Henry Ford Hospital Medical Journal

Volume 31 | Number 1 Article 8

3-1983

Current Concepts in Otitis Media

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Henry Ford Hosp Med J
Vol 31, No 1, 1983

Current Concepts in Otitis Media†

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Otitis media continues to be a common and disabling problem which has become, in recent years, a fertile area for research. Based on studies in animals and humans, otitis media is classified into four groups: acute purulent otitis media (POM), serous otitis media (SOM), and mucoid or secretory otitis media (MOM). Together, these are referred to as otitis media with effusion (OME). The types can overlap and evolve into another type to become chronic otitis media and mastoiditis, characterized by the presence of granulation tissue or cholesteatoma. The biochemistry, microbiology, and pathology as well as clinical features of the disease are discussed.

Otitis media, inflammation or infection of the middle ear, and its clinical subgroups are common problems throughout the world. In the United States it is estimated that 95% of all children have had one or more middle ear infections before age five, and approximately 10% of all school chidren have otitis media with effusion (OME). In recent years, otitis media research has made important advances.

We have studied pathological, chemical, and bacteriological aspects of the pathogenesis of otitis media in human subjects and various animal models. Longitudinal studies of various forms of the disease, acute purulent otitis media (POM), serous otitis media (SOM), mucoid or secretory otitis media (MOM), and chronic suppurative otitis media (COM) were especially evaluated for evidence of interrelated changes of various groups. Purulent otitis media was produced in chinchillas by direct inoculation of less than one hundred pneumococci into the middle ear space. Serous otitis media was produced in chinchillas and cats following the development of SOM in cats after two to four weeks of tubal occlusion. Material for evaluation of middle ear effusion (MEE) and serum was obtained from children with SOM and MOM after myringotomy for ventilation tube placement. Three components were studied: MEE, epithelium, and the subepithelial space (SES). Significant inflammatory changes in the SES, which characterized all forms of otitis media, were especially prominent in POM and SOM. Epithelial metaplasia of secretory cells was most prominent in MOM.

Pathology

The pathology of POM is characterized by the presence of pus in the middle ear (bacteria and polymorphonuclear leukocytes) along with acute inflammatory reaction throughout the organ, including the mucoperiosteum. Much inflammatory activity occurs in the subepithelial space. SOM as seen in some children and adults with OME following barotrauma (aerotitis), or with nasopharyneal tumors, is characterized by the presence of clear amber fluid. Here, the primary pathology occurs in the subepithelial space: transudation of fluid, demonstrated by direct visualization of vessels, rupture of the basilar membrane, and passage of fluid between cells, which was first demonstrated in our laboratory (Figs. 1,2,3). MOM is characterized by the change of cuboidal epithelium into secretory epithelium, which is characterized by the presence of many goblet cells and secretory glands. The SES also participates in the changes of MOM. These types of otitis media overlap, and one can evolve into another. Either as a group or individually, they can lead to permanent sequelae, which include ossicular fixation or erosion,

†This study is supported by an NIH Grant IP50-NS14528. This paper was presented at the Second Plenary Session of the Henry Ford Hospital 1982 Alumni Reunion on October 22, 1982.

Submitted for publication: October 25, 1982
Accepted for publication: January 24, 1983

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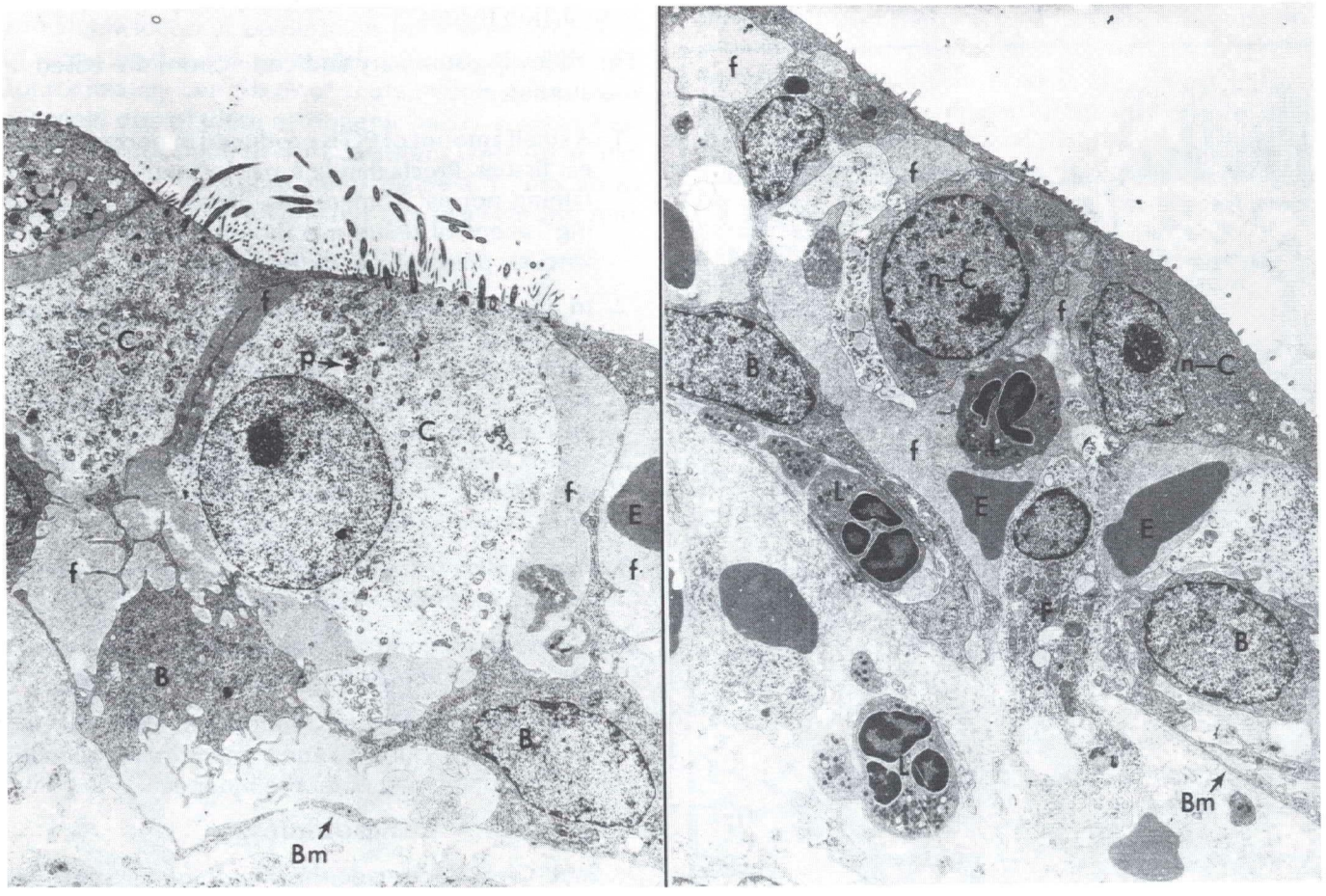
atelectasis, or tympanosclerosis resulting in conductive deafness. Inflammation of the round window can produce temporary or permanent sensorineural hearing loss (Figs. 4,5). Another important sequela of OME in childhood is chronic otitis media and mastoiditis, characterized by cholesteatoma and/or persistent granulation tissue. Granulation tissue forms in the subepithelial space, while cholesteatoma results from migration of keratinizing squamous epithelium from the adjacent canal wall into the middle ear space. Metaplasia of mucoperiosteum of the middle ear cleft into squamous cells with keratin may also contribute to formation of cholesteatoma.

Biochemistry

Dr. Steven Juhn, director of biochemistry research in our laboratories, employing animal models for serous, purulent, and mucoid otitis media, studied the sequential biochemical changes occurring with middle ear effusions (MEE). Levels of the enzyme lactate dehydrogenase (LDH) and of lysozyme were higher in effusions from POM than from SOM, indicating that the presence of microorganisms enhances the release of cellular enzymes. The hexosamine content of middle ear effusions was higher in MOM than in SOM.

In recent studies using combinations of models (SOM + POM), the levels of lysozyme in MEE were higher in animals whose middle ear infection was introduced after Eustachian tube obstruction than in those with primary purulent otitis media. The data strongly suggest that obstruction of ventilation through the Eustachian tube can enhance subsequent inflammatory changes of the middle ear cavity. Lysozyme, an enzyme found predominantly in neutrophils, is released in the process of phagocytosis.



A Fig. 1 B

Middle ear mucosa in serous otitis media in the monkey. A. Ciliated cells (c) 4,600X; B. Nonciliated cells (n-c) 4,800X. Expanded intercellular spaces are filled with fluid (f). A few leukocytes (L), erythrocytes (E), and free cells as fibroblasts (F) are shown. The basement membrane (BM) is disrupted in areas. The cytoplasm appears dark in basal cells (B) and nonciliated cells due to an increased number of ribosomes and density of ground substance. Pigment bodies (P) are also increased in number and size in the cytoplasm.

In correlated human studies, levels of LDH, lysozyme, and hexosamine were higher in mucoid effusions than in serous effusions, corresponding to the finding in the animal models. In patients with recurrent disease (requiring repeated surgery within 18 months), lysozyme levels were higher than those found with first attacks. Thus, high levels of lysozyme in MEE indicate either severe inflammation or chronic disease. Reasoning from animal experiments of combination models cited above, we consider that the recurrent group with high lysozyme levels might have the combination of Eustachian tube obstruction and bacterial infection.

The immunological characteristics of MEE in MOM are different than in SOM. The immunoglobulin content of MOM often is higher for IgA, IgG, and IgM than is similar fluid from SOM (Fig. 6). Thus, bacteriologic and biochemical study of inner ear cleft fluids assists in diagnosis and consequent treatment.

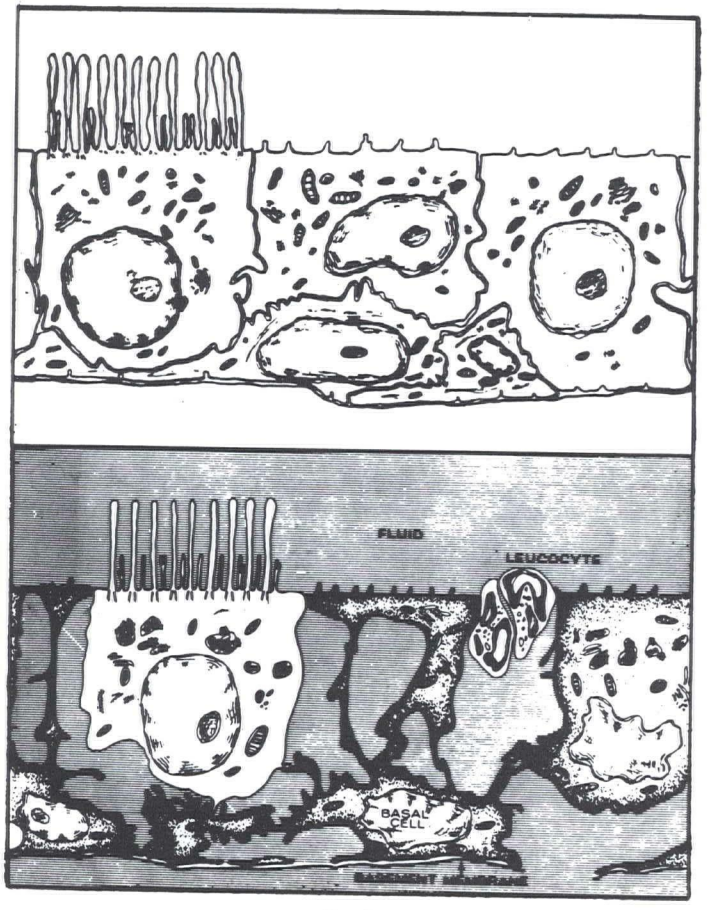


Fig. 2

Diagrammatic comparison between normal mucosa showing ciliated, nonciliated, and basal cells and mucosa-producing effusion. Note disruption of basement membrane, serous fluid flooding intercellular spaces, and the dark cytoplasm of basal cells and nonciliated cells.

Prostaglandins

The Nobel Prize in Medicine this year was awarded to two Swedish scientists and one English scientist for the discovery of prostaglandins. Dr. Timothy Jung, of our laboratories, has studied the significance of prostaglandins in the pathogenesis of otitis media for several years.

Prostaglandins (PG) are naturally occurring unsaturated fatty acids with a wide range of potent biological activity. In studies at our institution, PGs were measured in various types of otitis media fluid, choleosteatoma, and granulation tissues. Metabolites of the PG precursor, arachidonic acid, have been found in middle ear tissue, cholesteatoma, and granulation tissue. The effects of PG injection into the middle ear on the biochemistry of middle ear fluid and the histopathology of temporal bones have been evaluated. PG-forming cyclooxygenase is localized in middle ear mucosa and granulation tissues.

The following summary and conclusions are based on our studies:

1. A small amount of PG is produced in normal middle ear tissues. Prostaglandins may be involved in maintaining normal homeostatis, acting as a "fine tuning" agent of tissue metabolism, blood flow, and vascular permeability of the middle ear.
2. In disease states such as purulent otitis media and chronic otitis media, large quantities and abnormal combinations of PG may be produced, inducing acute inflammation, vasodilation, increased vascular permeability, and bone resorption. Some of the non-PG arachidonic acid metabolites act as a chemotactic factor for polymorphonuclear (PMN) leukocytes, intensifying acute inflammation.
3. Granulation tissue as well as cholesteatoma tissue can produce bone-resorbing PG.
4. PG and arachidonic acid introduced into the middle ear induce mucoid otitis media in chinchillas.
5. PG produced in the middle ear increases the permeability of round window membrane, allowing toxic substances to enter the inner ear.

Microbiology

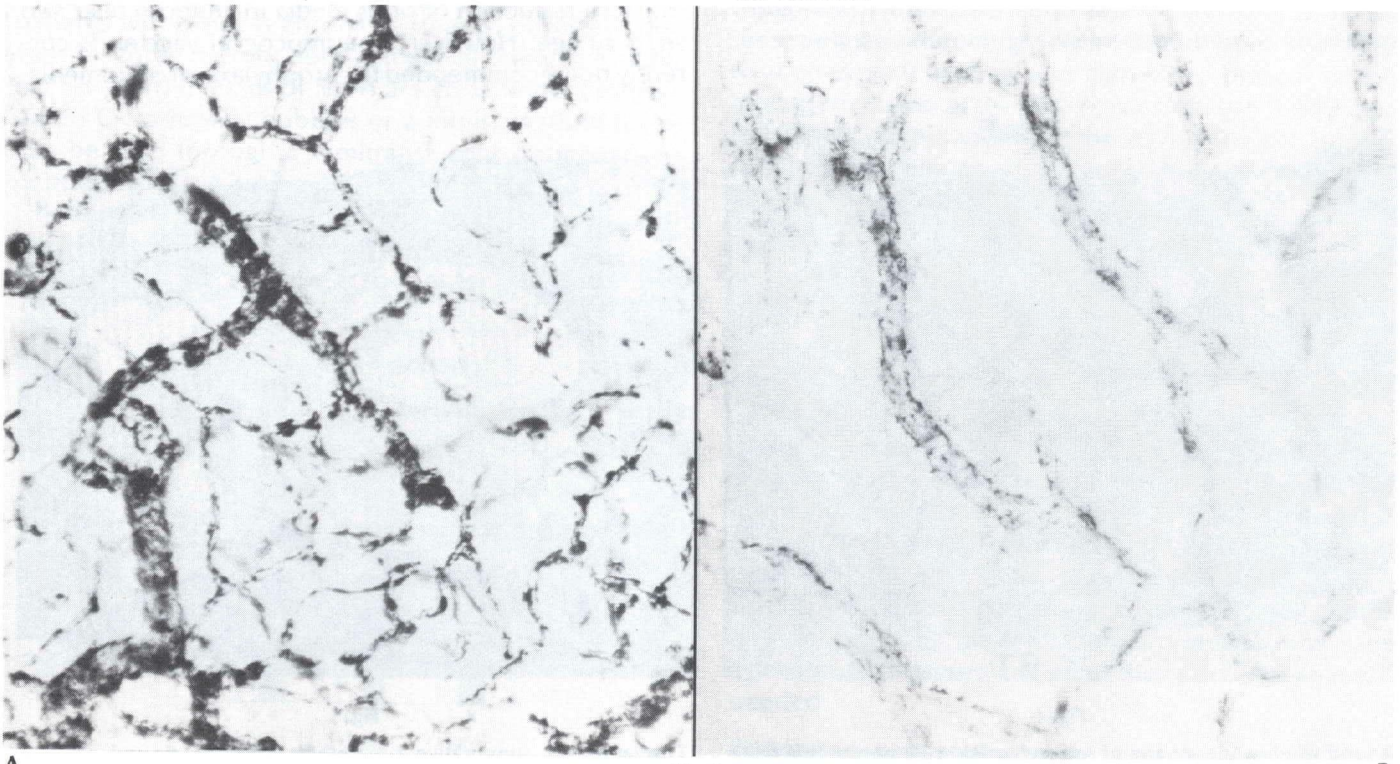
Dr. Scott Giebink directed the microbiologic studies of otitis media. His studies of middle ear effusion obtained from children with acute and chronic otitis media reveal that a variety of upper respiratory tract bacteria, viruses, and other non-bacterial agents contribute to the pathogenesis of otitis media. One of the earliest events is

thought to be the development of Eustachian tube dysfunction creating negative middle ear pressure during an upper respiratory viral infection. Human studies demonstrate that viral infection does lead to negative middle ear pressure. Infection of chinchillas with influenza A viruses also causes Eustachian tube dysfunction and negative middle ear pressure. If pathogenic bacteria are not present in the nasopharynx of the chinchilla during influenza A infection, the animal rarely develops acute otitis media. Similarly, in human subjects, viruses are infrequently recovered from acute middle ear effusions but are frequently present in the nasopharynx of the child with acute otitis media.

Bacteria recovered most frequently from effusions of children with acute otitis media include Streptococcus pneumoniae (40-50% of cases), non-typable Hemophilus influenzae (20-30%), and Streptococcus pyogenes (5-10%). Branhamella catarrhalis, Staphylococcus aureus, and Staphylococcus epidermidis have been implicated in occasional cases of acute otitis media. Whereas approximately two thirds of acute middle ear cultures will yield one of these pathogenic bacteria, middle ear effusion from children with persistent OME (of at least three months' duration) yields bacteria in only about half of the cases. Approximately 25% of all chronic middle ear effusions will yield Hemophilus influenzae, with a less percentage yielding Streptococcus pneumoniae, Branhamella catarrhalis, Staphylococcus aureus, and Staphylococcus epidermidis.

Anaerobic bacteria sought in acute and chronic middle ear effusions have been isolated infrequently. Mycoplasma pneumoniae has rarely been cultured from middle ear effusions, although approximately 15% of children with acute otitis media have serologic evidence of acute mycoplasmal infection. Similarly, Chlamydia trachomatitis has been cultured occasionally from middle ear effusions with accompanying serologic evidence of acute chlamydial infection.

Cytologic and biochemical studies of middle ear effusion obtained from children with acute and chronic OME support the concept of disease caused by pathogenic bacteria. In both acute and chronic middle effusions, abundant PMNs are present when Streptococcus pneumoniae and Hemophilus influenzae are recorded by bacterial culture. In chronic middle ear effusions, however, positive cultures of Branhamella catarrhalis and Staphylococcus epidermidis are not associated with abundant PMNs, suggesting that these bacteria may be merely "innocent bystanders" in chronic middle ear disease.



A

Fig. 3

B

Capillary permeability: A. Squirrel monkey (230X); B. Guinea pig (450X). Surface preparations of middle ear mucosa in the presence of serous otitis media after obstruction of Eustachian tube. Blackening of blood vessels with carbon deposits indicates increased vascular permeability.

Investigators have sought to determine whether bacteria cause the one third of acute middle ear effusions and one half of chronic middle ear effusions that are sterile. The capsular antigen of Streptococcus pneumoniae has been found in approximately 40% of such effusions, suggesting that cellular components of bacteria may persist in the middle ear cleft long after viable organisms have been eradicated. Conceivably, these persisting antigens may continue to stimulate host defense mechanisms and release potentially damaging oxidative and hydrolytic enzymes into the middle ear space.

Host defense mechanisms play a major role in clearing microorganisms from the middle ear cleft. In children with chronic OME and positive MEE cultures of Hemophilus influenzae, a transient depression in PMN function occurs. In chinchillas with experimental pneumococcal otitis media, similar transiently depressed PMN function has been observed. Chinchillas with influenza A infection manifest transiently depressed PMN function during the time of peak susceptibility to middle ear infection with Streptococcus pneumoniae.

We hypothesize that the development of acute otitis media begins with an upper respiratory virus infection with associated defects in epithelial ciliary function and mucosal clearance. These local host defense abnormalities allow the adventitious upper respiratory pathogen, such as the pneumococcus or Hemophilus influenzae, to enter the normally sterile middle ear space. Eustachian tube dysfunction and abnormalities of PMN function allow the invading bacterial pathogen to establish a focus of infection with the consequent release of inflammatory mediators, middle ear effusion, and destructive oxidative and hydrolytic enzymes.

Clinical Concepts Based on Pathogenesis Studies

Purulent otitis media (POM)

Acute purulent otitis media (POM) occurs most frequently in young children. Treatment consists of heat and analgesics, but especially appropriate antibiotics. Because bacterial pathogens have changed in recent years, the choice of antibiotic has necessarily changed. Currently, our first choice of treatment for POM is ampicillin or amoxicillin. Our second choice is an erythromycin-sulfa combination. Hemophilus influenzae is commonly encountered in children under five; however, we have recently found Hemophilus influenzae in older children as well, and 15% of all these organisms are resistant to ampicillin. Cefaclor (cephalosporin) or septra (combination of trimethoprim plus sulfa) can be used for ampicillin-resistant Hemophilus organisms.

Studies with anti-pneumococcal vaccines have demonstrated a reduction of otitis media in children over two years of age. However, pneumococcal vaccine is currently not recommended for prophylaxis of otitis media.

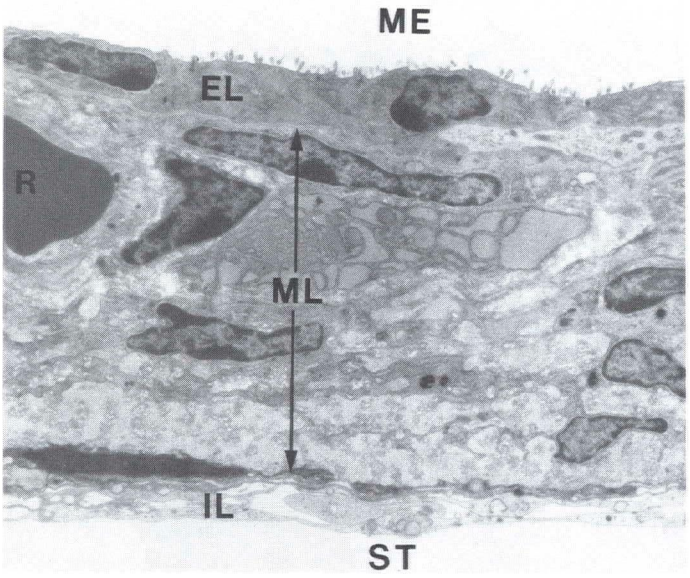


Fig. 4

Round window membrane of squirrel monkey demonstrating three layers: epithelial layer (EL) on middle ear side (ME), large middle layer, and inner layer lining scala tympani (ST); red blood cell (R).

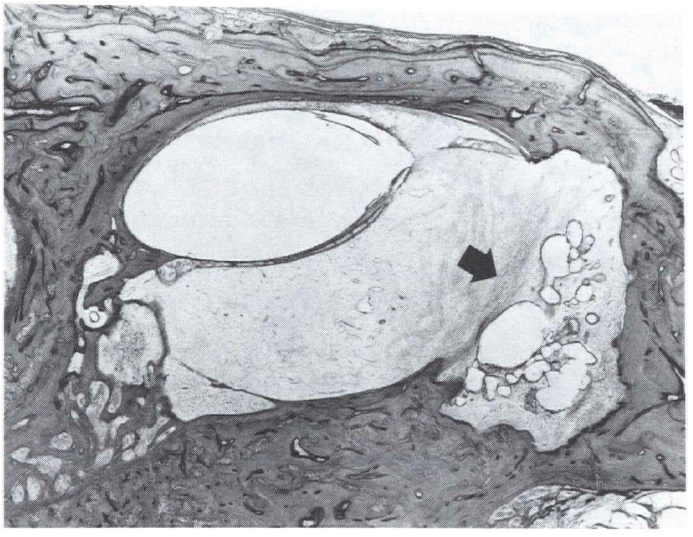


Fig. 5

Tympanogenic suppurative labyrinthitis (human). Round window membrane (arrow) is difficult to see and is surrounded by fibrous tissue in the round window niche (to the right) and in the scala tympani (to the left).

Tympanotomy Tubes

Repeated episodes of POM

Children up to five years of age have frequent and repeated episodes of acute purulent otitis media, especially for the first two years of life. Seen by the pediatrician or family physician, sometimes several times a month, such children may receive antibiotics almost constantly. Between episodes of middle ear abscess, the tympanic membrane usually appears normal although there may be persistent fluid. Among the many causes of these repeated episodes, Eustachian tube dysfunction is most important. Myringotomy and insertion of tympanotomy tube have great treatment value, and I use the following procedure: the child receives either ampicillin or erythromycin for at least ten days before the procedure. If hypertrophy or focal infection is present, a conservative midline adenoidectomy accompanies sterile placement of tympanotomy tubes. A tube must not be inserted if there is active middle ear infection. We have seen children who had multiple episodes of POM, up to twenty per year, who experienced very few episodes of POM after this treatment.

Seromucinous otitis media

The major indication for inserting a ventilation tube in patients with OME is chronicity, that is, persistent disease for three months despite medical therapy. Middle ear effusions in cases of SOM are clear, watery transudates. Occasionally bubbles or a miniscus (fluid level) can be seen through a semitranslucent drumhead. In contrast to MOM, such cases of middle ear effusion have a better chance of resolving either spontaneously or in response to conservative management; accordingly, tubes are not placed quite as soon as for MOM patients.

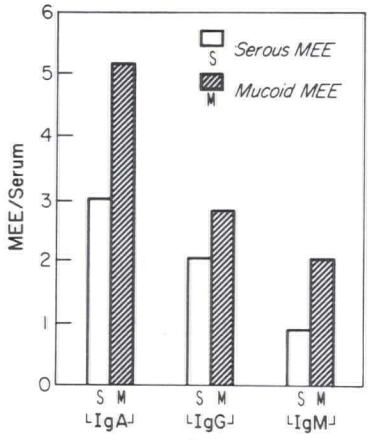


Fig. 6

Immunoglobulin levels (MEE/serum ratio) in serous and mucoid MEE in humans.

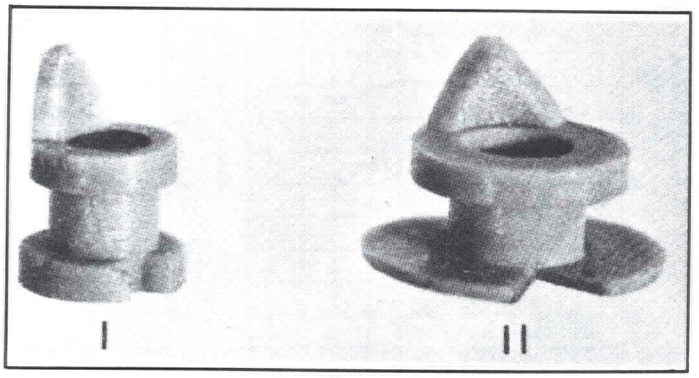


Fig. 7

Type I tube has an internal diameter of 1.2 mm and inner flange diameter of 2.4 mm. Type II tube, for obstinate cases, has an internal diameter of 1.5 mm and inner flange diameter of 4.2 mm.

On the other hand, in SOM the tubes are effective in arresting the pathological process. If either SOM or MOM persists for three months or more despite appropriate medical therapy, tube insertion is advised (Fig. 7). With a Juhn collector (Tymp Tap), the aspirated fluid is saved for laboratory studies. The fluid in MOM or secretory otitis media is a thick, cloudy exudate. Even in the absence of clinical evidence of infection, bacteria are commonly cultured. The fluid may be so thick, tenacious, and inspissated as to be termed a "glue" ear. Increased numbers of goblet cells and other secretory structures such as cysts and glands are present in the mucoperiosteum of the middle ear cleft. In MOM cases, I routinely advise antibiotic therapy. If the patient will require a tympanotomy tube, appropriate antibiotics are continued for at least one week before the procedure.

Persistent blue eardrum

Long-standing refractory SOM will occasionally result in the formation of cholesterin granuloma in the mastoid and middle ear. These unique pathological lesions form in an area devoid of oxygen in the presence of plasma or blood cells. The characteristic brown or "axle grease" granulations may be observed during routine mastoidectomy for chronic otitis media. Although these cases have been erroneously considered as "idiopathic hemotympanum," they actually represent changes resulting from long-standing SOM. Once this stage has been reached, treatment consists of exploratory tympanotomy followed by mastoidectomy, tympanotomy tube insertion, and reconstruction of the middle ear space, if needed.

Exploratory tympanotomy

Some patients in whom tympanotomy tubes have been inserted several times over a period of years experience

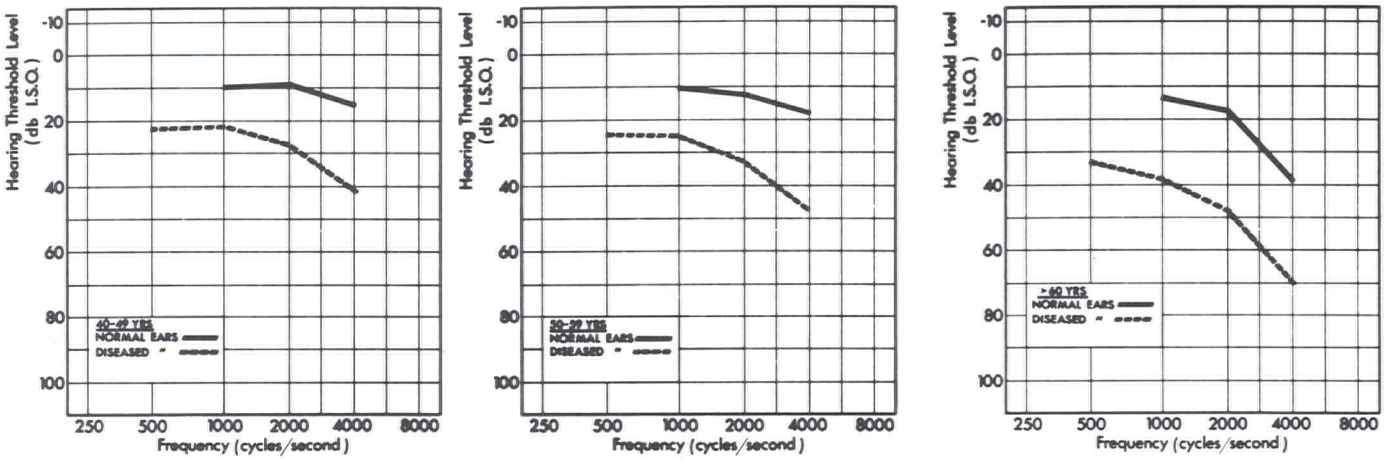


Fig. 8

The decade audiograms of COM compared to normal data. The difference between the two curves in each case represents sensorineural deafness due to chronic otitis media.

conductive hearing loss even though middle ear fluid is absent. The conductive loss (e.g., 50 dB SRT or more) may be greater than that which is expected to occur with fluid alone. In such instances, the middle ear effusions may have caused osteolysis and ossicular disruption, ossicular fixation (a result of fixation of the tensor tympani tendon and other ligaments), osteoneogenesis, or tympanosclerosis. In any case, when a conductive loss of such magnitude occurs, exploratory tympanotomy is indicated at the time a tympanotomy tube is inserted. The middle ear contents are assessed microscopically and corrected accordingly.

Atelectasis

Atelectasis, a common sequela of OME, may produce conductive hearing loss of 35 dB or more. An attic cholesteatoma is often suspected in these cases, and tympanoplasty has been successful. The procedure consists of reestablishing the mesotympanic space, strengthening the tympanic membrane by an underplant fascial graft, cutting the tensor tympani, extirpating abnormal tissue, reestablishing ossicular mobility and continuity, and inserting a number one ventilation tube in the anterior drumhead remnant, along with silicone rubber sheeting and a moist Gelforam implant. Methods and results were discussed in a recent study of 60 ears.

Chronic suppurative otitis media (COM)

COM is characterized by cholesteatoma, granulation tissue, or cholesterol granuloma. The disease may be active (with otorrhea) or inactive (without otorrhea) with similar pathological tissues. Occasionally, COM will result in a "burned out" process with a residual perforation and conductive hearing loss despite regression of pathological tissue (Fig. 8). The latter cases are ideal tympanoplasty candidates. Proper treatment of chronic otitis media and mastoiditis consists of closed or open cavity tympanomastoidectomy.

Eustachian tube dysfunction represents the chief difficulty in the surgical correction (tympanoplasty) of COM. Many of these patients have had Eustachian tube dysfunction earlier in their lives and by the time they receive a tympanoplasty, the Eustachian tube may appear to function appropriately. Unfortunately, the tube dysfunction usually persists in some form. For this reason, I use a tympanotomy tube in the anterior drumhead remnant whenever possible while performing tympanoplasty for otitis media. The tube must not be inserted through the graft. Silastic sheeting used routinely in the middle ear and the fascial graft, which extends to and, in some instances, around the tube, must not obstruct its internal lumen. The tube appears to assist the postoperative healing and improves hearing.

Acknowledgment

The contributions of my co-workers, Dr. Scott Giebink (microbiology), Dr. Steven Juhn (biochemistry), and Dr. Timothy Jung (prostaglandins), are gratefully acknowledged.

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