Pathogenesis of middle-ear effusion owing to the hydrops ex vacuo theory is now evidence-based from studies in humans and animals.

As summarized in Chapter 1, “Introduction,” many factors have been identified as being involved in the etiology and pathogenesis of middle-ear disease, other than dysfunction of the Eustachian tube (see Figure 1–7). The most important of these other factors would be host related, such as genetic predisposition, age, prematurity, gender, race, allergy, immunocompetence, and craniofacial abnormalities. Environmental factors are also important, such as upper respiratory tract infection, season of the year, attendance in child day care, number of siblings, exposure to smoking, absence of breast-feeding, socioeconomic status, and use of a pacifier (see Chapter 2, “Epidemiology”). In this chapter, I discuss the role of the dysfunctional Eustachian tube system in the pathogenesis of otitis media and certain related diseases and disorders. I proposed a few of these concepts many years ago, but now we have studies in both humans and animals to confirm some of the more common pathogenic sequences of events leading to otitis media. The reader should review my presentation of the pathophysiology of the Eustachian tube system in Chapter 5, “Pathophysiology,” to better understand the role of the tubal system in the pathogenesis of disease presented in this chapter; I also included some discussion of pathogenesis in that chapter.

As detailed in Chapter 5, many abnormalities of the Eustachian tube system can be attributed to the pathogenesis of middle-ear disease, some of which do not necessarily have to involve the existence of pathophysiology or pathology of the Eustachian tube itself to be present. The most obvious example of middle-ear infection that does not involve dysfunction of the tube in its pathogenesis is when there is a traumatic perforation of the tympanic membrane in an individual who has a Eustachian tube that functions normally; despite normal tubal function, the posterior, middle ear end of the system is open. These patients frequently develop an attack of acute otitis media, with otorrhea, at the onset of an upper respiratory tract infection. Infected nasopharyngeal secretions can reflux through the tube into the middle ear owing to the loss of the middle ear–mastoid gas cushion. Also, these patients can insufflate nasopharyngeal secretions through a normal tube into the middle ear by vigorously blowing the nose.

But, most commonly, Eustachian tube dysfunction is involved in the pathogenesis of middle-ear disease. I describe in detail the recent studies that have provided convincing evidence-based confirmation that the hydrops ex vacuo theory, first advanced by Adam Politzer over 100 years ago, is the most logical explanation for the development of middle-ear underpressures, which is the stage that precedes the most frequently encountered types of middle-ear disease: acute otitis media and otitis media with effusion. Clinical studies in adult volunteers and experiments in animal models have shown that Eustachian tube dysfunction is involved in the pathogenesis of middle-ear underpressures, otitis media with effusion, and acute otitis media. But first I provide an overview of the pathogenesis of middle-ear disease related to the various abnormalities of the Eustachian tube system as described in Chapter 5.

Overview of Pathogenesis Related to the Pathophysiology of the Eustachian Tube System

As summarized in Chapter 5, the Eustachian tube system can be either too closed or too open, or there is abnormal pressure at either end. The most common result of a dysfunction of the system is development of middle-ear underpressures, which can progress into middle-ear disease. But, as stated above, there are circumstances in which negative middle-ear pressure is not involved in the pathogenesis, such as when acute otitis media,
with otorrhea, occurs when the tympanic membrane is not intact, owing either to a perforation, a tympanostomy tube in place, or when the patient has had a radical mastoidectomy. The middle ear and mastoid can be infected by two major routes: reflux of infected secretions from the nasopharynx or contamination of the middle-ear cleft from the external auditory canal, most commonly from water in the ear canal. If the acute otitis media does not resolve spontaneously or following treatment, the acute disease can progress to chronic suppurative otitis media, as I discuss in this chapter. But dysfunction of the Eustachian tube system is most frequently the cause of underpressures developing in the middle ear, which can progress to middle-ear disease.

**Primary and Secondary Causes of Middle-Ear Underpressure Owing to Dysfunctions of the Eustachian Tube System**

Dysfunction of the system may be a primary or a secondary cause of middle-ear negative pressure. Abnormalities of the system that are a primary cause are due to either anatomic or functional obstruction of the tube or both. Anatomic obstruction is most frequently caused by inflammation, which is most commonly viral in etiology. Evidence for viruses as the cause of tubal dysfunction and middle-ear negative pressure has been demonstrated in studies that involved adult volunteers. However, as described below, subjects who had preexisting tubal dysfunction were at highest risk of developing middle-ear underpressures after being challenged with a respiratory virus inoculated into the nasal cavity. Development of underpressures in the middle ear could be from any of the intrinsic or extrinsic anatomic conditions that are related to pathophysiology of the tube itself (such as allergic inflammation); at either end of the tubal system, such as obstruction at the nasopharyngeal end, as might be caused by adenoids or tumor; or at the middle ear end of the system, such as cholesteatoma or polyposid granulation tissue.

Functional obstruction of the tube within its system can also cause primary development of middle-ear negative pressure. The possible underlying causes of functional obstruction of the tube are presented in Chapter 5 but include a floppy cartilage, dysfunction of the tensor veli palatini muscle, and constriction of the tube during swallowing. Functional obstruction of the tube has been identified by our team and confirmed by other investigators. A more dramatic and rapid example of a primary cause of middle-ear negative pressure by functional (as opposed to anatomic) obstruction is otitic barotrauma owing to “locking” of the tube during descent in an airplane, scuba diving, and hyperbaric oxygen therapy; the sudden negative pressure at the middle ear end of the tubal system functionally obstructs the tube. Patients who have preexisting dysfunction of the Eustachian tubes are at highest risk. Functional tubal dysfunction can also be induced at the proximal end of the tubal system and cause middle-ear negative pressure by either functionally obstructing the tube at the nasopharynx (the Toynbee phenomenon or in infants using a pacifier, thumb sucking, or sucking on a nonventilated milk bottle) or by aspirating gas out of the middle ear by sniffing.

A secondary cause of middle-ear underpressures would not be primarily related to anatomic or functional obstruction but secondarily to inflammation that occurs in the middle ear. Because middle-ear inflammation can obstruct the osseous portion of the tube, preventing adequate pressure regulation of the middle ear (anatomic obstruction at the middle ear end of the system, which can impair the pressure regulatory and clearance functions of the Eustachian tube), secretions are trapped in the middle ear. From my description of the inverted flask in Chapter 5, as liquid flows down the narrow neck, negative pressure develops in the bulbous portion of the flask. Negative middle-ear pressure has been identified in children who have otitis media with effusion. The most likely cause of inflammation occurring within the middle ear in this scenario is either from reflux (the tube is too open, too short, or both) of nasopharyngeal secretions into the middle ear or by insufflation of secretions from the nasopharynx into the middle-ear cavity by nose blowing or crying in infants or from the Toynbee phenomenon (if positive pressure is transmitted to the middle ear). From knowledge of fluid dynamics through a collapsible tube, liquid flows more readily than gas. Thus, if positive pressure has been identified in the middle ear during these events, nasopharyngeal secretions are even more likely to be forced into the middle ear.

**Middle Ear Negative Pressure Can Cause Otitis Media with Effusion and Acute Otitis Media**

The next step in the sequence of events leading to otitis media is the development of middle-ear effusion owing to the presence of underpressures in the middle ear; various mechanisms causing these pressures are discussed above. As postulated by Politzer, middle-ear negative pressure can cause transudation of fluid from the middle-ear mucosa into the cavity of the middle ear. Since his time, subsequent observations and now studies in humans and animals have provided evidence to support his hydrops ex vacuo theory. Obviously not available to Politzer 100 years ago, development of barotitis is a now a well-known complication of flying in an airplane (especially when the cabin is not pressurized), scuba diving, and during hyperbaric oxygen treatment in a pressure chamber. Another dramatic example of how middle-ear negative pressure can cause transudation of an effusion was shown by Ingelstedt and colleagues in which they aspirated the middle ear and mastoid with a syringe in aviators and produced middle-ear effusion. Even though these rapid alterations in pressures are impressive examples of effusion developing in the middle-ear cleft owing to the extreme and rapid onset of negative middle-ear pressure, they are not related to the pathogenesis of middle-ear disease in children and adults who have not been exposed to
these conditions. Therefore, we must turn to the studies in humans and animals described below. Also, the originally proposed classic ex vacuo theory does not explain if middle-ear negative pressure is a stage prior to an attack of viral or bacterial acute otitis media. But as shown below, following intranasal inoculation of a virus in an adult volunteer, Eustachian tube obstruction occurred, followed by middle-ear negative underpressure and the subject developing an attack of acute viral and bacterial otitis media. It is probable that the nasopharyngeal pathogens were aspirated into the middle ear. Thus, development of negative pressure in the middle ear can be an antecedent event for the pathogenesis of both otitis media with effusion and acute otitis media. As stated above, acute otitis media can be caused by other dysfunctions of the tube and pathogenetic mechanisms, such as reflux or insufflation of nasopharyngeal secretions into the middle ear, which do not have to have underpressures in the middle ear to occur. However, if negative middle-ear pressure is present, it will enhance reflux and insufflation into the middle ear.

Viral Nasal Challenge Studies in Adult Volunteers

Clinical studies of adult volunteers at our center have assessed nasal and Eustachian tube functions and the status of the middle ear following intranasal challenge with viruses. These studies demonstrated the role that the Eustachian tube plays in the pathogenesis of middle-ear underpressures, otitis media with effusion, and acute otitis media and are summarized in Table 6–1.

In an early study, Doyle and colleagues determined the effect of an upper respiratory tract infection (a cold) on Eustachian tube function and the status of the middle ear after intranasal challenge with rhinovirus in a group of 40 adult volunteers. After rhinovirus was inoculated into the nose, all subjects were found to be infected, but only 80% developed the signs and symptoms of a clinical illness. Before and periodically after this nasal challenge, assessments were made of Eustachian tube function (using sonotubometry and the nine-step test), middle-ear pressure (using tympanometry), and nasal patency (using active posterior rhinometry). All subjects who had a cold had decreased nasal patency, 50% had Eustachian tube obstruction, and 30% had abnormal negative middle-ear pressure for approximately 1 week after the inoculation. All outcomes completely resolved within 16 days, but none of the volunteers developed a middle-ear effusion.

In a subsequent study by McBride and colleagues that employed similar methods and design as described in the above-cited study, 32 adult volunteers were recruited. After the challenge with rhinovirus, abnormal findings were limited to the 24 (75%) subjects who developed clinical signs and symptoms of infection. After 2 days, 80% had Eustachian tube obstruction, 50% had high negative middle-ear pressure, and 46% had decreased nasal patency. Again, none of the subjects developed a middle-ear effusion. These abnormal findings resolved 6 to 10 days after the challenge.

A similar study by Buchman and colleagues evaluated 60 adult volunteers using a design and methods similar to the previous two studies. Figure 6–1 shows that after nasal inoculation with rhinovirus, 95% became infected and 60% had a clinical cold. Before the nasal challenge, three volunteers (5%) had abnormal middle-ear pressure, and in two of these subjects, a middle-ear effusion developed. Of the 60 subjects, 22 (39%) had high negative middle-ear pressure. None of the subjects who had normal middle-ear pressure before the challenge developed an effusion, indicating that a rhinovirus infection may result in a middle-ear effusion if the patient has a preexisting dysfunction of the Eustachian tube.

In still another study, but with a different respiratory virus, Doyle and colleagues reported that intranasal challenge with influenza A virus in 33 healthy adult volunteers resulted in

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Reference</th>
<th>Number of Subjects</th>
<th>Virus</th>
<th>Outcomes, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Doyle et al, 1988&lt;sup&gt;18&lt;/sup&gt;</td>
<td>40</td>
<td>Rhinovirus</td>
<td>ET OBS: 50, HNP: 30, MEE: 0, AOM: 0</td>
</tr>
<tr>
<td>2</td>
<td>McBride et al, 1989&lt;sup&gt;19&lt;/sup&gt;</td>
<td>32</td>
<td>Rhinovirus</td>
<td>ET OBS: 80, HNP: 50, MEE: 0, AOM: 0</td>
</tr>
<tr>
<td>3</td>
<td>Buchman et al, 1994&lt;sup&gt;20&lt;/sup&gt;</td>
<td>60</td>
<td>Rhinovirus</td>
<td>ET OBS: NT, HNP: 39, MEE: 3, AOM: 0</td>
</tr>
<tr>
<td>4</td>
<td>Doyle et al, 1994&lt;sup&gt;21&lt;/sup&gt;</td>
<td>33</td>
<td>Influenza A</td>
<td>ET OBS: 80, HNP: 80, MEE: 23, AOM: 0</td>
</tr>
<tr>
<td>5</td>
<td>Buchman et al, 1995&lt;sup&gt;17&lt;/sup&gt;</td>
<td>27</td>
<td>Influenza A</td>
<td>ET OBS: NT, HNP: 59, MEE: 25, AOM: 4</td>
</tr>
<tr>
<td>6</td>
<td>Doyle et al, 2000&lt;sup&gt;22&lt;/sup&gt;</td>
<td>18</td>
<td>Influenza A</td>
<td>ET OBS: Yes/no*, HNP: Yes/no*, MEE: 0, AOM: 0</td>
</tr>
<tr>
<td>7</td>
<td>Buchman et al, 2002&lt;sup&gt;23&lt;/sup&gt;</td>
<td>32</td>
<td>Respiratory syncytial virus</td>
<td>ET OBS: NT, HNP: 54, MEE: 0, AOM: 0</td>
</tr>
</tbody>
</table>

Adapted from Bluestone CD.<sup>78</sup>

AOM = acute otitis media; ET OBS = Eustachian tube obstruction; HNP = high negative pressure; MEE = middle-ear effusion; NT = not tested.

*Eustachian tube dysfunction and abnormal middle-ear pressures in individuals are more prevalent when the tube is found to have poor function prior to challenge (see text).
80% demonstrating Eustachian tube obstruction and 80% having negative middle-ear pressure. However, with this virus, 5 (23%) of 21 infected subjects also developed a middle-ear effusion. Most likely, influenza A virus is more virulent than rhinovirus in the pathogenesis of Eustachian tube and middle-ear abnormalities.

In a highly enlightening study, Buchman and colleagues demonstrated the events leading to the development of not only otitis media with effusion but, more importantly, an acute otitis media that developed in one subject. Using a design similar to the previous studies, they recruited 27 adult volunteers, in whom influenza A was inoculated into the nose. Figure 6–2 shows that all subjects developed a nasal infection and 16 (59%) subsequently developed high negative middle-ear pressure. In one subject, acute otitis media was present. Using polymerase chain reaction, a middle-ear aspirate revealed the virus and *Streptococcus pneumoniae*; traditional viral and bacterial culture methods failed to grow these organisms from the middle-ear effusion. It is possible that these microorganisms were aspirated from the nasopharynx into the middle-ear cavity owing to the high negative middle-ear pressure.

In a more recent study, Doyle and colleagues infected 18 adult subjects with influenza A, showing that those individuals who had preexisting good Eustachian tube function reduced the otologic complications of the viral upper respiratory tract infection. Also, Buchman and colleagues inoculated respiratory syncytial virus into the nasal cavities of 32 adult volunteers. Only 56% had detectable infection, but all of the subjects who did have infection had rather substantial signs and symptoms, and 54% of these subjects developed abnormal middle-ear pressures.

These studies in adult volunteers were unique because they demonstrated the relationship of viral upper respiratory

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**Virus-Induced Acute Otitis Media**

<table>
<thead>
<tr>
<th>Time Course</th>
<th>27 Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Intranasal Inoculation Influenza A Virus</td>
</tr>
<tr>
<td>24 Hrs.</td>
<td>Infected</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>4 Days</td>
<td>Abnormal Middle-Ear Pressure</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>5 (18%)</td>
</tr>
<tr>
<td>5-7 Days</td>
<td>Middle-Ear Effusion</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Acute Otitis Media</td>
</tr>
<tr>
<td></td>
<td>N0</td>
</tr>
</tbody>
</table>
|             | 3        | 1 (4%) *

* Middle-Ear Aspirate; PCR-Positive Virus + *S. pneumoniae*

---

**FIGURE 6–1.** Outcomes of an adult volunteer study following intranasal inoculation of rhinovirus related to development of negative middle-ear pressures and effusion in subjects who did and did not have preexisting abnormal middle-ear pressures. Adapted from Buchman CA et al.20

**FIGURE 6–2.** Outcomes of an adult volunteer study following intranasal inoculation of influenza A virus demonstrating not only development of abnormal middle-ear pressures and middle-ear effusion but also, importantly, an attack of viral and bacterial acute otitis media in one subject. Adapted from Buchman CA et al.17
tract infection, middle-ear negative pressure and effusion, and acute otitis media.

**Studies of Upper Respiratory Tract Infections in Children**

An informative clinical investigation by Moody and colleagues also demonstrated a similar sequence of events in children, as was documented in adult volunteers. In this study, the parents of 20 children between the ages of 2 and 6 years monitored the middle-ear status of their children every day using a tympanometer. They reported that when an upper respiratory tract infection developed in the children, many soon also developed middle-ear underpressures, and some then developed a middle-ear effusion.

In a follow-up study, Antonio and colleagues prospectively followed 40 children in their homes, using daily tympanometry, symptom diaries, and weekly otoscopic examinations, during the respiratory seasons (fall, winter, and early spring) and during periods of common cold, which occurred in 22%; 63% of all otitis media episodes occurred during an upper respiratory tract infection. Interestingly, 30% of the episodes of otitis media were evident 1 to 7 days prior to the onset of the cold, whereas in 26%, the middle-ear disease occurred between 8 and 14 days after the onset of the cold; the remaining 44% had otitis media on the same day or up to the seventh day after the onset of the cold. These prospective studies in children who developed a “wild cold”—not induced by intranasal inoculation of viruses, as in the adult studies—showed that almost one-third of episodes of middle-ear effusion occurred prior to the signs and symptoms being apparent. Thus, the virus had already caused Eustachian tube dysfunction and otitis media.

There is now equally convincing evidence from studies in adult volunteers that the Eustachian tube is involved in the pathogenesis of otitis media. These six experiments show that the Eustachian tube has an important role in the development of otitis media in animal models. This is described below.

**Experiments in Animals**

In our laboratory over the past 30 years, we successfully produced both underpressures and middle-ear effusion in animal models using several methods. Some of our more important studies are summarized in Table 6–2.

We demonstrated that when the tensor veli palatini muscle is experimentally impaired (altered or inactivated) in animal models, active opening of the Eustachian tube is impaired. This results in negative middle-ear pressure followed by middle-ear effusion. In one experiment, excision of a portion of the tensor veli palatini muscle at the pterygoid hamulus in the palate resulted in negative pressure in the middle ear followed by an effusion. A similar experiment in which the muscle was completely excised, the superficial muscle bundle was transected, or the tendon medial to the hamular process was transposed had comparable outcomes. Figure 6–3 shows the surgical procedures used and the number of animals in each group. Complete excision of the tensor tendon resulted in middle-ear underpressures followed by persistent middle-ear effusion. Transection of the muscle resulted in negative middle-ear pressure, or effusion, or both (and in some animals, the middle ear returned to nor-

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**Table 6–2. Animal Models of High Negative Middle-Ear Pressure and Middle-Ear Effusion**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Reference</th>
<th>Animal</th>
<th>Diagnostic Method</th>
<th>Method</th>
<th>HNP</th>
<th>MEE</th>
<th>Resolved</th>
<th>Long Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cantekin et al, 1977&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Monkey</td>
<td>Otomicroscope and tympanometry</td>
<td>TVP excised</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Cantekin et al, 1980&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Monkey</td>
<td>Otomicroscope and tympanometry</td>
<td>TVP Excised</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Transected</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Transposed</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Casselbrant et al, 1988&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Monkey</td>
<td>Otomicroscope and tympanometry</td>
<td>Botulinum into TVP</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Buchman et al, 1995&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Ferret</td>
<td>Otomicroscope and tympanometry</td>
<td>Influenza A nasal inoculation</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Swarts et al, 1995&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Monkey</td>
<td>MRI</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt; insufflation into ME</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Alper et al, 1997&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Monkey</td>
<td>MRI</td>
<td>Botulinum into TVP</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Bluestone CD.<sup>78</sup>

HNP = high negative middle-ear pressure; MEE = middle-ear effusion; TVP = tensor veli palatini muscle; ME = middle ear; MRI = magnetic resonance imaging; NA = not applicable (acute experiment).
mal after the muscle healed). When the tendon was transposed, outcomes were similar to surgical alteration, but the middle ear rapidly returned to normal in a few weeks. Using a noninvasive method, Casselbrant and colleagues injected botulinum toxin into the tensor muscle, which resulted in negative pressure and then effusion. When the effect of the botulinum toxin resolved, the middle-ear status returned to normal.

In these earlier studies, middle-ear status was diagnosed with otomicroscopy and tympanometry. We have also used magnetic resonance imaging (MRI) to more accurately diagnose the presence of effusion in the middle ear and mastoid. Figure 6-4 shows the flow diagrams for two such studies in the monkey. Alper and colleagues used MRI and tympanometry to identify middle-ear and mastoid effusion. These investigators also injected botulinum toxin into the tensor veli palatini muscle of monkeys, resulting in a Eustachian tube that failed to open, middle-ear underpressure, and effusion. In ears that developed underpressure within the middle ear, increased vascular permeability was observed on the MRI. These experiments created a functional obstruction of the Eustachian tube (ie, an impairment of the active opening of the tube) impeding pressure regulation of the middle ear and resulting in an effusion. As in the earlier study, when the effect of the botulinum toxin resolved, the middle-ear status returned to normal.

Using a different approach, Swarts and colleagues were also able to produce unilateral middle-ear effusion in the monkey shortly after inducing middle-ear negative pressure by inflating the middle ear with carbon dioxide. Increased vascular permeability was identified on the MRI using a contrast agent. None of these changes were found in the contralateral (control) ear. When the middle-ear cleft was flushed with oxygen, lesser middle-ear underpressures developed, but no middle-ear effusion or other changes on the MRI scan developed. Even though the Eustachian tube was not altered in this experiment, the study showed the effect of middle-ear negative pressure in the development of middle-ear effusion.

Buchman and colleagues, using a ferret, evaluated the effect of influenza A virus nasal challenge on the function of the Eustachian tube. The results were assessed by forced-response and inflation-deflation tests, and middle-ear status was evaluated by otomicroscopy and tympanometry. All 10 animals in the experiment became infected, and all had Eustachian tube dysfunction associated with middle-ear underpressures, although no middle-ear effusion developed in any of the ferrets. The investigation also showed that even though the Eustachian tube did not become totally obstructed, abnormally high negative pressures developed in the middle ear.

In an earlier study by Giebink and colleagues, the nasopharynx of 29 chinchillas was inoculated with influenza A, which resulted in histopathologic evidence of inflammation of the Eustachian tube and tympanic membrane; middle-ear underpressures were also documented by tympanometry. More recently, Piltcher and colleagues, in our laboratory, completely obstructed the Eustachian tubes of 164 rats, which resulted in tympanic membrane retraction and middle-ear effusion.

### Magnetic Resonance Imaging (MRI) in Animal Models Supports Hydrops Ex Vacuo Theory of Pathogenesis of Middle-Ear Effusion (MEE)

- **4 Monkeys**
  - Unilateral CO₂ Insufflation of Middle Ear
  - \(< -600 \text{ mm H}_2\text{O}\)
  - MRI Evidence of MEE

- **10 Monkeys**
  - Unilateral Botulinum Toxin Injection of Tensor Veli Palatini
  - \(< -600 \text{ mm H}_2\text{O}\)
  - MRI Evidence of MEE
  - Resolution of Toxin
  - Normal Middle Ear


Summary and Conclusions from Human and Animal Studies

These studies in both humans and animal models support the causal relationship between a viral upper respiratory tract infection, partial Eustachian tube obstruction, abnormal middle-ear underpressures, and otitis media with effusion and acute otitis media (Figure 6–5). It is important to note that this pathogenic sequence of events in humans affected subjects who had preexisting dysfunction of the Eustachian tube and that those whose function was normal had little or no middle-ear sequelae following induced viral upper respiratory tract infection. It is assumed that functional obstruction of the tube is the dysfunction that is present, which makes these individuals more susceptible than normal. Future research should be directed toward uncovering the underlying pathophysiology of functional Eustachian tube obstruction and reducing the severity, if not the occurrence, of viral upper respiratory tract infections. These studies lend convincing support for the hydrops ex vacuo theory.

Clinical Aspects of the Pathogenesis of Otitis Media and Certain Related Conditions

Acute otitis media, otitis media with effusion, Eustachian tube dysfunction, and chronic suppurative otitis media are the most frequent middle-ear diseases that clinicians encounter. Following the onset of either acute otitis media or otitis media with effusion, persistent middle-ear effusion may develop. The following describes these clinical types and stages of otitis media and relates them to the pathophysiology and pathogenesis related to the Eustachian tube, as described in this chapter and in Chapter 5. The pathogenesis of chronic suppurative otitis media, atelectasis, retraction pocket, and cholesteatoma is described in Chapter 10, “Role in Certain Complications and Sequelae of Otitis Media,” because management is related to pathogenesis.

Acute Otitis Media

As described above, the pathogenesis of acute otitis media usually occurs with the following pattern in most children: the patient has an antecedent event (usually an upper respiratory viral infection) that results in congestion of the respiratory mucosa of the upper respiratory tract, including the nasopharynx and Eustachian tube. Congestion of the mucosa of the Eustachian tube is followed by negative middle-ear pressure, and, if prolonged, potential pathogens (viruses and bacteria) are aspirated from the nasopharynx into the middle ear. Because the Eustachian tube is obstructed, the middle-ear effusion, owing to the infection, accumulates in the middle ear, and the clearance function of the tube is impaired. Microbial pathogens proliferate in the secretions, resulting in a suppurative and symptomatic acute otitis media.

For children with recurrent acute otitis media, an anatomic or physiologic abnormality of the Eustachian tube appears to be an important factor, if not the most important factor. In Sweden, Stenstrom and colleagues studied the pathogenesis of recurrent acute otitis media in 50 otitis-prone children (defined as greater than 11 episodes of acute otitis media). Using the pressure chamber to test Eustachian tube function, they found the otitis-prone children to have significantly poorer active tubal function than 49 normal (control) children who had no history of acute otitis media. This finding indicates that the pathogenesis of recurrent acute otitis media is the result of functional obstruction of the Eustachian tube, as opposed to mechanical obstruction. However, it is likely that infants and young children with their short, floppy Eustachian tubes can reflux or insufflate nasopharyngeal secretions into the middle ear during a viral upper respiratory tract infection. Another possible mechanism is an infection that progressively ascends from the nasopharynx into the mucosa of the Eustachian tube. This most likely occurs when an indwelling obstructing foreign object is in the nasopharynx, such as a nasogastric or nasotracheal tube.
**Otitis Media with Effusion**

At the onset of an episode of otitis media with effusion, the patient is usually asymptomatic (except for presence of hearing loss), but usually this condition has a sequence of events similar to that described above for acute otitis media. Bacteria can be isolated from middle-ear effusions of patients with otitis media with effusion,24-36 but prolonged negative pressure within the middle ear can cause a sterile middle-ear effusion. As described above, otitis media with effusion has been produced in the monkey animal model following excision of the tensor veli palatini muscle26 and injection of botulinum toxin into the tensor veli palatini muscle,28,31 which resulted in the Eustachian tube failing to open, middle-ear underpressures, and effusion. These experiments confirm the hydrops ex vacuo theory of the pathogenesis of middle-ear effusion. This theory postulates that when the Eustachian tube does not open, the gas exchange from the middle ear into the microcirculation of the mucous membrane causes a middle-ear underpressure, followed by transudation of effusion. Swarts and colleagues were also able to produce middle-ear effusion in the monkey by flushing the middle ear with carbon dioxide shortly after inducing middle-ear negative pressure.30 In the studies cited above by McBride and colleagues and Buchman and colleagues that involved adult volunteers, nasal challenge with rhinovirus resulted in Eustachian tube obstruction, negative middle-ear pressure, and, in two subjects, middle-ear effusion.19,20 Doyle and colleagues also demonstrated that intranasal challenge of influenza A virus in adult volunteers resulted in Eustachian tube obstruction, negative middle-ear pressure, and, in infected subjects, middle-ear effusion.21 Most likely, influenza A virus is more virulent than rhinovirus. Also, preexisting poor Eustachian tube function predisposes the individual to obstruction of the tube and middle-ear abnormalities.20,22

Episodes of upper respiratory tract infection can then result in atelectasis of the tympanic membrane—middle ear (ie, high negative middle-ear pressure), sterile otitis media with effusion, or acute bacterial otitis media. Because the tube can open when there is a middle ear with an effusion, nasopharyngeal secretions can be aspirated, creating the clinical condition in which otitis media with effusion and acute bacterial otitis media occur together.

In a study of Eustachian tube function in 163 ears of Japanese children and adults who had otitis media with effusion and chronic otitis media, Iwano and colleagues found an impaired active opening function of the tube in children and adults.37 They concluded that the tube was functionally obstructed. But organic (mechanical or anatomic) obstruction was also considered to be involved in the pathogenesis in adults.

**Persistent Middle-Ear Effusion**

The pathogenesis of persistent middle-ear effusion after the initial stage of a viral or bacterial infection in the middle ear or following transudation of effusion is multifactorial. In addition to impairment of clearance function of the tube and inflammatory obstruction at the protympanic (ossseous) portion of the tube, cytokines are stimulated, such as interleukins 1, 2, and 6; tumor necrosis factor; interferon-γ from inflammatory cells of the middle-ear mucous membrane; and growth factors,38-44 followed by two pathways of inflammation: (1) up-regulation of submuosal receptors, primarily selectins and integrins that trap lymphocytes into the mucosa, which also produce cytokines and inflammatory mediators, and (2) stimulation of inflammatory mediators, such as leukotrienes, prostaglandins, thromboxane, prostacycline, and platelet-activating factor,45,46 which, in turn, can promote fluid leakage from the mucous membrane. Nitric oxide47 and free radicals48,49 have also been implicated in the pathogenesis of persistent middle-ear effusion. At this stage, there is probably an increase in blood flow within the mucous membrane owing to engorgement of blood vessels and angiogenesis. This then results in further negative pressure within the middle ear owing to an increase in N2 into the microcirculation of the mucosa.50 There is some evidence that infection caused by *Haemophilus influenzae* predisposes the middle-ear cleft to persistent effusion.51 In addition, the effusion that is produced is “trapped” in the middle ear owing to the anatomy of the system, that is, a closed space with a narrow outlet—the Eustachian tube. Also, the mucociliary system and the pumping action of the tube are most likely impaired, causing persistent middle-ear effusion.

**Eustachian Tube Dysfunction**

Symptomatic Eustachian tube dysfunction can be due to either an obstruction (anatomic or functional or both) of the tube (too closed) or a patulous tube (too open). Signs and symptoms are referable to the ear, despite the lack of a middle-ear effusion. Obstruction of the tube can cause middle-ear negative pressure, retraction of the tympanic membrane, hearing loss, and, in its severe form, atelectasis of the middle ear (loss of the middle-ear space). Obstruction can be due to inflammation or failure of the opening mechanism. Obstruction can be acute or chronic, but infrequent periodic tubal opening probably occurs to prevent the accumulation of an effusion. A patulous tube can cause patients to complain of autophony and hearing their own breathing. Both conditions have been documented during the last trimester of pregnancy.52 Eustachian tube obstruction is common in girls during puberty and may be related to hormonal changes, but we do not know the underlying cause of this problem (see Chapter 5).

**Role of Allergy in Etiology and Pathogenesis**

Allergy is thought to be one of the etiologic factors in otitis media because otitis media occurs frequently in allergic individuals.53 The mechanism by which allergy might cause otitis media is hypothetical and controversial.54,55 Figure 6-6 illus-
trates my concepts of allergy’s role in the etiology and pathogenesis of otitis media by one or more of the following mechanisms:

- The middle-ear mucosa functioning as a shock (target) organ
- Inflammatory swelling of the Eustachian tube mucosa
- Inflammatory obstruction of the nose
- Aspiration of bacteria-laden allergic nasopharyngeal secretions into the middle-ear cavity

Doyle has also proposed another possible mechanism. This hypothesis is based on the possible increase in circulating inflammatory mediators from local allergic reactions in the mucosa of the nose or stomach, which, in turn, could alter the middle-ear mucosal permeability and result in altered gas exchange. Ohashi and colleagues found that allergic responses did not impair mucociliary activity but could adversely affect the structure of the Eustachian tube’s mucus blanket. More recently, investigators from Finland reported a higher incidence of recurrent otitis media in children who had a cow’s milk allergy in infancy.

As presented in Chapter 5, Bernstein and colleagues provided evidence that the Eustachian tube may be adversely affected by allergy, as opposed to the middle ear as a target organ (see Table 5–5). More recently, Hurst and Venge assessed the inflammatory response by eosinophils, neutrophils, and mast cells in the middle ear and found a difference between atopic and nonatopic individuals, which led to their conclusion that the middle-ear mucosa is capable of an allergic response, similar to other portions of the respiratory tract. But if the middle ear is a target organ, why is it that following tympanostomy tube placement in children who have allergic rhinitis and otitis media, a postoperative otorrhea is not a common complication? The target organ is the Eustachian tube.

Studies at the Children’s Hospital of Pittsburgh involving adult volunteers demonstrated a relationship between intranasal antigen challenge, allergic rhinitis, and Eustachian tube obstruction. Table 6–3 summarizes studies that demonstrated a relationship among intranasal challenge with allergens, virus, and mediators in volunteers who did and did not have allergic rhinitis and the effect on their nasal and Eustachian tube function. None of these allergy studies produced otitis media in the volunteers, but none had preexisting Eustachian tube dysfunction; we were concerned that challenging a volunteer with a susceptibility to middle-ear effusion (a preexisting Eustachian tube dysfunction) could be hazardous. It is possible that repeated challenge with antigen over a prolonged period of time would cause individuals who are hypersensitive to the specific antigen and who also have poor Eustachian tube function to develop middle-ear effusion (see Chapter 11, “Future Directions”). It seems reasonable that children with signs and symptoms of upper respiratory allergy may have otitis media as a result of the allergic condition, especially if they have underlying dysfunction of the tubal system.

Gastroesophageal Reflux

There has been a suggestion in the past that gastroesophageal reflux disease may be involved in the pathogenesis of Eustachian tube–middle-ear pathology. In the last few years, several reports have shown an association of otitis media with gastroesophageal disease in humans and animal models. In animals, Heavner and colleagues were able to demonstrate a transient inflammation of the Eustachian tube secondary to multiple exposures of a gastroesophageal refluxant instilled into the middle ears of a rat model. In a similar study, White and colleagues instilled gastric juice into the nasopharynx of the rat model that resulted in Eustachian tube dysfunction. In humans, Tasker and colleagues measured pepsin concentrations in middle-ear effusions from children using enzyme-linked

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<tr>
<th>Nasal Provocation</th>
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<tr>
<td>Allergens (pollens, mite)</td>
<td>Nonallergic 0</td>
<td>Allergic + 0</td>
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<td>Mediators</td>
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<td>Histamine</td>
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<td>Methacholine</td>
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Adapted from Friedman PA et al; Ackerman MN et al; Doyle WJ et al; Skoner DP et al; Skoner DP et al; Stillwagon PK et al.

+ = adverse effect; 0 = little effect; PGD₂ = prostaglandin D₂.
immunosorbent assay and enzyme activity assays; of the 54 specimens, 45 (83%) were positive.69 In another report from the same research group, Tasker and colleagues assessed the levels of pepsin and pepsinogen protein in 65 middle-ear effusions of children; 59 had levels 1,000-fold higher than serum levels, which were attributed to reflux of gastric contents into the middle ear.73 Poelmans and colleagues performed tests for reflux in adults who had chronic otitis media with effusion or Eustachian tube dysfunction and reported that there was an association and that treatment with antireflux medication was effective in relieving the otologic symptoms.74 This was not a randomized clinical trial. At this time, it is still uncertain that gastroesophageal reflux is involved in the pathogenesis of Eustachian tube–middle-ear disease, even though there appears to be an association in both humans and an animal model.75 These issues are future research goals (see Chapter 11).76

I routinely include questions concerning symptoms of reflux disease (arching the back and frequent vomiting in the infant, chronic or recurrent hoarseness, frequent belching and clearing the throat, recurrent croup, heartburn, stomach discomfort) in children who have recurrent acute otitis media and chronic otitis media with effusion. All young infants are especially prone to reflux because of their relatively short esophagus and other factors related to being "born too soon."77 Even if a cause-and-effect relationship between the two is lacking, there may be a cause-and-effect relationship in symptomatic patients. Thus, I treat these children for both diseases; even if there is only an association, both usually require management (see Chapter 9, “Role in Management of Otitis Media”).

References


CHAPTER 6: ADDITIONAL FIGURES

RELATION BETWEEN ALLERGIC RHINITIS AND CHRONIC OTITIS MEDIA WITH EFFUSION (OME)

77 Children with OME

- 42% Allergic rhinitis
- 58% Allergy absent
- 7% Middle ear target organ
- 35% Eustachian tube (?) target organ

(Modified after Bernstein et al, Am J Otol 1983;5:66-69.)

Surgery of the base of the skull can interfere with tensor veli palatini muscle attachments.