Paparella II: Section 3: Diseases of the Ear

Part 3: Middle Ear and Mastoid

Chapter 31: Complications of Suppurative Otitis Media

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In discussing complications of suppurative otitis media, it is important to understand the definitions of terms. Understanding the anatomy and the pathogenesis is important in classifying the different forms of complications, and more so in developing rational methods of prevention and treatment. Otitis media is defined as inflammation of the middle ear cleft as well as of the eustachian tube and mastoid, regardless of the cause or duration of the disease. A complication occurs when the infectious process extends beyond the mucoperiosteum; the term *sequela* refers to a process confined within the mucoperiosteum (mucoperiosteal changes) that has the capacity or potential for developing a complication. For example, granulation tissue is in itself a sequela (active sequela), but erosion of bone by granulation tissue is a complication.

In certain forms of otitis media, the complications caused by their "masked" persistence can be very subtle. It appears that toxins or enzymes may reach the inner ear, causing inapparent, nondevastating changes such as sensorineural hearing loss. These forms of otitis have been grouped under the term "silent otitis media", which refers to usually chronic pathologic conditions, behind an intact tympanic membrane, that are clinically "undetected" or "undetectable" (Paparella et al, 1986). The mechanism and manifestations of these subtle complications are discussed at the end of this chapter in Section II, "Subtle Inner Ear Complications of Otitis Media". Because there are so many studies on this subject reporting similar findings, the references in Section II are numbered sequentially and appear separately, following the references in Section I.

Complications of Suppurative Otitis Media

Overview

Historical Background

The existence of complications of suppurative otitis media and efforts to control it go far back into history. Ear surgery proper, or surgery for ear complications, may have started as early as the Carnac period of the neolithic age (Parry, 1914), in which there is evidence that trephining was performed on skulls. Whether this work was done for relief of suppuration in the mastoid region or for intracranial conditions is not definitely known (Sonnenschein, 1936). Trephining is also documented in the Inca Empire (McIntyre, 1975) and earlier in Indians of the Moche Valley in Peru, and in Bolivia (Stuart and Stuart, 1969). Writtent reports of this disease and its complications go as far back as the third earliest medical writings, the Egyptian papyrus of Ebers, believed to have been written about 1550 BC (Ebbell, 1937). In studies of Dinkha-tepe skulls from Iran, of individuals living approximately in 1300 to 1000 AD, up to 40 per cent of cases have shown temporal bone changes presumably secondary to otitis media (Ratbun and Mallin, 1977). The Babylonian Talmud (352-427 AD) also refers

to this subject (Stevenson and Guthrie, 1949). Hippocrates (400 BC) was well aware of otitis and brain abscess as caused by otitis (Lederer, 1960), but it was not until Morgagni, whose studies were published in 1736, that abscess of the brain was considered in many cases to be secondary to infections of the ear (Bolz, 1971).

Mortality and Morbidity of Complications

Clearly defining the potential seriousness of otitis media in the preantibiotic era, based on its anatomic location and its boundaries with vital structures, Politzer in 1869 (published in 1909) stated that "the temporal bone has four sides: the outside is bounded by life, from which there comes the opening of the auditory canal, one form of our appreciation of what life means; on the other three sides this bone is bounded by death" (Politzer, 1909; Lederer, 1960). The advent of antimicrobials, an increasing awareness on the part of physicians and the public regarding the potential seriousness of this disease, and diagnostic methods yielding earlier identification and treatment reduced immensely the incidence of its lethal complications. Prior to the antibiotic era, intracranial complications occurred in 2.3 per cent of cases of acute or chonic otitis media (Dowes, 1965), and acute otitis media resulted in mastoiditis in 25 to 50 per cent of patients (Boies, 1942). Antibiotics reduced this incidence to current figures of 0.15 per cent (Jeanes, 1962), 0.02 per cent (Prellner, 1985), and 0.04 per cent (Palva, 1985) and that of coalescent mastoiditis to 0.4 per cent (Palva and Pulkinen, 1959). However, it must be kept in mind that despite this dramatic decline, the complication rate in acute mastoiditis varies between 8 and 12 per cent (Ginsburg, 1980; Pfaltz and Griesemer, 1984).

The dramatic decline in mortality is exemplified in a report by Couville (1955) from the Los Angeles County Hospital. At this institution, between 1928 and 1933 (preantibiotic ear) 25 of every 1000 deaths were due to intracranial complications of otitis media; between 1949 and 1954 (antibiotic era), only 25 of every 10.000 deaths were due to such complications. This represents a 90 per cent decrease in mortality.

Despite an overall decline in the incidence of intracranial complications of otitis media with significant mortality, complications of otitis media in the temporal bone with significant morbidity occur quite frequently. Complications and/or sequelae of otitis media may have devastating effects physiologically as well as psychologically, resulting in behavioral complications. Unfortunately, severe complications still exist, and this cannot be emphasized enough. Although the statistical figures show a dramatic decrease in the absolute numbers of cases, those cases that still occur represent a significant medical problem. This is so in part because the physician confronted with such uncommon cases are obviously less experienced and may underestimate or misinterpret the symptoms. In many cases, not even the best treatment available will prevent sequelae. Important factors in the development of complications include the infecting agent, the adequacy and timing of treatment, and the resistance of the infected individual.

In a recent report of a study done in South Africa, Samuel and colleagues (1986) presented their experience with 224 otogenic intracranial complications occurring between 1978 and 1983. Their patient population comprised African blacks in whom otitis media had been neglected and who were reluctant to seek medical attention. This study represents a prevalent problem (which tends to be overlooked) in very many areas of the world. It reflects

in part the contrast between the incidence and prevalence of complications in a low socioeconomic group (analogous to patients in the preantibiotic era) and the results in this same group when subsequently exposed to modern medicine.

Of 85.000 patients attending the ear, nose, and throat clinic Samuel and coworkers reported that 335 had otogenic complications, 224 of which represented intracranial complications. Meningitis occurred in 83 patients, brain abscess in 53, extradural abscess in 49, and lateral sinus thrombosis in 39 patients. Of these patients, 74 per cent were children and young adults (under 15), which reflects conditions in the preantibiotic era. The actual tendency is that of an increasing number of complications in older individuals with chronic otitis. With modern-day evaluation and treatment, the overall mortality of 14 per cent reported by these investigators compares very favorably with current reports from American and European groups. While prevention and early diagnosis are crucial and remain most important, this study reflects the difference that modern-day medicine makes and is supportive of arguments for the existence of sophisticated facilities.

Anatomic Pathways of Infection

Spread of infection beyond the membranous lining of the middle ear cleft can occur through three basic pathways:

1. Extension through pre-formed pathways such as the round window, congenital bony dehiscences, or dehiscences resulting from fractures or surgery.

2. Extension by bony erosion secondary to inflammatory processes such as granulation tissue and cholesteatoma.

3. Extension by progressive thrombophlebitis through the haversian venous channels near the infected site, such as the lateral sinus.

Sites of extension will then necessarily be related to the anatomic vicinity of the various structures providing the pathways.

The middle ear cleft is separated superiorly from the middle cranial fossa by a thin plate of bone, and posteriorly from the posterior cranial fossa and lateral sinus by a thicker plate of bone. Inferiorly, the jugular bulb is separated from the hypotympanum by a thin, occasionally dehiscent plate of bone. Medially, the round window membrane and the footplate of the stapes are doors to the inner ear. Within the middle ear itself, the facial nerve traverses in its not uncommonly dehiscent bony canal, and the ossicles themselves are easily exposed to damage.

Acute infections are more likely to spread through pre-formed pathways or through progressive thrombophlebitis; therefore they develop early. Extension of chronic infection and/or active sequelae is most likely to be due to bony erosion, but evidence of persistent disease is usually seen before a complication develops. Because of the pathogenesis of otogenic extension, it is common to have multiple areas of complication; on the other hand, most types of complications may also lead to others. In the overall picture of the problem,

anatomy and pathogenesis are considered in dealing with complications. They are described separately in this chapter, for practical purposes.

Table 1. Complications and Sequelae of Otitis Media

Complications

Temporal Bone	*Extratemporal*
Middle ear:	Intracranial:
Facial nerve paralysis	Extradural abscess
Ossicular lesions	Subdural abscess
Perforation of the tympanic membrane	Brain abscess
	Meningitis
	Lateral sinus thrombophlebitis
	Otitis hydrocephalus
Mastoid:	Extracranial:
Petrositis	Bezold's abscess
Reduced pneumatization	Zygomatic abscess
Coalescent mastoiditis	Postauricular abscess
Inner ear:	Others:
Labyrinthitis	Developmental
Sensorineural hearing loss	Behavioral

Sequelae

Active:
- Recurrent attacks of otitis media
- Chronic otitis media with effusion
- Silent otitis media
- Masked mastoiditis
- Continuum of POM-SOM-SOM --> COM*

Inactive:
- Atelectasis
- Tympanosclerosis
- Adhesive otitis media

* POM = purulent otitis media; SOM = serous otitis media; MOM = mucoid otitis media; COM = chronic otitis media.

Classification

Based on the preceding discussion, complications of suppurative otitis media can be classified into two major categories (Table 1): inside the temporal bone (intratemporal) and

outside the temporal bone (extratemporal). *Intratemporal* bony complications include facial nerve paralysis, perforation of the tympanic membrane, ossicular lesions, reduced mastoid pneumatization, coalescent mastoiditis, petrositis, labyrinthitis, and sensorineural hearing loss. *Extratemporal* bony complications can be divided into intracranial, extracranial, and others. Intracranial complications include extradural abscess, subdural abscess, abscess of the brain, meningitis, lateral sinus thrombophlebitis, and otitic hydrocephalus. Extracranial complications include Bezold's abscess, zygomatic abscess, and postauricular abscess. Other complications include developmental and behavioral problems.

Facial Nerve Paralysis

In the preantibiotic era, facial nerve paralysis occurred in 0.5 per cent of cases of acute suppurative otitis media and in 1.7 per cent of cases with chronic suppurative otitis media, the majority of them (80 per cent) in relationship with cholesteatoma (Kettel, 1943).

Facial paralysis may occur during an episode of *acute* otitis media secondary to the spread of infection through a dehiscence of the bony facial canal, which is present in over 50 per cent of cases. The pathophysiology of facial paralysis secondary to acute infection is not clear. It is generally believed that venous congestion, tissue edema, and possible direct neural toxicity are the major factors that result in paralysis. Myringotomy for drainage of purulent effusion, placement of a large-bore tube, and antibiotic therapy will suffice in the great majority of cases. Decompression of the facial nerve is reserved for those cases in which, despite proper initial therapy, the nerve undergoes an axonal degeneration, as diagnosed by electrical testing. Complete evaluation including computerized tomography (CT) should be done if there is no neural response. What appears to be an acute condition may be an acute phase of an ongoing underlying process under an intact tympanic membrane.

Facial paralysis occurring as a result of *chronic* otitis media indicates a serious complication that demands prompt surgical decompression of the nerve. Facial nerve paralysis in this condition implies erosion of the bony canal by a chronic inflammatory process, with direct compression or infiltration of the nerve. In these cases, the nerve sheath (epineurium) should probably not be opened, because the ingrowth of fibrous tissue could potentially decrease the completeness of the overall recovery. If the facial neural impairment represents only a paresis, and excitability remains normal, a complete evaluation should be done, and surgery may be indicated according to those findings.

Labyrinthitis

Labyrinthitis, as the name implies, is an inflammation of the inner ear (labyrinth) and can be serous, suppurative, or localized (perilabyrinthitis). It may be caused by viruses or bacteria. A detailed discussion of this subject is included in Chapter 42 of this volume.

Serous, or toxic, labyrinthitis is a diffuse labyrinthine inflammation without pur or bacteria. Histologically, it is characterized by a serous, acellular precipitate in the labyrinth, whereas purulent labyrinthitis is characterized by the presence of inflammatory cells. Serous labyrinthitis is a form of sterile inflammation secondary to exposure to toxic materials that cross the round window membrane or the oval window annulus. Most commonly, serous labyrinthitis is a complication of otitis media. Paparella and colleagues (1972) found

histologic evidence of serous labyrinthitis in 83 per cent of cases of suppurative otitis media studied. It is usually self-limiting, with reversible damage; however, partial loss of hearing may be permanent.

Purulent labyrinthitis occurs as the result of direct spread of infection from the middle ear, retrograde invasion of infection through the internal auditory canal or cochlear aqueduct in patients with meningitis, or transmission of infection by way of vascular channels in patients with septicemia. Meningitis purulent labyrinthitis is usually bilateral, and tympanogenic purulent labyrinthitis is most commonly unilateral. The incidence of meningogenic labyrinthitis is more common than tympanogenic labyrinthitis (Nadol, 1978). Schuknecht (1974) described four histologic stages of purulent labyrinthitis characterized by (1) collection of polymorphonuclear leukocytes, (2) formation of precipitate and development of endolymphatic hydrops, (3) necrosis of the membranous labyrinth, and (4) fibrosis and osteogenesis. Purulent labyrinthitis usually results in total loss of hearing and equilibrium due to destruction of membranes of the inner ear. In cases of severe suppurative labyrinthitis, osteoneogenesis may totally replace the normal anatomical structures of the inner ear (labyrinthitis ossificans).

Symptoms of labyrinthitis include sensorineural hearing loss, tinnitus, and vertigo. Any patient with otitis media who develops spontaneous nausea, vertigo, sensorineural hearing loss, and tinnitus should be suspected of having labyrinthitis. Purulent labyrinthitis is more severe, with fulminating, incapacitating symptoms associated with spontaneous nystagmus. It is frequently impossible to differentiate (except in retrospect) serous from suppurative labyrinthitis until the episode has resolved.

Treatment consists of hospitalization, hydration, antimicrobial therapy, antivertiginous medications, and myringotomy (initially). When conditions persist, further surgical intervention should be considered, including mastoidectomy. When serous labyrinthitis occurs in chronic otitis media, early surgery is indicated.

Localized labyrinthitis (perilabyrinthitis) is due to erosion (fistula) of the cochlea or, more commonly, one of the semicircular canals, by an inflamatory process. A surgical fistula may also be created accidentally. A fistula in an unoperated patient is generally indicative of cholesteatoma, most commonly involving the horizontal canal. Involvement of the horizontal canal alone has been reported in up to 51 per cent of cases (Dawes and Watkins, 1978). Like the other forms of labyrinthitis, the localized type may result in vertigo and sensorineural hearing loss. In addition, the patient will have a positive fistula test. A positive test for fistula in the horizontal canal means horizontal nystagmus with a fast component to the ipsilateral ear when inward pressure is applied to the external ear canal.

Fistulas of the other canals may have a more vertical tendency for nystagmus. In combined fistulas, nystagmuc can be rotatory. However, abscence of indications by a fistula test does not rule out a fistula. Dawes and Watkins (1978) reported a negative test in 38 of 66 surgically proven fistulas. Therefore, when all the clinical elements are present except for a positive fistula test and a doubt exists, surgical exploration is indicated, whether or not there is chronic otorrhea.

Surgical treatment for fistulas basically implies mastoidectomy with thorough removal of pathologic tissue in the mastoid and middle ear, leaving the matrix of the fistula for last. Removal of such matrix depends on the size of the fistula. Two millimeters has been considered an arbitrary guideline (Gacek, 1974). Location of such a fistula is also of paramount importance.

Reduced Mastoid Pneumoatization

The question of whether pneumatization of the mastoid is purely hereditary or can be directly affected by chronic otomastoiditis used to be a subject of livery discussion (Wittmaack, 1918; Diamant, 1940; Tumarkin, 1959). However, based on ample evidence (Ojala, 1953; Diamant et al, 1958; Goro and Kaieda, 1958; Hussl, 1973; Hussl and Welzi-Muller, 1980; Tos et al, 1984, 1985; Stangerup and Tos, 1986; Qvarnberg et al, 1987), poor mastoid pneumatization can be considered a complication of chronic otomastoiditis.

Coalescent Mastoiditis

Acute otitis media is defined as an inflammation of the middle ear cleft as well as of the eustachian tube and mastoid. It implies an involvement of the mucoperiosteum lining these cavities. Treatment is intended to eliminate the symptoms and the infected effusion as well as to arrest the inflammatory process. When such an inflammation becomes persistent in the mastoi, it constitutes a mastoiditis proper. It can be either masked (discussed later) or clinically evident. This prolonged form has been termed granulomatous exudative mastoiditis. If the infected inflammatory process erodes the underlying bone, a mastoiditis ensures. If the bony partitions within the mastoid are eroded, it becomes a *coalescent* mastoiditis. Coalescent mastoiditis derives its name from the observation of resorption of the thin bony septa separating the air-cells, making the air-cells appear to coalesce. An acute otitis media requires the presence of air-cells in order to develop this complication; on the other hand, chronic otitis may result in a complication of bony erosion in a mastoid with poor or absent pneumatization. This clinical picture should be suspected in any patient who has had an episode of prolonged, purulent otitis media, with or without aural drainage, and who develops pain, fever, and tenderness in the mastoid region. One of the diagnostic pointers is persistence of low fever or recurrence after antibiotic therapy has been stopped. Bacterial cultures in coalescent mastoiditis reveal *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus pyogenes,* and occasionally *Proteus* and *Klebsiella* species and *Escherichia coli* (Hawkings et al, 1983; Holt and Young, 1981).

Maharaj and colleagues (1987) in South Africa did cultures for microorganisms in 35 consecutive patients undergoing surgery for mastoiditis. There were 87 isolates (36 aerobes and 51 anaerobes) for 32 culture positives (91.4 per cent). Speciments from three patients yielded no growth (8.6 per cent). Aerobes only were cultured in four patients (11.4 per cent); anaerobes only in six patients (17.1 per cent) and both aerobes and anaerobes in 22 (62.8 per cent). Thus, anaerobes were cultured from a total of 28 patients (80 per cent). The most common aerobes were Group A beta-hemolytic streptococci (9 cases), *Staphylococcus aureus* (7 cases), and *Proteus mirabilis* (5 cases). Anaerobes were most commonly gram-negative: *Bacteroides melaninogenicus* (10 cases), *B. fragilis* (9 cases), and other *Bacteroides* species (5 cases). These results, evidence of a polymicrobial flora, are suggestive that antimicrobial

agents against anaerobes should be used in these cases (eg, chloramphenicol, lincomycin, clindamycin, and metronidazole).

When infection surprasses the mastoid cortex, a subperiosteal abscess can occur. It may present as a postauricular abscess (swelling behind the ear with displacement of the auricle forward, outward, and downward), or a Bezold's abscess, formed by perforation of the tip of the mastoid with extension down to the posterior triangle of the neck (Bezold and Siebenmann, 1908; Mygind et al, 1910; Hawkins et al, 1983). Extension beyond the mastoid cortex following the same pattern as a Bezold's abscess can also occur secondary to an active sequelae such as cholesteatoma and granulation tissue (Godde, 1962; Luetje, 1979; Hughes et al, 1980; Ibekwe, 1988). These abscesses are treated by mastoidectomy and drainage; in patients with Bezold's abscess, exploration of the neck may be needed as well.

The diagnosis of coalescent mastoiditis is confirmed by x-rays of the mastoid area that demonstrate opacification of the air-cells and a decrease in the fine bony septations. However, radiography of the mastoid alone may not help differentiate a coalescing mastoiditis from a chronic mastoiditis. The treatment of choice is antimicrobial therapy and cortical mastoidectomy involving total exenteration of the diseased bone and membranes. Ample communication from mastoid to middle ear must be ensured. A large myringotomy and insertion of a tympanostomy tube at the time of mastoidectomy may help the drainage process.

Petrositis

The term *petrositis* refers to an inflammatory process that has spread to the air-cells of the petrous apex of the temporal bone. These air-cells are distributed in both the perilabyrinthine and the apical regions of the petrous bone; hence, their classification as either perilabyrinthine (supra and infra) or apical (apical and periapical). Petrositis is an uncommon and late complication of purulent otitis media. Pneumatization of the petrous apex is less common than in other areas of the temporal bone, and treatment for otitis media and mastoiditis usually also provides treatment for mild petrositis. It does occur, however, especially in relation to cholesteatoma and formation of granulation tissue.

Owing to its anatomic relationship to cranial nerves V and VI, this disease may result clinically in paralysis of the lateral rectus muscle and pain in the areas of the distribution of cranial nerve V (retro-orbital pain); in fact, a deep-boring pain may be the only persistent symptom. These symptoms plus otitis media, described by Giuseppe Gradenigo in 1904, constitute the classical clinical triad known as Gradenigo's syndrome that is characteristic of petrositis. Petrositis can exist without exteriorization beyond the apex; therefore, without the classical triad, petrositis is not synonymous with Gradenigo's syndrome. Petrositis can lead to other complications such as meningitis, extradural abscess, and labyrinthitis. The diagnosis can be confirmed by x-rays (Towne's and Stenvers' views of the mastoid), polytomography, and CT. CT is most useful in the diagnosis of petrositis. Bone-scanning using gallium-67 and technetium-99 can be helpful.

The treatment of choice includes intensive antimicrobial therapy (eg, against *S. pneumoniae, H. influenzae, Staph pyogenes*) and surgical intervention. A complete mastoidectomy with search and exenteration of cell-track extension around the semicircular

canals with curettage of fistulous tracts is indicated. If unsuccessful, a petrous apicectomy may be needed. Surgical approaches to the petrous apex include those through the sinodural angle, the subarcuate air-cell tract (Frenchner's aproach), the supralabyrinthine portion of the perilabyrinthine tracts (Thornvaldt's approach), the middle fossa (House, 1961; Glasscock, 1969), the sphenoid sinus, and an approach following the peritubal cells to the petrous apex between the cochlea and the carotid artery (Lempert-Ramadier's approach).

Lateral Sinus Thrombophlebitis

This is an uncommon complication that develops as a consequence of erosion in the bony covering of the lateral sinus. It can also be caused by infections extending through the mastoid emissary vein (from scalp or mastoid). Occasionally the reverse happens - that is, thrombophlebitis of the lateral sinus can extend to the mastoid emissary vein. The postauricular edema that ensues is called Griesinger's sign. In this complication, an initially localized phlebitis promotes development of a mural thrombus that can enlarge and occlude the lumen. The thrombus can propagate, become infected, and release septic emboli.

Since the advent of antibiotics, the incidence of lateral sinus thrombophlebitis has gradually declined (Teichgraeber et al, 1982); however, mortality remains extremely high, ranging from 10 per cent to 36 per cent (Samuel et al, 1986). The use of antibiotics has changed many other characteristics of this condition, which in the past was a complication of acute otitis in very young individuals (Rosenwasser, 1945). Over the years, it has become more common in adults with chronic otitis media. The classic sign in the preantibiotic era was a "picket-fence" curve in the patient's temperature, due primarily to periodic release of hemolytic streptococci from the septic sinus thrombus. Patients were described as progressively anemic and emaciated; blood cultures and Quekenstedt's test were helpful in diagnosis.

Beta-hemolytic streptococcus is no longer the most common organism (Teichgraeber et al, 1982). Cultures in chronic cases reveal mixed flora, including *Bacteroides* and *Streptococcus* species and gram-negative rods (de Lomvois, 1978; Jahrsdoerfer et al, 1968). In a large series of cases, Seid and Sellars (1973) cultured *Proteus* and *Pseudomonas* species frequently. Fever is still the primary sign, even though it may not manifest as a typical spiking curve. The second most consistent sign is pain in the mastoid and neck over the sternocleidomastoid muscle. Ocular abnormalities such as papilledema have been reported as ranging from 20 to 50 per cent (Teichgraeber et al, 1982). However, in one large series (Samuel et al, 1986) there are no reported findings of papilledema. This suggests that ocular changes are an unreliable sign.

With current revisions in bacterial agents and antibiotic therapy, changes in cerebrospinal fluid, which in the past used to be useful signs, are no longer as useful diagnostically.

Lateral sinus thrombophlebitis uncommonly progresses to embolization. Clinically, the most important sign is high fever in a patient with acute otitis, or a slight or intermittent fever in a patient with a chronically draining ear. This may be accompanied by tenderness in the mastoid and neck. Diagnostically, CT is the imaging procedure of choice (Venezio et al, 1982; Teichgraeber et al, 1982), and associated contrast studies are helpful in identifying not

only the thrombus but also any associated complications, the size of the thrombus, and surrounding edema. Such imaging allows proper timing and adequate planning of surgical intervention. Vascular studies such as arteriography and venous jugulograms are quite useful and specific; however they carry the risk of dislodging the thrombus, although their use in various series has no reported complications. Digilat subtraction venography can be used safely and accurately.

Treatment includes appropriate broad-spectrum antibiotic therapy and surgical intervention. Surgery involves a mastoidectomy with exposure of the posterior fossa plate and exploration of the sinus. The sinus can be needled for the presence of a thrombus, which, if present, should be removed. The question of ligation of the internal jugular vein remains controversial. There are strong arguments in favor (Cody et al, 1939) and against (Lyman, 1935) ligation. In general, ligation should be reserved for those unusual cases with evidences of septicemia and embolization that do not respond to treatment (Jahrsdoerfer et al, 1968; Alford and Pratt, 1966; Emery, 1962). Anticoagulants carry the risk of spreading the thrombus and are not recommended.

Meningitis

Meningitis is the most common intracranial complication of purulent otitis media (Gower and McGuirt, 1983; Samuel et al, 1986; Habib, 1988). It can follow either an acute or a chronic episode. Meningitis is an example of a complication in which mortality rates have been reduced dramatically; however, the rate of morbid complications remains excessively high. Inflammation of the meninges can occur by direct infection from the middle ear or by direct extension from bony erosion. Hematogenous dissemination also plays an important role in bacterial meningitis.

The main clinical signs are headache, fever, and nausea and vomiting associated with stiffness in the neck. Abnormal reflexes such as Kernig's sign, in which the leg cannot be completely extended when the thigh is flexed on the abdomen, or Brudzinski's sign, in which involuntary flexion of the ankles, knees, and hips occurs when the neck is flexed, may be present. Lumbar puncture will reveal high protein and low glucose levels, associated with the presence of bacteria and inflammatory cells. In early phases of meningeal infection, bacterial elements are not present. Any patient with unexplained meningitis should be carefully evaluated for otitis media.

When dealing with meningitis secondary to acute purulent otitis media, the treatment is medical unless there are recurrent episodes of meningitis. A large myringotomy with suction and evacuation of pus for Gram staining and culture is indicated in cases of acute purulent otitis media associated with meningitis. When there are recurrent episodes, exploration of the middle ear and mastoid is indicated in an effort to identify the pathway of communication. When meningitis occurs as a result of chronic otitis media, a complete mastoidectomy with a large myringotomy is required, in addition to antimicrobial therapy. In this cases, the organisms are usually gram-negative rods, whereas in acute cases those involved are usually *S. pneumoniae*, *H. influenzae*, and *Staph pyogenes.* To ensure the adequacy of antibiotic therapy, repeat lumbar punctures and cerebrospinal fluid analysis are important (Steele and Bradsher, 1983).

Intracranial Abscess

Intracranial abscess may occur at different sites. These may be extradural (most common), outside the dura mater; subdural, between the dura mater and arachnoid; or intracerebral or intracerebellar. Reports on the number of otogenic brain abscesses vary widely. Ayyagari and associates (1983) reported 45 patients with brain abscesses encountered in 21 months. Of these cases, 42 per cent were estimated to be otogenic. Hirsch and colleagues (1983) reported that 35 per cent of brain abscesses originate from infections of the ear, nose, and throat.

An extradural abscess may follow either acute or chronic infections. The dura is tightly bound to bone in the posterior fossa and loosely bound in the middle fossa. In the latter, an abscess can become quite large and can even cause compression over the temporal lobe; the signs and symptoms may be nonspecific; headache is by far the most common complaint, followed by fever (Kerr et al, 1958) and severe otalgia with general malaise. On occasion, headache is relieved by abundant pulsatile drainage from the ear. The treatment of abscesses includes antibiotic therapy and surgery.

Subdural abscesses are uncommon; however, they have a tendency to extend into nearby areas. They can occur as direct bony extension or as extension by thrombophlebitis. Symptoms include headache, fever, and general malaise. As these abscesses extend, they can present manifestations of compression such as hemiplegia. Treatment is initially oriented neurosurgically, the otologic focus being cleared surgically once the subdural space has been adequately drained.

Brain abscesses may occur in the temporal lobe (cerebrum) or the cerebellum as a direct extension (of infection or trauma) or due to thrombophlebitis. They are often associated with other intracranial complications such as extradural abscess. Temporal lobe abscesses are more common than cerebellar abscesses by a ratio of 2:1, but cerebellar abscesses more frequently result in fatal outcomes (Quijano et al, 1988). Mawson (1974) described four clinical stages in the development of brain abscess. The first stage is initial encephalitis, followed by a latent or quiescent stage (stage 2); stage 3 is that of enlarging abscess, and stage 4 occurs when the abscess ruptures. The clinical progression of these stages may vary from several days to several months, depending on the response of the host and the therapy (Proctor, 1966; Ward et al, 1969). On occasion, an unsuspected latent abscess can become manifest after a mastoidectomy for chronic suppurative otitis media (Cody et al, 1964).

There are no definite symptoms until stage 3, in which the patient develops compressive symptoms manifested by focal seizures and/or aphasia (abscess in the temporal bone) or ataxia and/or intention tremor (cerebellar) associated with fever, headache, nausea, vomiting, and mental compromise. Papilledema may be present. Examination of cerebrospinal fluid reveals elevated pressure and high protein content. Angiography and ventriculography assist in localizing the lesions. In these lesions as well as in almost all of these complications, advances in radiology, particularly CT, have become invaluable in optimizing the timing for medical and surgical management (Rosenblum, 1978; Som et al, 1978; Miyamoto and Worth, 1986; Maniglia et al, 1980). CT with contrast studies of the brain abscess shows a hypodense area encircled by an enhancing ring.

The treatment of abscesses is by a combined approach of otologic and neurosurgical drainage plus antimicrobial therapy. Advances in imaging and antibiotic therapy have resulted in a tendency toward reliance on medical treatment, and in some cases, abscesses have resolved through the administration of antibiotic therapy alone, thus obviating the need for intracranial surgery (Quijano et al, 1988). It is important to clarify that this statement refers only to intracranial surgery and only to related cases. Antibiotic therapy may very well control the infectious process at times, but it will never eradicate the cholesteatoma. Moreover, antibiotic therapy may have reduced the incidence of otogenic complications by eradicating the infection, but it does not always resolve the underlying inflammatory process. Cholesteatomas and granulation tissue cause the bone destruction that leads to complications, and they should be removed surgically. The otologic surgical approach is directed toward eradicating diseased tissue, draining infected secretions, performing functional reconstruction of the conductive system of the middle ear, and if necessary, repairing a dural defect. The extent and type of procedure done depends on the circumstances in a particular case. In the case of an acute infection with a destructive inflammatory reaction and necrosis of the dura mater, attempts to eradicate all diseased tissue may result in a large dural defect. Therefore, drainage should be done, and tympanomastoidectomy with repair of the dural defect should be reserved for a later time when the intracranial abscess has been controlled (Quijano et al, 1988). This complication has the highest mortality rate.

Otitis Hydrocephalus

Otitis hydrocephalus is characterized by increased pressure of cerebrospinal fluid, caused by failure of arachnoid granulations to absorb the fluid or by dural sinus thrombosis following meningeal infection and inflammation of the middle ear. This complication should be suspected in patients who develop headaches, paralysis of nerve VI, decreased consciousness or lethargy, and papilledema following an episode of several weeks of otitis media. The diagnosis is confirmed by lumbar puncture that reveals normal cellular elements and high levels of cerebrospinal fluid pressure.

Therapy includes eradication of suppurative ear disease with appropriate antibiotics and surgical therapy and treatment for the increased intracranial pressure with repeated lumbar puncture, systemic steroids, and/or shunting procedures. The pressure usually returns to normal after several weeks to months. It should be kept in mind that it is possible to herniate the cerebral peduncles through the foramen magnum when lumbar punctures are done in the presence of hydrocephalus.

Other Complications

Other, non-devastating complications of otitis media include sensorineural hearing loss, abnormalities of the ossicular chain, perforations of the tympanic membrane, and psychological and behavioral changes. Inflammatory processes can both disrupt and fix the ossicular chain, causing conductive hearing losses. Hearing loss by itself, even if mild and conductive in nature, can result in partial isolation from the environment, leading to psychological and behavioral complications. Bilateral hearing loss, even if mild and purely conductive in nature, occurring during the first year of life can result in problems in language acquisition and decreased academic skills (Teele et al, 1984; Eimas and Kavanagh, 1986; Downs et al, 1988; Gleason, 1988; and Roberts et al, 1988).

Latent Mastoiditis

While the advent of antibiotics has reduced the mortality and morbidity of otitis media, it has either resulted in the appearance of new forms of complications or made previously unrecognized complications more evident. This is particularly true in the case of masked mastoiditis and silent otitis media. Antibiotics are expected to eradicate infectious processes; however, in the case of otitis, at times they will only confine the infection to the middle ear cavity and/or mastoid. This does not necessarily eradice the underlying histopathologic changes or avoid exacerbations of a latent infection if conditions are favorable. When affecting the mastoid, this condition has been termed "latent or masked mastoiditis" (Mawson, 1963; Goodhill, 1979). According to Mawson, latent mastoiditis occurs following an antibiotic treatment that has not extinguished but merely damped down an infection, which remains smoldering and subclinical. Behind an intact tympanic membrane there may be little or no symptomatic indication of this potentially dangerous process. Clinically, persistence of pain or hearing loss, or discharge in the case of a perforated tympanic membrane, indicates an unextinguished infection. Hearing loss is the most common symptom. Occasionally there is low fever and/or slight tenderness over the mastoid process. Mastoid x-rays are not definite. Air-cells may have a hazy aspect. In patients with these symptoms and in whom this diagnosis is suspected, exploration is indicated. This is provided that a complete evaluation of the patient has been performed. Other elements, such as anatomic, immunologic, and allergic factors, may play a role in rendering the antibiotics ineffective.

The best treatment for this entity is prevention. Patients should be warned that antibiotic treatment for acute infections must be taken for the full extent prescribed and at the number of times a day recommended, regardless of whether the patient becomes seemingly asymptomatic.

Silent Otitis Media

Otitis media may be present in forms similar to that of a smoldering infection on the mastoid. These forms have been grouped under the term silent otitis media and usually refer to chronic pathologic conditions that are clinically "undetected or undetectable" behind an intact tympanic membrane (Paparella, 1986). Michael Paparella, who has set forth this concept, describes silent otitis media in a separate chapter. In these forms of otitis media, the complications caused by their masked persistence can be subtle. Based on clinical observations correlating otitis media with sensorineural hearing loss, a cause-and-effect relationship had been postulated. This concept has been the subject of controversy (Gardengli, 1955; Frickenger, 1957; Bluvshtein, 1963; Paparella et al, 1970, 1972, 1984; English et al, 1973; Moore and Best, 1980; Dumich and Harner, 1983; Walby et al, 1983; Walby et al, 1983; Kirtane et al, 1985; Dommerby and Tos, 1986; and Vartiainen and Karjalainen, 1987). The evidence is highly suggestive that such a relationship exists, but the evidence is not conclusive. The possible association of otitis media with endolymphatic hydrops has also been postulated (Paparella et al, 1979).

Subtle Inner Ear Complications of Otitis Media

The concepts of masked mastoiditis and silent otitis media lead to the hypotheses that subtle inner ear complications could develop as a consequences of noxious substances from

the middle ear reaching the inner ear (Paparella et al, 1972, 1979). What initially was the subject of interest of only a few investigators has evolved over time into the concept of middle and inner ear interactions. The extensive experimental work in this area is sufficient to suggest the concept, but there is not enough of it. For these reasons we have elected to describe systematically the experimental work available.

A most likely portal of entry for noxious substances is the round window membrane. It is the only soft tissue barrier between middle and inner ear. It is located inferiorly in the medial wall of the middle ear, lies in a niche in which effusions can accumulate, and is proximal to the sinus tympani. All of these anatomic factors render it susceptible to "noxious materials.

While working with fixed tissues can be viewed as a static descriptive discipline, this view changes dramatically if these tissues are evaluated as dynamic structures, based on the principle that structural organization represents function. The round window membrane should be seen as an armonic structure with interrelated cells and layers, which in turn interrelate as a unit with the middle and inner ear (which are in turn part of an overall system).

Experimental Evidence

Evidence for permeability of the round window membrane has come from different studies. Substances placed in the middle ear can be recovered in perilymph (directly or indirectly) and/or observed to caused morphologic inner ear changes, and/or noted to cause detectable neurophysiologic changes (Table 2). However, this evidence does not prove that such passage is through the membrane. A clear, irrefutable demonstration has to be morphologic.

Table 2. Substances Placed in the Round Window Niche That Have Been Detected Directly or Indirectly in the Inner Ear

Ceftemazole	^{22}Na
Gentamicin	^{131}I
Dimethyl tetracycline	NaCl
Neomycin-polymyxin B	KCl
Chloramphenicol	Cyclaine
Neomycin	Procaine hydrochloride
Streptomycin	Lidocaine
Staphylococcal exotoxin	Tetracaine hydrochloride
Pseudomonas aer. exotoxin A	Prilocaine
Lipopolyssacharide from *E. coli* (endotoxin)	Cocaine
	Quinine
S. typhimurium derived endotoxin	Bupranolol
Albumin	Triamcinolone
High-density lipoprotein	Dexamethasone
Tetraethylammonium chloride	Thorotrast
Povidone iodide	Sodium salicylate
Chlorhexidine	Indomethacin
Propylene glycol	Lipoxygensae products
	Rhodamine.

Ultrastructural studies of the round window membrane in different species (Table 3) have revealed a basic three-layered structure that has the anatomic potential for passage of substances from the middle to the inner ear, as well as from perilymph into the round window membrane. Despite similarities, there are significant differences between species, especially in terms of connective tissue layer thickness. This layer becomes thicker and better organized as the species is higher on the philogenetic scale. Within a species, the average thickness of a normal round window membranes remains constant with age.

Table 3. Reported Ultrastructures of the Round Window Membrane

Rat	Cat
Guinea pig	Squirrel monkey
Chinchilla	Rhesus monkey
Mongolian Gerbil	Human.

Passage of substances through the layers of the round window membrane has been demonstrated experimentally in animals and humans with tracers such as horseradish peroxidase (HRP), cationic ferritin, and 1-micron spheres (Table 4). These substances, when placed in the middle ear, have been observed to pass through the round window membrane. The mechanism of transport is pinocytosis by the epithelial cells. From the cytoplasm of such cells, vesicles are transported into the intercellular space or toward the basement membrane into the connective tissue layer. Once in the connective tissue, tracer can be taken up by cells, pass into blood or lymph vessels (by pinocytosis and through cell junctions), and/or (in the cases of tracer coming from middle ear), traverse theinner epithelial layer by pinocytosis and end up in perilymph. The reverse is also true, that is, tracers and spheres placed in perilymph traverse into the membrane (Table 5).

These studies have established morphologically the semipermeable nature of the normal round window membrane and the capacity to absorb substances from perilymph. However, they provide no information as to what occurs in pathologic membranes. Ultrastructural changes have been studied in humans with otitis, diabetes mellitus, and in animals with round windows exposed to staphylococcal exotoxin. In otitis media induced in cats, round window membrane changes have been evaluated by light microscopy, and the membrane was observed to undergo gradual changes similar as those of the mucoperiosteum. These changes suggest that perhaps at early stages there may be an increase in permeability, but as the inflammatory process develops, the changes in the membrane become protective in terms of decreased permeability. In cats, during very early stages of otitis media, increased permeability to tritiated albumin has been observed. In chinchillas with early stages (about 12 hours) of antigen-induced otitis media, permeability to human serum albumin increases.

Permeability of chinchilla round window membranes to tetraethylammonium chloride increases after application of exotoxins or endotoxins, whereas it diminishes after established inflammatory changes, such as after 2 weeks of eustachian tube obstruction. In otitis induced in chinchillas and guinea pigs, HRP placed at different intervals was observed to traverse the membrane in normal animals and in animals with early stages of otitis media. However, when the inflammatory changes were established in the membrane, the tracer would not go through it. Nomura has observed passages of both HRP and ferritin in otitis-induced guinea pigs in early stages as well. In established otitis media in the same animal species, Nomura reported

that the membrane seems to become less permeable to neomycin when compared with the membranes of normal animals.

Table 4. Substances Placed in the Round Window Niche That Have Been Observed Within the Round Window Membrane Layers

Substance	Species
Cationic ferritin	Guinea pig Chinchilla Cat Rhesus monkey Human
Horseradish peroxidase (HRP)	Guinea pig Chinchilla Cat
Neomycin-gold spheres	Chinchilla Rhesus monkey
1-micron Latex spheres	Chinchilla Rhesus monkey.

Histopathologic changes in the membrane during episodes of otitis media have been the basis for the suggestion that the round window membrane can participate in a middle ear, inner ear, and round window defense system. In animals with induced otitis media, at the initial inflammatory stage the nonspecific immunologic cells are represented by polymorphonuclear leukocytes that respond quickly, escaping between capillary and postcapillary venule walls to move into the connective tissue layer. From there, some migrate between the epithelial cells into the middle ear cavity, and some toward the scala tympani. In the perilymphatic space, these cells, together with lymphocytes and plasma cells, have been observed not only near the inner layer but also lining the undersurface of the basilar membrane, the osseous spiral lamina, Schuknecht's channels, habenula perforata, and surrounding the nerve endings. They are also present at the opening of the cochlear aqueduct. The number of cells observed is quite discrete and most probably represents migration due to the penetration of toxins into the scala tympani as a chemotactic effect. In otitis induced in cats, plasma cells become readily apparent in the membrane at 2 weeks and are more numerous, larger, and more "mature-looking" at 1 month. Only occasional plasma cells are identified at 3 months. Immunoglobulins in the round window membrane had not been evaluated until recently, when IgG-bearing plasma cells were identified. These same authors have shown that middle ear antibodies can cross the round window membrane and reach the perilymph. These sequential defense mechanisms do not suggest partial or isolated reactions, but rather a graduated and coordinated process involving all cells in each layer and occurring among all layers. Moreover, this process seems to be part of an overall reaction of the middle ear and inner ear.

Table 5. Substances Placed in Perilymph That Have Been Observed Within the Round Window Membrane Layers

Substance	Species
Cationic ferritin	Chinchilla Cat
1-micron Latex spheres	Chinchilla Cat.

Since the round window is a biological membrane, selectivity has to be involved. This is not a mere mechanical passage through an inert three-layered wall; both substance confronted with the epithelium (outer or inner) needs a "compatibility" password that will determine this interaction and its fate in terms of passage. Some of the factors determining this password are size, configuration, concentration, liposolubility, and electrical charge. Size and molecular weight are obvious factors; however, it must be remembered that structure, electrical charge, and possibly other unknown factors can be as important as size alone. While cationic ferritin traverses the membrane, anionic ferritin (which is identical except for its electrical charge) does not. The amount of passage of a tracer is directly related to the depth of the membrane. Therefore, an inflamed, thickened membrane should by itself be less permeable - regardless of all other defensive events occurring in a inflammatory reaction.

Table 6. Facilitating Agents for Round Window Membrane Permeability

Histamine	Endotoxins
Leukotrienes	Pontocaine
Prostaglandins	Propylene glycol.
Exotoxins	

In addition to the substance itself and the conditions of the membrane, there are other roles played by "facilitating agents" (Table 6). In one report, Thorotrast placed in the middle ear failed to diffuse through the membrane, but did so after application of 1 per cent Pontocaine. Histamine has been observed to cause a marked increase in permeability. Saijo and Kimura have considered that the histamine-like effect of HRP favors its penetration into the round window membrane. Additional facilitating agents have been considered, such as prostaglandins and leukotrienes. Propylene glycol has been shown to cause inflammatory reactions in the tympanic membrane. This raises questions as to the effect of propylene glycol (a common component of otic drops) on permeability of the round window membrane. *Escherichia coli* endotoxin and staphylococcal exotoxin significantly increase the permeability of the round window membrane to tetraethylammonium chloride. Some toxins by themselves can penetrate by altering the membrane without using a "compatibility password".

Following surface contact, and assuming that the substance is "able to penetrate", it is confronted with possible pathways or "doors" to be traversed. The two basic pathways are through cells (transcellular-intracellular-"closed system") or between cells (intercellular-"open system"). These mechanisms have all been established and/or postulated in different areas of the body and are not necessarily present in the round window membrane. The evidence

available using tracers suggests a closed system. Tracers observed between epithelial cells are believed to reach this position from the cells and not through the junctions. Subtending the epithelium are the basement membrane and connective tissue layers - bridges to be crossed with a password and a key. Within the connective tissue, the same applies for blood and lymph vessels, and also for the cell membranes of the inner epithelial cells facing the connective tissue layer.

Once a substance has reached the connective tissue layer, it can be phagocytized by cells, traverse toward perilymph, and/or penetrate blood or lymph vessels present in this layer (Table 7 to 8). There is experimental evidence for all these alternatives. The fate of a substance phagocytized by connective tissue cells would in most cases end there as lysosome. Passage into lymph vessels would mean transport toward regional lymph nodes, where macrophages would take it up. Despite the fact that the route of drainage of the lymphatics of the round window is not known exactly, a lymphatic connection between middle and inner ear has been postulated. However, it seems that drainage should be in a peripheral rather than in a central direction; the inner ear being of neuroectodermal origin, lymphatic conduits should not be prominent. Passage of tracers into blood vessels is an interesting area to consider as a conduit because of the abundant vascular connections in the round window membrane. Nakashima and Ito, in studies of guinea pigs based on direct visualization and documentation with motion pictures, have divided the blood vessels of the round window membrane into two groups: one connected directly to the vein of the round window in the scala tympani, and the other connected directly to the blood vessels of the middle ear. Moreover, the direction of the blood in the vein of the round window seemed to be toward the vestibulocochlear vein. Anatomic studies in guinea pigs and humans by Axelsson verify that at the basal end of the cochlea the collecting venules of the scala tympani empty into the vein of the round window, and that the round window membrane is supplied by such vein.

Table 7. Potential Routes of a Substance Once It Reaches the Connective Tissue*

Lymph capillaries
Blood capillaries
Connective tissue cells
Inner epithelium-perilymph

* Substance coming from the middle ear side.

If a substance reaches the perilymph, theoretically it could go out through the cochlear aqueduct toward cerebrospinal fluid, up in the scala tympani (to the perilymphatic space) from where it can become incorporated into cells lining such space, pass into vessels, be affected by defensive factors in perilymph, or find its way into endolymph (and be exposed to structures bathed by it and/or then flow toward the endolymphatic sac).

Saijo and Kimura have systematically addressed some of these questions of perilymphatic passage, utilizing HRP. When this tracer was injected into the middle ear cavity, scala tympani, and vestibule of guinea pigs, these authors observed the following: HRP entered the scala tympani through the normal round window membrane after repeated injections in the middle ear. The tracer appeared to pass through the epithelial cells of the membrane and not through the tight junctions. HRP deposits were localized in structures such

as the organ of Corti, spiral ligament, and Reissner's membrane (Table 9), but not in the stria vascularis. HRP deposits were found in the vestibular labyrinth (saccule, utricle, and ampullae), in phagocytes, and in the lumen of the endolymphatic sac, as well as in the epithelial cells and subepithelial connective tissue spaces after injections into the middle ear cavity or scala tympani. After injection in the vestibule, the organ of Corti did not pick up HRP. Closure of the round window by dental cement still allowed some HRP to pass into the scala tympani, but the density of the deposits was very low, whereas it remained high in the vestibular sensory epithelia. Blockage of the cochlear aqueduct did not prevent HRP from entering the endolymphatic sac from the middle ear cavity; however, when both the cochlear and vestibular aqueducts were blocked, no HRP deposits could be found in the sac.

Table 8. Potential Routes of a Substance Once it Reaches the Connective Tissue*

Lymph capillaries
Blood capillaries
Connective tissue cells
Outer epithelium-middle ear?+

* Substance coming from the inner ear side.
+ Not reported to date.

Based on the observation of passage of substances through the membrane and into perilymph, the existence of an "inner ear defense system" has been postulated. The ultimate fate of substances within the inner ear is unclear.

Table 9. Location of HRP Deposits in the Inner Ear*

Adjacent to round window
Perilymph, greatest in basal turn
Adjacent to cochlear aqueduct
Cochlea:
Basilar membrane, basilar crest, vestibular crest
Spiral limbus, spiral prominence, Reissner's membrane
Internal sulcus cells, external sulcus cells
Tunnel of Corti
None in stria vascularis or tectorial membrane
Vestibular labyrinth:
Saccule
Utricle
Ampullae
Endolymphatic sac.

* After placement in middle ear side for 24 hours. HRP = horseradish peroxidase.

Migration of polymorphonuclear leukocytes, lymphocytes, and plasma cells from the round window membrane to perilymph is well established. However, evidence of inner ear defensive reactions is scarce. Cationic ferritin in the scala tympani of chinchillas and rhesus monkeys is incorporated into the cytoplasm of the mesothelial cells on the scala tympani side of the basilar membrane. In chinchillas exposed repeatedly to staphylococcal exotoxin, consistent mesothelial cell activity with the appearance of long cellular projections has been noted. It has yet to be determined where the antigen processing occurs in the inner ear (if it does), what defensive steps occur in the inner ear, and what, if any, is the role of the endolymphatic sac in this defensive process. Different studies - beyond the scope of this review - have provided information (anatomic, cell responses and interactions, immunoglobulin identification and interactions, immunoglobulin identification and production, and so forth) suggesting that the inner ear has a defense system and that the sac may play an important role in these responses.

Summary

1. The ultrastructure of the round window membrane suggests the capability for substances to traverse from the middle to the inner side and vice versa.

2. Substances placed in the middle ear can be detected directly or indirectly in the inner ear side.

3. Tracers adn spheres placed in the middle ear traverse through the layers of the round window membrane.

4. Tracers and spheres placed in perilymph penetrate into the round window membrane.

5. The round window membrane has the capability of participating in the defense system of both the middle and inner ear.

6. Tracers placed in the middle ear and/or perilymph can be localized in the cochlea, vestibular labyrinth, and endolymphatic sac.

This experimental evidence supports the semipermeable nature of the round window membrane, its defensive capabilities, and the capability of some substances to traverse into both the perilymphatic and endolymphatic spaces.

Questions and Criticisms

Despite the wealth of reports, the experimental evidence presented does not prove that these round window membrane capacities have functional and/or clinical significance. Rather, it reflects only a capability that could very well be a common occurrence but could also be only occasional or supplementary functions, or that could even be potential functions made manifest by experimental challenges. The differences in experimental conditions and in animal species and the lack of established facts account for some of the variabilities observed. Experiments combining different methods of evaluation in a same animal group are needed.

Some substanmces may or may not penetrate, depending on the experimental conditions; furthermore, it is unclear how much of a role is played by local inflammatory factors (eg, pH, cell charge, and so forth). For the most part, substances placed in the middle ear have been at high concentrations, loading a system under unusual conditions. Morphologic tracer studies (in contrast to minute amounts of invisible substances) have the advantage of being visible and permanent. This limits the discussions to the methods, rationales, and the interpretation of findings.

The significance of the use of tracers, even if experimentally important, is physiologically relative. Substances that can traverse the membrane include water, ions, macromolecules (eg, toxins), and antibiotics - each of which uses different pathways and is affected by different factors. These factors have to be analyzed in perspective. Although it has been established that tracers pass through the round window membrane and into the perilymph, their rate and significance have not been defined. Studies with tracers obviously document specific pathways for such tracers with molecular weights in the thousands. However, this represents only part of the whole picture, and the significance of these observations can be relative for the study of substances such as water and ions, which represent most of the substances transported. In the case of the latter, it is quite possible that osmosis and hydrostatic pressure (perilymph or middle ear effusion) have a much more important effect than would be the case for a macromolecule, which would probably use a different pathway and be subjected to other interactions.

These observations do not prove that the round window membrane is the only route for passage of substances or that it is the most significant. The study by Saijo and Kimura suggests that there may be another route from the middle to the inner ear besides the round window membrane.

These studies have provided some basis for the assumption that otitis media can cause sensorineural hearing loss, and perhaps endolymphatic hydrops. They have also provided some basis for important concerns such as the potential ototoxicity of otic drops and bactericidal agents used topically in the ear. However, despite the observations accumulated, there is no evidence that otic drops are ototoxic when used to treat chronic otitis media, that otitis media is associated with sensorineural hearing loss or endolymphatic hydrops, or that what has been demonstrated in animals occurs in humans.

General Perspective and Future Research Aspects

It is important to point out that we are not suggesting that passage of substances from the middle to the inner ear is a normal function of the round window membrane. We consider this to be an anatomic accident with which the membrane has to deal because of its anatomic characteristics and location and because of the high prevalence of middle ear disease. While the middle ear epithelium of the round window membrane has the capacity for absorbing substances present in the middle ear cavity, its structure does not suggest that this is a normal function. In contrast, the inner ear epithelium of the round window membrane has an ultrastructure that definitively suggests that absorptive capabilities are a function of this layer. Suffice it to point out the long lateral extensions (increasing surface exposure) usually observed to contain abundant pinocytotic vesicles and loose cell junctions.

It is also important to reiterate that documentation of passage of a substance through the round window membrane has no significance by itself unless it is viewed in perspective - that is to say, unless an effort is made to understand the purpose, meaning, and significance of this passage. A number of other factors and aspects must be evaluated. It should be determined if specific substances that can potentially pass from the middle to the inner ear are harmful, beneficial, or indifferent. These substances' "passwords and keys" have to be defined, as well as their interaction with the defense system. What are the trigger factors? What are the factors that determine whether the aggressor of the defense system prevails? Once a substance passes, what does it affect? Why, how, and under what circumstances? Which are the target organs? Other pertinent questions are: How does it translate and what can be done to prevent or treat (in harmful cases), or to promote and control passage (in beneficial cases)?

These studies are important from the standpoint of passage of drugs - both therapeutic (intended to pass into the inner ear at known rates and concentrations) or ototoxic. The latter is particularly pertinent today because of the common use of otic drops for otitis media with perforation (either spontaneous or via pressure-equalizing (PE) tube), and also because of the use of germicidal agents prior to otologicl surgical procedures. Definitions of sizes of spheres with or without electrical charges that are impermeable to the round window and middle ear mucosa could allow the safe use of these drugs (provided that their activity would persist when attached and that they would stay attached). Attaching potentially ototoxic drugs to substances that do not traverse the round window membrane or middle ear mucosa, and attaching useful drugs to substances that do traverse the round window membrane is a long-term goal. One of these potential uses can be exemplified in the development of selective vestibulotoxic drugs for vertiginous syndromes, to date with no satisfactory surgical solutions. It may very well be that some of these syndromes involve neural pathways beyond the endolymphatic space, and that these could be reached by drug delivery. This subject is beyond the scope of this chapter. It involves evaluating pathogenesis, factors such as effectiveness of drugs with no tissue penetration and the stability of drugs linked to spheres. The question of whether the round window route is the most adequate (reaching primarily the scala tympani) or whether it is a fenestration of the lateral semicircular canal (reaching the vestibule) should also be addressed.

It should be emphasized that this concept of passage of substances from the middle to the inner ear does not imply that substances placed in the middle ear do not get absorbed and follow other routes. There is ample evidence that the middle ear mucoperiosteum absorbs substances placed in the middle ear cavity. Lim conducted several experiments in guinea pigs and observed that HRP particles placed in the middle ear are readily taken up by the middle ear mucosa and eustachian tube. The mechanism of transport is similar to that of the round window membrane: that is, pinocytosis by the epithelial cells facing the middle ear cavity. From there, these particles are either stored in vesicles or transported into the intercellular space or across the cell toward the basement membrane. It is noteworthy that absorption and transcellular transport is accomplished by all epithelial cell types, including secretory and nonsecretory cells. HRP did not pass through junctional complexes. Past the basement membrane and once in the connective tissue layer, the tracer is taken up by macrophages and/or enters the lymphatics or blood capillaries (by pinocytosis and through the tight junctions). In addition, the absorptive function seems to depend largely on the size of the

particles, since only a few particles of India ink (average 40 nanometers) were absorbed, compared with HRP (diameter 5 to 6 nanometers), which were readily absorbed.

This section has been written with the intent of keeping the information available in the strictes perspective. We believe that these concepts have immense potential, not only for the understanding to the subtle complications of otitis media and of the semipermeable nature of the round window membrane, but also for the understanding of inner ear function, inner ear syndromes, and the fascinating area of drug delivery (based on permeability) for prophylactic and therapeutic purposes. Keeping these studies in perspective will permit solid progress and will, it is hoped, allow us to use the round window not so much as a window but as a door that may open to lead us to fundamental knowledge.