Chapter 13

Summary and conclusions
Centuries before Prosper Menière described his classical triadic symptomatology Menière-like symptoms were already reported. In 1861 Prosper Menière was actually the first one who described a series of patients with the classical triadic symptomatology of hearing loss, vertigo and tinnitus. The essence of his hypothesis was that the symptoms were caused by a disorder of the labyrinth instead of a vascular cerebral dysfunction, as had previously been thought. This was published in the ‘Gazette Médicinale de Paris’ (Menière 1861). In this paper Prosper Menière concluded that the auditory apparatus may be suddenly affected causing tinnitus and diminution of hearing. He also stated that the inner ear was the site which can suddenly be affected causing attacks of vertigo, dizziness, uncertain gait, staggering and falling. The attacks may be accompanied by nausea, vomiting and syncope. He described that the attacks were intermittently followed by hearing loss of increasing severity. In the 20th century the interest to establish an exclusive diagnosis and an adequate therapy was growing. Although different definitions of Menière’s disease for diagnostic, therapeutic and evaluation purposes are proposed, unresolved issues on the definition of the disease are still persistent. A uniform applicability of the definition of Menière’s disease is obligatory for clinical and scientific purposes.

Chapter 2. History and definition
This chapter describes the history and evolution of defining Menière’s disease. During the last decades a lot of different definitions of Menière’s disease have been used. The development of these definitions is described and discussed. In 1972 in response to a large variability in defining Menière’s disease, the Committee on Hearing and Equilibrium of the American Academy of Ophthalmology and Otolaryngology (AAOO) defined Menière’s disease as a disease of the membranous inner ear with a characteristic set of symptoms and signs and with a pathological correlate of endolymphatic hydrops. This hydrops of the endolymphatic system in the temporal bones of patients with Menière’s disease was discovered by Hallpike and Cairns, and also Yamakawa, in 1938. Since then this endolymphatic hydrops has been generally accepted as the basic histopathological substrate of Menière’s disease. The definition of the disease has been revised in 1985 and in 1995 by the AAOO. Both definitions are described and discussed. The 1995 definition of Menière’s disease is still used at this moment.

Chapter 3. Definition Menière Groningen and Groningen Diagnostic Protocol
This chapter starts with a discussion on unresolved issues and shortcomings of the definition of Menière’s disease, with special interest for the 1995 definition of the American Academy of Ophthalmology and Otolaryngology Committee on Hearing and Equilibrium. Difficulties in defining duration, uni- and bilateral Menière’s disease, and the presence of aural fullness (if tinnitus is absent) are also addressed. The Definition Menière Groningen and the Groningen Diagnostic Protocol are introduced. The definition of Menière’s disease must basically include the clinical symptomatology as the direct consequence of the idiopathic endolymphatic hydrops as the basic histopathological substrate. Furthermore, a uniform applicability of the definition of Menière’s disease is obligatory for clinical and scientific purposes. The diffuse and
complex symptomatology of Menière’s disease requests an accurate diagnostic program to confirm the diagnosis and to exclude other pathology. With such a program it might be possible to obtain more information about the cause of the disease and to establish staging, allowing more specific treatment modalities for each particular stage. Menière’s disease was redefined and the Definition Menière Groningen was introduced. The criteria for a positive diagnosis are: a documented cochlear hearing loss (at least one threshold of 20 dB HL or worse in one of the six measured pure-tone audiogram frequencies) combined with tinnitus (being present now or in the past), vertigo attacks (at least two in the history), confirmed by the Groningen Diagnostic Protocol and other pathology excluded through this protocol. Definitions of the separate symptoms, affected and unaffected, uni- and bilateral disease, duration and severity of symptoms and disease are described.

The Groningen Diagnostic Protocol was part of the Definition Menière Groningen. The diagnostic protocol was developed to confirm the diagnosis Menière’s disease with the tests of the protocol and to exclude other pathology as defined in the Definition Menière Groningen. The protocol allowed a systemic evaluation of the diagnostic value of each different testmodality for the diagnosis of Menière’s disease. In addition, the contribution of each test separately and their correlations with regard to a possible classification was further subject of investigation. The Groningen Diagnostic Protocol contained the following tests: routine ORL-history and -examination, subjective audiometry (pure-tone and speech), objective audiometry (tympanometry, stapedial reflex measurements, BERA, otoacoustic emissions, electrocochleography), vestibular tests, perilymphatic pressure measurements, magnetic resonance imaging of the petrous bone and cerebellopontine angle, routine laboratory tests (including aldosterone assessment) and psychological consultation.

During a three and a half year period (from January 1994 to June 1997) patients suspected of having Menière's disease were admitted for four days at the Department of Otorhinolaryngology of the University Hospital Groningen, a tertiary referral center. During their stay in the hospital these patients underwent the tests that were required for the Groningen Diagnostic Protocol resulting in prospective clinical cohort studies as part of the Definition Menière Groningen.

A database was designed together with a special data management office. The database itself and the collection of the data were controlled and secured by the office. Statistical analysis of data was performed with the SPSS 10.0 program and the help of a professional statistician.

Chapter 4. Patients and characteristics
During a three and a half year period (from January 1994 to June 1997) 128 patients, suspected of having Menière’s disease, were admitted for four days at the Department of Otorhinolaryngology of the University Hospital Groningen, a tertiary referral center. Based on the criteria of the Definition Menière Groningen and the Groningen Diagnostic Protocol finally 111 patients were diagnosed with Menière’s disease. The fact that 17 out of 128 patients did not have Menière’s disease is illustrative for the usefulness of the Groningen Diagnostic Protocol as part of the Definition Menière Groningen.
Of the 111 included patients 57 patients were male (51%) and 54 patients were female (49%). There were 151 affected ears and 71 unaffected ears. Of all patients 36% was bilaterally affected. At the start of the disease the mean age of the studied group was 42.8 (±11.5) years. At the time of the hospital admission this was 50.3 (±10.9) years. The mean duration of the disease of all patients was 7.5 (±6.7) years. In this study specific attention is paid to differences between affected and unaffected ears, as well as uni- and bilaterally affected patients. To our knowledge such specific analysis on these issues has not been reported in the literature. In our population the duration of Menière’s disease in bilaterally affected patients was longer than in unilaterally affected patients. This was probably not caused by a change-over from an unilateral start of the disease to a bilateral involvment of the disease. The ears of the bilaterally affected patient were both affected almost from the beginning of the disease, suggesting a bilaterality as a separate entity. In this study there was no uniform initial presentation of the separate symptoms. Vertigo usually was the first presenting symptom (75%), but hearing loss (70%) and tinnitus (73%) scored an almost comparable percentage. At the start of the disease almost half of the patients suffered from the complete triad of symptoms. None of the three symptoms was among the first occuring in all patients. The severity of symptoms did not correlate with the duration of the disease. Aural fullness/pressure had a high correlation with tinnitus indicating that this symptom is not obligatory for the definition of Menière’s disease. Patients with a fluctuating hearing loss generally had a more severe tinnitus and aural fullness/pressure sensation. In contrast an ‘unchanged’ hearing was related to a ‘mild’ score in aural pressure/fullness. These findings may support the hypothesis that an actual endolymphatic hydrops is responsible for an increase of symptoms as hearing loss fluctuation, tinnitus and aural fullness/pressure, possibly indicating to an instable Menière’s disease, although no similar relation could be found with the symptom vertigo. The hospital admission caused a release in tinnitus and aural pressure/fullness, possibly by reducing stress, leading to a decrease in endolymphatic hydrops. Our patient group was found to be comparable to patient cohorts as reported in the literature with respect to gender distribution, age, duration and severity of the disease. The group can be regarded as representative with a high external validity.

Chapter 5. Pure-tone and speech audiometry
In this chapter the subjective audiometry study is discussed. The aim of this study was to reinvestigate many of the claims in the literature about hearing loss in Menière patients. A well defined group of patients under well controlled circumstances was subject of this study. As part of the Groningen Diagnostic Protocol pure-tone and speech audiometry was performed on 111 patients with Menière’s disease according to the Definition Menière Groningen. Affected ears of patients suffering from Menière’s disease showed reduced hearing, both in pure-tone and in speech audiometry. Correlations between pure-tone and speech audiometry were present as in non-Menière ears, and no indications have been found of reduced speech discrimination in relation to the expectation based on pure-tone loss. A classification method was devised to determine audiogram shape in
an objective manner. The results of this method indicated that affected ears more frequently showed ‘low’ or ‘low+high’ hearing losses. In patients with large average hearing loss more often had a flat shape of their pure-tone audiogram. The shape of the audiogram did not depend on the duration of the disease. Also the average hearing loss did not correlate with the duration of the disease. No relation was found between the duration of the disease and the subjective severity of the hearing loss over the three months before hospital admission, as given by the patients in a questionnaire. A relation between the audiometric data and the subjective severity of the hearing loss by the patient seemed to be present, but was not very strong. In conclusion; classification of hearing loss (shape, average hearing loss and subjective severity of hearing loss) can not be connected to the duration.

Chapter 6. Electrocochleography

This chapter describes a study that was performed to investigate whether electrocochleography (EcoG) could be helpful in classifying patients with Menière’s disease. As part of the Groningen Diagnostic Protocol, EcoG was performed on 111 patients with Menière’s disease, according to the Definition Menière Groningen. All patients underwent transtympanic EcoG in both ears. The protocol consisted of averaging 1500 responses to each of the following stimuli: clicks - alternating, condensation and rarefaction (duration 80 µs); alternating tonebursts - 1 kHz, 2 kHz, 4 kHz, 8 kHz (duration 10 ms, rise and fall time two cycles of the sinewave). The amplitude of the clicks and tonebursts was 90 dB nHL, except for 8 kHz bursts that were presented at 75 dB nHL. The stimuli were delivered to the ear at a rate of 11.3/s, using an insert earphone. Summation and action potentials (SP and AP) of clicks and tonebursts, and click latencies (alternating, condensation, rarefaction) were measured. The SP (tonebursts) was calculated in two fundamentally different ways (SP1, SP2). The results of affected and unaffected ears were systematically compared and related to the magnitude of hearing loss, the duration of disease and the severity of complaints. Comparing the affected ears with the unaffected ears, significant differences in SP and AP were found as well as significant differences in latency-differences between rarefaction and condensation-clicks. The most prominent features were the significant differences in both the SP2 and the ratio SP2/AP at 1 kHz and 2 kHz, a small latency difference for rarefaction clicks, the significant correlation between latency and average hearing loss for the three click stimuli, a significant correlation with hearing loss for SP2/AP at 2 kHz in both affected and unaffected ears and poor correlations with duration of disease only for the three click latencies. For the symptom ‘hearing loss’, the averages of the potentials for 2 kHz tonebursts plus the click potentials had the largest (absolute value of the) SP and SP/AP ratio in the ‘worse’ group. The smallest SP and SP/AP was observed in the ‘unchanged’ group. On an individual basis, EcoG parameters can not identify a diseased ear. The present results do not provide obvious clues for the staging of Menière’s disease. A possible approach to staging is the combined use of several test parameters instead of a single one.
Chapter 7. Otoacoustic Emissions
Click-evoked, as well as distortion product otoacoustic emissions (OAEs), were measured in 100 patients with Menière's disease according to the 'Definition Menière Groningen. The incidence of the emissions in affected ears (56%) was lower than in unaffected -or contralateral- ears (85%). The mean emission amplitude in affected ears was significantly lower also (2.6 dB), and, in turn, the mean amplitude in unaffected ears was lower than in normal-hearing ears (5.3 dB). These differences are likely to be caused by the hearing loss involved. Further, ears with OAEs clearly showed smaller hearing losses than ears without OAEs (24 dB difference). The average hearing loss did show correlations with the emission amplitudes, though not very strong; when plotted against the smallest hearing loss, a certain upper bound for the emission amplitude was present. Also, the amplitude of click evoked OAEs showed a considerable correlation with the largest of the three distortion product OAEs. These observations confirm the view that OAEs are associated with normal or near-normal hearing.

Chapter 8. Electronystagmography
In this study we performed standardized measurements of spontaneous nystagmus (SN), caloric tests and velocity step tests on a well-defined group of 92 Menière patients as part of a diagnostic protocol. The aim of the study was to look for results that could contribute to the diagnosis, but more specifically to a possible classification, of Menière’s disease. Relations with average hearing loss, shape of the audiogram, duration and severity of perceived symptoms of disease and differences between uni- and bilateral Menière’s disease were studied. Directional preponderance (DP) in unilaterally affected patients and labyrinthine preponderance (LP) in both uni- and bilaterally affected patients were significantly more often directed towards the unaffected (uni) or least affected (bi) side. DP was correlated with LP, which means that the DP can be seen as a latent SN, directed to the unaffected side. With the caloric test parameters LP and DP it was possible to find unilateral weakness. In unilateral disease a duration of disease <2 years resulted in small asymmetry in time constant (T_asym), large LP’s and LP’s not only directed to the unaffected, but also to the affected side, whereas a longer duration of disease gave large T_asym and small LP’s that were only directed to the unaffected side. Patients suffered more severe vertigo in the first two years of the disease. Studying the shape of the audiogram, it was found that patients having an LP to the affected side, suggesting that this was a hyperactive labyrinth belonging to a beginning of the disease, never had a flat audiogram.
In this study the LP was the best diagnostic parameter to find unilateral weakness in patients with Menière’s disease. Together with the duration of the disease, the severity of symptoms, the asymmetry in T and the shape of the audiogram, it was possible to find two subgroups in the group of patients with unilateral Menière’s disease. Vestibular data in association with other test results of the diagnostic protocol may contribute to a more sophisticated classification of Menière’s disease.
Chapter 9. 3DFT-CISS Magnetic Resonance Imaging
In this chapter 3DFT-CISS MRI was used to quantify the distance between the vertical part of the posterior semicircular canal and the posterior fossa as a measure of the endolymphatic sac and duct size in patients with Menière’s disease. Differences in this distance between affected and unaffected ears as well as differences between unilaterally and bilaterally affected patients were studied and compared to a control group. Also, possible correlations between the measured distance and the duration and severity of symptoms, age and average hearing loss were investigated within the Menière group. Of the initially included Menière population (111 patients), 90 patients underwent a 3DFT-CISS MRI scan. Finally, 86 patients were analyzed in this MRI study. Fifty-six patients suffered from unilateral and 30 patients from bilateral Menière’s disease (116 affected and 56 unaffected ears). Sixty-two ears of non-Menière patients were included as control. The distance between the vertical part of the posterior semicircular canal and the posterior fossa was determined by 3DFT-CISS MRI. Contiguous axial 3DFT-CISS MRI slices of 0.7 to 1.0 millimeter (mm) were made by a radiologist according to a strict protocol. Measurements were taken by two professionals, namely a radiologist and an otolaryngologist, using a ruler and the original scan. A significantly smaller MRI distance (2.9 mm) was found in Menière ears, compared to the control group (3.8 mm). In both uni- and bilaterally affected patients (n=56 and n=30, respectively) no significant differences in the distance were found between both ears. However, in bilaterally affected patients this distance (3.2 mm) was significantly larger than the distance in unilaterally affected patients (2.7 mm). There was no relationship between the MRI distance and duration of disease, age, average hearing loss or severity of symptoms, in both uni- and bilaterally affected patients. The difference in duration between the two ears of bilaterally affected ears rarely exceeded one year.

The difference in MRI distance between uni- and bilaterally affected patients strongly suggests that uni- and bilateral affection are two different entities. The size of the endolymphatic sac seems to be not the only factor in the pathogenesis of Menière’s disease. The fact that the MRI distance does not have any relationship to duration of the disease and age indicates that this distance is a congenital feature.

Chapter 10. Perilymphatic pressure measurement
In this chapter the MMS-10 Tympanic Displacement Analyser was used as a device to measure the perilymphatic pressure in humans. This instrument was used in a prospective cohort study of 70 patients with Menière’s disease (44 affected ears) according to the ‘Definition Menière Groningen’ and a group of 50 young normal hearing subjects. No significant differences were found in perilymphatic pressure measurements between the groups. Although measurement parameters showed large inter-individual variation in a subgroup of 25 patients, the intra-individual correlation in the subgroup was highly satisfactory. In patients with Menière’s disease no relationship was found between perilymphatic pressure and hearing thresholds, blood pressure, gender age. Also no relation as found with duration of the disease or with the severity symptoms. There was no difference between uni- and bilaterally affected patients.
Chapter 11. Aldosterone assessment

Manifestations of Menière’s disease are frequently observed in times of emotional stress. Mediated through the hypothalamus, stress leads to an increased secretion of the adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland followed by an increased adrenocortical production of glucocorticoids (cortisol and corticosterone) and mineralocorticoids (aldosterone). Although the etiology of Menière’s disease is still unsolved, cumulating evidence suggests that endolymphatic hydrops may arise as a result of the destabilization of natural regulation through overproduction and/or reduced absorption. The production of endolymph is thought to be regulated mainly by the enzyme Na/K-ATP-ase in the marginal cells of the stria vascularis of the cochlea, as well as in the dark cells of the utricle and the cristae ampullares of the semicircular canals. In earlier experiments a relationship between circulating adrenal steroids and Na/K-ATPase activity in the inner ear was observed. Emotional stress leads to the activation of neuroendocrine effector systems resulting in the increase of endolymph production. A borderline capacity of the endolymphatic sac in combination with a periodic increase of endolymph production caused by stressful situations is regarded to be responsible for the development of Menière’s disease.

Therefore, as part of the Groningen Diagnostic Protocol a study was performed on 89 patients with Menière’s disease to assess plasma aldosterone levels. Plasma aldosterone was not elevated in Menière patients compared to plasma aldosterone in a control group of 27 normal subjects. No statistically significant differences were found in plasma aldosterone between uni- and bilateral Menière’s disease. Plasma aldosterone levels did not correlate with age, average hearing loss, or duration or perceived severity of subjective complaints (vertigo, hearing loss, tinnitus and aural pressure). No elevated plasma aldosterone levels were found in patients with Menière’s patients during an attack-free period. The question whether plasma aldosterone and cortisol levels show variations before, during and after an attack remains to be answered. If so, this might contribute to a better understanding of the pathophysiological mechanism of Menière’s disease.

Chapter 12. The Definition Menière Groningen in future perspective

The definition of Menière’s disease is subject of continuous evolution as increasing information and knowledge is acquired regarding etiology, diagnosis and treatment. As many diseases can almost duplicate the symptoms of Menière’s disease an accurate assessment of the definition including the exclusion of other diseases is obligatory. The 1995 revised criteria for the diagnosis of Menière’s disease of the American Academy of Ophthalmology and Otolaryngology Committee on Hearing and Equilibrium provide uniformity and allow a more adequate comparison of clinical studies. However, the subdivision in four different categories and the absence of a diagnostic protocol to establish the diagnosis and to exclude other causes for the
symptomatology make the application in clinical and scientific practice still unsatisfactory.
The Definition Menière Groningen as used in this scientific project provided a fairly well-defined patient cohort allowing reliable and systematic analysis. Nevertheless, a more detailed characterisation of the specific symptoms of Menière’s disease and a revised diagnostic protocol based on the results of the thesis could further contribute to a uniform diagnosis. The Definition Menière Groningen 2001 including a diagnostic protocol is introduced for clinical purposes. The Definition Menière Groningen 2001 including an extended diagnostic protocol is proposed for scientific analysis. The Definition Menière Groningen 2001 for clinical purposes (diagnosis, treatment and reporting) includes a well-defined description of the correlating symptoms and a diagnostic protocol, which does not require a specialized test equipment (table 1).
A renewed Definition Menière Groningen including an extended diagnostic protocol for scientific purposes is proposed (table 2). The Definition Menière Groningen 2001 for scientific purposes includes the identical well-defined description of the correlating symptoms and an extended diagnostic protocol with emphasis on etiology and classification of the disease. The Definition Menière Groningen 2001 for clinical and scientific purposes may provide not only the accurate clinical assessment of the diagnosis of Menière’s disease, but also may contribute to further understanding of the etiology and pathogenesis of Menière’s disease.
**Table 1. Definition Menière Groningen 2001 for clinical purposes.**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
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<tbody>
<tr>
<td>Vertigo</td>
<td>spontaneous, not provoked</td>
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<td>at least two episodes (&gt; 20 minutes) in the past</td>
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<tr>
<td>Cochlear hearing loss</td>
<td>documented on at least one occasion</td>
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<tr>
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<td>total hearing loss of at least 60 dB over the three worst octaves in the standard pure-tone audiogram</td>
</tr>
<tr>
<td></td>
<td>present now or in the past</td>
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<tr>
<td>Tinnitus</td>
<td>ipsi- or bilateral</td>
</tr>
<tr>
<td></td>
<td>present now or in the past</td>
</tr>
</tbody>
</table>

**- Diagnostic Protocol:**

I. General and ORL-history
   - otological history
   - emotional stress related factors
   - personality features

II. General and ORL-examination
   - blood pressure measurement

III. Subjective audiometry
   - pure-tone audiometry
   - speech audiometry

IV. Objective audiometry
   - tympanometry
   - stapedial reflex measurements
   - brainstem evoked response audiometry (BERA)

V. Vestibular tests
   - electronystagmography
   - caloric tests
   - rotating chair

VI. Magnetic Resonance Imaging
   - T1, T2, gadolinium
   - petrosal bone, cerebellopontine angle, cerebrum

VII. Laboratory tests
   - full blood count
   - BSE
   - glucose
   - Lues serology
   - Borrelia burgdorferi serology
   - thyroid function test T3, T4, TSH

VIII. Consultation other disciplines on indication
   - internal medicine
   - neurology
   - ophthalmology
   - psychiatry
   - psychology
   - social worker
Table 2. Definition Menière Groningen 2001 for scientific purposes.

| - Vertigo | - spontaneous, not provoked |
| - at least two episodes (> 20 minutes) in the past |
| - Cochlear hearing loss | - documented on at least one occasion |
| - total hearing loss of at least 60 dB over the three worst octaves in the standard pure-tone audiogram |
| - Tinnitus | - ipsi- or bilateral |
| - present now or in the past |

- Extended Diagnostic Protocol:

I. General and ORL-history
   - otological history
   - emotional stress related factors
   - personality features

II. General and ORL-examination
   - blood pressure measurement

III. Subjective audiometry
   - pure-tone audiometry
   - speech audiometry
   - fine structure audiometry
   - low-frequency masking

IV. Objective audiometry
   - tympanometry
   - stapedial reflex measurements
   - brainstem evoked response audiometry (BERA) including threshold and latency measurement
   - otoacoustic emissions (OAEs) including postural changes

V. Vestibular tests
   - electronystagmography
   - caloric tests
   - rotating chair

VI. Magnetic Resonance Imaging
   - T1, T2, gadolinium, 3DFT-CISS, 0.7mm slices
   - petrosal bone, cerebellopontine angle, cerebrum
   - distance between vertical part of posterior semicircular canal and posterior fossa
   - hippocampus

VII. Laboratory tests
   - full blood count
   - BSE
   - glucose
   - Luces serology
   - Borrelia burgdorferi serology
   - thyroid function test T3, T4, TSH
   - cortisol assessment
- dexamethasone suppression test

VIII. Psychometric analysis
  - personality characteristics
  - coping
  - quality of life

IX. Symptomatology profile questionnaire (intake+follow-up)

X. Consultation other disciplines on indication
  - internal medicine
  - neurology
  - ophthalmology
  - psychiatry
  - psychology
  - social worker

XI. Donor codicil for post-mortem studies