerful device for congenital deafness in the other – has shown that the N1 wave does not appear when induced at a distance, in spite of good speech recognition performances.

The evaluation of brain plasticity can only be based on AEP studies. It is likely that functional imaging, which has so far not been used in studies on children, will be a source of complementary and more detailed data in the years to come.

Acoustics must meet a new challenge by developing new screening, diagnostic and management tools

Acoustics is one of the fundamental tools that has, for the last century and a half, allowed elucidating the workings of auditory receptors and the structure of the messages they transmit to higher brain centers. This has led to some degree of understanding of auditory perception mechanisms, at least concerning certain elementary perceptive attributes. In itself, and contrary to other disciplines mentioned in this report, acoustics is not an emerging field. But the rapid progression of other fields such as molecular biology, and the greater demand on the part of physicians and families for improved screening, diagnosis and management of hearing impairment have raised new challenges, as reflected by recent literature in the field.

The physiology of hearing, better understood thanks to a number of tools emanating from the field of physics, has led to update and deepen our comprehension of abnormal inner ear function in relation to the identification of dysfunction in child deafness genes. Even if this does not immediately lead to significant modifications in hearing impairment management (especially congenital deafness because the damage involved appears to be irreversible, in the current state of knowledge), this understanding is a prerequisite for subsequent progress, if only because the precision of diagnosis depends on it.

More complete identification of perception and cognition mechanisms involved in the analysis of sound messages (the field of psycho-acoustics) is increasingly necessary: for any given auditory loss, with a characteristic origin, degree, onset and duration, one needs to know which aspects of sound processing are affected (time or frequency-related for instance, or more complex as in the analysis of auditory scenarios in the presence of noise or competing sources), and how nerve center function is modified when the messages received are impoverished or have disappeared. Answering theses questions is crucial for determining how device fitting can counter deficits, which device is the most appropriate and which type of reeducation is likely to accelerate installation or resumption of optimal performance. New functional imaging tools now allow undertaking innovative research in this field but the results in 2005 are still embryonic.

In order to evaluate the impact of hearing impairment and, just as importantly, the benefit brought by its management, it is naturally necessary to have new physical acoustics and biological tools, not for use on a day-to-day basis. For everyday use, one must be able to measure simple responses of the auditory system with a view to make a general evaluation of any hearing loss and its consequences (electrical and acoustic measurements). The tools required, invented 2 to 3 decades ago, are well anchored in clinical practice but can be perfected technically as can the analysis of the results they produce. Both of these aspects are beginning to be represented in current research.

Among non-invasive tests for cochlear exploration, distortion products are the most promising; they involve a class of acoustic otoemissions that probe by frequency variation for the different types of cochlear sensory cells responsible for the selective amplification of

sound. Study of this class of otoemissions in adults and animal models recently uncovered new links between different types of cochlear mechanical performance, usually measured by longer or more invasive means. Thanks to distortion products, it also seems possible to detect conduction problems that are frequently observed in children and prevent the detection of otoemissions nonetheless emitted by the cochlea. Development of these techniques could render neonatal screening more efficient by producing results giving rise to fewer false alarms.

The steady state potential method explores means of evaluating hearing loss earlier and more thoroughly. However, this technique is neither reliable enough at conversational frequencies for the time being nor routinely useable since it involves an examination during prolonged sleep.

Functional imaging (magnetoencephalographic imaging in particular) combined with the use of classical psychoacoustic techniques has proven to be both feasible and reasonably efficient for understanding cortical representations of auditory messages, and assessing the respective importance of analyses based on spectral and temporal indices and their interaction (especially when the coding strategy of a device disturbs its natural coherence). The practical interest of other brain functional imaging techniques (fMRI, PET) remains to be proven in children.

Analysis of recent publications also reveals a lack of application of research on screening tools. Indeed, the few studies (around ten) aiming at maximizing the conditions for collecting and using signals, as well as subsequent tasks, stick out in a sea of hundreds of thousands or even millions of OAE and AEP results collected worldwide in the course of universal screening. This suggests on the one hand that auditory screening, once performed, has so far not led to changes in audiological practices (the question whether evaluation is correct is still rarely addressed), and that on the other hand practitioners in charge currently tend to have confidence in the material available without trying to detect their flaws or improve their operation. Similarly, there is little data available to estimate the proportion of hearing-impaired children left undetected by current techniques.

Deficits can either be compensated by acoustic amplification or by fitting electronic or electroacoustic implants in the vicinity of structures unaffected by the pathology. The principle of electroacoustic amplification is intrinsically limited by the fact that the sound processed by the device is applied to a pathological ear, which distorts and degrades the signals it receives. However, the current generation of devices has gained from digital technology and notices for prosthetic devices are now appearing with the mention that they are equipped with intelligent signal processing features capable of anticipating and countering certain defects inherent to the auditory receiver organ. Evaluation of such devices is still generally very difficult due to industrial secrecy, which does not help scientific research. Profound deafness – and severe deafness when acoustic amplification does not give good results – can benefit from another strategy, namely implants, when fitted sufficiently early. Implants, and in particular cochlear implants, circumvent the difficulty of having to go through a pathological cochlea since they short-circuit this structure. Cochlear implants have met with remarkable success in the last decades. This field has been very active over the last few years, with the identification of numerous characteristics that now allow considering an improved list of specifications for more appropriate performance and new indications.

Cochlear implant performance are improved by new coding and novel implantation techniques are emerging

Analysis of recent publications clearly shows the emergence of two strategies: one consists in refining the tools for early diagnosis of hearing impairment (since screening worldwide has recently been propelled to the forefront), and the other, necessarily derived from the former, aims at providing more efficient early management thanks to the fitting of more appropriate devices (the exponential development of cochlear implants being its most blatant illustration). Two new approaches are being grafted onto these emerging strategies: trying to understand the flaws of current devices in order to find remedies, and launching new indications for prosthetic devices.

The study of conventional devices (electro-acoustic amplifiers) is not an emerging field. Its activity remains modest in the academic world, which in no way reflects the speed with which new devices are launched on the market. This is no doubt due to the difficulties involved in designing experimental protocols to study devices the functioning rationale of which is not part of the public domain (and even more so when devices or their algorithms are still being developed). The lesson gained from device evaluation is that basic and theoretical knowledge in acoustics cannot as yet provide all the clues necessary to know and possibly understand and control complex sounds such as speech and music. Spectrotemporal analysis remains the basis for our understanding. The precise rules that govern such analysis are continuously subject to major advances that guide the development of coding and tuning strategies for acoustic audioprosthetic devices and cochlear implants. Classical tuning adjustments for audioprosthetic devices can bring significant improvement and remain the subject of many ongoing studies. In particular, such adjustments bear on the level of dynamic compression combined with various time constants, microphone directionality and automatic signal detection in a noisy environment. The idea of implanting a transducer directly into the middle ear in order to remove certain acoustic distortions is still theoretically valid but the most recent studies are still unable to make the awaited improvements with classical audioprosthetic devices.

Research on cochlear implants has been intensified as a result of its success as a means of rehabilitation for hearing-impaired children. Subjects with implants often display impressive performances in favorable acoustic situations, thanks to the numerous studies on the respective and combined roles of frequency and time-related coding, combined with the important increase in technical possibilities offered by digital systems. This has led to perform implantations in cases of partial deafness, which used to be managed only with conventional devices, with very modest results.

However, people with implants have great difficulties in a noisy environment, in the presence of a competing sound source, or with complex sounds such as music. These limitations can now be clearly attributed to the insufficient number of independent functional canals in currently available implants and to the lack of temporal resolution of their coding technology. Remedies are being developed in several ways, such as increasing the number of independent electrodes, using coding that involves more impulses per second, better management of rapid frequency variations and using more physiological methods for stimulating auditory neurons. Without waiting for such remedies to be implemented, new indications have emerged, either because their efficiency is immediately obvious (electroacoustic implants with electrodes restricted to lesional zones in adults), or by analogy with already validated advances for conventional hearing aids, which is the case for the binaural device. It is therefore hoped that using bilateral cochlear implants might also allow spatial localization of sounds, which is crucial under certain conditions in everyday life, and detection of signals such as speech coming from a particular person in a noisy environment.

The particularly strong development of imaging of auditory cerebral activation, previously mentioned, is providing basic knowledge that will undoubtedly give objective means for the fine-tuning of devices in young children.

Recent research offers new cochlear therapeutic prospects

Hearing disorders can affect organs involved in sound transmission (outer and middle ear) or/and organs that analyze and transform sound into biological processes and ensure its neural coding (inner ear and central auditory system). A large proportion of hearing disorders involve alterations in sound transmission, in which case a surgical approach is usually possible and gives satisfactory results. When sensory organs or neural pathways (responsible for transducer functions, and the analysis and coding of sound) are affected, therapeutic approaches are far more difficult and usually fail to give satisfactory results. However, the many fundamental scientific advances over the last few years will no doubt lead to the emergence of new highly promising therapeutic approaches.

Auditory disorders can be classified into two major categories: deafness and tinnitus. Deafness can itself be divided into deafness of known origin (sound trauma, ototoxic drugs or genetic abnormalities) or deafness of little understood or unidentified origin (sudden deafness and Ménière's disease). Auditory ageing, which is bound to be multifactorial, occupies a place of its own. When causes are known, it is possible to reproduce them experimentally and therefore have models available allowing real progress to be made. The great majority of pathophysiological processes associated with the different types of deafness and tinnitus seem to come from inner ear dysfunction, which in turn affects the function of brain auditory pathways. The various deafness and tinnitus disorders present perception alterations that can be very different, suggesting that the underlying pathophysiological mechanisms are also different.

Exposure to noise is one of the major causes of auditory disorder in our society today. It has been known for some years that there is a relationship between physiological damage and quantity of acoustic energy and sound levels and times of exposure representing limits that should not be crossed have been determined. However, these limits only have statistical value and great individual variability is observed in vulnerability to noise. One of the more important aspects remains the determination of exact acoustic parameters influencing the degree of induced sound trauma, since the principle according to which equal acoustic energy levels correspond to equal physiological damage is not always verified. New audiometric measurements such as acoustic otoemissions allow better understanding and differentiation of underlying cochlear dysfunction. Physical protection, sound source attenuation, wearing ear plugs or protective ear muffs, have made little progress and attention is being focused on environmental factors (hypoxia, chemicals including certain solvents, etc.) that can increase sound trauma. However, it has been observed that sound exposure can generate acquired resistance to sound trauma and studies are being carried out to try and understand the physiological processes associated with this phenomenon. Efferent sympathetic innervations of the cochlea have been identified in connection with such processes and are currently under study. Several drugs for sound trauma have been identified, such as anti-inflammatory, antioxidant and antiapoptotic drugs, neurotrophic factors and neuromodulators, and have been found to be efficient. Certain genes, such as genes involved in early ageing and oxydative stress or coding for cellular adhesion molecules, seem to influence sensitivity to sound trauma.

The ototoxicity of certain antibiotics, and in particular the aminoglycosides, has been known for many years. It essentially affects hair cells and can also alter proper function of cochlear

nerve cells. Considerable individual variability to antibiotic ototoxicity has been observed but it is not known whether this is due to intrinsic individual susceptibility or punctual physiological states at the time of treatment. In animal models, it would appear that males are more sensitive and that protective pretreatment is effective. Over sixty antidote molecules have been tried with variable success and, when administered jointly with aminoglycosides, have been demonstrated to induce a marked decrease in antibiotic ototoxicity. These molecules present antioxidant, anti-inflammatory or antiapoptotic properties. There is to date no equivalent published study in man. In addition, genetic factors appear to influence ototoxicity, particularly in relation to mitochondrial function, natural antioxidizing agents, pigmentation, and neurotrophic factors.

The antineoplastic drug, cisplatin, unfortunately has ototoxic effects and the mechanisms underlying these effects are beginning to be elucidated. The drug affects vascularization, the organ of Corti and cochlear nerve cells. Carboplatin, an antineoplastic drug similar to cisplatin, seems to be selectively toxic for inner hair cells. The cellular and molecular processes of cisplastin ototoxicity involve oxidative mechanisms and mitochondria as well as apoptosis. Over forty antidote molecules have successfully been used with success, the majority of which have antioxidant or antiapoptotic properties. These studies, conducted in animals, open hopeful perspectives for man.

Over the last few years, a great deal of knowledge has been gained on processes of inner ear cellular and tissue regeneration. It is now well established that almost all inner ear disorders involve an irreversible loss of sensory cells or nerve cells. It had been known for more than twenty years that natural sensory cell regeneration could occur in birds and perhaps to some extent in the vestibular apparatus of mammals. However, it was shown only recently that natural continuous regeneration of ciliary tufts and interciliary bridges occurs in mammals. The two phenomena are probably associated with the functional recovery observed after certain reversible sound trauma. Neurons are also capable of natural regeneration and studies are being carried out to continue identifying the factors that control their regrowth and the formation of new connections. Significant progress has also been made to prevent the degeneration of cochlear neurons. Growth factors and cellular adhesion molecules have been found to prevent nerve cell degeneration. The use of stem cells or embryonic cells is also bringing new encouraging results. Finally, the transfer of the *Math1* gene after selective destruction of sensory cells has allowed the regeneration of functional sensory cells.

Tinnitus, whistling or buzzing in the ears, are a very common hearing disturbance in adults but that remains poorly understood. It can also occur in children but its incidence and impact are practically unknown in this population. Sometimes, a triggering factor can be identified (sound trauma, drug, vascular malformation, otosclerosis, myoclonus, etc.). Progress is being made to characterize tinnitus from the psychoacoustic standpoint. This should help make quantitative measurements and possibly draw up a useful classification of underlying pathological processes. Recent studies in man have shown an association between certain stress conditions and the occurrence of tinnitus on the one hand, and the occurrence of tinnitus-specific anomalies in acoustic otoemissions and evoked potentials on the other hand. Brain imaging has shown cortical tonotopic disorganization in certain cases of tinnitus. Therapy remains quite insufficient even though peripheral electrical stimulation, which regenerates lacking spontaneous activation (a phenomenon thought to be involved in the suppression of tinnitus by cochlear implants), seems to be offering new prospects. In addition, some degree of success has been obtained by electrical and/or magnetic stimulation of the auditory cortex in association with cortical functional imaging, allowing the decrease or suppression of tinnitus perception. Over the last few years, reliable animal models have been developed and are being used by several research teams. Experimental induction of tinnitus is achieved with strong doses of salicylate or by sound trauma. Data

from such animal models have shown multiple cochlear alterations at the vascular, sensory and neural level, exploration of the central auditory pathways revealing involvement of secondary auditory structures and various types of functional reorganization.

The benefit of new mixed electroacoustic audioprosthetic devices for children remains to be validated

In many cases of inner ear hearing impairment, audioprosthetic devices remain the only therapeutic solution that can be considered at present. Although remarkable progress has been made, audioprosthetic devices are far from being entirely satisfactory in spite of the fact that the technical possibilities available with the advent of digital techniques are enormous. Besides the technical problem previously mentioned in relation to signal processing, it is still unclear whether there is a relationship between the number of functionally competent neural fibers and the benefit a cochlear implant can bring, partly probably because autoptic studies in man are very rare. Interesting studies are currently being conducted to conserve the cochlea as well as possible when a cochlear implant is being fitted (by local administration of cortisone or neurotrophic agents and use of soft surgery techniques). The very promising development of the mixed electroacoustic audioprosthetic device follows the same logic of conserving as much as possible what remains of the cochlear auditory structure. In the case of partial deafness, where the loss of high-pitch frequencies is severe while hearing is well preserved at low-pitch frequencies, one may combine a cochlear implant restricted to the base of the cochlea with a classical hearing device for low-pitch frequencies. The first results obtained indicate that careful fitting of a short implant does not deteriorate cochlear function and brings considerable benefit in terms of intelligibility associated with a degree of music perception that is clearly superior to the benefit derived from the hearing device or the classical cochlear implant alone.

Recommendations

Whatever the origin of hearing impairment, all studies agree that screening for deafness in children should be done as early as possible in order for all hearing-impaired children to benefit from auditory rehabilitation from a very young age. Early rehabilitation is one of the major factors influencing the quality of oral language development in deaf children. Indeed, because of the plasticity of auditory centers changes with time, there are critical periods beyond which rehabilitation will be less efficient. The quality of audioprosthetic devices, whether they be hearing aids or cochlear implants, requires to be perfected and further research appears to be necessary in this area.

The analysis and synthesis the group of experts has carried out lead to a number of propositions for public health actions in view of promoting early and systematic screening for hearing impairment with a variety of prevalidated tools. Setting up early screening will require further research in order to define the modalities of generalized or partial application to the population of newborn infants, especially since there is still insufficient fundamental data concerning deaf children. The group of experts has also drawn up propositions to carry out research for improving molecular diagnosis of genetic deafness. It should be kept in mind that while numerous genes responsible for early deafness have been identified, their exact function remains to be determined.

Basic research in psychoacoustics appears to be essential in order to acquire the basic knowledge necessary for understanding the various auditory deficits, thus allowing restitution of the most pertinent acoustic information to hearing-impaired people according to the type of hearing device used (acoustic and/or implanted). The current absence of curative treatment for perception deafness is an incentive for developing basic research and getting a better understanding of interactions between sensory cells, toxic or protective molecules and environmental factors (noise, most prominently) predisposing to a loss in hearing acuity.

Developing public health actions

CREATING A NATIONAL CHILD HEARING IMPAIRMENT REGISTER

In spite of the high prevalence of deafness, probably around 1.5 to 2/1,000 in the first years of life, and the prolonged management such children require, no health insurance fund (whether local or regional) is currently able to estimate rigorously the costs generated by hearing handicaps and their management for this age group.

Even though the group of experts is aware of the organization difficulties involved in a census program (legal protection of families, scattering of data, variety of personnel with various degrees of competence), the group of experts strongly recommends the creation of a national child hearing impairment register. This action, inspired by the experience acquired in other countries (Australia, Canada, Sweden, Great-Britain), would help public authorities plan the provision of more appropriate health care, better coordinate educational management according to the handicaps incurred, and identify emerging needs for professional training in particular areas.

The register would allow making a census of all hearing impairment cases in France, thus helping to draw up relevant public health policies on the basis of epidemiological knowledge. The request for full reimbursement of health and educational management for hearing-impaired children being a central issue, health insurance funds could participate in maintaining such a register. The audiograms provided to request and renew rights to reimbursement could be collected in order to record the degree of hearing impairment and follow its progression. The mode of educational management could also be recorded.

STANDARDIZING THE DATA COLLECTION METHOD FOR ESTABLISHING THE PREVALENCE OF THE VARIOUS FORMS OF HEARING IMPAIRMENT IN FRANCE

The prevalence of congenital deafness needs to be brought to the attention of public health authorities in order to help them to judge the efficiency of neonatal screening programs and adjust prevention and educational management policies to the needs of the population. It is therefore important to validate prevalence figures by having precise information on the conditions in which they were obtained. In order for the prevalence figure to be really meaningful, one needs to know the age at which the estimate was made, the auditory exploration technique chosen (otoacoustic emissions, auditory evoked potential, behavioral audiometry), the characteristics of deafness (hearing level and audiometric frequencies chosen, sensorineural/conductive/mixed nature of deficit, restriction to bilateral disorders or not) and the characteristics of the living area (socioeconomic deprivation, culturally related inbreeding).

Prevalence studies in newborn infants, now possible thanks to the development of automated techniques, should also provide further information to limit interpretation errors. When prevalence is studied by otoemissions, the condition of the middle ear (otoscopy and/or tympanometry) and the postnatal day of examination should be available. If on the other hand automated auditory evoked potentials are used, the level of stimulation should be indicated.

Given the absence of international consensus on severity criteria in audiometric screening, studies aiming at refining the prevalence according to the degree of hearing loss (moderate, severe, profound) should always mention the frequencies chosen to determine the mean hearing loss, as well as the hearing level thresholds of the different categories of hearing impairment. These details are essential for estimating management needs since it is becoming increasingly apparent that moderate hearing impairment is the most common. Knowing the distribution of the various degrees of hearing impairment should also allow better structuring of professional training for people taking care of such children.

The group of experts recommends that the method for collecting information be standardized to ensure the development of a quality public health policy.

PROMOTING EARLY AND SYSTEMATIC SCREENING OF HEARING IMPAIRMENT WITH VALIDATED TOOLS

In spite of the recommendations in each child's health care notebook to carry out hearing examinations during the first year of life, the majority of bilateral cases of perception hearing impairment ≥40 dB HL are still being diagnosed after 12 months when the child was not systematically screened at birth. The lack of reliable behavioral tools for all pediatricians, the absence of risk factors in at least half of hearing-impaired children, the often astonishing capacity of many hearing-impaired children to reinforce other sensory abilities to counter

their deficiency, parental hope that their initial doubts will be contradicted by the physician's diagnosis, the possible mistaking of perception deafness for a banal serous otitis media, and reassuring words unconfirmed by precise auditory examination, can all contribute to delay diagnosis. While a simple initial measure to improve the situation would be to coordinate action with respect to these factors, this turns out to be difficult in practice.

The advent of reliable objective techniques, automated and therefore applicable from the first few days of life – otoacoustic emission (OAE) and brainstem auditory evoked potential testing (BAEP) – now make screening of hearing deficit possible in the maternity setting. This type of public health approach requires rigorous organization for the performance of tests, the collection of individual data, the repetition of tests in the maternity setting when the apparatus fails to detect a response, organizing referral of children testing positive to a diagnostic center and identifying those that do not show up.

The ongoing experimental CNAMTS/AFDPHE program chose the automated AEP technique rather than otoacoustic emissions (OAEs) for a number of scientific reasons: the percentage of false positives (children presenting suspect neonatal test results but shown not to have bilateral perception hearing impairment ≥40 dB HL upon further examination) is lower, the predictive positive value (PPV) is higher (over 15% in most programs using two-step automated AEP testing), and it is possible to identify forms of deafness that conserve OAEs.

Other local or regional screening programs using OAEs have been set up across the country. OAE data are collected more rapidly and associated consumables are not as costly. A rigorous comparison of the OAE and AEP techniques should bear on the number of deaf children identified (deviation from the expected prevalence), PPV and a precise quantitation of false negatives.

Whatever the degree of hearing impairment, early management (from 3 months for profound deafness) has proved to be beneficial according to most studies for the development of auditory capacities and oral language. Such management therefore requires the setting up of early screening with tools of proven efficiency. The group of experts recommends early neonatal screening to warrant the most exhaustive analysis.

Because hearing impairment may occur as a result of secondary development, the medical profession and parents must be highly vigilant with respect to auditory responses and language development in young children. Several simple clues can draw attention and motivate the request of an audiophonological exam for a child who:

- does not produce double syllables at 9 months;
- does not say "dadda" or "mamma" at 14 months and does not respond to being called by name;
- does not produce two-word combinations at the age of 2 and does not point to the different parts of the body when asked to do so;
- is not intelligible at the age of 3 (or is only understood by its own parents).

The group of experts insists on the usefulness of generalized screening in a school setting at the beginning and at the end of day nursery.

LOOKING FOR AN ASSOCIATED SYNDROME IN HEARING IMPAIRED CHILDREN AS SOON AS A HEARING DEFICIT IS CONFIRMED

In the context of increasingly early diagnosis (after neonatal screening), the group of experts recommends primarily focusing etiological analysis on two syndromes that present as isolated deafness:

- Usher's syndrome: while the fundus oculi in very young children may appear normal, there may be signs that the vestibular apparatus is affected (the child does not hold its head up at 3 months, does not sit at 9 months, and does not walk at 18 months) and an electroretinogram should be performed;
- the Jervell and Lange-Nielsen syndrome: an electrocardiogram should systematically be performed in order to look for lengthening of the QT interval.

Other frequent syndromes must be looked for by questioning and clinical examination (branchio-oto-renal syndrome and Waardenburg syndrome), by imaging of the temporal bone (syndromes with inner ear malformation such as Pendred's syndrome), by urine examination (to look for hematuria/proteinuria, as in Alport's syndrome).

PROPOSING A MEDICAL GENETICS CONSULTATION

Medical genetics consultation allows determining whether the hearing impairment is of genetic origin by exploring family history (genealogy) and closely examining any clinical signs suggesting a syndrome disorder.

Imaging of the temporal bone can help the genetician in his/her etiological search.

The consultation allows giving indications for molecular diagnostic testing and informing the family about the risk of recurrence.

As a complement to the previous recommendation, the group of experts advocates refining etiological search by proposing medical genetics consultation.

INFORMING FAMILIES EARLY ABOUT POSSIBLE COMMUNICATION AIDS FOR THEIR CHILD

Deficits can be compensated by acoustic amplification or by fitting electronic/electroacoustic implants in the vicinity of healthy structures. Early auditory rehabilitation has been recognized for many years as one of the major factors influencing the quality of oral language development in hearing-impaired children. As soon as diagnosis is confirmed, the parents should be informed of the various aids available for communication and cognitive function development in relation to the severity of the hearing impairment and any other associated handicap. Although the parents sometimes favor sign language, most families choose auditory rehabilitation aiming at acquiring oral language.

The great majority of studies demonstrate the benefit of fitting auditory devices early on for the development of oral language, in practice from the age of 4-6 months.

In the case of profound deafness, early cochlear implantation (between 12 and 24 months) has been shown by all studies to give excellent results on oral language (in the absence of an associated mental handicap).

In cases where a cochlear implant is indicated, the group of experts recommends that it be fitted from the age of one.

INFORMING THE POPULATION ABOUT HEARING IMPAIRMENT LINKED TO SOUND TRAUMA

In the absence of knowledge at present on the genes predisposing to sound trauma, which would possibly allow identifying a population incurring a higher risk, it is desirable to multiply preventive and educational actions on hearing impairment linked to sound trauma among the general population of children and adolescents (school programs, conferences, temporary or permanent exhibitions in science and technology or health-oriented museums).

The group of experts recommends learning to recognize, avoid and protect oneself from dangerous sound levels, particularly in the case of amplified music.

REMINDING HEALTH PROFESSIONALS ABOUT THE RISK OF HEARING IMPAIRMENT ASSOCIATED WITH THE USE OF AMINOGLYCOSIDES

Iatrogenic hearing impairment occasioned by taking aminoglycoside antibiotics must be prevented in genetically at-risk individuals. The group of experts stresses the usefulness of reminding health professionals about the risk of hearing impairment linked to the use of aminoglycosides and about considering the use of alternatives. In the short term, protocols involving aminoglycosides antibiotics for treating neonatal infections could be reevaluated. In the longer term, the pharmaceutical development of new antibiotics could avoid or limit the use of aminoglycosides. In cases where such antibiotics cannot be avoided, it will be necessary to develop the quick molecular diagnosis of the 3 mutations in the mitochondrial 12S rRNA gene involved, for all patients at risk. These include families with maternal transmission of deafness and/or triggering of deafness by an antibiotic from this group, and more generally any individual for whom treatment with aminoglycoside antibiotics is being considered (suspected neonatal infection, mucoviscidosis, urinary tract infection, etc.).

Developing research

DEVELOPING RESEARCH ON STRATEGIES OF REHABILITATION AND DEFINING THE MOST FAVORABLE AGE BRACKETS FOR FITTING THE VARIOUS TYPES OF DEVICES

Detailed knowledge about the plasticity of auditory centers determines several aspects of hearing impairment management once early detection has been achieved. Certain teams across the world advocate very early implantation, well before the age of one. In view of this, the group of experts believes it is important to refine knowledge on the critical periods beyond which fitting certain types of devices will be less efficient. This remark is also valid for new indications such as binaural implantation for which there are so far no studies demonstrating a real communication benefit.

Furthermore, the group of experts recommends comparing the long-term benefits of the various rehabilitation and reeducation strategies in children in order to further knowledge in this field.

IMPROVING OUR KNOWLEDGE OF PERCEPTION PROCESSES IN HEARING-IMPAIRED INDIVIDUALS

Current studies indicate that each hearing-impaired individual is affected by multiple perception deficits, which vary a great deal from one person to another. Furthermore, hearing-impaired people are particularly subject to hearing deterioration in the presence of noise or competing sound sources. The technical possibilities offered by digital systems are currently greatly underexploited essentially because knowledge on the algorithms that need to be set up in such systems is lacking.

The group of experts recommends developing studies on the specific psychoacoustic processes that take place in given individuals under noisy and non-noisy conditions in order to try and compensate for noise interference by appropriate signal processing algorithms in audioprosthetic devices.

Not enough basic research is being done in psychoacoustics, i.e. the study of normal processes associating acoustic parameters and auditory perception, especially for complex sounds such as speech and music. The group of experts therefore advocates further development of psychoacoustic research. This is essential for making progress and acquiring sufficient basic knowledge to study and understand various auditory deficits so as to allow hearing-impaired individuals to receive the most relevant acoustic information through hearing aids and/or implanted devices. Such studies will need to rely on the various decompositions of time/frequency provided by mathematical and physical tools, and on research in communication engineering.

DEVELOPING RESEARCH TO IMPROVE THE CHARACTERIZATION OF EACH FORM OF GENETIC HEARING IMPAIRMENT

Characterizing each form of genetic hearing impairment requires:

- defining specific clinical profiles (in as much as possible) in order to target the molecular diagnosis of hearing impaired children (for example, looking for minimal signs of associated vestibular apparatus pathology or inner ear morphological abnormalities detectable by scanner, or for characteristic audiometric profiles);
- developing functional imaging: this technique has only recently been applied to the field of audition and has so far brought rudimentary results. Numerous studies seem to be necessary, particularly normative studies; their potential impact is particularly important for children by allowing to make objective measurements both for characterizing different types of hearing impairment and for rehabilitation;
- looking for possible genotype-phenotype correlations with prognostic value;
- measuring the prevalence of each genetic form of hearing impairment: the prevalence of the different forms of genetic hearing impairment in France needs to be precisely known, particularly for dominant forms, which often appear later in childhood and have a poorly understood genetic epidemiology.

The group of experts advocates applying the above measures for characterizing the various genetic forms of hearing impairment.

DEVELOPING EFFICIENT TECHNIQUES FOR MOLECULAR DIAGNOSIS

The development of efficient techniques for molecular diagnosis is necessary in order to:

- allow genetic counseling and prognostic evaluation;

- diagnose particularly invalidating syndromic forms of deafness, which may justify voluntary interruption of pregnancy. This is the case for Usher's syndrome, which combines congenital deafness and a later-onset retinal disorder leading to blindness. The difficulty for molecular diagnosis resides in the number of genes responsible, most of which are very large, and the diversity of possible mutations in each gene. The use of DNA chips is promising but is hampered at present by the fact that as complete an inventory as possible of the mutations present in the population concerned still needs to be done (ideally, on a European scale).

The group of experts recommends thinking about the usefulness of the various molecular diagnoses. The techniques involved will need to be evaluated in order to determine which diagnoses should be reimbursed by health insurance funds.

While it is already technically possible to carry out prenatal molecular diagnosis for deafness, one needs to examine whether this is justified in the case of isolated deafness. In addition, the future identification of genes predisposing to presbyacusis, a form of perception affecting a large fraction of the elderly population, will allow considering presymptomatic molecular diagnosis. One should however consider whether this diagnosis should be proposed in the absence of preventive measures of proven efficiency.

The group of experts advocates starting reflexion immediately on ethical questions raised by molecular diagnosis of deafness.

DEVELOPING THE ANALYSIS OF GENETIC DEAFNESS IN MICE

Developing the analysis of genetic deafness in mice involves:

- pursuing the identification of genes responsible for deafness in mutants emanating from European large-scale mutagenesis programs (this approach allows accelerating the identification of candidate genes for human deafness, and in particular those involved in rare genetic forms of deafness, for which positional cloning by studying large affected families is difficult);

- conducting morphological and functional studies on murine models for deafness in order to try and understand the pathology of the corresponding forms of deafness at the cellular level, a prerequisite for specific therapeutic research;

- producing late conditional murine mutants for genetic forms exhibiting an abnormal development of the cochlea in order to invalidate the corresponding gene in the mature cochlea and look for a possible extra deleterious effect of the mutation on mature cochlea function. This type of late effect is important to identify in order to develop therapies that will not only correct the early developmental anomaly. Late conditional mutants could be obtained by the Cre-Lox system (where the difficulty lies in choosing an adequate promoter to control the expression of the Cre recombinase, hence the necessity to intensify the detailed characterization of the spatiotemporal expression profile of genes expressed in the mature cochlea) or an inducible system (induction-repression controlled by the administration of tetracycline);

- looking for modifier genes, i.e. genes that can modify the different forms of genetic deafness, since these genes constitute potential therapeutic targets for the corresponding forms of human deafness. Murine genetics is the tool of choice for this type of research, which is often difficult to conduct in man because of the small size or the small number of families available. One hopes therapeutic solutions can be found thanks to the identification of modifier genes for the most common form of genetic deafness, DFNB1

(due to a mutation in the connexin-26 gene), which leads to various types of cochlea dysfunction that are difficult to correct by a simple therapeutic approach given the multiplicity of cellular types involved.

The group of experts stresses the importance of developing the analysis of genetic deafness in mice in order to further pathophysiological knowledge and identify therapeutic targets.

DEVELOPING PATHOPHYSIOLOGICAL RESEARCH FOR THERAPEUTIC PURPOSES

Hearing deficits result from dysfunction that affects the inner ear in most cases and has repercussions on central auditory pathways. There is to date no curative treatment for the various types of sensorineural deafness. The only form of management currently available is auditory device rehabilitation. Over the last few years, there has been considerable progress in knowledge and the development of techniques in health-related biology, including the development of functional imaging and cellular/molecular physiology. Numerous interdependent pathophysiological processes affecting the inner ear appear to be involved in deafness and tinnitus (inflammation, oxidative stress, hormonal dysfunction, apoptosis). Thus dysfunction that initially only affects a particular cell type or cellular metabolism can often lead to disturbance of other cellular entities and metabolic pathways. The group of experts advocates furthering our knowledge on the interactions between such pathophysiological processes in order to control them more readily.

TESTING MOLECULES LIKELY TO REDUCE THE OTOTOXIC PROCESS

Diverse possibilities for reducing ototoxic processes leading to hearing impairment such as sound trauma and drug-induced hearing loss (antibiotics, anticancer agents), using antioxydative, anti-inflammatory, neuromodulator and antiapoptotic agents, open particularly promising perspectives in man. Numerous studies remain to be performed in order to determine which substances are the most active before exploring whether their combined use might cumulate their respective benefits.

With this in mind, the group of experts recommends evaluating the efficiency and innocuousness of various modes of intracochlear administration of active substances (diffusion via the round window, coupling with the implant, osmotic micropumps) with a view to applying these to man. Such techniques could also be used in the treatment of certain genetic forms of deafness.

DEVELOPING RESEARCH ON THE DIFFERENCIATION OF SENSORY CELLS

Knowledge about phenomena such as continuous renewal of the molecular components of ciliary tufts in normal sensory cells on the one hand, and regeneration of functional hair cells induced by transfer of the *Math1* gene after destruction of these cells, opens new perspectives for therapeutic research.

The group of experts advocates developing research on genes involved in early differentiation of auditory sensory cells and on the characterization of progenitor cells that might possibly persist in the mature cochlea, with a view to develop a therapeutic approach whereby damaged sensory cells might be replaced.