

Chapter 176: Sensorineural Hearing Loss in Children

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Early identification of educationally significant sensorineural hearing impairment in young children, which varies in incidence from 1:1000 to 1:2000 depending on the population studied, should be a major public health priority. Early (re)habilitative intervention, as provided under Public Law 94-457, is a prerequisite for the development of age-appropriate speech and language skills by school age, to provide a basis for attaining literacy skills. Credible research supports the existence of a critical period in the first years of life for optimal acquisition of speech and language. The absence of adequate auditory stimulation in the young infant may also impair the full development and maturation of central auditory pathways. Universal hearing screening for all newborns would be a laudable goal, but behavioral measures (both automated and direct observation) have proven too labor intensive, as well as unreliable, and auditory brain stem response testing is too technologically sophisticated and costly for general acceptance by clinicians. Evoked otoacoustic emission testing may prove to be the long-awaited, cost-effective objective evaluation tool, but present clinical practice focuses on evaluation of neonates and infants who are identified as being at risk for hearing impairment. The major argument against limiting early identification efforts to such targeted testing of high-risk populations is data indicating that as many as 50% of infants with significant hearing loss may be missed.

In 1982 the Joint Committee on Infant Hearing recommended seven criteria for identifying infants at risk for hearing impairment. Revised recommendations were published in 1991 (Bess, 1991) that expand the risk criteria to include not only neonates (birth to 28 days) but also infants (29 days to 2 years). As many as 2% to 5% of neonates manifesting high risk factors can be confirmed as having moderate to severe sensorineural hearing loss. Additionally, recommendations were made regarding optimal audiologic screening protocols and early intervention strategies for hearing-impaired infants and their families.

The high risk factors identified for neonates can be broadly classified in four categories: family history, physical findings, events during birth and postnatal hospital stay, and infections. A family history of congenital or delayed-onset childhood sensorineural hearing loss (SNHL) should serve as a red flag for referral of the infant for early audiologic evaluation. High-risk physical findings include birth weight less than 1500 g (3.3 lb); craniofacial anomalies involving the ear, skull, and mouth region; and stigmata associated with a hearing loss syndrome, such as white forelock Waardenburg's syndrome). Severe depression of vital body systems at birth is reflected by a low Apgar score (0 to 3 at 5 minutes), delayed spontaneous respirations (beyond 10 minutes), and persistent hypotonia during the first 2 hours of life. In addition to these indicators, significant occurrences during the neonatal period include hyperbilirubinemia requiring exchange transfusion, prolonged mechanical ventilation, and treatment with ototoxic medications (for example, gentamicin, tobramycin, kanamycin, streptomycin). Infections with the potential to damage hearing may be acquired prenatally (for example, toxoplasmosis, syphilis, rubella, cytomegalovirus, herpes) or postnatally (for example, bacterial meningitis).

In addition to risk factors for neonates, infants (29 days to 2 years) may sustain skull/temporal bone trauma or contract other infectious diseases with potential for causing SNHL (for example, measles or mumps). Neurodegenerative disorders in infancy (for example, Tay-Sachs disease, myoclonic epilepsy) should also prompt a referral for hearing evaluation. Finally, concern expressed by a parent or surrogate care giver about an infant's hearing, speech and language acquisition, or general development should alert the clinician to the need for audiologic evaluation. The axiom "moter is always right" is worth remembering when deciding whether to refer an infant for testing. Because behavioral audiologic testing of hearing in neonates and some infants is fraught with methodologic problems, it is essential to refer the high-risk neonate for auditory brain stem response (ABR) evaluation, optimally before hospital discharge. If this is not feasible, evaluation by 3 months of age is acceptable, but a delay beyond 6 months is unwarranted. It is important to continue follow-up of those infants with absent or abnormal ABRs or a family history of progressive hearing loss. The conventional "click" stimulus used to elicit an ABR in most centers is accurate in assessing auditory acuity for higher frequencies (that is, above 2000 Hz), so that a valid and repeatable behavioral audiogram should be obtained as soon as practicable. Appropriate (re)habilitative intervention should be initiated immediately after a sensorineural hearing loss has been confirmed. Local school districts are obligated to provide and coordinate such intervention programs for hearing impaired children living within their boundaries.

The risk factors that identify those neonates, birth to 28 days, who are at risk for sensorineural hearing impairment include the following (ASHA, 1991):

1. Family history of congenital or delayed-onset childhood sensorineural impairment.
2. Congenital infection known or suspected to be associated with sensorineural hearing impairment such as toxoplasmosis, syphilis, rubella, cytomegalovirus, or herpes.
3. Craniofacial anomalies, including morphologic abnormalities of the pinna and ear canal, absent philtrum, and low hairline.
4. Birth weight less than 1500 g (3.3 lb).
5. Hyperbilirubinemia at a level exceeding indication for exchange transfusion.
6. Ototoxic medications including but not limited to the aminoglycosides used for more than 5 days (for example, gentamicin, tobramycin, kanamycin, streptomycin) and loop diuretics used in combination with aminoglycosides.
7. Bacterial meningitis.
8. Severe depression at birth, which may include infants with Apgar scores of 0 to 3 at 5 minutes or those who fail to initiate spontaneous respiration by 10 minutes or those with hypotonia persisting to 2 hours of age.
9. Prolonged mechanical ventilation for a duration equal to or greater than 10 days (for example, persistent pulmonary hypertension).

10. Stigmata or other findings associated with a syndrome known to include sensorineural hearing loss (for example, Waardenburg or Usher syndrome).

The factors that identify those infants, 29 days to 2 years, who are at risk for sensorineural hearing impairment include the following:

1. Parent or care giver's concern regarding hearing, speech, language, or developmental delay.

2. Bacterial meningitis.

3. Neonatal risk factors that may be associated with progressive sensorineural hearing loss (for example, cytomegalovirus, prolonged mechanical ventilation, and inherited disorders).

4. Head trauma, especially with either longitudinal or transverse fracture of the temporal bone.

5. Stigmata or other findings associated with syndromes known to include sensorineural hearing loss (for example, Waardenburg or Usher syndrome).

6. Ototoxic medications including but not limited to the aminoglycosides used for more than 5 days (for example, gentamicin, tobramycin, kanamycin, streptomycin) and loop diuretics used in combination with aminoglycosides.

7. Children with neurodegenerative disorders such as neurofibromatosis, myoclonic epilepsy, Werdnig-Hoffmann disease, Tay-Sachs disease, infantile Gaucher's disease, Niemann-Pick disease, any metachromatic leukodystrophy, or any infantile demyelinating neuropathy.

8. Childhood infectious diseases known to be associated with sensorineural hearing loss (for example, mumps, measles).

Neonates, birth to 28 days, who manifest one or more items on the risk criteria should be screened, preferably under the supervision of an audiologist. Optimally, screening should be completed before discharge from the newborn nursery but no later than 3 months of age. The initial screening should include measurement of the auditory brain stem response (ABR) (ASHA 1989). 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, ongoing assessment and observation of the infant's auditory behavior are recommended during the early stages of intervention. If the infant is discharged before screening or if ABR screening under audiologic supervision is not available, the child should be referred for ABR testing by 3 months of age but never later than 6 months of age.

The acoustic stimulus for ABR screening should contain energy in the frequency region important for speech recognition. Clicks are the most commonly used signal for eliciting the ABR and contain energy in the speech frequency region (ASHA, 1989). Pass criterion for ABR screening is a response from each ear at intensity levels 40 dB nHL or less.

Transducers designed to reduce the probability of ear-canal collapse are recommended.

If consistent electrophysiologic responses are detected at appropriate sound levels, then the screening process will be considered complete except in those cases where there is a probability of progressive hearing loss (for example, family history of delayed onset, degenerative disease, meningitis, intrauterine infections, or infants who had chronic lung disease, pulmonary hypertension, or received medications in doses likely to be ototoxic). If the results of an initial screening of an infant manifesting any risk criteria are equivocal, then the infant should be referred for general medical, otologic, and audiologic follow-up.

Infants, 28 days to 2 years, who exhibit one or more items on the risk criteria should be screened as soon as possible but no later than 3 months after the child has been identified as at risk. For infants less than 6 months of age, ABR screening is recommended. For infants older than 6 months, behavioral testing using a conditioned response or ABR testing is appropriate. Infants who fail the screen should be referred for a comprehensive audiologic evaluation. This evaluation may include ABR, behavioral testing (6 months), and acoustic immittance measures (see ASHA 1989 Guidelines for recommended protocols by developmental age).

Evaluation of Young Hearing Impaired Child

The comprehensive evaluation of a child with educationally significant hearing impairment requires the coordinated efforts of a specialty team that should include an otolaryngologist experienced with children, a pediatric audiologic team competent with both behavioral and electrophysiologic testing, a pediatrician skilled in detecting subtle findings associated with deafness syndromes, a genetic counselor, a pediatric ophthalmologist with competence in electroretinography, a psychologist to assess the child's cognitive abilities, an educator of the deaf with expertise in early intervention, and a speech/language pathologist to assess oral motor function and linguistic development. Consultation in pediatric neurology and neuroradiology should also be easily available.

A thorough case history provides the foundation for the remainder of the evaluation. In addition to a detailed prenatal, birth, and postnatal history for the child, a complete family history should be obtained that includes hearing loss; speech/language disorders; ear, nose, and throat disorders; and craniofacial deformities; as well as features that accompany syndromes, such as kidney disorders, sudden death at a young age, thyroid disease, intracranial tumors, progressive blindness, and café-au-lait spots. Because the majority of genetic hearing loss is inherited in a recessive manner, it is very important to rule out marital consanguinity in the family history. If a family history of hearing loss is identified, an exhaustive pedigree should be constructed, including at least three generations. It is important to realize that many families with genetic deafness fail to recognize the heritable nature of the disorder, because family oral tradition ascribes each case to an extrinsic cause such as mastoid disease, head trauma, or noise damage.

A careful physical examination must involve not only an assessment of the ears but also a search for subtle findings such as preauricular or branchial pits, heterochromia iridis, blue sclerae, dystopia canthorum, facial asymmetry, and café-au-lait spots. Specific physical findings associated with deafness syndromes are detailed in the subsequent text, but no

finding should be disregarded until genetic consultation has been obtained. Ophthalmologic evaluation is critical because the visual system assumes an even more important neurosensory role in a child with impaired auditory acuity. Additionally, early detection of coexisting retinitis pigmentosa, with electroretinography, can influence (re)habilitative decisions.

Basic laboratory studies should include complete blood count with differential and sickle cell preparations, if indicated; basic blood studies: chemistries, lipids, blood sugar, creatinine, BUN, and thyroid studies; and urinalysis. If hematuria is present, additional renal studies (such as ultrasound) should be undertaken. Serologic tests aimed at detecting congenital syphilis and toxoplasmosis, both of which are potentially treatable, are advisable. Knowledge of the rubella vaccination status of the mother should determine the necessity for pursuing that diagnosis. Cytomegalovirus infection presents a diagnostic quandary. It is likely that CMV accounts for a significant percentage of childhood deafness, but confirmation of true congenital infection must be based on positive serology obtained very early in life, probably within the first month or two. After that, antibodies to perinatally or postnatally acquired CMV can obscure the diagnosis. The role that autoimmune disorders play in the etiology of SNHL in children is presently unclear, and judgments regarding the cost effectiveness of studies aimed at detecting such disease processes must await evidence regarding their prevalence.

The pediatric audiologic evaluation must determine the type of hearing loss (that is, conductive, sensorineural, or mixed); the degree of loss (that is, mild, moderate, severe, profound, or anacusic); the audiometric configuration and symmetry of the impairment; and finally, with serial assessment, the stability or progression of the loss. Vestibular dysfunction may coexist with hearing loss in some children with genetic deafness (for example, Usher's syndrome, type 1) and with hearing loss attributable to such nongenetic etiologies as bacterial meningitis. The availability of computerized rotational testing has facilitated vestibular system evaluation in young children, which may also be important in determining the cause of delayed gross motor skill development (such as sitting unsupported, walking, standing on one foot). Progressive and fluctuating SNHL, with or without vertigo, in children raises the specter of possible perilymphatic fistula (PLF). Although preoperative confirmation of PLF remains elusive, a monitored fistula test seems a reasonable course in these cases. A positive fistula test may be helpful, but a negative result must be considered inconclusive on the basis of reported series.

Temporal bone imaging studies are helpful in identifying middle ear anomalies in children with conductive or mixed losses, as well as inner ear or internal auditory canal anomalies or lesions in cases of SNHL. The relatively low yield and high cost of such studies make their uniform application problematic. The utility of CT scans for assessing profoundly deaf children for cochlear implant candidacy has resulted in increased use of this diagnostic modality in recent years.

A diligent search for etiology of SNHL in a child, utilizing state of the art techniques, will prove inconclusive in 30% to 40% of cases. With the declining incidence of non-genetic etiologies such as prenatal rubella, measles, mumps and *Haemophilus influenzae* meningitis, genetic hearing loss will affect an increasing percentage of newly identified cases. Many parents are anxious to determine the etiology of their child's loss for prognostic and family planning considerations. Clinicians serving the needs of these families must be prepared to

address their concerns regarding the lack of a definitive diagnosis.

Several detailed etiologic classifications of SNHL in children have been suggested. The use of terminology such as genetic versus acquired and congenital versus acquired can be confusing. It would seem most helpful to classify SNHL cases broadly in a matrix as genetic versus nongenetic and congenital versus delayed (that is, postnatal) onset. Clearly, many genetic hearing losses are not congenital, whereas certain nongenetic hearing impairments (for example, rubella deafness) are present at birth. Rapidly expanding knowledge regarding genetic hearing loss should lead to techniques for the prenatal or early postnatal diagnosis of these disorders even if clinical manifestations are delayed for months or years.

Genetic Hearing Loss

It has been estimated that 50% of childhood sensorineural hearing impairment is due to genetic factors; 20% to 25% of cases are attributable to identifiable environmental causes, occurring prenatally, perinatally, or later in life; and 25% to 30% are sporadic cases of uncertain etiology.

Genetic forms of hearing loss may be congenital or delayed in onset, progressive or nonprogressive, and unilateral or bilateral; they may be part of a syndrome (that is, involving other identifiable physical characteristics in other systems), or there may be no associated syndrome, (that is, there is only hearing loss). At least 100 genetic syndromes that involve hearing loss have been identified, and they may be classified on the basis of other organ systems involved; craniofacial/cervical, skeletal, integumentary, ocular, neurologic, renal, metabolic, and "other". Classifications of hearing impairments not associated with syndromes (that is, hearing loss only) are generally based on audiologic characteristics, presence or absence of progression, age of onset, and mode of inheritance. Approximately 75% to 80% of genetic hearing loss is generally attributed to autosomal recessive genes and 18% to 20% to autosomal dominant genes, with the remainder classified as X-linked, or chromosomal, disorders.

Patterns of Dysmorphology

Based on the classification by Spranger et al (1982), a number of terms can be used to describe patterns of dysmorphology.

Individual alterations of forms or structure

A *malformation* is a defect in the morphology of an organ or body region occurring because the underlying developmental potential of the involved organ was intrinsically abnormal.

If an organ's developmental potential was normal and extrinsic factors, such as trauma, infections, radiation, or pharmaceuticals, cause the defect, the resulting morphologic anomaly is called a *disruption*. By definition, disruptions cannot be inherited because they are sporadic occurrences.

Intrinsic or extrinsic mechanical forces can produce a *deformation* in which a part of the body assumes an abnormal position, shape, or form. Intrauterine constraint is an example of such a deforming force.

Abnormal cellular organization within tissues is classified as a *dysplasia*, as exemplified by osteogenesis imperfecta resulting from a defect in connective tissue. A dysplasia may involve multiple organs, may be sporadic or multifactorial in etiology, and may result from a genetic mutation. Solitary acoustic neuromas and multiple neurofibromatoses are examples of dysplasias.

Patterns of morphologic defects

A *polytopic field defect* results from perturbation of a single developmental field, whereas the term *sequence* describes a pattern of several anomalies resulting from a single cause such as a preexisting anomaly or a mechanical force. A malformation or disruption may be the underlying cause of a sequence. The Robin sequence (also known as Pierre Robin syndrome), consisting of micrognathia, cleft palate, and glossoptosis, can result from various intrinsic and extrinsic forces operative in several different developmental environments.

A *syndrome* is a pattern of multiple anomalies presumed to be pathogenetically related but not meeting the qualifications for classification as a single sequence or a polytopic field defect. Malformation syndromes usually have an identifiable cause, which could include disorders resulting from chromosomal abnormalities or genetically determined morphogenetic deviances.

Association describes a nonrandom occurrence of multiple anomalies, not meeting strict criteria for classification as a polytopic field defect, sequence, or syndrome, in two or more individuals. In reality, association is a statistical instead of an etiopathogenetic construct that serves to alert clinicians to possible occult associated anomalies after one defect has been identified. CHARGE association consists of the following: C - coloboma, H - heart defects, A - choanal atresia, R - retarded growth and development and/or CNS anomalies, G - genital hypoplasia, and E - ear anomalies and/or deafness.

Basic Genetic Principles

Human genes are arranged linearly on 22 pairs of autosomes and 1 pair of sex chromosomes, which taken together constitute what might be called a design manual for the human body. Each pair of chromosomes carries a distinctive set of gene loci for which there may be several alternative codes or alleles. For any particular trait, the *genotype* may be comprised of two identical alleles (homozygous) or two different alleles (heterozygous). The physical expression of the trait in an individual is called the *phenotype*, which is determined by the nature and interaction of the two alleles. An autosomal dominant allele is phenotypically expressed in either the homozygous or heterozygous state, whereas an autosomal recessive allele is expressed only in the homozygous state. An X-linked (that is, sex chromosome-linked) recessive gene will also be expressed in the hemizygous condition in the male because the Y chromosome does not carry a complementary allele. A parent who is heterozygous for an autosomal dominant gene has a 50% chance of transmitting it to each

child (Fig. 176-1). Offspring of heterozygotic carriers of an autosomal recessive gene have a 25% recurrence risk (Fig. 176-2). An X-linked recessive trait is not usually expressed in a heterozygous female, but each male child has a 50% chance of inheriting the gene, which would be phenotypically expressed. There is a 50% chance that each of a female carrier's daughters would also inherit the gene, but 100% of the daughters of an affected male will inherit his only X chromosome and thus carry the abnormal gene. None of an affected male's sons inherit his X chromosome with the abnormal gene.

Dominant genes may not be phenotypically expressed in all individuals who are heterozygous for the gene, a phenomenon called decreased penetrance. Variable expressivity is also characteristic of dominant genes in that different family members may show diverse manifestations of the gene. Phenotypic expression may be modified by environmental influences or interaction with other genes.

Chromosomal abnormalities involving autosomes result from extra or deficient chromosomal material being present in each cell, and the phenotypic expression may be quite severe or even fatal. Phenotypes associated with abnormalities of sex chromosomes are generally less severe. In patients with trisomy, three copies of a given chromosome are present. *Trisomy 21* or *Down's syndrome* is the least severe autosomal trisomy, whereas *trisomy 13* (*Patau's syndrome*) and *trisomy 18* (*Edward's syndrome*) are less common and more severe. Other autosomal trisomies are almost always lethal, as is the presence of a single chromosome of a pair, monosomy. Chromosomal deletions (absent segments) or duplications (extra material) may be present, with the nature and severity of each phenotype depending on the amount and origin of the material involved.

Genetic Linkage Analysis

Genetic linkage analysis is the process of determining the precise chromosomal location of a specific gene. Genetic material may be randomly exchanged (that is, crossover) between two members of a chromosome pair during cell mitoses, and two genetic loci are said to be linked when their alleles are transmitted together more frequently than expected by chance. If the chromosomal location of one gene is known (a marker gene), the linked focus can be determined. Restriction fragment length polymorphisms are markers based on variations in DNA sequence rather than on gene product. These DNA probes have already played an important role in linkage studies successfully identifying specific chromosomal loci of multiple genes responsible for Usher syndrome (USH 1 and USH 2), Waardenburg syndrome (WS 1), and branchio-oto-renal syndrome (BOR).

Inner Ear Structural Malformations

By the beginning of the ninth week of gestation, the cochlea reaches full growth (2.75 turns). Arrest in normal development (agenesis) or aberrant development (dysgenesis) of inner ear structures may result in hearing impairment. Studies utilizing modern temporal bone imaging reveal subtle or severe anomalies of the inner ear in about 20% of children with congenital sensorineural hearing loss, with about 65% being bilateral and the remainder unilateral.

Complete agenesis of the petrous portion of the temporal bone occurs in *Michel's aplasia*, which is inherited as an autosomal dominant trait. Temporal bone imaging plays an essential role in confirming the diagnosis, although labyrinthitis ossificans, as occurs following meningitis, can present a similar appearance. Affected ears are anacusic because of the absence of sensory and neural inner ear structures. Vibrotactile devices have been of some benefit with these patients, but conventional amplification and cochlear implantation are not efficacious for obvious reasons.

In *Mondini's aplasia* the basal coil of the cochlea can be clearly identified, but the interscalar septum is absent in the upper coils, which assume a cloacal form. It is postulated that the deformity results from a development arrest at approximately the sixth week of gestation. The anomaly is inherited in an autosomal dominant fashion, may be unilateral or bilateral, and has been described in a number of disorders, including Pendred's, Waardenburg, Treacher Collins, and Wildervank's syndromes. An aggressive program of early intervention with conventional amplification is advisable in cases with residual neurosensory structures.

The bony labyrinth and superior portion of the membranous labyrinth, including the utricle and semicircular canals, are normally differentiated in patients with *Scheibe's aplasia*. The organ of Corti is generally poorly differentiated with a deformed tectorial membrane and collapsed Reissner's membrane. Inherited as an autosomal recessive trait, Scheibe's is the most common aplasia and has been observed in temporal bones from patients with Jervell and Lange-Nielsen, Refsum's, Usher's, and Waardenburg's syndromes.

In *Alexander's aplasia*, cochlear duct differentiation at the level of the basal coil is limited, with resultant effects on the organ of Corti and ganglion cells. High-frequency hearing loss is the rule in these patients, with enough residual low-frequency hearing to benefit from amplification.

An enlarged vestibular aqueduct, observed radiographically, has been associated with early-onset SNHL, which is usually bilateral and may be accompanied by vertigo. Initial hopes that endolymphatic sac surgery in these patients might be beneficial proved incorrect, and such intervention is contraindicated.

Autosomal Dominant Disorders

An autosomal dominant syndrome might be expected to be easily identified by a positive family history of classical dominant inheritance and a recognizable phenotype. In fact, variation in expressivity may be reflected in different phenotypic characteristics in affected family members. An obligate carrier may not have any detectable phenotypic expression because of decreased penetrance. If a new mutation has occurred, the family history might be negative, but the disorder is still transmitted in a dominant fashion.

Variable expressivity is observed with *Waardenburg's syndrome*, which includes unilateral or bilateral sensorineural hearing loss in 20% of cases, as well as pigmentary anomalies: white forelock in 20% to 30% of cases, heterochromia iridis, premature graying, and vitiligo; and craniofacial features such as dystopia canthorum, broad nasal root, and synophrys. Clinically, two distinct types of Waardenburg's syndrome are distinguishable, based on the presence (WS-1) or absence (WS-2) of dystopia canthorum, with hearing loss

being more frequent in WS-2. Initial linkage analysis results assign a locus for WS-1 to the 2q37 region of the number 2 chromosome (Foy et al, 1990).

Features in individuals with *Stickler's syndrome* may include a small jaw, often with a cleft palate (Robin sequence), myopia that may be accompanied by retinal detachment or cataracts, hypermobility and enlargement of joints with early adult-onset arthritis, and occasional spondyloepiphyseal dysplasia. Sensorineural or mixed hearing loss is present in about 15% of cases.

In *branchiootorenal (BOR)* or *Melnick-Fraser syndrome*, ear pits (possibly tags) or cervical fistulas are present as are renal findings ranging from agenesis with renal failure to minor asymptomatic renal dysplasia, detectable by ultrasound or intravenous pyelography. The hearing loss may be sensorineural, conductive, or mixed. Linkage analysis studies have recently identified the responsible gene to be on chromosome 8q (Kimberling, 1992).

The craniofacial features of *Treacher Collins syndrome* (mandibulofacial dysostosis) may include microtia, aural meatal atresia, and conductive hearing impairment about 30% of the time. Sensorineural loss and vestibular dysfunction may also be present. Malar hypoplasia, with underdeveloped zygomatic arches, downward slanting palpebral fissures, coloboma of the lower eyelids, and a hypoplastic mandible, characterizes the face of affected individuals. Symmetric facies and bilateral eyelid coloboma distinguish Treacher Collins from *Goldenhar's syndrome* and other oculoauricular vertebral syndromes that involve similar, but unilateral, microtia and craniofacial abnormalities. The oculoauriculovertebral (OAV) spectrum is sporadic and thought to be multifactorial, whereas Treacher Collins syndrome is transmitted as an autosomal dominant trait.

Persons affected by *neurofibromatosis* may present with café-au-lait spots (light brown, variable-sized pigmented spots) and multiple fibromatous tumors. Cutaneous tumors are most common, but the central nervous system, peripheral nerves, and viscera may also be involved. Mental retardation, blindness, and SNHL may result from CNS lesions. Two distinct forms have been identified clinically, the more common benign classic neurofibromatosis (*von Recklinghausen's disease*), with an incidence of about 1:3000 persons, which generally includes many café-au-lait spots and cutaneous neurofibromas but acoustic neuromas (typically unilateral) in only 5% of cases. Bilateral acoustic neuromas are present in 95% of cases with central neurofibromatosis (NF-2), which is genetically distinct from the classical form. Presenting signs and symptoms of the bilateral lesions may not be noted until early adulthood. Café-au-lait spots and cutaneous neurofibromatosis in NF-2 patients are fewer than observed in von Recklinghausen's disease. Both types of neurofibromatosis are inherited as autosomal dominant traits with high penetrance but variable expressivity. High mutation rates characterize both disorders. The gene for at least one form of NF-2 has been assigned to chromosome 22 by linkage analysis.

Otosclerosis appears to be transmitted by an autosomal dominant pattern with decreased penetrance, so that only 40% of gene carriers will actually demonstrate the phenotype. Delayed-onset conductive or mixed hearing impairment may begin in childhood but usually presents in adulthood.

Osteogenesis imperfecta is characterized by bone fragility, blue (clear) sclerae, hearing loss (conductive, mixed, or sensorineural), and hyperelasticity of joints and ligaments. This disorder is transmitted as an autosomal dominant trait with variable expressivity and incomplete penetrance. A severe congenital type may present with intrauterine fractures severe enough to threaten fetal viability. The age at which the more common "tarda" variety becomes clinically apparent is variable. *Van der Hoeve's syndrome* is a subtype of osteogenesis imperfecta in which progressive hearing loss begins in early childhood. Although some investigators have postulated a relationship between osteogenesis imperfecta and otosclerosis, histopathologic studies of stapedial foot plates in each disorder demonstrate significant differences. Minimal peripheral fixation of a markedly thickened stapedial foot plate is present in a typical case of osteogenesis imperfecta hearing loss.

Nonsyndromic Autosomal Dominant Hearing Loss

Dominant progressive hearing loss (DPHL) is a type of nonsyndromic, noncongenital sensorineural hearing loss, variable in age of onset and rate of progression, transmitted as an autosomal dominant trait. It is idiopathic and differs from otosclerosis by the absence of ossicular and otic capsule involvement and from presbycusis by the earlier age of onset. All types of DPHL eventually progress to severe or profound hearing loss, but initial frequency involvement and the rate of progression vary among families. Konigsmark and Gorlin (1976) defined four types of DPHL: early onset, high frequency, mid frequency, and low frequency.

About 80% of genetic deafness in childhood is inherited in an autosomal recessive fashion, with approximately one half of cases involving recognizable syndromes. Variation in penetrance and expressivity is less pervasive than with dominant disorders, but carriers are asymptomatic, making definitive diagnosis in small kindreds difficult unless other syndromic components are identified.

Sensorineural hearing loss and retinitis pigmentosa characterize *Usher syndrome*, which has an estimated frequency of 3.0/100,000 in Scandinavia and 4.4/100,000 in the USA. This disorder affects about one half of the 16,000 deaf/blind persons in the USA. Clinically, at least two subtypes, USH 1 and USH2, are distinguishable, based on severity of the hearing loss and the extent of vestibular system involvement. Patients with USH 1 present with congenital, bilateral profound hearing loss and absent vestibular function, whereas USH 2 patients have moderate hearing losses and normal vestibular function (Fig. 176-3). Linkage analysis studies have localized the gene for USH 2 to the 1q32 region of chromosome 1 (Kimberling, 1990). More recently, Kimberling and coworkers have identified chromosome 11q as the probable site of the gene for USH 1 that occurs in patients who are not of Acadian background and do not reside in Louisiana (Kimberling, 1992). Ophthalmologic evaluation is an essential part of the diagnostic workup, and subnormal electroretinographic (ERG) patterns have been observed in affected children as young as 2 to 3 years of age, before retinal changes are evident fundoscopically.

In the autosomal recessive disorder *Pendred's syndrome*, SNHL is associated with abnormal iodine metabolism resulting in a euthyroid goiter. The perchlorate discharge test demonstrates abnormal organification of nonorganic iodine in these patients, and exogenous thyroid hormone is the therapy of choice.

In patients with *Jervell* and *Lange-Nielsen syndrome*, a severe, congenital sensorineural hearing impairment is inherited in a recessive pattern together with a cardiac conduction defect that can produce syncopal episodes early in life and even sudden death. Electrocardiographically, large T waves and prolongation of the QT interval are observed, so that an electrocardiogram should be performed on all children with early-onset hearing loss of uncertain etiology. Beta-adrenergic blockers have proven effective in treating the disorder.

Konigsmark and Gorlin (1976) described three subtypes of *nonsyndromic recessive SNHL*: *congenital severe*; *congenital moderate*; and *early-onset*, which usually progresses rapidly from onset at age 1.5 years to profound loss by 6 years of age.

Sex-Linked Disorders

Approximately 6% of nonsyndromic profound losses in males may be attributable to sex-linked disorders. In *Norrie's syndrome* congenital or rapidly progressive blindness, development of pseudoglioma, opacification, and ocular degeneration resulting in microphthalmia are observed. Progressive sensorineural hearing loss, with onset in the second or third decade, affects approximately one third of individuals with this sex-linked disorder.

Characteristics associated with *otopalatodigital syndrome* may include hypertelorism, craniofacial deformity involving the supraorbital area, flat midface, small nose, and cleft palate. Affected individuals are also short in stature with broad fingers and toes that vary in length, with an excessively wide space between the first and second toe. An associated conductive hearing loss usually results from an ossicular malformation.

Wildervaank's syndrome is comprised of the Klippel-Feil malformation involving fused cervical vertebrae, sensorineural or mixed hearing impairment, and cranial nerve VI paralysis causing retraction of the eye on lateral gaze. *Wildervaank's syndrome* is almost always observed in females because of the high degree of lethality associated with the X-linked dominant form in males.

In *Alport's syndrome* SNHL is associated with renal impairment of varying severity. The progressive hearing impairment may not become clinically evident until the second decade of life. The renal disease may cause hematuria in infancy but generally remains asymptomatic for several years before onset of renal insufficiency. Renal involvement is especially severe in males, and death from uremia before 30 years of age was the rule before the availability of renal dialysis and kidney transplantation. Although genetic heterogeneity may be involved in some cases, the gene for the X-linked form of Alport's codes for a collagen gene (COL4A5) on the X chromosome.

Two types of *nonsyndromic congenital severe sensorineural hearing loss* have been described: *early-onset, rapidly progressive* and *moderately slowly progressive*.

Multifactorial Genetic Disorders

Some genetic disorders appear to result from a combination of genetic factors interacting with environmental influences. Such multifactorial disorders associated with hearing loss include clefting (that is, cleft lip/palate) syndromes, involving conductive hearing loss, and the *microtia/hemifacial microsomia/Goldenhar's spectrum*.

Findings may include preauricular tags/pits, vertebral anomalies such as hypoplastic vertebrae or hemivertebrae in the cervical region, epibulbar dermoids, and coloboma of the upper lip. *Goldenhar's syndrome* (oculoauriculovertebral dysplasia) has also been described as being inherited in an autosomal dominant pattern in some families.

Autosomal Chromosomal Syndromes

Middle ear and mastoid disease is often observed in Down's syndrome children. *Turner's syndrome* patients, monosomic for all or part of one X chromosome (X0), generally present as females with gonadal dysgenesis, short stature, and often a webbed neck or shield chest. Sensorineural, conductive, or mixed hearing loss may be seen with Turner's syndrome.

Genetic Evaluation and Counseling

Family histories of persons with genetic hearing impairment often involve a number of marriages between deaf individuals, with hearing losses of uncertain etiology. Reasonable criteria for obtaining cytogenetic studies would be the presence of two major malformations or a single major malformation with two or more minor malformations. The specific etiology of a hearing loss may still remain uncertain after an intensive, and often expensive, evaluation. A complete genetic evaluation involves diagnosis, including careful delineation of the phenotype, prognosis, and estimation of recurrence risk. Consideration of the usual pattern of penetrance of a gene must be considered in counseling regarding recurrence risks for autosomal dominant disorders. Recurrence risk for children of an individual with recessively inherited deafness depends on the genetic status of his or her mate. The recurrence risk in deaf x deaf marriages entirely depends on the etiology of the deafness. If both parents have identical recessively inherited deafness, for example, the recurrence rate would be 100%, but if parents have disparate etiologies, the risk may be quite small.

Bieber and Nance (1978) developed empiric risk tables based on an "averaged" risk, taking into account various possibilities, including the number of affected and unaffected children in the family. For instance, the range of recurrence risk for future offspring in a family whose only child has an unexplained hearing impairment is 10% to 16%. Each additional normal hearing child born to such a family reduces the probability of a genetic etiology with a consequent decrease in estimated recurrence risk.

If a normal hearing individual marries a person with sensorineural hearing loss of uncertain etiology, their risk of having a hearing-impaired child could range from negligible (nongenetic or uncommon recessive) to 50% if the gene is a fully penetrant dominant one. The averaged empiric risk cited for such a couple is 6%, which would decrease with each unaffected child born to them.

When both husband and wife have hearing losses of uncertain etiology, most counselors assign an empiric risk for a deaf child of about 10%. The risk declines with the birth of each hearing child but increases to 62% if their firstborn is hearing impaired.

Infectious Diseases

Congenital and early-onset infectious disease

Congenital and neonatal infections

Infections acquired during the prenatal or perinatal/neonatal period occur in about 10% of all live births. In most instances these infections are asymptomatic or present non-specific findings. New diagnostic techniques, including fetal ultrasound, sampling of peripheral umbilical blood, and polymerase chain reaction technology, hold promise for more specific diagnostic capability in the future.

Viral infections

A number of viruses have been implicated as etiopathogenic agents for congenital and acquired hearing loss. Cytomegalovirus has been isolated from human labyrinthine fluids. Seroconversion studies and virus isolation from urine and nasopharyngeal secretions have confirmed an association of labyrinthitis with rubella, rubeola, mumps, influenza, varicella-zoster, Epstein-Barr, poliomyelitis, variola, adenoviruses, and parainfluenza viruses. Before the advent of an effective vaccine, mumps was a common etiology of acquired profound unilateral sensorineural hearing loss in childhood. Effective immunization programs for rubella, rubeola, and mumps in developed countries have decreased their importance in the etiology of childhood hearing loss, but these infections continue to play a significant role in the Third World.

Histopathologic studies of temporal bones from patients who were affected by prenatal rubella, mumps, rubeola, or cytomegalovirus (CMV) reveal evidence of an endolymphatic labyrinthitis with pathologic changes limited to the cochlear duct, saccule, and utricle. These findings are consistent with a blood-borne spread of infection most likely via vessels of the stria vascularis. Measles, mumps, and CMV may also present with a meningoencephalitis, permitting direct spread along meningeal and neural structures into the perilymphatic spaces, where inflammatory changes may later progress to fibrosis. Bordley and Kapur (1972) studied temporal bones of patients who suffered acute smallpox, varicella (chickenpox), or measles and found the most severe pathologic changes in the middle ears, although two measles patients also revealed histopathologic evidence of endolabyrinthitis.

Davis and Johnson (1976) demonstrated selective vulnerability of inner ear structures of experimental animals to specific viruses. In newborn hamsters, influenza virus infected mesenchymal cells in the perilymphatic system, whereas mumps virus infected principally endolymphatic structures. Rubeola and vaccinia viruses infected both perilymphatic and endolymphatic cells, whereas herpes simplex involvement was essentially limited to the sensory cells of the labyrinth.

Cytomegalovirus infection

Cytomegaloviruses (CMVs) are members of the herpes family that are widely prevalent in human populations in both developed and developing countries. Human CMV appears to be species specific with no known external reservoirs or animal vectors involved in transmission. CMVs may be transmitted either vertically (that is, from mother to child) or horizontally from person to person, and primary infection is accompanied by viral shedding that may persist for months to years. Congenital CMV infection differs from rubella and toxoplasmosis in that the virus can be transmitted in utero in the course of both primary maternal infection and infection resulting from reactivation of latent virus in immune women. The probability that her baby will have a harmful congenital CMV infection is decreased in the mother with recurrent infection, being approximately one ninth as great as after primary infection.

In populations of higher socioeconomic status (SES) approximately 55% of women of childbearing age are CMV immune, with the remaining 45% susceptible to primary CMV infection. In lower SES groups, fully 85% of fertile women demonstrate immunity.

About 1% to 4% of susceptible women will experience primary CMV infection during pregnancy, with a resultant fetal infection rate of 40%. Higher SES women with evidence of CMV immunity at conception will deliver infants with congenital infection in 0.15% of cases, whereas the congenital infection rate among offspring of immune lower SES mothers varies from 0.5% to 1.0% (Fig. 176-4). Although Hardy (1973) found that the gestational age of the fetus is the most important factor determining the extent and long-range consequences of congenital viral infections, the time of greatest susceptibility for CMV is not known.

CMV infection is endemic in child day-care centers, and transmission of the virus from young children who acquire CMV at such centers to their pregnant mothers is important epidemiologically.

Congenital CMV infection, which is definitely diagnosed by isolation of the virus from neonates in the first few weeks of life, is currently the most common cause of intrauterine infection in humans, occurring in approximately 1% of all live births. An additional 4% to 10% of infants acquire the infection during and after birth through such sources as cervical virus shedding, virus in breast milk, and blood transfusions. Perinatally infected infants usually begin to excrete virus between 3 and 12 weeks of age, making early viral isolation studies essential to the diagnosis of a true congenital infection. Of congenitally infected infants, 10% to 15% are symptomatic, and 90% of those demonstrate typical cytomegalic inclusion disease (CID), characterized by involvement of the central nervous system and reticuloendothelial system, with hepatosplenomegaly, petechiae, and jaundice as common presenting findings. Microcephaly, intrauterine growth retardation, and prematurity also characterize the CID population, which may experience a mortality rate as high as 30%. As many as 90% of children with true CID will develop severe mental and perceptual deficits by 2 years of age, including severe to profound sensorineural hearing impairment and such ocular abnormalities as chorioretinitis and optic atrophy in 25% to 30% of cases.

Before current viral isolation techniques were available, speculation regarding the dire outcome of congenital CMV infection was based solely on data from the 10% of congenitally infected infants who are symptomatic. Investigators were unaware of the large percentage of asymptomatic infected neonates. Such subclinical infections, which account for 90% of congenitally infected infants, may become apparent months to years after birth. Although prognosis for life with normal neurologic development among these infants is better, approximately 10% to 15% will develop significant SNHL, ranging from mild to profound. SNHL is the most common irreversible sequela of congenital cytomegalovirus infection, with an estimated 30% to 50% incidence in symptomatic cases and 10% to 15% in asymptomatic infants with congenital infection. It is bilateral in about 50% of cases, varying in magnitude from 50 to 100 dB. Stagno and coworkers (1982) found that nearly 25% of SNHL either develops or increases in severity after the first year of life, reiterating the need for longitudinal screening programs during the preschool years. With the vaccine-related decline in congenital rubella, congenital CMV infection is likely the most common cause of nongenetic congenital sensorineural deafness in developed countries. Whereas rubella occurs in epidemic cycles, CMV infection extracts an annually recurring toll on the newborn population. Thus far, research directed toward developing a clinically effective vaccine, as well as a safe and effective treatment regimen, has yet to bear fruit.

Histopathologic study of temporal bones of infants dying of CID has revealed characteristic inclusion bodies in the superficial cells of the stria vascularis, Reissner's membrane, the limbus spiralis, saccule, utricle, and semicircular canals. Although no inclusion-bearing cells were present in the organ of Corti, cristae, or ganglia, endolymphatic hydrops was noted to be present in at least a portion of each cochlear duct.

Congenital rubella

During the Australian rubella epidemic of 1941, the ophthalmologist Gregg (1941) first recognized the teratogenic potential of prenatal maternal infection; Swan and coworkers (1943) were first to describe deafness as a component of the rubella triad, along with congenital cataracts and heart defects. Initial estimates of fetal damage following first-trimester maternal rubella ranged from 16% to 59%. Following isolation of the rubella myxovirus in 1962, clinically applicable methods for confirmation of infection by serologic and virus isolation techniques became feasible. Laboratory-based case identification permitted documentation of subclinical rubella infection in expectant mothers, as well as confirmation of congenital rubella infection in infants who did not manifest all components of the classical rubella syndrome. During the 1963-1965 rubella epidemic in the USA, these laboratory methods for documenting the presence and timing of rubella infection led to the description of rubella-related disorders in addition to the classical triad. Included in the expanded rubella syndrome are deafness, eye defects, congenital heart defects, microcephaly, mental or motor retardation, newborn hepatosplenomegaly, thrombocytopenia, radiolucencies in long bones, interstitial pneumonitis, encephalitis, and low birth weight. Prospective studies were carried out by obtaining paired sera samples from pregnant women, thus pinpointing the exact timing of maternal rubella infection, clinical or subclinical. Of 165 laboratory-documented cases of maternal rubella in one study, 49% were clinically apparent and 51% were subclinical. Maternal rubella during the first trimester of pregnancy exacted the greatest toll on the fetus, but some offspring of mothers with second-trimester infection were also found to have deafness, microcephaly, cataracts, and mental-motor retardation. Infants with only one or two

components of the rubella triad were clearly demonstrated to be victims of congenital rubella infection.

Hearing loss was the single most common deficit in the laboratory-documented congenital rubella population, being the only defect found in 22% of cases. Among those infants from whom rubella virus was isolated, 57% had hearing impairment, whereas 41.5% of infants in whom only serologic confirmation could be obtained were hearing impaired. Approximately 30% of babies born of mothers with subclinical but laboratory-confirmed infection had hearing loss. The hearing loss was typically sensorineural in character, ranging in severity from patient to patient and to a lesser extent between the ears of the same patient. Some patients showed no response at any frequency, but the most frequently observed audiometric curves were of the "cookie-bite" type with greatest loss in the middle frequencies between 500 and 2000 Hz. Serial audiograms demonstrated a progressive decrease of auditory acuity in 25% of cases.

Prolonged virus shedding was observed in many infants who failed to thrive, most of whom were progeny of mothers with first-trimester rubella. Viral excretion can pose a hazard to rubella-susceptible health care and child care personnel interacting with infected babies. A general miniaturization of organs from rubella-infected fetuses and infants was noted at autopsy, and histopathologic examination revealed hypocellularity. Highly specialized cells, such as fiber cells in the lens of the eye, appear to become more susceptible to the effects of intracellular virus with increasing cellular specialization. As a consequence, gradual progression in cataract formation was noted in the postnatal period.

Temporal bone histopathologic findings in rubella infants include Scheibe-type cochleosaccular changes, but the utricle, semicircular canals, and spiral ganglion were unaffected. Partial collapse of Reissner's membrane with adherence to the stria vascularis and organ of Corti was observed in a number of cases. In some sections the tectorial membrane was found to be rolled and lying in the internal sulcus. Saccular collapse with histologic evidence of recent acute inflammation was documented in a number of temporal bones. The organ of Corti per se was relatively unaffected but the stria vascularis was noted to be smaller than normal and areas of cystic dilatation were observed at the junction of Reissner's membrane and the spiral ligament.

Before the availability of an effective rubella vaccine, epidemics in most developed countries occurred at 6- to 9-year intervals. Up to 60% of cases of newly identified deafness in infants and young children were attributed to prenatal rubella in epidemic years, falling to less than 1% in non-epidemic years. Widespread and, in some instances, mandatory administration of the rubella vaccine to children and nonpregnant women of childbearing age in the USA has markedly decreased the incidence of rubella. In some parts of the world, however, prenatal rubella still poses a threat to hearing, and it must be considered as an etiologic possibility in immigrant children with sensorineural hearing impairment.

Herpes simplex encephalitis

Herpes simplex encephalitis (HSE) is uncommon, but 25% to 30% of cases involve the pediatric age group. As anticipated in light of the rapidly rising incidence of genital herpes infection in women of childbearing age, recent studies reveal a tenfold increase in the incidence of neonatal HSV (herpes simplex virus) infection. A large percentage of HSV-infected neonates are born prematurely of young, often nulliparous mothers. Neonatal HSV patients may present with mucocutaneous involvement or disseminated infection, with one fourth to one third of the infants also affected by meningoencephalitis. On the other hand, up to 20% of newborns with HSV infection never manifest cutaneous involvement. The route by which the HSV reaches the brain during primary infection is not clear, although hematogenous dissemination, direct spread from the nasopharynx via the cribriform plate, and retrograde spread from infected ganglia have all been postulated. The infection has demonstrated a predilection for the temporal and frontal areas of the brain.

Herpes simplex meningoencephalitis, which has an incubation period ranging up to 4 weeks, is most likely to occur in the second or third postpartum week. Epidemiologically, only 50% of neonatal HSV infections can be related by history to a definite maternal or paternal infection, so that the absence of a positive history does not exclude the disease. Nonspecific clinical findings, including fever and an altered mental state, are accompanied by abnormal CSF findings in over 90% of patients. Electroencephalography and imaging studies, computerized tomographic scanning, and magnetic resonance imaging are of benefit in detecting focal meningoencephalitis. Brain biopsy, which is positive in 33% to 55% of HSE cases, represents the only definitive means of diagnosing HSE, as well as excluding other disease processes that may mimic the condition. Chemotherapy for HSE involves the antiviral drug acyclovir for a 10- to 14-day period. Clinicians caring for a child with undiagnosed focal encephalitis are advised to introduce broad-spectrum antimicrobial therapy, in addition to acyclovir, until definitive diagnostic tests have been completed. Effective team management of a child with HSE requires the involvement of neurologists, neurosurgeons, pulmonologists, intensivists, and infectious disease specialists.

Congenital toxoplasmosis

Toxoplasmosis is spread by the ingestion of oocysts on food contaminated by cat feces or consumption of tissue cysts in undercooked meat products, as well as by congenital transmission. The cat is the definitive natural host for the protozoan organism *Toxoplasma gondii*, and ingested feline fecal material containing oocysts leads to the liberation of organisms that invade human intestinal mucosa and are widely disseminated. Cysts may be formed in all tissues of the body including the human placenta, through which fetal infection occurs. Except in immunocompromised mothers, fetal infection is usually the result of primary maternal infection during gestation. Although the incidence of fetal infection is greater if maternal infection occurs during the third trimester, greater fetal damage follows first-trimester infection. Two clinical forms are recognized, the more common neurologically dominant type and a disseminated variant with multiple organ system involvement. Clinical presentation of congenital *Toxoplasma* infection may include chorioretinitis, hydrocephalus, and generalized intracranial calcifications. Such infants have a very poor prognosis for normal development. In 90% of cases, congenital toxoplasmosis is subclinical and must be confirmed by laboratory studies. If subclinical infection is unrecognized and consequently untreated,

there is a high likelihood of subsequent chorioretinitis with decreasing visual acuity, progressive CNS involvement with decreased intellectual function, deafness, and precocious puberty.

French investigators conducted extensive studies of pregnancies at risk for congenital toxoplasmosis, and compulsory programs for the identification of seronegative women early in pregnancy have been implemented in that country (Daffos, 1988; Decoster et al, 1988; Desmots and Couvreur, 1974; Stepick-Biek, 1990). Maternal infection is confirmed by the appearance of specific IgG in a previously seronegative patient or a rising IgG titer after a 3-week or greater interval. Prompt and intensive maternal treatment with a combination of pyrimethamine plus a sulfonamide of the sulfapyrimidine type is advocated as a means of decreasing the likelihood and mitigating the effects of fetal infection. Prenatal diagnosis of fetal infection is accomplished by acquisition of amniotic fluid through amniocentesis and fetal blood samples from the umbilical cord under ultrasound control. Inoculation of fetal blood and amniotic fluid into mice, IgM immunosorbent assays, and quantitative maternal and fetal IgG studies are utilized to document the presence of fetal infection. In the French studies, which included prenatal treatment of maternal infection, congenital infection occurred in 0.6% of cases with documented maternal infection during the preconceptual/early pregnancy period, in 3.7% of fetuses carried by mothers who were infected from the sixth to the sixteenth week of gestation, and in 20% of infants born after maternal infection during the sixteenth through the twenty-fifth week of pregnancy. The relatively low incidence of fetal infection among the 16- to 25-week group was 70% less than reported in previous studies, demonstrating that adequate treatment of primary maternal infection during pregnancy reduces the likelihood of transmission to the fetus. Extended treatment is also advocated for congenitally infected infants, in the form of alternating courses of pyrimethamine and sulfonamide. Infected infants should receive very careful follow-up, including CT scans to assess central nervous system status and ophthalmologic examination for chorioretinitis. French investigators found that treatment of congenitally infected infants, begun at birth, reduced the frequency of chorioretinitis from 60% to 10%.

Accurate incidence figures for congenital toxoplasmosis in the USA are elusive, with estimates ranging from 1:1000 to 1:8000. It is estimated that as many as 85% to 90% of American women of childbearing age may be previously uninfected and consequently at risk for primary infection. The most effective strategy for control of fetal damage is prevention of maternal infection by careful attention to hygienic measures, including cleaning of fruits and vegetables and thorough cooking of meat products. Expectant mothers should be especially careful when cleaning cat litter boxes. Careful serologic testing of women at the time of diagnosis of pregnancy and during prenatal visits will facilitate accurate identification of seroconverters and prompt institution of maternal treatment during pregnancy. Prenatal and neonatal evaluation of the fetus and infant can document congenital infection so that postnatal treatment can be instituted as early as possible. Longitudinal follow-up studies in France should further demonstrate the effectiveness of recommended treatment regimens in preventing sequelae, including deafness.

Syphilis

Congenital syphilis, resulting from the transplacental transmission of the causative organism *Treponema pallidum* to the fetus after the fourth month of gestation, may be manifest at birth or may be inapparent until as late as the fifth decade of life. Recent reports indicate a rapid increase in the number of acquired and congenital syphilis cases. There is evidence that concurrent human immunodeficiency virus (HIV) infection in patients with acquired syphilis may increase the likelihood of early progression to neurosyphilis and be associated with failure to respond to penicillin therapy. Although SNHL has been reported in patients with primary, secondary, and later acquired syphilis, the primary concern in children is congenital infection.

Classic stigmata of congenital syphilis include deafness, interstitial keratitis, Hutchinson's teeth (notched incisors), and nasal septal perforation. Prevalence estimates of hearing loss among patients with congenital syphilis range from 3% to 38%, with about 37% of cases presenting before 10 years of age, 51% between 25 and 35 years of age, and 12% becoming apparent even later in life. In some instances, sensorineural hearing loss may be the only presenting symptom. A commonly reported audiometric configuration is a bilateral, flat sensorineural hearing loss, which may present in children as a sudden, bilateral profound impairment, usually without vertigo. In late congenital syphilis the hearing loss may be sudden, asymmetric, fluctuating, or progressive, accompanied in many cases by episodic tinnitus and vertigo. Speech discrimination scores tend to be poorer than expected from the audiometric configuration, loudness recruitment severe, and caloric responses weak to absent. A positive labyrinthine fistula test may be present (Hennebert's sign), and Tullio's phenomenon (dysequilibrium in response to loud sounds) may be observed.

Because any attempt to carry out direct dark-field examination of perilymph for *Treponema pallidum* would present an unacceptable risk of additional hearing loss, serologic tests present the best alternative means for diagnosing otosyphilis. *Treponema pallidum* infection gives rise to both nonspecific reagin antibody and specific antitreponemal antibodies. Nonspecific tests are utilized for screening large numbers of patients from low-incidence populations, such as state-required tests of cord blood from all newborns. On the other hand, reports from large otologic centers indicate a prevalence of 570/100,000 of presumed otosyphilis among otologic referrals, justifying the use of more expensive treponema-specific procedures. The most widely utilized treponema-specific test is the fluorescent treponema antibody absorption test (FTA-ABS) with a high sensitivity rate to all stages of syphilis and a low rate of false-positive results; the specificity rate approaches 98% in large studies. Most instances of false-positive results involve autoimmune or drug-induced collagen vascular diseases, such as systemic lupus erythematosus. Other treponema-specific tests that may be used to confirm FTA-ABS results are the micro-hemagglutination assay for *T. pallidum* (MHA-TP) and the *T. pallidum* inhibition test, a complex and costly but highly specific (99%) procedure. Because the treponema-specific tests may remain positive following adequate treatment, Birdsall and coworkers (1990) introduced a western blot assay to identify antitreponemal antibody isotype and determine whether or not the infection remains active. In the presence of active infection, both antitreponemal IgM and IgG antibodies are present. After successful treatment, only IgG antibodies persist.

High-dose parenteral penicillin is the treatment of choice in all nonallergic patients with a presumptive diagnosis of otosyphilis, and consideration must be given, in dosage determination, to the potential limits on penicillin diffusion posed by the blood-CSF and blood-perilymph barriers. The discovery that treponemes may lie dormant for as long as 90 days between replications in late congenital syphilis cases dictates the necessity for longer-term treatment schedules than formerly recommended. Current recommendations for dosage and treatment course may be found in publications from the Centers for Disease Control, which should be consulted before initiating therapy.

As an adjunct to adequate antimicrobial therapy, systemically administered corticosteroids (generally oral prednisone) have demonstrated effectiveness in stabilizing or improving hearing in approximately 50% of patients with syphilitic deafness. Greater improvement is usually observed in speech discrimination scores than in pure-tone thresholds. The mechanisms of steroid action in these cases are uncertain but may involve nonspecific reduction of vasculitis, suppression of immune reaction to spirochetal antigens, or enhancement of penicillin diffusion into the perilymph. Relative contraindications to steroid therapy include lack of immunity to varicella, recent vaccination, hypertension, diabetes mellitus, glaucoma, pregnancy, and peptic ulcer disease. Fatal cases of varicella have been reported in young children receiving steroid therapy, and careful case selection is essential. Steroids, initially administered in a gradually tapered dosage regimen, are usually discontinued after 4 to 8 weeks if hearing does not improve. On the other hand, long-term maintenance therapy may be required to sustain hearing improvement. Alternate-day dosage appears to carry less risk of sequelae, such as cataract formation, bone growth disturbance, and adrenal suppression.

Temporal bone histopathologic features in cases of congenital otosyphilis include obliterative endarteritis, as well as mononuclear cell infiltrates, osteitis of the otic capsule, and varying degrees of tissue necrosis. Early congenital syphilis may involve the labyrinth, as well as the eighth nerve, with round cell infiltration but may also present as a meningolabyrinthitis. Osteitis of the temporal bone with secondary involvement of the membranous labyrinth can also be found in late congenital otosyphilis. Atrophy of the organ of Corti, as well as involvement of the stria vascularis, spiral ganglion, and eighth nerve fibers, has been reported. Gummatous changes may be found in all bones of the ear including the ossicles, which may add a conductive component to a preexisting sensorineural hearing loss.

Neonatal sepsis

Neonatal sepsis, characterized by signs of infection and septicemia in the first month of life, carries a significant mortality, ranging from 10% to 50%, with an inverse relationship to the age and weight of the child. The bacterial pathogens involved may vary from center to center, but group B streptococci and gram-negative enteric bacilli are most commonly observed. Meningitis is a common outcome of bacteremia in these infants, and uncommon organisms such as *Listeria monocytogenes* may play a significant role in such cases. Postmeningitic deafness should be suspected in all survivors of neonatal meningitis, and appropriate evaluation with techniques such as auditory brain stem response testing should be undertaken.

Later-onset infectious disease

Mumps and measles

Measles and mumps immunization as part of standard well-baby care has effected a 90% to 95% decrease in the incidence of these diseases in the USA. Before the availability of an effective vaccine for mumps, the most common otologic sequela attributed to this virus was unilateral profound SNHL or unilateral anacusis without vertigo or vestibular impairment. Data from adults suggest that the time of onset of mumps hearing loss is usually within a few days after the disease has reached the acute stage.

Two distinct pathogenetic mechanisms have been implicated in SNHL as a sequela of measles or mumps. In cases of SNHL without signs of meningoencephalitis, the virus appears to access the inner ear via the stria vascularis during viremia. Sluggish strial circulation, coupled with an intraepithelial capillary network, predisposes to the onset of inflammation in this structure, which is followed by degeneration and scarring. The resultant change in the volume and constitution of endolymph has been invoked to explain subsequent degeneration of the stria vascularis, the organ of Corti, the tectorial membrane, and peripheral cochlear neurons, proceeding from the cochlear base to the apex. Collapse of Reissner's membrane with adherence to underlying structures has also been described. The perilymphatic system, the vestibular sensory organs, and the internal auditory canal contents are generally uninvolved. These histopathologic changes are also compatible with findings in cases of SNHL caused by prenatal rubella.

Temporal bone findings in patients who suffered meningoencephalitis in conjunction with measles or mumps are substantially similar to those associated with meningogenic bacterial labyrinthitis. It appears that direct extension of the viral inflammatory process occurs along the nerves and vessels in the internal auditory meatus into the inner ear. Findings compatible with such a transmeatal route of infection include severe degeneration of neural elements in the modiolus, contrasted with lesser degrees of involvement of neural structures in the cochlear duct. Temporal bones from infants who died during the acute stage of meningoencephalitis demonstrate lymphocytic infiltration along nerves and vessels in the internal auditory canal without concurrent involvement of the stria vascularis. Intralabyrinthine fibrosis and osteoneogenesis in perilymphatic spaces were found in patients who had survived the acute disease process.

Bacterial meningitis

Bacterial meningitis in young children was associated with a 90% to 100% mortality during the preantibiotic era. By 1986, clinical investigators reported a mortality of 2% to 3% among children over the age of 1 month with bacterial meningitis that had been adequately treated. In cases of neonatal meningitis, *Escherichia coli* and group B beta-hemolytic streptococci are the most common causative organisms. The highest percentage of childhood meningitis cases in the USA occur in children 6 to 9 months of age, with *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae* collectively accounting for 84% of cases. Among this group of infants, *H. influenzae* is the most commonly isolated pathogen.

Unfortunately, the dramatic decline in mortality was not accompanied by a concomitant decrease in the incidence of immediate and long-term sequelae of the disease. Seizures are experienced by 28% to 40% of meningitis patients before or during their hospital stay, and at least one handicap was detected during a 1-year follow-up in 57% of pneumococcal meningitis survivors and 14.5% of children in which *H. influenzae* was the etiologic agent. Apart from sensorineural hearing impairment, meningitis sequelae may include mental retardation, hydrocephalus, seizure disorders, motor abnormalities (hemiparesis, diplegia, quadriplegia, cerebral palsy), vestibular deficits, speech defects, language disorders, hyperactivity, poor impulse control, visual impairment, and learning disabilities. Computerized tomographic imaging studies of the CNS in children with severe sequelae reveal evidence of brain infarction, arterial occlusion, and brain/spinal cord necrosis.

The reported incidence of SNHL following meningitis varies from 3% to 40%, with most reports clustered in the 15% to 20% range. In my series of 280 meningitis survivors, 89% of those who experienced postmeningitic hearing loss contracted the disease before their third birthday (Brookhauser et al, 1988). The majority of patients with post-meningitic hearing loss sustain permanent, bilateral, severe-to-profound sensorineural impairment, but in a series of 64 carefully documented cases, coworkers and I found 38% to have bilateral, asymmetric SNHL and 11% to have unilateral SNHL. Some reports have documented improvement in hearing acuity in a small number of cases observed longitudinally, whereas in other patients hearing losses fluctuated or progressed. These reports can be broadly classified into those using behavioral audiologic tests and those using primarily ABR (Tables 176-1 and 176-2).

A number of observations can be drawn from these studies. The onset of hearing loss associated with bacterial meningitis usually occurs early in the course of the disease, and no particular regimen of antibiotic therapy appears to offer any degree of protection against this sequela. These findings are consistent with recent observations regarding the role that the host's initial inflammatory response may have in damage sustained by neural tissue. Direct spread of the infection to the labyrinth from the middle ear during a bout of otitis media is much less likely than (1) the penetration of bacteria and toxins along the cochlear aqueduct or internal auditory canal leading to a suppurative labyrinthitis, perineuritis, or neuritis of the eighth nerve; (2) serous or toxic labyrinthitis that constitutes a sterile inflammatory response; (3) septic thrombophlebitis or embolization of small labyrinthine vessels; and (4) hypoxic insult to the eighth nerve or central auditory pathways.

Meningitis patients who exhibit normal ABR after the first few days of hospitalization and antibiotic therapy are unlikely to develop later SNHL. Late-onset SNHL, after discharge from the hospital, is also distinctly uncommon. Some patients whose ABR results are abnormal early in their hospital course may demonstrate a normal ABR by the time of discharge or in follow-up evaluation. These observations may, in some cases, reflect the resolution of a co-existing conductive loss caused by middle ear effusion. Most patients with postmeningitic losses who show improvement of auditory thresholds over time initially demonstrate mild or moderate, rather than severe or profound, SNHL. Thresholds in patients who exhibit improvement, deterioration, or fluctuation of auditory acuity often require a year or more to stabilize following meningitis. Some patients with improving thresholds continue to exhibit absent vestibular responses. The likely pathophysiologic explanation for changing bone conduction thresholds during and after an episode of bacterial meningitis is the occurrence of serous labyrinthitis. All meningitis survivors should have careful evaluation of

auditory function, initially by ABR in younger children, to be followed by behavioral audiologic testing when the child's condition permits. Because postmeningitis hearing losses may assume a wide range of audiometric configurations, click-evoked ABR, which assesses hearing sensitivity primarily in the high-frequency region (2000 to 4000 Hz) may lead to erroneous conclusions regarding auditory acuity at lower frequencies. Careful longitudinal follow-up of postmeningitis children will avoid diagnostic errors.

Neurologic sequelae of bacterial meningitis, including sensorineural hearing loss, may be attributable to direct bacterial action on nervous tissue, the patient's inflammatory response, or a combination of both factors. Studies of the progression of events at the molecular level during an episode of bacterial meningitis suggest that significant injury to the central nervous system occurs during the first hours of antibiotic therapy. Experimental animal models demonstrate that bacterial surface components, including endotoxin and cell wall structures, are sufficient to produce the symptom complex of meningitis even in the absence of viable bacteria. Bacterial disintegration resulting from antibiotic action produces a veritable flood of cell wall antigens and endotoxins, stimulating an intense immunologic response by the host. The damage attributable to such an inflammatory reaction was first demonstrated in animal studies of pneumococcal meningitis and later with gram-negative pathogens. Reports involving neonates and young children with meningitis have also documented a rapid host inflammatory response following antibiotic-induced release of bacterial components. It is hypothesized that inflammatory exudate that forms as a result of meningeal invasion by bacteria is potentially harmful and is not critical for containment of the infection. By studying paired CSF samples drawn at admission and 18 to 30 hours later, clinical investigators have found a correlation between the intensity of inflammation as reflected in CSF findings and subsequent clinical outcome. Poorer outcome observed in neonates receiving intraventricular gentamicin rather than just intravenous antibiotics may also be attributable to the patient's response to an additional load of bacterial degradation products in the CSF.

The local production of interleukin-1B (IL-1B) and tumor necrosis factor (TNF) in response to CNS tissue interacting with bacterial breakdown products is thought to be the first step in a complex series of molecular events that result in inflammation and tissue destruction. Based on the hypothesis that down-modulation of the host inflammatory response could ameliorate the severity of postmeningitic sequelae, corticosteroids have been used as adjunctive therapy to the usual course of bactericidal antibiotics. Corticosteroids act to inhibit the activity of phospholipase with a consequent decrease in prostaglandin E₂, thromboxane, and leukotriene formation. Dexamethasone has also been shown to decrease the production of IL-1B and TNF. In double-blind, placebo-controlled trials with bacterial meningitis patients, CNS indices of infection severity, such as decreased glucose levels, elevated protein, and increased lactate levels, were significantly less pronounced after 24 hours of combined therapy with antibiotics and dexamethasone than with antibiotics alone (Odiro et al, 1991; Laebel et al, 1988). In a population of 200 infants and older children, patients receiving dexamethasone became afebrile earlier and were less likely to suffer moderate to severe sensorineural hearing loss than controls. Fourteen percent of patients in the placebo group had severe or profound hearing loss, whereas only 1% of the steroid-treated group were affected (Laebel et al, 1988). Because of a natural reluctance by some clinicians to administer steroids in the face of a potentially life-threatening infection, other strategies for downmodulating host response to the infection are being explored in current studies.

Ototoxic Drugs and Chemicals

As a result of more accurate reporting of adverse effects of pharmaceutical agents mandated by federal regulations, a steadily increasing number of potentially ototoxic drugs and chemicals are being identified. Some medications, such as thalidomide, taken early in pregnancy produce severe embryopathic effects that may include deformities of the external, middle, or inner ear with associated sensorineural hearing loss. Other ototoxic drugs and chemicals produce more profound effects after the sensory end-organ of the inner ear has reached a greater degree of differentiation later in pregnancy.

A partial listing of drugs and chemicals with ototoxic potential follows:

1. Antibiotics
 - a. Streptomycin
 - b. Dihydrostreptomycin
 - c. Neomycin
 - d. Gentamicin
 - e. Kanamycin
 - f. Vancomycin
 - g. Polymyxin B
 - h. Erythromycin

2. Chemicals
 - a. Carbon monoxide
 - b. Mercury
 - c. Gold
 - d. Lead
 - e. Arsenic
 - f. Aniline dyes

3. Loop diuretics
 - a. Ethacrynic acid
 - b. Furosemide

4. Other drugs
 - a. Cisplatin
 - b. Quinine
 - c. Chloroquine
 - d. Salicylates
 - e. Polybrene
 - f. Nitrogen mustard
 - g. Thalidomide.

Aminoglycosides

Aminoglycoside antibiotics are administered parenterally because they are poorly absorbed from the gastrointestinal tract, with only 3% actually entering the bloodstream. Normal serum half-life is about 2 hours in patients with unimpaired renal function. This class of antimicrobials is not metabolized in the body and is excreted almost entirely by glomerular filtration so that urinary concentrations can approach 100 times serum levels if renal function is impaired. Hemodialysis and peritoneal dialysis are effective in lowering serum levels in renal-compromised patients. It has been documented that aminoglycosides may also accumulate in the perilymph, particularly in patients with suboptimal renal function. Schacht (1986) demonstrated that the drugs are transmitted into hair cells by an energy-dependent process involving binding to the phospholipid phosphatidyl-inositol biophosphate. Histopathologic evidence of injury has been observed in the stria vascularis, suprastrial spiral ligament, pericapillary tissues in the spiral prominence, the outer sulcus, and Reissner's membrane. Cochlear damage usually proceeds from the basilar turn toward the apex with initial destruction being observed in the inner row of outer hair cells. Although the remaining rows of outer hair cells may also be destroyed, inner hair cells are usually spared except in cases of overwhelming toxicity. In the vestibular system, type I hair cells of the crista ampullaris appear to be more sensitive to damage by streptomycin, kanamycin, and gentamicin than type II.

Streptomycin, gentamicin, and tobramycin are primarily vestibulotoxic, whereas kanamycin and amikacin are principally cochleotoxic. Fee (1980) observed that gentamicin was significantly more vestibulotoxic than tobramycin, the toxicity being further potentiated by high hematocrit, elevated creatinine clearance, criticality of illness, and duration of therapy beyond 10 days. The margin between therapeutically effective blood levels and potentially toxic concentrations for aminoglycosides is relatively small, so that careful monitoring of peak serum levels (30 minutes after intravenous administration) and trough levels (immediately before the next IV dose) is essential. Dosage levels must be adjusted downward appropriately in patients with renal dysfunction. In addition to compromised renal function, other factors thought to predispose to aminoglycoside ototoxicity include preexisting hearing loss, temporally related noise exposure, age, duration of therapy, prior use of aminoglycosides, or concomitant use of additional ototoxic drugs such as other aminoglycosides and loop diuretics (for example, ethacrynic acid and furosemide).

Aminoglycosides are utilized with some regularity to treat serious infections in neonates and young infants, but controversy exists as to the inherent risk posed to hearing and balance function. On the basis of extensive studies, Finitzo-Hieber and colleagues (1985) concluded that aminoglycosides at appropriate dosage levels pose little risk of ototoxicity in children. Eviatar and Eviatar (1982), however, conducted controlled prospective studies of infants receiving aminoglycosides for neonatal sepsis, evaluating such parameters as acquisition of head control and nystagmus induced by position change, perrotatory stimulation with a torsion swing, and caloric irrigations. Nearly 10% of the infants who had received aminoglycosides demonstrated vestibular abnormalities and delay in acquisition of head control as would be compatible with vestibulotoxicity. Prolonged administration of the drugs (that is, 25 to 45 days) increases the risk of damage as does concomitant administration of other ototoxic drugs. Serial audiometric screening, including frequencies above 12,000 Hz, and vestibular evaluation may be of benefit for providing early warning of impending damage.

Some investigators report partial return of vestibular function after an initial deficit has been demonstrated during extended gentamicin therapy.

Loop diuretics

Powerful "loop" diuretics, such as ethacrynic acid and furosemide, promote the rapid excretion of large amounts of isoosmotic urine. Early clinical observations of a transient ototoxic effect associated with the use of these agents were followed by reports of permanent ototoxicity, particularly when these diuretics are used concurrently with apparently safe levels of aminoglycosides. Estimates of the incidence of ototoxic effects with this class of pharmaceuticals reported by Matz (1990) range from 0.7% with ethacrynic acid to 6.4% with furosemide. Temporal bone histopathology in animals treated with toxic levels of these drugs reveals changes in the stria vascularis and significant hair cell loss, Rybak and coworkers (1990) postulate that furosemide and ethacrynic acid have different mechanisms of action on the cochlea. Because of the repeatedly documented synergy between the ototoxic effects of loop diuretics and aminoglycosides, the respective dosages of these medications should be carefully adjusted when they are administered concurrently.

Erythromycin

The ototoxic potential of erythromycin became evident with the relatively large intravenous dosage levels utilized to treat pneumonia caused by *Legionella pneumophilla*. Bilateral SNHL, often accompanied by tinnitus and vertigo, was noted in adults with erythromycin doses of 2 g/day, particularly in patients with concomitant renal or hepatic failure. Blood levels at which ototoxic effects were observed ranged upward from 63 mg/L.

Salicylates

High therapeutic doses of salicylates (levels exceeding 20 mg/dL) are known to be associated with reversible hearing loss and tinnitus in humans. Hawkins' work (1973) demonstrated that salicylates in the perilymph can lead to a reduction in transaminases, cochlear adenosine triphosphate levels, and cochlear blood flow. Changes in cochlear function have been attributed to a salicylate-mediated increase in the membrane conductance of outer hair cells. The association of the ingestion of therapeutic doses of salicylate in young febrile children with the occurrence of Reye's syndrome has led to a marked decrease in the utilization of this class of drugs in the pediatric and adolescent age groups without strict indications.

Vancomycin

Nephrotoxicity and ototoxicity have been reported in patients receiving vancomycin, particularly if blood levels exceed 45 mg/L. Adults have described tinnitus at slightly lower serum levels, which could serve as early warning of impending damage. Matz (1990) reports that premature infants are more susceptible to the ototoxic effects than full-term babies because they have larger volumes of distribution of the drug, which has a longer half-life in these neonates.

Cisplatin

Cisplatin (cis-diaminoedichloroplatinum), which is utilized for treating a range of neoplasms, has been implicated as an ototoxic agent, with the potential for permanently affecting both cochlear and vestibular function. Studies employing serial high-frequency audiometry demonstrate that the hearing loss usually begins in the 10.000 to 18.000 Hz range, gradually involving frequencies below 8.000 Hz if treatment continues. Audiometric screening at 12.000 Hz and 14.000 Hz has proven helpful in early identification of ototoxicity. The pathophysiologic mechanism by which damage occurs involves drug-mediated blockade of outer hair cell transduction channels, coupled with a decrease in adenylate cyclase. Histopathologically, outer hair cell loss is observed, particularly in the basal turn of the cochlea. Estimates of the risk of ototoxicity posed by cisplatin vary with the audiometric frequencies that are evaluated. Early estimates placed the risk at 20% or less. In a study evaluating thresholds from 8 to 20 kHz, Dreschler and colleagues (1985) utilized conservative criteria for damage, including deterioration of 20 dB or more at one frequency, 15 dB at two frequencies, or 10 dB at four frequencies. They found that 46% to 83% of patients in the various study groups demonstrated some degree of loss, principally at higher frequencies. Eighty percent of these losses were bilateral, with the remainder having unilateral involvement. Most investigators agree that dosage levels exceeding 3 to 4 mg/kg of body weight carry a definite risk of ototoxicity. In one report of 54 cases, no ototoxic changes were noted in patients where the peak plasma concentration of cisplatin did not exceed 1 microg/L. Davidson and coworkers (1989) reported that permanent, bilateral, high-frequency sensorineural hearing loss was detected in 88% of children receiving cisplatin doses over 450 mg/m². Cochlear damage, which was related to cumulative doses exceeding 279 mg/m², was inversely proportional to the age of the child. Animal studies have confirmed that the ototoxic effects of noise exposure (85 dB SPL or greater) and cisplatin are synergistic, producing greater hair cell loss and hearing impairment at high frequencies in combination than is observed with either agent alone. Although conclusive human studies addressing this issue are not available, prudence would dictate avoidance of exposure to potentially damaging sound levels during cisplatin treatment.

Quinine and chloroquine

The antimalarial agents quinine and chloroquine phosphate have both demonstrated ototoxic potential. Mothers receiving quinine during pregnancy may give birth to infants with varying degrees of severe to profound hearing impairment. Both retinopathy and hearing loss have been observed in offspring of pregnant mothers treated with chloroquine. The pathophysiologic mechanism involved with both drugs appears to be vasculitis and ischemia in the inner ear, with subsequent degenerative changes of the stria vascularis, organ of Corti, and neuronal elements.

Anoxia/Hypoxia

Anoxia and hypoxia during the perinatal period, resulting from such factors as cord compression and neonatal seizures, are strongly correlated, statistically, with subsequent SNHL in young adults. Objective evidence of anoxia/hypoxia in the neonatal history can include meconium staining, primary apnea, a history of resuscitation at birth, low Apgar scores at 1 and 5 minutes, postnatal apneic episodes, and the need for prolonged postnatal

ventilatory assistance. Histopathologic evidence demonstrates that anoxic damage occurs in the brain stem reticular formation and cochlear nuclei, which show decreased cell numbers and volume in direct proportion to the length and severity of oxygen deprivation. In some cases of perinatal anoxia, infants may have multiple high risk factors, making the precise role of oxygen deprivation in the etiology of hearing loss unclear. On the other hand, recent studies among neonates with chronic hypoxemia resulting from persistent fetal circulation revealed a 20% incidence of SNHL, three fourths of which was moderate to severe and one fourth of which was profound.

Hyperbilirubinemia

A causal relationship between elevated bilirubin levels in neonates, with associated kernicterus, and SNHL has been appreciated for decades. Whether resulting from inadequate conjugation, impaired albumin binding, or increased unconjugated bilirubin production, the bilirubin that crosses the blood-brain barrier may be deposited in the basal ganglia, particularly the ventrocochlear nucleus, resulting in neurologic sequelae including SNHL. Histopathologically, the middle and inner ears of these patients are generally free of abnormality. Improved prenatal care including the introduction of Rh immunoglobulin, exchange transfusion, and phototherapy has markedly decreased the importance of hyperbilirubinemia as a cause of early acquired SNHL. Recent studies suggest that therapeutic intervention should be instituted at lower serum bilirubin levels in premature neonates than was previously thought necessary.

Prematurity and Full-Term Low Birth Weight

Although a number of high risk factors, such as perinatal hypoxia, sepsis, and kernicterus, may be present in premature and dysmature neonates, prematurity itself constitutes a reliable risk indicator. Admission to a neonatal intensive care unit (NICU) is standard care for these small infants, and NICU outcome studies reveal that premature infants may be as much as 20 times more likely to be severely hearing impaired than infants of normal weight and gestational age. As many as 2% of all infants with birth weight of 3 pounds or less manifest significant SNHL. Audiologic evaluation and habilitation of these hearing impaired infants may be further complicated by the presence of additional handicaps.

Recurrent Otitis Media and Mastoid Disease

Conductive hearing loss is the usual sequela of recurrent otitis media and mastoiditis, but studies by Paparella et al (1970, 1984) and others indicate that otitis-prone children showed an increased likelihood to have a coexisting sensorineural loss than would be predicted by incidence figures for the general population. Mechanisms postulated to account for this observation include penetration of the labyrinthine windows (particularly the round window membrane) by infectious by-products or toxins, topical medications with ototoxic potential, or a combination thereof. Studies of round window permeability in experimental animals suggest a greater risk for penetration by middle ear contents into the inner ear than has been observed empirically in humans. It has been postulated that edema and granulation tissue that accompany middle ear infection may actually help prevent transmission of unwanted substances through the round window membrane.

Ear and Head Trauma

Middle ear and inner ear trauma can result from diverse etiologies, including a slap in the ear, a foreign body (for example, cotton swab) inserted in the external canal, impact against water while diving or water skiing, and skull trauma, which may include temporal bone fracture. An infant's foreshortened ear canal can predispose to transcanal injury, whereas head trauma is a more common etiology in older children and adolescents. Youngsters may be able to report symptoms such as acute pain, bloody otorrhea, hearing loss, tinnitus, and possibly vertigo. Mild to moderate conductive hearing loss is the most common audiometric finding, but intralabyrinthine injury may produce a concurrent, usually high-frequency, sensorineural component. More severe conductive impairment suggests possible ossicular damage, and labyrinthine membrane disruption, including perilymphatic fistula, should be suspected in patients with fluctuating or progressive sensorineural losses. Large traumatic tympanic membrane perforations, particularly if accompanied by ossicular injury, may require surgical intervention, but most heal with surprisingly little residual scarring.

Motor vehicle accidents, bicycle or skateboard mishaps, and falls are among the common etiologies for temporal bone fractures in children and adolescents. Such fractures are broadly classified as longitudinal or transverse with respect to the long axis of the temporal bone, with the longitudinal variety accounting for 70% to 90% of these injuries. Longitudinal fractures are associated with middle ear and ossicular damage, usually sparing inner ear and internal canal structures. Transverse fractures often disrupt labyrinthine integrity or transect neural structures in the internal auditory canal, leading to permanent sensorineural deafness or facial nerve paralysis, as well as vertigo.

Temporal bone fractures have been reported to occur in 7% of children who were admitted to the hospital following head injury, and 13% of these patients sustained SNHL. In a group of 324 children and adolescents with unilateral SNHL, 10.8% of losses were attributed to head trauma, which in 35% of cases had been sustained at or before 6 years of age.

Noise-Induced Hearing Loss

Sounds of sufficient loudness and duration will produce ear damage resulting in temporary or permanent hearing loss, often accompanied by tinnitus. Irreversible inner ear damage from loud sounds is cumulative over time, can occur at any age, and is not presently amenable to medical or surgical treatment. An important consequence of a typical noise-induced hearing loss (NIHL) is difficulty in understanding speech sounds, which could impair classroom performance. Utilizing current knowledge about ear protection, NIHL is entirely preventable except in rare cases of accidental exposure.

About 10,000,000 Americans have hearing losses that are at least partly attributable to damage from loud sounds. More than 20 million Americans, including children and adolescents, are exposed on a regular basis to hazardous sound levels that could result in hearing loss. Much of this noise exposure occurs in the workplace, but the proliferation of potentially harmful noise sources at home, on the farm, and in recreational environments has placed increasing numbers of unsuspecting children and adolescents at risk (Table 176-3).

Table 176-3. Loud noises signal danger

	dB	Noise
D	140	Firecrackers, gunshot blast, jet engine
A	130	Jackhammer
N	120	Boom cars, band practice, headphones, and rock concerts
G	110	Shouting in ear, disco, chain saw
E	100	Snowmobile, subway, woodworking shop
R	90	Traffic, lawn mower, motorcycle, orchestra
85 dB-----		
	80	Alarm clock, hair dryer, assembly line
	70	Restaurant, vacuum cleaner, sewing machine
	60	Conversation, air conditioner
	50	Average home, refrigerator
	40	Principal's office
	30	Quiet library, soft whisper.

Current US Department of Labor regulations set the boundary between acceptable and damaging noise in the workplace at 85 dB(A) for continuous exposure during a full workday. Because the decibel scale is exponential, a change of a few decibels can represent a significant change in loudness, for example, a 20 dB sound is 10 times as loud as a 10 dB sound. The "A" refers to a type of sound filter used in a sound level meter when measuring potentially damaging sound in the laboratory or workplace. These devices can measure both continuous loud noise, as produced by amplified music, and intermittent, short-duration noises with very loud peak components, as exemplified by gunfire or a firecracker. Individual susceptibility to the damaging effects of loud sounds is variable, so that it is difficult to predict the precise magnitude of hearing loss that will result from exposure of a specific individual to a potentially damaging sound. Damage risk criteria are based on the average responses of large numbers of subjects.

Ear damage resulting from exposure to hazardous noise levels may be classified as either acoustic trauma or noise-induced hearing loss (NIHL). The pattern of damage resulting from a specific exposure to a particular sound source depends on the frequency, content, intensity (that is, loudness), duration, and scheduling (that is, continuous or intermittent) of the exposure, as well as the susceptibility of the ear involved. Exposure to intense sounds (greater than 140 dB(A) of short duration, such as gunfire or an explosion, can produce immediate, severe, and permanent hearing loss, which is termed acoustic trauma. By means of direct mechanical destruction, such high-intensity sound waves can disrupt virtually any structure in the ear, ranging from the tympanic membrane and ossicles to the organ of Corti.

Moderate exposure to less intense but potentially damaging sounds may cause a temporary threshold shift (TTS). With additional exposure, NIHL gradually becomes permanent, initially involving frequencies in the 3,000 to 6,000 Hz range, as reflected in a characteristic "notch" audiometric configuration. Experimental evidence indicates that hair cells are the inner ear components most vulnerable to damage, with outer hair cells being initially affected. Disruption of intracellular organelles, including endoplasmic reticulum, lysosomes, nucleus, and mitochondria has been observed with electron microscopy, as have

disorganization, fusion, and loss of stereocilia. The stereocilia rootlet structure, which anchors it into the top of the hair cell, appears to be affected first. Degeneration of damaged hair cells may lead to eventual loss of auditory nerve fibers and changes in auditory areas of the central nervous system. With repeated exposure, hair cell loss will continue to increase, and there is no evidence that degenerated hair cells are ever replaced in mammals. Recent studies in birds, however, have documented some hair cell regeneration after initial loss following noise exposure. The anatomic and physiologic changes that occur in the inner ear during a TTS are quite subtle and may be limited to swelling of hair cells and underlying afferent nerve fiber terminals that resolve during a rest period away from loud sounds. Acute changes in stereocilia rootlets might alter cochlear micromechanics, whereas vascular spasm and metabolic exhaustion could also play a role in TTS.

Impulse noises, as generated by gunfire or an exploding firecracker, are characterized by short duration and very high sound intensity levels, 132 to 170 dB(A) during the initial acoustic pulse of a typical gun discharge. Large-caliber rifles and shotguns are particularly hazardous, having the potential to produce immediate and permanent injury to sensitive inner ear structures. Sound levels produced by toy weapons measured at a distance of 50 cm showed mean peak values from 143 to 153 dB(A), while firecrackers produced peak levels measured at 3 m of 125 to 156 dB. Adolescents employed in noisy environments, who also engage in shooting or setting off firecrackers, may add to whatever hearing loss they sustain as a result of occupational exposure.

Whereas an explosion poses an obvious hearing risk to an unprotected ear, other potentially damaging environmental sounds may be less readily apparent. Parents and public policy makers have expressed concern about hearing risks posed by exposure to rock music, "boom" cars, motorcycles, and personal cassette players (for example, "Walkman").

Average sound levels in a typical discotheque approximate 95 dB(A), but at rock concerts it is common to experience amplified sound as loud as 105 to 115 dB(A), well above the discomfort level for most people. Not only the audience but also the rock musicians, stagehands, ushers, and concessionaires are at risk for acquiring NIHL after prolonged exposure to these very high sound levels. Short periods of exposure during a typical concert can be experienced by most children and youth without suffering a permanent hearing loss, but practically everyone exposed to such sound levels will experience a temporary loss (TTS) often accompanied by tinnitus.

Personal cassette players are capable of producing sound levels in excess of 110 to 115 dB(A) at the ear. Because they are portable and often used by listeners to drown out loud background noises, exposure time can be quite long. A child may unwittingly compensate for a temporary threshold shift by simply turning up the volume to even more hazardous levels. Surveys reveal that about 80% of children in the middle elementary school age group own or use personal cassette players and 5% to 10% listen for extended periods at potentially dangerous volume settings. A child who experiences a full feeling in the ear, muffled hearing, or tinnitus following use of a personal cassette player should be cautioned to modify listening habits to avoid NIHL. Sound levels attained in many "boom" cars containing very powerful stereo amplifiers and speakers may exceed 120 dB(A). All individuals, including children, exposed to such high ambient sound levels for prolonged periods risk permanent NIHL.

In a recent paper my coworkers and I (Brookhauser et al, 1992) reported results of a study of 114 children and adolescents (19 years old and younger) who were diagnosed as having NIHL on the basis of history and audiometric configuration. In 42 children the loss was unilateral, and bilateral losses were present in 72. The gender distribution of the sample was consistent with the findings of other investigators, in that 90.3% of the affected children were males. The mean age of referral for evaluation was 12.7 years (range of 1.2 to 19.8 years; standard deviation of 4.21 years), but 26% of these losses were diagnosed in children aged 10 years or younger. Parents or guardians were asked to identify the potentially damaging noise sources to which their children was exposed. Among 70 children for whom very reliable information was available, fireworks or firearms were identified as the sole noise source in 21 of 58 (36%) children with bilateral losses and 8 of 12 (67%) youngsters with unilateral losses. Histories of 14 of 19 children (74%) with exposure to multiple noise sources also mentioned fireworks or firearms. Consequently, noise exposure histories on 43 of 94 children (46%) included exposure to impulse sounds produced by fireworks or firearms. Although cap pistols and noisy toys have been identified in the literature as possible hazardous noise sources, none of the histories mentioned either. Such an omission may reflect a lack of caregiver awareness of the noise levels produced by such devices. Live or amplified music was identified in 11 of 94 (12%) cases as the principal source of noise exposure.

The age of identification of the hearing loss in relation to the type of noise source implicated in the history was also examined (Table 176-4). Although the "loud music" category contained only youth age 10 years or greater, all other categories included youngsters in the preschool and early elementary age groups. The noise exposure histories were replete with descriptions of children riding with a parent on a recreational vehicle (for example, motorcycle, snowmobile), assisting a parent in a home workshop, or accompanying a parent on a hunting trip or a visit to a target range. Eight of forty-seven children (17%) for