Review Article

Procedures for restoring vestibular disorders

Leif Erik Walther[1*]

[1]Department for Otolaryngology and Head and Neck Surgery, University Hospital Aachen

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Abstract

This paper will discuss therapeutic possibilities for disorders of the vestibular organs and the neurons involved, which confront ENT clinicians in everyday practice. Treatment of such disorders can be tackled either symptomatically or causally. The possible strategies for restoring the body's vestibular sense, visual function and co-ordination include medication, as well as physical and surgical procedures. Prophylactic or preventive measures are possible in some disorders which involve vertigo (bilateral vestibulopathy, kinetosis, height vertigo, vestibular disorders when diving (Tables 1 (Tab. 1) and 2 (Tab. 2)). Glucocorticoid and training therapy encourage the compensation of unilateral vestibular loss. In the case of a bilateral vestibular loss, it is important to treat the underlying disease (e.g. Cogan's disease). Although balance training does improve the patient's sense of balance, it will not restore it completely.

In the case of Meniere's disease, there are a number of medications available to either treat bouts or to act as a prophylactic (e.g. dimenhydrinate or betahistine). In addition, there are non-ablative (sacculotomy) as well as ablative surgical procedures (e.g. labyrinthectomy, neurectomy of the vestibular nerve). In everyday practice, it has become common to proceed with low risk therapies initially. The physical treatment of mild postural vertigo can be carried out quickly and easily in outpatients (repositioning or liberatory maneuvers). In very rare cases it may be necessary to carry out a semicircular canal occlusion.

Isolated disturbances of the otolith function or an involvement of the otolith can be found in roughly 50% of labyrinth disturbances. A specific surgical procedure to selectively block the otolith organs is currently being studied. When an external perilymph fistula involving loss of perilymph is suspected, an exploratory tympanotomy involving also the round and oval window niches must be carried out. A traumatic rupture of the round window membrane can, for example, also be caused by an implosive inner ear barotrauma during the decompression phase of diving. Dehiscence of the anterior semicircular canal, a relatively rare disorder, can be treated conservatively (avoiding stimuli which cause dizziness), by non-ablative „resurfacing" or by „plugging" the semicircular canal. A perilymph fistula can cause a Tullio-phenomenon resulting from a traumatic dislocation or hypermobility of the stapes, which can be surgically corrected. Vestibular disorders can also result from otosurgical therapy. When balance disorders persist following stapedectomy it is necessary to carry out a revision operation in order to either exclude a perilymph fistula or shorten the piston. Surgically reducing the

[*]**Corresponding Author:**
PD Dr. med. Leif Erik Walther, Department for Otolaryngology and Head and Neck Surgery, University Hospital Aachen, Pauwelsstraße 30, 52074 Aachen, Telephone: (0241) 8085080, Telefax: (0241) 8082523, eMail: LWalther@ukaachen.de

size of open mastoid cavities (using for example porous hydroxylapatite or cartilage) can result in a reduction of vertiginous symptoms while nursing or during exposure to ambient air. Vestibular disturbances can occur both before and after vestibular nerve surgery (acoustic neuroma). Initially, good vestibular compensation can be expected after surgically removing the acoustic neuroma. An aberrant regeneration of nerve fibers of the vestibulocochlear nerve has been suggested as a cause for secondary worsening. Episodes of vertigo can be caused by an irritation of the vestibular nerve (vascular loop). Neurovascular decompression is generally regarded as the best surgical therapy. In the elderly, vestibular disturbances can severely limit quality of life and are often aggravated by multiple comorbidities. Antivertiginous drugs (e.g. dimenhydrinate) in combination with movement training can significantly reduce symptoms. Administering antivertiginous drugs over varying periods of time (e.g. transdermal scopolamine application via patches) as well as kinetosis training can be used as both prophylactically and as a therapy for kinetosis. Exposure training should be used as a prophylactic for height vertigo.

Keywords: neurootology vestibular disturbances labyrinth, rehabilitation therapy oto-surgery vestibular compensation

1. Introduction

A person's sense of balance is related to labyrinth function, the visual system and cervical deep sensibility. These sensory modalities work in an interconnected manner to control visual motor activity in order to provide spatial orientation in all positions and during head movement. In addition, muscular co-ordination allows standing and walking while simultaneously moving the head. When the co-ordination between these sensory functions is disturbed, a person will experience a sensation which is individually interpreted as some form of dizziness. This is neither a diagnosis, nor is it a finding, but rather a multi-faceted subjective symptom involving many disciplines. This is not just the case for balance disorders, but also for diseases unrelated to otology. Vestibular disorders, more precisely, can also be seen in terms of postural regulation. This is the result of lesions within the vestibular system. „Being off balance" therefore can have all manner of causes.

Dealing with dizziness and balance disorders is generally regarded as difficult. The subjective nature of the term „dizziness", coupled with the fact that it is a widely and poorly defined term, leads to an array of problems within clinics [1], [2], [3].

Dizziness and balance disorders are two of the most common complaints, turning them into endemic diseases. There could be over 300 reasons behind the complaint [4].

Acute or constant vertigo may manifest itself as disorders affecting spatial orientation and perception (e.g. rotation vertigo), gaze stabilization (e.g. nystagmus), postural regulation (ataxia and tendency to fall), as well as the vegetative nervous system [5]. The patient may be severely debilitated by these symptoms. In addition to the physical, psychological factors also play an important role [6]. The patient will almost certainly suffer repercussions in his/her everyday and professional lives.

The vestibuloocular reflex (VOR) is a central part of the sensomotoric system. It carries the information from the labyrinth over the vestibular nerve and its nucleus area in the brain stem to the eye muscles (Figure 1 (Fig. 1)). Forms of vestibular vertigo are linked to disorders in the VOR. Based on this, the commonly used differentiation between peripheral and central disorders no longer appears relevant. While being didactically appropriate, the differentiation is not relevant when understanding the causes and interpreting functional diagnostic findings.

Many methods can be employed for restoring vestibular function: medication, physical measures, non-ablative surgical procedures, as well as procedures to unilaterally disable the function of the labyrinth. The prerequisite which decides which method is used is the individual's capacity for vestibular compensation; a process organized through the central nervous system in the case of unilateral and bilateral functional disturbances of the vestibular system coupled with a restructuring of the VOR.

The past years have seen new impulses towards explaining vertigo from both within our own discipline, as well as neurology. It is now widely accepted that finding a solution to the problem of

vertigo can only be achieved by working together with other disciplines.

This paper concentrates primarily on diseases of the labyrinth with vestibular disturbances. Both past and present treatments will be presented, and controversial attitudes will be compared and critically discussed. Our treatment of this topic is directed towards ENT practitioners and clinicians.

Where available, sources from evidence-based medicine will be used to assess the success of individual therapeutic measures.

2. Basic principles

2.1 Development of the structure of the vestibular organ

The embryonic development of the inner ear is a complicated process. Growth of the labyrinthine structures is three dimensional. The otocyst is the embryonic beginning. Initially, this divides into a ventral section, consisting of saccule and cochlear duct, and a dorsal component, the utricle. Signs of adult stem cell have since been found in the utricle. The inner ear begins to develop in the sixth week. All three semicircular canals develop simultaneously from three outpocketings of the utricle. The further development of the semicircular canals is a process involving fusion and simultaneous growth. The lateral semicircular canal is the final structure to develop during the embryonic phase of the inner ear. A malformation of the lateral semicircular canal can be an isolated anomaly [7]. A malformation of all three semicircular canals is described in the Goldenhar-syndrome and the CHARGE Association [8], [9].

2.2 Anatomy, physiology and pathophysiology of the vestibular system

The osseous labyrinth surrounds the membranous labyrinth, which appears as a correspondingly complex fluid-filled system. The endolymph filled semicircular canals open into the utricle by means of five openings (common crus, non-ampullary end of the anterior and posterior semicircular canals). What is clinically important (balance disorders post stapes operations) is the area immediately around the otolith organs to the fenestra vestibuli. According to a summary by Lang, the distance to the oval window is smallest (0.3 mm) from the top edge of the oval window to the utricle (medial and superior). The average is 1.4 mm from the lower posterior edge and 1.6 to 2 mm from the lower wall. The saccule is situated roughly 1 mm from the central part of the stapes footplate. The smallest distance is from the anterior edge (roughly 0.75-1 mm) [10].

The labyrinthine artery is responsible for the blood supply of the vestibular organs. The vestibular artery branches off from the labyrinthine artery and its branches in turn anatomize with the vestibuloocular artery via the ramus vestibularis. Variations of the vascular anatomy and looping around the brain stem (neurovascular compression) could cause vertigo as part of vestibular paroxysm.

The vestibular labyrinth's sensory epitheliums are situated in the otolith apparatus (maculae of the utricle and saccule) as well as in the ampulla of the three semicircular canals (cristae). Humans have two types of hair cells: the flask or bottle shaped type I hair cell and the cylinder shaped type II hair cell. Both act as mechanic sensory receptors. Stimulation caused by rotational or linear acceleration results in a mechanic electrical transduction. According to a current study, this is greater in type I hair cells (500 pA) than in type II hair cells [11]. The receptorpol of both cell types contains stereocilia, which are arranged in a hexagonal pattern. The stereocilia are embedded either in the honeycomb-like gelatinous membrane, which is covered with otoliths (statoliths) or in the gelatinous mass of the cupula. A shearing movement of the sensory hairs will provide adequate stimulation. In a similar fashion to functional cell polarisation, a kinocilia can be located laterally to the stereocilia bundle (deflection toward the kinocilia = depolarisation, in opposite directions = hyperpolarisation). While the polarisation of the sensory cells in the cristae is unified, it is more complicated in the maculae due to functional requirements. Here we find a curved border line (striola) which divides the sensory epithelia into two halves. Instead of being parallel, the polarisation of the sensory cells of the otolith organs is also curved, making it present in all directions of a plane [12], [13].

Information of the otolith organs, positioned somewhat at right angles to one another (sacculus upright), is passed through the nerve fibers of the utricular and saccular nerves to the upper part of the vestibular ganglion (scarpae). There is another nerve that runs from the saccule to the inferior vestibular ganglion. A nerve also comes out of all the cristae. The frontal and lateral ampullar nerve runs to the upper edge of the vestibular ganglion. The posterior semicircular canal releases the singular and ampullar nerves to the inferior vestibular ganglion. The nerve cells of the second neuron are situated in the vestibular ganglion. The fibers of the vestibulocochlear nerve (pars vestibularis superior, pars vestibularis inferior, pars cochlearis) rotate slightly before entering the brain stem. The individual fiber bundles can be identified around the fundus meatici acustici. A number of the many anastomoses can be found between the pars vestibularis superior and the intermediate nerve, as well as the top part of the saccular and intermediate nerves. In addition to the afferent fibers, there are also efferent pathways in the vestibular nerve. The nerve endings spread in the vestibular organ in no specific manner and connect to both type I and type II cells. It is suspected that the efferent fibers are responsible for minute adjustments of the vestibular organ [10], [14].

The most important structure of the vestibular system, the VOR, is responsible for transmitting information from the labyrinth (semicircular canals, otolith organs on both sides) over the vestibular nerve, the vestibular nucleus, the vestibular area of projection in the brain stem (fasciculus longitudinalis medialis, brachium conjunctivum, ascending Dieter's tract) to the nucleus of the eye muscle nerves via the so-called „three neuron arc" (N. trochlearis, N. oculomotorius, N. abducens). The paramedian pontine formatio reticularis (PPRF) is an important centre for eye movement and controls, for example, horizontal saccades by means of pre-motoric burst neurons with monosynaptic axons to the abducens nerve. The VOR is also responsible for visual stabilization. Images are simultaneously reproduced on the same parts of the retina during all bodily movements. Other pathways lead to the vestibular cortex (spatial orientation and perception) as well as to the vestibulospinal pathways (postural regulation) [5], [15].

Recent studies using functional magnetic resonance imaging and positron emission tomography post visual and vestibular stimulation of the brain centre have been able to demonstrate that different stimuli are processed centrally and in an intersensoric manner. Vestibular stimulation (thermal stimulation) resulted in signals to the parieto-insular areas (parieto-insular vestibular cortex). Activation of the visual system leads to a reduction in circulation in the post-insular cortex. When the vestibular system was stimulated, the visual cortex was partially deactivated. This so-called reciprocal inhibitor interaction between the visual and vestibular systems is said to serve an important function for processing conflicts caused by different sensory inputs [16], [17], [18], [19], [20], [21], [22]. It is therefore likely that such mechanisms could also play a role in vestibular compensation.

Balance disturbances are a result of lesions in the structures of the vestibular system and lead to a disruption of the vestibular function's balance. The VOR operates at three levels, sagittal (pitch), frontally (roll) and horizontally (yaw). Well-defined topical function disturbances sometimes determine certain nystagmus direction. This clinical allocation of eye movements and types of injury was primarily developed for central nervous syndrome (brain stem lesions) and also aids in diagnosing disturbances of the labyrinth (e.g. benign paroxysmal positional vertigo) [5], [15], [23] (Figures 2a, b (Fig. 2)). Pathological eye movements in the *pitch plane* are due to bilateral pontomedullary, pontomesencephalic and flocculus damage. Vestibular syndromes in the *roll plane* represent unilateral damage to the ascending pathways (of the semicircular canals and otolith organs). Disturbed eye movements in the *yaw plane* can be caused either by unilateral lesions around the entry area of the vestibular nerve into the brain stem, by damage to the central and/or upper vestibular nucleus, or by the parapontine formatio reticularis [5], [15], [23].

Endolymph and perilymph have roughly the same specific weight and are under the same amount of pressure which is influenced by the subarachnoid space. This is located very close to the labyrinth. The cochlear aqueduct provides a connection between the perilymph and subarachnoidal spaces, formed during ontogenesis. In adults this connection is closed. Communication between the perilymph and the subarachnoidal space above the cochlear aqueduct plays a role in perilymphatic hypertension [24]. The hypothesis of an interlabyrinthine connection between the perilymph spaces of both ears via the perineural lymph sheath has also been discussed for some time ("Schreiner-Effect", sympathetic

cochleo-labyrinthitis) [25], [26].

The vestibular aqueduct leads the endolymph canal (endolymphatic duct). This is formed by a joining of the utricle and saccule passages. The distal endolymphatic sac lies beneath the dura mater of the posterior cranial fossa. It forms a roughly 10mm intracranial extension of the membranous labyrinth. Functionally significant characteristic epithelia can be found in three areas: the pars rugosa, the pars intermedia and the pars lateralis of the endolymphatic sac. Transport movements between the endolymph and perilymph spaces result in volume shift and liquid flow. There are various functions carried out by the endolymphatic duct and sac, such as regulation of volume and flow (valve system), resorption of the endolymph, secretion, as well as immune processes in the inner ear (pars rugosa) [11], [27], [28]. An ectactic or obliterated duct may be present, for example, in the case of endolymphatic hypertension.

2.3 Vestibular diagnostic

Labyrinthine and neurogenic disturbances of the vestibulocular reflex can now be diagnosed thanks to modern techniques. Due to their central position, the otolith organs are more often affected by a range of functional disturbances than the cristae. Indications, for example, for the insertion of tympanic tubes, exploratory tympanotomy and niche covering, as well as endolymphatic shunt surgery can only be conducted once the complete neurootological diagnostic and sub-classification of labyrinth disorders have been exhausted.

Static tilt and excentric rotation, caloric assessment in both pronation and supination positions using video nystagmography and assessment of the subjective vertical all enable the unilateral assessment of the macula function [29]. Modern thermal stimulation methods (e.g. Infrared stimulation) make the diagnostic process more targeted, does not involve contact, can be more optimally dosed, and is silent and generally more comfortable for the patient. In addition the uncomfortable phenomenon of cooling due to evaporation is avoided [30], [31], [32].

Modern rotational testing can assess the cristae dependent (frequency selective rotation pendel test) and macular dependent vestibuloocular reflex (OVAR). Vestibular evoked myogenic potentials (VEMP) can be derived through the averaged EMGs. These can be allocated to the saccule function.

High resolution computer tomography is suited for diagnosing labyrinth anomalies and neoplasia. Fibrosis of the endolymphatic and perilymphatic spaces can be viewed using magnetic resonance imaging and maximum intensity pixel projection. Three-dimensional images make it easier to spatially assess the findings.

Many diseases affect labyrinth function gradually, beginning with the otolith organs and moving on to semicircular canal function. Therefore, it is recommended that tests be repeated over time and their findings compared, especially when assessing certain, in particular pressure-related, labyrinth function disturbances [29]. Diagnostic methods including reviews are also necessary in order to objectively assess the success and quality of therapy in individual cases.

Examination of the vestibuloocular reflex has been improved over the past decades with a new generation of three-dimensional video nystagmography, which, in the future, could contribute to the differential diagnosis of vestibular disturbances.

3. Acute unilateral vestibular disorders

3.1 Diagnosis and causes

In the majority of cases of a sudden onset of unilateral labyrinth disturbance we are actually looking at an idiopathic loss of vestibular function. The synonyms "acute isolated loss of vestibular function", "vestibular neuritis" and vestibular neuropathy are actually used to describe one and the same thing in clinical practice. They are, however, generally considered etiologically unclear diseases.

It is relatively easy to diagnose loss of vestibular function. In the early phase there may be intermittent or sudden vertiginous symptoms with primarily horizontal spontaneous nystagmus, a lateropulsion

towards the affected side together with vegetative symptoms (Figure 3 (Fig. 3)). The Halmagyi-Curthoys test is suited for screening to assess whether unilateral labyrinth function disorders are present (testing of the horizontal VOR). The examiner holds the patient's head with both hands while he/she fixes on a point near by. A series of rapid horizontal head movements follow (3000 to 4000 °/s) to the left and right (10 to 20 degrees). An undisturbed horizontal VOR is shown through rapid compensatory eye movements in the opposite direction of the head's rotation. A pathological horizontal VOR (e.g. in the case of unilateral vestibular disorders) is shown through the eyes remaining positioned in the opposite direction (correction of gaze direction through refixation saccade) [33].

Various forms of *neurogenic lesions and labyrinth disorders* have been described. A complete "failing" of the vestibular organ is not the case in the majority of patients. More often, we are dealing with a lack of thermal stimulation of the lateral semicircular canal; its caloric response in practice is wrongly extrapolated onto the entire vestibular organ. In such cases we are likely to see a type of disorder which includes an isolated lesion of the vestibular nerve's pars superior, which supplies the lateral and anterior semicircular canals, the utricle as well as parts of the saccule. Singular disorders of the vestibular nerve's pars inferior with selective failure of the posterior semicircular canal [34] combined with a functional disorder of the posterior semicircular canal and the cochlea [15] can also found described in the literature as a form labyrinthine vestibular dysfunction. In addition to impairment of semicircular function, dysfunction of the otolith organs can often be observed in the case of vestibular failure [35].

In the case of *vertebrobasilar vascular processes*, 60% of patients will suffer isolated vertiginous symptoms as a precursory symptom [36], [37], [38], [39], [40], [41]. Vertebrobasilar vascular processes should also be considered as the cause of vertiginous episodes in elderly patients when the indication is an apparent classic case of vestibular failure. The therapy of choice for intracranial vascular occlusion in the vertebrobasilar circulation is anti-coagulation. Stenosis of the branches of the vestibular artery can be dealt with surgically. Percutaneous transluminal angioplasty is another possible treatment for extra- and intracranial stenosis of the large vertebrobasilar vessels [39].

A further well known cause of vestibular failure is *blunt head trauma involving the inner ear* (labyrinth contusion). This results in hemorrhage or micro fissures in the labyrinth. It is recommended to use cortisone therapy in the early phase (150 mg over 3 days, then decreasing orally) [42]. In addition to resulting from trauma, isolated hemorrhage in and around the labyrinth can also occur spontaneously. In MRI T1 weighted sequence a signal enhancement of the labyrinth prior to contrast application can be observed [43], [44]. Scherer and Helling suspect that a *spontaneous detachment of the cupula from the ampulla wall* may be the cause of vestibular failure. Because differences in the structure of the cupulae of the three semicircular canals have been proven, this could be an explanation for varying courses. Animal models were able to demonstrate vestibular failure by detaching the cupula of the lateral semicircular canal in pigeons [45], [46], [47].

In addition, there is evidence that the so-called vestibular failure is linked to a *viral infection*, thus justifying the term "vestibular neuritis". Herpes simplex virus type 1 (HSV 1) especially, which can latently infect the ganglia of the vestibular nerve, is considered to play a role in reactivation [15], [48], [49]. Contrast enhancement of the inner acoustic canal has also been described, which is considered an indication for a suspected viral infection of the vestibular ganglion (ganglionitis, neuritis) [50]. Other studies, however, were not able to demonstrate an inflammation related enhancement [51]. Serological examinations have also failed to show clear and uniform results [52], [53]. There are signs that the varicella zoster virus (VZV) might be involved in recurring vestibular failure [53].

In addition to disturbances of the microcirculation and viral infections of the labyrinth, autoimmune disorders are also being discussed as possible causes [42].

In many cases of acute unilateral vestibular disorders we can often see a return of thermal stimulation. The percentages published in the literature vary somewhat. Haid and Mirsberger found a return of thermal stimulation of the labyrinth in 57% of cases (n=47) [54]. After an initial complete failure of thermal stimulation, 75% to 81% (n=252) of patients showed an increase after various therapy methods were applied [55]. Herzog and co-workers observed a normalization of vestibular function after acute labyrinth dysfunction in 46% of cases (n=79) up to four months after the acute event [56].

3.2 Medical therapy

Independent of the above discussed causes, it is recommended that the early phase of acute vestibular failure should be treated with electrolyte substitution, as well as therapy involving antimetica, antivertiginosa (e.g. dimenhydrinate i.v. or suppository for a maximum of three days) and glucocorticoids (100 mg Methylprednisolone in reducing doses for one to two weeks) [15]. In addition, we treat the early stages with blood flow enhancing medication [42]. Some authors regard this therapy as ineffective [15].

In the case of viral related diseases, virostatics in combination with glucocorticoid are a causal treatment approach. The antiviral, virostatic efficient medications which can be administered and purchased are only effective if the virus has reached the extracellular space in the sense of reactivation and reproduction. A recent study has shown that administering methylprednisolone does contribute to a significant improvement of vestibular function in the case of vestibular failure, whereas administering an antiviral medication does not (valacyclovir) [57]. Local application of medications (e.g. gancyclovir) through a special tympanic tube (MicroWick®) is currently being discussed in the literature as a possible future therapy when the unilateral vestibular disturbance is clearly related to a viral infection [58].

Administering a fixed combination of cinnarizine (20 mg) and dimenhydrinate (40 mg) has resulted, after only one week, in a greater reduction of acute vestibular vertiginous disturbances compared to a monotherapy with these same medications [59]. According to a recent study, cinnarizine, dimenhydrinate, and also Beta-histine only affect vigilance slightly [60]. In a randomized double blinded study, significant improvement in acute vertiginous disturbance was shown [61].

3.3 Vestibular compensation

Mechanisms of vestibular compensation will follow all cases of damage to the labyrinth, provided the central nervous system is able carry out such a function. Vestibular compensation is a plastic neuronal, central process, dependent on both time and age, and involving various sensory modalities. Changes to the sensitivity of the primary vestibular sensory cells in the inner ear through the ipsi- and contra laterally running efferent fibers of the vestibular nerve are said to influence this process considerably [14]. Vestibular compensation is aided by a special vestibular *training*, something which has been proven in animal models, leading to the recovery of the disturbed tonus balance following a unilateral lesion of the vestibular organ [14], [15], [62], [63].

As early as 1964, Gramowski remarked on the importance of habituation during the rehabilitation of vestibular disturbances. He recognized in the phenomenon of habituation a change in the regulating range on different level of sensitivity. Repeated stimuli in short intervals translate into a „central process", which in turn reduces the stimulated response and minimizes the reaction (habituation). In patients with a unilateral vestibular lesion, this minimized reaction translates to an increased capacity when the vestibular system is challenged [64].

Vestibular compensation is carried out in phases and takes, in the case of continuing loss of thermal stimulation response of the lateral semicircular canal, several weeks. The most effective physical therapy for training central vestibular compensation is the gradual, systematic and individual search for situations which, in effect, will involve the entire vestibular system (conflict identification) [65]. The early use of antivertiginosa following labyrinth disturbances is not recommended because they can delay the process of vestibular compensation [15], [66]. Curthoys and Halmagyi have appropriately described this period as a "critical phase" [67], [68]. Subsequently, active head movements can be carried out to encourage vestibular compensation. In a further phase, the vestibulospinal and vestibulocerebellar connections can also be activated through fixation and directional motor activity.

The purpose of this particular physical therapy is to encourage the readjustment of the vestibulo-ocular reflex. Due to the plasticity of the central nervous system it is indeed possible to reorganize the vestibulo-ocular reflex [69].

Based on Cawthorne, Cooksey and Sterkers' work, Hamann developed a training program in the 80's

which lead to an improvement of roughly 90% of vertiginous disturbances. A range of other, more complex physical training programs can be found in the literature [70], [71], [72], [73], [74], [75], [76].

Vestibular compensation in patients' thermally proven recovery of labyrinthine function has more success through the application of training programs with a gradual increase of the challenges placed on the body's sense of balance than those without such features [77], [78].

Animal models were able to show a positive influence of glucocorticoids on compensation [79]. According to current understanding, glucorticoids are also likely to encourage compensation in humans following a unilateral labyrinth lesion [15], [57]. Caffeine and amphetamines are said to play a similar role [66], [78]. In animal models, it was shown that alcohol, diazepam and phenobarbital have a negative effect [15].

Scherer makes the distinction between five stages of compensation following an acute unilateral vestibular lesion [14]. The compensation process can be a rapid one, being completed in just a few weeks. However, it may also take months or even years to complete and remain at the incomplete compensation stage (partial compensation). The reason why some compensation remains incomplete within the expected period is not fully understood. A delayed or incomplete compensation has been noted in patients suffering a combination of disorders of the vestibular system, for example simultaneous functional disturbances of the labyrinth, the central nervous system and the occular, as well as in those under the influence of alcohol [80], [81]. The cervical spine should also be taken into consideration as a possible "disturbing factor". Such influences will be discussed in another paper contained in this volume. In the case of an incomplete compensation process and the suspicion of multitopical disorders, it is necessary to carry out a multi-disciplinary vertigo diagnosis, in order to research possible alternative therapies. Otherwise, a different form of rehabilitation, based on Stoll's assessment criteria, may be necessary, such as looking for alternative employment [82], [83], [84]. There are various diagnostic methods available for assessing the effectiveness of vestibular compensation, for example following unilateral vestibular disorders. We use the frequency selective rotation pendle test with a frequency of 0.01 to 0.16 Hz [85]. This allows us to objectively assess the involvement of the vestibuloocular reflex because the test is very similar to everyday patterns of movement [86]. In addition, we also recommend posturografic and stabilometric processes.

4. Benign paroxysmal positional vertigo

4.1 Causes

Otoliths are composed of calcium carbonite crystals embedded in a protein matrix. They have a characteristic shape and size. Until now, it was not known which factors shaped the particles and controlled their size. Recently, a gene has been identified in the zebra fish which has been characterized as necessary in forming the otoliths in fish. The genetic product Starmaker has been identified as the component of the organic protein matrix of the otolith. It has been proven that changes to the shape of the otolith can result from a gradual reduction in the activity of the starmaker gene. Such morphological changes to the otolith (from rounded to star-shaped) are caused by a change in the lattice structure of the otolith. A reduction of the concentration of the starmaker gene will also result in a strong and uncontrolled growth of calcium carbonate crystals [87].

According to other animal models, the growth and number of otoconia should be completed by birth, after which it appears that no new otoliths are formed [88]. In the course of time, especially during middle age and later years, it is thought that their number reduces, especially in the saccule [89]. The dark vestibular cells, which are also responsible for endolymph production, can apparently absorb calcium ions which are set free. It is therefore assumed that they are also involved in the resorption of degenerated otoliths [90]. Proof of a calcium turnover allows us to assume a dynamic process involving not only the regeneration of the otoliths, but also their break down. The ability of the otoliths to reabsorb the calcium ions decreases with age [91], [92]. A spontaneous recovery from benign paroxysmal positional vertigo seems to be more common than initially thought; something which has been confirmed in a series of observations [93]. Roughly a third of people over 70 have experienced such symptoms at some time [15]. An explanation for this is the ability of the endolymph to reabsorb

otoconia debris [94]. It is currently not possible to fully intervene pharmacologically in this as yet only partially understood metabolic process.

Lindsay and Hemenway have reported of several patients whose symptoms of a benign positional vertigo have occurred predominantly on the side of the primary lesion within days or months following an acute isolated vestibular failure. The disease is now often referred to as the Lindsay-Hemenway-syndrome [95], [96]. We have been able to observe spontaneous, reversible symptoms of benign positional vertigo, which mostly does not need to be treated, roughly ten days after the early stages of acute vestibular failure. Whether these symptoms are due to inflammation or a virus remains to be explained.

Parnes and McClure, as well as Welling, were able to intraoperatively observe particles in the posterior semicircular canal ("free-floating particles") during occlusion surgery on the posterior semicircular canal ("canal plugging"), which has expanded and confirmed existing understanding of the clinical picture's pathogenesis [97], [98]. It has, however, not yet been possible, using magnetic resonance imaging, to visualize the particles either in the endolymph tube or cupula during an attack of vertigo.

4.2 Symptoms and variations

The pathophysiological basis for the disease is the dystopic presence of otoliths in one or more semicircular canals. Otolith particles can be present in the semicircular canals as a result of head trauma, degeneration or also as a result of diseases in the inner ear. Patients suffering from benign positional vertigo often have attacks of vertigo during the night while turning or changing position in bed, after lying down or standing up quickly while moving their head [99]. They report severe and „threatening" vertigo of a spinning nature, attacks which increase and decrease, and generally do not last longer than one minute.

There are several variations of benign positional vertigo depending on which semicircular canal contains the free floating otolith fragments on which side. In clinical practice, it is by far most common that only the posterior semicircular canal is involved (roughly 90%), because its caudal crus marks the lowest point of all semicircular canals. Due to gravitational forces, it is easy for the particles from the utricle to end there.

The lateral semicircular canal is affected in fewer cases (5-10%) [93], [100]. Although some authors regard the existence of positional vertigo of the anterior semicircular canal as insufficiently described [101], some case reports do indeed exist. In a study of 122 patients suffering benign positional vertigo, the otoconic deposits were found in the posterior semicircular canal in 110 cases, in the horizontal canal in ten cases and in only two cases were the deposits found to be in the anterior semicircular canal [102], [103].

In addition to the unilateral form of positional vertigo of the semicircular canal, there is also the bilateral variation (especially following head trauma). Although seldom, in practice it is also possible to have the combination of two different semicircular canals affected (after treatment, the otoliths on one side may move from the posterior to the lateral semicircular canal, or vice versa) [93], [104]. This diagnosis can often cause difficulties. However, it is important that it be taken into consideration. When the nystagmus reaction is not typical, it may be the case of an atypical form of positional vertigo, which could be mistaken for benign proxysmal positional vertigo [99], [105], [106], [107].

4.3 Diagnosis

In order to accurately assess and localize a classic case of benign *positional vertigo of the posterior semicircular canal*, it is necessary to carry out a positional test, as described by Hallpike, using Frenzel glasses (in a darkened room). In the case of a unilateral variation of the posterior semicircular canal, it is typical, after a latency of a few seconds, to see torsional nystagmus, not lasting longer than a minute, in the direction of the dependent ear (geotropic) or the affected side. The accompanying vertiginous sensation follows a crescendo-decrescendo pattern. The direction of the nystagmus changes when the patient is returned to an upright position (ageotropic nystagmus). The change in

position should be carried out quickly. Abruptly stopping the head movement increases the possibility of a nystagmus, as well as the intensity of the vertiginous sensation. The Hallpike maneuver, when carried out incorrectly (a lack of or insufficient head rotation before positioning) can mislead by presenting as a bilateral variation of the posterior semicircular canal [108]. It is not possible to continually provoke positional nystagmus in the posterior semicircular canal variation (due to habituation), making it necessary to wait several hours before it can be reproduced. For this reason, the suspicion must remain even if initially there is no proof of positional nystagmus with a positive case history (anamnesis). A fatiguing of the nystagmus can, for example, mean that nystagmus is not present during the diagnosis of attacks of vertigo suffered shortly before [99]. The diagnosis of benign proxysmal positional vertigo must be carried out before any other diagnostic methods of vestibular assessment. In this way, we are able to minimize the effect habituation may have [99], [108]. Because the symptoms are generally more severe on the affected side, this can often be assessed in an explorative manner. The Hallpike test should be carried out on the suspected side first [99].

It is also possible to diagnose benign positional vertigo involving the *anterior semicircular canal* using the Hallpike maneuver. Compared to the posterior semicircular canal, this can show inverted symptoms. The vertical component of the nystagmus is not in a geotrope direction but the opposite (ageotropia). The non-dependent ear is subsequently affected.

The rarely benign positional vertigo involving the *lateral semicircular canal* presents certain peculiarities. Symptoms are provoked through head rotation along the body's longitudinal axis in a supine position. It is diagnosed by laying the patient on her back and rotating the head and body quickly along the body's longitudinal axis (roughly 90 degrees) in the direction of the side where the lesion is suspected. If the particles are situated in the endolymph canal of the lateral semicircular canal (canalolithiasis), a purely horizontal nystagmus in the direction of the affected ear will result. Compared to the variation affecting the posterior semicircular canals, the intensity of the attacks in this case will be stronger and the latency shorter. In addition, the tendency for fatiguing is either not present or reduced. When the variation affecting the posterior semicircular canal is suspected, it should always be checked before the lateral [93], [99], [100], [108]. If the otoconia are situated directly on the cupula instead of moving freely in the endolymph tube, the examiner will be faced with an ageotropic nystagmus on the side of the lesion. A good rule of thumb is always to assess the side of the disturbance based on where the greatest intensity of the nystagmus (and vertigo) is. A right cupulolithiasis (geotropic nystagmus) and a left canalolithiasis (ageotropic nystagmus) in the lateral semicircular canal would therefore result in maximum nystagmus intensity on the left side. We are obviously dealing with a conglomerate of particles (canalith jam). Small particles are said to be expelled from the semicircular canal during head movements. The more forceful intensity of nystagmus in this form can primarily be related to the greater sensitivity and enhancement of the horizontal vestibuloocular reflex [108], [109].

In addition to canalolithaisis and cupulolithiasis, it is also possible to encounter the so-called „otolith jam" in every day practice; in other words, a blockage of the canal or cupula (canalith jam) (Figure 4 (Fig. 4)). Epley has described the respective diagnostics and therapy in detail [110].

4.4 Physical therapy

Physical therapy procedures, or so-called „maneuvers" have been developed for all forms of benign paroxysmal positional vertigo. The aim of each of these treatments is to redirect these „lost" particles from the semicircular canals to the utricle. The treatment uses the forces of acceleration and gravity.

The Semont or Epley maneuver can be applied when the *posterior semicircular canal* is involved [111], [112]. The Semont maneuver („liberatory maneuver") uses primarily acceleration (rapid, abrupt passive head and body movements) as well as gravitational force („liberatory maneuver"). In comparison, the Epley maneuver is a „repositioning maneuver" which primarily uses gravity to „move" the otolith particles out of the semicircular canals. Acceleration is employed only moderately in this method. In the vast majority of cases, both techniques result in a rapid and impressive therapy for the patient. Extreme vegetative reactions can, in some cases, create difficulties and delay the therapeutic process. We prefer the Epley maneuver (Figure 5 (Fig. 5)).

The Semont maneuver is carried out in the following steps:

1st step: Patient sits on an examination bed in front of the doctor, head is turned 45 degrees towards the healthy side, the affected ear is facing the examiner, who holds the head.

2nd step: Abrupt side-ways positioning in the direction of the affected side. The patient's head, still held by the doctor, should rest on the occiput, ideally stretching over the edge of the bed (105 degrees). After a latency period, nystagmus will appear (as in the case of the Hallpike test) in the direction of the dependent ear. Duration: roughly 3 minutes.

3rd step: Rapid side-ways positioning (195 degrees) to the other side. The nystagmus is now in the opposite direction (towards the non-dependent ear). Duration: roughly 3 minutes.

4th step: Quickly sitting up again. Duration: until dizziness stops.

The success rate for this method of treatment is very high. Only a few patients need to be treated more than twice. Relapses do, however, occur. Although extremely seldom, in practice it is possible to encounter resilient therapeutic cases which can then be treated surgically. It is controversial whether head shaking or oscillation, as used by Epley in his initial description, is able to increase the rate of success [113], [114]. The success of the therapy should be assessed some days later using the Hallpike maneuver.

The Brandt-Daroff maneuver is ideal as an initial therapy [115]. Using this technique, the authors have been able to cure 90% of patients after a 14 day therapy.

A modified form of the Semont or Epley maneuver can be used as a physical treatment for benign positional vertigo of the *anterior semicircular canal.*

Canalolithiasis or cupulolithiasis of the *lateral semicircular canal* can be treated using various positioning techniques [116], [117]. The Vannicchi's so-called prolonged positional maneuver is an involved procedure, in which the patient lies on the healthy ear for 12 hours. A success rate of over 90% was achieved using this technique. However, there have been cases reported of conversion in variations involving the posterior semicircular canal [116]. Another procedure is described by Epley and involves a log rolling rotation along the body's longitudinal axis (360 degrees). The patient is „rolled away" from the affected ear in 90 degree stages [110]. This method also makes use of gravitational force („repositioning maneuver").

It is interesting that many patients suffer a vertiginous sensation for hours or even days following a successful positioning maneuver, which is similar to an otolith vertigo and substantially different from positional vertigo. Empirical studies have shown that antivertiginous therapy can reduce the symptoms [99].

Benign positional vertigo can be treated using repositioning and liberatory maneuvers entirely on an outpatient basis. This is a very efficient form of neurootological therapy. It is not recommended that further diagnostic tests be carried out once the therapy has been successful. Instructions, such as sleeping with the head elevated, following treatment do not influence the success of the therapy [118].

4.5 Surgical therapies

Rarely is there an indication for the surgical treatment of benign positional vertigo, and it remains reserved for cases which have proven to be resistant to other forms of therapy [99], [119]. It should only become an option once physio-therapeutic rehabilitation has not succeeded and once other, more seldom, forms of benign positional vertigo have been ruled out, including other differential diagnoses. It may be necessary to carry out imaging studies in order to exclude central disturbances (tumors) [99], [120]. One of the rarer differential diagnoses is, for example, vestibular paroxysm.

Singular nerve section is said to be an effective surgical procedure for selectively ablating the function of the posterior semicircular canal [121], [122]. This nerve, coming from the inferior vestibular nerve, can be exposed and sectioned transtympanally at the lower edge of the round window [119]. Anatomically, the singular nerve is an accessory nerve from the posterior crista ampullaris, which transects its own bony canal, and which joins the sacculo-ampullar nerve some millimeters after the inferior saccular nerve and the posterior ampullary nerve join. The nerve cells can be found in the

inferior vestibular ganglion [24], [120]. A complete sensory block would require the section of the posterior ampullary nerve. Examination of petrosal bone specimens have demonstrated that it was possible to easily reach the singular nerve transtypanically for neurectomy at the lower edge of the round window in only a fifth of cases [123]. It is therefore sometimes necessary to drill and „open" the round window niche. The procedure can also be carried out using laser surgery (Argon laser), during which the nerve is ablated [124]. This procedure, however, still remains uncommon. A decisive disadvantage to this method is that it can result in some degree of hearing impairment [125]. For this reason, *occlusion surgery* is preferred. Plugging the posterior semicircular canal can also be carried out using either conventional surgery or laser techniques [93], [126], [127]. Parnes and McClure developed the concept of occlusion surgery of the posterior semicircular canal [127], [128], [129], which involves fenestration of the posterior semicircular canal via a mastoidectomy and blocking the lumen with bone pate` and fibrin glue. The result is an obliteration of the endolymphatic tube and a „fixing" of the cupula. Strutz and Menke have tested various materials for blocking the semicircular canal in animal models. Teflon and titanium have proven ideal and lead to a strong induction of connective and bony tissue within the semicircular canal [130]. All patients undergoing the surgery will suffer a period of four to six weeks post-operative with vertiginous disturbances. It is therefore also recommended that these patients undergo training therapy to assist compensation. Possible complications include the development of a temporary or permanent hearing impairment, a perilymph fistula or labyrinthitis [126], [131]. Other studies have confirmed the low rate of complications coupled with a high success rate of this surgical procedure - a treatment which we have found to rarely be indicated [131]. This makes it a better choice than the neurectomy of the singular nerve. References to the bilateral occlusion of the posterior semicircular canal and plugging of the anterior semicircular canal can also be found in the literature [126], [132].

In fact, *laser assisted posterior semicircular canal plugging* was found to be the better choice in a study comparing conventional surgical occlusion of the posterior semicircular canals [133]. The procedure is based on studies carried out by Wilpizeski and Anthony [134], [135]. Both Argon and CO_2 laser systems are suited for the obliteration of the endolymphatic tube [136], [137]. Argon laser obliteration of the endolymphatic tube histologically assures fibrosis and subsequent ossification of the lumen of the semicircular canal [136]. *Maculectomy of the utricle (selective laser labyrinthectomy)* is also referred to in the literature as a possible treatment for benign positional vertigo [137].

Although rare, benign proxysmal positional vertigo can also affect children aged between one and four years of age [138]. A form of migraine (without headaches) has been discussed as one possible cause [139], [140], [141]. Hamann has observed episodes of vertigo in childhood, which he was clearly able to differentiate as benign paroxysmal positional vertigo and not vertigo associated to migraines [142].

4.6 Facts from evidence-based medicine

Although few in number, the facts resulting from a research of evidence-based medical sources regarding benign positional vertigo are interesting.

Today, the diagnosis of "benign paroxysmal positional vertigo" involves a clearly defined disease, with equally well designed clinical tests, and quick and easy treatments which can be carried out in less than five minutes. Diagnosis is only difficult and complicated in the exceptional case. The term „benign" is generally justified with a few exceptions which are secondarily diagnosed (so-called malignant paroxysmal positional vertigo in the case of central lesions, "pseudo-benign paroxysmal positional vertigo" in the case of cerebellar disorders, difference: there is generally no habituation) [143], [144], [145], [146]. The prognosis for traumatic or labyrinthitis induced benign variations of positional vertigo is worse than those resulting from Menière's disease [147].

Based on an analysis of all studies carried out until January 2004, the Epley maneuver seems to be the most secure form of treatment from an evidence-based point of view [148]. Within a period of three months following treatment, repositioning maneuvers resulted in a greater level of comfort for patients compared to those who had not been treated [149]. Compared to those patients who were treated, untreated patients' symptoms improved when they avoided body positions which could provoke attacks. Many of the untreated patients still had a positive Hallpike maneuver after several weeks [150].

A treatment for benign positional vertigo based exclusively on antivertiginous medication has been assessed as ineffective and we would go so far as to say it is contra-indicated. Self-treatment (e.g. the Brandt-Daroff maneuver) is recommended in evidence-based sources [151]. Misdiagnoses and inappropriate therapeutic strategies for treating benign paroxysmal positional vertigo result in unnecessarily high costs (according to a US study from 2000 over $2000) [152].

5. Menière's disease

5.1. Differential diagnosis and treatment options

The understanding of what illness exactly lies behind the words "Menière's disease" has decidedly changed over the past decades. 100 years ago, the term "Menière's disease" was used to describe a number of diseases involving the triad vertigo, tinnitus and hearing loss, which cannot be clearly allocated etiologically. Over time, several differential diagnoses were viewed individually and today have clearly been separated from Menière's disease. It is still possible, however, that sudden attacks of vertigo, hearing loss and tinnitus appearing simultaneously can cause differential diagnostic difficulties.

The primary symptom of Menière's disease is sudden attacks of vertigo, which also create the greatest impairment for the patient. Stoll has observed 15 patients over a period of 10 to 15 years and, based on the vertiginous attacks, was able to identify four types:

• regressive type: as the disease progresses the attacks become less intense and less frequent (20%),

• variable type: frequency and intensity of attacks vary in intervals (13%),

• progressive type: monosymptomatic beginning, increase in frequency of attacks, then developing into a fast or slow type 1 (27%) and

• periodic type with attack-free periods (40%) [125].

The classic triad was only observed in a fifth of cases. The different types point to a high variability of the clinical picture. This leads to questioning of the nosological unit of the disease and to the suggestion that the term "Menière's syndrome" might be more appropriate than „Menière's disease" [153].

It can be problematic deciding which therapy to adopt due to the fact that symptoms come in cycles and that, especially during the early stages of the disease, it is difficult to make a prognosis regarding the development of the disease [154]. Generally, there is the danger that a unilateral manifestation can later develop into a bilateral disease. In the literature the frequency of such cases is reported as being extremely variable between 2% and 47% [119], and in some studies from 15% to 50% [155].

Recurring low-frequency hearing loss is rarely the first sign of Menière's disease (3.7%, n=27; five year period of observation) [156].

Immunological hypotheses regarding the etiology of Menière's disease support therapy with steroids [157], [158]. As part of the MALT system, the endolymphatic saccule is able to react immunologically ("inner ear tonsil") [158], [159], [160]. Vascular causes [161], a viral infection (herpes simplex virus type 1) [162], [163] and hereditary factors are also discussed [164].

A pressure-sensitive, calcium dependent potassium channel in vestibular hair cells has recently been proven. Changes in the hydrostatic pressure of the endolymph, such as in the case of endolymphatic hydrops, is said to increase potassium efflux and subsequently the spike frequency of the vestibular nerve on the affected side. This would also explain the stimulated nystagmus in acute episodes. Modulation of the calcium influx affects the voltage in the pressure sensitive channel [165], [166]. In the future, calcium antagonists approved for treating vertigo and vestibular disorders (e.g. flunarizine, cinnarizine), may possibly be used to treat attacks [167].

The differential diagnosis of Menière's disease currently profits from new imaging studies which have decidedly influenced therapeutic decisions [168], [169]. This enables the diagnosis of rare disorders such as neurovascular compression around the cerebellopontine angle (vestibular paroxysm) [170].

Directives for the diagnosis and assessment along the lines of study results should be based on the criteria stipulated by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) [171].

5.2 Medical therapy

The medical treatment of Menière's disease includes treatment of attacks as well as prophylaxis [172], [173]. A causal therapy is currently being actively researched.

Attacks can be treated using antivertiginous medication (e.g. dimenhydrinate, orally or as a suppository). Self-treatment is possible for vertiginous aura attacks.

Calcium antagonists block the voltage dependent calcium influx channel of the vestibular hair cells and are likely to subsequently stop the increased potassium efflux during repolarisation in acute attacks [174]. In practice, a combined preparation (cinnarazine 20 mg with dimenhydrinate 40 mg) has proven effective in treating attacks. The fixed combination of cinnarizine and dimenhydrinate is, according to evidence-based criteria, a safe and effective method for treating acute episodes of Menière's disease [175].

The effectiveness of betahistine (H1 antihistamine) as a *prophylactic against further attacks* is based on its H1 receptor agonism and an H3 receptor antagonism. It has, however, virtually no effect on H2 receptors. The effectiveness is based on an increase in the microcirculation within the inner ear [176]. It has also been described as having an influence on central vestibular neurons [177]. It has been proven that betahistine has a positive effect on the frequency and intensity of vertiginous attacks of Menière's disease. The quality of many studies, however, has been rightly criticized [178]. An advantage is the fact that betahistine appears to have few side-effects and is said to even encourage vestibular compensation [179]. Betahistine can be prescribed long term in the dose recommended by the manufacturer (3x8 mg to 3x16 mg). According to our experience, the dosage may even be increased when the therapy does not achieve the expected success (it is necessary to inform the patient, off label use, take care: in case of bronchial asthma contra-indicated). Brandt et al. recommend 3x12mg to 3x24 mg betahistine over a period of 4 to 12 months. When this therapy fails, therapy may be continued with diuretics (hydrochlorothiazide and triamterene) [15], [180], [181]. Hydrochlorothiazide and triamterene, however, only have a proven positive effect on the vertiginous symptoms and not on the hearing loss [180]. According to Vollrath, low-frequency hearing loss with an increased SP/AP ratio responds better to a dehydration therapy (mannitol and acetacolamide) than rheological treatment. If the vasoactive therapy fails, it may be possible in some cases to achieve an improvement of the hearing threshold with diuretics [182].

The dehydrating effect, resulting from glycerol with the Klockhoff test, seems to primarily have a positive effect on hearing. Acetacolamide can be administered as a mono-therapy (20-25mg/d) [181]. Corticosteroids are used based on the immunological etiology of Menière's disease. It can be administered in various ways with decreasing doses and usually in combination with other medications. [183], [184]. In the case of inner ear disturbances including Menière's disease, and based on the results of a study of the cortisol level of the perilymph, Niedermeyer et al. recommend administering 250 mg prednisolone intravenously [185].

Vasoactive substances are said to improve the cochlear blood flow [181]. Changes in diet (low-sodium diet, avoiding caffeine) can in some cases lead to an improvement.

5.3 Intratympanic application of medication

5.3.1 Aminoglycoside therapy

After the development of streptomycin in 1944, symptoms of vertigo and especially hearing loss were reported as disturbing and unwanted side-effects of the treatment for tuberculosis [186]. The idea of using the unwanted side-effects of aminoglycoside treatment therapeutically came about after it was objectively proven that this antibiotic was able to cause a disturbance in labyrinthine function [187], [188]. In 1948, Fowler was the first to systematically administer *streptomycin*, for the treatment of vertigo and vestibular disturbances [189]. Schuknecht used it in 1956 to treat Menière's disease.

Instead of administering the antibiotic intravenously, he injected it twice daily intramuscular. A year later, Schuknecht was the first to describe the intratympanic use of streptomycin sulfate [190], [191]. However, neither the intravenous nor the intratympanic application will lead to the desired selective vestibular toxicity. *Gentamycin*, developed in 1963, proved to be less cochleo-toxic [192]. The later developed aminoglycosides, amicaine and netilmicin, also had a lower ototoxic potential [193]. In 1966 using animal models, Holz et al. were able to prove that it is possible to protect cochlear hair cells by administering streptomycin simultaneously with ozothine [194]. Two years later, Lange reported on a selective medical ablative treatment of the vestibular organ using streptomycin in combination with ozothine [195]. The intratympanic application of gentamycin was first published in 1976 by Lange, who then went on to develop the procedure which has since been modified by many authors [196], [197], [198], [199], [200], [201]. Gentamycin can be placed in the tympanic cavity using various techniques. Katzke (1982) used a *grommet* and slowly pushed the gentamycin with the aid of a *Politzer balloon* along the auricular canal into the tympanic cavity [202]. *Inserting tubes* into the middle ear and using *infusion pumps* to aid in the application have also been described [201], [203], [204]. It remains unknown how long the medication is in contact with the semipermeable membrane of the middle ear during such forms of intratympanic application. For this reason, a connective tissue plug is placed to *seal off the round window niche* before administering gentamycin [205], [206]. This delays diffusion into the inner ear. Recently, there have been reports on the use of *micro catheters* to assist with the microdosage, which can be placed directly in the round window niche [207]. Whenever a catheter is inserted or similar measures undertaken, the result may be a swelling of the middle ear mucosa and formation of granulation tissue in the middle ear. An additional tympanotomy is said to be particularly damaging, making diffusion of the antibiotic into the inner ear unpredictable. Therefore, Lange prefers the application through a traumatic, simple tympanic puncture at the antero-superior quadrant of the ear drum, based on Tjell's technique. During treatment (in a supine position) the head is turned 45 degrees towards the healthy side in order to achieve a maximum diffusion into the inner ear window [208], [209], [210].

Gentamycin diffuses through the tympanic membrane into the inner ear fluid, primarily through the round window. It is likely that the vascular connections between the middle ear mucosa and the labyrinth also play a role in the transport. Aminoglycosides are highly water soluble, which means they dissolve in the inner ear fluid and thus spread. A further advantage is that they cannot pass the blood-brain barrier. The problem is situated in the dark vestibular cells, which are assumed to be responsible for endolymph production [211], [212], [213], [214].

Ozothinoil protects the inner ear and should be administered roughly 30 minutes before the aminoglycoside. In addition, neurotropic vitamins, vasoactive substances and minerals (magnesium and zinc) are said to protect against damage to the cochlear hair cells. Calcium, as well as magnesium, is seen as able to effectively compete against aminoglycosides [193], [208].

Acute cochlear damage can, with small doses of calcium at the beginning of treatment, be reversible by electrostatically binding the aminoglycosides to the external hair cells [211], [212], [213]. Higher toxic doses can irreversibly damage the external hair cells, which are based on a selectively high binding affinity of the gentamycin for PIP2 (Phosphatidylinositbiphosphate) [215]. A decisive factor, therefore, is the timing of the gentamycin application for the rehabilitation of vertigo attacks. Both location of the application and the dose also play an important role in avoiding irreversible cochlear damage through accumulation or overdose of the medication. The fact that the medication is eliminated renally should also be taken into account [193]. There are currently five types of intratympanic application [216].

• applications several times a day (three doses daily for 4 days or longer) [217],

• weekly applications (a maximum of four doses per week) [218], [219],

• low dose applications (one to two doses, repeated only in the case of further attacks) [220],

• continuous microcatheter assisted applications [207], [221], [222] and

• titrated application (daily or weekly doses until spontaneous nystagmus, vertiginous symptoms or hearing impairment sets in) [223].

In 1991, Magnusson et al. were able to prove that the ototoxic effect only sets in several months later.

They applied the medication for two consecutive days and then ceased treatment. All patients developed vertiginous symptoms but hearing was not impaired [224]. Ödkvist and coauthors recommend therapy in stages. After two doses on continuous days, therapy was discontinued for four weeks when the ototoxic effects set in within ten to fourteen days. Further applications were recommended only if vertiginous symptoms persisted, even when thermal stimulation was still present [225]. Lange et al. recently reported on an intratympanic treatment in intervals, which avoided hearing impairment by administering low doses of gentamycin (titrated application). 0.3 ml of gentamycin sulphate was applied intratympanically on the first day. The injection was repeated on the eighth day provided no reaction had set in (nystagmus or vertiginous symptoms). Treatment was not continued if the patient suffered either subjective or objective vestibular symptoms (nystagmus). If on the 15th day no inner ear symptoms had set in (roughly a quarter of patients), one final treatment is administered and a period of at least two to three months elapses before further treatment is considered. According to Lange, it is possible now to be more generous when assessing indications for Menière's disease. Treatment in the early stages of the disease is possible [226], [227]. The authors would not hesitate in treating the other side when the unilateral treatment was successful [226], [227]. We must ask ourselves the question, however, whether the patient's quality of life will indeed improve with the induction of a bilateral vestibulopathy.

When the degree of toxicity for the inner ear is unclear, therapy should be ceased and the relevant audiological and vestibular diagnostic tests carried out. Therapy should aim to maintain hearing which can respond to rehabilitation [226], [227]. The success of therapy does not depend on the loss of thermal stimulation. It is quite likely that the attacks can cease even when thermal stimulation is still present [226], [227], [228], [229], [230].

In the case of bilateral Menière's disease, Jahnke and Arweiler recommend intravenous applications when the episodes of vertigo are associated with a pancochlear hearing loss of over 40 - 50 dB, when conservative therapies have not been successful, and when a saccotomy is no longer an option. A debatable indication can be the unilateral disease of the last functioning ear. The intravenous dose administered daily was 2x120 mg gentamycin, dissolved in 500 ml Ringer solution, titrated over two to three hours, for a period of five to six days. The success rate was high. Five in every six patients were free of symptoms (period of observation was roughly five years post-treatment). After completion of this treatment, thermal stimulation was also still present. Significant loss of hearing was avoided [205], [206]. Even in the case of residual thermal function, training to encourage central compensation following treatment remains necessary [225], [226], [227].

The success rates for the intratympanic application of gentamycin are high. Küppers reports an 89% success rate (n=28). In over half of these cases, thermal stimulation was preserved [203], [204]. Using the interval therapy, Lange et al. were able to achieve a success rate exceeding 95% (n=57) [226], [227]. In a 2004 published meta-analysis of intratympanic gentamycin therapy (1978-2002, 27 studies, n=980) an average success rate of 90,2% was reported [216]. The best rehabilitation results were achieved with the tritrated application (96,3%). The results of other therapies including the percentage of hearing impairments can be found in Table 3 (Tab. 3).

In a retrospective analysis, Blakley found the success rate for the intratympanic treatment of Menière's disease to be between 78% and 100% (13 studies). The results were not able to clearly recommend one particular treatment. There is also currently no clear consensus regarding dose and method of application [229].

Other techniques involving the combination of aminoglycoside have been mentioned in the literature. Shea and Norris carried out mastoidally a fenestration operation of the lateral semicircular canal (labyrinthotomy) and directed streptomycin into the perilymph. A multi-centre study showed that 80% of patients could be cured of their vertiginous symptoms using this technique. It was, however, necessary to carry out a further treatment in 20% of cases. 57% lost hearing on the treated side [199], [200], [231], [232].

There are only a few studies looking at the long term effects of gentamycin on the crista and macula function based on thermal stimulation and other test methods. Animal models have shown that vestibular hair cells can begin to regenerate as early as 24 weeks after gentamycin was administered [233]. Forge and Nevill have confirmed this result based on their own studies. Regeneration of the

cochlear hair cells, however, was not found [234].

De Waele et al. treated 22 patients with intratympanic gentamycin therapy. Roughly a third of patients had returning function within two years. There were no vertiginous symptoms when a complete loss of semicircular canal function was the result of therapy [235]. In several cases, Westhofen was able to observe a return of otolith function some years after gentamycin therapy [35]. Other authors believe that otolith function vanishes prior to the crista function in gentamycin therapy [225].

An intact otolith function could be the cause of unsuccessful intratympanic therapy. A further possible explanation for an unsuccessful therapy is the partial or complete obstruction of the round window niche in some patients suffering Menière's disease [236]. Despite these arguments and in accordance with the findings of a systematic review conducted by Diamond et al., transtympanic gentamycin therapy remains an effective method of treating the symptoms of Menière's disease [237].

5.3.2 Labyrinth anesthesia

Labyrinth anesthesia is another form of treatment of Menière's disease, based on applying local anesthetic (e.g. lidocaine, xylocaine) to the middle ear [238]. Once it has diffused in the inner ear, the local anesthetic will spread to the melanocytes of the vascular stria and lead to a blocking of the vestibular organ [239]. This both explains vertiginous symptoms following procedures carried out under local anesthetic and warns of caution in the case of defective ear drums. In 1968, Ristow reported an 83.3% success rate (n=12). His patients were intratympanically injected with a mixture of 0.7cm^3 2% tetracaincaine or 4% xylocaine solution with furfuryladenine (kinetin). A worsening or substantial worsening of hearing was registered in 33% of cases two years after treatment [240]. Fradis et al. were able to note a rapid improvement of vertiginous attacks in 82% of cases involved in their trial. [241].

In 2003, Adunka et al. published a retrospective analysis of patients (n=24) suffering unilateral Menière's disease, treated with 4% lidocaine and kinetin. 87.5% of patients reported an improvement in vertiginous symptoms. 66% suffered no attacks of vertigo [242]. Sakata and co-workers also recommended labyrinthine anesthesia based on the positive results of lidocaine on vertiginous symptoms [243].

5.3.3 Glucocorticoid therapy

The development of effective locally applied medications is likely to be the future treatment directions for both Menière's disease as well as other diseases of the labyrinth. There are currently high expectations regarding glucocorticoids. There is, however, still a great deal of problems associated with the exact dose, something which has become the centre of intense work [244], [245]. There are special tympanic tubes (MikroWick®) [246] or microcatheters (RWµCath®) available for application [207], [221], [222], [247], [248]. A catheter can be placed under local anesthesia during a tympanotomy around the area of the round window niche (beware: ossicular chain luxation). The round window niche can be clearly seen and the condition of the membrane assessed using a micro-endoscope. The rest of the procedure is described in the literature. The transtympanic endoscopy allows the correct placement of medication systems [249]. An exact dose can be administered using an external pump.

The round window membrane is permeable for a range of substances: antibiotics, toxins, albumin, oxygen or glucocorticoids [250]. It is assumed that the effect of the glucocorticoids dexamethasone, methylprednisolone and hydrocortisone in the inner ear is conducted through proven receptors [251]. The effectiveness of glucocorticoids in treating certain vestibular diseases ("vestibular neuritis", Menière's disease) has been proven [57], [252], [253], [254]. However, in order to achieve an optimal concentration of the substance in the inner ear fluid, high doses are necessary, which can only be achieved through transtympanic application [245]. Animal models have been able to show that local applications of high glucocorticoid doses through the round window do indeed lead to a high concentration in the perilymph [255]. In one single application over three hours, Bachmann was able to achieve a concentration of 1g/l perilymph which remained effective for roughly 16 hours [245]. Dodson et al. were able to achieve a rapid improvement of the vertiginous symptoms in 54.2% of their patients suffering Menière's disease by transtympanically applying methylprednisolone and dexamenthasone

256]. Barss et al. also reported the successful use of dexamethasone (4mg/ml over four weeks) [257]. Plontke and Salt simulated the corticoidsteroid-pharmacokinetic and were able to prove that the measured drug level in the inner ear could be controlled through a defined contact time in the inner ear. Even small changes to the virtually administered dose caused large differences to the drug level in the inner ear [258]. Differences in the anatomical structure of the middle ear windows play an important role. Variations in the shape of the round window niche can be found in roughly a third of patients [259].

5.3.4 "Osmotic induction"

In 1971, Arslan propagated a therapeutic method which was easily carried out and avoided high surgical risks. The choice of therapy depended on the patient's hearing. He reported 95 cases, in which, after a tympanotomy, he filled the round window niche with sodium chloride crystals. He assumed that this would cause an osmotic imbalance between the endolymph and the perilymph, which would subsequently have an effect on the endolymphatic hydrops. A nystagmus towards the treated ear set in only a few seconds after application. The nystagmus was reversed after 12-16 hours. Vertiginous symptoms disappeared within one to two days after the operation. An improvement in vertiginous symptoms was achieved in over 90% of patients [260]. Although this procedure is clearly effective, it is no longer used in clinical practice.

5.4 Influence on middle ear pressure, -mechanism and -hydrodynamics

Under normal atmospheric conditions, changes in ambient pressure do not affect the inner ear because the ossicle joints act as a protective mechanism. However, inflammation or arthritic changes in the ossicle joints can lead to a hindering of the glide mechanism and, subsequently, to a reduction in the protective mechanism [261]. Unphysiological increases in the movements of the stirrup bone foot plates were induced from experiments under such conditions. Changes in the ambient pressure resulted in repeated (100 µm) changes to the physiological normal entad and ectad movements of the stapes (5-30 µm) in an artificially stiffened hammer amboss joint [261]. In patients with a piston prosthesis after stapes plastic, nystagmus was registered using a tympanometry. Significant vestibulospinal changes have been noted in patients suffering from unilateral Menière's disease following rapid pressure changes (positive-negative pressure). Therefore, depending on pressure, changes in the middle ear mechanism can result in vertiginous symptoms [261], [262], [263], [264].

Due to their aerating function, *tympanic tubes* subsequently have an effect on the middle ear pressure. Several studies have described that „dizziness" as a symptom of Menière's disease improved after a tympanic tube was inserted [265], [266], [267]. Rates of success up to 82% have been reported [268], [269]. A eustachian tube dysfunction, however, is said to be present in roughly a third of patients suffering Menière's disease [270].

A *tenotomy* of the tensor tympanic muscle and the stapedius muscle tendons had a positive effect on both hearing and vertiginous symptoms in patients suffering Menière's disease (n=45). An inflammatory reaction of the tympanic cavity was observed in many patients [271].

In patients with endolymphatic hydrops, *varying ambient pressure changes (positive-negative air pressure application)* have a positive effect on the hydrodynamics of the labyrinth. Both vertiginous symptoms and hearing impairments caused by the disease were improved through controlled changes in air pressure. Recently, a method was developed in Sweden which, in combination with a previously inserted tympanic tube, applies pressure pulses using a maximum of 12 cm/H$_2$0 to the external acoustic canal. It was proven that this therapy significantly reduces the symptoms of vertigo [272], [273], [274], [275], [276], [277], [278].

Treating Menière's disease patients in a *hypobaric chamber* demonstrated that vertiginous symptoms could be influenced according to pressure. There was an improvement in 30% of cases [278].

5.5 Surgical therapy

5.5.1 Non-ablative labyrinth surgery

5.5.1.1 Saccotomy

There are both ablative and non-ablative surgical procedures available for treating Menière's disease. Saccotomy is one of the non-ablative surgical procedures. In 1895, Gruber postulated a hydrops theory regarding Menière's disease which assumed that disturbances in the endolymphatic flow to the endolymphatic sac would lead to an endolymph over-production [279]. Previously it was referred to as "glaucoma of the inner ear" [280]. Portmann assumed that the endolymphatic sac was involved in the endolymphatic pressure regulation. A few years following successful animal models in the 1920's, he successfully carried out the first saccotomy on a human [281], [282], [283]. The purpose of this procedure is endolymphatic decompression. This is achieved either through decompression without incision by mastoidally draining the endolymph, or by opening the saccus subarachnoidally (inserting a shunt valve). In addition, opening up and inserting a strip of silicon creates a larger resorption surface (forming a neosaccus) [284], [285], [286], [287] (Figure 6 (Fig. 6)). Both House and, here in Germany, Plester have modified the saccotomy and saccus decompression thus making it an increasingly popular procedure [288], [289].

The saccus can be reached transmastoidally by identifying and demonstrating the contours of the lateral semicircular canal, the sigmoid sinus and the posterior semicircular canal. The endolymphatic sac can be found medially and dorsally to the posterior semicircular canal in the form of a duraduplicature of the posterior cranial fossa. Before incising the endolymphatic sac, it is recommended that antibiotics be administered, as well as a one off application of corticosteroids [290].

An animated and, in part, emotional debate centering on this method flared up in the 1980's around discussions for and against the various surgical treatments of Menière's disease. During initial analyses, a placebo controlled double blinded study was carried out, in which a group of patients was examined, 15 of which underwent a saccotomy as well as a mastoidectomy. Roughly 70% of patients from both groups reported improvements in vertiginous symptoms. The success of surgery was assessed as being unspecific, causing the authors to term it a „placebo effect". Neurectomy of the vestibular nerve was then suggested as the procedure of choice for surgically treating Menière's disease [291], [292], [293], [294]. The heated debate continues today [295], [296], [297], [298]. Brandt et al. have stated that, currently, only between one and three percent of patients should be considered candidates for surgical therapy [15]. Before the neurectomy, Kerr et al. carried out a simple mastoidectomy, resulting in only 57% of patients reporting the disappearance of symptoms [299]. Silverstein et al. compared patients after an endolymphatic shunt operation (subarachnoid shunt insertion) and post neurectomy with the natural development of Menière's disease (n=83). Two years after saccus surgery, 40% were found to be free of symptoms and after 8.7 years, the number had risen to 70%. In the group which did not undergo surgery (n=50) 57% were free of vertiginous symptoms after 2 years and 71% after 8.3 years. In comparison, a total of 93% of patients had no symptoms after 4.4 post neurectomy. According to the authors, endolymphatic shunt surgery does not alter the long-term development of the disease [300].

Fibrotic transformations around the endolymphatic sac (sac fibrosis) in the case of Menière's disease have been described as having various rates of success [301], [302]. Ußmüller et al. posed the question whether it is possible to prove developmental anomalies of the saccus and subsequently examined 46 petrosal bone specimens from the Wittmaack collection in Hamburg. They were able to prove that with increasing years, an aging process affects the endolymphatic sac, increasing the stenosis of the lumen, even in patients with healthy ears. Therefore, the authors propose critically assessing indications for surgery in patients over 50 years of age. The success of treatment via saccotomy depends on a wide, normally formed endolymphatic sac [303].

In 2000, Welling und Nagaraja [304] reevaluated the effectiveness of the saccotomy, based on the data published by Bretlau und Thomsen [291], [292], [293], [294] at that time. They subsequently dispelled the idea of the saccotomy as a placebo procedure. An evidence-based analysis of 96 saccotomies also showed an improvement in vertiginous symptoms ranging between 68% and 92 % of cases [305].

In a retrospective study of patients who had undergone endolymphatic shunt surgery to treat Menière's disease (n=159) after medication had been unsuccessful, Kato et al. were able to prove that the quality of life had improved in 87% of the patients, worsened in 9% with 3% registering no change

]. Based on his experience of conducting over 3000 saccotomies, Huang believes that this technique, in the hand of an experienced micro-surgeon is low in risks, highly effective and safe [307]. It is said that saccotomy has long-term better results on the „dizziness" symptom when carried out in the early stages of the disease as opposed to later [308], [309]. Intraoperative electrocochleography during sac decompression can confirm the decompression of the endolymphatic hydrops and thus also the success of the surgery [310]. Avoiding complications such as intraoperative trauma of the endolymphatic sac are seen as a possibility of increasing the rate of success for this procedure [311]. According to Yin et al., saccotomy will also have an effect on vertiginous symptoms in the long term (n=6, endolymphatic decompression and sac-mastoid shunt, follow-up average 10 years) [312].

A combined therapy with medication has also been described. Therefore, during the saccotomy procedure, steroids have additionally been administered in the saccus [313]. Other authors have used mitomycine C and an antibiotic (cephalosporin). The positive short-term effects (<3 years, n=103) speak for this method. Relapses were not observed [314].

In 1996, Welling described a procedure which involved the removal of the extra osseous endolymphatic sac. No differences were noted compared to mastoid shunt surgery [315].

In the vast majority of cases following saccotomy, the lack of attacks trains stable vestibular compensation. Training therapy is indicated here also in order the accelerate and support the compensation mechanisms [316].

Saccotomy can often lead to a normalization of labyrinthine function (maintenance of function). Patients' vertiginous symptoms alone, which are often used as criteria for many studies, are not sufficient to assess the success of the operation. Documenting vestibular functions and, in particular, assessing thermal stimulation is necessary when judging the success of surgery in relation to vertigo [316].

Schwager et al. examined 29 patients retrospectively after revision saccotomy. After 20 months, 62% were free of symptoms. 14% reported an improvement in symptoms. 7% found themselves free of vertiginous symptoms temporarily for a period of 18 months. 17% reported no improvement. The authors found that the formation of bone around the area where the shunt surgery was carried out as one reason for the failure of the therapy. They, however, recommend a revision saccotomy as the procedure of choice before other therapies, such as neurectomy, are considered [317].

In the case of unilateral Menière's disease, saccotomy can be the first choice in surgical therapy [318].

5.5.1.2 Cochleosacculotomy

Cochleosacculotomy is more common in America than in Europe. The aim of this method is to establish a permanent endo-perilymphatic shunt in order to avoid an endolymphatic hydrops [319]. The procedure can be carried out under local anesthetic. A sharp rectangular-shaped bent hook (2-3 mm) is inserted into the round window membrane in such a way that the point is situated in the middle of the footplate. The hook is then moved slightly to the right and left, provoking a fracture of the lamina spiralis ossea and the cochlear duct. The procedure is then repeated and the window is closed with connective tissue. Some patients notice a clicking noise during the operation while the hook is being inserted, however, no vertiginous sensations have been reported [320], [321]. The long-term success rate lies between 82% and 89% [321]. The effect on hearing, however, is insignificant. Indeed, Schuhknecht has reported a worsening in hearing of 25% in a group of 60 patients [319]. Many authors, therefore, consider factors such as advanced age or the inability to undergo an anesthetic as being indications for this procedure [322], [323], [324], [325]. Due to the high percentage of hearing loss, in our opinion, this procedure is most suited for patients with a high hearing impairment or loss.

5.5.2 Ablation of labyrinthine function

5.5.2.1 Neurectomy of the vestibular nerve

The unilateral, selective sectioning of the vestibular nerve (vestibular neurectomy) is one of the most effective ablative surgical treatments of Menière's disease. The nerve can be sectioned in a variety of ways. Neurectomy, especially in the case of Menière's disease can be traced back to Dandy's work [326]. He reported success rates exceeding 90%. Dandy preferred the approach through the posterior

cranial fossa [327]. McKenzie developed the vestibular neurectomy via a suboccipital approach [328]. House and Fisch further modified the procedure. They approached the vestibular nerve transtemporally via a middle fossa craniotomy [329], [330]. After non-ablative methods have failed and in the case of functional residual hearing, additional transtemporal or suboccipital access is recommended [276], [331]. It is also possible to conduct a transmeatal or translabyrinthine neurectomy if the patient is functionally deaf [332], [333].

The neurectomy's high rate of efficiency has been documented in many studies: Molony (95%, n=27), Thomsen et al. (88%, n=42), Hillman (95%, n=39) [334], [335], [336]. This makes neurectomy of the vestibular nerve the therapeutic procedure with the highest rates of success for treating Menière's disease.

Rosenberg et al. found that patients undergoing a neurectomy had a lower chance of developing bilateral Menière's disease than those treated exclusively with medication (17% versus 0%, 6.3 year period of observation) [337].

Fewer than 10% of patients will not profit from a neurectomy. The method has no affect on the pathomechanism of Menière's disease, therefore providing *no* "protection" against fluctuating hearing impairments as a result of a continuing endolymphatic hydrops ("cochlear Menière attacks"). Currently, American studies are discussing whether the saccotomy should be the first step in the staged approach in treating Menière's disease, which, in the case of failure, would be followed by a neurectomy. In one study 36% of the otosurgeons carried out endolymphatic shunt surgery first, while 24% chose the neurectomy as a first step [338], [339]. The post-operative condition after a neurectomy is equal to unilateral vestibular failure. Therefore, the medical and physical therapies mentioned in the respective sections need to be carried out even after vestibular neurectomy until optimal vestibular compensation has been achieved. In the case of a low residual vestibular function, the patient hardly notices any postoperative symptoms.

5.5.2.2 Labyrinthectomy

Labyrinthectomy as a procedure was first carried out through the transmeatal route by Schuknecht and Cawthorne. This involves the complete destruction of the labyrinth and removal of the neuroepithelia of the maculae and cristae [340], [341]. Indications for a labyrinthectomy in the case of vestibular disorders include a virtually complete labyrinthine failure, a severely reduced quality of life as a result of recurring or permanent vertiginous symptoms, and when the patient is unfit for a general anesthetic in order to undergo a neurectomy of the vestibular nerve [342].

An incomplete removal of the membranous sensory structures can lead to persistent vertiginous symptoms. Postoperatively, it is often impossible to distinguish between an incomplete labyrinthectomy from an incomplete vestibular compensation [343]. Silverstein combined the labyrinthectomy with a transmeatal cochleovestibular neurectomy and achieved good results (89%) [332]. Modifications to the labyrinthine destruction by combining surgery to remove the neuroepithelia with additional alcohol instillation or electro-cauterization have been discontinued due to the negative effect on the facial nerve [344], [345], [346]. Surgical labyrinthectomy, also in combination with ototoxic medication, does not ablate the labyrinth as effectively as the neurectomy does [342].

5.6 Further therapeutic procedures

Fenestration surgery, vestibulotomy, "tack"-operation, otic-perotic-shunt

Over the years, various methods of treatment have been used which, due to their rate of side-effects, are no longer considered appropriate [276]. In the 1940's and 50's surgeons attempted to alleviate a pressure labyrinth by fenestrating the lateral semicircular canal with a more or less restricted removal of the semicircular canal or vestibulum. Later, the sacculotomy was introduced which involved piercing the saccule above the oval window [276], [347]. As a consequence, many patients became deaf. In the case of the "tack operation", introduced by Cody, a small "nail" was inserted into the saccule [348]. Pulec developed the "otic-perotic shunt" procedure which created a connection between the scala media and the scala tympani, held open by a platinum tube [349].

Ultrasonic destruction of the labyrinth

There are other procedures, which remain of purely historical value, such as the direct application of ultrasound on the bony labyrinth (labyrinth destructive procedure). Arslan applied the ultrasound using a machine which he administered directly onto the lateral semicircular canal after antrotomy with local anesthetic. In this way, the ultrasound was applied to the vestibular section of the bony labyrinth. Nystagmus was observed after one to two minutes. Initially an "irritative" nystagmus was observed, which then developed into a „paralytic" nystagmus to the opposite side as a sign that the labyrinth had failed. The entire ultrasonic irradication period lasted up to 22 minutes. None of the 45 patients observed for a period of one year after the procedure continued to have vertiginous symptoms. In all cases, lack of thermal stimulation was detected within a few weeks. The cause is said to be the destruction of the ampullary neuroepithelia. Hearing and tinnitus also showed improvement. Due to the resulting improvement in hearing, it is assumed that the procedure has a direct effect on the impaired resorption or hypersecretion in endolymphatic hydrops [350], [351], [352], [353].

5.7 Variations of Menière's disease

Lermoyez syndrome

An indication of Lermoyez syndrome is the development of tinnitus and hearing impairment before attacks of spinning vertigo appear. Once the patient begins suffering spinning vertigo, the reduction of the intensity of tinnitus and an improvement in hearing appear in an opposite order compared to Menière's disease [354].

It is still open to debate whether this is a separate disease, or whether we are dealing with a variation of Menière's disease. The negative glycerol test and electrocochleographic findings would contest the idea that this is a separate disease, while the course of the phases of nystagmus supports it [355], [356], [357], [358]. Initially, Lermoyez suspected a vaso spasm in the inner ear [354]. Boenninghaus and Feldmann, however, assumed it was correlated to a regulatory disorder leading to a slowed reduction of endolymph volume. According to this theory, vertiginous symptoms and vestibular disturbances are due to endolymph flow, when the utriculus suddenly decompresses during positive pressure resulting from an insufficiency of the utriculo saccular (Bast`schen) valve, located in front of the endolymphatic sac ostium [359]. Just as in the case of Menière's disease, treatment during the acute phase is directed towards treating the symptoms (anti vertiginous drugs). In addition, rheological therapy is recommended. A saccotomy is said to greatly reduce vertiginous symptoms [355], [360].

Tumarkin's otolithic crisis

This is caused by a sudden stimulation of the otolith organs during the latter phases of Menière's disease [14]. The result is an extremely rapid loss of tone of the muscles supplied by the vestibulospinal tract, causing patients to suddenly and unexpectedly fall [14], [361]. The resulting vertiginous attacks are generally described as a lifting or tilting sensation which leads to a loss of spatial orientation. The attacks are so sudden that it is often impossible to activate protective reflexes. It is not uncommon for such fall to result in serious head trauma. These symptoms generally only appear in the latter stages of Menière's disease [362]. A nystagmus may temporarily appear towards the affected ear. Opinions represented in the literature appear to be unanimous that medication will have no effect [362], [363], [364]. Depending on the severity of the disease, Ödkvist and Bergenius have, at times, been able to successfully apply gentamycin therapy [363]. Neurectomy of the vestibular nerve is the most effective way to treat the disease.

It is important, however, to distinguish the symptom of „drop attacks" in a differential diagnostic way. This is a sudden loss of tone in the leg extensor muscles without sensations of vertigo, nystagmus or loss of consciousness, caused by blood flow disturbances in the formation reticularis [365].

Delayed endolymphatic hydrops (DEH)

Patients who, after labyrinthitis or trauma involving the inner ear, suffer from a progressive unilateral loss of hearing, may experience episodes of vertiginous symptoms involving either the same (ipsilateral DEH) or opposite ear (contralateral DEH), thus mirroring Menière's disease [366].

Schuknecht recommends labyrinthectomy for the ipsilateral form. Our approach in such cases is similar to the staged approach used to treat Menière's disease [364].

5.8 Summary

Still today we do not yet completely understand the etiology of Menière's disease. There are a number of conservative, non-ablative and ablative therapies available for treating the vertiginous symptoms of the disease. A subtle differential diagnostic is necessary before beginning to treat Menière's disease.

Practical experience has shown us that, even at an early stage, psychological effects may be felt. Menière's disease is still diagnosed too often and the varied conditions in respect to both physical and psychological factors are insufficiently taken into account. Fear of the vertiginous symptoms can be so great that they often cause insecurity. Psychogenic vertiginous symptoms can still manifest themselves even when the vestibular organ has long lost its function [4], [6].

If the disease involves a high rate of attacks over a lengthy period, it is not uncommon for the patient to be unable to carry out his/her work on a regular basis, and there is a real threat of disablement or, indeed, disability. The aim must be to rid the patient of symptoms quickly and effectively, while maintaining function and avoiding the potential of serious complications (such as becoming deaf). The irregular course of the disease, its high variability and the difficulty of assessing a prognosis mean that currently no one method is able to stand up to all these challenges.

The most important factors to consider when choosing a therapy include the patient's condition, how long the patient has been afflicted, the past success of conservative (medical) therapies, hearing, as well as the location and the degree of otolith dysfunction.

We conduct a staged otomicrosurgical therapy concept here at the ENT university department in Aachen. Indications for the surgical therapy of Menière's disease include:

• patient not reacting or insufficiently reacting to *conservative therapy* (roughly 6-12 months),

• impairment resulting from progressive worsening of cochlear function,

• and severe restrictions to patient's quality of life and/or work (relative indication) resulting from a high rate of attacks (<2 weekly).

Patients with a proven temporary otolith dysfunction have *tympanic tubes* inserted either unilaterally or bilaterally when either a shift in the maximal compliance of over 50 daPa can be reproduced in the impedance audiometry (during at least two separate examinations) or a reduction of tube function can be objectively proven. The otolith organs, due to their central position, are most likely to be involved and affected by both endolymphatic and perilymphatic hypertension. However, we see no indication for surgery for tympanic drain solely in the case of semicircular canal dysfunctions. Aerating the tympanic cavity can, however, in conjunction with other therapeutic measures, lead to a significant improvement in symptoms. In the case of a therapy refractory endolymphatic hydrops, we recommend *non-ablative endolymphatic shunt surgery*. The minimum prerequisite for this, however, is the residual function of the macula and/or crista. Pressure is released by incising the sac transmastoidally. Inserting a thin wedge-shaped silicon strip resembling a christmas tree into the sac offers, in our opinion, greater security compared to simply decompressing the sac. According to our observations, this leads to the formation of a neo-sac. During revisions of the sac, we found a greatly enlarged pars lateralis of the endolymphatic sac around the silicon strip.

An *ablation of labyrinthine function* is indicated when conservative rehabilitation and non-ablative measures have not produced the desired rehabilitation results. Indication for a *neurectomy* of the vestibular nerve is preserved social hearing. Bilateral disease is not a contra-indication. *Ablative labyrinth surgery becomes the primary therapy* when hearing is lost. We recommend *cochleosacculotomy* in the case of normal contralateral but non existent ipsilateral social hearing [35], [364].

Physiotherapy training to encourage compensation for acute isolated vestibular failure with acute unilateral dysfunction and reduced thermal sensitivity is equally the method of choice for treating Menière's disease.

6. Dysfunction of the otolith organs

50% of patients with labyrinthine vertiginous symptoms also have isolated otolith dysfunction or an involvement of the otolith. Diseases of the otolith organs may be the sole cause of vertiginous symptoms, but can also be in combination with cochlear and/or semicircular canal dysfunction [35], [364]. Around a fourth of all patients who come to our hospital complaining of vertiginous symptoms, name symptoms such as lift vertigo or a tilt in certain positions, or even unspecific symptoms, which can be related to otolith dysfunction. Today, macula dysfunction can be qualitatively assessed using screening methods or quantified using other, more time intensive, diagnostic tools [35], [364]. Another possibility of otolith diagnosis (utricle), which has yet to be fully researched, is thermal testing in pronation and supination. Vestibular evoked myogenic potential (VEMP) is a response to saccule stimulation [367].

A specific surgical therapy for the selective ablation of the otolith organs is currently still being studied in animal models [368], [369]. Laser surgery can be used to treat isolated disorders of the otolith apparatus. It has been shown in guinea pigs that using an Argon laser through an intact footplate to destroy the otolith organs does not result in hearing impairment [368]. There have also been animal models involving laser therapy and the temporary removal of the footplate [369]. This procedure, termed "selective labyrinthectomy", has until now only been performed successfully on one patient [370], [371]. In a similar fashion to semicircular canal failure, otolith disorders result in a form of compensation. The interval of time for compensation, however, is only roughly three days [368]. Artificial ablation of the otolith organs on one side simultaneously results in a reduction of the semicircular canal response because the otolith organs modulate the semicircular canal responses [372], [373].

7. Bilateral vestibulopathy

In addition to bilateral labyrinthine causes (malformation, basal skull fracture involving the labyrinth, labyrinthitis, Menière' disease), central nervous disorders (meningitis) or metabolic diseases (vitamin B6 and B12 deficiency) can also be responsible for the relatively rare disorder of bilateral vestibular dysfunction [374]. In our own research involving 64 patients, we found that the most common known cause was vestibulotoxic medication (12%) and meningitis (8%). In most cases (62%), however, the etiology remained unclear. Rinne et al. discovered that in 39% of cases there was a central nervous cause, in 17% the administering of ototoxic antibiotics, and in 9% the cause was an autoimmune disease (n=53). In roughly a fifth of cases (21%) no direct cause could be isolated [375]. Damage to both labyrinths can be acute or can manifest itself slowly. Both vestibular organs can be affected simultaneously or sequentially. The Bechterew phenomenon can be observed in the case of a slowly developing loss of vestibular function, with alternating sides affected and periods of vestibular compensation [374], [376], [377]. Acquired disorders are accompanied by gait insecurity (ataxia) and visual perception disturbance (oscillopsia). This symptom, described by Dandy, was first observed following the bilateral section of the vestibular nerve [378].

Thermal stimulation of the lateral semicircular canal does not need to be fully „extinguished". Even a residual stimulation can result in the typical symptoms involved in bilateral vestibulopathy [379]. In two cases of loss of thermal stimulation, which we chanced upon, both patients were amazingly free of symptoms (congenital form of bilateral vestibulopathy).

Today, it is necessary to monitor (plasma level) the administering of ototoxic drugs, especially aminoglycosoids. Risk factors include advanced age, renal insufficiency, and the additional administering of diuretics (furosemide) or salicylates (accumulation) [380].

In the case of Cogan's syndrome, high doses of cortisone are administered (1g urbason over five days) and a few authors recommend azathioprine or cyclophosphamid under certain conditions [15], [374], [381].

Physical therapy is recommended for a proven partial or complete loss of thermal stimulation. Vestibular training aids in becoming accustomed to the dysfunction. Brandt refers to visual and somatosensory substitution [15]. According to Herdmann, however, there is no significant difference

between treated patients' sense of balance compared to those untreated [382]. When function in both vestibular organs has been lost, the term "habituation" replaces the notion of compensation.

8. Vestibular disorders in the elderly

Vertiginous symptoms are particularly common with increased age. Vertiginous sensations and vestibular disorders (balance disorders) are by far the most common reason for over 65's to visit their doctor. More than half of all hospital patients over 75 years of age complain of vertiginous symptoms. Recent studies have shown that such symptoms severely limit a person's quality of life. In one observational study, one to two slow-release dimenhydrinate tablets were administered per day for eight weeks. A number of patients were also given physiotherapy. The results showed that the patients treated with medication felt considerably better in various situations. 95% of patients tolerated the medication well. The addition of physiotherapy guaranteed an even better quality of life score [383].

Physical training does not only protect the elderly from cardiovascular risks. Continual balance training helps improve the neuromuscular performance components, such as co-ordination and flexibility. The notion of the central nervous system being a static organ needs revising. We now know that, even with increased age, it possesses a surprising level of plasticity, which can be taken advantage of through training [384], [385].

It is not uncommon for the elderly to fall as a result of staggering and gait insecurity. Patients suffering from vertiginous symptoms are ten times more likely to fall compared to those without such symptoms. Regular balance training can result in roughly 50% less falls in older patients, which translates into a considerable saving.

Prescribing medication known to cause vertiginous symptoms in a sensible manner is one way of preventing falls [386]. Vestibular prosthesis can help prevent falls in the future when compensation is incomplete ("cochlea implant for the vestibular organ") [387].

9. Kinetosis

Kinetosis is the result of an optical-vestibular discrepancy, for example when traveling by car, train, plane and ship, „sea sickness" resulting from linear and angular acceleration of a low frequency (<1 Hz). Optokinetic stimulation is responsible for the so-called simulation disease [14], [15].

There are two grades of kinetosis syndrome. The „sopite syndrome" involves compulsive yawning, lack of energy, fatigue, tiredness, while the „nausea syndrome" involves nausea and vomiting.

In theory, every person can develop a kinetosis (coriolis effect) [14], [388]. Individual susceptibility, however, differs. Otolith asymmetry, especially of the utricle, are said to play a role [389], [390]. Kinetosis is referred to as space-motion-sickness or space-adaptation-syndrome when there is zero gravity [388], [391].

Therapy can be in the form of medication. A very practical and simple treatment is the transdermal application of parasympatholytica (scopolamine). It works for roughly 72 hours applied behind the ear, where the skin is most permeable. For the medication to work optimally, it should be applied roughly six hours before travel. A series of other available medication can be found in Table 4 (Tab. 4). Most antivertiginous drugs, however, begin to take effect more quickly (roughly 30 minutes after being taken).

Before traveling, it is recommended that only small amounts of lights foods be eaten. Dairy products should be avoided. While traveling, the person should try to fix his/her gaze on the horizon or on one particular object and sit in the direction being traveled (visual control). This is possibly the reason why drivers seldom suffer from kinetosis [388], [391].

The symptoms of kinetosis take up to 24 hours after traveling to pass [15].

Kinetosis induced training (repeated trigger exposure) it is possible to delay the threshold for the development of kinetosis [15].

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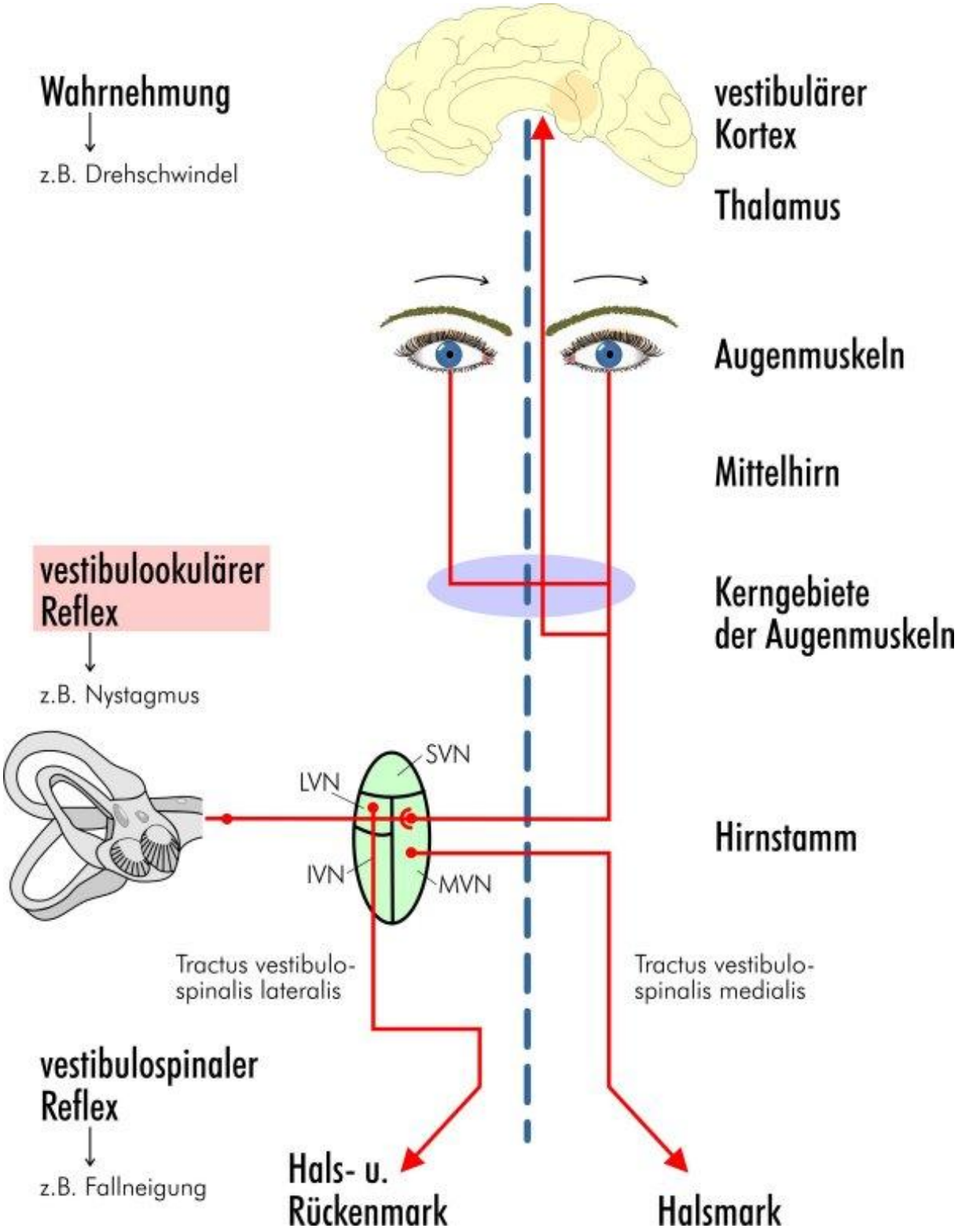

Figure 1: Vestibuloocular reflex (VOR) from the labyrinth to the cortex

The VOR is a central component of the sensomotoric system responsible for spatial orientation and perception (vestibular projection in the cortex, perceptive crus of the VOR), postural regulation (vestibulospinal projection, postural crus) and gaze stability. The VOR transmits information from the semicircular canals and otolith organs via the vestibular nerve, the brain stem nuclei and vestibular projection to the nuclei of the three eye muscles (Three-neuron arc, oculomotor crus). The short conduction velocity of the VOR (approx. 20 ms) guarantees a well defined retinal image during head movements [5, 15]. (SVN; IVN; LVN; MVN: superior, inferior, lateral, medial vestibular nucleus).

Figure 2a: The three planes of operation of the vestibuloocular reflex (VOR). Sagittal pitch plane (green), frontal roll plane (gray), horizontal yaw plane (green) [23].

Figure 2b: Nystagmus in defined disorders in the three planes of operation of the VOR. Tonus imbalance in the pitch plane leads to a vertical nystagmus (upbeat or downbeat nystagmus). Disorders in the roll plane cause a torsional nystagmus while disorders of the VOR in the yaw plane cause a horizontal nystagmus.

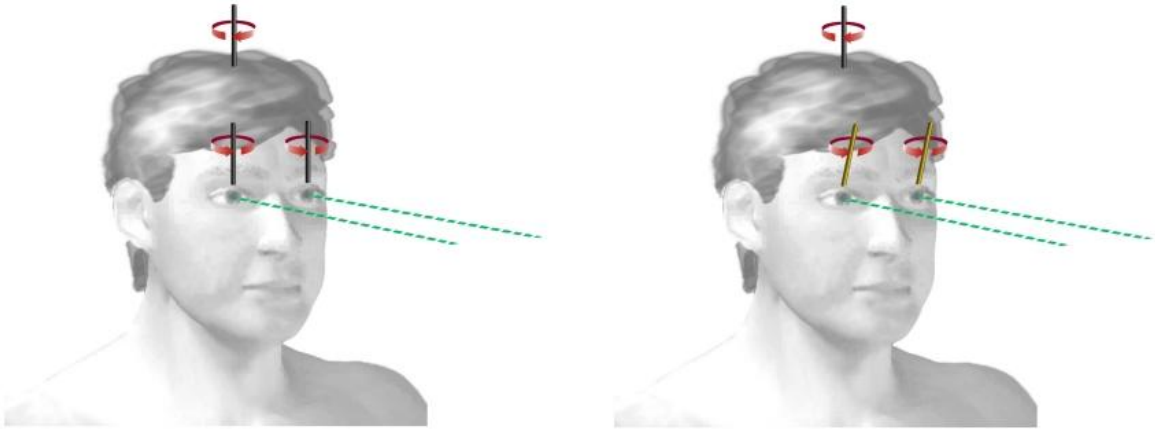

Figure 3a: In a healthy person, both eyes will rotate in an opposite to direction to the rotation of the head. The rotational axis of the head and eyes are parallel to one another. The speed of the eye rotation is equivalent to that of the head rotation [after 68].

Figure 3b: In the case of unilateral vestibular failure, the eyes rotate more slowly than the speed which the head moves. The rotation axis of the head and eyes are different. Both result in a diffused and blurred retinal image. [after 68].

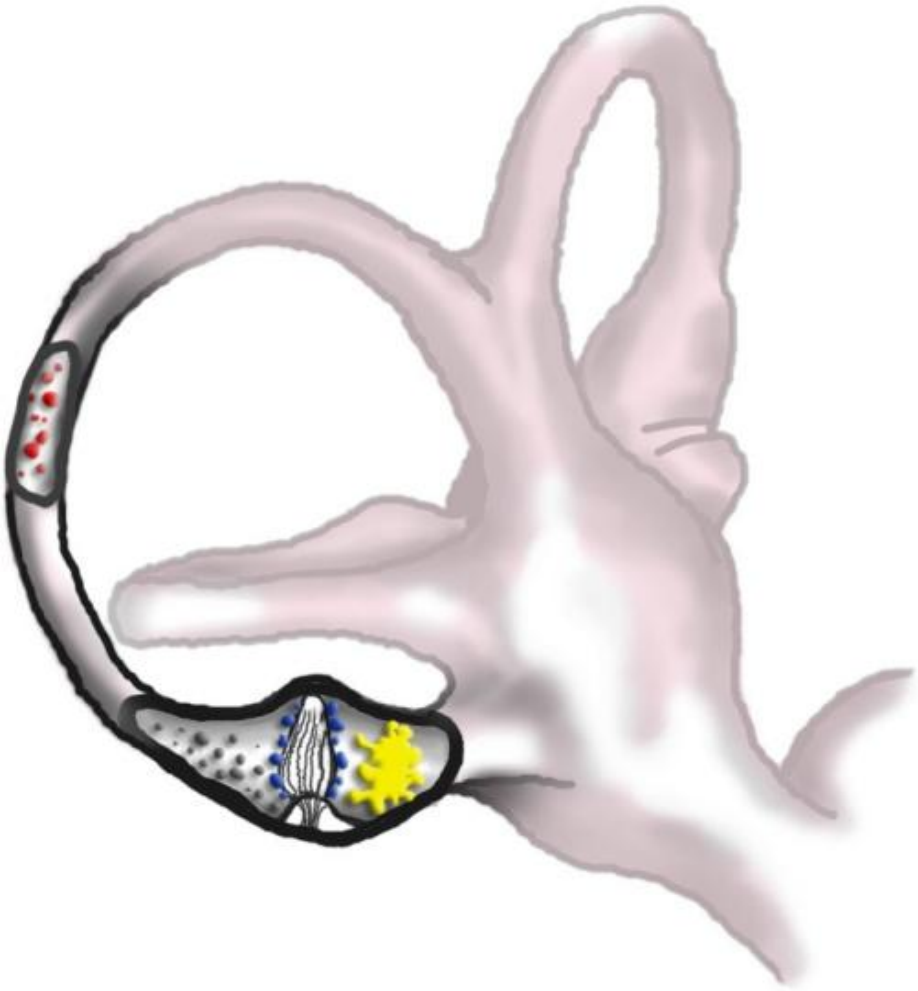

Figure 4: Canalolithiasis (red and grey pictured particles), cupulolithiasis (blue particles) and „canalith jam" (yellow particle mass) around the posterior semicircular canal

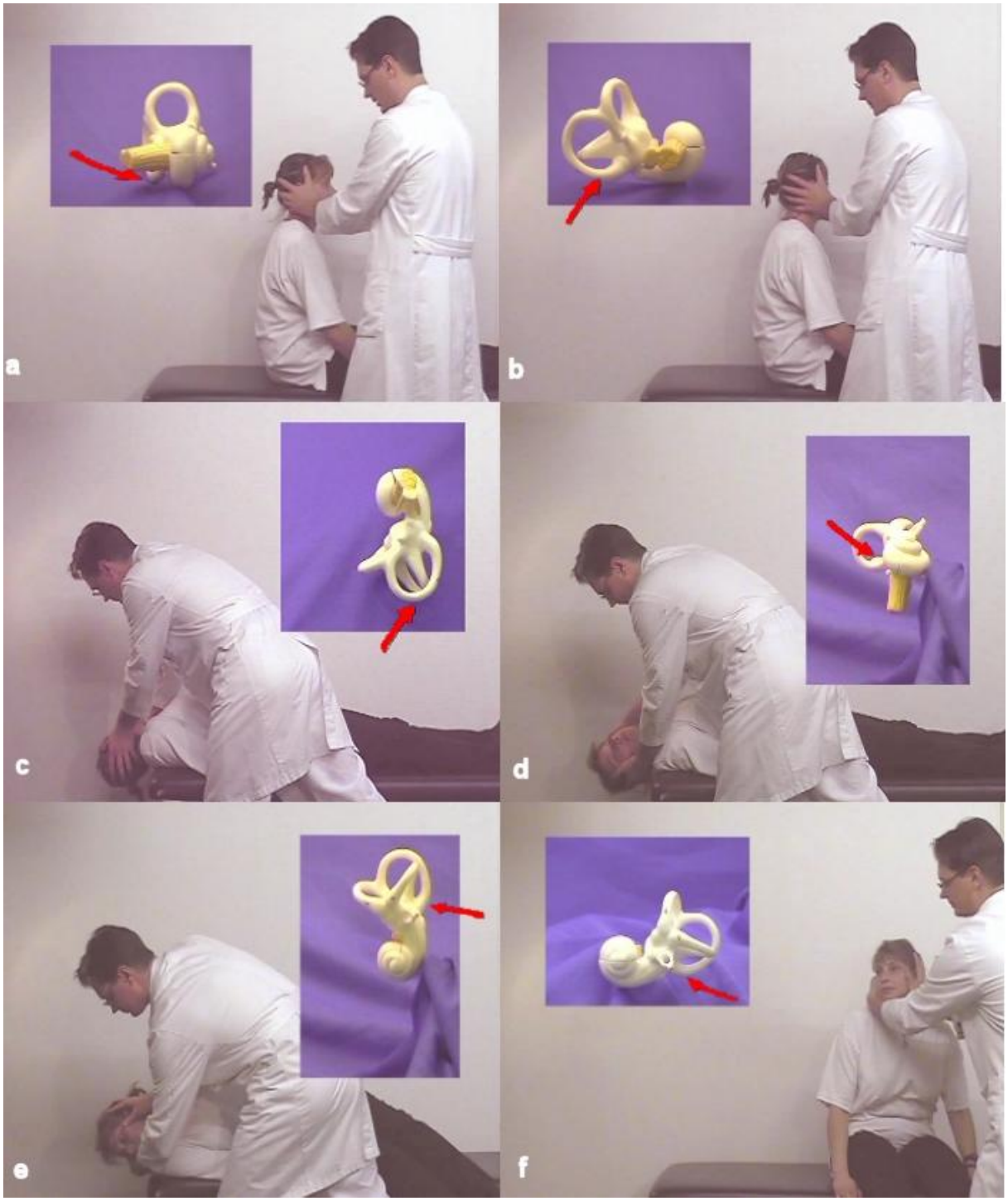

Figure 5: Epley-reposition maneuver. Sequences of physiotherapy for the left posterior semicircular canal (red arrow).

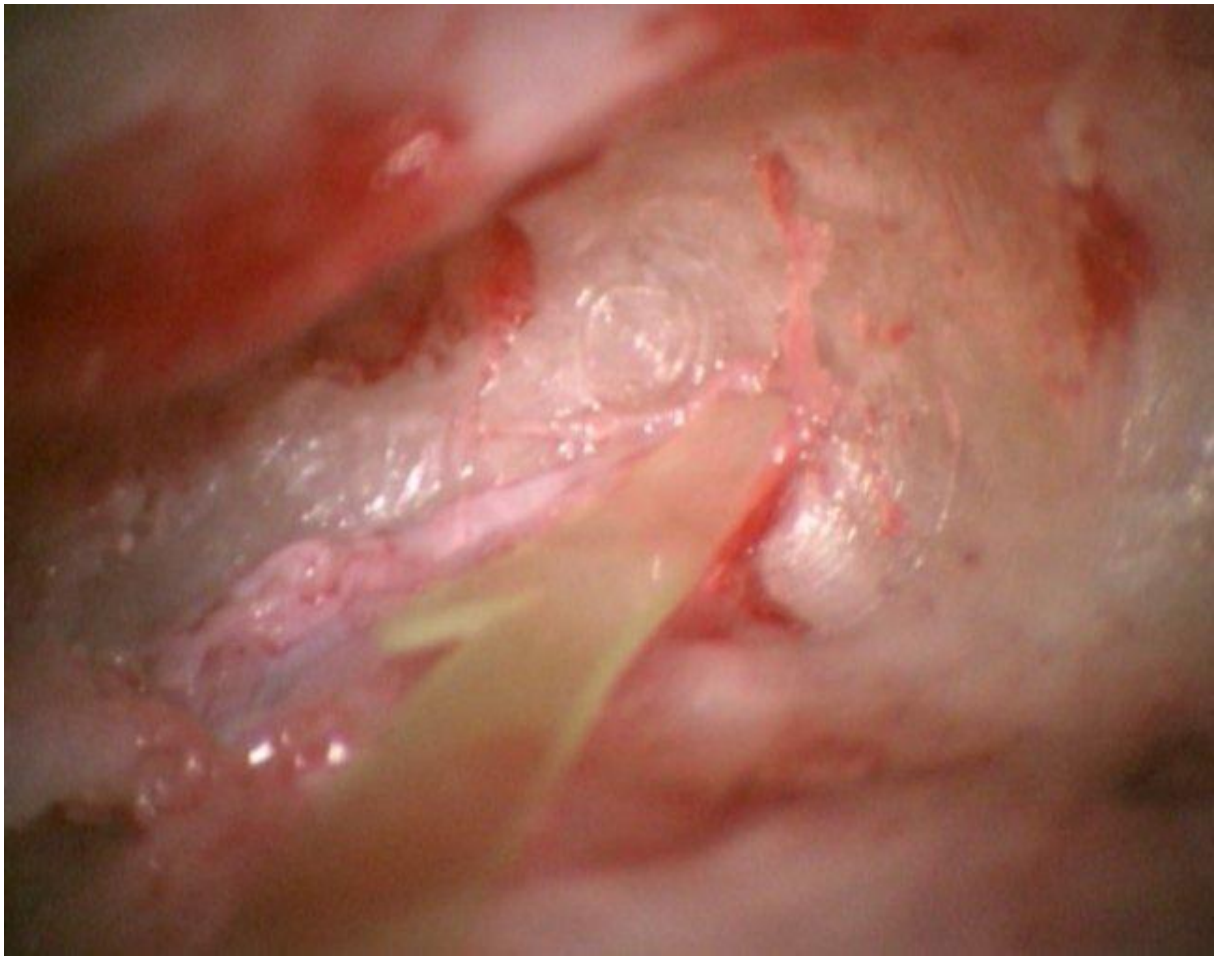

Figure 6: Inserted silicon sheet in the endolymphatic sac (red arrow) during saccotomy. Intraoperative situs

disease	medical therapy	physical therapy	surgical therapy
acute unilateral vestibular loss	e.g. antivertiginous drugs, glucocorticoids	vestibular training	-
Menière's disease	attack therapy: antivertiginous drugs (e.g. dimenhydrinate) attack prophylaxis: e.g. cinnarizine and dimenhydrinate, betahistine, diuretic	-	function-preserving: e.g. saccotomy, ablative: e.g. neurectomy of vestibular neuritis; medical-surgical: issue of intratympanal gentamicin- or lidocaine
benign paroxysmal positional vertigo	contraindicated as stand-alone therapy, in individual cases: one-time issue of antivertiginous drug after physical therapy	after participation of respective semicircular canal: e.g. Semont maneuver or repositioning maneuver (e.g. Epley's or Vannuchi's)	in individual cases: conventional-surgical occlusion of respective semicircular canal („plugging") or laser-surgical (argon-, CO_2-laser) occlusion

Table 1:Therapies for diseases involving vestibular disturbance (vestibular failure, Menière's disease, benign paroxysmal positional vertigo)

disease	prevention/prophylaxis
bilateral vestibulopathy	serum level check (gentamicin), prevention of cumulative effects (e.g. when issueing loop diuretics at the same time)
equilibrium disturbances after implantation of cochlear implant	involving results of thermal vestibular check as well as otolith function tests in chosen side of implant
borreliosis	antibiotics (one-time issue), adequate treatment of erythema chronicum migrans
kinetosis	kinetosis training specifically aimed at travelling (repetitive stimulus exposition: habituation), careful accelerating and braking, prevention of additional accelerating powers (e.g. head motion while driving), prevention of optic-visual conflicts (e.g. reading while driving, visual checks during the ride), head fixation during the ride, antivertiginous drugs prior travelling
batophobia	prevention of intense head-tilting, sitting or lying down, holding down or leaving ajar, prevention of motion, close contrasts should stay in field of vision
equilibrium disturbances while diving	examination of diving capabilities, no diving sessions in case of diseased upper airways with tube function disorders
disturbed equilibrium at older ages	physical and equilibrial training, prevention of cambers by means of proper medicine prescriptions

Table 2: Prevention of and prophylactic for selected vestibular disorders

type of application	average rate of succes (vertigo disorders) [%]	average rate of hearing disorders after treatment [%]
multiple times, daily	91.1	34.7
weekly	89.3	13.1
low dosed	86.8	23.7
continous	88.3	24.4
titrated	96.3	24.2

Table 3: Therapy success rates (vertiginous symptoms) following various methods of intratympanic gentamycin treatment and hearing impairment. As per Chia et al. 2004 [215]

substance group	medicine	example	dosage	duration of usage before travelling (hours)	effective for (hours)
H_1-antihistaminics	dimenhydr-inate	Reisetabletten ratiopharm®	50 mg per os	0.5	8
	meclozine	Peremesin® N	25 mg per os	0.5	12
	scopolamine	Scopoderm TTS®	1.5 mg transdermal retro-auricular	6	72
serotonine-($5\text{-}HT_3$) antagonists	tropisetrone	Navoban®	5 mg per os	prior to exposition	24
herbal antiemetics	ginger rhizome	Citona®	500 mg per os	0.5	4
homoeopathics	cocculus	Hervertigon SL Tabletten®	250 mg per os	0.2	0.25-6
neuroleptics (only as combined preparation)	promethazine	Atosil®	25 mg per os	prior to exposition	6-8

Table 4: Medication as prophylactic and therapy for motion sickness [Source: Rote Liste 2004]