SPECIAL ISSUE
Update on Infant Hearing
I am pleased to present in this special issue of *Audiology Today* the keynote and selected special session presentations from The 2nd International Newborn Hearing Screening (NHS) Conference held in beautiful Cernobbio, Italy on Lake Como, May 30 Through June 1, 2002. The NHS 2002 Conference is the result of coordinated efforts of international and national institutions, research laboratories, clinical centers, projects, consortia, health care providers and individuals in the European area working together within the framework of the European Commission - Project AHEAD II, Contract n. QLG5-CT-2000-01613.

The organization of this 2nd International NHS 2002 Conference was made possible only thanks to the cooperation with Dr. Deborah Hayes who has been involved in planning and “engineering” this meeting from the very beginning.

I would like to thank all my colleagues and coworkers here at the CNR Institute of Biomedical Engineering who have enthusiastically cooperated in the organizing committee, namely Marta Parazzini, Paolo Ravazzani, Gabriella Tognola, and particularly Sharon Scagnetti deserve my most grateful acknowledgment. Finally, ARSI-ONLUS, the Association for Research on Infant Hearing, a non-profit organization based in Milan, gave a fundamental contribution to make this Conference feasible.

More than 90 papers and 130 posters were presented to 550 delegates on a wide variety of topics. The organization, the level and the venue were witnessed by many delegates as “simply great.”

Ferdinando Grandori
NHS 2002 Conference Chairman

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**In This issue**

- Introduction – Ferdinando Grandori
- The Role of the Joint Committee on Infant Hearing in the Development of Early Hearing Detection and Intervention Programs in the USA – Patrick E. Brookhouser
- Historical Landmarks in European Otoacoustic Emissions – A. Roger D. Thornton
- Auditory Neuropathy in Infants and Children: Implications for Early Hearing Detection and Intervention Programs – Yvonne S. Sininger
- Otoacoustic Emissions and the Auditory Descending Pathway: Characterization and Influence of Age – L. Collet and E. Veuillet
- Possible Roles for the Auditory Steady-State Responses in Identification, Evaluation and Management of Hearing Loss in Infancy – Terence W. Picton, M. Sasha John & Andrew Dimitrijevic
- Early Cochlear Implantation in Congenitally Deaf Children – Richard T. Miyamoto, Derek Houston & Karen Iler Kirk

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*update on infant hearing* 3
Distinguished panel members Rene´ Dauman, Jay Hall, Susan Norton, Yvonne Sininger, Gerry Popelka and Paul Kileny discuss issues relevant to universal newborn hearing screening.

Marion Downs and Judith Marlowe enjoy the dinner cruise on Lake Como.

Deborah Hayes and Jerry Northern enjoy the dinner cruise on Lake Como.

NHS 2002 delegates enjoy lunch in historic 18th century Villa Erba.

Jay Hall, Yvonne Sininger, NHS 2002 Chair Ferdi Grandori and René Dauman.

Distinguished panel members René Dauman, Jay Hall, Susan Norton, Yvonne Sininger, Gerry Popelka and Paul Kileny discuss issues relevant to universal newborn hearing screening.
In the USA, the Joint Committee on Infant Hearing (JCIH) has provided a useful forum in which stakeholders representing an array of interested disciplines have been able to carry out objective evaluation of advances in technology for newborn hearing screening and EHDI program management while developing recommendations regarding implementation. The publication and dissemination of sequential JCIH position statements have served as a catalyst to focus the attention of practitioners and policy makers alike on the most current recommendations for Early Hearing Detection and Intervention (EHDI) programs. A review of the history of the JCIH's efforts as an instrument for changing public policy regarding early identification of hearing loss in infants provides useful guidance as to how such beneficial advances can be accomplished.

The Joint Committee on Infant Hearing traces its origin to the late 1960’s, during a period of rapid change in the scope of knowledge regarding childhood hearing loss. The mid-1960’s witnessed the last great rubella epidemic in the United States before the development and widespread utilization of an effective rubella vaccine. The availability of serological and viral isolation techniques to provide laboratory confirmation of prenatal rubella infection allowed clinical researchers to demonstrate that congenital deafness, often occurring in isolation, was the most common permanent sequela of congenital rubella infection. Descriptive studies being undertaken by geneticists shed light on the array of deafness syndromes, as well as the prevalence of nonsyndromic deafness. Advances in the developing specialty of neonatology were making possible the survival of increasing numbers of high risk neonates, including those who required prolonged mechanical ventilation, treatment with potential ototoxic medication, and exchange transfusions for Rh incompatibility.

It was clear to audiologists, most notably Marion Downs, and otolaryngologists interested in childhood deafness, that developing an effective program for early identification of deaf and hard of hearing infants would require them to enlist efforts of neonatologists and primary care pediatricians, as well as public health officials and health policy makers. The first formal action by the American Speech and Hearing Association (ASHA) regarding formation of a Joint Committee on Newborn Hearing was initiated in November 1969.

In the June 1971 issue of *Pediatrics*, the American Academy of Pediatrics (AAP) published "Joint Statement on Neonatal Screening for Hearing Impairment" which had been completed by the initial meeting Joint Committee on September 16, 1970. The following quotations from the statement reveal the Joint Committee's careful pursuit of evidence-based recommendations from its inception.

"Review of data from the limited number of controlled studies which have been reported to date have convinced us that results of mass screening programs are inconsistent and misleading."

"To determine whether mass screening programs for newborn infants should indeed be instituted, intensive study of a number of variables is essential. These should include stimuli, response patterns, environmental factors, status at the time of testing and behavior of observers. Furthermore, confirmation of results obtained in the nursery must await data derived from extended follow-up studies which involve quantitative assessment of hearing status."

"In view of the above considerations and despite our recognition of the urgent need for early detection of hearing impairment, we urge increased research efforts, but cannot
recommend routine screening of newborn infants for hearing impairment.”

Because the need to make some progress toward effective early identification of hearing loss was viewed as increasingly urgent, a multidisciplinary conference was held in February 1971 which was cosponsored by the State Public Health Department of California and the Joint Committee with funding from the federal Maternal and Child Health Bureau. Drawing upon information shared at the conference, a “Supplementary Statement” was issued in April 1973 by the Joint Committee on Infant Hearing Screening. The Supplementary Statement reads as follows:

“The committee recommends that, since no satisfactory technique is yet established that will permit hearing screening of all newborns, infants AT RISK for hearing impairment should be identified by means of history and physical examination. These children should be tested and followed-up as hereafter described:

I. The criterion for identifying a newborn as AT RISK for Hearing Impairment is the presence of one or more of the following:
   A. History of hereditary childhood hearing impairment.
   B. Rubella or other non-bacterial intra-uterine fetal infection (e.g., cytomegalovirus infections, Herpes infection).
   C. Defects of ear, nose, or throat. Malformed, low-set or absent pinnae; cleft lip or palate (including submucous cleft); any residual abnormality of the otorhinolaryngeal system.
   D. Birthweight less than 1500 grams.
   E. Bilirubin level greater than 20 mb./100 ml. serum.

II. Infants falling in this category should be referred for an in-depth audiological evaluation of hearing during their first two months of life and, even if hearing appears to be normal, should receive regular hearing evaluations thereafter at office or well-baby clinics. Regular evaluation is important since familial hearing impairment is not necessarily present at birth but may develop at an uncertain period of time later.”

### The 1982 Joint Committee on Infant Hearing Position Statement

The 1982 Joint Committee on Infant Hearing Position Statement expanded the list of high risk criteria from five to seven, stating: “Since the incidence of moderate to profound hearing loss in the at-risk infant group is 2.5 to 5.0%, audiologic testing of this group is warranted.” Screening, under the supervision of an audiologist, was to occur optimally by 3 months but, in any event, not later that 6 months of age. These revised and expanded risk criteria were as follows:

1. Family history of childhood hearing impairment
2. Congenital perinatal infection (e.g., cytomegalovirus, rubella, herpes, toxoplasmosis, syphilis)
3. Anatomic malformations involving the head or neck (e.g. dysmorphic appearance including syndromal and nonsyndromal abnormalities, overt or submucous cleft palate, morphologic abnormalities of the pinna)
4. Birth weight <1500 gm
5. Hyperbilirubinemia at level exceeding 20 mb. -2 years.
6. Bacterial meningitis, especially Haemophilus influenzae.
7. Severe asphyxia which may include infants with Apgar scores of 0 to 3 or who fail to institute spontaneous respiration by ten minutes and those with hypotonia persisting to 2 hours of age.”

As far as screening procedures were concerned, the Committee stated that: “The initial screening should include observation of behavioral or electrophysiologic response to sound.” Although the Committee acknowledged that “Early detection of hearing impairment in the affected infants is important for medical treatment and subsequent educational intervention to assure development of communication skills,” the 1982 Statement included the caveat: “Acoustic testing of all newborn infants has a high incidence of false positive and false negative results and is not universally recommended.”

Over time, the Joint Committee assumed a slightly more formal structure and other stakeholders were invited to the table, the current membership consisting of representatives of: the American Academy of Audiology, the American Academy of Otolaryngology-Head and Neck Surgery, the American Academy of Pediatrics, American Speech-Language-Hearing Association, the Council on Education of the Deaf (member organizations: Alexander Graham Bell Association for the Deaf and Hard of Hearing, American Society for Deaf Children, Conference of Educational Administrators of Schools and Programs for the Deaf, Convention of American Instructors of the Deaf and Hard of Hearing, National Association of the Deaf, and Association of College Educators of the Deaf and Hard of Hearing) and, finally, the Directors of Speech and Hearing Programs in State Health and Welfare Agencies.

By the time the 1990 Position Statement was issued, the Joint Committee felt it was important to distinguish between a list of ten risk criteria for neonates (birth -28 days) and eight risk criteria which targeted infants (29 days - 2 years). The optimal time recommended for screening of neonates who manifested one or more of the risk criteria was prior to discharge from the newborn nursery but not later than 3 months of age. The issue of methodology to be utilized for neonatal screening was dealt with as follows: “The initial screening should include measurement of the auditory brainstem response (ABR). Behavioral testing of newborn infants’ hearing has high false-positive and false-negative rates and is not universally recommended. Because some false-positive results can occur with ABR screening, on-going assessment and observation of the infant’s auditory behavior is recommended during the early stages of intervention. If the infant is discharged prior to screening, or if ABR screening under audiologic supervision is not available, the child ideally should be referred for ABR testing by 3 months of age but never later than 6 months of age.” The importance of continued follow-up in cases where there is a probability of progressive hearing loss was noted.

Issues of feasibility, cost effectiveness and workforce availability to accomplish
the recommended screening procedures were also addressed: “The protocols recommended by the Committee are considered optimal and are based on both clinical experience and current research findings. The Committee recognizes, however, that the recommended protocols may not be appropriate for all institutions and that modifications in screening approaches will be necessary to accommodate the specific needs of a given facility. Such factors as cost and availability of equipment, personnel and follow-up services are important considerations in the development of a screening program.”

In 1993, an important milestone was reached when an NIH Consensus Development Conference was held on the topic of early identification of hearing impairment to address the following issues: “(1) the advantages of early identification of hearing impairment and the consequences of late identification; (2) the issue of which children should be screened for hearing impairment and when; (3) the advantages and disadvantages of current screening methods; (4) the question of which model for hearing screening and follow-up is preferred; and (5) future directions for research in diagnosis and management of hearing impairment in infants and young children.”

The Panel observed that, “There is a clear need in the United States for improved methods and models for the early identification of hearing impairment in infants and young children. Approximately 1 of every 1,000 children is born deaf. Many more are born with less severe degrees of hearing impairment, while others develop hearing impairment during childhood. Reduced hearing acuity during infancy and early childhood interferes with the development of speech and verbal language skills. Although less well documented, significantly reduced auditory input also adversely affects the developing auditory nervous system and can have harmful effects on social, emotional, cognitive, and academic development, as well as on a person’s vocational and economic potential.” They further noted that, “During the past 30 years, infant hearing screening has been attempted with a number of different test methods, including cardiac response audiometry, respiration audiometry, alteration of sucking patterns, movement or startle in response to acoustic stimuli, various behavioral paradigms, and measurement of acoustic reflexes. For the past 15 years, auditory brainstem response (ABR) audiometry has been the method of choice. More recently, attention has turned to the measurement of evoked otoacoustic emissions (EOAE), which shows promise as a fast, inexpensive, noninvasive test of cochlear function. Each method is effective in its own way, but technical or interpretative limitations have impeded widespread application.”

Because of the availability of better screening methods, the panel concluded that “the systematic evaluation of the effects of earlier identification and earlier intervention can now be conducted. Because such data are not presently available, it is difficult to evaluate fully the effectiveness of early identification and intervention on language development. There are, however, a wide range of clinical observations, a number of descriptive studies, and a few statistically controlled, nonrandomized trials that support the benefits of early identification and intervention. The benefits to be gained from early intervention may vary, depending on the severity and type of hearing impairment. Children with sensorineural hearing loss who receive early amplification, when indicated, and a comprehensive habilitation program may show improved speech and language skills, school achievement, self-esteem, and psychosocial adaptation when compared to hearing-impaired children who do not receive amplification until 2 to 3 years of age.”

The NIH Consensus Panel recommended: “… that all infants admitted to the NICU be screened for hearing loss prior to discharge. Infants in the well-baby nursery with diagnoses of craniofacial anomalies, family history of hearing loss and diagnosis of intrauterine infection comprise a special high-risk category. Thus, they should be screened using the same protocol and follow-up vigilance as the NICU population.”

In addition to all NICU babies being screened, the members of the panel “... strongly recommend that universal screening be implemented for all infants within the first 3 months of life.” They also observed that “Even though we recommend universal screening within the first 3 months, as a practical matter this is most efficiently achieved by screening prior to discharge from the well-baby nursery. The disadvantages of hospital well-baby screening, such as missed screening because of early discharge and the possibility of higher false-positive rate, are outweighed by the accessibility of all newborns to testing at this time.” They concluded that “Infants who are not screened in the hospital should be screened by 3 months of age.”

The panel identified two techniques - EOAE and ABR – as showing maximal promise as universal screening tools for the newborn. While EOAE appeared most promising as a rapid, cost-effective tool for screening all newborns, the Panel felt that the relatively large number of false positives resulting from EOAE screening dictated that a second or confirmatory second stage screen with ABR be made available. Babies who passed the second stage ABR screen could be discharged but should be flagged for rescreening at 3-6 months. Babies who failed the ABR screen were to be referred for diagnostic evaluation. The consensus panel noted that while neonatal screening is best accomplished before the baby leaves the hospital, identification of delayed onset or progressive losses must be accomplished through systematic education of primary caretakers, medical and nursing personnel, and all other professionals “who have opportunity to observe the child must be relied upon to recognize factors that place the child at high risk for hearing impairment and behavioral signs of a possible change in hearing status.” The Consensus Panel also recognized the need for carefully controlled research
The 1994 Position Statement was clearly a transitional document which took into account the time which would be required to put the necessary legislative and organizational infrastructure into place to mount an effective universal newborn hearing screening program in many parts of the U.S. and other countries.

"With these concerns in mind the Position Statement:
1. endorses the goal of universal detection of infants with hearing loss and encourages continuing research and development to improve techniques for detection of and intervention for hearing loss as early as possible;
2. maintains a role for the high-risk factors (hereinafter termed indicators) described in the 1990 Position Statement, and modifies the list of indicators associated with sensorineural and/or conductive hearing loss in newborns and infants;
3. indicators associated with late-onset hearing loss and recommends procedures to monitor infants with these indicators;
4. recognizes the adverse effects of fluctuating conductive hearing loss from persistent or recurrent otitis media with effusion (OME) and recommends monitoring infants with OME for hearing loss;
5. endorses provision of intervention services in accordance with Part H of the Individuals with Disabilities Act (IDEA); and,
6. identifies additional considerations necessary to enhance early identification of infants with hearing loss."

In February 1999, the American Academy of Pediatrics’ Task Force on Newborn and Infant Hearing Screening published a Policy Statement entitled “Newborn and Infant Hearing Loss: Detection and Intervention (RE0846).”

"To justify universal screening, at least five criteria must be met:
1. An easy-to-use test that possesses a high degree of sensitivity and specificity to minimize referral for additional assessment is available.
2. The condition being screened for is otherwise not detectable by clinical parameters.
3. Interventions are available to correct the conditions detected by screening.
4. Early screening, detection, and intervention result in improved outcome.
5. The screening program is documented to be in an acceptable cost effective range."

The statement continues: “Although additional studies are necessary, review of both published and unpublished data indicates that all five of these criteria currently are achievable by effective universal newborn hearing screening programs (UNHSP). Therefore, this statement endorses the implementation of universal newborn hearing screening. In addition this statement reviews the primary objectives, important components, and recommended screening parameters that characterize an effective UNHSP.”

The AAP Policy Statement asserts that a minimum of 95% of newborns must be screened, with a false positive rate of 3% or less and a false negative rate of zero, before a program can be considered effective. The high profile support of universal newborn hearing screening by the AAP represented an important milestone in gaining support for EHDI among pediatricians and other primary care providers, hospitals, legislators, health policy makers and third party payers.

Another important milestone achieved in 1999 was the enactment by the federal government of the “Newborn Screening and Intervention Program Act” which mandated the U.S. Department of Health and Human Services to provide assistance to states in establishing programs for early detection of hearing loss in infants through universal screening and to promote appropriate treatment and intervention for infants with hearing loss.
The high level of congressional interest in early identification of hearing loss with prompt intervention prompted important dialogue regarding the scope of interest and level of priority being accorded this topic by government agencies and institutes. Maternal and Child Health section of the U.S. Heath Resources and Services Administration, and the Centers for Disease Control and Prevention which, through its Early Hearing Detection and Intervention (EHDI) Program, assists states in implementing screening and intervention programs and supports research and data collection on EHDI programs. A large and representative cross section of extramural stakeholders have been included in these discussions to help avoid duplication of efforts and assure appropriate allocation of scarce financial resources.

As development of the Joint Committee On Infant Hearing 2000 Position Statement proceeded, it was evident that more than simply endorsement of nationwide EHDI programs was called for. The core of the Position Statement included the following:

“The Joint Committee on Infant Hearing (JCIH) endorses early detection of, and intervention for infants with hearing loss (early hearing detection and intervention, EHDI) through integrated, interdisciplinary state and national systems of universal newborn hearing screening, evaluation, and family-centered intervention. Without appropriate opportunities to learn language, children who are hard of hearing or deaf will fall behind their hearing peers in language, cognition, and social-emotional development. Such delays may result in lower educational and employment levels in adulthood. Thus, all infants’ hearing should be screened using objective, physiologic measures in order to identify those with congenital or neonatal onset hearing loss. Audiologic evaluation and medical evaluations should be in progress before 3 months of age. Infants with confirmed hearing loss should receive intervention before 6 months of age from health care and education professionals with expertise in hearing loss and deafness in infants and young children. Regardless of prior screening outcomes, all infants who demonstrate risk indicators for delayed onset or progressive hearing loss should receive ongoing audiologic and medical monitoring for 3 years and at appropriate intervals thereafter to ensure prompt identification and intervention.”

Eight principles provide the foundation for effective EHDI systems (from 2000 Position Statement):

1. All infants have access to hearing screening using a physiologic measure. Newborns who receive routine care have access to hearing screening during their hospital birth admission. Newborns in alternative birthing facilities, including home births, have access to and are referred for screening before one month of age. All newborns or infants who require neonatal intensive care receive hearing screening before discharge from the hospital. These components constitute universal newborn hearing screening (UNHS).

2. All infants who do not pass the birth admission screen and any subsequent rescreening begin appropriate audiologic and medical evaluations to confirm the presence of hearing loss before 3 months of age.

3. All infants with confirmed permanent hearing loss receive services before 6 months of age in interdisciplinary intervention programs that recognize and build on strengths, informed choice, traditions, and cultural beliefs of the family.

4. All infants who pass newborn hearing screening but who have risk indicators for other auditory disorders and/or speech and language delay receive ongoing audiologic and medical surveillance and monitoring for communication development. Infants with indicators associated with late-onset, progressive, or fluctuating hearing loss as well as auditory neural conduction disorders and/or brainstem auditory pathway dysfunction should be monitored.

5. “Infant and family rights are guaranteed through informed choice, decision-making, and consent.”

6. Infant hearing screening and evaluation results are afforded the same protection as all other health care and educational information. As new standards for privacy and confidentiality are proposed, they must balance the needs of society and the rights of the infant and family, without compromising the ability of health and education to provide care (AAP, 1999).

7. Information systems are used to measure and report the effectiveness of EHDI services. While state registries measure and track screening, evaluation, and intervention outcomes for infants and their families, efforts should be made to honor a family’s privacy by removing identifying information wherever possible. Aggregate state and national data may also be used to measure and track the impact of EHDI programs on public health and education while maintaining the confidentiality of individual infant and family information.

8. EHDI programs provide data to monitor quality, demonstrate compliance with legislation and regulations, determine fiscal accountability and cost effectiveness, support reimbursement for services, and mobilize and maintain community support.”

The statement acknowledges the U.S. government’s new goals in Healthy People 2010, which are:

“To increase to 100% the proportion of newborns served by state-sponsored early hearing detection and intervention programs.

To provide 100% of newborns access to screening.

To provide follow-up audiologic and medical evaluations before 3 months for infants requiring care.

To provide access to intervention before 6 months for infants who are hard of hearing and deaf.”

The Joint Committee went on to state that “We must assure quality in EHDI services through available benchmarks and standards for each stage of the EHDI process. Accountability for the outcomes of audiologic and medical evaluation and intervention services as
well as the screening process itself must be documented. Outcomes and quality indicators obtained at the hospital, community, state, and national levels should permit the community to draw conclusions about the EHDI process, including its fiscal accountability.”

Although much has been achieved in the 30 years of the Joint Committee on Infant Hearing’s existence, much remains to be accomplished to guarantee the on-going success of EHDI programs in the United States. Organizations which scrutinize health expenditures will continually revisit this topic as they search for potential areas of savings, as evidenced by a recent statement from the U.S. Preventive Services Task Force (USPSTF) which stated:

“The USPSTF concludes the evidence is insufficient to recommend for or against routine screening of newborns for hearing loss during the postpartum hospitalization.”

“The USPSTF found good evidence that newborn hearing screening leads to earlier identification and treatment of infants with hearing loss. However, evidence to determine whether earlier treatment resulting from screening leads to clinically important improvement in speech and language skills at age 3 years or beyond is inconclusive because of the design limitations in existing studies.”

“Although earlier identification and intervention may improve the quality of life for the infant and family during the first year of life, and prevent regret by the family over delayed diagnosis of hearing loss, the USPSTF found few data addressing these benefits. The USPSTF could not determine from existing studies whether these potential benefits outweigh the potential harms of false-positive tests that many low-risk infants would experience following universal screening in both high- and low-risk groups.”

A particularly controversial portion of the document focused on the effectiveness of early intervention in improving language outcomes. The statement including the following assertions:

“There are no prospective, controlled studies that directly examine whether newborn hearing screening and earlier intervention result in improved speech, language, or educational development.”

“Although several retrospective studies have variously concluded that infants entering treatment programs at younger ages, or infants identified in hospitals with universal screening programs, have better long-term language outcomes, all of these studies have significant methodological flaws.”

“A number of interested parties have already responded publicly to the USPSTF Statement particularly regarding the non-feasibility, both ethical and practical, of carrying out a prospective, randomized controlled study of intervention with deaf and hard of hearing children to assess longitudinal language outcomes. On the other hand, such public dialogue can result in more federal research dollars being made available for large scale follow-up studies which will be necessary to assess.

Among the challenges which continue to bedevil EHDI programs across the country is the difficulty of achieving appropriate levels of timely follow-up evaluations for children who are identified at increased risk for hearing loss by newborn hearing screening programs. Cultural and socioeconomic factors which may impede an infant’s return for timely follow-up evaluations and intervention must be systematically addressed to ensure that a smooth continuum of diagnostic and intervention services are made available to these children and their families. The Joint Committee on Infant Hearing will continue to play an important catalytic role in pointing out potential solutions to these challenges as they arise.

References
1. Personal Communication from ASHA
4. Joint Committee on Infant Hearing Screening Supplementary Statement, American Academy of Pediatrics Newsletter Supplement, October, 1973
Introduction

The brief for this paper, commissioned for the NHS-2002 conference in Milan, was to highlight the landmarks in otoacoustic emissions (OAEs) that have appeared as part of the various concerted action programmes which have taken place within the European Community. Of course, the first and most notable landmark is the fact that there were these concerted action programmes in the first place. These programmes provided the infrastructure that enabled researchers to have exchanges of views and laboratories, attend conferences and workshops. Clearly this has had a significant impact on the quality and quantity of European research. Many people have worked on management committees and as individuals to support these enterprises. However, there is one individual who conceived the ideas, bullied the rest of us into helping and is, above all, responsible for these initiatives. It would be inexcusable to record some of the achievements of these action programmes without first acknowledging our debt of gratitude to Ferdinando Grandori.

Technical developments

As expected, there have been notable achievements at the technical level, and a workshop, held in Lyon in May 1993, was devoted to recording techniques for otoacoustic emissions. The importance of recording system properties, particularly the probe characteristics, on the OAE waveform has been reported by Lutman et al, (1994). An example is given in Figure 1A which shows recordings made on an ILO88 machine. In the top trace an ILO88 probe was used and in the lower trace one of the POEMS probes was used. The higher frequency content present in the ILO88 probe recording can clearly be seen. Even different probes supplied from the same manufacturer can cause some waveform differences and examples are shown in Figures 1B and 1C respectively.

The data from Grandori et al (1994) (Figure 1B) show changes in spectra when three different ILO88 probes were used in a 1cc cavity and similar results were found by Harris and Probst (1994) (Figure 1C) who also examined spectral differences for three different ILO88 probes. The overall morphology of the responses is similar but there are subtle differences in the spectral measures as can be seen in the Figure.
These studies underlined the need for a more standardised approach in this area and have led to improvements in production and quality control.

The Southampton team of the MRC Institute of Hearing Research, has reported their new maximum length sequence (MLS) stimulation technique (Thornton et al, 1994, Thornton, 1994). Figure 2 shows OAEs recorded conventionally using the MLS technique at rates up to 5000 clicks/s. This has enabled the testing of those with good OAEs to be completed some 13 times faster than testing conventionally but, more importantly, when recording for the same time as the conventional test, this technique will detect responses that are only 20% of the amplitude of those which could be detected by the conventional method. It has been shown that this leads to a worthwhile reduction in false alarm rates when screening very young babies.

**Suppression of otoacoustic emissions**

Suppression of OAEs was the topic of another dedicated workshop, held at Puerto de la Cruz in May 1994, which was organised within the concerted action programme. As the group in Lyon had carried out a great deal of the early work on contralateral suppression, it was fitting that Lionel Collet (Collet et al, 1994) should have presented a review of the results and findings in humans.

The basic suppression effect is shown in Figure 3A and operates so that, when contralateral broadband noise is presented, the otoacoustic emission in the opposite ear decreases in amplitude. The majority of papers dealt with various aspects of contralateral suppression in animals and in both human subjects and patients using mainly TEOAE measures (Aran et al, 1994; Chéry-Croze et al, 1994; Graham and Hazell, 1994; Lind, 1994; Prasher et al, 1994; Thornton, 1994).

In contrast, Cianfrone et al, 1994 described an ingenious experiment in which DPOAE suppression tuning characteristics could be measured and one of the results is illustrated in Figure 3B. Tavartkiladze et al, 1994 reported new data on the ipsilateral suppression of TEAOEs. An illustrative result is shown in Figure 3C where the OAE is suppressed by a 1.5 kHz tone. The proceedings of this workshop provided an excellent summary of the body of knowledge as it was at that time.

**Neonatal screening**

Screening neonates for hearing loss is the largest clinical application of OAEs and its importance has been reflected in the number of research projects in this area, carried out in Europe. Under the auspices of the European Biomedicine and Health Programme, a European consensus development conference was organised in May 1998. Evidence from a wide range of specialists was presented in an open forum to a distinguished panel of experts and a consensus statement produced. The resulting publication has had a significant influence on the various screening programmes that have since been set up in Europe and further afield.

In order to follow up the issues raised in the consensus conference, a second meeting was organised in October 2000 and was attended by 350 delegates from 50 countries. This second meeting, presented screening methods but also went on to deal with assessment techniques and with ways of providing early intervention.

The benefits of neonatal screening, which in turn enable early diagnosis and intervention to occur, were disseminated as conference abstracts and the keynote addresses were published more widely (Seminars in Hearing, 2000). The world-wide influence achieved by these publications is certainly a landmark for the European joint programme.

**Clinical applications of OAEs**

There has been much progress in the application of OAE methods to various types of clinical disorders. Two conferences were organised to address this area; the first in 1994 in Pécs, Hungary and the second in 1995 at Noordwijkerhout, Netherlands. A selection of papers from these meetings was published under the title "Clinical Applications of Otoacoustic Emissions".

Two papers reported that DPOAEs could reflect the
changes occurring with temporary threshold shift due to disco music and noise. Engdahl and Kemp (1995) reported changes in DPOAE amplitudes following noise exposure. An example of their results is shown in Figure 4A.

The data from Döring et al (1995) are presented in Figure 4B and show good correspondence between the TTS measures and the DPOAE findings. The characteristics of audiometric patterns created by long-term occupational noise exposure could also be seen in TEOAE spectra and in DP-grams for those cases where the degree of hearing loss permitted the measurement of OAEs (Sliwinska-Kowalska, 1995). The similarities between the two can clearly be seen in Sliwinska-Kowalska’s data shown in Figure 4C.

The use of OAEs in monitoring changes due to intracranial hypertension was described by Avan and his team (Avan, 1995) who found a relationship between OAE phase and intra-cranial pressure. Similar monitoring of the effects of ototoxic drugs was described by Katona et al (1995), Noszek et al (1995) and Rácz (1995), and it was shown that this was another clinical application in which OAEs have a useful role to play. A paper on the epidemiology of hearing loss completed the first section of this volume (Farkas et al, 1995).

The second section focused on procedures for the analysis of click-evoked OAEs in both time and frequency domains with contributions from Tognola et al (1995) and Pytel et al (1995). Some of the data presented by Tognola are shown in Figure 5. Clear distinctions, between the adult data on the left and the neonatal data on the right, can be made.

Modelling and insights into cochlear function
More fundamental work, involving theoretical considerations of modelling cochlear functions, has been encouraged by the concerted action programmes.

Avan et al, (1994) elegantly related the temporal structure of OAEs to basal cochlear function showing simpler emission structure in hearing loss cases that involved all of the basal end. However, if some high-frequency, residual basal activity remains then the waveform exhibits a more complex temporal structure. This can be seen in the recorded OAE and the corresponding audiogram shown in Figure 6A.

Various mechanical models from Brass and Kemp (1994), van den Raadt (1994) and Fritze (1994), were used to explain various properties of the cochlear amplifier and the nature of OAEs. Figure 6B illustrates the fluid flow model of Brass and Kemp which was used to model a mechanically active cochlea to predict cochlear travelling wave velocity.

A meeting, held in Basel in 1998, was devoted to OAEs and psychoacoustic performance. This provided many opportunities not only for experimental papers but also for work on modelling to provide further insights into OAE
who had normal audiograms and normal OAEs.

Avan et al (1998) compared theoretical and actual aspects of cochlear filter bandwidth and Upfenkamp (1998) investigated the relationship between the critical band estimated psychoacoustically and from OAE measures. A result from Avan et al (1998) is shown in Figure 6D. This gives the frequency spacing between TEOAE components which is about 65 Hz for adults and 45 Hz in neonates. A basic model of OHC populations (Fritze and Steurer, 1998) provided an interesting approach to the relationship between inner ear function and OAEs.

### Conclusion

The concerted action programmes have had a hugely positive and successful effect on European research into OAEs. They have provided an excellent example of what can be achieved when such collaborations are well organised and executed.

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### Neonatal screening


### Clinical applications


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Great Moments in Pediatric Audiology

1944: The Ewings of England elicit aural reflex responses in infants
1960: In Sweden, a gong and mallet (130 dB SPL) used to screen infants
1964: Downs and Sterritt screen 17,000 infants for hearing in Denver
1969: Joint Committee on Infant Hearing develops first High Risk Register
1974: Northern and Downs publish First Edition of Hearing in Children
1976: Jerger and Hayes advocate “Cross-check Principle” in pediatric testing
1986: Public Law 99-457 enacted as Education of the Handicapped Act
1986: First automated ABR infant hearing screening device introduced
1992: OAEs used to screen hearing in newborn infants
1993: NICDC Consensus Committee recommends universal newborn hearing screening
1998: Cochlear implants approved for children less than 18 months of age
2000: 1st International Newborn Hearing Screening (NHS) Conference held in Milan, Italy
2002: 4th National Symposium on Hearing in Infants sponsored by The Colorado Hearing Foundation
Introduction
The early hearing detection and intervention (EHDI) process has made significant strides in the last 10 years. Currently, more than 40 of the 50 states in the U.S. have active programs for universal screening. Throughout the world, infants are being screened for hearing loss and generally, all infants are screened rather than just those with specific risk indicators. In addition, guidelines for follow-up audiological procedures are being established (Joint Committee on Infant Hearing, 2000) and are generally followed. Increasing numbers of infants are being referred for and enrolled in early intervention programs for hearing loss before 6 months of age.

As the EHDI process moves forward and matures, it is important that professionals re-examine basic principles on which those programs are founded, and make appropriate modifications in program. Such decisions should be based on valid new information and assessment of outcomes of children identified and served by programs. Specifically, in the zeal to move forward rapidly with EHDI programs, some disease processes that lead to hearing loss may have been inadvertently, or purposefully, left off the list of target disorders. Most screening protocols will identify unilateral and mild hearing loss but not slight hearing loss or loss that is isolated to narrow frequency regions. In addition, many currently recognized protocols will not detect the condition known as auditory neuropathy (AN).

No detection/intervention program can do everything. However, an important part of any comprehensive EHDI program is continual review and update. Auditory neuropathy is found in a substantial subset of children for whom special considerations must be taken to avoid misclassification. Further special considerations must be given to accurate diagnosis and to adjustment to rehabilitation protocols based on the unique physiology and auditory limitations of this disorder.

Auditory Neuropathy Definition
Patients with auditory neuropathy have pure-tone audiograms that show any degree of hearing loss from slight to profound. The audiograms have a sensorineural pattern with air and bone conduction thresholds intertwined. Patients with auditory neuropathy can be distinguished from those with sensory (hair cell) loss in several ways. Patients with AN have evidence of normal hair cell function, either in the form of normal-amplitude otoacoustic emissions, which are indicative of outer hair cell (OHC) function, or clearly recorded cochlear microphonic, indicative of inner and/or outer hair cell function, or both. The outer hair cells perform as amplifiers in the sensory process and are responsible for adding about 30-50 dB of auditory sensitivity. The OAE is a reflection of that amplification process. When outer hair cells are absent or non-functioning, the OAE will be gone and a mild to moderate elevation in hearing threshold will exist. In other words, without the aid of the OHC, the hearing process will be initiated in the IHC only when the stimulus exceeds normal auditory threshold levels by 30-50 dB. The presence of otoacoustic emissions in combination with sensorineural loss of more than 30-50 dB, consequently, points to a site of lesion other than the outer hair cell.

The cochlear microphonic (CM) is an electrical potential generated by the inner and outer hair cells in response to sound stimulation. This potential is generally only recorded in response to high level sound and is often obscured by the N1 response of the auditory nerve (Wave I of the ABR), when it is present. The CM may be visible in patients having AN because of the lack of time-locked activity from the auditory nerve in that condition which would otherwise hide the CM. Otoacoustic emissions sometimes diminish or disappear in children with AN (Deltenre et al., 1999), for reasons that are unclear, while the CM
has been more stable. When OAEs disappear, the CM can suffice as evidence of good hair cell function for purposes of AN diagnosis (Rance et al., 1999). Patients with AN invariably show evidence of poor neural function on the auditory brainstem response (ABR) as well as an absence of brainstem reflexes such as the middle ear muscle reflex and oculo-cochlear reflex. In some cases the ABR is completely absent and in others it shows very poor morphology. In all cases, the ABR threshold does not reflect the psychophysical threshold and should not be used to predict psychophysical hearing levels, as it often is for infants and children with sensory hearing loss.

An example of an ABR from a patient with AN is shown in Figure 1. The prominent cochlear microphonic can be seen in the first 5 ms. The CM follows the polarity of the stimulus and appears as a mirror-image of several peaks when responses to rarefaction and condensation clicks are superimposed. However, no neural (ABR) activity follows the CM as is typical in many patients with AN in whom the neural response is not precisely time-locked to the stimulus.

The same lack of consistent time-locked response from the auditory nerve that renders the ABR abnormal, causes the severely impaired speech perception on patients with AN (Starr et al., 1996; Sininger and Oba, 2001). The importance of the encoding of exact temporal information from the speech signal at the level of the auditory nerve is demonstrated by dramatically reduced speech perception scores, especially relative to degree of hearing loss in patients with AN. Poor temporal encoding is a hallmark of AN as demonstrated by Zeng and colleagues (Zeng et al., 2001).

Another feature of AN that can be attributed to the neural rather than sensory site of lesion, is the volatile nature of the symptoms. AN patients are known to demonstrate fluctuations in hearing and in speech perception capacity on a day-to-day basis (Sininger and Oba, 2001). Some children with AN have dramatic fluctuations in hearing and auditory capacity reported by parents or documented in audiometric test results. These fluctuations often lead to misdiagnosis of malingering or poor cooperation on the part of the patient. The most dramatic of these fluctuations has been documented in cases of children who suffer traumatic deafness, most likely due to demyelinating pathology, during occasions of increased core temperature from fever (Starr et al., 1998).

Physiology of Auditory Neuropathy

Controversy still exists on the nature of the physiologic basis of AN. The probes into the system are not perfect and the candidate structures cannot be viewed directly. The nature of the symptoms that demonstrate normal function up to and including the outer hair cells and poor function starting with wave I of the ABR, points to either the inner hair cell (IHC), the synapse at the IHC/auditory nerve junction or the peripheral portion of the auditory nerve as the site of lesion. Precise measures that would distinguish IHC from OHC function are not currently obvious. The summating potential (SP) and previously described cochlear microphonic (CM) are generated by both IHC and OHCs.

Indirect evidence from patients with auditory neuropathy, points to the peripheral portion of the auditory nerve as the site of lesion. Starr (2001) has found that eighty percent of adults with auditory neuropathy demonstrate peripheral nerve disease. In addition, temporal bone pathology in patients with documented hearing disorders has shown that it is possible for patients to have a loss of auditory neurons and spiral ganglion cells and yet show a relatively full complement of hair cells (Spoendlin, 1974; Nadol, 2001). Starr has identified a patient with auditory neuropathy, on whom post-mortem auditory nerve biopsy showed reduced neurons and evidence of demyelination. This same patient was found to have normal inner and outer hair cells in the organ of Corti (Starr, personal communication). Starr has also performed sural nerve biopsy on a number of well-documented patients with AN. The pathology identified in all cases was either axonal or demyelinating neuropathy (Starr, 2001).

Evidence of other nerve disease in patients with AN and direct evidence of isolated peripheral auditory nerve disease with preserved hair cell in a few patients with hearing loss, points to the auditory nerve as the most likely site of lesion. Some would argue that the inner hair cell is a viable candidate for the site of lesion in AN. In contrast to many reports of isolated auditory nerve disease, review of many years of study of human temporal bones reveals only one report of human temporal bones, which described isolated absence of inner hair cells (Amatuzzi et al., 2001). This condition was found only in a very few premature infants who did not survive and whose auditory status was not well defined. This study does not provide adequate evidence that isolated inner hair cell loss exists in adult humans. Certainly, this condition would have revealed itself in human temporal bone studies before now.

The lack of similar anatomical findings in humans leaves naturally-occurring animal models of isolated IHC loss, such as the Bronx-waltzer mouse, unattractive for study or for drawing conclusions regarding human AN. Animal experiments that can produce isolated IHC loss with spared OHC function, have also been used in attempt to model human auditory neuropathy. Results from these animal experiments are not similar to findings from humans that we would label as having “auditory neuropathy.” For example, Harrison and colleagues (Harrison, 2001; Harrison, 1999) have used carboplatin in guinea pigs to produce isolated IHC damage while sparing OHCs. These
animals demonstrated otoacoustic emissions and elevated ABR thresholds. However, their ABRs, when present, were normal in appearance. This is in stark contrast to the ABR results described in humans in which no clear response or very poor ABR morphology is seen regardless of stimulus level.

Other studies of isolated inner hair cell loss in animal models have shown that the hearing thresholds are only mildly elevated even with as much as 70% loss of cells (Schrott et al., 1989; Phillips et al., 2001) that the frequency tuning mechanism is intact and that sensitivity to temporal stimulus features, such as rise time, are unaffected by partial loss of inner hair cells (Phillips et al., 2001).

In summary, no convincing evidence exists that adult humans have a condition of isolated inner hair cell loss with any regularity. In addition, the symptoms of IHC loss do not include poor ABR morphology or abnormal temporal processing which are hallmarks of the human disorder known as auditory neuropathy. At this time it is more prudent to assume that patients with unexplained ABR abnormality, present OAE and significant temporal processing dysfunction have a neural rather than sensory disorder.

It is clear that patients with what we call AN will have a variety of pathologies and auditory characteristics. Without better technology, we cannot rule out the possibility that some persons with this disorder have isolated IHC loss, with normal OAEs, elevated hearing thresholds, elevated ABR thresholds and reasonably normal temporal processing. We know that many of these patients have neural disease. More evaluation of temporal processing ability and neural function may help to sort out the physiologic basis for the symptoms in these patients.

Regardless of the exact site of lesion of AN, it is clear that the majority of these patients will show a normal OAE and abnormal ABR. Screening protocols for hearing loss in neonates have falsely assumed that either technology would identify all infants with hearing loss. In addition, diagnostic audiology protocols for follow-up of screening failures on infants, have assumed that ABR thresholds would be indicative of hearing sensitivity. Neither of these assumptions holds for children with AN.

**How Many Children Have Auditory Neuropathy?**

Gathering of appropriate data on incidence/prevalence of auditory neuropathy has been difficult for a number of reasons. As previously mentioned, newborn screening protocols that allow an infant with a present OAE to pass, will not identify those with AN. According to a recent survey in the U.S. by Karl White (personal communication), approximately 70% of newborn hearing screening programs would allow an infant to pass based on OAE results alone. Consequently, gathering accurate incidence data on infants with AN from newborn screening programs may be problematic.

A few studies have utilized ABR technology in screening programs and specifically sought to determine how many infants might be considered to have AN. The results of three studies of infants enrolled in high-risk nurseries can be found on Table 1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Hearing Loss #</th>
<th>Auditory Neuropathy</th>
<th>Auditory Neuropathy/100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kraus et al., 1984</td>
<td>48</td>
<td>7</td>
<td>14.6</td>
</tr>
<tr>
<td>Cone-Wesson et al, 2000</td>
<td>56</td>
<td>3</td>
<td>5.3</td>
</tr>
<tr>
<td>Rance et al., 1995</td>
<td>109</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>213</strong></td>
<td><strong>22</strong></td>
<td><strong>10.3</strong></td>
</tr>
</tbody>
</table>

Table 2. Three studies which determine the number of cases of AN among the children found with hearing loss from neonatal screening. The combined data indicate that just over 1 in 10 (10.3/100) children with congenital hearing loss will have AN.

Rance et al., (1999) report results of assessments on 5199 high-risk infants. One hundred and nine of these infants were found to have hearing loss. Of those twelve were found to have ABR results consistent with auditory neuropathy. This translates to 2.3 cases of auditory neuropathy per 1000 high-risk infants. Two other studies evaluated smaller groups of high-risk infants. Stein et al., (1996) found 4 of 100 infants from a neonatal intensive care unit (NICU) demonstrated characteristics of AN and Psarommatas et al. (1997) found 2 cases of AN in a study of 100 NICU infants. In total these studies represent 5401 at-risk infants and found 18 to have AN. From this data we could assume that approximately 3.1 of 1000 infants, enrolled in an NICU will demonstrate characteristics of AN.

Another way to look at incidence of AN is to determine the percentage of children with known sensorineural hearing loss who have AN. Data from three studies are shown in Table 2. As previously discussed, of the 109 patients with hearing loss studied by Rance et al., 12 had symptoms of auditory neuropathy. Kraus et al., (1984) found 7 of 48 patients on whom no ABR could be obtained, demonstrated hearing levels that were not in line with ABR results. This study was performed before the routine use of otoacoustic emissions but the definition of AN, based on mismatch of hearing thresholds and ABR results, is still valid.

Cone-Wesson et al., (2000) describes the characteristics of 56 infants with confirmed hearing loss on follow-up from neonatal hearing screening. Of these infants, 3 had some evidence of present otoacoustic emissions in combination with absent auditory brainstem response at 70 dB nHL. Combining data from these three studies reveals a total of 213 children with hearing loss of whom 22 demonstrated AN. This translates to approximately 10.3 children of every 100, or 1 in 10 children with sensorineural hearing loss demonstrating characteristics of AN.
What are the Risk Indicators for AN?

Risk indicators for AN are difficult to determine for the same reasons that incidence and prevalence are difficult. Few large-scale studies have investigated risk indicators prospectively and systematically and methods for determining the presence of AN vary. Sininger and Oba described 59 carefully studied patients with AN (Sininger and Oba, 2001). A breakdown of risk indicators from the histories of those patients is shown in Table 3. By far the factor most often cited was family history with 20 of the 59 subjects showing either dominant or recessive family history. We did have several pairs of siblings in this study and that fact may tend to overemphasize this factor. However, it is clear that genetic disorder will play an important role in the etiology of AN (Kalaydjieva et al., 1996; Lopez-Bigas et al., 2001; Oshima et al., 1996) (Rogers et al., 2001; Butinar et al., 1999).

A number of genetically-based neural disorders have been frequently associated with hearing loss. A summary of the most common genetic diseases that demonstrate peripheral neuropathy and hearing disorder can be found on Table 4. A number of chromosome locations have been associated with AN and it is clear that no one single genetic mutation will be found responsible for the symptoms we group as AN.

After family history, the most common single medical history item noted among our patients with AN was hyperbilirubinemia (see Table 3). Shapiro and Nakamura (2001) have recently published a complete discussion of the toxic effects of bilirubin on the auditory system. In their words "Bilirubin selectively damages the brainstem auditory nuclei, and may also damage the auditory nerve and spiral ganglion containing cell bodies of primary auditory neurons. The inner ear, thalamic and cortical auditory pathways appear to be spared."

Descriptive information on the variability and progression of auditory system damage due to bilirubin toxicity in neonates and young children is not available. Methods of measuring bilirubin levels are not well standardized across medical facilities making characterization of the risk difficult. Many reports have been circulated of infants, who initially show symptoms of AN including absent or poorly formed ABRs with present OAEs, but who later to recover normal or near-normal function (ABR and/or hearing). These reports are not well-documented and these findings that change over time may often be dismissed as inaccurate testing. It is clear that much more information and data regarding the variability and progression of bilirubin toxicity in the auditory system is needed.

A questionnaire was sent to a group of parents of children with AN who have gathered on an email group to share information regarding their children. These parents were asked about their experiences and about risk indicators and medical problems that their children with AN displayed. Answers were received from 12 families. Results of that survey regarding risk indicators are found in Table 5. All but one of these children had hearing loss in the neonatal period and more than half were enrolled in a newborn intensive care unit (NICU). Hyperbilirubinemia was found in half of these children as was ventilator use and prematurity. In the original study, we found that half of our subjects had no obvious risk indicators (see Table 3) whereas the survey found 2 in 12 with no medical or family issues related to hearing loss.

In summary, far more data is needed to determine if it is possible to find consistent risk indicators for AN, especially in the newborn population. It seems clear that hyperbilirubinemia and family history are the most common factors found among patients with AN but the degree of elevated Bilirubin that puts a child at risk is not clear. It is not yet known what percentage of children will be born with AN and no other medical or family risk indicators. Given the severity of the symptoms that usually accompany this disorder, it will be important to understand how best to identify it as early as possible. A clear understanding of risk indicators will be needed to do so.

Interest in Auditory Neuropathy

Hearing disorders due to neural rather than sensory loss have been described for decades. However, it was not until otoacoustic emissions were used routinely in audiology clinics that the proportion of cases that could be attributed to neural pathology has been appreciated. Figure 2 graphs the number of dele-
been linked for several decades. The first extensively studied case by Starr et al., (1991) is indicated on the plot. At that time, the patient described had no other signs of neural disease and the term "Auditory Neuropathy" was not used. Later this same patient did develop other signs of peripheral neuropathy and the same was demonstrated in many other patients. The term "Auditory Neuropathy" was later coined by Starr et al.(1996) and has gained general acceptance. Since that time the number of publications on this issue has risen dramatically and only recently has this type of hearing disorder been accepted as worthy of special consideration by virtue of the number of publications and patients being found.

Of the five infants who referred on ABR, the average age of diagnosis was much lower; overall it was 4.4 months. One of these parents reported that her infant was retested with OAEs and sent home with a clean bill of health. If this infant is omitted from the ABR-screened statistics, the average age of diagnosis is 2 months. Based on this data, an ABR-only protocol would dramatically reduce the age at diagnosis for patients with AN (from 11 to 2 months of age).

The Joint Committee on Infant Hearing (JCIH) 2000 position statement specifically omits AN from the definition of target disorder for newborn hearing screening programs.

"Based on investigations of long-term, developmental consequences of hearing loss in infants, current limitations of physiologic screening techniques, availability of effective intervention, and in concert with established principles of health screening......, the JCIH defines the targeted hearing loss for UNHS programs as permanent bilateral or unilateral, sensory or conductive hearing loss, averaging 30 to 40 dB or more in the frequency region important for speech recognition (approximately 500 through 4000 Hz)."

At the time of writing no consensus could be reached on the inclusion of AN because data on the nature, prevalence and even treatment for this disorder were sparse and inconclusive. The position statement points out that some auditory disorders like AN will not be detected by all technologies. The JCIH placed responsibility on individual hospitals and professionals to choose screening protocols based on current information but did not suggest that OAEs were not appropriate for neonatal hearing screening. They also emphasized the need to obtain data on these disorders, including incidence/prevalence and risk indicators for future position statements to draw upon. Clearly, data is needed on this disorder and this information will eventually allow for consensus on whether current screening protocol modifications are necessary.

It is clear that audiologic and re-screening protocols for determination of degree and type of hearing loss in infants and children must take the unique quality of AN into consideration. It is no longer acceptable to use either OAE or ABR in isolation as an indicator of hearing levels. Infants who fail an ABR screening should not be retested (or re-screened) with OAEs alone. Hearing health care professionals must acquaint themselves with the idiosyncrasies of neural hearing loss such as the possibility of dramatic changes in function over time. Changes in hearing are possible from day to day, or even minute to minute, in patients with AN as the parents of these children will attest. We must listen to parents’ reports regarding their children and be open for new interpretations.

One parent sent the following comment with the questionnaire, which should illustrate some of the concerns. Not only was determination of degree of hearing loss made with inadequate information, but also the reports from these parents were ignored. The child’s name has been replaced with MYSON.

"As the ABR came back negative, we were told by the audiologist at the hospital that MYSON was deaf. My husband and I were, at first, in shock, and then I was angry. MYSON was definitely hearing SOMETHING, but I knew that he wasn’t hearing everything. I
knew that he wasn’t totally deaf, but people kept telling us that we were just in denial. Later the testing in the booth showed hearing at around 50-60 decibels.”

Another parent sent this comment:

“She was tested at 14 months in the booth which was inconclusive due to her age and activity. They also performed four OAE’s, which she passed at normal levels. I was told “at those levels there is no way she cannot be hearing. H failed the ABR only getting a response in the 80-90 db range. The audiologist said this proved hearing loss in the moderately severe to severe range. He questioned all of our previous results and asked if he might be able to perform the OAE’s again in his office. We walked down to his office and she passed the OAE’s again. “Amazing,” was his response. “

As professionals we must continue to learn about the nature of auditory system features and disorders. As health administrators we must constantly seek to revise our procedures based on current information and consensus.

Summary

The disorder we call auditory neuropathy may have one or more physiologic bases. Regardless of the exact physiology, the disorder will cause significant disruption of the development of communication skills in infants, especially if not detected at an early age. Auditory neuropathy appears to be present in about 3 of every 1000 infants enrolled in the NICU and may be the etiology in 1 of every 10 children with bilateral hearing loss. Many health factors are candidates for risk indicators of AN, but hyperbilirubinemia and family history appear to be the most often associated with the disorder.

Finally, auditory neuropathy cannot be reliably detected by OAE-type screening and cannot be diagnosed without a combination of ABR and OAE testing. It is important for audiologists and other hearing health care professionals to consider this disorder carefully and to develop consensus on its detection, diagnosis and management. This should be possible in the near future as important data on the topic emerges.

References


update on infant hearing 21
Abstract

The mammalian cochlea receives innervation from the CNS via two efferent systems: the lateral and the medial olivocochlear bundles (MOCS). The peripheral effects of medial olivocochlear system activation have been described, but the role of this inhibitory feedback onto the cochlea is still unclear. Suppression of the amplitude of otoacoustic emissions (click and tone evoked otoacoustic emissions, spontaneous OAEs, and Distortion Product OAEs) is induced by the MOCS neurons during contralateral (and also ipsi- and bi-lateral) stimulation, presumably by modification of OHC motility. The suppression effect is intensity-dependent and frequency-specific. The most efficient contralateral acoustic stimulus for suppressing OAEs is noise, and broad-band more than narrow-band. This overview summarizes the main results of several studies performed in humans characterizing the contralateral suppressive effect and also the influence of age on this activation.

Key Words: contralateral acoustic stimulation, otoacoustic emissions, medial efferent system.

Otoacoustic emissions (OAEs) constitute a unique tool to explore the medial olivocochlear system in humans. This system (together with the lateral olivocochlear system) is the terminal part of the descending auditory system starting from the auditory cortex [Spangler et al, 1991]. This part synapses with outer hair cells of the organ of Corti by axon terminals coming from neurons of the superior olivary complex [Rouiller, 1997]. Two-thirds of the medial olivo-cochlear neurons cross the midline and project on the contralateral cochlea [Guinan et al, 1984]. These fibers are vehicled along the vestibular nerve. A cochleotopic organization of the efferent innervation is almost observed.

Part of the medial neurons respond at an acoustic stimulation. Liberman and Brown [Liberman and Brown, 1986] have shown that 69% of the neurons respond better at an ipsilateral acoustic stimulation and 31% at a contralateral stimulation in the cat. So two ways are allowed to elicit medial olivocochlear bundle (OCB) responses: An ipsilateral or a contralateral acoustic stimulation. But in both cases the pathways are not similar. In the contralateral auditory suppression the uncrossed OCB is involved while in the ipsilateral suppression it is the crossed OCB which is involved [Liberman, 1989].

At last as the projections of the medial OCB system are on the outer hair cells and as these cells are supposed to be at the origin of otoacoustic emissions several authors have shown an alteration of OAEs under electrical [Mountain, 1980; Siegel et al. 1982] and acoustical [Puel and Rebillard, 1990] stimulation in animals.

The present paper aims to characterize the contralateral auditory suppression in humans to allow to use it from basic research to clinical routine.

Characterization of the contralateral auditory suppression on OAEs in humans.

Mott et al. [1989], Collet et al. [1990a], Moulin et al. [1993a, 1993b], and Souter [1995] have been the first authors to publish an effect of contralateral auditory stimulation respectively on spontaneous, transient evoked, distortion products and stimulus frequency OAEs.

As transient evoked OAEs are present in almost all normal hearing subjects [1993c], it seems to constitute one of the best tools to use in clinical practice.
Amplitude decrease.

The decrease is intensity dependent (Fig. 1). The greater the contralateral auditory stimulus intensity, the greater the decrease in EOAEs. The decrease appears as soon as the contralateral noise becomes audible [Collet et al., 1990a, 1990b].

Temporal alterations
A contralateral broadband noise induces a phase shift of EOAEs which mainly corresponds to an advance of signal [Giraud et al., 1996, Ryan and Kemp, 1991].

Characterization of the stimulus.
All the kinds of contralateral acoustic stimulation do not suppress EOAEs in the same way. A broadband noise gives the greater suppression. Narrow band noises elicit a smaller suppression [Veuillet et al., 1991]. Continuous tones do not suppress EOAEs or with a very slight decrease. But amplitude modulated tones suppress EOAEs [Maison et al., 1997]. This last effect increases with the depth modulation and with a modulation frequency nearby 100 Hz.

So the present results suggest to use a broadband noise as a contralateral auditory stimulation and a level of 30 dB SL is sufficient to evoke a suppression of the OAEs obtained in response to non filtered clicks. But it must be taken care of the hearing loss of the contralateral ear to avoid a cross talk.

Influence of the ipsilateral stimulus intensity.
As seen in Fig. 2, suppression is greater when EOAEs are elicited with low level ipsilateral stimulation [Veuillet et al., 1991, Hood et al., 1996, Ryan and Kemp, 1996, Williams et al., 1994, Veuillet et al., 1996]. Similar results have been described with acoustic distortion products [Moulin et al. 1993a, Williams and Brown, 1995]. The influence of click-rate must be taken in account as when click rate increases, suppression decreases [Ryan and Kemp, 1996, Thornton and Slaven, 1994, Thornton, 1994a, 1994b, Lina-Granade et al., 1997].

Involvement of the OCB in this effect has been demonstrated in patients with vestibular neurotomy (as we have shown upper the anatomical link between OCB and the vestibular nerve). These patients (Fig.5) present a diminution or an abolition of the contralateral suppressive effect [Williams et al. 1993, Scharf et al. 1997, Giraud et al. 1995]. This is a major argument in favor of the involvement of medial OCB in the suppressive effect but it doesn’t prove that this effect is exclusively imputable to the medial efferent fibers. Anatomical data

Is the medial OCB responsible of the suppression?
First at all cross-talk has been easily ruled out as this effect appears as soon as contralateral noise become audible and as there is no suppression in subjects with contralateral total hearing loss when noise is applied on the impaired ear [Collet et al., 1990].

There are several arguments against an exclusive role of middle ear reflexes. Veuillet et al. [1991] have shown a frequency specific effect (Fig.3) which has been also demonstrated on acoustic distortion products [Chery-Croze et al., 1993] and as it is shown in Figure 4, the presence of the suppressive effect in subjects with abolition of the stapedial reflex [Veuillet et al. 1991].

Involvement of the OCB in this effect has been demonstrated in patients with vestibular neurotomy (as we have shown upper the anatomical link between OCB and the vestibular nerve). These patients (Fig.5) present a diminution or an abolition of the contralateral suppressive effect [Williams et al. 1993, Scharf et al. 1997, Giraud et al. 1995]. This is a major argument in favor of the involvement of medial OCB in the suppressive effect but it doesn’t prove that this effect is exclusively imputable to the medial efferent fibers. Anatomical data

update on infant hearing 25
but also experimental works [Veuillet et al., 1992] do not rule out the possibility of a combination of both medial OCB and middle ear effect.

**Audiological protocol.**

The use of a 30 dB SL contralateral noise and of low-level EOAEs seem to be a convenient way to evaluate the medial OCB functioning. But to objective the effects three opportunities have been described: the absolute difference of the EOAE amplitude; the equivalent attenuation [Collet et al, 1992] or the Euclidean distance [Chery-Croze et al, 1994].

**Age - effects.**

In neonates: Lavigne-Rebillard and Pujol (1988) have shown that, in humans, some synapses between MOCS neurons and OHCs appear around 20 weeks GA (Gestational Age). However, in newborns some authors have not found a suppressive effect [Morlet et al., 1993] (Fig. 6) while authors have shown an effect [Ryan and Piron, 1994]. Methodological differences could explain this controversy. In several pre-term neonates, no clear efficient suppression effect was seen by Morlet et al. (1993). This result has been supported by Goforth et al. (1997). In full-term neonates, a suppression effect has been found in more than half the tested ears (Ryan and Piron, 1994, Goforth et al, 1997, Hamburger et al, 1998). Morlet et al (1999) have shown a relationship between CA (Conceptional Age) and suppression effect. The greater the CA the greater the suppression. But they also pointed out a great interindividual variability of this suppression.

In elderly: there is a reducing of the suppressive effect obtained on EOAEs [Castor et al. 1994].

**Sleep effect.**

A suppressive effect can be found during almost all the sleep [Froehlich et al. 1993].

**Cochlear action site.**

Contralateral acoustic stimulation exerts the greater suppressions on the EOAE frequency components between 1 and 2 kHz (Fig. 7) but is less effective on EOAE frequencies around 4 kHz [Veuillet et al. 1992].

**Lateralization.**

In right handed subjects, suppression is greater in the right ear [Khalfa and Collet, 1996, Khalfa et al. 1997, 1998a, Philibert et al. 1998] and in left handed subjects no laterality is observed (Khalfa et al., 1998b). This peripheral auditory asymmetry has been studied in infantile autism (Khalfa et al., 2001) and in schizophrenia (Veuillet et al, 2001).

**Psychoacoustical data.**


**Clinical data.**


**Conclusions**

The evaluation of medial olivocochlear system functioning can be done in a non-invasive and objective way by...
studying the effect of contralateral auditory stimulation on OAEs. Some recent papers extend this use to the ipsilateral auditory stimulation [Tavartkiladze et al., 1994, 1996, Berlin et al, 1995] allowing to study the crossed medial OCB and also to be able to explore patients excluded from an exploration by contralateral acoustic stimulation (i.e. patients with total or profound unilateral hearing-loss).

The suppression effect of OAEs appears around the term of birth in humans (Morlet et al, 1999) and can be easily explored in neonates. The clinical value of MOCS testing at birth merits some more extensive work to study if it could help to assess future auditory dysfunctions.

References


Possible Roles for the Auditory Steady-State Responses in Identification, Evaluation and Management of Hearing Loss in Infancy

Terence W. Picton
M. Sasha John
Andrew Dimitrijevic

Rotman Research Institute
Baycrest Centre for Geriatric Care
University of Toronto, Canada

Abstract
Steady-state responses evoked by regularly repeating stimuli are most easily evaluated in the frequency domain, where the spectrum shows peaks at the rate of stimulation and its harmonics. Auditory steady-state responses can be reliably evoked by tones that have been modulated in amplitude and/or frequency at rates between 75 and 110 Hz. These responses show great promise for objective audiometry since they can be readily recorded in infants and are unaffected by sleep. Responses to multiple tones presented simultaneously can be independently assessed if each tone is modulated at a different modulation-frequency. This makes it possible to estimate thresholds at several audiometric frequencies in both ears at the same time. Response to amplitude-modulated wideband noise may be recognized rapidly, and these may prove helpful in screening for newborn hearing loss. Since tones that have been sinusoidally modulated are not significantly distorted by free-field speakers and microphones, they can be used to evaluate the performance of hearing-aids. Responses to amplitude- and frequency-modulation may help determine how well hearing aids improve the discriminability as well as the audibility of sounds.

Introduction
The past decade has seen a great push to screen all newborn infants for hearing loss. The justification for this early screening is twofold. First, many infants with hearing loss would not otherwise be detected until they were several years of age. Second, beginning the treatment of hearing-impaired infants at an earlier age enhances their ability to communicate. Hearing-impaired infants detected by the screening procedures will need management by several months of age. Screening protocols must therefore be closely associated with other services that assess the degree of hearing impairment, and that provide the necessary treatment and training.

We do not know the optimal protocols for identifying and then managing hearing impairment in infancy. Most present screening protocols use click-evoked otoacoustic emissions (OAEs) to determine whether a hearing impairment is present, followed by click-evoked auditory brainstem responses (ABRs) to confirm the hearing impairment and assess its severity. Tone-evoked ABRs can then be used to assess the hearing loss at the different audiometric frequencies and provide a basis for prescribing hearing aids, or a justification for cochlear implants. Once a management program is initiated, the results of this treatment program are generally monitored by behavioral testing, although this remains difficult in young infants.

Such protocols may run into problems. OAEs will miss infants with auditory neuropathy. Such infants might be better detected if ABRs were used to screen for hearing impairment and OAEs then used to diagnose the disorder. Click-ABR can miss hearing losses with elevated thresholds at low- and mid-frequencies and normal hearing at high-frequencies. Although tone-ABRs can provide reasonably accurate frequency-specific thresholds, the testing procedure is slow and thresholds at some audiometric frequencies may not be measured before the baby wakes up. The performance of aids and implants in terms of the infant’s ability to discriminate sounds cannot be easily monitored in infants and younger child, whose behavioral responses can be variable.

Steady-state responses may help with some of these problems. Steady-state responses are evoked by regularly repeating stimuli and are measured in the frequency domain as the energy in the response at the frequency of stimulation (Picton et al, 2002c). These responses have several advantages over the more commonly recorded transient evoked
These findings have led to the commercialization of auditory steady-state responses in subjects with hearing loss. In newborn infants and Rance et al. showed that the technique worked well with young children. Rickards et al. (1994) demonstrated how this technique could be used to assess thresholds in hearing-impaired subjects. Cohen et al. (1991) showed that steady-state responses evoked by tones modulated at frequencies greater than 70 Hz did not change with the state of arousal and might therefore be useful as an objective test of auditory thresholds in infants and young children. Rickards et al. (1994) showed that the technique worked well in newborn infants and Rance et al. (1995) demonstrated the validity of the technique in subjects with hearing loss. These findings have led to the commercially available Audera instrument, manufactured by Grason-Stadler Incorporated.

Lins and Picton (1995) demonstrated that multiple steady-state responses could be recorded simultaneously and demonstrated how this technique could be used to assess thresholds in hearing-impaired subjects. Lins et al. (1996). A research instrument designed and evaluated by John and Picton (2000) has recently been further developed into a clinical instrument by Biologic Systems Corporation. The Audix instrument marketed by Neuronic S.A. also uses multiple response techniques.

Figure 1 illustrates what happens when recording multiple auditory steady state responses (Picton et al., 2002a). Each stimulus is constructed by modulating the amplitude and frequency of a tone. The stimulus is then characterized by a carrier frequency (the tone) and a modulation frequency (the envelope). For each ear, four carrier frequencies are chosen at the most important audiometric frequencies (e.g., 500, 1000, 2000 and 4000 Hz). Each carrier frequency is associated with a different modulation frequency that serves as its “signature” in the recording. The four stimuli are added together to provide the auditory signal for one ear. The signal for the other ear is made up in a similar manner except that different modulation-frequencies are chosen so that there are eight different modulation frequencies in total. The stimuli are presented to the ears and activate the basilar membranes in regions determined by the carrier frequencies. The brain’s response to these stimuli is recorded and viewed in the frequency domain. The responses to the eight stimuli are then identified at the eight modulation frequencies. A response is deemed present if it is significantly larger than the activity in adjacent frequency bins using an F-test.

Auditory steady-state responses can be recorded down to intensities close to behavioral thresholds. Herdman and Stapells (2002) have provided a meta-analysis of the results of multiple studies evaluating the relationship between the thresholds for detecting a steady-state response and behavioral thresholds. The physiological threshold is on average 8 dB higher than the behavioral threshold. The standard deviations of this estimate are around 10 dB. Steady-state responses may successfully demonstrate thresholds in infants and children with no demonstrable click-evoked ABRs (Rance et al., 1998).

The responses in subjects with sensorineural hearing loss are larger than those with normal hearing when the stimuli are presented simultaneously. The response to a 60 dB SPL sound will have approximately the same amplitude in someone with recruiting hearing loss and a threshold 50 dB SPL as in someone with normal hearing, even though the stimulus is only 10 dB above threshold in the subject with the hearing loss and 50 dB above threshold in the subject with normal hearing. Responses at intensities close to threshold in patients with hearing loss are therefore easy to recognize in a short recording period. Responses close to threshold in normal-hearing subjects are smaller and may take longer to recognize. Determining that a stimulus is below threshold will depend upon how small a response needs to be ruled out. It takes longer to rule out a 10 nV response than to rule out one at 20 nV in order to decrease the background noise to be below the level of the smaller response. The time for obtaining an audiogram will depend on how accurate one wishes to be at low intensities. Herdman and Stapells (2002) estimated about 50 minutes for four frequencies in a single ear using multiple stimuli. Estimating two ears simultaneously

**Evaluation — Frequency-Specific Audiometry**

Over the last decade, research in Australia, Cuba and Canada has led to techniques for assessing frequency-specific thresholds using auditory steady-state responses. Cohen et al. (1991) showed that steady-state responses evoked by tones modulated at frequencies greater than 70 Hz did not change with the state of arousal and might therefore be useful as an objective test of auditory thresholds in infants and young children. Rickards et al. (1994) showed that the technique worked well in newborn infants and Rance et al. (1995) demonstrated the validity of the technique in subjects with hearing loss. These findings have led to the commercially available Audera instrument, manufactured by Grason-Stadler Incorporated.

Lins and Picton (1995) demonstrated that multiple steady-state responses could be recorded simultaneously and demonstrated how this technique could be used to assess thresholds in hearing-impaired and in infants (Lins et al., 1996). A research instrument designed and evaluated by John and Picton (2000) has recently been further developed into a clinical instrument by Biologic Systems Corporation. The Audix instrument marketed by Neuronic S.A. also uses multiple response techniques. The responses in subjects with sensorineural hearing loss are larger than those with normal hearing when the stimuli are presented simultaneously.

**Figure 1. Multiple auditory steady state responses.** Diagrammatic representation of the stimuli (left), the activation of the cochlea (middle) and the steady-state responses generated in the brain and viewed in the frequency-domain (right).
A good screening test is fast, easy, inexpensive and accurate. OAEs and click-ABRs can rapidly provide information about whether hearing is normal or not with relatively low levels of false positive outcomes (hearing loss detected in infants with normal hearing) and very low levels of false negative outcomes (normal hearing detected in infants with a hearing loss). The decision can be made within several minutes using automatic techniques. However, several phenomena can disrupt the smooth flow of newborn hearing screening using OAEs. Conductive hearing loss is the most common cause of false positive results, and this is relatively common in newborn infants, particularly if they are in an intensive care nursery. Auditory neuro-pathy requires that both ABRs and OAEs be recorded.

Steady-state responses might also be used to screen for hearing loss. Basically one would have to decide on a stimulus (or stimuli), choose a level to use for the screening test, and choose some decision rules for deciding whether responses are present or not. For example, one might decide to present multiple AM tones at 60 dB SPL, and decide that a hearing loss is present if any one of these does not show a significant response after a 10-minute recording. One would then have to find out how well the screening test works by following up the screened infants to measure the rate of false positive and false negative outcomes. The first step would be to find levels at which most normal infants pass. Cone-Wesson et al (2002b) have shown that responses to single AM tones at moderate levels of intensity (50 – 75 dB SPL) are easily recognized in 80 - 90% of newborn infants when decision are based on a recording lasting less than 2 minutes.

Getting significant responses at all frequencies in both ears may take longer than is reasonable for a screening test. Another approach might therefore use the time to recognize the noise response should therefore be about 1/9 the time taken to recognize the tone response. Indeed only one of tone responses is recognizable after 15 sweeps (about one minute) whereas both noise responses are clearly recognizable at this time. We have shown that noise stimuli also evoke large responses in newborn infants, but we have not yet evaluated a sufficient number of infants to estimate how variable these responses are in a population of infants, or how long it takes to recognize them when they are present.

Our work with noise stimuli has led us to study how long it takes to recognize a
response. If one tests whether a response is present after every recorded sweep, one can monitor when the response reaches significance. Then one can stop recording as soon as the response is recognized rather than continuing to the end of a preset protocol. This is illustrated in Figure 3 for the same responses that are shown at two times in the averaging process in Figure 2.

Significance testing was performed using the F-test, which estimates the probability that the measured response is part of the background EEG noise as measured in the adjacent frequency bins of the spectra. The graphs plot how these probabilities change as the recording progresses and more and more sweeps are accumulated. The responses to right ear stimulation (dashed lines) become significant at p<0.05 more rapidly than the responses to left ear stimulation (continuous line). Also the responses to tones take much longer to become significant than the responses to noise.

One problem with this type of study derives from repeating statistical test. (Lütkenhöner, 1991). If one repeats a test 100 times one would expect about 5 significant results at p<0.05 even if no responses were present. One solution to this problem was proposed by Carlo Emilio Bonferroni (1892-1960), who was born in Bergamo, just a short distance away from the site of the NHS2002 meeting. Dividing the desired probability criterion on a single test by the number of tests performed maintains the overall error rate at a constant level. This criterion is shown in the graphs by the line labeled Bonferroni. Any estimate falling below this line would be significant at p<0.05, even considering that tests of significance had been performed after every sweep.

The major difficulty with using amplitude-modulated noise in a screening test is that it likely will not demonstrate hearing losses that spare hearing in one frequency region. In this regard, the test is similar to using the click-ABR, since both responses may be mediated through any region of the cochlea activated by the broad-band stimulus. The advantage of the steady-state technique is that detecting the response does not require sophisticated pattern detection and does not require normative data specific to the stimuli or the age of the subject. Detection simply depends on recognizing a response at the frequency of the envelope. The disadvantage of the technique is the lack of any normative data to determine what intensity-levels should be used to screen for hearing impairment. Furthermore, the problems of auditory neuropathy remain. Steady-state responses, like the click-ABRs, are absent in these patients.

Management — Monitoring Hearing Aids

At present, the most important role for the auditory steady-state responses in fitting hearing aids is providing an accurate and objective assessment of hearing thresholds at different frequencies. The proper fitting of a hearing aid is largely based on an accurate audiogram. Combining the thresholds in the audiogram with real-ear measurements of the gain of the hearing aid at different frequencies, the audiologist can adjust the aid so that normal speech sounds become optimally audible. Auditory steady-state responses may also demonstrate the functioning of hearing aids. Amplitude-modulated tones, which are frequency-specific and stable over time are much less likely to be distorted by amplification in either a sound-field speaker or a hearing aid than transient stimuli such as clicks. Picton et al (1998) showed that auditory steady-state responses to amplitude-modulated tones with modulation-frequencies between 80 and 105 Hz can be recorded when multiple stimuli are presented simultaneously through a sound-field speaker and amplified using a hearing aid. Responses were recorded down to intensities close to the behavioral thresholds for sounds in the aided condition. These measurements are helpful in demonstrating that the hearing aid is working. This is particularly useful in patients who do not have clear or reliable thresholds (either behavioral or physiologic) without aids. However, such measurements do not really assess how well the aid is working since the gain of the aid is usually not linear (varying with the intensity of the sounds).

A more important application of the steady-state responses would be to assessing supra-threshold hearing. Even though the gain of an aid can be adjusted on the basis of within-the-canal acoustic measurements, one still does not know how the aided sound is processed within the brain. The most important fact is whether the amplified sounds are optimally discernable. The sounds might be adequately amplified so that they are above the threshold for detection and yet might not be discernable due to distortion in the aid or in the physiological processing. Adequate word recognition scores provide a simple way of demonstrating discriminability in subjects who can process words, but this is not possible in young subjects.

We have begun to study the responses to multiple AM and FM stimuli presented simultaneously (Dimitrijevic et al. 2001). A basic test may use four carrier frequencies and modulate each carrier in amplitude and frequency, using a different modulation frequency for frequency and for amplitude - “independent amplitude and frequency modulation” (IAFM). Our initial studies of patients using hearing aids demonstrated that the number of recognizable responses to these stim-

32 special issue: picton, john, dimitrijevic
related to the word-recognition score when word recognition is manipulated by masking noise. We must be clear that this test is not directly related to speech perception but only to the discrimination of those acoustic parameters necessary for speech perception. The process of speech perception likely involves many stages. First, the sounds must be “audible”. Second, different sounds must be “discernable” from each other along the dimensions that are important for speech. Third, the sounds must be “perceptible” as representations of phonemes and sequences of phonemes (words) in memory. Determining thresholds for the steady-state responses can demonstrate the audibility of sounds. Measuring steady-state responses to modulations in the amplitude and frequency of sounds should demonstrate their discriminability.

Concluding Comments
This paper has reviewed the possible uses for the steady-state responses in the context of newborn hearing loss. Of the three areas covered, the use of these responses to measure the audiogram of an infant identified as hearing-impaired is most justifiable. Even here, much more research needs to be done to determine the accuracy of the various techniques and to improve them with better stimuli and more efficient recording-methods. Using steady-state responses to screen for hearing loss and to monitor the function of hearing aids are presently in the realm of the possible.

Figure 4. Independent amplitude and frequency modulation (IAFM). The figure shows the spectrum of the stimulus presented in free-field. Each of the four carriers (500, 1500, 2500 and 4000 Hz) is modulated in amplitude and frequency causing the energy to be distributed around the carrier. The long term average speech spectrum (LTASS) is from Cornelisse et al (1991).

Figure 5. IAFM responses and word recognition scores in masking noise. The responses to the eight different IAFM stimuli are shown in polar format with the AM responses above and the FM responses below. As masking noise is added to the stimuli the number of recognizable responses (shaded circles) decreases, just as the word recognition score (WRS) decreases.

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The widespread application of newborn hearing screening programs has resulted in many more infants with congenital hearing loss being identified within the first few months of life. Early identification must be coupled with an effective early intervention program. The Joint Committee on Infant Hearing Loss has recommended that children with hearing loss be identified by the age of three months, and that appropriate intervention should begin by the age of six months [1]. When sufficient residual hearing is present, the fitting of hearing aids before the age of 6 months can have a significant impact on language development in children with hearing loss [2]. However, for infants whose degree of hearing loss exceeds the limits of conventional amplification no treatment was available prior to the advent of cochlear implants.

Since cochlear implantation involves an elective surgical procedure performed under a general anesthetic, an appropriated risk:benefit ratio must be established. Advantages of intervention with cochlear implants have been demonstrated through improvements in speech perception, speech production, and language acquisition in older children. However, new measures must be developed and detailed longitudinal studies performed to quantify the benefits in infants.

The clinical trials performed for US Food and Drug Administration approval of cochlear implant systems have demonstrated that implantation is safe and effective for children as young as 12 months of age. (At the time of this writing, the lower age limit for the Nucleus device is 12 months but for the Clarion and Med El devices 18 months.) However, the prevailing emphasis placed on early identification of hearing loss has mandated a re-evaluation of the lower age limits appropriate for cochlear implantation. A trend toward even earlier cochlear implantation in children has emerged in an attempt to ameliorate the devastating effects of early auditory deprivation. A small but growing number of infants younger than 12 months of age have received implants. It is our opinion that in experienced hands, surgical risks down to the age of six months are no greater than for 12 month old children. However, there may be a slightly greater anesthetic risk in children less than one year of age [3]. It is obviously imperative that a pediatric anesthesiologist experienced with this age group be an integral part of the operative team.

**Selection of Patients**

The selection of cochlear implant candidates is a complex and ever-evolving process. The minimum age for implantation has decreased while the level of residual hearing in potential candidates has increased. Cochlear implants are no longer restricted to children who are anacusis. Current candidacy criteria differ according to the age of the patients being considered. The current pediatric cochlear implant criteria are listed in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Pediatric Candidacy Criteria for Cochlear Implantation</th>
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<tr>
<td>Children aged 12 mos to 24 mos</td>
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<tr>
<td>Bilateral profound hearing loss</td>
</tr>
<tr>
<td>Lack of auditory skills development and minimal hearing aid benefit (documented by parent questionnaire)</td>
</tr>
<tr>
<td>No medical contraindications</td>
</tr>
<tr>
<td>Enrollment in a therapy of education program emphasizing auditory development</td>
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Implantation of Very Young Children

Implantation in very young congenitally or neonatally deafened children may have substantial advantages because the development of speech perception, speech production, and language competence normally begins at a very early age. In addition, electrical stimulation appears to be capable of preventing at least some of the degenerative changes in the central auditory pathways [4]. Although implanting very young children has become more routine for experienced cochlear implant teams, it remains somewhat controversial because the audiological assessment, surgical intervention and post implant management in this population is challenging. Profound deafness must be substantiated and the inability to benefit from conventional hearing aids demonstrated. This can be difficult to determine in young children with limited language abilities. For very young children, parental questionnaires are commonly used to assess amplification benefit.

When implanting very young children, special consideration must be given to the small dimensions of the temporal bone and to potential problems from postoperative temporal bone growth. None-the-less, extension of implant candidacy to the six-to-12 months age group is feasible on an anatomic basis. The cochlea is adult size at birth and by age one year, the facial recess and mastoid antrum, which provide access to the middle ear for electrode placement, are adequately developed [5].

Early implantation may be particularly important when the etiology of deafness is meningitis, as progressive intra-cochlear ossification can occur and preclude standard electrode insertion. A relatively short window of time exists during which this advancing process can be circumvented. Thus, infants with deafness secondary to meningitis may be implanted prior to the age of one year if they have completed a brief hearing aid trial with no evident benefit.

Cochlear Implant Systems

Electrical stimulation of the auditory system is effective because the vast majority of cases of sensorineural deafness are due to receptor cell dysfunction while the auditory nerve remains responsive. Cochlear implants seek to replace a non-functional inner-ear hair-cell transducer system by converting mechanical sound energy into electrical signals that can be delivered to the cochlear nerve in profoundly deaf patients. In this way, damaged or missing hair cells of the cochlea are bypassed.

Multichannel, multi-electrode cochlear implant systems are designed to take advantage of the tonotopic organization of the cochlea. The incoming speech signal is filtered into a number of frequency bands, each corresponding to a given electrode in the array. Thus, multichannel cochlear implant systems use place coding to transfer spectral information in the speech signal as well as encoding the duration and intensity cues of speech.

All current generation multichannel cochlear implant systems consist of a surgically implanted internal and an external portion. The essential components include:

- A surgically implanted electrode array that is placed in the cochlea near the auditory nerve;
- An external microphone, which picks up acoustic information and converts it to electrical signals;
- An externally-worn speech processor that processes the signal according to a predefined strategy and produces stimuli for the electrode array;
- A transmission link between the external components and the surgically implanted array.

The processed speech signal is amplified and compressed to match the narrow electrical dynamic range of the ear. The typical response range of a deaf ear to electrical stimulation is on the order of only 10 to 20 dB, even less in the high frequencies. Transmission of the electrical signal across the skin from the external unit to the implanted electrode array most commonly is accomplished by the use of electromagnetic induction or radio frequency transmission. The critical residual neural elements stimulated appear to be the spiral ganglion cells or axons.

Nucleus Cochlear Implant Systems

The Nucleus 22-channel cochlear implant [6] was the first multichannel cochlear implant to receive FDA approval for use in adults and children and it has been used in more patients than any other cochlear implant system worldwide. The Nucleus CI24M cochlear implant received FDA approval for adults and children in 1998.

Early speech processing strategies (F0F2 and F0F1F2) used with the Nucleus 22-channel cochlear implant used feature-extraction strategies that conveyed information about key speech features such as the amplitude and frequency of vowel formats and the fundamental frequency of voiced sounds. The third generation speech processing strategy, MPEAK, encoded additional high frequency information by stimulating two of three more basal fixed electrodes; the goal was to provide additional information that would yield improved consonant recognition scores.

Three processing strategies are currently available for use with the Nucleus cochlear implants. Two of the strategies utilize the n-of-m approach in which the speech signal is filtered into m bandpass channels and the n highest envelope signals are selected for each cycle of stimulation [7]. The spectral peak, or SPEAK strategy is the most widely used with the Nucleus 22-channel cochlear implant and is available to users of either the Nucleus 22-channel or the Nucleus CI24M system. This strategy filters the incoming speech signal into 20 frequency bands; on each stimulation cycle an average of six electrodes are stimulated at a rate that varies adaptively between 180-300 pulses per second. An n-of-m strategy using much higher rates of stimulation, known as Advanced Combined Encoder (ACE) strategy can be implemented in the new Nucleus CI24M device. The third processing strategy available with the Nucleus CI24M system is the Continuous Interleaved Sampling or CIS strategy [8]. The CIS strategy filters the speech signal into a fixed number of bands, obtains the speech envelope, and then compresses the signal for each channel. On each cycle of stimulation, a series of interleaved digital pulses
rapidly stimulates consecutive electrodes in the array. The CIS strategy is designed to preserve fine temporal details in the speech signal by using high rate, pulsatile stimuli.

Two different speech processors are available for new Nucleus cochlear implant recipients. The body-worn SPRINT processor can implement any of the three current speech processing strategies. The ear-level ESPRIT speech processor currently can implement only the SPEAK processing strategy.

**Clarion Cochlear Implant System**
The Clarion multichannel cochlear implant system [9,10] is manufactured by the Advanced Bionics Corporation. This device has been approved by the FDA for use in adults (1996) and children (1997). The Clarion multichannel cochlear implant has an eight-channel electrode array. Two processing strategies can be implemented through a body-worn processor. The first is CIS, described above, which is used to stimulate monopolar electrodes. The second strategy, Simultaneous Analog Stimulation (SAS) filters and then compresses the incoming speech signal for simultaneous presentation to the corresponding enhanced bipolar electrodes. The relative amplitudes of information in each channel and the temporal details of the waveforms in each channel convey speech information.

**Medical Electronic (Med-El) Cochlear Implant System**
The Combi 40+ cochlear implant system manufactured by the Med-El Corporation in Innsbruck, Austria is currently undergoing clinical trials in the United States. The Med-El cochlear implant has 12 electrode pairs and has the capability of deep electrode insertion into the apical regions of the cochlear 8[11]. This device uses the CIS processing strategy and has the capacity to provide the most rapid stimulation rate of any of the cochlear implant systems currently available. Both a body-worn and ear level speech processors (the CIS Pro+ and Tempo+, respectively) are available for this the Med-El cochlear implant.

**New Developments in Cochlear Implant Electrode Design**
New designs of the internal electrode array have recently been introduced for the Nucleus and Clarion cochlear implants. The Nucleus Contour electrode array is a curved electrode which is straightened by a stylet for insertion purposes. After surgical placement into the scala tympani, the stylet is withdrawn. The electrode then assumes its preformed shape more closely approximating the modiolar wall of the cochlea. The Clarion HiFocus electrode is positioned closer to the modiolar wall by inserting a separate positioner into the scala tympani. Because the spiral ganglion cells are thought to be the sites stimulated by cochlear implants, directing the electrodes toward the modiolarus and further positioning the array may improve spatial specificity of stimulation and reduce the current needed to drive the electrodes [12].

**Previous Auditory Experience**
The current impetus for early cochlear implantation has been driven, in part, by the suboptimal performance of congenitally or early deafened children who have had little or no previous auditory experience and rely primarily on sign language who elect to have a cochlear implant during adolescence or early adulthood. This group has not demonstrated high levels of success with electrical stimulation of the auditory system. On the other hand, adolescents with profound hearing loss who have a history of consistent hearing aid use and who communicate primarily through audition and spoken language can experience significant benefit.

Children who become deaf at or after age 5 years generally are classified as postlingually deafened. These patients have developed many or all aspects of spoken language before the onset of their deafness. However, once they lose access to auditory input and feedback, they frequently demonstrate rapid deterioration in the intelligibility of their speech. Implantation soon after the onset of deafness potentially can ameliorate this rapid deterioration in speech production and perception abilities [13].

**Medical Assessment**
The medical assessment includes the otophologic history and physical examination. Routine otoscopic evaluation of the tympanic membrane is performed. An otologically stable condition should be present prior to considering implantation. The ear proposed for cochlear implantation must be free of infection, and the tympanic membrane should be intact. If these conditions are not met, medical or surgical treatment before implantation is required.

Radiologic evaluation of the cochlea is performed to determine whether the cochlea is present and patent and to identify congenital deformities of the cochlea. High-resolution, thin-section computed tomography (CT) scanning of the cochlea remains the imaging technique of choice [14]. Congenital malformations of the cochlea are not contraindications to cochlear implantation. Several reports of successful implantations in children with inner-ear malformations have been published [15-20]. Likewise, intracochlear bone formation resulting from labyrinthitis ossificans can usually be demonstrated by CT scanning and can be circumvented surgically.

**Audiological Assessment**
The audiological evaluation is the primary means of determining suitability for cochlear implantation. Audiological evaluations should be conducted in both an unaided condition and with appropriately fit conventional amplification. Thus, all potential candidates must have completed a period of experience with a properly fit hearing aid, preferably coupled with training in an appropriate aural re(habilitation) program. The audiological evaluation includes measurement of pure tone thresholds along with word and sentence recognition testing appropriate for the age group under consideration. Aided speech recognition scores are the primary audiological determinant of cochlear implant candidacy. For very young children or those with limited language abilities, parent questionnaires are used to determine hearing aid benefit.

**Surgical Implantation**
Cochlear implantation in children requires meticulous attention to the delicate tissues and small dimensions. Skin incisions are designed to provide access to the mastoid process and coverage of the external portion of the implant package while preserving the blood supply of the postauricular skin. The incision used at the Indiana University Medical Center has eliminated the need to develop a large postauricular flap. The inferior extent of the incision is made well posterior to the
mastoid tip to preserve the branches of the postauricular artery. From here the incision is directed posterior-superiorly. In children, the incision incorporates the temporalis muscle to give added thickness. A subperiosteal pocket is created for positioning the implant induction coil. A bone well tailored to the device being implanted is created. The induction coil is fixed to the cortex with a fixation suture or periosteal flaps at the completion of the procedure.

Following development of the skin incision, a mastoidectomy is performed. In infants, care must be exercised because the mastoid process is short and shallow and the facial nerve may exit the temporal bone superficially. The horizontal semicircular canal is identified in the depths of the mastoid antrum, and the short process of the incus is identified in the fossa incudis. The facial recess is opened using the fossa incudis as an initial landmark. The facial recess is a triangular area bound by (a) the fossa incudis superiorly, (b) the chorda tympani nerve laterally and anteriorly, and (c) the facial nerve medially and posteriorly. The facial nerve usually can be visualized through the bone without exposing it. The round window niche is visualized through the facial recess about 2 mm inferior to the stapes. Entry into the scala tympani is accomplished best through a cochleostomy created anterior and inferior to the annulus of the round window membrane. A small fenestra slightly larger than the electrode to be implanted (usually 0.5 mm) is developed. This approach bypasses the hook area of the scala tympani, allowing direct insertion of the active electrode array. After insertion of the active electrode array, the cochleostomy area is sealed with small pieces of fascia.

Clinical Results

Although cochlear implants are now an established therapeutic option for deaf children, considerable variability exists in pediatric cochlear implant performance. With current cochlear implant technology, more children than ever before have the potential to develop spoken word recognition.

In contemporary practice, the majority of children who receive cochlear implants have congenital or prelingually acquired hearing loss. These children must use the sound provided by a cochlear implant to acquire speech perception, speech production and spoken language skills. Since young deaf children have limited linguistic skills and attention spans, the assessment of performance in this population is quite challenging. To effectively evaluate the communication benefits of cochlear implant use in children, a battery of tests that are developmentally and linguistically appropriate should be employed [21,22].

A number of demographic factors influence performance results in children with cochlear implants. Age at the time of implantation is one factor which influences communication skill development. Although the critical period for implantation of congenitally or prelingually deafened children has not been determined [23], it is now apparent that earlier implantation yields superior cochlear implant performance in children [24-33]. In a longitudinal analysis of 73 children who were prelingually deafened and received current implant technology and processing strategies before 5 years of age, we have shown that children who underwent implantation before 3 years of age had significantly faster rates of language development than did children with later implantation. In addition, children using oral communication demonstrated more rapid gains than did children using total communication [34]. The variables of communication mode and/or unaided residual hearing also influence speech perception performance [35-38]. Oral children, and those who have more residual hearing prior to implantation, typically demonstrate superior speech understanding.

Measuring and tracking the perceptual and linguistic development of prelingually deaf infants who receive cochlear implants has both clinical and theoretical importance. With new measures of speech perception, clinicians will be able to assess the development of speech perception of infant cochlear implant users. From a theoretical perspective, it is of interest to compare language development of normally hearing infants to infants who are first deprived of auditory input and then gain access to sound at a later age via a cochlear implant. To address these issues, a new laboratory at Indiana University School of Medicine has been established to carry out behavioral procedures that have been used successfully for several years to assess linguistic skills of normal hearing infants [39].

Visual Habituation Procedure. One of these procedures is the Visual Habituation procedure. The goals of this project are to (1) validate visual habituation as a technique to measure detection and discrimination of speech sounds by deaf and hard-of-hearing infants, and (2) use visual habituation to track speech perception and language skills before and after cochlear implantation.

In a standard visual habituation procedure for testing speech discrimination, a repeating speech stimulus paired with a visual display (e.g., a checkerboard pattern) is presented to infants until their looking time to the visual display decreases to the point of reaching a habituation criterion. Then a novel speech sound paired with the same visual display is presented. An increase in looking time to the visual display in the presence of the novel speech sound indicates procedure has been modified to assess speech detection as well as speech discrimination. Speech detection is assessed by presenting half of the habituation trials with no sound. Thus, the infant’s looking time to the visual display in the presence of sound is compared to looking time in the absence of sound. To validate visual habituation with this population of infants, we selected two simple speech One is a 4 second continuous vowel (“ahhh”) vs. a 4 second discontinuous syllable repetition (“hop hop hop”) contrast. The other was a 4 second rising /i/ vs. 4 second falling /i/ intonation contrast. To date 11 prelingually deaf infants who are enrolled in the IU Medical School cochlear implant program (mean age = 173, range 6-31.3 months) have been tested. Nine of the infants were tested prior to cochlear implantation; seven at both the 1-month and 3-month post-CI interval; and eight at the 6-month post-CI interval. One participant, (CI01), who was the youngest cochlear implant recipient at IU School of Medicine received a CI at 6 months of age. We have followed CI01 closely and will report his individual data collected across several testing sessions. Finally, for comparison, we have also
tested 24 normal 6-month-olds and 24 normal hearing 9-month-olds.

The preliminary results from this investigation are promising. The participant attrition rate (due to crying, failure to reach habituation, or fussiness) is relatively low (~25%) and similar across normal hearing and cochlear implant infants, suggesting that visual habituation is a viable technique for assessing speech perception skills in deaf infants before and following cochlear implantation. As expected, the normal hearing infants attended significantly longer to the sound than to the silent trials and longer to the novel than to the old trials, demonstrating that they detect and attend longer to speech sounds than silence and that they can discriminate these speech contrasts. At pre-implantation intervals, deaf infants did not attend longer to sound trials or to the novel trials. By contrast, deaf infants at all of the post-cochlear implant intervals attended longer to the sound trials and to the novel trials but not to levels that were statically significant. CI01, who was followed more intensively, did not attend longer to sound trials or to novel trials at early post-CI intervals (months 1-3) but attended much longer to sound trials and to novel trials at later post-CI intervals (months 6-15). These findings suggest that after a few months of experience with CIs, deaf infants are demonstrating detection of speech and discrimination of gross-level speech contrasts. However, additional data are needed from more deaf infants to document and verify these trends.

Conclusion
Cochlear implants are an appropriate sensory aid for selected deaf children who receive minimal benefit from conventional amplification. Improvements in technology and refinements in candidacy criteria have secured a permanent role for cochlear implantation. With improved postoperative performance, a clear justification for implanting not only patients with bilateral profound sensorineural hearing but also patients with severe sensorineural hearing has been reached. Patients as young as 12 months of age may be implanted under current FDA guidelines and experience with even younger children is accumulating. Wide intersubject performance variability continues to exist. However, many children using cochlear implants have acquired speaking and listening skills and have developed a spoken language system which is beyond what previously could be achieved with hearing aids. Children who are implanted at a young age and use oral communication have the best prognosis for developing intelligible speech and age appropriate language abilities.

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References