CHAPTER SEVEN

Pathology

The pathology of the Eustachian tube may or may not be involved in the pathogenesis of otitis media, whereas the pathophysiology of the tubal system usually is.

Pathologic changes in the Eustachian tube can be involved in the pathogenesis of otitis media and Eustachian tube dysfunction, but intrinsic (intramural, mural) or extrinsic (extramural) tubal pathology does not have to be present for the development of middle-ear disease. As described in Chapter 5 "Pathophysiology," and Chapter 6, "Pathogenesis," the tubal system can either be too open (nonintact tympanic membrane) or too closed (nasopharyngeal obstruction at the pharyngeal tubal opening) at either end without any pathologic changes in the tube itself, which can result in middle-ear disease. Also, the tube may be functionally obstructed owing to failure of the opening mechanism (failure of tubal dilatation or tubal constriction on swallowing), without any direct evidence of pathology of the tubal mucosa or extramural disease. Thus, histopathologic studies of the Eustachian tube may not show any pathologic changes even though disease is present in the middle ear and mastoid. Also, functional obstruction of the tube can be caused by diseases or disorders of the tensor veli palatini muscle distant from the Eustachian tube, such as by tumor, trauma, or surgery involving the palate or base of skull, without any pathologic changes in the tube itself (see Tumors and Irradiation).

However, it has been shown that a viral upper respiratory tract infection can result in partial tubal obstruction, as evidenced by the development of Eustachian tube dysfunction, diagnosed by manometric testing of the tube. Also, following viral challenge of the nose in adult volunteers, tympanometry identified middle-ear negative pressure, which was followed by the development of an effusion or infection in the middle ear (see Chapter 6). As described below, there are many diseases and disorders that can affect the Eustachian tube that can result in middle-ear disease, as demonstrated on human histopathologic temporal bone specimens. Most of these reports have been from the laboratory of Professor Isamu Sando at the Eye and Ear Institute of the University of Pittsburgh School of Medicine.

Effect of Inflammation on the Middle-Ear Cleft

Acute Otitis Media

The following are the generally accepted stages of inflammation that occur in the middle-ear cleft. In the initial stages of classic acute otitis media, the mucoperiosteum of the middle ear and mastoid air cells is hyperemic and edematous. This is followed by an exudation of polymorphonuclear leukocytes and serofibrinous fluid into the middle ear. The quantity of fluid increases until the middle ear is filled and pressure is exerted against the tympanic membrane. If the disease progresses, the bulging tympanic membrane may rupture spontaneously. The resultant discharge is at first serosanguineous but then becomes mucopurulent. Throughout the middle ear and mastoid, the mucosa becomes markedly thickened by a mixture of inflammatory cells, new capillaries, and young fibrous tissue. Tos and Bak-Pedersen described an increase in goblet cell population in the Eustachian tubes and middle ears in temporal bone specimens from children and adults who had a middle-ear infection. In the rat model of acute otitis media, Cayé-Thomasen and Tos recently reported that goblet cell density and mucous gland volume in the Eustachian tube increased up to 6 months following infection when the animal was inoculated with Streptococcus pneumoniae or Haemophilus influenzae; Moraxella catarrhalis did not induce the same degree of these inflammatory changes, which supports the belief that this bacterium is not as virulent in the middle ear as S. pneumoniae or H. influenzae. They postulated that these pathologic changes in the Eustachian tube can compromise the ventilatory (pressure regulatory) and drainage (clearance) functions of the tube following an attack of acute otitis media. An earlier study from the same laboratory demonstrated in the rat model of acute otitis media that increased mucosal goblet cell density caused by H. influenzae can result in secretory otitis media that can progress to the chronic stage (see Otitis Media with Effusion). The acute middle-ear infectious process may become associated with blockage of the aditus ad antrum, resulting in inadequate drainage of the mastoid gas cells and a consequent mastoiditis. Extension beyond the mucoperiosteum may lead to intratemporal complications, such as facial paralysis, labyrinthi-
Eustachian Tube: Structure, Function, Role in Otitis Media

Otis Media with Effusion

The pathologic findings associated with the serous and mucoid types of chronic middle-ear effusion are similar. Early pathologic changes include hyperplasia, differentiation of epithelial cells, and gland formation. There is an increase in the number of secretory cells, including glands and ciliated cells. Tos and Bak-Pedersen described the increase in goblet cells and gland density in biopsies obtained from children's middle ears that had chronic otitis media with effusion. The lamina propria or connective tissue layer becomes thickened by edema and infiltration of numerous inflammatory cells consisting of lymphocytes, plasma cells, macrophages, and polymorphonuclear leukocytes. These changes are more striking in the presence of a mucoid effusion than for a pure serous effusion, in which tissue edema is the predominant finding in addition to the presence of chronic inflammatory cells. It is generally believed that mucoid effusions are mainly the result of secretion, whereas serous effusions are mostly transudates. Persistent atelectasis of the middle ear, chronic middle-ear effusions, or both are associated with a number of intratemporal complications and sequelae, including hearing loss, tympanosclerosis, adhesive otitis media, perforation with discharge, chronic mastoiditis, and cholesterol otitis externa.

Pathology of Post–Tympanostomy Tube Placement

It is assumed that middle-ear pathology caused by chronic otitis media with effusion is resolved in the majority of patients following myringotomy and tympanostomy tube insertion. Indeed, most clinicians would agree that the tympanic membrane and hearing are restored to normal following tympanostomy tube surgery. Also, I have had the opportunity to operate on the middle ears of many children (eg, exploratory tympanostomy for perilymphatic fistula) who had had tympanostomy tubes previously inserted for chronic otitis media with effusion. Kamimura and colleagues examined histopathologic sections from 263 temporal bones of children with and without evidence of otitis media. Of the 65 specimens that had otitis media, MALT was present in 30 (46.2%) Eustachian tubes and in 19 (29.2%) middle ears, whereas in the 98 cases in which no otitis media was present, MALT was relatively rare or nonexistent. In a follow-up study, Kamimura and colleagues concluded that MALT has a close relationship to otitis media and might be a local response to recurrent infection in the Eustachian tube and middle ear. Employing similar histopathologic studies of temporal bones, with and without otitis media, in the same laboratory, Haginomori and colleagues hypothesized that cellular proliferation of MALT within the middle ear and Eustachian tube might reflect the activity that produces immunoglobulin A against invasion of foreign antigens.

Cleft Palate

I describe here the histopathologic findings from human temporal specimens from individuals who had cleft palate, but in Chapter 5, I describe how these congenital abnormalities are related to the development of middle-ear disease. The infant with an un repaired cleft palate has been reported to have a universal incidence of a middle-ear effusion, which has been associated with a functional obstruction (failure of normal tubal dilation during swallowing) of the Eustachian tube. It is my contention that understanding the underlying structural and functional abnormalities that lead to middle-ear disease in the child who has a cleft palate will aid in finding answers to the development of otitis media in children who have an intact palate. Indeed, there is some evidence that the Eustachian tube dysfunction identified by tubal function tests of patients who have a cleft palate is similar to that of children who have chronic otitis media with effusion but no cleft palate.

Histopathologic Studies of Human Temporal Bones

Using extended temporal bone histopathologic specimens from infants with cleft palate, computer-aided three-dimensional reconstructions have shown anatomic differences between specimens with and without a cleft palate. Sando and colleagues described in detail the procedure of removing and processing
these human extended temporal bone specimens. These findings help us understand the pathophysiology of tubal dysfunction and pathogenesis of middle-ear disease in infants who have a cleft palate. Table 7–1 is a summary of these findings from Professor Sando’s laboratory at the Eye and Ear Institute of Pittsburgh and from our other studies conducted in the Anthropology Department at the University of Pittsburgh.

There are at least nine known abnormalities in the structure of the Eustachian tube associated with cleft palate (compared with specimens without a cleft palate). These have been identified from studies of extended histopathologic specimens taken from individuals with cleft palate:

1. **Eustachian tube length.** Sadler-Kimes and colleagues and Siegel and colleagues compared the length of the tube between individuals with and without a cleft palate and found that the tube was shorter in specimens from infants and young children with a cleft palate than in age-matched controls. The significance of this finding is discussed below.

2. **Angle between the tensor veli palatini muscle and the cartilage.** Sadler-Kimes and colleagues reported that the angle at which the tensor veli palatini muscle attaches to the Eustachian tube cartilage was larger than control specimens without a cleft palate.

3. **Deformed cartilage.** Shibahara and Sando described the angle between axial lines through the lateral lamina and the medial lamina of the cartilage as wide in the cleft palate specimens compared with age-matched controls. In a similar follow-up study, Sando and Takahashi examined three specimens from patients who had a cleft palate and found the cartilage deformed; the angle between lines along the upper half of the luminal side of the medial lamina of the cartilage and the luminal side of the lateral lamina of the cartilage was different than in specimens without a cleft palate.

4. **Cartilage cell density.** Shibahara and Sando assessed the cross-sectional area of the cartilage between cleft and non–cleft palate specimens and reported it to be greater in cleft palate patients.

5. **Ratio of area of lateral and medial laminae of the cartilage.** Matsune and colleagues measured the areas and ratio of the lateral and medial laminae of the tubal cartilage and reported that the ratio of the areas of the cartilage was smaller than in specimens with a cleft palate when compared with cases without a cleft palate. In a later similar study, Takasaki and colleagues evaluated the cartilage of the Eustachian tube in 10 specimens with a cleft palate and compared them with 34 non–cleft palate cases. They found that the ratio of the lateral and medial laminae of the cartilage was smaller in the specimens with a cleft palate.

6. **Curvature of the lumen.** Matsune and colleagues evaluated the shape of the lumen of the Eustachian tube in 10 cleft palate specimens, which was compared with non–cleft palate (control) specimens. Of the 20 specimens without a cleft palate, 18 (90%) had the classic normal “C-shaped” lumen, whereas of the 10 cases with a cleft palate, only 5 (50%) had the normal C-shaped lumen, whereas the other 5 had an abnormal, straight-appearing lumen (Figure 7–1).

7. **Elastin in the cartilage.** Matsune and colleagues examined the elastin at the hinge portion of the cartilage in cleft palate specimens and found less elastin in these patients than in specimens without a cleft palate.

8. **Insertion of the tensor veli palatini into the tip of the lateral lamina of the cartilage.** Matsune and colleagues determined if the tensor veli palatini muscle inserted into the tip of the lateral lamina. In all 20 specimens without a cleft palate, the muscle did insert into the tip, but in only 6 of the 10 cases with a cleft palate did this occur (Figure 7–2).

Table 7–1. Summary of the Differences in Structures of the Eustachian Tube in Extended Temporal Bone Specimens from Infants and Young Children with Cleft Palate Compared with Specimens without Cleft Palate

<table>
<thead>
<tr>
<th>Abnormality Compared with Specimens without Cleft Palate</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Length of tube shorter</td>
<td>Sadler-Kimes et al, 1989; Siegel et al, 1988</td>
</tr>
<tr>
<td>Angle between cartilage and TVP larger</td>
<td>Sadler-Kimes et al, 1989</td>
</tr>
<tr>
<td>Cartilage deformed</td>
<td>Shibahara and Sando, 1988; Sando and Takahashi, 1990</td>
</tr>
<tr>
<td>Cartilage cell density greater</td>
<td>Shibahara and Sando, 1988</td>
</tr>
<tr>
<td>Ratio of lateral and medial laminae area of cartilage smaller</td>
<td>Takasaki et al, 2000; Matsune et al, 1991</td>
</tr>
<tr>
<td>Curvature of lumen less</td>
<td>Matsune et al, 1991</td>
</tr>
<tr>
<td>Elastin at hinge portion of cartilage less</td>
<td>Matsune et al, 1992</td>
</tr>
<tr>
<td>Insertion of TVP into tip of lateral lamina abnormal</td>
<td>Matsune et al, 1991</td>
</tr>
<tr>
<td>Insertion ratio of TVP to cartilage less</td>
<td>Matsune et al, 1991</td>
</tr>
</tbody>
</table>

TVP = tensor veli palatini.
FIGURE 7–1. Photomicrograph of cross sections through the midcartilaginous portion of the Eustachian tube. A, A control subject (6-week-old female) and, B, a cleft palate case (7-week-old male) that show the difference in curvature of the lumen and cross-sectional area of the Eustachian tube development of the cartilage between the normal child and the child with a cleft palate (hematoxylin-eosin stain). ETC = Eustachian tube cartilage; L = Eustachian tube lumen; LL = lateral lamina of Eustachian tube cartilage; ML = medial lamina; TVPM = tensor veli palatini muscle. Courtesy of L. Sando, MD.

FIGURE 7–2. A, Photomicrograph of histologic sections showing normal insertion of the tensor veli palatini muscle into the tip of the lateral lamina of the Eustachian tube cartilage in a temporal bone specimen from a child without a cleft palate. B, Section at a similar site in a specimen from a child with a cleft palate showing deficient attachment into the tip. Reproduced with permission from Matsune S et al. 37

FIGURE 7–3. Insertion ratio represented schematically showing the length of the Eustachian tube cartilage involved by the insertion of the tensor veli palatini muscle (TVP) (B) divided by the total length of the Eustachian tube from the nasopharyngeal orifice to the isthmus portion (A). Reproduced with permission from Matsune S et al. 37
9. Insertion ratio of tensor veli palatini muscle. Matsune and colleagues evaluated the ratio made up by the length of the Eustachian tube cartilage with the insertion of the tensor veli palatini muscle to its total length for the pharyngeal end to near the tubal isthmus in 10 temporal bone specimens from cases with a cleft palate and 20 non–cleft palate specimens (Figure 7–3); this insertion ratio was statistically smaller in individuals with a cleft palate (Figure 7–4).

Significance of Pathologic Temporal Bone Findings
These histopathologic findings in the Eustachian tubes of temporal bone specimens provide at least some explanation for the extremely high incidence of otitis media in this special population, which is also consistent with the pathophysiologic findings following testing of the tube in humans. It has been shown that the Eustachian tube in infants and young children is shorter than in older children and adults without a palatal cleft, but in the cleft palate patient, the tube is even shorter than normal in this young age group. This finding is important in understanding some aspects of the pathophysiologic and pathogenesis of otitis media in children who have a cleft palate. The shorter tube in these patients is most likely related to aspiration and especially to reflux of nasopharyngeal secretions into the middle ear (see Chapter 5). Also, as reported by Doyle and colleagues, there is histopathologic evidence of middle-ear disease associated with abnormalities of the tubal structure. But inflammation of the middle ear and bony middle-end of the Eustachian tube was found to be more severe than the cartilaginous portion by Kitajiri and colleagues (Figure 7–5). This observation would indicate that it is not severe inflammatory obstruction of the cartilaginous portion of the tube primarily involved in the pathogenesis of the middle-ear disease in the patients with a palatal cleft, but more likely functional obstruction (failure of normal dilation during swallowing) is involved, as described in Chapter 5.

Other Possible Differences between Patients with and without a Cleft Palate
It has been suggested from assessments of middle-ear aspirates from children with and without a cleft palate that mucin in middle-ear effusions in the cleft palate population has larger glycopeptide units forming intact mucin of a larger hydrodynamic size than either mucoid or serous middle-ear effusions aspirated from the ears of children with chronic otitis media with effusion who have normal palates. Confirmation and the possible cause of this difference are yet to be established.

Other Congenital Syndromes and Chromosomal Abnormalities
At least one report has described pathologic changes in the Eustachian tube in individuals who had a variety of congenital syndromes and chromosomal abnormalities other than cleft palate. Shibahara and Sando described the histopathologic temporal bone findings of a fetus that had Down syndrome (trisomy 21 syndrome) in which the Eustachian tube was described, compared with a control specimen, as being extremely small and collapsed in the midcartilaginous, isthmus, and tympanic portions, with poorly developed lateral cartilage in the midcartilaginous area. The cartilage of the tube was also described as being malformed in temporal bone specimens from older children with Down syndrome. This is an interesting finding because manometric testing of children who have Down syndrome has shown them to have a patulous tube. In another histopathologic study, Sadler-Kimes and colleagues compared temporal bone specimens from children with and without Down syndrome and found that the Eustachian tube in the Down syndrome specimens was shorter than in age-matched controls. Miura and colleagues reported that temporal bones from individuals with chromosomal abnormalities, including Down syndrome (trisomies 13, 18, 21, and 22 and inversion of chromosome 1), had similar Eustachian tube anomalies, which might explain their tubal dysfunction. In still another report, Miura and colleagues studied the temporal bones of two individuals with trisomy 22 and found severe inner ear anomalies, malformations of the Eustachian tube cartilage, and a lack of an attachment of the tensor veli palatini muscle to the lateral lamina; the latter finding is similar to the deformity identified in some cleft palate specimens.

Miura and colleagues described anomalies of the Eustachian tube and associated structures in temporal bones from a patient who had oral-facial-digital syndrome and another patient with Townes’ syndrome. In a similar study of temporal bone specimens from a patient who had oculoauriculovertebral spectrum, Miura and colleagues reported that the Eustachian tube had several anomalies, including a widely opened cartilaginous portion of the tubal lumen and absence of the lateral lamina of the tubal cartilage. Ganbo and colleagues assessed the inflammatory response to chronic otitis media in DiGeorge syndrome and reported that even if T lymphocytes are depressed, as in this cell-mediated immunodeficiency disorder, expression of intercellular adhesion molecule expression can be induced in the middle ear with otitis media.

Tumors and Irradiation
The most reasonable explanation for otitis media to occur when a tumor of the skull base is present, especially when it involves the Eustachian tube, is that the tumor anatomic (mechanically) obstructs the tubal lumen. Indeed, Schuknecht and Kerr demonstrated from their histopathologic assessment of the temporal bone of a patient who had a squamous cell carcinoma that the tumor had invaded the Eustachian tube. Figure 7–6 shows a carcinoma invading the Eustachian tube, which is consistent with anatomic (mechanical) obstruction of the tube causing middle-ear disease. Also, Cundy and colleagues reported on a histopathologic study of a temporal bone of an individual who...
**FIGURE 7–4.** The insertion ratio in 10 cleft palate specimens was statistically shorter than that in non–cleft palate specimens. Reproduced with permission from Matsune S et al. 37

**FIGURE 7–5.** Evidence that despite a lack of significant inflammation of the lumen of the Eustachian tube, otitis media occurs in a child with a cleft palate; functional obstruction of the tube is the most likely explanation. Photomicrograph of a histopathologic section from a temporal bone specimen from the left Eustachian tube of a 5-day-old infant with a complete cleft palate (hematoxylin-eosin stain; ×12.5 original magnification). There is moderate subepithelial inflammatory round cell inflammation (arrow) in the middle ear, whereas very slight inflammation is noted in both the bony (*) and cartilaginous (**) portions of the Eustachian tube. Reproduced with permission from Kitajiri M et al. 40

**FIGURE 7–6.** Photomicrograph of a histopathologic section through the Eustachian tube showing anatomic (mechanical) obstruction of the tubal lumen (hematoxylin-eosin stain; ×5.2 original magnification). Carcinoma (T) in the subepithelial layer of the Eustachian tube. Columnar epithelium (arrow) being invaded by tumor. C = carotid artery. Reproduced with permission from Cundy R et al. 49
had received radiation for a carcinoma of the pharynx and described nasopharyngeal carcinoma invading the Eustachian tube and the middle ear having otitis media.\(^49\) Also, benign neoplasms of congenital origin have been reported to have arisen from the Eustachian tube, such as a hairy polyp or dermoid tumors.\(^{50-52}\)

On the other hand, Takahara and colleagues described a histopathologic specimen from an individual with a lymphoma invading the anterior Eustachian tube that involved the tensor veli palatini muscle but spared the lumen (Figure 7–7).\(^{53}\) Otitis media was present, and the conclusion was that the patient had a functional obstruction of the Eustachian tube owing to inactivation of the tensor muscle (see Chapter 6).

A recent report addressed the appearance of the Eustachian tube in patients with otitis media who had been irradiated. Takasaki and colleagues described the effect of irradiation of the oropharynx on the Eustachian tube from histopathologic assessment of temporal bones and reported that the tubal lumen was patulous and wider and that the Ostmann’s fatty tissue, levator veli palatini muscle, and submucosal glands around the tubal cartilage were replaced by more dense connective tissue when compared with control cases.\(^{54}\)

**Other Diseases and Disorders**

Systemic disease can affect the Eustachian tube, as demonstrated by Takasaki and colleague, who studied specimens from two patients who had chronic renal failure and found ossification in the medial lamina of the Eustachian tube and in Ostmann’s fat pad.\(^{55}\) They postulated that this was possibly associated with tubal dysfunction in this condition. In a study of 20 patients from India who had scleroma, Soni identified 6 (30%) who had nasopharyngoscopic evidence of involvement of the Eustachian tube in the granulomatous stage, which was characterized as atrophic changes with crusting and granuloma with areas of thick fibrotic tissue; the effect of this disease on the middle ear was diagnosed by tympanometry.\(^{56}\) Miura and colleagues reported on the histopathologic findings of six children who had cholesterol granuloma.\(^{57}\) The disease was primarily in the mastoid cells and epitympanum, and in all cases, otitis media was present, along with inflammatory changes in the Eustachian tube; in some of the specimens, there were malformations of the tube. The authors concluded that Eustachian tube dysfunction was the most likely cause of the chronic middle ear and mastoid disease that resulted in cholesterol granuloma.

**Cystic Fibrosis**

Recent histopathologic studies of temporal bones of individuals who had cystic fibrosis revealed an infrequent occurrence of otitis media and low densities of goblet cells, which may contribute to reduced amounts of viscous mucus. This, in turn, may be related to the low incidence of otitis media in this population.\(^{58}\) It is an interesting research question to investigate the underlying cause of the relative lack of otitis media in these patients compared with the population without cystic fibrosis, especially when rhinosinusitis is almost universal in individuals with cystic fibrosis (see Chapter 11, “Future Directions”).

**References**

CHAPTER 7: ADDITIONAL FIGURES

Cartilage Cell Density in Individuals with Trisomy and Cleft Palate

- CP
- CP with microtia
- Trisomy 21
- Control

Sagittal section through Eustachian tube showing inflammatory stenosis. L, lumen; S, stenosis
CT scan showing neurofibroma (arrow) obstructing osseous portion of tube.

Close-up CT scan of neurofibroma (arrow) obstructing the osseous portion of tube.