Ductus Reuniens and Its Possible Role in Menière's Disease

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Objective: After 160 years the true underlying cause of Meniere's disease remains enigmatic. The aim of our study is to discuss the possible implication of an obstruction of the ductus reuniens as a cause in Menière's disease.
Methodology: We first conducted an historical study of the description of the ductus reuniens. We then reviewed the literature regarding ductus reuniens obstruction in animal experiments, human post-mortem studies and living ear imaging. We completed its description by modern microCT imaging. Limited knowledge on the fate of dislodged saccular otoconia is summarized. The possible implications for Meniere's attacks are discussed.
Results: Victor Hensen was the first to describe the ductus reuniens in 1863. He described its length and width and predicted that saccular otoconia might enter the ductus and the cochlea. On microCT the narrowest width of the human ductus reuniens was 0.14 mm. The literature reports cochlear endolymphatic hydrops occurring after animal experimental obstruction of the duct. Human postmortem studies have confirmed saccular otoconial clumps entering the ductus and the cochlea. A postmortem study has shown sites of endolymphatic obstruction, and imaging speculates on blockages in ears with Meniere's disease. Dislodged utricular otoconia can be in clumps of otolithic membranes.
Conclusion: Blockages of the ductus reuniens and at other endolymphatic system sites appear to be a feature in Meniere's disease ears. The blockages have been postulated to be saccular otoconia either causing or aggravating hydrops. This could be consistent with observed nystagmus reversals during attacks as the endolymphatic sac attempts to clear the hydrops and the otoconia. **Key Words:** Cochlea—Ductus reuniens—Menière's disease—Otoconia—Saccule—Vestibular.

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INTRODUCTION

After 160 years the true underlying cause of Meniere's disease remains enigmatic. Briefly, theories have been inner ear ischaemia, a variation in the size or position of the endolymphatic duct or sac, a viral infection of the endolymphatic sac, an autoimmune or allergic condition, or (assuming a provable family history) a genetically determined abnormality of endolymph control The aim of our study is to discuss the possible implication of an obstruction of the ductus reuniens as a cause in Menière's disease.

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METHODOLOGY

We first conducted an historical study of the description of the ductus reuniens. We then reviewed the literature regarding ductus reuniens obstruction in animal experiments, human postmortem studies and living ear imaging. We completed its description by modern microCT imaging.

History of the First Descriptions of Inner Ear Structures

Modern knowledge concerning the anatomy of the ear began in the sixteenth century. The Italian anatomist Andreas Vesalius (1514–1564) was the first to remove the human organ of hearing from the skull for dissection and recognised the middle ear, malleus, incus (but not the stapes), tensor tympani muscle, oval and round windows, cochlea, vestibule, semicircular canals, and the acoustic nerve (1). In the seventeenth century there were only scant references to ear anatomy outside Italy. Attention turned to animal dissections where there followed a long period of descriptions of ear structures and speculation on their function by Italian, German, British, Dutch, and French

investigators. Of note Guichard Joseph Duverney (1648–1730) in France dissected and anticipated the true function of the cochlea (2). Italian Domenico Cotugno (1736–1822) was the first to establish the dimensions of the vestibular aqueduct and its communication with the endolymphatic sac under the posterior fossa dura, and with mercury injections identify veins and lymphatic vessels (3). Cotugno also confirmed the cochlear aqueduct, first identified by Duverney.

By the nineteenth century, the accepted theory of cochlear function was for its role in the perception of sound pitch. Various notions concerning the role of the semicircular canals and the otolith organs prevailed. Antonio Scarpa (1747–1832) from Italy has been described by Politzer as being one of the ''greatest anatomists of all time'' (4). Insisting on examining fresh specimens, using a primitive microscope, he discovered the membranous labyrinth. He demonstrated that the membranous labyrinth in man and higher animals was similar to the bony labyrinth and consisted of ''three semicircular tubes'' and two small sacs in the vestibule (5). He named the anterior sac the saccule, and the posterior sac that was connected to the ampullae of the semicircular canals the ''the common sac,'' later called the communis utriculus (utricle) by Samuel Thomas Soemmerring (1755–1830) in Germany (6). This new structure was probably the one identified by Giovanni Battista Morgagni (1682–1771) as ''particular canals containing particular threads, fine, quite long, curved, white in colour and very similar to small nerves'' (7). He was familiar with ''labyrinthine humour'' (perilymph) and then observed an inner ''limpid humour'' (endolymph). Scarpa also described a white, oblong, shiny spot which he considered to be produced by expansion of the auditory nerve. It was later named the otoconia by Gilbert Breschet (1784–1845) in France (8), and identified as being similar to the otolith in fish and amphibians. Breschet was among the first to investigate otoliths as being crystals of calcium carbonate and named them otoconia in higher mammals. He was the main proponent of the otolith organs in the mammalian ear as being for the perception of the loudness of sound. Similarly the German physician John Heinrich Ferdinand von Authenreith (1772–1735) believed that, due to their anatomical configurations, the function of the semicircular canals was to recognize the direction of sound (9,10). This theory was overturned in 1824 by the experiment of Pierre-Marie Flourens (1794–1867) who lesioned semicircular canals inducing violent head turns in the plane of the canal (11). Although it was not his conclusion Flourens has been credited with establishing the semicircular canals have a role in balance function and not hearing.

The Description of the Ductus Reuniens by Hensen

Three hundred years of overlapping discoveries of ear structures by many investigators in many countries can lead to argument as to originality. For the most obscure inner ear structure there is no debate. Victor Hensen (1835–1924) (Fig. 1) studied medicine in Berlin, but was best known as a zoologist at the University of Kiel, Germany.

Among many accomplishments he is considered the father of biological oceanography and coined the term plankton (12). In 1863, he published *Zur Morphologie der Schnecke des Menschen und der Saugethiere* on the structure of the cochlea in humans and mammals (13). In this study, he described several rows of cells in the organ of Corti, which are elongated in the basal turn and increase in height toward the cochlear apex (14), and a new structure—the ''canalis reuniens'' (Fig. 2). Hensen states:

> Here [at the root of the cochlear canal], however, as Fig. 1 shows, the membrane [i.e., Reissner membrane] produces a sac backwards, which one, over the last cartilage teeth, manages a connection, the ''canalis reuniens'', with the Sacculus rotondus. This is about 0.7 mm long canal, the narrowest part of which is 0.225 mm, after the fluid has been removed, its walls are only 0.015 mm thick. It is continuous, which, apart from the fact that a closure was nowhere to be seen, hence the fact that I succeeded with the needle at 50 times. Enlargement of getting from the Sacculus into the cochlear canal, whilst I gradually lifted the upper wall from the lower one. *Without a doubt, the otoliths can be driven into the cochlear canal, as well, as they are usually pressed into the semicircular canals in certain otological sections of the labyrinth! [The exclamation mark is Hensen's]*

The presence of the canalis reuniens was confirmed by other German investigators. Jean Cruveilhier (1791–1874) in France was the first to use the term ductus reuniens (15), the official name most commonly used thereafter as well as the reuniting duct.

Into the twentieth century, the emergence of temporal bone laboratories saw the duct depicted in numerous

FIG. 1. Christian Andreas Victor Hensen (1835–1924).

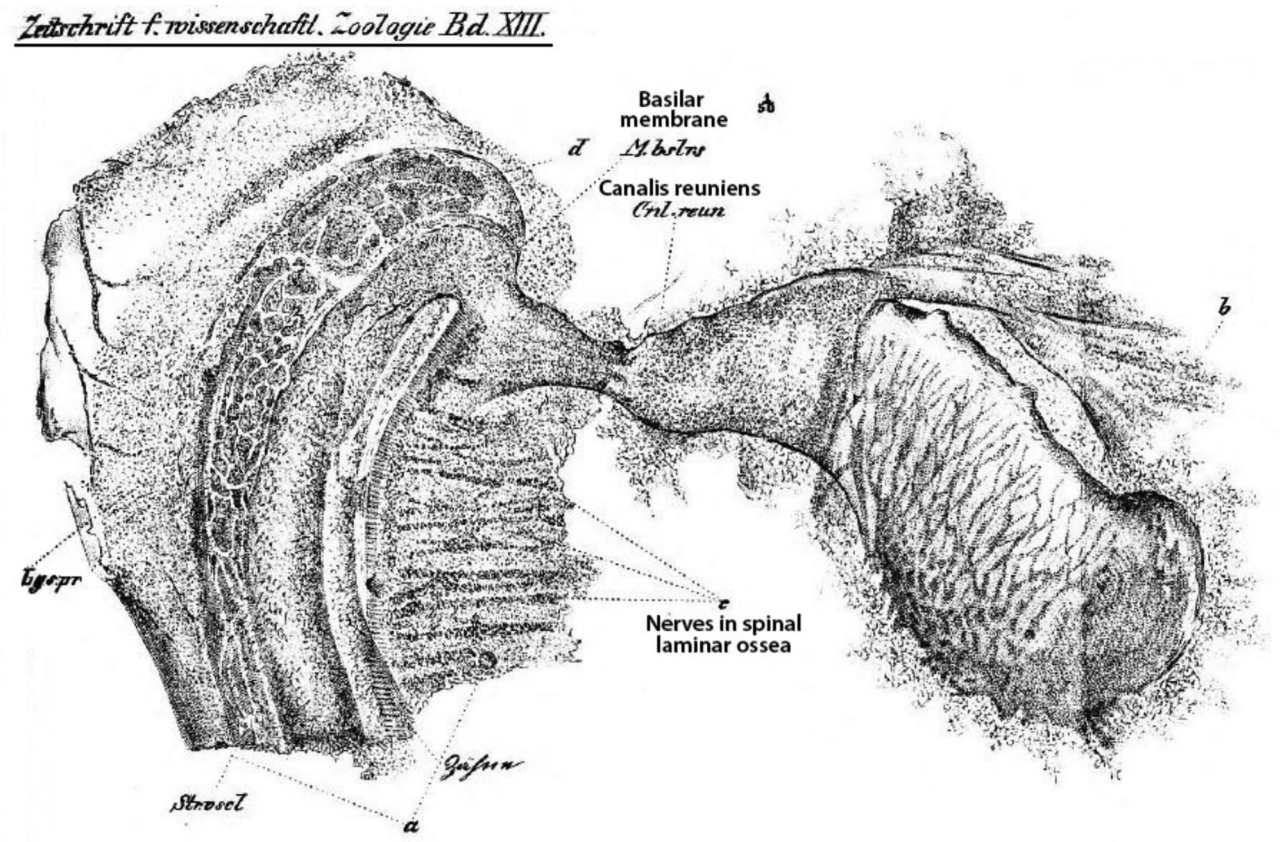

FIG. 2. Hensen's 1863 pen and ink drawing with the first depiction of the canalis reuniens (13).

histological specimens available only to experts. The Johns Hopkins Professor of Art as Applied to Medicine Max Brödel (1870–1941) became interested in the ear late in his career. His pen and ink sketch of inner ear structures and 1946 unpublished antero-medial drawing of membranous structures in the vestibule (Fig. 3), completed after his death by P.D. Malone (16), have served as the main *conceptual* images of a tiny structure.

Live Human Imaging of Ductus Reuniens

Using 3D cone beam CT scanning of human normal ears and ears with Meniere's disease Yamane and colleagues have attempted to image the endolymphatic system in living human ears. In one study (17), they describe the ductus reuniens, saccular duct, and endolymphatic sinus as showing a loss of continuity being a feature of Meniere's disease compared with normal inner ears. The implication is that there are blockages, but the images are of insufficient clarity to convincingly demonstrate blockages and what they might be. Although MRI inner ear imaging is now becoming commonplace, in our opinion a clear MRI image of a normal ductus reuniens in a living human ear has yet to be published.

MicroCT of Guinea Pig and Human Inner Ear of Ductus reuniens

MicroCT Images of Guinea Pig Inner Ear

The images in Figure 4 are from reconstructions of previously published microCT data of the labyrinth of guinea pigs and human (18,19). Figure 5 shows the reconstruction of the whole guinea pig ductus reuniens from the cochlear duct to the saccule. The scanning methods and reconstructions were similar for both species and the methods are summarized in Supplemental Digital Data—Methods, http://links.lww.com/MAO/B336.

MicroCT Images of the Human Inner Ear

The Methods including details about the scanning parameters are described in detail in earlier publications (20,21) and are summarized in Supplemental Digital Data—Methods, http://links.lww.com/MAO/B336. Figure 6A shows a microCT section through a human temporal bone to show the ductus reuniens. The length of the slender portion of duct is 1.12 mm and minimum diameter 0.14 mm. Figure 6B is a three dimensional reconstruction of the ductus reuniens in the human temporal bone, in relation to other major inner ear structures. As in the

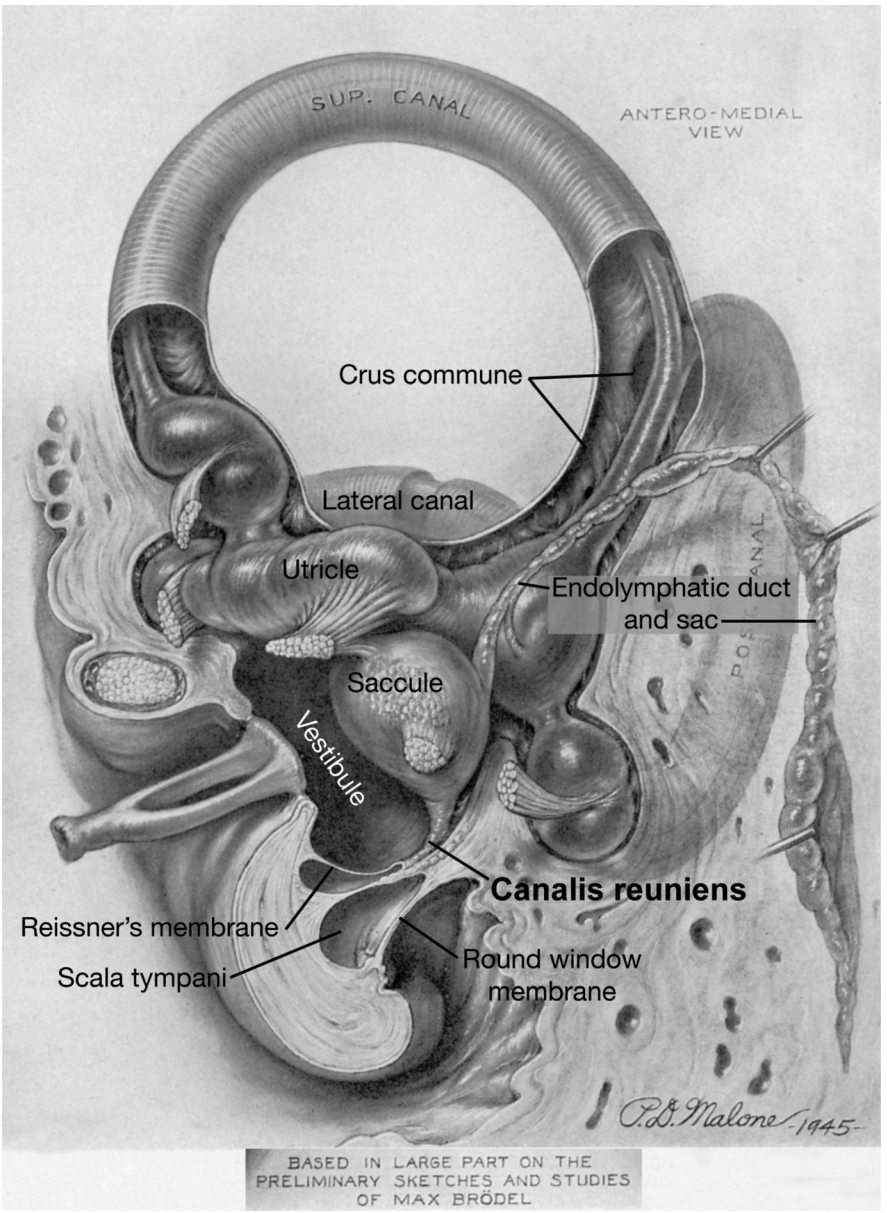

FIG. 3. Brödel's unpublished drawing of the membranous labyrinth (book completed by P.D. Malone) from a copy of the book in the possession of the authors. This is an antero-medial drawing of membranous structures in the vestibule showing the canalis reuniens (16).

guinea pig the ductus courses in close proximity to the medial wall of the labyrinth.

The Theory of Obstruction of Ductus Reuniens

Schuknecht and Ruther (22) examined 46 temporal bones with a premortem history of Meniere's disease for blockages. Blockages were seen in the endolymphatic duct, endolymphatic sinus, utricular duct, saccular duct, saccule and in 27/46(59%) of ductus reuniens. Kitamura et al. (23) studied 5 temporal bones with hydrops limited to the cochlea, all of which had a collapsed saccule and blocked ductus reuniens. Kimura et al. (24) attempted obliteration of the ductus reuniens in 52 guinea pigs. In 35/52 (67%), there was cochlear hydrops, saccule collapse and a normal utricle. When the endolymphatic duct was blocked 2 months later the utricle became involved. Ductus reuniens obstruction had to be total for significant cochlear hydrops to occur. In a human cadaver study, Ishiyama et al. (25) sought the potential electrode causes for delayed loss of residual hearing in cochlear implant recipients. Round window insertion was associated with no fibrosis or cochlear hydrops. In those who had a cochleostomy insertion 17/29 (59%) had hydrops from ductus reuniens obstruction.

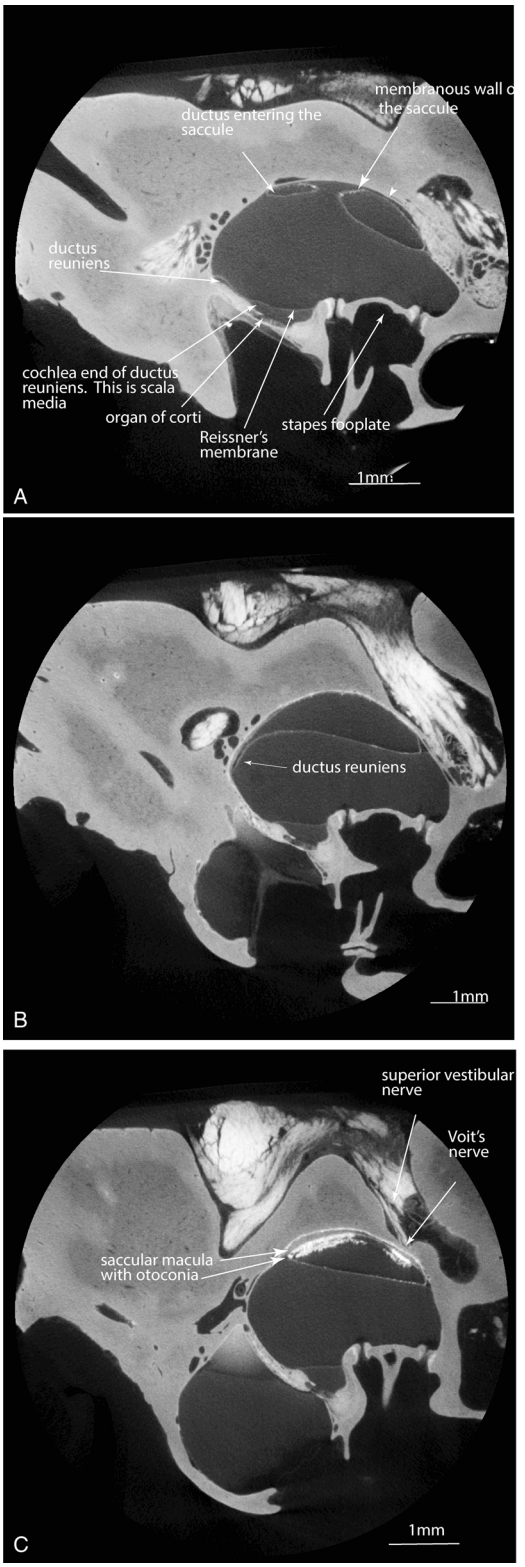

FIG. 4. Three sequential microCT sections through the guinea pig labyrinth showing the ductus reuniens connecting the cochlear duct and the saccule. *A*, Horizontal cross-section through the guinea pig stapes, saccule, and the basal turn of the cochlea. The features of the cochlea are visible (Reissner's membrane, organ of Corti). The thin tube of the ductus reuniens can be seen as an extension of the cochlear duct, coursing against the medial wall of the labyrinth to the membranous wall of the saccule. *B*, The thin tube of the ductus is visible against the medial wall of the bony labyrinth, coursing toward the cochlea. The tube of the ductus as it enters the saccule is clearly distinguished. *C*, The adjacent saccular macula in the saccule, with the macula and the otoconia visible as two distinct layers. This section is close to the caudal end of the saccule where the ductus reuniens enters the sac of the saccule just at the location of the arrowhead labelled otoconia. Osmium is taken up by myelin so the superior vestibular nerve (and the branch known as Voit's nerve) appears as the whitish strands to the right.

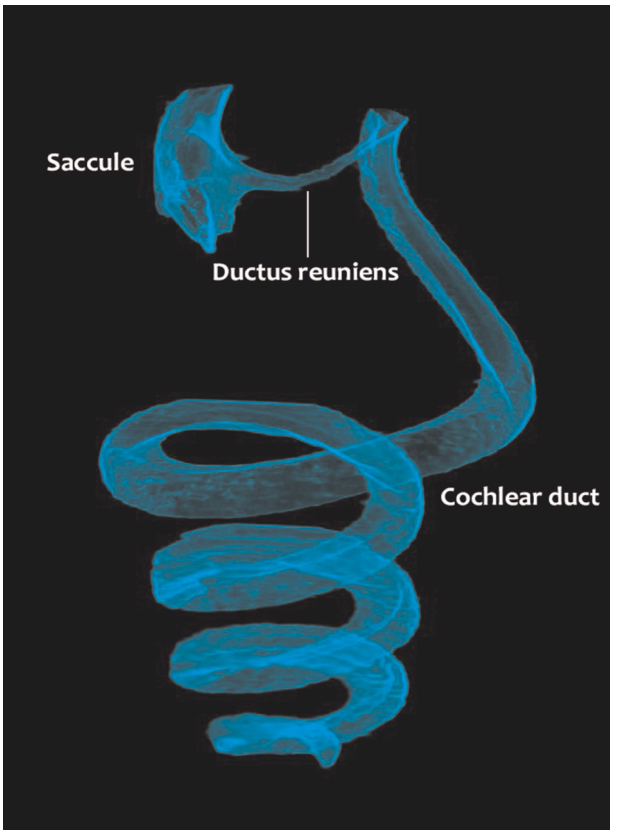

FIG. 5. Three-dimensional reconstruction of the guinea pig ductus reuniens alone (after digital deletion of the surrounding tissue) coursing from the scala media of the cochlea duct to the membrane of the saccule.

DISCUSSION

An abnormal accumulation of endolymph called endolymphatic hydrops is recognized as the pathological feature of Meniere's disease (26). After injecting a blue dye into the guinea pig cochlea, in 1927 Guild proposed that there is constant flow of endolymph from the stria vascularis from which ''The endolymph in the cochlear duct moves toward the basal end and passes through the canalis reuniens into the sacculus, and from the sacculus through the ductus endolymphaticus into the saccus endolymphaticus'' (27). Guild also noted that ''crystals [presumed to be otoconia] embedded in a gelatinous

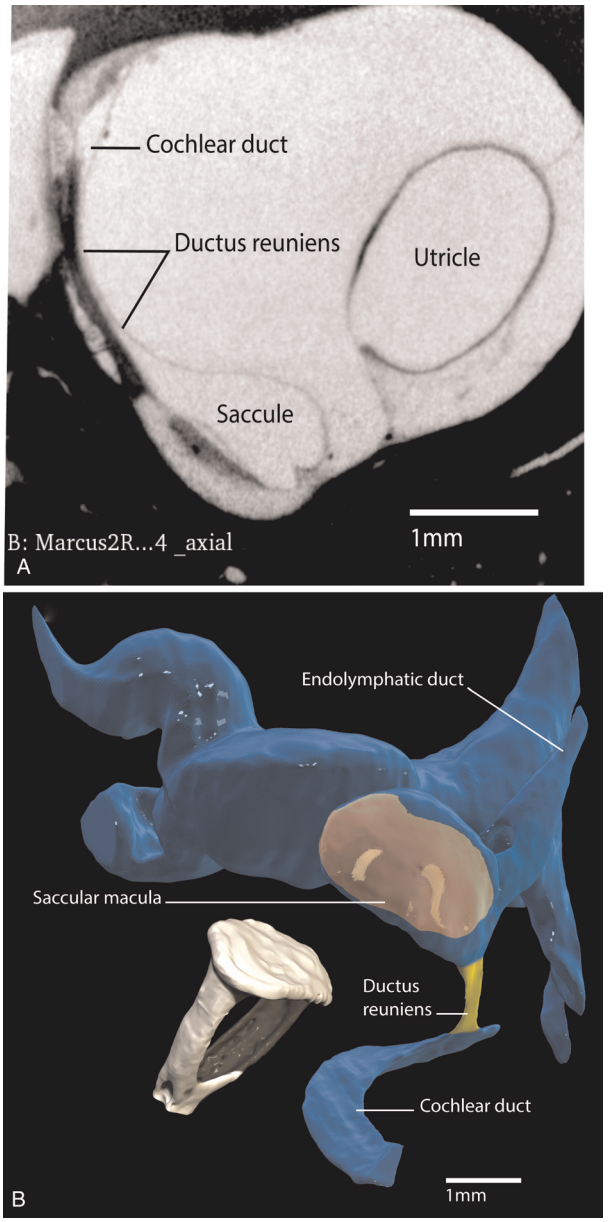

FIG. 6. *A*, Image from microCT scan of the human labyrinth showing the ductus reuniens and its connection between the cochlear duct and the saccule. The length of the slender portion of the duct is 1.12 mm and minimum diameter 0.14 mm. From these images, a 3D reconstruction was made. *B*, Three-dimensional reconstruction of the human membranous labyrinth showing the ductus reuniens. The major structures are labeled, and the wall of the membranous labyrinth is shown in blue.

mass. . ..in the enlargement of the ductus endolymphaticus near the superficial oriface'' have been seen in some nonmammalian species, and could support what has been termed his longitudinal flow theory.

Until recently, there have been two predominant competing theories as to the mechanism of Meniere's vertigo attacks. The first is Schuknecht's potassium intoxication theory (28). Assuming constant longitudinal flow Schuknecht proposed that ''endolymphatic hydrops of the progressive type. . ..appears to be the result of *permanent impairment* of endolymph resorption and is caused principally by disorders of the endolymphatic sac.'' Increasing hydrops results in a rupture of Reissner's membrane in the cochlea, allowing potassium-rich endolymph to enter the perilymph. The initial (assumed) ipsilateral nystagmus is postulated to be caused by potassium stimulation of vestibular endorgans, and the reversal to contralateral nystagmus by a central compensation mechanism. Practical counter arguments to the Schuknecht rupture theory are the remoteness of a rupture in the cochlea, and that anatomically discrete losses of hearing or total hearing losses are not typical. Brown et al. (29) injected endolymph into the guinea pig cochlea and made electrophysiological measurements from utricular afferent nerves. Changes in utricular function implied a sudden endolymph escape through the utriculo-saccular duct into the utricle. MicroCT on the ears showed no ruptures. Transtympanic electrocochleography is an evoked response electrophysiological test of inner ear function. In Meniere's ears a 1 kHz tone burst elicits a measurable large negative summating potential (SP) which implies basilar membrane distortion from hydrops. Gibson (30) identified 87 patients tested 1 to 24 hours before an attack, during an attack and up to 72 hours after. SP measurements imply that there is a sudden increase in hydrops prior to an attack, a decrease with the attack and then a slow increase over 72 hours. The action potentials (cochlear nerve function) were unaltered, making ruptures unlikely. In a patient with bilateral Meniere's disease Nakada et al. (31) accomplished MRI inner ear imaging of an attack, and no ruptures were seen.

The second theory is the Gibson-Arenberg drainage theory (32) based on the evidence that ruptures do not usually occur, and that the endolymphatic sac can act rapidly to clear hydrops when it occurs. Salt and DeMott (33) have challenged Guild's theory of constant longitudinal flow of endolymph. Microinjections of artificial endolymph containing an ionic flow marker into the second turn of the guinea pig cochlea suggest that small volume disturbances are corrected locally by radial flow in the cochlea. Larger volume disturbances stimulate longitudinal flow towards the endolymphatic sac. The drainage theory is that when significant endolymphatic hydrops occurs in the cochlea (from whatever cause) the endolymphatic sac attempts to clear it. The sac contains hydrophilic proteins (34) and natriuretic peptides that may have a role in controlling cochlear endolymph (35). It may clear it, but if the sac is dysfunctional, or if the duct is narrow (36) or blocked, excess endolymph fills the endolymphatic sinus. If it cannot be cleared by the sac endolymph refluxes though the utricular valve of Bast and past the utricle and into the horizontal canal ampulla explaining nystagmus. Two MRI inner ear imaging studies on Meniere's ears have shown hydrops into the horizontal canal only (31,37). If the duct and sac regain function the endolymph direction and nystagmus

direction reverse. Animal experiments and fortuitous nystagmus recordings in the clinic (38–45) have been used to both support and refute a rupture mechanism. Varying descriptions of initial nystagmus direction and reversals may depend on the phase of attack recorded. Using a continuous ambulatory nystagmus monitor Phillips et al. (46) have recorded an entire attack. From the prodrome (preceding vertigo) over the next three hours eight nystagmus reversals occurred, most likely explained by an alternating flow of endolymph mechanism.

There is a very recent third theory. In 1927, Guild (27) stated ''[the saccus endolympaticus] serves as the principal outflow of endolymph; *not, as some have thought, as the place of origin of endolymph*.'' The new theory is based on a venous plexus around the human endolymphatic duct demonstrated by microCT and synchroton techniques (47). The plexus is speculated to cause an uncontrolled endolymphatic sac secretion of endolymph and a sudden increase in endolymph pressure initiating a vertigo attack (48).

The utricle and saccule contain thousands of calcite-based otoconia of varying size embedded in an acellular matrix with connecting fibrils which creates a flexible, deformable network. Their mean size is about 10 μm (0.01 mm) (49). Experimental immersion of mammalian otoconia has shown they usually dissolve in normal endolymph in 20 hours (50). The effects of undissolved free utricular otoconia as the cause of benign paroxysmal positional vertigo are beyond doubt, but the fate of saccular otoconia is seldom questioned. The endolymphatic sac has morphological features suggesting its role in the absorption of endolymph and digesting cellular debris (51). The duct and sac have been observed to contain otoconial bodies (52–55) suggesting they may play a role in the absorption of free otoconia. In a temporal bone of a female with a vertigo history, Gussen (56) found unilateral saccule degeneration with clumped otoconia obliterating the cochlear end of the ductus reuniens and mild hydrops of the basilar end of the cochlear duct. In a further study of eight temporal bones with varying degrees of cochleosaccular degeneration, five exhibited otoconial obstruction of the ductus reuniens and the cochlear duct as far as the ascending basal limb (57). Using scanning electron microscopy, Kao et al. (58) have shown that dislodged utricular otoconia in posterior semicircular canals can be in large clumps in otolithic membranes.

The narrowest human ductus dimension found in the present study is 0.14 mm, so it would require a width of approximately 14 otoconia, possibly in clumps, to cause obstruction. Based on a two-institutional postmortem temporal study (59) it appears that hydrops always occurs in the cochlea before the saccule, and then in the utricle. This is supported by one MRI inner ear imaging study (60). Chen et al. (61) measured cVEMPs (saccular function) and oVEMPs (utricular function) in Meniere's subjects at an early and late stage of disease and in normal control ears. In the early disease stage abnormal saccule function occurred earlier than in the utricle, and the saccule remained more involved than the utricle in the late disease stage. This could be explained by the observation of saccular otoconia in the ductus reuniens (23,56,57), other postmortem studies (22,23) and imaging speculations (17) on what might be later endolymphatic system blockages.

It is accepted that utricular otoconia can become detached for reasons other than trauma, so it is likely that saccular otoconia can do so. If the endolymphatic sac does produce a backflow of endolymph (47,48), damage to the saccule could account for its initial loss of otoconia. That free otoconia might be a cause of endolymphatic hydrops and even Meniere's disease has been suggested (17,62–64). Yamane (17), Hornibrook and Bird (63), and Hornibrook et al. (64,65) have postulated that detached saccular otoconia might be at least one cause of initial cochlear hydrops. This could be consistent with observed nystagmus reversals during attacks as processes within the endolymphatic sac are acting to clear the hydrops and the otoconia (30,31,37). With normal bilateral horizontal canal function a unilateral utricular dysfunction alone can cause horizontal nystagmus (66). Assuming no ruptures and a drainage mechanism, the multiple nystagmus directions in a Meniere's attack may be complicated by additional utricular and central compensation mechanisms.

CONCLUSION

In 1863, Victor Hensen discovered the ductus reuniens and predicted that saccular otoconia could enter the duct and the cochlea. Hensen also commented on seeing otoconia in semicircular canals at least a 100 years before the suspected cause of benign paroxysmal positional vertigo was confirmed. There is strong evidence that cochlear endolymph ruptures are not the cause of Meniere's attacks. Multiple nystagmus direction changes during an attack could be explained by endolymph movements in one direction, and then in the opposite direction. Observation of saccular otoconial debris in the ductus reuniens makes possible partial or total obstruction, as well as at other sites in the endolymphatic system. One possible function of the endolymphatic sac is to clear dislodged saccular otoconia. Dislodged utricular otoconia have been observed to be in clumps, raising the likelihood that saccular otoconia can be. Significant advances in internal imaging of the living human inner ear will be required to provide further in vivo proof or disproof of endolymphatic blockages in Meniere's ears and what they might be. It is acknowledged that this paper is an historical study of one structure, and not a comprehensive review of the literature on Meniere's disease. The possible relevance of the ductus reuniens has been discussed in the light of the main theories.

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