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The Chorda Tympani Nerve

*Role in Taste Impairment in Middle Ear Disease and
after Ear Surgery*

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Abstract

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The chorda tympani nerve, also known as the taste nerve, runs uncovered through the middle ear cavity, a localization that exposes the nerve to pathological processes and surgical trauma in the middle ear. People operated on for otosclerosis tend to complain more about postoperative taste disturbances than those operated on for chronic otitis media. It has been suggested that this difference may be explained by gradual deterioration of chorda tympani nerve function caused by chronic otitis media infection and that further impairment caused by surgery is less noticeable in these patients.

This thesis aimed to evaluate the function of the chorda tympani nerve, the effects of middle ear disease on taste and complications resulting from ear surgery for chronic otitis media or otosclerosis. This information will help to improve the ear surgeon's ability to predict the prognosis of iatrogenic taste disturbances in patients with middle ear disease and after ear surgery.

Taste was assessed using electrogustometry and the filter paper disc method before and after surgery for chronic otitis media or otosclerosis. Patients also completed questionnaires about symptoms and quality of life. The status of the chorda tympani nerve upon surgical opening of the ear and grading of the trauma to the nerve during the surgery were recorded. The ultrastructure of the chorda tympani nerve from healthy ears and from ears with chronic otitis media was examined. Electrogustometry and the filter paper disc method were evaluated.

The results of electrogustometry and the filter paper disc method were highly reproducible, although their correlation was moderate. Patients with chronic otitis media, patients with a more traumatized nerve, female patients and younger patients were more likely to report postoperative taste disturbances. Most of the patients recovered their taste after 1 year. The quality of life study showed only minor changes after surgery. Electron microscopic observations of nerves from ears with chronic otitis media showed signs of structural degeneration, although signs of regeneration, such as sprouting were also observed. This results may explain the recovery of taste postoperatively and indicate that the nerve should be carefully handled during surgery.

Keywords: Chorda tympani nerve, ear surgery, taste, chronic suppurative otitis media, otosclerosis, electrogustometry, filter paper disc method, quality of life, transmission electron microscopy, degeneration, sprouting

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Berling K, Knutsson J, Rosenblad A, von Unge M. Evaluation of electrogustometry and the filter paper disc method for taste assessment. *Acta Otolaryngol* 2011. May 131(5) 488-493.
- II Berling K, Mannström P, Ulfendahl M, Danckwardt-Lillieström N, von Unge M. The chorda tympani degenerates during chronic otitis media: an electron microscopy study. *Acta Otolaryngol* 2015. Jun 135(6):542-548.
- III Berling Holm K, Knutsson J, Strömbäck K, Danckwardt Lillieström N, Rosenblad A, von Unge M. Taste disturbance after stapes surgery – an evaluation of frequency, severity, duration and quality of life. *Acta Otolaryngol* 2017 Jan 19;137(1):39-43.
- IV Berling Holm K, Knutsson J, Rosenblad A, von Unge M. Surgery for chronic otitis media causes greater taste disturbance than surgery for otosclerosis. Submitted for publication.

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Abbreviations

ENT	Ear, nose and throat
CTN	Chorda tympani nerve
EGM	Electrogustometry
FPD	Filter paper disc method
CSOM	Chronic suppurative otitis media
QoL	Quality of life
HRQoL	Health-related quality of life
SF-36	Short form 36 health survey
TEM	Transmission electron microscopy
TM	Tympanic membrane
CN	Cranial nerve
VAS	Visual analog scale

Introduction

Background

The chorda tympani nerve (CTN) runs uncovered through the middle ear cavity, which makes it vulnerable to disease and surgical trauma. This thesis project derived from discussions at our ear, nose and throat (ENT) Department about how middle ear disease and surgery may affect taste.

The thesis begins with discussion of some general aspects of taste. Taste is an important sense that is required for life. People can live without sight, hearing, or smell but, for people without taste, the urge to eat is missing. According to Halliday (1), without medical intervention people without a sense of taste can starve and eventually die from malnutrition (2 -4). The importance of taste may explain why taste involves input from three cranial nerves (CN). Taste is the main sensory modality by which we evaluate whether a potential food is edible. Everything eaten normally passes through the oral cavity, where its flavor is registered as a gestalt comprising taste, odor, somatosensation, and pain. Taste sensations can be divided into different psychological attributes such as quality, intensity, oral location and timing. All of these sensations are rapidly evaluated during eating, and a decision is made about whether a food is edible. For example, a sweet taste indicates that a food contains calories and is therefore accepted, but a strongly bitter taste may indicate the presence of toxins and that food is rejected (4). These actions reflect brain stem reflexes, which are apparent in humans prenatally, and adult food preferences are built on these reflexes, which can be modified by experience but never eliminated.

The qualities of taste are divided into the modalities sweet, sour, salty, bitter, and umami (or savory). Earlier, it was believed that humans have sensors in different regions of the tongue and mouth that can recognize only those first four basic tastes. A fifth taste, umami, is now also recognized. Umami was first identified scientifically in 1908 by Professor Kikunae Ikeda, at Tokyo Imperial University. He found that glutamate was responsible for the palatability of the broth from a type of seaweed (kombu dashi). Umami is described as a pleasant savory or meaty taste.

Ikeda noticed that the taste of kombu dashi was distinct from sweet, sour, bitter, and salty and named it umami (5 -6). The taste of the fat has been suggested as a sixth taste, but evidence demonstrating that the sensation of fat taste differs qualitatively from other tastes is lacking (7). There is also a belief that the ability of taste sensation of the tongue can be mapped in four areas, the so-called “taste map” which involves sweet taste on the tip of the tongue, salty taste on the sides of the anterior part of the tongue, sour taste on the sides of the posterior part of the tongue and bitter taste on the most posterior part of the tongue (8). The theory behind the taste map originated in a translation from German, that misrepresented the 1901 publication *Zur Psychophysik des Geschmackssinnes* (8). In 1974, Collings investigated the topic again and confirmed that all the tastes exist on all parts of the tongue (9). It is now accepted that the different taste qualities are perceived on all tongue areas displaying taste buds (9 -11). Most taste buds on the tongue and other regions of the mouth can also detect umami taste, irrespective of their location (12). The taste sensation emerges when a substance in the mouth reacts chemically with receptors in taste buds. Taste sensations are complex; placement of food or beverages in the mouth stimulates olfaction, touch, temperature, and pain sensations in addition to taste (13 -17). Taste and olfaction are closely related, and loss of olfaction often describes as even loss of taste (13, 18). Gustatory and olfactory receptors are located in two positions: the former in the oral cavity and the latter in the olfactory mucosa high in the nasal cavity.

The CTN, a branch of the facial nerve, is the most important taste nerve. The CTN innervates the taste buds on the anterior two-thirds of the tongue and runs uncovered through the space of the middle ear. This location can expose the nerve to bacterial toxins, enzymes, and mechanical damage related to inflammatory middle ear pathologies such as chronic suppurative otitis media (CSOM), with or without cholesteatoma. Injury of the CTN is a common risk associated with middle ear surgery. The nerve is almost always touched and stretched to some degree by the instruments, desiccated under the light of the operating microscope, or even severed. It is not clear to what extent different manipulations during surgery impair CTN function and cause discomfort for the patient.

In the field of otosurgery, although opinions differ about how to handle the CTN, the topic is rarely addressed in the literature and many clinical questions remain unanswered. It is not clear to what extent patients with CSOM experience CTN malfunction before surgery or to what extent different manipulations of the CTN during surgery impair nerve function and whether this recovers over time. We examined also whether

the nerve status when the ear is opened during surgery predicts the outcome of taste function and whether there are age and sex differences with regard to postoperative taste disturbance. A further aim of this thesis was to investigate to what extent malfunction of the CTN affects quality of life (QoL).

Some otosurgeons believe that patients operated on for CSOM seldom complain about taste disturbances even though the CTN is often extensively manipulated during surgery (14, 19 -23). Earlier studies suggested that patients with CSOM exhibit preoperative changes in taste sensation related to the inflammatory process in the middle ear (24 -27). Compared with patients with CSOM, patients operated on for otosclerosis complain more often about postoperative taste disturbances, although the CTN is manipulated less during surgery for otosclerosis than during that for CSOM (14, 23, 28 -31).

The structural changes related to CTN impairment are poorly described in the literature. A few studies have shown various degrees of pathological CTN changes in CTN in patients with CSOM and describe signs of disarrangement in the nerve, thickening of the perineural and epineural connective tissues, cellular and myelin degeneration, increased amount of collagen and connective tissue, and edema (24 -27).

Clinical taste examination is performed in different contexts throughout the world. In Japan, in contrast to most Western countries, different procedures for taste assessment are in clinical use, and EGM and the FPD test have become the gold standards for taste assessment (16, 32 -43). However, there is a lack of systematic evaluation of the reproducibility of EGM and FPD test, and of the extent to which measurements may be biased by everyday activities performed by the patients before testing. To evaluate whether EGM measures taste only and no other sensations, such as trigeminal tactile response, correlational analysis was applied to the results of a test of EGM thresholds and compared with those for the thresholds obtained using the FPD test, which used specific flavors on a normal control group.

Taste anatomy

The specialized sense organ for taste comprises about 10 000 multicellular rosette clusters or taste buds. The lingual papillae were described in 1664 by Malpighii, and the taste buds were first discovered in 1867 by the German anatomist and anthropologist Schwalbe together with the Swedish doctor Lovén (44). There are four morphologically distinct

types of cells within each taste bud: basal cells, dark cells, light cells, and intermediate cells. The basal cells are small round cells at the base of the taste bud. The other three cell types are elongated cells that stretch from the basal to the apical ends of the taste bud; these appear as dark, light, or intermediate in colour and are referred to as cell type I, II, and III, respectively. The basal cells do not extend processes in the taste pore and are likely to be undifferentiated or immature taste cells. The other three cell types are sensory neurons that respond to taste stimuli or flavors (referred to as gustatory cells, transitional cells and hair cells in Figure 1).

The receptor cells within a taste bud are not neural cells but instead are specialized epithelial cells that exhibit almost all of the normal neural cell properties except the absence of an axon. Each taste bud contains receptor cells that are sensitive to a wide array of taste stimuli. The taste buds are located in several fields: in the oral cavity, on all edges of the tongue, on the upper surface of the tongue, on the soft palate, and in the pharyngeal and laryngeal regions of the throat. Most taste buds are located on raised protrusions of the tongue surface called papillae (Figure 1). Taste fields in the soft palate and the pharynx reside in the epithelium and not within a papilla. There are four types of papillae. Fungiform papillae are present mostly on the dorsal surface and the sides of the tongue. Filiform papillae are the most numerous of the tongue papillae. They do not contain taste buds and are not involved in gustation, but these papillae serve to make the tongue surface mechanically rough, which facilitates manipulation of food and fluids. Foliate papillae are located on the posterior part and lateral border of the tongue. Only 10–14 circumvallate papillae are found in the posterior part of the tongue in most people.

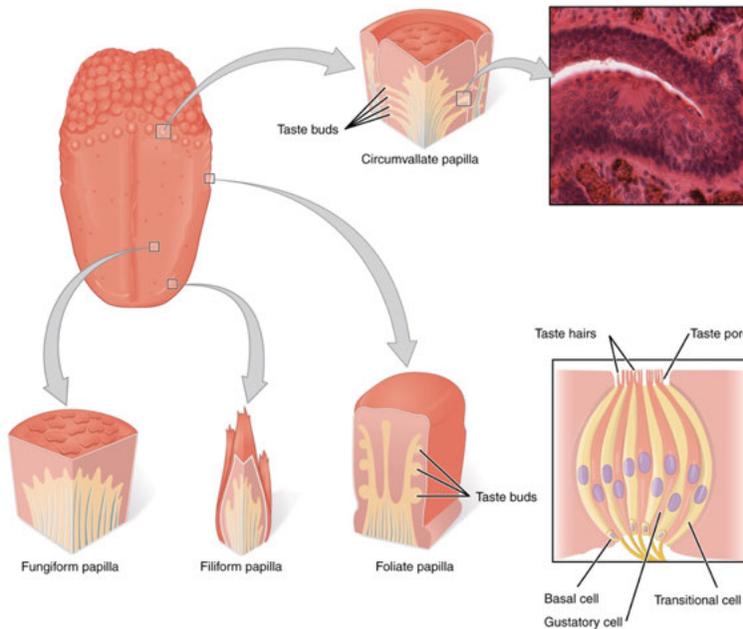


Figure 1. The anatomy of the tongue, papillae and taste buds. www.wikipedia.org, public access.

Taste sensations are carried to the brain stem and subsequently to the cerebral taste centre by three CN: the facial nerve (CN VII), the glossopharyngeal nerve (CN IX), and the vagal nerve (CN X). The CTN, which is a branch of the facial nerve, innervates the anterior two thirds of the tongue and is the major taste nerve. It runs uncovered through the middle ear cavity between the malleus and incus (two of the three sound-conducting ossicles) (Figure 2).

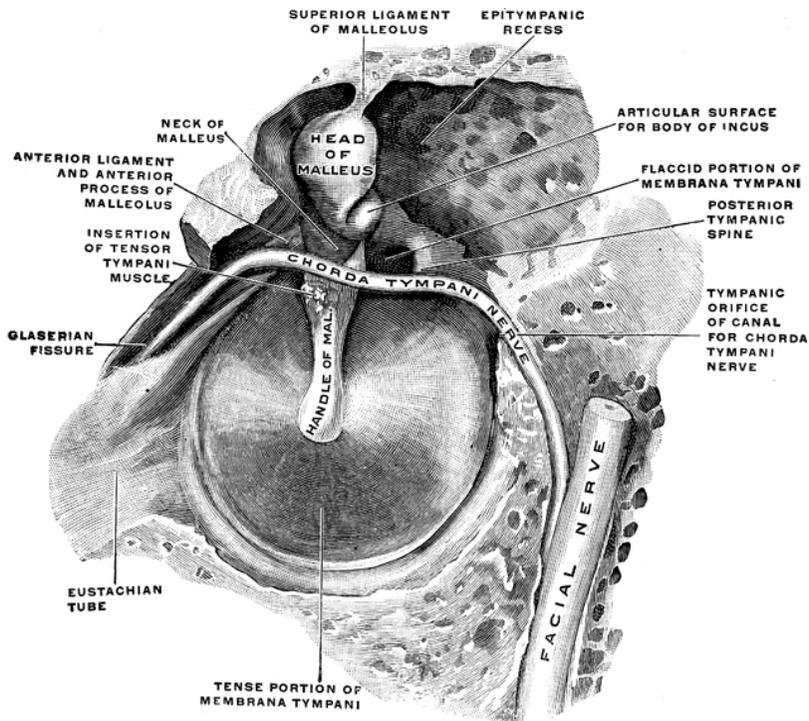


Figure 2. The chorda tympani in relation to the tympanic membrane and the ossicles. Viewed from inside the middle ear. www.wikipedia.org, public access.

The greater superficial petrosal nerve is a branch of the facial nerve and carries taste stimuli from the soft palate. Its cell bodies are located in the geniculate ganglion. The glossopharyngeal nerve innervates the posterior third of the tongue and carries taste sensations from taste buds located in that area; its cell bodies are located in the petrosal ganglion. The vagal nerve innervates the pharynx and larynx via the superior laryngeal nerve and its cell bodies are located in the nodose ganglion. Neurons from all three CNs project to rostral and lateral regions of the nucleus of the solitary tract in the medulla, which is also known as the gustatory nucleus of the solitary tract complex. Axons from the rostral (gustatory) part of the solitary nucleus project to the ventral posterior complex of the thalamus, where they terminate in the medial half of the ventral posterior medial nucleus. This nucleus projects to several regions of the neocortex including the gustatory cortex (the frontal operculum and the insula), which becomes activated as a person eats and experiences taste sensations.

Taste measurement

Different methods are used to assess taste. One method is to assess the taste intensity of solutions of different concentration and the quality in the entire mouth using a mouthwash or when applied to specific parts of the oral mucosa using filter paper discs or strips. Another method is EGM, which uses an electric current to stimulate the taste receptors. In Western countries taste is not routinely measured in medical clinics. The two methods used in this study, EGM and the FPD test, are considered to be the gold standards (16, 33 -45). For example, in Japan taste examination performed using EGM and the FPD test are routine procedures in otorhinolaryngology departments in almost all university hospitals and in many private clinics (32 -34, 40, 45).

Anatomy of the ear

The ear is traditionally divided into three parts: the outer ear, middle ear, and inner ear. The outer ear and middle ear are aerated compartments, and the inner ear is filled with fluid (Figure 3).

The outer ear comprises the auricle and the outer ear canal, which measures 2.5 -3 cm in length in humans. The tympanic membrane (TM) constitutes the border between the middle ear and the outer ear, and has two major functions as a protector of the middle ear and in sound transmission. The TM also allows the clinician to evaluate middle ear status.

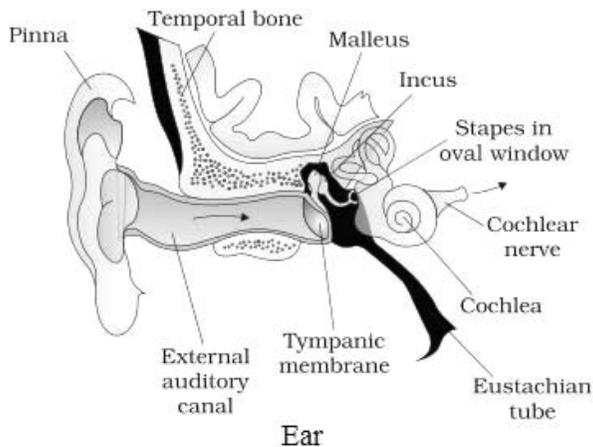


Figure 3. The anatomy of the outer, middle and inner ear. www.wikipedia.org, public access.

The middle ear is located in the temporal bone and is divided in two aerated compartments: mastoid cells and the tympanic cavity, which are connected by the antrum. The tympanic cavity is limited laterally by the TM and medially by the promontory of the cochlea, where the mobile round and oval windows constitute the borders with the fluid-filled inner ear. The tympanic cavity is connected to the rest of the upper airway through the eustachian tube, which plays an important role in pressure changes in the middle ear and thereby in middle ear pathology. The tympanic cavity contains three ossicles: the malleus, incus, and stapes. The long process of the malleus is attached to the superior part of the pars tensa of the TM. The incus forms a bridge between the malleus and the stapes, and the footplate of the stapes connects to the inner ear via the oval window. The middle ear also contains the CTN, which runs between the handle of the malleus and the long process of the incus (Figure 2). The CTN separates from the facial nerve just before entering the tympanic cavity and leaves the cavity through the petrotympanic fissure to join the lingual nerve.

The inner ear is located in the temporal bone and comprises the cochlea, vestibule and semicircular canals. The cochlea translates sound into nerve impulses. The vestibule, contains the saccule and utricle, and the semicircular canals are responsible for receiving sensory inputs related to linear and rotatory motion changes and thereby balance. The spiral-shaped cochlea is divided into three compartments: the scala vestibuli, scala media and scala tympani. The scala media is filled with endolymph and is separated from the scala vestibuli by the Reissner's membrane and from the scala tympani by the basilar membrane; the scala vestibule and scala tympani contain perilymph. The basilar membrane is attached to the organ of Corti where mechanical inputs are transformed into nerve signals that are conveyed to the central nervous system by the vestibulo-cochlear nerve.

Middle ear diseases

The middle ear is susceptible to microbial invasion because both bacteria and viruses can invade the tympanic cavity. The eustachian tube is the only route for such invasion if the TM is intact, but bacteria and viruses can enter the middle ear if the TM is perforated. Most middle ear diseases are associated with bacterial or viral infection, but others are caused by other mechanisms, such as a defect in mineralization of the ossicles or anomalies during development.

Otitis media

Otitis media is a collective name covering for the various middle ear conditions that can elicit an inflammatory tissue reaction. The main forms of otitis media are classified according to the clinical characteristics and symptoms. These comprise purulent otitis media, secretory otitis media, and chronic otitis media with or without cholesteatoma, and are discussed below.

Purulent otitis media

Bacterial infection of the middle ear may result in empyema. Often the disease is preceded by a viral infection, which makes the middle ear mucosa less resistant to the infecting bacteria. The most common pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* (46). Patients in the lower age of the pediatric spectrum are at highest risk. In most countries, purulent otitis media is treated with antibiotics to prevent the serious complications that appear in a limited number of cases. Transmyringal insertion of ventilation tubes is often used for patients with repeated episodes of purulent otitis media. A well-known complication of recurrent acute otitis media and insertion with ventilation tubes is a prevailing perforation of the TM which can lead to the development of chronic otitis media. Persistent perforation of the TM and chronic otitis media can be indications for surgery with myringoplasty.

Secretory otitis media

Transudate in the middle ear can be termed secretory otitis media but is commonly known as otitis media with effusion. The pathogenesis is thought to be multifactorial. Incompetence of the eustachian tube plays an important role in secretory otitis media and is common. In cases of mucosal swelling in the eustachian tube, most often as a result of upper respiratory infection, the ability to transport air into the middle ear is impaired and transudate may develop (47).

If the eustachian tube blockage persists, chronic changes in the tissue of the middle ear begin to develop. The mucous secretions become thicker and therefore less likely to drain via the eustachian tube, which increases the chance of development of acute otitis media. Secretory otitis media normally resolves over time but, in long-standing cases associated with impaired hearing, insertion of transmyringal ventilation tubes is often the treatment. The impaired hearing then often resolves within the immediate postoperative period (48). Prevailing perforation of the TM and

development of chronic otitis media are risks of treatment with ventilation tubes.

Chronic otitis media

Chronic otitis media is the term used to describe a variety of symptoms, signs, and physical findings that result from the long-term damage to the middle ear by infection and inflammation. It is characterized by a long-standing perforation of the TM with drainage. Intermittent or sometimes permanent drainage or secretion from the middle ear with a TM perforation is classified as CSOM. The disease can cause scarring or erosion of the sound-conducting bones (ossicles) of the middle ear, which results in hearing loss. The inflammatory process can cause erosion, which can cause the infection to spread to the meninges or brain, and other severe complications.

An altered pressure in the middle ear may deform the TM, which may become severely retracted, thinned out, or even perforated. Perforation of the TM can cause loss of the natural zone that protects the middle ear from the environment. Entry of water containing bacteria into the middle ear through the perforation may cause infection, inflammation, and subsequently drainage from the ear. CSOM might lead to damage of the hearing bones, which can cause hearing loss and severe discomfort for the patient.

At present, surgery is the only effective treatment for CSOM with perforation of the TM and persistent infection. Myringoplasty is commonly performed, in which a graft material, usually endogenous muscle fascia or cartilage, is placed to close the perforated TM.

Cholesteatoma

An acquired cholesteatoma is the formation of keratinizing squamous epithelium retracted from the TM into the middle ear cavity. This formation is called the cholesteatoma matrix. Different definitions of cholesteatoma are used in the otology literature; for example, retention of keratin debris encapsulated by the matrix is required in one definition, and an infection within the retraction is required in another. When the cholesteatoma is trapped by a deformed TM or migrates through a perforation, its growth can become uncontrolled and can cause significant damage to the structures of the middle ear and mastoid.

The acquired form of cholesteatoma is the most common type. It usually develops because of negative pressure in the middle ear, which may be

secondary to a chronic eustachian tube dysfunction or altered gas diffusion over the middle ear mucosa, which can induce prolonged negative pressure in the middle ear and cause a retraction of the TM (49, 50). Retraction is most common in the upper part of the TM (pars flaccida) or in the posterior superior part of the TM (pars tensa). Local inflammatory processes are believed to stimulate keratin production and exfoliation, and thereby cholesteatoma growth. Continuing growth of the cholesteatoma often proceeds in a tumor-like fashion and may cause destruction of the ossicles and the bone surrounding the mastoid bone, fistulation or invasion of the labyrinth, and cortical bone destruction with intracranial complications.

Preoperatively it can be difficult to differentiate between CSOM and cholesteatoma, and the diseases are referred to as CSOM, with or without cholesteatoma, as used in papers II and IV.

Another type of cholesteatoma with completely different pathogenesis, the primary congenital form, is not addressed in this thesis.

Surgery is the ultimate treatment for cholesteatoma and is usually necessary. The main goal of the surgery is to eradicate all keratinizing epithelium from the middle ear because this is likely to produce a residual cholesteatoma. Different techniques are used: the wall-down procedure, which allows for easier visual access to most parts of the tympanic cavity; and the wall-up procedure, which allows for easier reconstruction of the ear anatomy. Endoscopic techniques have been developed recently and may complement microscopy-based surgery for easier visualization of parts of the ear. A mastoidectomy is performed when necessary. If the ossicles are destroyed, a remnant ossicle or prosthetic can be used to restore the ossicular chain. If conductive hearing loss is not managed completely, a hearing aid can also be used.

Otosclerosis

Otosclerosis is a condition that affects the mineralization of the ossicles and leads to fixation of the ossicular chain, mainly the stapes. To deliver normal sound transmission to the inner ear, the ossicular chain must be able to move freely in response to sound waves. In otosclerosis, new bone is formed. The footplate of the stapes is usually where the condition starts; the stapes becomes fixated and fails to transmit sound energy to the inner ear. The hearing loss is known as conductive hearing loss, in which the sound vibrations cannot be conducted fully from the stapes to the cochlea.

In most cases, stapes fixation causes the hearing loss. However, sometimes, over time, otosclerosis may also affect the bony shell of the cochlea and thereby impair inner ear function. In such cases, damage to the inner ear function can affect the transmission of nerve impulses to the brain. This is a different type of hearing loss, called sensorineural hearing loss. In most cases, both ears are affected by otosclerosis but, in the early stages, symptoms may be restricted to one ear only (51).

The treatment involves either surgery or the use of hearing aids. Surgery involves removal of the immobilized stapes, of part it, and replacement with a prosthetic device, or a stapes piston. The prosthetic device allows the bones of the middle ear to resume movement and to transfer sound energy to the fluids of the inner ear (52).

Quality of life

QoL refers to the general well-being of individuals and populations, and include both negative and positive features of life, such as emotional, social, and physical aspects of life. QoL includes factors that can affect life satisfaction, such as physical health, family, education, employment, wealth, religious beliefs, finance, and the environment. In health care, health-related quality of life (HRQoL) provides an indication of how a person's well-being may be affected over time by a disease, disability, or disorder. Early versions of HRQoL tools referred to the assessment of physical abilities by means of an external rater (for example, the patient's ability to arise, eat, drink, and attend to personal hygiene without help from others) or to a single measurement (for example, the angle to which a limb can be flexed). Current assessment of HRQoL is based on the concept that people can evaluate their actual situation in relation to their personal expectations. This can vary over time, and may change in response to external influences, such as the duration and severity of illness, family support, and other factors. As with any situation involving multiple perspectives, patient's and physician's rating of the same objective situation have been found to differ significantly. Consequently, HRQoL is now usually assessed using patient questionnaires. Hundreds of validated health-related quality of life questionnaires have been developed for various illnesses. The questionnaires can be generalized into two categories: generic instruments and those that are specific for a disease, disorder, or condition.

The short form 36 health survey (SF-36) questionnaire, used in the present thesis, is a generic HRQoL questionnaire about general health, and

is the most frequently used questionnaire in otorhinolaryngology research (53 -61). It comprises eight scaled domains, which are scored as the weighted sums of the questions in each domain. Each question is transformed into a 0 -100 scale. The lower the score, the greater the disability; that is, a score of zero indicates maximum disability, and a score of 100 indicates no disability. The eight domains are: physical function (10 questions); role limitations relating to physical problems (four questions); role limitations related to emotional problems (three questions); energy/fatigue (four questions); emotional well-being (five questions); social function (two questions); pain (two questions) and general health (five questions) (62, 63).

Aims of the studies

The aims of the studies included in this thesis were as follows.

- To clarify the types of impairment of the CTN in different types of middle ear disease and as a complication of middle ear surgery.
- To evaluate the symptoms and consequences for patients with different types of middle ear diseases, after different types of middle ear surgery and after different degree of manipulation of the nerve during surgery.
- To provide surgeons with better tools for predicting the risk of CTN impairment and for managing the CTN during surgery.
- To enable better prognosis for patients regarding risks for CTN impairment after middle ear surgery.
- To evaluate methods for measurement of taste to ensure validity of the results.
- To evaluate histopathological changes of the CTN in CSOM, with or without cholesteatoma.
- To evaluate the QoL before and after ear surgery.

Materials and methods

Paper I

Evaluation of electrogustometry and the filter paper disc method for taste assessment

Thirty-nine participants without any history of chronic middle ear disease were recruited from the author's ENT Department staff.

EGM was performed on groups of 10 participants in different substudies to evaluate possible methodological bias that may have been induced by actions preceding the taste measurement. EGM was performed before and after the participants ate salty, sweet, sour, bitter, hot spicy and neutral-tasting food. EGM was performed on 10 participants before and after smoking and taking Swedish dry snuff ("snus"), and before and after anesthetization of the anterior two-thirds of the tongue with three doses (30 mg) of lidocaine spray (Xylocaine® 10mg/dose, Astra Zeneca, Sweden) on each side of the tongue. EGM was performed 2 minutes after anesthetization of the tongue.

The reproducibility of EGM was evaluated with a decay test performed on 10 participants using 10 unilateral, repeated EGM measurements. The time-dependent variability during 1 day and the variability between different days were evaluated in 10 participants each.

A correlation study was performed to evaluate whether the EGM thresholds correlated positively with taste, as assessed using the FPD test. The two methods were used on both sides of the tongue in the same sequence in 30 participants. The intraindividual thresholds observed using EGM and the FPD test were then compared.

Paper II

The chorda tympani degenerates during chronic otitis media: an electron microscopy study

CTN specimens were collected by otosurgeons at the ENT Department at Uppsala Academic Hospital. We obtained five specimens from patients with no earlier middle ear disease undergoing translabyrinthine surgery for acoustic neuroma, which requires sacrifice of the CTN. These specimens were used as normal controls. Five CTN specimens were collected from patients undergoing middle ear surgery for CSOM, with or without cholesteatoma, in which the nerves could not be spared because of the pathology. The study population comprised 10 patients (seven females; three males) with a mean age of 44 years (range, 7-65 years).

After harvest, the nerve samples were fixed and transferred to Karolinska University Hospital, Stockholm. The specimens were prepared for light microscopy and transmission electron microscopy (TEM) according to standard procedures. A cross-sectional view of the nerve was obtained and photographed using a light microscope, and the areas were measured. The sections were then studied and photographed using TEM. Digital images of the CTN were compared between the diseased middle ears and those of the normal controls. Morphometric evidence of degeneration, such as myelin sheath disintegration, increased vacuoles in the cytoplasm, and shrunken axon nuclei, and the occurrence of nerve sprouting, total cell count per section, and percentage of myelinated versus unmyelinated axons in the specimens were compared.

Paper III

Taste disturbance after stapes surgery: an evaluation of frequency, severity, duration and quality of life

One hundred and fifty-six patients undergoing primary stapedotomy at the ENT departments of Västmanland Hospital Västerås, Uppsala Academic Hospital and Karolinska University Hospital Stockholm, were included from November 2009 to April 2015. Twenty-two patients were excluded because of loss to follow-up, the need for revision surgery during the study period, or inability to comprehend the questionnaires. The final study population included 134 patients.

At inclusion, the patients signed an informed consent form and were given a study subject number. All collected study data were anonymized. Participants answered a symptom questionnaire about taste disturbances before surgery and a validated QoL questionnaire (SF-36). The status of the nerve and the degree of nerve traumatization during surgery were recorded by the surgeon using a form. The symptom questionnaire was repeated at 1 week, 6 weeks and 1 year after the operation. At 1 year, the participants repeated the QoL questionnaire.

Paper IV

Surgery for chronic otitis media causes greater taste disturbance than surgery for otosclerosis.

Seventy-five patients undergoing primary middle ear surgery because of CSOM or otosclerosis at the ENT Department of Västmanland Hospital Västerås were included from November 2009 to April 2016. Ten patients were excluded because of loss to follow-up, the need for revision surgery during the study period, or inability to comprehend the questionnaires. The final study population included 65 persons.

At inclusion the patients signed an informed consent form and was given a study subject number. All collected study data were anonymized. The patients underwent taste measurement with EGM and the FPD test, and answered the symptom questionnaire about taste disturbances before surgery and the QoL questionnaire (SF-36). The status of the nerve and the degree of nerve traumatization during surgery were recorded by the surgeon using a form. The taste measurements and the symptom questionnaire were repeated at 1 week, 6 weeks, 6 months and 1 year after the operation. At 1 year, the participants repeated the QoL questionnaire.

Electrogustometry

EGM was performed using the Rion TR-06[®] instrument (Sensonic Inc, Haddon Heights, New Jersey, USA). The taste buds at the surface of the tongue were stimulated with a calibrated electrical current lasting 2 seconds, delivered by a metal probe with a flat circular contact surface, 5 mm in diameter. The lateral side of the tongue was stimulated about 2 cm from its tip in the area innervated exclusively by the CTN. Both sides of the tongue were assessed independently of each other. The current level was increased stepwise from 4 to 400 μ A as used in pure-tone

audiometry. The current readings were converted into a logarithmic dB scale in which 4 μA corresponds to -6 dB and 400 μA to 34 dB. Steps of 2 dB were used. The lower the reading of dB, the better the taste. The participant's perception of a sensation was indicated by pressing a button. The threshold value was defined as the lowest current level that twice elicited a positive response, interspersed with a current at one level below the threshold level that did not elicit a response. The test person was blinded to the stimulation time and levels.

Filter paper disc method

The FPD method measures the ability to recognize the four flavors, sweet, salty, sour and bitter. Circular FPDs with a diameter of 5 mm were soaked in solutions of one of the four flavors, each in five different concentrations. The FPD was then placed on the lateral side of the tongue, about 2 cm from its tip. The lowest concentration level was applied first, followed by the next higher level, until the participant indicated his/her perception of the correct flavor. The threshold level was established for each of the flavors. A scoring system ranging from 1 to 6 was used, in which 1 represented the lowest threshold, 5 the highest measurable threshold, and 6 an immeasurably high threshold, meaning that no flavor was perceived even at the highest concentration. The scores for all four flavors were summed to create a total score for each side. The total scores could vary from 4 to 24, in which a score of 4 was equivalent to maximum taste ability and a score of 24 was equivalent to no ability to perceive flavors. The Central Pharmacy in Stockholm, Sweden, prepared the solutions. The concentrations used (substance to create this taste) were as follows: salty (sodium chloride) 0.5%, 2.5%, 5%, 10% and 25%; for sweet (sucrose) 0.5%, 2.5%, 10%, 20% and 50%; for sour (citric acid) 0.1%, 1%, 2%, 5% and 10%; and for bitter (quinin hydrochloride) 0.05%, 0.25%, 0.5%, 1% and 2.5%.

Transmission electron microscopy

In the study described in paper II, both TEM and light microscopy were used. TEM achieves greater magnifications than light microscopy. An electron microscope employs a particle beam of electrons with a wavelength that is about 100 000 times shorter than the photons of visible light. Under optimal conditions, the electron microscope can magnify up to one million times compared with the light microscope, which is limited to a maximum magnification of 1000 times.

The transmission electron microscope is the original form of electron microscope. It uses a high-voltage electron beam, that is focused by electrostatic and electromagnetic lenses. When the beam of electrons hits the specimen, some of the electrons pass through and others are scattered. The deflected electrons carry information about the structure, which is converted by the microscope's objective lens system into a gray-scale image. To enhance the ability of specimens to scatter electrons, they are stained with a heavy metal such as lead, uranium, or tungsten. In the study described in paper II, ultrathin sections were placed on formvar-coated grids and stained with uranyl acetate and lead citrate. The sections were then studied and photographed in a JEOL 1230 transmission electron microscope (JEOL GmbH, Eching, Germany).

Symptom questionnaire

A symptom questionnaire was used in the studies described in papers III and IV; one version was used for evaluation of preoperative symptoms and another for postoperative symptoms. Boxes were ticked to indicate taste disturbances and the degree of the disturbance was indicated on a visual analog scale (VAS) from 1 (no disturbance) to 100 (maximum disturbance). The participant was asked to indicate disturbances such as loss of taste, metallic taste sensation, numbness, tingling, or "other types" of disturbance; for the latter, space was provided for the patients to describe the disturbance(s) in his/her own words.

Surgeon's form

The surgeon's form was used in papers III and IV and includes the surgeon's description of the status of the CTN immediately upon elevation of the tympanomeatal flap. The surgeon ticked boxes to indicate the presence or absence of CTN atrophy, dislocation, and adherence. The surgeon also ticked boxes to indicate the extent of surgical trauma: CTN untouched, touched and stretched only, visually injured, severed, or shrunk because of desiccation under the light beam of the operating microscope.

Quality of life questionnaire (SF-36)

The studies described in papers III and IV used the SF-36, a QoL questionnaire about general health. The participants completed the questionnaire preoperatively and at 1 year postoperatively.

Statistical analyses

All statistical analyses were performed in cooperation with a registered statistician and using IBM SPSS Statistics (version 22, 23 and 24). For all statistical tests, two-sided *P*-values <0.05 were considered to be significant. For descriptive statistics, categorical variables are given as percentages and number (percentages). For ordinal and continuous variables, the values are given as the mean. Comparisons between two groups were made using Pearson's χ^2 test for independent categorical data. The Mann –Whitney U test and Wilcoxon signed ranks test were used for independent and dependent and for ordinal and continuous data. In paper I, Friedman's test and ANOVA were used to analyze the data by considering the variability within and between days. Spearman's correlation coefficient was used to examine associations between variables.

Ethics approval

The studies were performed in accordance with Swedish ethics legislation and with approval from the local ethics committee in Uppsala, Sweden (dnr 2007/250 and no. 99398, 22/9 1999).

Results

Paper I

Evaluation of electrogustometry and the filter paper disc method for taste assessment

EGM was used for 772 measurements. Based on 220 primary measurements performed before any taste provocations, the normative EGM threshold was calculated as -0.5 dB with a standard deviation of 6.3 dB.

The measurements before and after eating different flavors showed no significant changes, with one exception: eating the bitter sample caused a minor, but significant, threshold increase. Smoking or taking snus did not affect the threshold. Local anesthesia of the tongue caused a significant increase in the threshold. The decay test showed no significant threshold shift, as was the case with the comparison between days and within a day.

Correlational analysis showed moderate correlations except for the bitter taste, for which the correlation was close but not significant: 0.311 ($P<0.05$) for sour taste, 0.293 ($P<0.05$) for sweet taste, 0.265 ($P<0.05$) for salty taste, and 0.237 ($P=0.068$) for bitter taste.

Paper II

The chorda tympani degenerates during chronic otitis media: an electron microscopy study

The light microscopy examination showed that the cross-sectional area of the CTN was larger in the patients with disease than in those in the normal control group. There was substantial interindividual variation within the diseased group (CSOM with or without cholesteatoma). Electron microscopy showed, substantial ultrastructural differences between CTNs in the patients with disease compared with the normal control group (Figures 4 and 5).

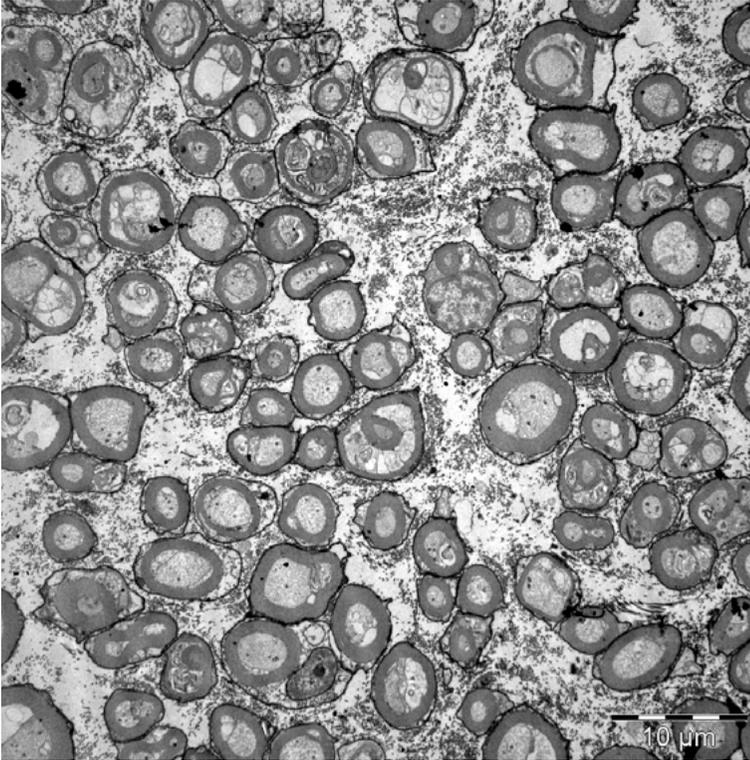


Figure 4. Electron micrograph of the CTN from a normal control participant. Note the round, regular axons in normal bundles. Original magnification, x2500; stained with uranyl acetate and lead citrate.

The percentage of unmyelinated axons was significantly lower in the patients with disease compared with the normal control group. The percentage of nerves showing signs of degenerative processes present in the myelin sheets, such as disintegration or edema, was higher in the diseased group than in the normal control group. The percentage of axons showing signs of degenerative processes, such as increased vacuoles with degenerative material in the axons, was significantly higher in the disease group than in the normal control group. Other signs of structural degeneration that were seen more frequently in the disease group included disarranged structure of the axon bundles, spatial separation with increased connective tissue between the axons in the endoneurium, more divergent shapes of the axons; and more divergent myelin thickness (figure 4 and 5).

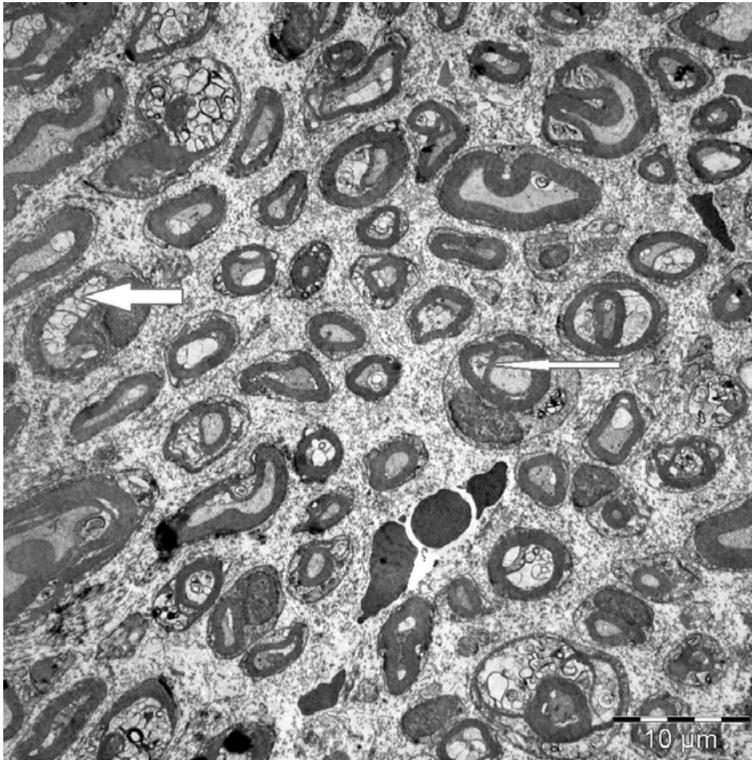


Figure 5. Electron micrograph of the CTN from a patient with CSOM. Note the degenerative signs, such as disintegration and edema in the myelin sheath (thin arrow), vacuoles, degenerative material in axons (thick arrow), increased connective tissue in the endoneurium, and irregular shape and arrangement of the axons. Original magnification, x2500; stained with uranyl acetate and lead citrate.

Axon sprouting, a sign of regeneration after previous damage of the nerve, was found exclusively in the diseased group, and in the most samples from this group (figure 6).



Figure 6. Electron micrograph of the CTN from a patient with CSOM showing signs of sprouting (arrow). Original magnification, x20 000; stained with uranyl acetate and lead citrate.

Paper III

Taste disturbance after stapes surgery: an evaluation of frequency, severity, duration and quality of life.

Of the 134 participants, 83 (61.9%) reported taste disturbances postoperatively: 57 (68.7%) reported loss of taste, 56 (67.5%) reported metallic taste sensation, and 16 (19.3%) reported some other types of disturbance. These were described as bad taste, poison, licorice, salty, vinegar, vapid, bile and “ghost taste;” that is, an experience of a taste between meals. The numbers (percentage) of patients reporting taste disturbance were 67 (50.0%) at 1 week after the operation, 51 (38.1%) at 6 weeks and 7 (5.2%) at 1 year.

Sixty females (66.7%) and 23 males (52.3%) reported postoperative symptoms. At 1 week, 48 females (53.3%) and 19 males (43.2%) reported symptoms, and at 6 weeks, 36 females (40.0%) and 15 males

(34.1%) reported symptoms. At 1 year only seven patients (5.2%) reported symptoms, and all were female. There were no significant age or sex differences in VAS scores at any time point.

In 126 (94.0%) ears, the CTN was assessed as normal by the surgeon upon opening the middle ear. In nine ears (6.7%) the CTN was assessed as abnormal. In four ears (3.0%) there was adherence to the CTN. One of these four patients reported symptoms, although this was only at 1 and 6 weeks after the operation. In five ears (3.7%) the CTN was displaced. Three of these five patients reported no symptoms, one reported symptoms up to 6 weeks and another patient reported symptom up to 1 year after the operation. No significant difference was seen between the group with CTN judged as normal and the group with abnormality of the CTN (adherences or displacement).

In 127 ears (95%) the CTN was handled mildly: untouched in two patients and touched and stretched only in 125 patients. Of the 127 patients whose CTN was handled mildly, 64 (50.4%) reported symptoms at 1 week, 48 (37.8%) at 6 weeks, and 6 (4.7%) at 1 year after the operation. The CTN was traumatized severely during surgery in seven ears (5.2%): visually injured in three, severed in one, and shrunk by desiccation in four. At 6 weeks, these patients had a significantly higher VAS score ($P=0.005$) compared with those with mild CTN trauma.

QoL, differed significantly only for the patients whose symptoms remained at 1 year after the operation. They had a significantly lower score for the physical function domain of QoL compared with the group without remaining symptoms ($P=0.048$).

Paper IV

Surgery for chronic otitis media causes greater taste disturbance than surgery for otosclerosis

The study population of 65 adults comprised 36 women (55%) and 29 men (45%) with a mean (SD) age of 46 (± 15.67) years (range 17 -74). Thirty-seven patients (57%) had CSOM and 28 (43%) had otosclerosis. Only four patients (6%) reported preoperative taste disturbance: one had CSOM and three had otosclerosis. However, their preoperative EGM and FPD scores did not differ significantly from those of the other patients.

More than half of the 65 patients (n=36, 55%) reported taste disturbances after the operation. Of these 36 patients, 30 (83%) reported taste disturbance, 27 (75%) reported loss of taste and 23 (64%) reported metallic taste sensation, 32 (89%) reported sensitivity disturbance, 28 (78%) reported numbness and 13 (36%) reported tingling. Six patients (17%) reported other types of disturbances, which were described as bad taste, poison, salty, sour, and “ghost taste;” that is, an experience of a taste between meals.

Eight patients (12%) reported remaining symptoms at 1 year, and six of them were in the CSOM group. Six others, of the eight patients, had only mild CTN trauma during surgery. Three had worse EGM and/or FPD scores (higher scores) at 1 year. Two of these patients had a severed CTN, and the third patient reported having impaired taste and had worse than normal EGM and FPD scores before surgery.

The operated side scored generally worse on the EGM and FPD test at every postoperative follow-up time point compared with the contralateral side. The difference was significant at two and at three follow-up time points, respectively.

Comparison between patients according to the diagnosis of CSOM and otosclerosis, showed that the CSOM group was more prone to report postoperative taste disturbance: 23 (62%) of the patients with CSOM reported taste disturbance postoperatively, and six of these (16%) reported symptoms remaining 1 year postoperatively. Of the patients with otosclerosis, 13 (46%) reported taste disturbance postoperatively, two of whom (7%) reported taste disturbance remaining at 1 year postoperatively. The CSOM group had significantly worse EGM and FPD scores than the otosclerosis group at two and four follow-up time points, respectively. The CSOM group also had worse VAS scores at all follow-up time points postoperatively, although the difference was not significant. The deterioration of VAS scores from before to 1 week after the operation was significantly larger in the CSOM group. At 1 year postoperatively, the CSOM group scored worse on the FPD test (significant) and VAS (not significant), but not on the EGM. Patients with CSOM also had worse taste ability preoperatively, as measured with the FPD test.

Twenty-four women (67%) and 12 men (41%) reported postoperative taste disturbances. The men had significantly worse EGM and FPD scores at two and at three follow-up time points, respectively. The VAS scores did not differ significantly between men and women. Contralateral EGM and FPD scores were worse in men than in women at all

follow-up time points; the differences were significant at all time points for the FPD test and at two time points for EGM.

The cohort was divided into two groups according to age: 28 patients (43%) were aged >50 years and 37 (57%) were ≤50 years. The older group had worse EGM and FPD scores overall, and these were significant at 1 year for EGM and at 1 week for the FPD test. The VAS scores were worse (higher values) for the younger group, although the difference was not significant. Contralateral EGM and FPD scores were worse in the older group than in the younger group at all follow-up time points, and the difference was significant at three time points for EGM and at all time points for the FPD test.

The CTN was assessed by the surgeon as normal upon tympanotomy in 39 (60%) ears and as abnormal because of adhesions, dislocation, or atrophy in 26 (40%) ears. The group with abnormal CTN had generally worse EGM and FPD results, although this was significant only for FPD test at three follow-up time points. The group with abnormal CTN also had worse VAS scores at all follow-up time points, although the differences were not significant. The deterioration of VAS scores from before to 1 year after the operation was significantly larger in the group with an abnormal CTN.

The CTN was handled mildly (un-touched or touched and stretched only) in 57 ears (88%) and traumatized severely (visually injured, severed or shrunk by desiccation) in eight ears (12%). Four CTNs were severed, and all were in patients with CSOM. Two of those patients reported no symptoms at 1 year, and one of them had normal EGM and FPD scores. The group that had received severe trauma to the CTN had generally worse EGM and FPD scores; these differences were significant at four follow-up times for EGM and at all time points for the FPD test. The VAS score did not differ significantly according to the handling of the CTN.

The only significant finding for QoL was the comparison between the two CTN status groups. The abnormal CTN group reported worse post-operative changes in mean QoL score (from 89.0 to 86.6 (±8.35)) compared with the normal CTN group (from 79.2 to 81.2(±14.77)) ($P=0.028$).

Discussion

Taste and taste measurements

Despite the impression given by the mass media and the weekly magazines replete with recipes and cooking programs and competitions, importance of taste is not reflected in the clinical routines or in research in Western medicine. Although EGM was first used in the 1950s, the use of clinical taste measurements is limited in Western countries. By contrast, Japan is at the forefront in including the assessment of taste as part of the clinical routine in ENT departments. Most related scientific articles also derive from Japan, and the state-of-the-art EGM instrument (Rion TR -06) used in this thesis was developed in Japan in 1990 (32 - 40, 42, 43, 64).

EGM is the first choice to measure taste because the range of measurements can be kept constant, the stimulus may be calibrated, and the method is a quick procedure with high sensitivity that can be used for even subclinical taste disorders. It has been suggested that performing both EGM and the FPD test increases the credibility of the results (33, 40).

Although there is no established standard for the FPD test in terms of the concentrations of different flavors, they were similar to those used in previous reports and included the four recognized flavors, sweet, salty, sour and bitter; the fifth flavor umami was not used. The FPD protocol used in papers I, III, and IV applied flavor concentrations that were similar to those used in commercial Japanese FPD test kits and in previous studies (15, 22, 33, 37, 65 -66). The FPD stimulation levels (i.e., the flavor concentrations) increase logarithmically similarly to the increments in the EGM protocol.

It is debatable what EGM actually measures. In one study, 22 subjects were asked to describe the EGM sensation, which was most often described as the sensation of an electrical shock, a tingling sensation, a buzzing vibration, or a metallic sensation. This raises the question whether the sensation really is transmitted through the taste system or through a tactile or another sensory system (34, 35, 37-40, 42, 43, 67 -

69). These uncertainties were the reason for using correlational analysis in this thesis to compare the results of EGM with those of the FPD test, which undoubtedly assesses taste and no other type of sensation. This comparison showed, for three of the four flavors, a significant correlation between the thresholds obtained in the two tests, which indicates that EGM actually measures taste.

Ear surgery: CTN impairment

In the field of otosurgery, opinion differ about how to handle the CTN during surgery; that is, whether to preserve a partially damaged nerve or to sever it completely (70 -79). Historically, the CTN was often sacrificed in middle ear surgery by a clean cut under the opinion that an injured CTN would cause more taste symptoms (67, 80 -82). In 1963, Rice reported that severing or preserving the nerve made little difference to postoperative symptoms (29). In the studies described in papers III and IV, we found that greater surgical trauma was associated with more postoperative symptoms. The intention in our otosurgery clinic is to preserve the CTN if possible, and our results reflect that objective in that the CTN was severed in only a few patients. Our study included some patients with severed CTN who experienced remaining symptoms 1 year postoperatively, although there were too few patients with a severed CTN to show statistical significance.

In clinical practice, patients operated on for CSOM seldom complain about taste disturbances even though the CTN is sometimes traumatized severely during surgery. By contrast, patients with otosclerosis seem to complain of postoperative taste disturbances more often even though the CTN is less frequently traumatized severely during surgery in these patients (14, 15,19, 23, 28, 52, 83 -91). One theory is that patients with CSOM have impaired taste ability before the operation because of the pathology and are thus less prone to experience taste disturbance postoperatively. A few studies have reported preoperative taste disturbances in patients with CSOM and even functional improvement postoperatively (15, 91, 92). One of the aims of the study described in paper IV was to resolve this matter. Earlier studies have reported morphological changes in the CTN in patients with CSOM (25 -27), and the results in paper II agree with these findings. Contrary to this belief, paper IV showed that patients with CSOM were more likely to experience taste disturbance postoperatively. The EGM and FPD test results showed that patients with CSOM had more taste disturbance postoperatively than did patients with otosclerosis. We also found that

patients with CSOM had worse taste ability preoperatively, as measured with the FPD test.

The functional impairment of the CTN in patients with CSOM may be explained by the presence of pathogens in the affected middle ear, which produce toxins or enzymes that affect CTN function. If a disease has already reduced the nerve's function, further loss of function by surgical trauma would presumably be less. The structural changes in the CTN reported in patients with CSOM in paper II may explain the reduced gustatory function and thus more taste disturbances preoperatively.

Histological changes of CTN

To evaluate the histopathological changes in the CTN in ears affected by CSOM, we collected samples from patients undergoing translabyrinthine surgery for acoustic neuroma, in which the procedure requires sacrifice of the CTN. These specimens were used as normal controls. CTN specimens were also collected from patients undergoing middle ear surgery for CSOM, with or without cholesteatoma, whose CTN could not be spared because of the pathology.

It is difficult to access the CTN without ultrastructural changes in healthy ears. The use of CTNs from otosclerotic ears as normal controls is controversial. Comparison between patients with facial paralysis (in which the CTN branches off from the facial nerve to enter the middle ear cavity) and those with otosclerosis has shown similar degenerative morphological changes associated with both diseases (93). These structural changes in the CTN from otosclerotic ears indicate that ears affected with otosclerosis are not optimal for use as normal controls in ultrastructural studies. Therefore, in paper II, we used CTN samples from patients with acoustic neuroma whose middle ears were unaffected by the disease.

Degeneration

There are only a few published studies of the CTN histology in patients with CSOM, we found only four studies that assessed structural and ultrastructural changes in CTN. In one study, CTNs obtained in otosclerosis surgery were used as controls (26). In a second study, specimens from patients with dry chronic otitis media were compared with those from CSOM ears (25). A third study used no controls (27). The fourth study was performed on temporal bones

from patients with CSOM and from patients with facial paralysis, who were the normal controls (24).

The study reported in paper II found degenerative signs in all specimens but also in the normal controls. To avoid causing degenerative changes in the specimen, tissues should be fixed immediately after harvest. The fact that nerves from healthy middle ears show degenerative signs might be explained by trauma during surgery or the handling of the specimen during fixation. Significantly more degenerative signs were observed in the CSOM group than in the normal control group, even though the number of specimens was small.

There are also few papers that describe degeneration of the taste buds and decreased taste ability as a consequence of severing of the CTN and papers that describe signs of regenerated taste buds and recovered taste function after surgery (92, 94 -100).

Regeneration

In clinical practice, postoperative taste symptoms often decrease or disappear with time, possibly because of nerve repair or adaption of central mechanisms. Earlier studies on postoperative taste disturbances showed that most patients recover their taste function within 1 year postoperatively (15, 23). The results of paper IV also showed recovery of taste function by 1 year postoperatively as measured with EGM and the FPD test.

One study reported that, in patients with preoperative impaired nerve function and intraoperative injury to the CTN, the decrease in postoperative nerve function was only temporary. After surgical treatment of the inflammation, taste measurement showed improved nerve function 1 month postoperatively (15). This finding suggests that the inflammatory process causes the taste impairment and, after surgical treatment of the inflammation, the CTN regenerates and taste function recovers. Indications of nerve regeneration observed at second-look surgery have also been reported (101 -105).

Nerve sprouting may be an important repair process in CSOM, in which the nerve function is restored after elimination of the suppressing inflammatory pressure. The findings of CTN sprouting in CSOM specimens in paper II support this idea. However, the mechanisms responsible for CTN regeneration, recovery of taste thresholds, and relief of taste symptoms postoperatively in CSOM remain unclear.

Sex and age differences

Earlier studies have shown that females have better taste ability than males (41, 80, 105 -107), and that taste decreases with age (108-111). The findings reported in paper IV are consistent with these sex differences and age trends. We found a significant difference between age groups and sexes on the contralateral side. That is, the younger group and females had better EGM and FPD scores compared with the older group and males. These findings suggest that these differences exist even in the normal population. This suggests that females and younger persons can be at higher risk of experiencing postoperative taste impairment.

Quality of life

The effects of taste disturbance on QoL have rarely been addressed in the literature. In the few available reports, olfaction was also involved (60). Papers III and IV examined the impact on QoL in relation to taste disturbance before and after middle ear surgery and to the surgical CTN trauma.

The SF-36 comprises general questions about QoL and is not specific for taste disturbance. It has been used in previous otorhinolaryngology-related studies (53-57); no more specific QoL questionnaire has been developed for taste disturbance. One weakness related to the use of the SF-36 in the present thesis is that the postoperative hearing gain may confound the QoL results (53, 54).

Interestingly, in paper III, the seven patients who reported remaining taste symptoms at 1 year postoperatively were all women and they were older than the rest of the study population. They also had a lower mean QoL score both before and after surgery, with a significantly lower QoL score for the physical function domain postoperatively at 1 year compared with the group without postoperative symptoms. This seems to support House et al.'s finding that postmenopausal women are at higher risk for postoperative taste disturbance after stapes surgery (80).

Conclusions

EGM is a reliable and reproducible method for measuring taste. The correlation between the EGM and FPD test thresholds indicates that EGM actually measures taste. The combination of both methods enhances the credibility of results obtained in clinical trials aiming to monitor CTN function.

CSOM causes ultrastructural degenerative changes in the CTN that may explain impairment of taste preoperatively.

Nerve sprouting, as a sign of regeneration, was found for the first time in human CTN and was found exclusively in specimens from patients with CSOM regardless of the presence or absence of cholesteatoma. The signs of nerve regeneration may explain why most patients with postoperative taste disturbance recovered during the first year postoperatively. These results support the opinion that the CTN should be spared during surgery if possible.

Most patients (62%) operated on for otosclerosis, experienced subjective taste disturbance after stapes surgery, whereas only 5% still experienced disturbance 1 year postoperatively.

Patients operated on for CSOM seem to be more prone to experience both subjective and measurable taste disturbances postoperatively than are patients operated on for otosclerosis. The FPD test indicated that CSOM patients exhibit CTN impairment before the operation.

Severe surgical trauma of the CTN was a significant predictor of more severe symptoms postoperatively, which indicate that the CTN should be carefully handled during surgery. Patients with abnormal CTN status were more likely to report postoperative taste impairment.

Sex seems to predict outcome because the seven patients with remaining symptoms at 1 year postoperatively in paper III were all female. EGM and FPD scores were generally worse in males and older people than in females and younger people. This was true for both for the operated side and the contralateral side and at most follow-up time points.

These findings suggest that there is a real difference according to age and sex in the entire population.

Minor changes in QoL were seen postoperatively. The seven females with symptoms that remained at 1 year after stapedotomy scored worse in the physical domain of the SF-36 questionnaire compared with those without symptoms. The QoL was significantly worse in the group with an abnormal CTN than in the normal group in paper IV.

Summary in Swedish (Sammanfattning)

Korda tympani-nerven, den viktigaste smaknerven, passerar oskyddat genom mellanörat. Den passerar mellan hörselbenen, hammaren och städet, vilket gör det svårt för öronkirurgen att lämna den orörd i samband med öronoperationer. Vid operation i mellanörat rensas nerven ofta från sjukliga processer och kan därför utsättas för olika grad av manipulation. Den kan skäras av, sträckas ut, vidröras eller torka ut under ljuset av operationsmikroskopet. I samband med sjukdomar i mellanörat så som öroninflammation (kronisk otit) med eller utan cystbildning (kolesteatom) kan nerven även vara påverkad av sjukdomen i sig.

Öronkirurger har noterat att patienter som opereras för öronsjukdomen otoskleros i högre grad påtar smakpåverkan efter operation än patienter som opereras för kronisk otit med eller utan kolesteatom. Detta trots att nerven ofta manipuleras i lägre grad i samband med operation av otoskleros jämfört med operation av kronisk otit. En förklaring till detta har föreslagits vara att nerven i samband med kronisk otit redan innan operationen är påverkad av sjukdomen i sig. Dessa patienter kan därför ha sämre smakförmåga redan innan operationen och ej vara lika benägna att uppleva smakpåverkan efter operationen.

I klinisk praxis testas nervfunktionen mycket sällan. I litteraturen beskrivs två metoder som gold standard för mätning av funktionen; elektrogustometri (EGM) och filterpapperdisc metoden (FPD). Dessa metoder har utvärderats i studie I för att säkerställa att de är trovärdiga mätmetoder av smak och har därefter använts i studie IV.

Denna avhandling syftar till att klargöra graden av påverkan på korda tympani-nerven samt konsekvenserna för patienterna vid olika former av öronsjukdom och som komplikation till öronoperation. Denna kunskap ger öronkirurger bättre möjligheter att ställa prognos inför öronoperation avseende nervens funktion och hur nerven bäst ska hanteras under operationen. Därigenom kan kirurgen ge patienterna bättre information kring risk och prognos för smakpåverkan i samband med öronoperationer av de olika formerna av öronsjukdom.

Avhandlingen är baserad på fyra delarbeten, studie I - IV.

I studie I ingår 30 friska frivilliga personer som genomgår ett antal mätningar med EGM och FPD för att etablera normativa värden samt för att evaluera mätmetoderna. Reproducerbarhet testas samt möjliga felkällor vid EGM mätningar med avseende på exposition för sött, salt, surt, beskt, kryddstark och neutral mat samt för rökning, snusning och efter lokalbedövning av tungan. En evaluering av korrelationen mellan EGM och FPD genomförs.

Studie II utgörs av en histologisk undersökning av korda tympani-nerver från fem friska öron och från fem öron med kronisk otit (med eller utan kolesteatom) för att utvärdera graden av histologisk påverkan av nerven i samband med sjukdomen. Nervbiopsier undersöktes med elektronmikroskopi i samarbete med Karolinska Institutet Stockholm.

Studie III utgörs av en enkätstudie där symtom av smakstörning och livskvalitet undersöks på 134 patienter som genomgår operation för otoskleros. Ett formulär angående upplevd smakpåverkan före och vid tre uppföljningstillfällen, upp till ett år, efter öronoperation ifylles samt ett livskvalitetsformulär före och ett år efter operationen. Operatören fyller i ett formulär angående nervens status samt hur nerven hanterats i samband med operationen.

I studie IV ingår 65 försökspersoner som genomgår operation för kronisk otit (med eller utan kolesteatom) och otoskleros. De genomgår smaktesterna EGM och FPD samt besvarar en enkät angående upplevd smakstörning före och vid fyra uppföljningstillfällen, upp till ett år, efter operationen. Före operationen och ett år efter operationen besvarar de även ett livskvalitetsformulär (SF-36). Operatören fyller i ett formulär angående nervens status vid början av operationen samt hur nerven hanterats under operationen.

Resultaten har visat att EGM är en pålitlig och reproducerbar mätmetod av smak. Korrelationen mellan EGM och FPD indikerar även deras trovärdighet som mätmetoder av smak. Kombinationen av båda mätmetoderna i studie IV ökar trovärdigheten av resultaten.

Kronisk otit med eller utan kolesteatom orsakar ultrastrukturella förändringar av korda tympani-nerven som kan förklara en smakpåverkan innan operation hos dessa patienter. Nervsprouting, som ett tecken till regeneration, påvisades exklusivt i nerver från kronisk otit med eller utan kolesteatom. Dessa tecken till regenerationsförmåga hos nerven kan förklara varför smakstörningen återhämtar sig inom ett år efter operation.

Studie III visade att nästan 62% av patienterna med otoskleros upplever smakstörning efter operation och drygt 5% har kvarstående störning ett år efter operation. Studie IV visade att patienter med kronisk otit med eller utan kolesteatom är mera benägna att få både subjektiv och mätbar smakstörning efter operation än vad patienter med otoskleros är. FPD mätningar påvisar en försämrad smakförmåga redan innan operation för patienter med kronisk otit med eller utan kolesteatom. Mera uttalat kirurgiskt trauma mot nerven samt onormalt status av nerven vid operationens början ger signifikant mer uttalad smakstörning postoperativt. Kön och ålder verkar också vara av betydelse för postoperativ smakpåverkan. I studie III var alla sju patienter med kvarstående smakpåverkan ett år postoperativt kvinnor. Män och äldre personer visade generellt sämre smakförmåga i studie IV, mätt med EGM och FPD, än kvinnor och yngre.

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