INTRODUCTION

The Panel considered certain categories of complications and sequelae of otitis media (OM). They were organized according to the anatomic pathology from tympanic membrane (TM) to intracranial complications.

Published reports for the past 5 years were included for sequelae or complications ensuing from OM in childhood to adulthood.

TYMPANIC MEMBRANE

Sequelae of OM manifested in the TM include atrophy, myringosclerosis, retraction, adhesion and perforation.

In a paper from the Dutch group\(^1\) long-term consequences of tympanostomy tube treatment is reported. Three hundred fifty-eight subjects with a positive and negative history of OM or tympanostomy tube insertion derived from a birth cohort had been followed-up from preschool to adult age. TM abnormalities were investigated at ages of 8 and 18 years. The occurrence of myringosclerosis was 6 times as common in the tube treated OM ears (56%) compared to the non-OM ears (9%) and the frequencies were not changed throughout the follow-up period. In contrast the frequencies of atrophy, atelectasis and pars flaccida retractions diminished throughout the follow-up period. Atrophies were more common in tubulated ears compared to the nontubulated, 20% vs. 7%, but in contrast to myringosclerosis the occurrence of atrophies decreased with time. Atelectasis and retractions of pars tensa as well as the pars flaccida showed similar dynamics as atrophies but with less differences between the tubulated and non-tubulated ears.

In a study by Johnston LC et al.\(^2\) on children with persistent MEE and tympanostomy tube treatment in the first 3 years of life the TM abnormalities were followed up at the age of 5 years. The children had been grouped in an early-treatment group, a late-treatment group and a non-trial group. One or more types of TM abnormalities in one or both ears, among children who received tubes, were 70.7%, 42.5% and 9.5%, respectively. Within the 3 groups, among children who received tubes, the proportions who had an abnormality of some type were similar, namely, 82.6%, 80.4%, and 83.3%, respectively. The corresponding proportions among children who had not received tubes were 15.4%, 19.3% and 7.2%, respectively. Segmental atrophy and tympanosclerosis were the most common abnormalities found.

In a retrospective study by Ryding M et al.\(^3\) on thirty-four patients, aged 16-25 years, with previous chronic OME persisting at least 6 years it was found that 76% of tube-treated exhibited TM abnormalities 18 years after surgery, compared to 0% in the control group. Similar figures for TM pathologic abnormalities after tube treatment was reported by Stenstrom et al.\(^4\)

A Danish study\(^5\) presented at the present symposium described in a 25-year follow-up that the pathology of the TM after treatment with grommets changes over time. While the occurrence of retractions decreases over time, atrophy increases and sclerosis remains grossly stable.
Tos and Cayé-Thomasen proposed a new 6-staged classification for posterior pars tensa retractions, which is based on their long-term epidemiological studies on secretory otitis and eardrum pathology, as well as studies on the pathogenesis of cholesteatoma. A report by Awad and Pothier suggests that digital photography of TM changes is considerably more accurate than the generally used clinical drawings and that its use should be encouraged.

Oktay et al. evaluated the histopathological changes in central TM perforations caused by chronic otitis media without cholesteatoma. Twenty-nine temporal bones from 25 patients (13 male patients and 12 female patients) with central TM perforations; 18 chronic otitis media with perforation and 11 chronic otitis media with perforation caused by ventilation tubes and 30 aged-matched normal temporal bones were included in this study. An extension of the migration of stratified squamous epithelium at the inner surface of the TM was observed in 11 of the 29 perforations (38%). The thickness of TM was significantly different between the perforation groups and the control group. Of the 29 TMs, 13 (44%) had tympanosclerosis and 8 (28%) revealed papillary projections of squamous epithelium. Most of the TMs showed one or more signs of sequelae or persistent abnormalities such as tympanosclerosis, papillary projections, thickening, and ingrowth without significant differences whether caused by tympanostomy tube treatment or the disease per se.

The efficiency of a subannular tube insertion technique in a group of pediatric patients with adhesive otitis or severe atelectasis of the TM was evaluated in a retrospective nonrandomized case series. The study group consisted of 190 patients (316 tubes) aged between 3 and 19 years (average 9 years old) and operated on between 1993 and 1999 by four pediatric otolaryngologists. The average follow-up was 53 months. The tubes remained in place for an average of 21.8 months, with fluoroplastic tubes lasting 17.8 months and Goode T tubes lasting 23.8 months. When used in children between 5 and 9 years of age and in cases of adhesive otitis, Goode T tubes showed statistically significantly better results than fluoroplastic tubes. The complications of this technique were otorrhea (17.7%), perforation (7.9%), a plugged tube (7.0%), and cholesteatoma (1.6%). The 5- to 9-year-old group and the reintervention group of patients showed statistically higher complication rates compared with all other groups. Sixty-four patients (128 tubes) were eligible for audiogram analysis, which showed a gain of 13.4 dB (speech reception threshold). The technique of subannular tube insertion is a safe and effective method for long-term middle ear ventilation in cases of adhesive otitis or severely atelectatic tympanic membranes or for patients with pathology related to dysfunction of the Eustachian tube.

The diffusion of gas across the TM in humans and animals is slow. However, structural changes caused by repeated TM perforations could affect gas diffusion rates. This possibility was evaluated by Felding et al. using a chinchilla model. The study showed an increased rate of diffusive gas exchange across TMs that had been repeatedly perforated. This effect may be caused by a structural thinning secondary to scar formation and could have implications for middle ear pressure regulation in ears with a history of repeated myringotomies and/or tympanostomy tube insertions.

Of certain interest is the report of Ibekwe TS et al. concerning persistent perforations among adults in West Africa. The majority of the perforations were caused by infections.

A study on surgical removal of tympanostomy tubes by Adkins and Friedman included 92 pediatric patients. It was shown that the overwhelming majority of patients who undergo surgical removal of tubes will show complete tympanic membrane healing independent of technique at the time of removal, duration of intubation, patient age, or indication for removal.

Goode’s T-Tubes have a bad reputation because their residual tympanic perforation rate. Carignan et al. reported on a modified Goode’s T-tube that had a comparable perforation rate to that of short-term tubes despite the tubes had been in place at an average of 2.9 years.

Stenfeldt et al. analyzed the distribution of 3 collagen types; I, II and III, in healthy TMs, during healing of a perforation, and during infection with Streptococcus pneumoniae. In normal TMs Type II collagen was a main
constituent of the lamina propria of the pars tensa, whereas type I collagen was found mainly in the pars flaccida. Collagen types I and III were found at the insertion to the malleus handle and in the loose connective tissue surrounding the main collagen layer of the pars tensa. After myringotomy, collagen types I and III were found at the perforation border and around dilated blood vessels early in the healing phase. During infection, the collagen layer was thickened and stained strongly for type II collagen. Collagen types I and III were found in the edematous connective tissue around the main collagen layer and around dilated blood vessels. Three months after perforation or infection, all 3 collagens were present in the lamina propria of the TM. Extensive amounts of all 3 collagen types were present in the scar tissue in the TMs of rats that had undergone myringotomy during the presence of acute otitis media.

Several studies have investigated effects of various compounds on the healing of TM perforations in animal models. In a study by Eken et al. the effects of insulin on the healing of acute traumatic TM perforations were tested in guinea pigs. The treatment showed an increased activity of the fibroblasts in lamina propria as well as an increased content of collagen. It was concluded that topical insulin treatment may be beneficial in the treatment of atrophic membrane, which is a sequel of perforation. Ramalho and Bento studied the effect of epidermal growth factor (EGF) and pentoxifylline on subacute TM perforations in chinchillas and quantified the healing rate of such perforations treated with these drugs alone or in combination. EGF promoted healing of the TM perforations and the use of pentoxifylline did not. The combination of the two had no synergistic effect on the healing.

Ramahn et al. investigated if the short-term healing scar that forms after experimental laser myringotomy will revert to a normal lamina propria in the long run.

Potassium titanyl phosphate laser myringotomy was made on one side of the TM in rats and the stiffness and strength of the healed TMs were measured. The interferometry readings showed a slightly reduced strength in the myringotomized and healed TMs. After half a year, still there were immense structural changes including an increased thickness over a wide area of the pars tensa with increased amounts of fibers. An obvious reorganization of the fiber layer was lacking. It was concluded that laser myringotomy causes profound, long-standing, or permanent structural changes in the lamina propria of the pars tensa, whereas the strength of the TM may become slightly reduced.

In a series of clinical studies Turkish groups have tested various substances interfering with the formation of oxygen radicals on patients with chronic otitis media in attempts to hinder development of myringosclerosis. Also animal experiments have been performed to study if myringosclerosis can be prevented. Some positive results were obtained by administration of L-carnitine, vitamin E and alpha-tocopherol. In a study by Uneri et al. it was shown that the vitamin E also reduced the formation of myringosclerosis in tympanostomy-treated TMs in humans. The authors however, concluded that further clinical studies consisting of a larger patient population are needed to bring about routine clinical use of antioxidants in myringotomy and VT insertion. The same group investigated the effects of vitamin E-coated tympanostomy tubes in a series of rat TM perforations. The results indicated that vitamin E-coated tube insertion decreases the quantity of reactive oxygen species in TM after myringotomy and tympanostomy tube insertion.

In a study by de Carvalho Leal et al. the influence of hypercalcemia in the development of tympanosclerosis in rats with or without acute otitis media was assessed. One group of rats was subjected to hypercalcemia status through calcium diet supplementation and the other used as a control group (normal calcium content diet). Both groups were subjected to induction of tympanosclerosis by inoculation of Streptococcus pneumoniae on the right middle ear only. The group subjected to hypercalcemia presented a prevalence of tympanosclerosis of 25% against 16.7% in the control group, presenting a relative risk of 1.27 (p=0.72). The results suggest that hypercalcemia may have an influence in the development of tympanosclerosis.
In rats Raustyte et al.\textsuperscript{27} investigated the calcification process in the formation of myringosclerosis by use of the expression of three bone modelling markers: osteopontin (OPN), osteoprotegerin (OPG) and osteonectin (ON). Calcium depositions were initially accumulated in the cytoplasm of macrophages and dispersed in the connective tissue layers of the pars flaccida and pars tensa. Late accumulation occurred in the lamina propria of pars tensa, more extensively in myringotomized ears. OPN expression was found early in inflammatory cells including especially macrophages and late in pars tensa fibrocytes. OPG expression was initially located to inflammatory cells and late to pars tensa fibrocytes and the inner basal membrane of pars flaccida. Some ears displayed a marked pars flaccida expression of ON in the connective tissue matrix on early days and at the inner basal membrane on later days. The latter cases were from myringotomized ears. Otherwise, no apparent differences of marker expression occurred between myringotomized and non-myringotomized animals. The authors concluded that osteopontin, osteoprotegerin and osteonectin are expressed by different cell types in the TM during calcification in association with AOM, with or without myringotomy. These molecules may accordingly play a role in the pathogenesis of myringosclerosis, in which macrophages and fibrocytes appear as potential major players.

A challenge in healing of TM perforations is to create an animal model for a chronic perforation. Kaftan et al.\textsuperscript{28} made an attempt to inhibit the epidermal growth factor receptor (EGFR) which may arrest wound healing. The EGFR tyrosine kinase inhibitor (erlotinib) was administered. However, systemic application of erlotinib was not suitable for creating a chronic TM perforation in rat.

Hebda et al.\textsuperscript{29} studied the effects of the ciprofloxacin-dexamethasone (CDX) combination applied ototopically after myringotomy on TM healing in rat ears with Eustachian tube obstruction (ETO) and unobstructed ears. Animals were randomized into three groups to receive no treatment or bilateral once daily ototopical treatment with balanced salt solution (BSS, vehicle) or CDX for 13 days. On day 14, TM perforation healing rates were 100% in all ears of untreated and BSS-treated animals, 89% (8/9) in CDX-treated obstructed ears, and 30% (3/10) in CDX-treated unobstructed ears (P < .05 vs. BSS). On day 28, 100% (5/5) of the CDX-treated unobstructed ears and 80% (4/5) of the CDX-treated obstructed ears were healed. Histology showed initial TM postmyringotomy thickening in all ears but no significant qualitative differences between groups on day 28. The authors concluded that myringotomy healing was transiently modulated by treatment with CDX but proceeded normally after CDX discontinuation. This early modulation might enhance middle ear drainage and middle ear concentrations of CDX when tympanostomy tube surgery is performed in patients with active OME and ETO, thus potentially reducing otorrhea and preventing or treating infection. It would not be expected to increase the risk of premature tube extrusion or adversely affect normal healing of the TM after the usual spontaneous extrusion.

The Umeå-group has proposed plasminogen to play an important role in different tissue remodeling processes such as wound healing and tissue regeneration after injuries including the healing of TM perforations.\textsuperscript{30} It was shown that the healing of TM perforations is completely arrested in plasminogen-deficient mice, with no signs of any healing even 143 days after perforation. Inflammatory cells were recruited to the wounded area, but there were no signs of tissue debridement. In addition, removal of fibrin, keratinocyte migration and in-growth of connective tissue were impaired. This contrasts with skin wound healing, in which studies have shown that, although the healing process is delayed, it reaches completion in all plasminogen-deficient mice. The finding that keratinocyte migration and re-epithelialization were completely arrested in plasminogen-deficient mice indicates that plasminogen/plasmin plays a more profound role in the healing of TM perforations than in the healing of other epithelial wounds.

In studies by Rahman et al.\textsuperscript{31} the long-term influence of embryonic stem cells on acute perforations and the effect of gelatin as a vehicle for applied stem cells were investigated. The possibility of teratogenic effects of the stem cells was also observed. Bilateral laser myringotomy
was performed in adult Sprague-Dawley rats. Stem cell treated ears did not show any enhanced healing of the perforation although a marked thickening of the lamina propria was observed compared with control group. After half a year the strength and the stiffness of the tympanic membrane was almost the same for both treated and untreated ears. No evidence of teratoma was found after half a year. The study suggests that the stem cells stimulate the proliferation of connective tissue and fibers in the lamina propria, possibly mediated by secreted substances, although the stiffness properties do not seem to be altered. The use of gelatin does not seem to enhance the healing process of the TM perforation.

CHOLESTEATOMA

Based on epidemiological, clinical and immunohistochemical studies Sudhoff and Tos\textsuperscript{32} proposed a four-step pathogenesis for cholesteatoma, combining the retraction and proliferation theory. The basic mechanism is the same as the same authors\textsuperscript{33} earlier suggested for attic cholesteatoma. However the anatomical conditions especially the shape and severity of retractions around the incudostapedial joint and around the stapes differ from the attic cholesteatoma.

Tokuriki et al.\textsuperscript{34} investigated the genes regulated in human cholesteatoma compared with normal skin tissue using complementary DNA arrays. The observed alteration in gene expression suggested a role in various mechanisms of pathogenesis in cholesteatoma.

Rochetti et al.\textsuperscript{35} investigated the possible relationship between \textit{Chlamydia pneumoniae} and the development of cholesteatoma. Tissue was studied in three different layers by polymerase chain reaction analysis. Four specimens contained \textit{Haemophilus influenzae}, always in the external layer, whereas none contained \textit{Mycoplasma pneumoniae}.

Kim et al.\textsuperscript{36} identified upregulated proteins in human cholesteatoma in comparison with canal skin using proteomic analysis with 2D electrophoresis and matrix-assisted laser desorption and ionization time-of-flight mass spectrometry (MALDI-TOF MS). The authors concluded that proteomic analysis may be a powerful tool for the identification and characterization of many promising candidate proteins relating to cholesteatoma.

Ozturk et al.\textsuperscript{37} determined the micronucleus (MN) frequency of acquired cholesteatoma tissue using an MN assay on 18 patients diagnosed as having chronic otitis media with acquired cholesteatoma and were divided into primary and secondary acquired cholesteatoma groups. These results indicate that there could be associations between MN frequency and acquired cholesteatoma and between MN frequency and complications.

Lee et al.\textsuperscript{38} studied telomerase activity in cholesteatoma and its relationship with cellular proliferation and clinical findings of 40 patients. As a cellular proliferation index, expression of Ki-67 was measured by means of immunohistochemical staining. The clinical features did not show a relationship with either telomerase activity or the cellular proliferation index.

Kobayashi et al.\textsuperscript{39} examined whether Vitamin D3 (VD3) could suppress matrix metalloproteinases (MMPs) production from cholesteatoma keratinocytes \textit{in vitro}. Addition of VD3 into keratinocyte cultures caused the suppression of MMP and TIMP production, which was increased by LPS stimulation. This was dose-dependent. The present results showing the suppressive activity of VD3 on the production of MMPs, which are responsible for tissue remodeling, strongly suggest that VD3 would be a good candidate for an agent in the medical treatment of, or prophylaxis for, cholesteatomas.

Raynov et al.\textsuperscript{40} investigated the presence of progesterone receptor (PGR) and oestrogen receptor (EGR) in human middle-ear cholesteatoma (MECh) tissues and to compare their expression between male and female patients. The preliminary experimental results give us ground to assume that female sex hormones may stimulate proliferation and affect differentiation of MECh keratinocytes.

Daudia et al.\textsuperscript{41} investigated the matrix metalloproteinases (MMP) in 11 cholesteatoma specimens, ten deep meatal skin and ten
postauricular skin specimens with immunohistochemistry using monoclonal antibodies to MMP-8 and MMP-13. Expression of MMP-8 and MMP-13 were found to be significantly higher in cholesteatoma compared to postauricular skin, suggesting that both MMP's are possible components of the destructive process seen in cholesteatoma.

Hwang et al. evaluated localization and expression of the peroxidase proliferator-activated receptor (PPAR)gamma in cholesteatoma epithelium with reverse-transcription polymerase chain reaction performed on cholesteatoma tissues from 10 adult patients undergoing tympanomastoid surgery for middle ear cholesteatoma and on 10 samples of normal external auditory canal skin tissue. PPARgamma is up-regulated in the cholesteatoma epithelium compared with normal external auditory canal skin. These results suggest that PPARgamma may play an important role in the pathogenesis of cholesteatoma.

Tinling and Chole reported the sequence of gross and histopathologic change to the normal middle ear (ME), TM, and external auditory canal (EAC) during spontaneous gerbilline cholesteatoma development. They reported that cholesteatoma development followed the sequence of: 1) slightly thickened pars flaccida (PF) without ME effusion, 2) thickened PF with ME effusion, 3) continuous buildup of EAC debris, and 4) complete occlusion of the lateral EAC.

Yoshikawa et al. investigated the role of fibroblasts in the pathogenesis of cholesteatoma on tissue specimens obtained from four patients using the human genome U133A probe array (GeneChip) and real-time polymerase chain reaction. These results suggested that fibroblasts may play a role in hyperkeratosis of middle ear cholesteatoma by releasing molecules involved in inflammation and epidermal growth.

Cho et al. investigated the expression and localization of placenta growth factor (PlGF) within cholesteatoma on tissue samples from human cholesteatoma and normal auditory meatal skin were obtained from patients during surgery for cholesteatoma of the middle ear.

Ozturk et al. investigated the status of c-MYC oncogene in primary acquired cholesteatoma in 15 patients using fluorescence in situ hybridization with a mixed DNA probe, which is specific for c-MYC located on 8q24 and chromosome 8 specific-alpha-satellite DNA probe. These findings suggest that the ability of hyperproliferation of primary acquired cholesteatoma might have been related to c-MYC copy number by deregulating c-MYC expression.

OSSICULAR PROBLEMS

Ossicular problems due to either fixation or discontinuity or resorption can cause conductive or mixed hearing loss. In a retrospective study on 315 operated ears of 305 patients by Yusan the predictive role of the audiometric Carhart's notch for the assessment of middle-ear pathology prior to surgical intervention was investigated. In patients with otosclerosis and tympanosclerosis, a Carhart's notch was seen at 2 kHz in 28 (93 percent) patients but at 1 kHz in only two (7 percent). However, in patients with chronic otitis media, a Carhart's notch was seen at 1 kHz in 10 (55 percent) patients and at 2 kHz in eight (45 percent) patients. Otitis media with effusion, tympanosclerosis and congenital malformations should be considered in the differential diagnosis of a patient with a Carhart's notch seen on pure tone audiometry. A Carhart's notch at 2 kHz indicates stapes footplate fixation, whereas one at 1 kHz indicates a mobile stapes footplate; the footplate mobility can thus be predicted preoperatively.

MUCOSAL SEQUELAE

Middle ear mucosal changes are other important sequelae of OM inducing hypertrophy and/or hyperplasia, adhesion, or tympanosclerosis. In a study by the Umeå group the role of the plasminogen (plg)/plasmin system for the spontaneous development of chronic otitis media was investigated in plg-deficient mice. Whereas essentially all of the wild-type control mice kept a healthy status of the middle ear, all the plg-deficient mice gradually developed chronic otitis media with various degrees of inflammatory changes during an 18-week
observation period. Five bacterial strains were identified in materials obtained from the middle ear cavities. Morphological studies revealed the formation of an amorphous mass tissue and inflammatory changes in the middle ears of plg-deficient mice. Immunohistochemical studies further indicate a mass infiltration of neutrophils and macrophages as well as the presence of T and B cells in the middle ear mucosa of these mice. These results suggest that plg plays an essential role in protecting against the spontaneous development of chronic otitis media.

In a study by Sancovic S et al., the number, distribution and degranulation frequency of mast cells were studied in the middle ear mucosa biopsies of patients with chronic otitis media. The number of mast cells increased in all areas of middle ear cleft in chronic inflammation of the middle ear mucosa. In chronic otitis media of atticotympanal and tubotympanic type mast cells were present in 91.5% of samples, the cells with heparin granules were present in 62.2% and degranulation frequency was 37.8%. In secretory otitis media 33 mucosal samples were analysed and all samples contained mast cells with predominance of histamine granules and with a degranulation frequency of 81.8%. These findings indicate that mast cells have complex function in pathophysiology of chronic inflammation of the middle ear mucosa: it may take part in amplification of inflammation as well as in its limitation. The studies confirm what has earlier been stated in animal models concerning mast cells and middle ear inflammation.

INNER EAR SEQUELAE

Vestibular Disturbances. In a study by Waldron et al. on children, aged 6-10 years, with clinically and audiometrically proven OME, a universal effect on balance was shown. A reduced effect on optic fixation and a reduced proprioception was shown. Insertion of grommets normalized the situation. Another study by Engel-Yeger B et al. in children with MEE was performed with Bruininks-Oseretsky Motor Performance Test. Children with MEE had poorer muscle strength than the control group, though not significantly. In a review on vertigo in children Niemensivu R et al. described that balance disturbances may occur in children with otitis media.

Hearing and Auditory Sequelae. During this symposium Casselbrant M et al. reported that behavioural hearing thresholds in the high frequencies, 12 kHz to 20 kHz, is significantly higher in children with histories of otitis media.

Lauritzen M-BG et al. showed that the “Galker test of speech reception in noise” is a valid and reliable measurement of speech reception in noise. The method may potentially be useful to detect children who are disabled by otitis media in their daily communication.

Two reports on the same cohort of 429 children randomized to receive early or later tympanostomy tube treatment were reported by Paradise and colleagues. Johnston et al. reported that at the age of 6 years, hearing thresholds averaged 6.2, 6 and 4.3 dB in right ears of children who received early, later and no treatment with tubes, respectively. Paradise et al. did not show any difference between otitis media children with early vs. late insertion of tympanostomy tubes with regards to hearing, speech, language and behavioural testing.

The MRC MultiCentre Otitis Media Study Group reported on improvement in conductive hearing loss immediately and over time in 233 children aged 3.5 to 7 years enrolled in the TARGET trial (Trial of Alternative Regimens of Glue Ear Treatment) with persistent OME and bilateral hearing loss >= 20 dB HL, who had been randomized to receive either myringotomy and tubes alone or accompanied by adenoidectomy. Tubes that were functioning during follow-up assessment improved hearing an average of 12 dB, thus tubes did not completely alleviate the conductive hearing loss. Tubes functioned in both ears for only 12 weeks on average. The authors concluded that recurrence of effusion and residual viscous effusion coating the ossicles was the most likely explanation for remaining conductive loss even with functioning tubes.

Rovers et al. conducted an individual patient data (IPD) meta-analysis on seven randomised controlled trials (n = 1234 children in all), focusing on interactions between treatment and baseline characteristics--hearing level (HL). The
effects of conventional ventilation tubes in children were small and limited in duration. Observation, watchful waiting, therefore seems to be an adequate management strategy for most children with OME. Ventilation tubes might be used in young children that grow up in an environment with a high infection load (for example, children attending day-care), or in older children with a hearing level of 25 dB HL or greater in both ears persisting for at least 12 weeks.

A meta-analysis of the effect of tube treatment on hearing levels was published by Lous et al. The meta-analysis found that mean hearing levels improved by 9 dB (95% CI 4 dB to 14 dB) after the first six months, and 6 dB (95% CI 3 dB to 9 dB) after 12 months. The combined effect of tubes and adenoidectomy was an additional 3 to 4 dB improvement in hearing (95% CI 2 dB to 5 dB) at six months and about 1 to 2 dB (95% CI 0 dB to 3 dB) at 12 months. The benefits of tubes in children appear small and diminished during the first year.

Gravel et al. reported on conventional and extended high frequency hearing thresholds, electrophysiological measures of auditory function, and higher order auditory processing measures in a prospective cohort of children in North Carolina and New York. Results showed an association between early life OME and extended high frequency hearing thresholds at school age and auditory brainstem responses which indicated a central conduction delay. No relationship was found between early life OME and higher order auditory processes at school age.

Two studies of auto-inflation were reported during this period. Arick and Silman conducted a randomized, controlled trial with a modified Politzer device used in the home setting over a 7-week period in 94 children aged 4 to 11 years. At study's end, the hearing sensitivity of 73.9% of the treated ears was within normal limits, compared with only 26.7% of the control ears.

Perera et al. reported a meta-analysis of randomised controlled trials that compared any form of autoinflation to no autoinflation in individuals with ‘glue ear.’ Improvement was found for the composite measure of tympanogram or audiometry at less than one month (Relative Risk of Improvement (RRI) 2.47, 95% confidence interval (CI) 0.93 to 6.58) and at more than one month (RRI 2.20, 95% CI 1.71 to 2.82), and no significant increase in risk, thus this may be considered a conservative treatment in children being watched for persistent OME.

SPEECH AND LANGUAGE DEVELOPMENT

The years 2003-2007 were marked by a limited number of research endeavors that examined the developmental outcome of otitis media with effusion (OME), especially those that utilized prospective designs. There were a total of nine original research reports that examined the developmental sequelae of OME, of which five used a prospective research design. We are including research that has employed retrospective designs based on the following rationale. Although in the four retrospective reports, OME was retrospectively documented, the other variables were collected contemporaneously. Moreover, in these studies the hypotheses are well-stated, the outcomes are specific to the hypotheses being tested, and the measures appear to be carefully assessed. Nevertheless, we will weigh more heavily evidence from prospective studies. In addition to these nine studies, there were two reports that considered opinions of parents and professionals regarding sequelae and two research reviews that will be briefly described. Thus, we will summarize the findings of the reports that directly assessed children’s development, concentrating on the prospectively designed studies, and will briefly describe the conclusions of the surveys and the reviews. Reports that included outcomes in different domains are discussed in each of the topic areas.

Speech Perception and Production. During the time period surveyed, there was only one prospective study that examined speech production. Paradise and colleagues studied speech development as part of their longitudinal study that included a randomized cohort and an observational cohort. In the randomized trial, children with persistent OME had tympanostomy tubes inserted either promptly or up to 9 months later if the effusion persisted. The follow-up at 6-
years of age included 395 children on whom speech samples were collected during conversations. No differences in the percentage of consonants correctly produced were found between children who received tympanostomy tubes in the early vs. delayed treatment groups. Neither was there any association between percentage of time with OME and percent consonants correct in the observational sample of 233 children.

In addition, there were two research studies that used a retrospective design—one examining speech perception and one examining speech production. In a study of 5-year olds with varying histories of OME and SES, Nittrouer and Burton found that the OME group used more immature strategy for speech perception than did the control group. Shriberg and colleagues64 examined children with speech impairments who were 3 to 5.5 years of age, half of whom had histories of OME. Their analysis of conversational samples indicated that the OME group was more likely to use backing of obstruents (e.g., cable for table). As indicated above, results of such studies carry less weight in coming to a consensus regarding the impact of OME. However, their exploration of specific aspects of speech development that were hypothesized to be affected by OME suggests that these might be fruitful areas to examine in future prospective investigations.

In summary, the one prospective study of speech production reported a relation with early OME, whereas the retrospective study did find an association. However, the inclusion of a sample of children with speech delays in the retrospective study reported by Shriberg and colleagues may be one reason why their findings differed from the Paradise study. Moreover, the type of production deficit they described was rather subtle in contrast to the overall measure of consonant production in the Paradise study.

Language. There were five studies detailing relations between OME and language development reported in the literature, of which two were prospective designs. The language outcomes were collected from infancy through school age. There were varied measures including standardized test scores, naturalistic language samples, and narrative retelling.

Vernon-Feagans and her colleagues examined language development as a function of OME and childcare in a cohort followed since infancy. Naturalistic language samples were collected at 18, 24, and 36 months of age while children were playing with a familiar adult at their childcare center. Samples were coded for a variety of syntactic, morphological, and semantic markers of language development. Although there were differences in many of the language measures between children in high-quality and low quality child care, there were no main effects or interactions as a function of OME at any time point.

Paradise and colleagues examined language at 6 years of age in both their correlational and randomized controlled studies described above. In the correlational study, they reported that children with a history of OME scored lower on a standardized measure of receptive vocabulary as well as number of different words and utterance length in a conversational sample even when demographic and hearing status were controlled. However, the percentage of variance explained was low. These researchers did not find that the early and late treatment groups differed on any language measures.

There were three studies that employed a retrospective design. Majerus and colleagues examined a group of 8 year old children with histories of OME matched for age, gender, SES, and non-verbal cognitive ability with a group of children with negative OME histories. They found no differences between these groups in either receptive or expressive vocabulary skills. Winskel, who compared 6-8 year old children with and without histories of OME matched for age, gender, and SES, reported differences between OME groups in word naming and definitions but not in receptive vocabulary or narrative skills. Finally, Nittrouer and Burton examined comprehension of complex syntax in their sample, with a non-significant difference reported between OME positive and control groups.

In the research cited, a variety of language skills were measured using both standardized measures and naturalistic language samples. In the one prospective study to document any
association between OME and language skills, the variance explained was minimal. Hearing was examined in all of these studies and during the period when OME was documented in the prospective reports as well. However, hearing was not included as a dependent or mediating measure, although it is hearing loss which is hypothesized to affect children’s language development. Feagans and colleagues did report that hearing and OME were highly related, which was their justification for only using OME classification in the analyses. Based on these findings, there is limited evidence to conclude that early otitis media has a lasting impact on language skills.

Phonological Processing. There were four studies that considered measures of phonological processing of which only one was prospective. All but one of these studies involved school age children; the remaining study included preschool age children. A variety of different measures were used including rhyme judgment, syllable counting, syllable manipulation, phoneme detection, and initial sound recognition.

Paradise and colleagues followed their cohorts who were part of the randomized trial and the representative correlational study when they were between 9 and 11 years of age. They failed to detect any relationship between OME and phonological awareness or rapid naming in either the randomized or the representative cohorts. In the three studies with OME that were retrospectively documented (Maejerus and colleagues, Nittrouer and Burton, and Winskel, all described previously), the groups with histories of OME performed more poorly than the control samples on a variety of different phonological processing measures including rhyme judgment.

In summary, it may be premature to conclude anything about the effect of OME on phonological processing. Despite the failure to find an association in the large, carefully documented cohort of Paradise and colleagues, it would be worthwhile to examine skills such as rhyme judgment in other prospective samples before concluding that there is no impact of OME on phonological processing. It would also be useful to examine in relation to hearing as that is the putative variable that is thought to affect phonological abilities.

Cognition and Academics. There were four investigations of cognitive and academic skills in relation to a history of OME that were published. There were three prospective studies, two of which were the follow-up studies of Paradise and colleagues. All reports involved school age children and the outcomes included IQ, reading, spelling, writing, and mathematics.

In the studies reported by Paradise and colleagues, there was no association between intelligence and either timing of tube placement or the percentage of time with middle ear effusion at either 6 years or between 9 and 11 years of age. In their sample at 9-11 years of age, Paradise et al. reported significant but low associations between the percentage of time with OME and both reading fluency (in 3rd grade children only) and spelling in the representative subgroup, but they failed to find any differences in these and other academic measures (i.e., word identification, word attack, reading comprehension, and writing). IQ scores were not found to be different between the groups randomized for tube insertion and there was no association between IQ and OME in the representative subgroup. A third report by McCormick, Johnson, and Baldwin also included a prospectively documented cohort seen at 7 years of age. McCormick and colleagues administered a variety of measures of reading skills and mathematics. No relationship was detected between any academic achievement measure and percent of time with OME in the first three years of life; neither did they find any differences in academic achievement between extreme OME groups. In contrast, Winskel, in whose sample OME was retrospectively documented, found group differences in reading fluency and comprehension as a function of OM.

Based on the findings of these studies, there is very limited evidence that OME is linked to intellectual or academic outcomes. In the one prospective study to report a relationship between OME and academic outcomes, the investigators only found it in one of the two subgroups they were following and they indicated that although significant, the associations were
low. None of the studies considered hearing in relation to OME reducing the ability to interpret the lack of findings.

**Memory and Attention.** There were five studies examining outcome in these domains, three of which were prospective. Three reports included memory skills and two reports included attention. The children who were the focus of these investigations were all school aged.

Of the three studies reporting memory, only Paradise and colleagues' study was prospective. They administered a nonword repetition test to their 6-year old sample. No relationship was found between performance on this task and the percentage of time with OME, and contrary to expectation, the group randomized to delayed treatment repeated significantly more nonsense words than did the early treatment group. Majerus and colleagues administered five different measures of verbal short-term memory and failed to find any association with OME. Only Nittrouer and Burton reported that children with reported OME made more errors on two measures of verbal working memory than did the control group.

Two prospective reports included measures of attention. Paradise and colleagues administered both visual and auditory continuous performance tests to their 9 to 11 year old sample and obtained ratings of inattention from parents and teachers. The continuous performance tasks involved attending to either verbal or visual material and responding when preceded by a valid cue; derived scores include inattention and impulsivity. No differences were detected between the groups randomized for treatment or between the children randomized and the observational cohort; nor was the percentage of time with OME associated with verbal or visual attention or on the ratings of children’s inattention. The second study of attention was reported by Hooper and colleagues who reported on their prospectively followed sample, initially recruited from child care centers. When in second grade, they were administered several measures of auditory attention as well as parent and teacher ratings of sustained attention. These investigators not only studied the percentage of time with OME during the first 4-years of life, but they also examined the percentage of time with hearing loss during the same time period. Neither OME nor hearing loss was found to relate to attention in the early school years, whereas the home environment and mother’s education were related to several of the outcomes. However, there was an interaction reported between hearing loss and the home environment on one of the measures of auditory attention. Specifically, children with hearing loss from less responsive and supportive home environments demonstrated poorer attention than children with hearing loss from more responsive and supportive homes. In summary, there is a lack of evidence that OME has a negative impact on memory and attention in the school years. There is some evidence that hearing loss may have a synergistic effect with environment in the development of attention.

**Behaviour.** The only two studies that included behavioral functioning as an outcome were reported by Paradise and colleagues. They administered several questionnaires to parents and teachers regarding the children’s behavior at both time points (i.e., 6-years and 9-11 years). At 6-years, there was no difference between the early and delayed treatment group on any measure of behavior. The authors report that there were some low, but significant correlations in the representative subgroup. At 9 to 11 years of age, Paradise et al. indicate that children who had delayed tube insertion had significantly fewer parent-reported problems than the early treatment group. The group not eligible for randomization had more favorable scores on a parent rating of impulsivity and on a teacher rating of impairment. In this representative subgroup, there were low but significant correlations between the percent of time with OME and behavioral outcomes, accounting for no more than 6% of the variance in behavior. In summary, there appears to be only a weak association between otitis media and behavioral adjustment.

**Parent and Professional Opinions about Sequelae of OME.** Two papers were published that queried different groups of individuals regarding the impact of otitis media on development. Sonnenschein and Cascella asked a small group of pediatricians their opinions about the relationship between otitis media (both acute
and OME) and children’s hearing and speech-language development. Results of their survey indicate that while these pediatricians thought that otitis media occurring in the first two years of life could impact speech-language development, they were less inclined to agree that otitis media would have an effect in general. Moreover, they felt that parents and childcare environments could lessen the impact of otitis media on speech-language sequelae. The second paper by Higson and Haggard examined the differences between parents, teachers, and otolaryngologists in rating the importance of symptoms and developmental impact of OME. Among their findings, they report that the three groups differed on all four areas of impact (i.e., hearing, language-education, behavior, and balance). Both parents and teachers rated OME as having an impact on behavior. They also reported that teachers weigh language and education symptoms much more heavily than do parents and otolaryngologists and that parents tend to rate language-education impacts with decreasing importance as children age. The conclusions reached in both of these papers reflect findings in the research literature that indicate that by school age, there is little impact of OME on speech and language development.

Summary. In the past four decades, there have been a host of research endeavors examining the relationship between a history of OME and developmental outcomes. Although there have been considerably fewer studies that appeared in the literature from late 2003 through mid 2007, the conclusions reached are similar to those that have been reached previously; namely, findings indicate that OME has no more than a minimal impact on developmental outcomes. In the prospectively followed samples, only one found any association between OME and speech-language outcomes; the variance explained was minimal. Likewise, there was only one prospective study in which there was a suggestion that OME may be related to academic outcomes. There were no prospective studies in which memory or attention was impacted by OME, although hearing loss was related only when the home environment was also considered. Finally, there were low but significant correlations between the percent of time with OME and behavioral outcomes reported in one prospective study. On the other hand, there is some evidence from retrospective studies that specific measures of phonological processing, speech, and working memory may be associated with OME. In general, the studies reported here support the conclusions of the meta-analysis performed by Roberts and colleagues and the published review based on data reported at an NIH conference. Specifically, these conclusions were that there are at most very small negative relationships between OME or its associated hearing loss and children’s development and that a history of OME may not be a substantial risk factor for later speech-language development or academic achievement. However, since hearing was inconsistently included as a variable in many studies, this conclusion should be interpreted cautiously. These conclusions are also consistent with the views of professionals and parents reported in surveys, many of whom did not believe OME would have long-term impacts on language or academic outcomes.

FUTURE RESEARCH

In the previous post-symposium meeting in 2003, a set of recommendations were provided that called for future studies to use a variety of research designs with varied populations, to design research that is hypothesis driven, to include reliable and valid measures of OME, hearing, and development, to include mediating and moderating measures that may impact the relationship between OME and developmental outcomes, and to provide adequate information in research reports, including power for non-significant findings, so that research synthesis may be completed. Several of these goals were met. Most of the studies were designed to examine specific hypotheses and utilized outcome measures to examine these effects. Populations included both middle-class and less advantaged groups, but only in one study was a clinical sample included. Many of the investigators examined hearing at the time of the developmental assessment to ensure that when outcomes were measured their samples had hearing in the normal range.

However, hearing during the time when children experienced OME was included as an
independent variable in only two studies—Hooper et al.\textsuperscript{69} and Paradise et al.\textsuperscript{55} Aside from SES, only Feagans et al.\textsuperscript{65} and Hooper and colleagues\textsuperscript{69} considered other environmental variables to account for development.

Our recommendations for future studies are to more consistently apply to the suggestions made previously. We encourage investigators to use more specific measures that may be more sensitive to the effects of OME effects as have been used in retrospective studies such as rhyme detection, working memory, and verbal attention. It is possible that the effects of OME are more subtle, and only apparent in acoustical analyses, although the importance of those effects may not be clear. We again strongly recommend that hearing be measured concurrently with OME and be included as the mediating variable that may explain the relationship between OME and developmental outcomes. Given the host of other variables that affect later development, it is critical that investigators include possible confounding factors that may mediate or moderate the relationship between OME and later development. These are variables such as the quality of mother-child interaction, quality of childcare experiences, as well as factors such as gender and the child’s cognitive level. Similarly, it will be important for investigators to include a variety of populations. As we indicated, it is important to include children at the most risk for OME, such children with Down syndrome or cleft palate who have considerable speech, language, and/or learning difficulties. In addition, understudied populations (children who are of Hispanic origin and Native Americans) should also be included in research studies. Finally, researchers must be diligent in providing detailed information about their participants and analytic procedures so that meta-analyses can be performed.

EXTRACRANIAL COMPLICATIONS

\textbf{Mastoiditis}. In a study by I Brook\textsuperscript{75} the bacterial flora in acute mastoiditis has been investigated. The author states that the incidence of mastoiditis has decreased since the advent of antimicrobial agents. In the last decade, however, there has been a marked increased in the incidence of acute mastoiditis in several communities, sometimes in association with the growing resistance of pneumococci. \textit{Streptococcus pneumoniae}, \textit{Streptococcus pyogenes}, \textit{Staphylococcus aureus} and \textit{Haemophilus influenzae} are the most common organisms recovered in acute mastoiditis. Several recent studies demonstrated the predominance of \textit{Pseudomonas aeruginosa} in this infection. However, because \textit{P. aeruginosa} colonizes the ear canal it can contaminate specimens obtained through the non-sterile ear canal. \textit{P. aeruginosa}, \textit{Enterobacteriaceae}, \textit{S. aureus} and anaerobic bacteria are the most common isolates in chronic mastoiditis. Anaerobes predominate in studies where adequate methods for their isolation are employed.

A retrospective study\textsuperscript{76} on 37 infants, who were operated for acute mastoiditis during 2000-2004, were performed in Belgrade, Serbia and Montenegro. All patients had local and general symptoms. It was concluded that making a diagnosis of acute mastoiditis might not be easy since there are no specific symptoms. It was emphasized that acute mastoiditis should always be considered as a differential diagnosis in cases of prolonged acute otitis media with no improvement after 10 days of antibiotic treatment, in particular when accompanied with weight loss and general condition worsening.

The restrictive use of antibiotics for acute otitis media in certain countries has been claimed to increase the number of acute mastoiditis. This initiated a registry based study\textsuperscript{77} with complete data on hospitalization for acute mastoiditis and cortical mastoidectomy in Norway during 1999-2005. Three hundred and ninety-nine Norwegian children aged 0-16 years were included. The incidence of acute mastoiditis in children below 2 years of age ranged from 13.5 to 16.8 per 100,000 during the study period. Corresponding numbers for children 2-16 years were 4.3-7.1 per 100,000 children. No incidence increase was found during the study period. Age-specific incidence revealed a peak during the second and third year of life, and acute mastoiditis was most common in boys. Cortical mastoidectomy was equally common in the young and older age group, 22% received surgery. Despite the introduction of restrictive Norwegian guidelines for antibiotic treatment of
acute otitis media in children aged 1 year and above, our data did not give evidence for an increase in acute mastoiditis.

Similarly a registry based study in Italy, the “Ferrara” experience, between 1994 and 2005 could not confirm a real increase in the incidence of acute mastoiditis. The authors however stress that careful attention must be paid to the clinical assessment of children who are 2-years old or under with suspect acute meningitis, as they seem to be more exposed to the risk of clinical complications like meningitis, meningoencephalitis and sigmoid sinus thrombosis.

In contrast Benito and Gorricho reported a progressive increase in the incidence of acute mastoiditis. These authors reviewed the cases of mastoiditis in the last 10 years (1996-2005) at The Niño Jesús University Children Hospital in Madrid to confirm the clinical impression, the bacteriology, treatment and evolution of the children and analyze the causes of this clinic situation. They studied 215 cases of mastoiditis (0.6-17 years), 67.4% less than 3 years old and 69.3% males. The number of cases every year was the double since 1999 with the same percentage of admissions in the Pediatric service, and the triple in 2005. The percentage of surgical treatment grew from 4.3% to 33% in the last years and to 70% in 2005. Most cases (80%) had received prior antibacterial agent therapy, but individual pathogens and current complications of periostitis or subperiosteal abscess formation were equally distributed between the two groups. Streptococcus pneumoniae was detected in 28.6% of the cases and Staphylococcus aureus in 16.3%. A 53.7% of cases had negative cultures. The authors concluded that there is a progressive increase in the incidence of acute mastoiditis and an increase of the surgical treatments. Ten years ago the process was controlled with antibiotic therapy only, but now the number of interventions has been eight times the previous years. Most cases of acute mastoiditis have responded well to medical management alone. But if higher levels of resistance predominate, more severe forms of pneumococcal or other pathogen like S. aureus disease are likely to be seen, these would be less likely to respond to oral or parenteral antibiotic therapy, so, tympanocentesis for middle ear culture may become more valuable and more frequently used in cases of antibiotic treatment failures, and surgical therapy may be necessary more often in the future.

In a Danish study sixty-seven patients with acute otitis media and thirty-nine patients with acute mastoiditis were studied. The overall bacterial flora found was dominated by S. pneumococci, all 100% susceptible to penicillin. However, Staphylococcus aureus was the primary bacterial pathogens cultured from patients treated with preadmission antibiotics. It is concluded that if a specimen from an AOM patient is obtained after the initiation of antibiotic treatment one should consider the possibility of the culture found being a result of the initial led treatment and not the causative AOM pathogen. The Danish data suggests that a restricted use of antibiotics in children with AOM may be associated with a higher incidence of acute mastoiditis. It was also found that a significant higher leucocytes count and CRP are found in the acute mastoiditis group compared to the AOM group.

It is now well accepted that most cases of acute mastoiditis can be successfully treated by parental antibiotics in combination with myringotomy. In a report by Spermo and Udovic it is however concluded that in coalescent mastoiditis, which has not responded to intravenous antibiotics within 48 hrs requires mastoid surgery. Studies by Zanetti and Nassifi showed that acute mastoiditis can fully recover with conservative treatment and myringotomy with tympanostomy tubes. Immediate surgical treatment is indicated for intracranial complications. A mastoidectomy with tympanoplasty is warranted in: (1) exteriorization, if the child is older than 30 months or >15 kg of weight, (2) intracranial complications (combined with a neurosurgical procedure as needed) and (3) cholesteatoma or granulation tissue.

In a study of Casula et al. a fatal case of acute mastoiditis was obtained in a person with HIV infection. The mastoiditis was complicated by thrombosis of the sigmoid sinus and an intracerebral abscess caused by an unusual pathogen – Nocardia asteroids. Sulfonamides have remained the first-line agents for the management of Nocardia infections, but mortality
remains high in patients with intracerebral infection.

A few reports related to cochlear implantation concern children with otitis media. In a study by Lunz et al.\(^8\) the risk for otitis media after cochlear implantation in otitis media (OM)-prone and non-OM-prone children was assessed. Onehundred and thirteen children were referred for cochlear implantation during the study period, and were implanted under the age of 7 years, 70 were classified as OM-prone and 43 as non-OM-prone. Postimplantation follow-up ranged from 6 to 75 months (average 35.5 months). During the first month after implantation 18 children suffered from acute otitis media, the vast majority of them (n=16) belonged to the OM-prone children (22.8% of this group) and 2 subjects belonged to the non-OM-prone children (4.6% of this group). During the late post-operative period 28 of the OM-prone children (40%) and 4 of the non-OM-prone children (9.3%) developed acute OM in the implanted ear. Eleven (9.7 %) of these cases, 10 belonging to the OM-prone (14%), and one belonging to the non-OM-prone group A (2.3%) proved to be recurrent and therapeutically challenging. Three subjects developed acute mastoiditis without intracranial complications. Each episode of mastoiditis or otitis media was controlled conservatively without any need of surgical drainage of the mastoid. It is concluded that early referral led to early implantation, even in children susceptible to OM. The incidence of OM decreased after implantation in both groups, but was still significantly higher in the OM-prone group. Meanwhile, prior to CI it is not possible to predict the cases that become therapeutically challenging at a later stage.

In another retrospective study\(^6\) from Israel the complication rate of cochlear implantation (CI) was evaluated and two different surgical approaches compared. The patients underwent CI between 1989 and 2003 and were followed-up for at least 18 months. The patients were divided into two groups according to the surgical technique that had been used for the implantation: the mastoidectomy with posterior tympanotomy approach and the suprameatal approach (without mastoidectomy). The incidence of complications following CI was compared between the two groups and between children and adults. Facial nerve paralysis, electrode misplacement, injury to the chorda tympani nerve and mastoiditis occurred only in the mastoidectomy with posterior tympanotomy approach group. Acute middle ear infection with or without mastoiditis emerged as the most common complication in both groups, followed by vestibular and wound problems. The suprameatal approach was demonstrated as being a good alternative technique to the classical surgery for CI.

Facial Paralysis. Facial paralysis is another serious but uncommon complication of OM. Nowadays, facial paralysis in relation to acute OM occurs at an estimated incidence of 0.005%, which should be compared to 0.5-0.7% in the pre-antibiotic era. A retrospective study by Popovtzer et al.\(^6\) on children with facial palsy and acute OM showed antibiotic therapy and myringotomy to be the first-line procedures. Surgery should be employed in case of acute or coalescent mastoiditis, supplicative complications and lack of clinical regression.

In a retrospective study by Evans et al.\(^7\) the causes and treatment of facial paralysis was characterized in pediatric patients. Thirty-five patients identified with partial or complete facial paralysis were evaluated between 1997 and 2003. A review of the medical records including sex, age, laterality, etiology, therapy, severity of paralysis according to House-Brackman (HB) six-point grading scale, duration, and degree of recovery was performed. The causes of facial paralysis were infectious (n=13), traumatic (n=7), iatrogenic (n=5), congenital (n=4), Bell's/idiopathic (n=3), relapsing (n=2) and neoplastic (n=1). Peak age distributions for both infectious and traumatic etiologies were bimodal: 1-3 and 8-12 years. Of the 13 infectious cases, 11 were associated with acute otitis media in combination with OME. Four (4/11) were bacterial-culture negative. Seven (7/11) were bacterial-culture positive, four (4/7) of which required prolonged, broth-medium culture. Bacteria cultured predominantly included *Staphylococcus non-aureus* species (5/7) and *Propionobacterium acnes* (3/7). One (1/13) was viral culture positive (*Herpes simplex* virus). All six patients who received intravenous steroids for OME-associated facial paralysis received the
doses within the first week of presentation and had complete recovery (HB I/VI); three of five patients who did not receive steroids had complete recovery. There were five iatrogenic cases; two (2/5) were planned surgical sacrifices and three (3/5) were complications of middle ear/mastoid surgery. Facial nerve function associated with infection returned in 0.5-2 months while, when associated with trauma, returned in 0.25-30 months. The study concluded that in infectious or traumatic facial paralysis, children aged 1-3 and 8-12 years are the primary groups involved. In acute otitis media alone or mixed with OME the culture-identified organisms may not be representative of traditional pathogens. Infectious facial paralysis averaged 1 month for recovery while traumatic facial paralysis averaged 9 months. Intravenous steroid therapy may improve the outcome. Recovery was complete (HB I/VI) in 8/10 infectious and in 4/6 of the traumatic cases.

Hydén et al.\textsuperscript{88} described inner ear complications and and/or facial paralysis secondary to acute otitis media in 20 patients. Nineteen patients had inner ear symptoms. Eight of them had a unilateral sensorineural hearing loss and vertigo, three had vertigo as an isolated symptom and one, with bilateral AOM, had bilateral sensorineural hearing loss. Seven patients had a combination of facial palsy and inner ear symptoms (unilateral sensorineural hearing loss in three, unilateral sensorineural hearing loss and vertigo in two, bilateral sensorineural hearing loss and vertigo in one with bilateral AOM, and vertigo alone in one). One patient had an isolated facial palsy. Healing was complete in 11 of the 20 patients. In seven patients a minor defect remained at follow-up; a sensorineural hearing loss at higher frequencies in all. Only two patients had obvious defects, a pronounced hearing loss in combination with a moderate to severe facial palsy in one (House-Brackmann grade 4), distinct vestibular symptoms and a total caloric loss in combination with a high-frequency loss in the other. Eight patients had positive bacteriological cultures from middle ear contents: \textit{Streptococcus pneumoniae} in two, beta-hemolytic \textit{Streptococcus} group A in two, beta-hemolytic \textit{Streptococcus} group A together with \textit{Staphylococcus aureus} in one, \textit{Staph. aureus} alone in one and coagulase-negative \textit{staphylococci} (interpreted as pathogens) in two. In the 12 patients with negative cultures, there was a probable bacteriological cause due to the outcome in SR/CRP and leukocyte count in five. In four patients serological testing showed a concomitant viral infection that was interpreted to be the cause; varicella zoster virus in two, herpes simplex virus in one and adenovirus in one. In three there was a probable viral cause despite negative viral antibody test due to normal outcome in SR/CRP, normal leukocyte count, serous fluid at myringotomy and a relatively short pre-complication antibiotic treatment period. Although the number of patients in this study is relatively low the findings show that inner ear complications and facial palsy due to AOM can be of both bacterial and viral origin. Severe sequelae were found only where a bacterial origin was proven.

The functional recovery in patients with facial paralysis due infective causes were reported in a retrospective study by Makeham et al.\textsuperscript{89} The patients were identified from a database of 1074 patients with facial paralysis. One hundred twenty of the 150 patients identified as having facial paralysis due to an infectious disease caused by \textit{Herpes zoster} oticus were excluded from the study. The remaining 30 patients were included in the study. Patients were treated both operatively and nonoperatively. Operative treatment included myringotomy and ventilation tube placement, cortical mastoidectomy, modified radical (canal wall down) mastoidectomy, petrous apicectomy, and lateral temporal bone resection. The House-Brackmann (HB) grade of facial function at 1 year after initial assessment was used to evaluate the outcome. The causes of facial paralysis were acute otitis media (n = 10); cholesteatoma (n = 10 [acquired, 7; congenital, 3]); mastoid cavity infections (n = 2); malignant otitis externa (n = 2); noncholesteatomatous chronic suppurative otitis media (CSOM; n = 2); tuberculous mastoiditis (n = 1); suppurative parotitis (n = 1); and chronic granulomatosis (n = 1). The patients with noncholesteatomatous CSOM who presented sooner after the onset of facial nerve symptoms had greater facial nerve recovery when assessed using the HB grade at 1 year. It is concluded that facial paralysis due to infective causes other than
Herpes zoster oticus is rare. Patients with noncholesteatomatous CSOM and FNP have a better outcome than those with facial paralysis due to cholesteatoma. Patients with facial paralysis due to acute otitis media tend to have a good prognosis without surgical decompression of the facial nerve being required.

In a case study from Sweden a patient presented with facial palsy after an acute otitis media episode. The facial palsy was shown to be the first symptom of Wegener’s granulomatosis. The clues leading to diagnosis consist of the practitioner’s suspicion of the disease, the use of appropriate serological measurements, and the histological confirmation. The early initiation of treatment leads to high rates of remission of an otherwise lethal disease.

INTRACRANIAL COMPLICATIONS

Leskinen and Jero published a paper on complications of acute otitis media. The retrospective chart review showed all pediatric patients treated for intratemporal and intracranial complications of AOM over a 10-year period; 1990-2000. The only intracranial complication was an extradural abscess with meningitis. In a review by Leskinen he summarizes that intracranial complications are encountered today only rarely in developed countries. Meningitis is found in 1-4% of the patients with AOM. Sinus thrombosis, intracranial abscesses and otic hydrocephalus are reported in 0 to 5%, 0 to 7% and 0 to 6%, respectively in children with acute otitis media. Encephalitis associated with AOM has been reported only occasionally during the past decade.

In a study by Redaelli de Zinis et al. two cases of internal jugular vein thrombosis without sigmoid sinus thrombosis were described secondary to acute mastoiditis. This complication was successfully treated with anticoagulation therapy and antibiotics. The authors claimed that surgery should only be performed to eliminate the source of infection from the middle ear and mastoid.

In a study from Ireland over a 7-year period showed twelve cases, 6-73 years of age. Five had brain abscesses, four had lateral sinus thrombosis and 3 had petrous apicitis. Eight were secondary to chronic otitis media and 4 were secondary to acute otitis media.

Miura et al. reported six cases during a 2-year period in Brazil. The most common complication was meningitis, which was detected in all cases. Five of them had abscesses, three cases manifested as hydrocephalus. Lateral sinus thrombosis occurred in 2 patients.

In a retrospective study by Kim et al. cochlear implantation in patients with a history of chronic otitis media was analysed. Four hundred eighteen cochlear implantations were investigated and nine patients who had chronic otitis media in the ear to be implanted were included. Of these, three showed active inflammation at presentation; the other six cases had undergone previous tympanomastoidectomy surgery and did not show active inflammation at presentation. Five patients with active inflammation or without an adequate soft tissue layer in the mastoid bowl underwent a two-stage procedure. Four cases who showed inactive inflammation and had an adequate tissue layer to protect the electrode array underwent a single-stage technique, although two of them showed dry TM perforation. No local or intracranial inflammation recurred.

GOALS FOR FUTURE RESEARCH

Research goals for the sequelae and complications due to otitis media are listed as follows. The list resembles that of the Panel from 2003. Despite some of the goals have been addressed however, further studies to increase our understanding are still needed.

1. The sequelae of OM have to be better understood. The sequelae related to AOM, SOM and treatment should be differentiated, and studied separately.

2. The pathogenesis of TM atrophy has to be studied in experimental models in order to prevent or treat TM atrophy.

3. Tympanic membrane retraction pockets have to be studied further clinically and with the new animal models.
4. Pathogenesis of adhesive otitis has to be further studied to develop preventive strategies.

5. The pathogenesis of and myringosclerosis and tympanosclerosis needs to be clarified. Treatment methods to prevent these conditions have to be studied in terms of safety and efficacy.

6. The mechanisms of change in mastoid pneumatization secondary to OM should be investigated. Animal models should be developed to confirm this hypothesis.

7. The transient and permanent effects of OM in the vestibular system should be clarified.

8. The transient and long-term effects of inflammatory mediators of OM in the ME and the inner ear need to be studied further.

9. Though rare, the severe complications of OM needs to be further investigated. The potential underlying mechanisms; such as high resistance rates, overdiagnosis, or delayed treatment, need to be documented and clarified.

10. A need to develop consensus for the best and minimally invasive method of treatment for acute complication of OM such as mastoiditis, facial palsy, or intracranial involvement deciding when to perform surgery or myringotomy and antibiotics.

PARTICULAR RESEARCH NEEDS FOR HEARING LOSS AND AUDITORY FUNCTION ASSOCIATED WITH OTITIS MEDIA WITH EFFUSION

1. There continues to be a dearth of developmental studies examining effects of OME on hearing as a function of onset, severity, and duration of hearing loss. A better understanding of the natural history of hearing loss including these variables is necessary in order to understand any potential impact of OME and how many children will be affected by various degrees and duration of hearing loss. Current research indicates that hearing thresholds should be routinely tested in children with OME rather than relying on parents’ judgments, even if formal questionnaires and parental education about symptoms are used.

2. Prospective studies are needed that investigate the required frequency of hearing testing over time to adequately describe the burden of hearing loss.

3. There is an urgent need for development of valid methods for describing longitudinal variations in hearing of children with OME over time.

4. Further research on sensorineural hearing loss using randomized controlled trials is needed to determine whether high-frequency sensorineural hearing loss is a result of the disease or of treatment with ventilation tubes.

5. Future studies of OME and development should include hearing level as a mediating variable.

6. Future studies should examine whether central auditory function is causally related to OME and, if so, how laboratory measures of complex auditory processes relate to functional ability to process speech in natural environments.

7. There is a need of validated questionnaires to determine the quality of life in children with SOM as this will influence the decision of tympanostomy treatment or not.

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