2. EUSTACHIAN TUBE, MIDDLE EAR, AND MASTOID: ANATOMY, PHYSIOLOGY, PATHOPHYSIOLOGY, AND PATHOGENESIS

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PANEL OBJECTIVES

1. Summarize important new contributions to our understanding of the anatomy, physiology, and pathophysiology of the middle ear (ME) system relevant to otitis media (OM) and certain related diseases and disorders, published since the Eighth International Symposium on Recent Advances in Otitis Media in June 2003.

2. Determine whether the short- and long-term research goals identified at the previous meeting of this Panel have been met.

3. Identify deficiencies in our understanding of the anatomy, physiology, and pathophysiology of the ME System related to OM.

4. Define and prioritize research goals that address deficiencies in our knowledge for investigation during the next 4 years.

5. Identify the short- and long-term goals for the future and methods by which they can be accomplished.

The following are publications related to the Eustachian tube (ET), middle ear and mastoid gas-cell system reported in the literature since the last research meeting in 2003. They include the anatomy, physiology, pathophysiology, and tests of function of the tube, as well as the role of the ET in the pathogenesis of middle-ear disorders and diseases. Also, these aspects related to the middle ear and mastoid gas-cell system are reviewed. But, there has been no attempt to include every publication reported during this time. This review is meant to be a state of knowledge since the last research conference up until the deliberations at this meeting.

EUSTACHIAN TUBE

Certain aspects of the ET were addressed in a recently published book by Bluestone (Eustachian tube: structure, function and role in otitis media), which viewed the ET as part of a system in which the nasal cavities, nasopharynx and palate are at the tube's anterior end and the middle ear and mastoid gas cells are at its posterior end. Also, a summary of research on otitis media, including the ET, middle ear and mastoid, conducted at the Children's Hospital of Pittsburgh and University of Pittsburgh since 1969 has been published.

Anatomy. Human babies are born with immature structures and functions which includes the ET and its immature immunity. This fact contributes to a high incidence of otitis media in human during the first year of life. Abe assessed the origin and insertion of the human tensor veli palatini muscle from an anatomic standpoint and confirmed that the dilator tubae of the tensor muscle acts to dilate the tube. They concluded the hamulus of the pterygoid acts strictly as a pulley for the tensor tendon and that its function could be maintained by preserving or reconstructing the maxillary placing during a pushback procedure for cleft palate repair, even if a hamulectomy is performed, it should not affect the function of the tensor. Studies of human temporal bone specimens from fetus to adults have shown that Ostmann's fat pad could vary in its location, which hypothetically could enhance or deter ET function. Orita reported that incomplete development of connective tissue in the region lateral to the ET
could be related to dysfunction of the tube. In addition, Suzuki examined the ratio of the tensor veli palatini muscle insertion to the length of the cartilaginous ET in human temporal bone specimens and found the ratio increased from infancy to adulthood, but then decreased with age. They postulated that this change may have some effect on pressure-regulation function in the elderly. Renko and colleagues used MRI imaging to investigate the nasopharyngeal airway in healthy children and compared the findings with their history information. They found that the dimension from caudal edge of septum to the midpoint of sella, which reflects the height of the nasopharynx, was on average 2.2mm smaller in children with history of OM, and that the nasal base angle was on average 2.1 degrees smaller in children with OM in the prior year.

**Physiology.** At the Symposium that preceded this Panel, two reports considered the physiology of the human ET: one was related to the impact of human evolution and the other compared the ET function between species. Bluestone presented the hypotheses that humans are the only species afflicted with otitis media, in particular with its extraordinary rate in infants and young children, in other species, such as non-human primates, otitis media associated hearing loss would more likely lead to death due to their natural predators. Differences in comparative anatomy and physiology were proposed as the cause of relatively poor ET function in humans. Indeed, Swarts and Ghadiali, using the forced-response test, described interspecies differences in function which and showed that the human functioned relatively poor compared with the monkey. In an ET compliance model of the monkey, Ghadiali and co-workers described the viscoelastic properties of the ET using pressure-flow hysteresis loops and a computer model. Later, the same group, developed a computational technique, which quantified the structure-function relationships of ET and, which the investigators believed, could be helpful in targeting treatment. Compliance of the ET was also assessed with a new functional 3-D model digital image system with the emphasis on the role of the medial pterygoid muscle. It concluded that this muscle may influence the opening of the ET, and this could be related to the patulous ET disorder and to patients with cleft palate. Brattmo fitted tympanostomy tubes in healthy volunteers in which the external canal was plugged with a pressure transducer. They found negative pressure in the ME and difficulty in equilibrating pressure differences through the ET. For the first time in humans, surfactant proteins have been detected in the Eustachian tube as well as in the organ of Corti and kidney. Mandell and colleagues (2003) reported that there is an effect in ambient oxygen concentration on the bioelectric properties of the middle-ear mucosa in experiments on the gerbil, which suggested a role for calcium-activated chloride channels in the middle ear. Franz and Anderson, (2007) demonstrated that sympathetic axons were sparse, but CGRP-immunoreactive, nociceptive axons formed a dense subepithelial plexus beneath the ET epithelium, and that capsaicin alone did not affect ET function but capsaicin applied with an alpha adrenoceptor agonist impaired ET function.

Picciotti and colleagues using a novel electromyography technique for TVP muscle, studied electrophysiological parameters in patients affected by chronic OM and in normal subjects. No differences were found between the affected by OM and the normal subjects. However, significant differences were found in the OM group between normal and affected sides. Didyk investigated the role of atmospheric pressure fluctuations (APF) in developing psychophysiological and autonomic reactions. Their results suggest that humans react to slight APF at the subcortical level.

**Pathophysiology.** Thirty-eight older children, adolescents and adults who had tympanostomy tubes placed for chronic otitis media with effusion were found to have ET dysfunction, primarily paradoxical constriction of the tube upon swallowing, as opposed to normal dilation. In studies in the monkey model, Ghadiali and co-workers injected botulinum into the tensor veli palatini muscle then assessed compliance using a new test of this function, continuous pressure—flow rate, and reported the lack of tubal dilation, increase in tubal compliance and abnormal forced-response ET function, but the tube did not abnormally constrict when the animal swallowed. Investigators from Iran reported that children with a deep dental overbite were 10.6 times more likely to have ET...
dysfunction than those without this dental abnormality.\textsuperscript{22}

Using Bluestone’s 9-step inflation-deflation ET test in patients with or without ventilated intranasal packs showed no difference in ET function; the authors noted that this is the first ET function test reported for packs, as previous studies only used tympanometry.\textsuperscript{23}

There were many reports concerning the patulous ET, especially from Japan. A patulous ET was reported as a sequela following a Le Fort 1 osteotomy in a cleft palate patient.\textsuperscript{24} Also, in a review article on ET dysfunction, Grimmer and Poe reported a patulous ET is associated with a defect in the longitudinal scaphoid in the antero-lateral wall of the cartilaginous portion of the ET which results in a closing failure of the tube; they identified this with endoscopy and reported that there is now CT scan evidence of this defect.\textsuperscript{25} In an earlier study, Yoshida and co-workers also used high resolution CT scans, with multiplaner reconstruction technique, to identify a patulous ET.\textsuperscript{26} An earlier study from this group compared the outcomes of sitting versus recumbent positions during the imaging.\textsuperscript{27} In an interesting report from Japan, investigators found that 8.8\% of 147 patients undergoing hemodialysis had a patulous ET and considered this as the dysfunction associated with patients who report ear symptoms during this procedure.\textsuperscript{28} In an earlier report from the same group, Kawase and co-workers using an artificial middle ear studied autophony associated with a patulous ET.\textsuperscript{29} Also from Japan, an interesting risk factor for the occurrence of a patulous ET was a previous episode of otitis media, which was attributed to a pathologic sequela of infection in the ET.\textsuperscript{30} Again from Japan, Kikuchi and colleagues reported that three-dimensional CT scans were able to diagnose (100\% specificity) the patulous ET in patients in the sitting position.\textsuperscript{31} An unusual cause of a patulous ET was identified on the CT scan of a patient with oculoauriculovertebral spectrum in which the osseous portion, as opposed to the usual cartilaginous portion, was grossly enlarged, which indicates that imaging in these patients with symptomatic patulous ET could be diagnostic of an unusual cause.\textsuperscript{32} And still another interesting report from Japan described a patient who had a patulous ET as the presenting symptoms related to an underlying intracranial hypotension syndrome which resolved after an epidural blood patch.\textsuperscript{33} The development of the patulous ET was attributed to changes in venous blood distribution which led to collapse of the dural sac of the cervical spine which presumably caused decreased size of the pterygoid plexus around the ET.

Yoshida and colleagues examined the bony portion of stenotic ETs, as defined by high opening pressures using multiplanar CT.\textsuperscript{34} They found that the bony framework was smaller and the soft tissue ratio was greater in patients with stenotic tube than in normals.

Models of the ET and middle ear are being developed to better understand the physiology and pathophysiology of the system. Kanick and Doyle developed a mathematical model to estimate the probability of otic barotrauma based on ET function and concluded that individuals with obstructed ET would be less likely to experience this problem than those who have difficulty in dilating the tube during swallowing.\textsuperscript{35} This is consistent with the report that children with middle-ear effusion usually do not have symptoms during air flight, whereas those who have recurrent otitis media, but who have no effusion at the time of flight, frequently do have complaints referable to the ear. Using a physical model of the middle-ear cleft, Cinamon determined that when the ET is blocked, the smaller the mastoid gas system, the greater the negative middle-ear pressure change.\textsuperscript{36} Also, with the aid of this model, these investigators concluded that under physiologic conditions, the amount of gas flow through the ET is more than sufficient to equalize middle-ear negative pressure that might occur when the tube is very narrow or only open for a very short time, but flow will not occur if the ET is completely occluded.\textsuperscript{37} In a unique study using the Visible Woman Project, a virtual reality model of ET dilator function was developed and used to assess methods of cleft palate repair.\textsuperscript{38}

Similar to flying, alternobaric vertigo (i.e., unequal ET equilibration function between the two middle ears during rapid atmospheric pressure changes) can occur in scuba divers which was studied by investigators from Turkey who identified a past history of otitis media, ET dysfunction (as determined by Bluestone’s 9-step test and Toynbee test), and difficulty clearing ears during diving were risk factors.\textsuperscript{39} In a later study from Germany, investigators tested 63 sport scuba divers and
reported that 27% had alternobaric vertigo, more common in females than males, but this disorder was not life-threatening. A case was reported in the neuroradiology literature describing severe middle-ear barotrauma in a scuba diver that resulted in rupture of the tegmen tympani with blood and gas in the epidural space of the middle cranial fossa. Also, a report from Denmark described 4 cases of cabin attendants who developed a perilymphatic fistula during air flights after which the authors advised against those who have poor ET, especially during a period of an upper respiratory tract infection to fly.

In a case report in the radiology literature, the authors described a habitual sniffer for chronic ET dysfunction who developed vertigo associated with calvarial (occipitoparietal) and upper cervical hyperpneumatization due to the Valsalva maneuvers.

Investigators from Turkey demonstrated, using a radionuclide in patients without any head and neck pathology, that nasopharyngeal secretions do not reflux into the middle ear during the recovery phase from a general anesthesia.

From Italy, employing audiometry and tympanometry, orthodontists studied children with maxillary constriction during rapid maxillary expansion and reported that there was improvement in conductive hearing loss, which was attributed to changes in palatal-paratubal musculature. Even though this was an uncontrolled study without valid evidence of ET function and presence of middle-ear effusion, it provides possible insight into the pathogenesis of otitis media in some children.

The pathophysiology of the ET associated with cleft palate in children continues to be an area of interest. From Pittsburgh, Gungor and associates reported at the Symposium that preceded this Panel meeting that ET dysfunction can be assessed using not only manometric tests, but also that MRI of the tube is a potential method to evaluate structure of the tube.

Pathology. In a recently reported temporal bone study of a term fetus with bilateral cleft palate from Germany, the levator palatini muscle was found to have an abnormal course, which was postulated to possibly related to the high incidence of otitis media in these children. In a brief report of an apparently unique case of a 35-year old male with relapsing polychondritis had a symptomatic patulous ET associated with an anacoustic ear as well as vertigo and tinnitus. From Korea, investigators exposed the ET of rats to relatively short-term cigarette smoke and found histologic changes in the tubal mucosa, e.g., squamous metaplasia. Also from Korea, Baek and colleagues described only the fourth reported case of a melanoma arising from the mucosa of the ET. In a rare case report from Taiwan, using CT scans and MRI, a nasopharyngeal carcinoma was identified as spreading along the ET into the middle ear and mastoid, which caused a middle-ear effusion. From China, surgeons reported that the pathologic changes in the ET following radiotherapy for carcinoma of the nasopharynx is not always obstructive, but may result in a patulous ET and concluded that examinations (e.g., tubal endoscopy) of the tube should be performed to determine the type and severity of the ET pathology for appropriate treatment. A case of a mature teratoma of the ET was reported from Thailand.

Pathogenesis. In a study in children who had recurrence otitis media following extrusion of tympanostomy tubes, Straetemans and colleagues determined that the combination of ET dysfunction and low IgA or low IgG2 levels, and decrease in mannose-binding protein was associated with recurrence. From Japan, investigators identified 20 patients with eosinophilic otitis media who had an associated patulous ET, diagnosed by sonotubometry, and who also had bronchial asthma; they posited the eosinophilic-laden secretions entered (refluxed) into the middle ear.

Investigators from Pittsburgh demonstrated on rat otitis media model that while gastroesophageal reflux do induce Eustachian tube dysfunction, this response is insufficient to cause otitis media with effusion or prolong an episode of acute otitis media. From Serbia, surgeons assessed mucociliary transport through the middle ear and ET in patients with chronic suppurrative otitis media with the saccharine test and found that transport was dramatically decreased, compared to control patients who had traumatic perforations of the tympanic membrane. In a study of 7047 Japanese Air Force trainees tested in a hypobaric chamber, 6.1% had ear pain and of these airmen there was an association between the presence of allergic rhinitis and
otalgia, especially in the spring of the year, which suggested ET dysfunction. From Pittsburgh, exposure of middle ear epithelial cells to physiologically relevant negative pressure was shown to trigger the release of key inflammatory mediators, which may be analogous to the middle ear underpressure in Eustachian tube dysfunction.

Tests of Function. In addition to the new tests of function described above (see Physiology), especially to assess compliance of the ET there have been other new, or modifications of old, ET function tests described. Radiopaque contrast material was placed at the nasopharyngeal orifice of the ET, which refluxed into the middle ear during swallowing and yawning as demonstrated on CT scans; this finding was similar tests in the past that used standard radiographs or fluoroscopy. Also, 3-dimensional CT scans were reported to be diagnostic in identifying the patulous ET. Another diagnostic test to identify a patulous tube used the acoustic transfer function of the ET using audiometric measurements, which also was purported to assess severity of the disorder. Employing Bluestone’s 9-step ET inflation-deflation function test, Adali and Uzun evaluated the effect of dry versus wet swallows on the outcome and concluded the dry swallows provided more accurate assessments of function when only one test is performed. Using a 2.5-mm flexible endoscope, seven normal adults had a successful examination of the structure and function of the ET and in some, topical anesthesia was needed. From China, surgeons, using a rhinopharyngoscope, compared the nasopharyngeal orifice of the ET in patients with otitis media with effusion to a control group, and reported the shapes in the otitis media group were abnormal, and variable in shape, compared to the control group. Ghadiiali investigated the physical properties that may influence ET opening phenomena, including tissue mechanical properties (viscoelasticity), micro-scale adhesion properties within mucosa. The standard force-response test was modified to generate oscillatory pressure-wave forms in the ET. Analysis of the FRT results of adults using a mathematical model provided important insights into the mechanisms responsible for ET dysfunction.

In monkeys, Alper and colleagues (2003) assessed the accuracy of tympanometry in correctly measuring middle-ear underpressures and concluded it was an unbiased, accurate and non-invasive method and that tympanometry could be used in other species, as well. In a report from Denmark, the rapid rate of pressure change in the newer tympanometers did not decrease the accuracy of measuring the middle-ear pressure.

Investigators in Germany used sonotubometry with a 8 kHz signal in healthy adults, but reported that it was not reliable. But, in another updated sonotubometry test in healthy adults (and a later publication in healthy children) was found to have high reproducibility, but was not tested in patients with middle-ear disease. One test thought to be an effective test of middle-ear ventilation through the ET was scintigraphy using technetium-99m, but a study in the rabbit model failed to demonstrate effectiveness. Investigators from Japan used several tests of ET function, including an updated sonotubometry, which they termed tubo-tympanum-aero-dynamography, which was useful to diagnose various ET disorders, especially patulous ET.

Investigators from Japan reported that audiometry with nasally presented noise was successful in diagnosing a patulous Eustachian tube. In a report from the Netherlands, a study of Eustachian tube function testing (forced-response, pressure equilibration, protective function) was not predictive of recurrence of otitis media with effusion in children.

Using the tests of ET function (forced-response, pressure equilibration, sniff), van Heerbeek and colleagues showed that children, who had tympanostomy tubes in place for otitis media, had different function test results between ears, thus the authors recommend against using split-level design studies.

From India, investigators used slow motion video endoscopy to assess the function of the ET in patients with and without middle-ear disease which was reported to be helpful in the diagnosis of ET dysfunction.

Management. There have been studies addressing the potential treatments for ET dysfunction. The efficacy of direct application of dexamethasone into the middle ear through a tympanostomy tube in 11 patients with ET dysfunction appeared to be promising in the short-term but long-term, randomized, placebo-controlled trials are yet to be
reported for this promising therapeutic option. In a study of 40 patients who had intra-nasal surgery for nasal obstruction and reported “ear fullness” preoperatively showed improvement of their symptoms and ET function postoperatively, but no improvement in tympanometric findings. In one study in the monkey, Ghadiali and colleagues performed experiments with surfactant and concluded this therapy might only be beneficial in rigid and inelastic ETs.

Five-fluorouracil (5FU) ointment was reported to be effective for prolonging the opening time of the myringotomy, thus effective for the treatment of OME.

In an effort to determine the efficacy of a gold tube wire (tube conductor), which was previously recommended for chronic ET dysfunction, investigators in Germany found it to be ineffective. From a study of rats, investigators from Japan showed that the ET possesses the immunologic characteristics of a mucosal effector site which responds to P6 outer-membrane protein of Haemophilus influenzae, lending support to the development of a vaccine against this bacterium.

Surfactant therapy for otitis media continues to be a subject of interest. Indeed, in a randomized, double-blind, placebo-controlled study of exogenous surfactant administered into the middle ear of rats, the surfactant decreased closing forces of the ET, but had no significant effect on mucociliary clearance. Indeed, intranasal aerosolized surfactant, alone or in conjunction with steroids, was employed in gerbils and mice reduced the passive ET opening pressure in normal animals and duration of middle-ear effusion in animals with experimental effusions. In an earlier experiment using guinea pigs, artificial surfactant was as effective as natural surfactant in facilitating ET opening function.

In an effort to alleviate the symptoms of a patulous ET in 10 patients (15ears), investigators in Japan ligated the pharyngeal end of the ET with the aid of an endoscope, and reported this method to be effective in nine ears. In another report from Japan, surgeons using a modification of the previously reported transcranial method to plug the middle-ear end of the ET in patients with a patulous tube (see: Bluestone CD, et al. Management of the patulous Eustachian tube. Laryngoscope 1981; 91:149-152.), was successful in relieving symptoms in 60% of 37 patients. In a similar surgical treatment, a patient with intractable tinnitus secondary to palatomyoclonus was corrected by blocking the protympanic portion of the ET with bone cement. Approaching the patulous ET from the nasopharyngeal end, surgeons inserted an autologous fat plug prior to cauterizing the proximal end of the tube, which was successful in 2 patients. Also approaching the ET from the nasopharyngeal end, Orlandi and Shelton, using an endoscope, cauterized the lumen and sutured the proximal end with success in 3 cases of cerebrospinal fluid otorhinorrhea and one patient with a patulous ET.

Surgeons in Japan found that patients who had cholesteatoma and were habitual sniffers due to closing failure of the ET had relief of their habit following surgery when there was an expanded air-bone gap in the lower frequencies of hearing after surgery.

In a review of autoinflation of the ET and middle ear for hearing loss due to otitis media with effusion, the Cochrane Database concluded that despite the small size of the published studies, limited follow-up and treatment duration, auto-inflation seems a reasonable option while awaiting natural resolution of the effusion; further research was recommended, especially related to the duration of treatment and long-term impact of this management on developmental outcomes. But, at the Symposium that preceded this Panel discussion, Alper and colleagues presented the results of a randomized clinical trial of air inflation with the Otovent inflator, with and without corticosteroid therapy, compared with placebo, for otitis media with effusion, in which they concluded the treatment is very limited in its practical applicability to children, not acceptable to most parents, and holds little or no promise of efficacy. Interestingly and related to the previous report, Mudry reviewed the contributions made by Adam Politzer in developing inflation techniques to inflate the middle ear through the ET which dates back to 1863.

In a review of three randomized clinical trials of decongestant therapy to prevent otic barotrauma during flying, Mirza and Richardson found in one study of oral pseudoephedrine, adults had reduced symptoms, but the same medication and route in children did not prevent this complication. The third trial showed that oxymetazoline nasal spray taken 30 minutes before the flight did not prevent ear pain.
In Denmark, investigators assessed the gland tissue changes in the ET of a rat model of acute otitis media, and reported that goblet cells increased in density for up to six months after a pneumococcal acute otitis media, and a second similar experiment showed this sequela after the infection irrespective of the bacterial etiology except for Moraxella catarrhalis which lasted only a few weeks. This finding is consistent with clinical observations that this bacterium is not as virulent as the other common otic bacteria. In a follow-up study, Andersen and co-workers demonstrated that penicillin treatment of rats reduced the gland tissue changes in the mucosa of the ET during a pneumococcal acute otitis media; they posited that penicillin could reduce ET dysfunction by this process.

Even though nasopharyngeal carcinoma is relatively uncommon in the West, it is quite common in Asia and thus is a therapeutic challenge. Indeed, investigators in China reported success in dilating the ET that was obstructed following radiotherapy using a Swan-Gans thermodilution catheter. In a later report, investigators reported that patients who had had nasopharyngeal radiotherapy were possible candidates for tympanostomy tube placement to prevent otic barotrauma if they were to receive hyperbaric oxygen therapy. Investigators found that slow compression during hyperbaric oxygen therapy was helpful in prevention of otic barotrauma. Evidently slow compression prevents the ET from locking or near locking, which is consistent with the mechanics of the ET.

The use of lasers to ablate a portion of the nasopharyngeal end of the ET has been reported in 56 adults with chronic otitis media, with a reported 68.51% improvement, but the study was not a randomized, control clinical trial. More recently but still without a control, these surgeons reported 13 adults had this procedure performed with success in some, and that those who failed had allergic rhinitis or laryngopharyngeal reflux. In a later report, these investigators used the microdebrider to excise a portion of the proximal end of the ET in 20 patients which had a 70% rate of improvement in symptoms.

MIDDLE EAR

Even though there has been very little in the literature related to the anatomy of the middle ear during the last four years, there has been significant advances in our state of knowledge of its physiology, pathophysiology and role in middle-ear diseases and disorders related to ET function.

Anatomy. In a potentially very useful method to study the middle-ear anatomy, investigators from Taiwan, using 3-dimensional reconstructions and modeling of the middle-ear biomechanics was performed using high-resolution CT scans and finite analysis after which the investigators concluded that this method is quick, practical, low-cost, and most importantly noninvasive as compared with histologic sectioning. Anatomists in Hungary studied 70 macerated temporal bones stereomicroscopically to understand the protympanum of the middle ear and found the main structures of the medial wall of the protympanum are the carotid canal with the internal carotid artery and concluded that the presence of the artery is necessary for development of the canal, and if the artery takes an aberrant pathway, or is absent, there is no sign of the carotid canal. In study of human cadaver crania, Todd attempted to answer the question as to why the manubrium of the malleus appears to be pointing downward and posterior, but could only conclude that its orientation is widely variable. Hypothetically, the fore-shortening position of the malleus could be explained by the presence of commonly encountered, subclinical middle-ear underpressures, but this explanation does not explain the persistence of this deformity in the presence of a functioning tympanostomy tube. Palva and Ramsay dissected 145 temporal bones and described, in detail, the state of the soft tissue structures of the epitympanum, especially Prussak’s space, which is relevant for surgery of this anatomic area.

Physiology and Pathophysiology. From France, investigators using the experimental rat and a mathematical model studied the role of nitrogen in transmucosal gas exchange rates in the middle ear,
and concluded that gas absorption of the rat middle ear during steady-state conditions is governed mainly by diffusive nitrogen exchange between the middle-ear gas and its mucosal blood circulation.\textsuperscript{108} There was an earlier similar report from this team related to the latest publication.\textsuperscript{109} Herman demonstrated in vitro and in vivo fluid absorption through epithelium sodium channel during otitis media.\textsuperscript{110} Variation of fluid volume after LPS inoculation compared to control side was monitored by a special capillary tube. Compared to the control side, the fluid absorption rate in the LPS-treated middle ear was dramatically affected, but recovered over the 3 days, suggesting that function of sodium channel is well preserved and is a major factor in elimination of fluid development. Ar et al. (2007) utilized a rat experimental model to study trans-mucosal gas exchanges by measuring volume changes in the middle ear. Middle ear gas exchange was recorded after resolution of effusion caused by LPS inoculation.\textsuperscript{111} The middle ear gas volume decreased significantly faster with time in inflamed ears compared to the normal control. Mucosal thickness was significantly greater in the inflamed ears. These changes are consistent with increased mucosal blood flow. Also from the same group and reported at the Symposium that preceded this Panel’s deliberations, Kania and colleagues, employing similar methods and animal model as described above, as well as a mathematical model, concluded that transmucosal gas absorption in the middle ear during steady state conditions is governed mainly by diffusive N\textsubscript{2} exchange between the middle ear and its mucosal blood circulation.\textsuperscript{112} From the same group in another report in the Symposium, Ar compared the mucosal blood flow in normal and inflamed ears, concluding that the increased gas exchange, despite the doubling of the mucosal thickness may be explained by doubling the mucosal blood flow.\textsuperscript{113}

Another report from Pittsburgh also addressing middle-ear gas exchange of nitrogen, Doyle and colleagues, measured the nitrous oxide time constant for middle ear transmucosal gas exchange in monkeys and using a mathematical model concluded that there is an asymmetric rate of nitrous oxide and by extension, nitrogen exchange for the middle ear.\textsuperscript{114} In an earlier report from the same laboratory, Doyle and Banks, using monkeys, showed that breathing gas mixtures containing nitrous oxide causes predictable and quantifiable increases in middle-ear pressure.\textsuperscript{115} Middle-ear gas loss was assessed when its mucosa was inflamed in the rat, and from a mathematical model investigators in Israel concluded the model predicts that despite almost doubling mucosal thickness in the middle ear the increased gas loss may be explained by increased blood flow rate.\textsuperscript{116} Yuksel demonstrated that nasal inflammation induced by bradykinin and prostaglandin D2 challenge increased the inert gas exchange rate, indicating that persistent nasal inflammation would increase the demand on the Eustachian tube for the gas supply, and may result in otitis media with effusion when this demand is not met.\textsuperscript{116} Investigators from Israel also used a mathematical model to determine that diffusive gas transfer in relation to blood gas content is the leading mechanism to alterations in middle-ear pressure and volume in patients with tympanostomy tubes in place.\textsuperscript{117} The mechanism and rate of middle-ear fluid absorption was assessed in guinea pigs by investigators in Israel who reported that absorption is related to osmotic gradients within the middle ear.\textsuperscript{118} High resolution measurements of middle-ear gas volume changes enabled investigators in the Netherlands to estimate the mucosal CO\textsubscript{2} conductance in the rabbit.\textsuperscript{118}

Periodic assessments of middle-ear function using tympanometry over a five-year period in older adults, 28-92 years of age, were essentially stable.\textsuperscript{120} Gaihede and co-workers (2005) reported that viscosity and amount of middle-ear effusion can influence the tympanogram by increasing the peak pressure difference and that errors of more than 100 daPa can be anticipated.\textsuperscript{121}

Pathogenesis. In a study from Japan, Noda and colleagues reported at the Symposium that preceded this Panel’s discussions, sonotubometry did not reflect the precise condition of the cholesteatoma, but was helpful in assessing the prognosis for hearing levels and recurrence of the disease.\textsuperscript{122} An article was published that addressed the unresolved question as to why Australian aborigines have such a high rate of chronic suppurative otitis media, but a low incidence of cholesteatoma. Surgeons from Australia observed the aborigines had “crowding” of the posterior attic, due the incudostapedial assembly, which compromised drainage that hypothetically could result in non-cholesteatomatous disease,
whereas these structures supported the tympanic membrane preventing cholesteatoma.

The possible role of gastrointestinal reflux in the pathogenesis of otitis media continues to be investigated. From Egypt, investigators performed dual 24-hour pH probe testing for reflux in 31 children with otitis media with effusion, of which 71% were considered having the disorder. Also, the middle-ear effusions were tested using ELISA for pepsin/pepsinogen concentrations and they reported that there was a significant positive correlation between the presence of reflux and middle-ear levels, after which they concluded that children with otitis media should be suspect for reflux.

A study of adults with otitis media with effusion in Japan also revealed high pepsinogen levels in the middle-ear effusions which was common in those patients who also had symptoms of gastroesophageal reflux by questionnaire, but not by pH probe testing. In an earlier report, *Helicobacter pylori* was detected in middle-ear effusions in children. The problem with these reports is that we remain uncertain if these contents from the stomach are just refluxing through the ET and entering the middle ear, or are these findings indicative of a true pathogenesis of middle-ear disease. Indeed, stomach contents were not detected in post-tympanostomy tube otorrhea by Antonelli and colleagues.

**Management.** To date, attempts to employ preoperative ET function testing in predicting the outcome of tympanoplasty have been a subject that has not generated any specific recommendations. But, Takahashi and colleagues (2007) report that preoperative ET function tests (inflation-deflation and passive opening via the middle ear) were predictive of outcome; ET mechanical obstruction was associated with failure, and poor inflation-deflation testing and decreased mastoid aeration were also correlated with less favorable outcomes. In a related study, surgeons assessed the predictive value of tympanometric volume in children prior to tympanoplasty and reported that the larger the volume the better the success rate of the procedure. No doubt the volume size is related to the size of the mastoid gas-cell system.

**MASTOID GAS-CELL SYSTEM**

There are several lingering controversies regarding the mastoid gas-cell system. One is the role of the size of the mastoid system related to middle-ear disease. A recent study of 41 adult crania, without apparent clinical otitis media, were examined for the degree of attic (pars flaccida) retraction related to the degree of aeration of the mastoid system, found no relationship.

Another controversial issue is the role of the mastoid gas-cell system, and its size, related to the pressure regulation function of the middle-ear cleft. Doyle and colleagues (2003) measured the rate of nitrous oxide exchange across the middle ear mucosa in monkeys before and after blocking the mastoid antrum, which essentially sealed off the mastoid gas-cell system from the middle ear, and reported that the experiment did indeed decrease the middle-ear volume but did not affect the time constant for transmucosal nitrous oxide exchange. Also, in an attempt to resolve this question, Doyle (2007) developed a mathematical model of the system and fit an equation to published human pressure-regulation data and concluded that the larger the volume of the gas-cell system the longer will be the time required to develop sufficient middle-ear underpressures to cause otitis media by the ex vacuo theory or prolonged periods of ET dysfunction; the mastoid is a rate-limiter of middle-ear pressure. This model implies the mastoid gas-cell system is a “gas sink.” In an earlier study using a model of the middle-ear cleft, Cinamon and Sade (2003), using mastoids of various sizes concluded that the volume of the mastoid “dilutes” pressure changes, which may be related to middle-ear atelectasis and retraction of the tympanic membrane.

In a study in air-dried temporal bones of monkeys, Felding and co-investigators (2003) assessed the air-phase gas exchange between the tympanic cavity and the mastoid gas-cell system, which they found to be rapid. Magnuson (2003) posits that one of the functions of the mastoid gas cell-system is to protect the sensitive vestibular system from stimulation by external temperature changes, and also postulated the system acts as pressure regulator. In a study of
submariners, Toklu and associates (2005) assessed the susceptibility for otic barotrauma related to mastoid pneumatization and reported that mastoid aeration had no relationship.\(^{136}\)

Still another persistent controversial issue is the role of early otitis media on mastoid gas-cell-system growth: one school of thought posits no correlation (i.e., nature) and the other that early ET dysfunction and otitis media inhibits mastoid aeration (i.e., nurture). From Israel, Sade and colleagues (2006) compared mastoid radiographs of two groups of children, 2-11 years of age, in which one group with a history of otitis media and the other group without such a history, and concluded otitis media in infancy inhibits growth of the mastoid system could not be accepted.\(^{137}\) But, there was no documentation (other than a subjective history) of the presence or absence of otitis media in infancy. Indeed, a 5-year prospective study from Finland did conclude that otitis media in infancy (<17 months of age) was associated with a small mastoid gas-cell system from which the investigators recommended early tympanostomy tube placement with repeat insertions if necessary.\(^{138}\) One variant that could be improved in these studies of mastoid volume would be to use newer technology, such as proposed by investigators in Turkey who used high resolution CT scans in a 3-dimensional multiplaner volume rendering technique.\(^{139}\) Also, in a later report from Korea investigators used and now advocate three-dimensional reconstructions of the mastoid using CT scans.\(^{140}\) In another method, but in human temporal bone specimens, Oishi and colleagues (2003) used a computer-aided surface area measurement of temporal bone pneumatization from histologic sections.\(^{141}\)

**Management.** For establishing a method for regenerating mastoid air cells after mastoidectomy in chronic otitis media, Kanemaru and colleagues, after in vitro experiments, applied a collagen-coated honeycomb-structure hydroxy apatite containing calcium phosphate in three patients with cholesteatoma, and they found that recovery of mastoid aeration and restructuring of mastoid air cells were observed in two patients.\(^{142-144}\)

**PROGRESS ON GOALS OF THE 2003 PANEL REPORT**

There has not been any report on the role of progenitor cells in the ET and ME epithelium. However this goal may not be a high priority. Similarly there were no reports on the lymphatic system of the ET-ME-mastoid and its role in the pathogenesis of ME disease. Further, no studies of temporal bone specimens from patients in special populations with a known high incidence of OM, such as the Aborigines of Australia and certain Native North Americans have been performed. The Panel still feels that this goal is important, but because of the limitations of temporal bone studies, an increased emphasis on evaluating temporal bones with imaging modalities is warranted. The Panel suggests the inclusion of subjects with cleft palate and other maxillofacial anomalies that predispose subjects to ear disease. There have been a couple of publications identifying the essential structural properties that govern ET function with the goal of elucidating which components could be targeted for treatment. There has been an interest on developing experimental and computational tools to evaluate the relative importance of the various ET structure-function relationships, however more work needs to be done.

There have been a number of publications and progress on determining the relative contributions of ET gas transfer and ME mucosa in the maintenance of ME gas composition and pressure under normal and inflammatory conditions, however more work needs to be done on the actual measurement of gas transfer and the ratio and relative importance of each in the disease state. Some studies were done on the physiology of ion and fluid transport in ET-ME epithelium in normal and diseased states, but this subject remains unexplored. The Panel feels that determining the response of ME mucosal cell cultures to under pressures and changes in gas composition needs to be expanded by applying the concept of “mechanotransduction” in this research.

Assessing ET function in special populations known to have a high incidence of OM, and comparing these findings with function in
individuals without OM, in order to ascertain the underlying pathophysiology in these special populations is still considered important. Evaluation of agents shown to moderate ciliary beat frequency, ET clearance function or ET pressure-regulating function by means of standard models of OM pathogenesis has not been done and panel encourages this research. Due to the ethical and technical limitations of studying ciliary clearance, in humans, novel methods need to be developed.

The Panel feels that designing studies on the ME secretory conditions of mucopolysaccharidoses and management of these conditions before and after blood, marrow, and stem cell transplantation does not fall under its purview. Identifying the progressive stages in the pathogenesis of OME in a manner similar to the recent progress made in elucidating these stages in the development of AOM needs to be expanded to infants and young children. Investigating certain anatomical and physiological markers making some subgroups more susceptible to OME is thought to be important. The Panel suggests continuing to investigate the role of viruses in the pathogenesis of OM and identify targets or promising interventions designed to prevent development of OM during a viral upper respiratory tract infection. The Panel feels that studying the role of OM in the pathogenesis of meningitis in patients with and without inner ear malformations, and with and without cochlear implants is also not relevant to its mandate and suggests they be assessed by the panel on sequelae. The Panel still feels that more studies are needed to evaluate possible role of gastroesophageal reflux in the pathogenesis of OM. Conducting definitive, targeted randomized clinical trials was also found to be not within the scope of this panel.

FUTURE GOALS

1. Investigate the normal anatomy of the ET-ME-mastoid lymphatic system and determine the system’s possible role in the pathogenesis of ME disease.

2. Study histologic temporal bone specimens from patients in special populations that have a known high incidence of OM, such as the Aborigines of Australia and certain Native North Americans. Assess ET function in special populations known to have a high incidence of OM, and compare these findings with function in individuals without OM, in order to understand the pathophysiology of ear disease in these special populations.

3. Identify the essential structural properties that govern ET function with the goal of elucidating which components could be targeted for treatment.

4. Develop experimental and computational tools to evaluate the relative importance of the various ET structure-function relationships.

5. Determine the relative contributions of ET gas transfer and ME mucosa in the maintenance of ME gas composition and pressure under normal and inflammatory conditions with special attention to the actual measurement of gas transfer and the ratio and relative importance of each in various conditions of disease in each disease condition.

6. Study the physiology of ion and fluid transport in ET-ME epithelium in normal and diseased states.

7. Determine the response of ME mucosal cell cultures to underpressures and changes in gas composition and apply the “mechanotransduction” concept to investigate the effect of underpressures on cell function. Evaluate this mechanism with respect to the transduction of deficient ME pressure regulation into OM.

8. Evaluate those agents shown to moderate ciliary beat frequency, ET clearance function or ET pressure-regulating function by means of standard models of OM pathogenesis.

9. Identify the progressive stages in the pathogenesis of OME in a manner similar to the recent progress made in elucidating these stages in the development of AOM, expanding in infants and young children and investigating certain anatomical and physiological markers making some subgroups more susceptible to OME.

10. Investigate the role of viruses in the pathogenesis of OM and identify targets or promising interventions designed to prevent development of OM during a viral upper respiratory tract infection.
11. Study the possible role of gastroesophageal reflux in the pathogenesis of OM, with special attention on the pathogenesis.

12. Investigate trans TM gas exchange, with respect to its exchange or buffer or role in pressure regulation. And impact of TM inflammation or sequela ( tympanosclerosis, or atelectasis) on this function.

13. Investigate the pathogenesis of patulous ET, and its impact on ME pathophysiology.


15. Investigate the role of Tensor tympani muscle and pars flaccida on MEP regulation and its mechanisms. Include these in the computational models of MEP regulation.

16. Differentiate between pathophysiology of MEP regulation system in recurrent AOM and OME.

17. Investigate the role of neurogenic inflammation in MEP regulation, potential role of naso-ME cleft reflex.

18. Investigate the impact of negative MEP and gas composition on biofilm formation. Impact of biofilms on MEM gas exchange and ETF.

19. Develop novel methods to measure surface area, mucosal blood vessel density and distribution in the ME cleft.

The long-term objective of this research remains a better understanding of the physiology and pathophysiology of the ME system in relation to the pathogenesis of OM. To accomplish that objective, it is important that we refine our current models of ME pressure regulation, include as extensions to those models the mucosal changes that are precipitated at threshold underpressures, define rational interventions that reestablish adequate pressure regulation, and evaluate those interventions in the clinical population. The long-term goal of the research is to implement this paradigm and thereby define rational treatments for OM.

REFERENCES


12. Swarts JD, Ghadiani SN. Interspecies comparisons of eustachian tube flow patterns during swallowing in the forced-response


56. Chi D, Alper CM, Yuksel S, Swarts JD. The effects of gastroesophageal reflux on Eustachian tube function, the development of otitis media and the resolution of an induced episode of acute otitis media. Paper presented at: 9th International Symposium on Recent Advances in Otitis Media; June 3-7, 2007; St. Petersburg Beach, FL.


59. Hebda PA, Barsic M, Singh T, Dohar JE. Negative pressure-induced secretion of inflammatory mediators by cultured middle ear epithelial cells: relevance to Eustachian tube dysfunction and otitis media with effusion. Paper presented at: 9th International Symposium on Recent Advances in Otitis Media; June 3-5, 2007; St. Petersburg Beach, FL.


104. Alper CM, Mandel EM, Casselbrant ML, Doyle WJ. Efficacy of air inflation with and without corticosteroids for treating otitis media with effusion. Paper presented at: 9th International Symposium on Recent Advances in Otitis Media; June 3-7, 2007; St. Petersburg Beach, FL.


122. Kania R, Herman P, Huy PTB, Ar A. Transmucosal gas exchange rate of the middle ear is nitrogen dependent. Paper presented at: 9th International Symposium on Recent Advances in Otitis Media; June 3-7, 2007; St. Petersburg Beach, FL.

123. Ar A, Herman P, Lecain E, Wassef M, Huy PTB, Kania R. Gas loss from the middle ear in normal and inflammatory conditions: The role of mucosa thickness and blood flow. Paper presented at: 9th International Symposium on Recent Advances in Otitis Media; June 3-7, 2007; St. Petersburg Beach, FL.

124. Doyle WJ, Yuksel S, Banks J, Alper CM. Directional asymmetry in the measured nitrous oxide time constant for middle ear


