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Sketches of Otohistory

Part 8: The Emergence of Vestibular Science

Joseph E. Hawkins   Jochen Schacht

Kresge Hearing Research Institute, University of Michigan, Ann Arbor, Mich., USA

The Beginnings

In the 2nd century AD, the Greek physician-anatomist Galen, in the course of his osteological study of the skull, took a look into the inner ear. Its curving passageways reminded him of the Cretan 'Labyrinthos', said to have been built by the fabled Daedalus for King Minos. Galen decided that the inner ear also deserved the name of *labyrinth*, but he seems to have gone little further in his examination of it. By the end of the 18th century, after the exhaustive labors of the renaissance anatomists and their successors, many features of the inner ear had been described and pictured, but no one suspected it of having any function apart from that of hearing. Discovery that its membranous sacs and canals had a different role was reserved for the 19th century.

Explaining Vertigo

Although Julien Offray de la Mettrie (1709–1751), a highly controversial minor prophet of the Enlightenment, may have been unaware of the vestibular system, he is included here for his long-forgotten *Traité du vertige* [1737]. He attributed vertigo solely to a disturbance of visual function. During his studies in Leiden, he became a devoted disciple of Boerhaave, professor in medicine, botany and chemistry, and esteemed teacher, whose writings he translated into French. He returned to France in 1742 but was forced to leave Paris because of his views on the close relation between psychic disturbances and organic ills, as expressed in his *Histoire naturelle de l'âme* (1745), and returned to Holland. There, the atheistic materialism of his 'Man a Machine' (*L'Homme Machine,* 1747) soon caused a second banishment. In 1748, at the invitation of Frederick the Great, he moved on to the Prussia court as physician and court reader, where he pleased his host but angered his fellow-guest, Voltaire. A practicing hedonist and voluptuary, La Mettrie's sudden death at Frederick's court 3 years later was attributed by his enemies to the deadly sin of gluttony, but its probable cause was food poisoning.

Erasmus Darwin (1731–1802), grandfather of Charles, was a leading intellectual in England, a practicing physician in Lichfield (Shropshire) and a well-known poet. As a philosopher, he was an evolutionist long before his more famous grandson. It was his belief that animals change and evolve by adapting to the conditions of their environment, and even stated that 'The final course of this contest among males seems to be, that the strongest and most active animal should propagate the species which should thus be improved'. He included a chapter on vertigo in his *Zoonomia, or, the Laws of Organic Life* (1794–1796). Unfortunately, his classification of three types may have contributed more to confusing than to clarifying the problem:

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Jochen Schacht, PhD
Kresge Hearing Research Institute, University of Michigan
1301 East Ann Street
Ann Arbor, MI 48109-0506 (USA)
Tel. +1 734 763 3572, Fax +1 734 764 0014, E-Mail schacht@umich.edu

1 Flight vertigo, which affected the elderly, and was caused by beginning defect of sight, but wrongly attributed to indigestion;
2 Auditory vertigo, 'which is called a noise in the head… which is also very liable to affect people in the advance of life and is owing to their hearing less perfectly than before';
3 'Another kind of vertigo begins with the disordered action of some irritative muscular motions, such as those of the stomach from intoxication'.

Defining the Organ of Balance

Among the first to dissociate the semicircular canals from the sensation of hearing was Marie-Jean-Pierre Flourens (1794–1867), one of the earliest neurophysiologists. He obtained his MD at Montpellier, where he was inspired by Georges Cuvier, the influential natural historian. By removing various portions of the brain in pigeons and rabbits, Flourens determined the functional significance of the cerebral hemispheres, cerebellum and medulla. He located the respiratory center *(noeud vital)* near the emergence of the vagi. In 1824, Flourens first told of the remarkable effects of cutting the semicircular canals on the posture and behavior of pigeons and showed how the loss of each of the ducts affected postural equilibrium, flight and movement, but not the hearing, with which they had always been thought to be associated [Flourens, 1824]. When stimulated, each canal caused eye movements (nystagmus) in its own plane. He published details of additional experiments in birds and rabbits in 1830 [Flourens, 1830]. Among his other contributions was his examination of the role of the periosteum in the formation of bone, and the use of chloroform as an anesthetic.

His fellow scientists seem to have taken little notice at that time, but 30 years later Ménière recalled Flourens when he insisted that the human complaint widely known as 'apoplectiform cerebral congestion' had to be a disorder of the labyrinth and not of the brain. In 1840, Flourens became one of the French 'immortals' when chosen a member of the Académie française. Upon his death, he was succeeded by Claude Bernard, who pronounced an eloquent eulogy, but somehow failed even to mention his predecessor's pioneer work on the vestibular organs.

The Czech physiological genius Jan Evangelista Purkyně (more commonly spelled Purkiné or Purkínje; 1787–1869) has lent his name to many well-known physiological phenomena and anatomical structures. He was educated by Piarist monks, but chose a career in philosophy, eventually graduating in medicine from Prague. His doctoral dissertation and early scientific interest in vision and optics was inspired by Goethe's *Farbenlehre*. It was through Goethe that he met important scientists and other intellectuals in Berlin, and came to be appointed as professor of physiology in Breslau, where he created the first department of physiology. His German colleagues deeply resented having the foreign colleague in their midst, but at the same time he pleased the Ministry of Education by bringing laboratory work and demonstrations into his teaching. He also obtained a compound microscope and is credited with the first use of the microtome, potassium bichromate and Canada balsam for histological studies.

While best known for his discovery of the Purkinje cells in the cerebral cortex and the Purkinje fibers in the heart, he also published studies on vertigo [Purkinje, 1920, 1827]. In his strenuous and exacting experiments of nystagmus and vertigo, Purkyně used only himself as his subject. A revolving stool served as his equipment for observing the effects of rotation, with his head in various positions; he also employed galvanic stimulation. Later he abandoned this interest.

Towards an Understanding of Vestibular Function

Although earlier scientists like Purkyně had experimented on human sensations, it was the physiological studies on animals that paved the way for groundbreaking clinical studies in the latter half of the 19th century. Friedrich Leopold Goltz (1834–1902) received his medical degree from Königsberg in Germany and worked in the surgical clinic there, while carrying out physiological experiments with frogs as his subjects. In his vestibular study of 1870, Goltz followed Flourens in the use of pigeons [Goltz, 1870]. He could not entirely rule out the possibility that the semicircular canals have some auditory function, but he was able to show that they serve for the maintenance of the equilibrium of the head, and indirectly for that of the entire body. In 1870, on the recommendation of Helmholtz he received an appointment in physiology at the University of Halle, and 2 years later as professor at the newly founded University of Strasburg, where he stayed until his retirement in 1900.

Josef Breuer (1842–1925), a physiologist and practicing physician in Vienna, followed the lead of Flourens and Goltz in studying the effects of cutting the individual semicircular canals in pigeons. He published his first results between 1873 and 1875 [Breuer, 1874, 1875]. Unlike Goltz, he recognized that directional currents in the endolymph in response to head movements, rather than variations in its hydrostatic pressure, must be the effective stimuli for equilibrium control by the canals. In subsequent publications in 1889 and later, he considered the function of the saccular and utricular otoliths, suggesting that because of their weight they exert pressure on the hair cells beneath them. Their degrees of pressure must vary with slight shifts of the otoliths in response to head movements and these changes must constitute the adequate stimuli for their control of head position.

As a student, Breuer had worked with his teacher, Ewald Hering, on the control of respiration, and had revealed the reflex self-regulation of breathing via the vagi. As a collaborator and friend of Sigmund Freud, who greatly admired him, Breuer was also interested in psychology, and especially in hysteria. Freud's famous Frl. Anna O. was actually a patient of Breuer's; it was Breuer who devised for her the 'talking cure' method known as 'catharsis'. Ernest Jones, a contemporary, friend and coworker of Freud, calls the years 1882–94 Freud's 'Breuer period', but Breuer himself eventually lost his faith in psychoanalysis, and with it Freud's friendship.

Ernst Mach (1838–1916), primarily a physicist and mathematician at the universities of Prague, Vienna and Graz, was a man of far-ranging scientific interests. He was fascinated by the physiological mechanisms of sensation and movement, and published books on his analyses of both. Quite independent of Breuer, he conducted similar experiments, observing the responses of birds and fishes to angular acceleration in his 'cyclostat' (fig. 1). Their papers appeared almost simultaneously in 1873 and 1874 and they conveyed almost identical conclusions concerning the actions of the canals and the otolith organs [Mach, 1873; Breuer, 1874]. Their interpretation, that the vestibular organs had nothing to do with hearing but only with postural equilibrium and head position, became recognized as the 'Mach-Breuer hypothesis'. It soon came to be widely accepted, despite the skepticism and outspoken opposition of Viktor Hensen. As a philosopher of science, Mach pointed out that all knowledge arises from sensations. He insisted that no scientific statement is admissible unless it is empirically verifiable. His rejection of absolute space and time is said to have paved the way for Einstein.

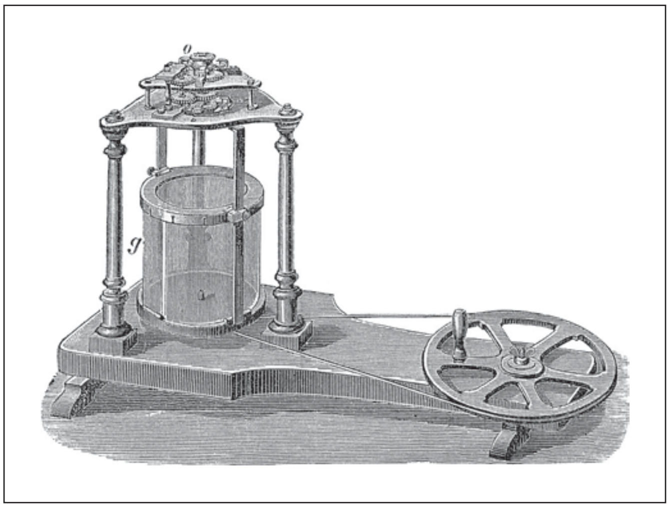

Fig. 1. Ernst Mach's 'Cyclostat' for the vestibular stimulation of small animals. From Mach E: Beiträge zur Analyse der Empfindungen. Jena, Fischer, 1886, p 71.

Clinical Vestibular Science

The experiments that Alexander Crum Brown (1838–1922) reported in his paper, *On the sense of rotation and the anatomy and physiology of the semicircular canals of the inner ear* [Crum Brown, 1874], were performed on a rotating table, with human subjects rather than with animals. Crum Brown had received his medical degree from Edinburgh with a thesis entitled *The theory of chemical combination*. He became the professor of chemistry there, after further studies with Bunsen and Kolbe in Germany, and he never practiced medicine. In his studies of the vestibular sensations [1874], his patients were blindfolded, and the head was placed in various positions, so as to make the vertical axis coincide with any hypothetical straight line in the head. He stated that 'rotation of the head about an axis at right angles to the plane of a canal will produce, on account of the inertia of the liquid, &c. motion of the contents relative to the walls of the canal, and this may be expected to irritate the terminations of the nerves in the ampulla'. He concluded that one canal could be affected by and transmit the sensation of rotation about one axis and in one direction only. Therefore, 'six semicircular canals are required, in three pairs, each pair having its two canals parallel (or in the same plane) and with their ampullae turned opposite ways'.

William James, the Harvard psychologist and vigorous exponent of pragmatism, who transformed psychol-

Fig. 2. Newspaper announcement of Robert Bárány's Nobel Prize. Photo by Bain News service.

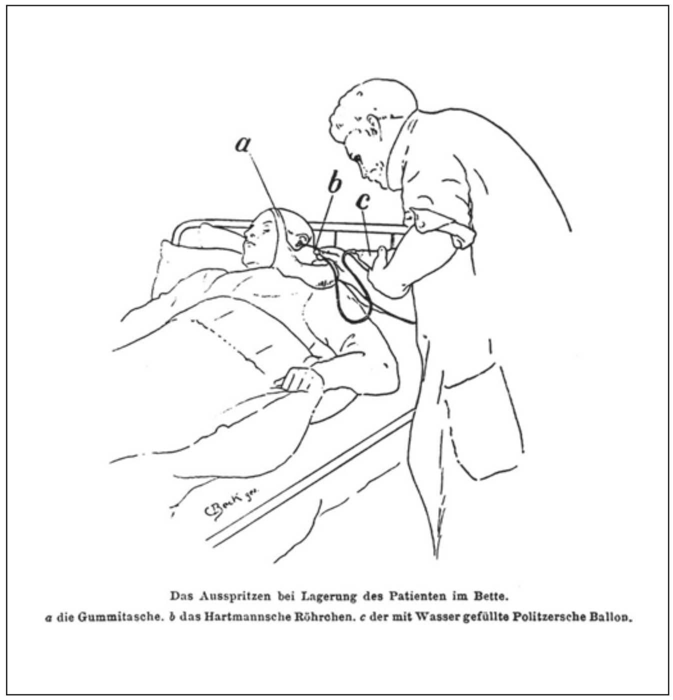

Fig. 3. Bárány's caloric test. The legend reads: Irrigation while the patient is lying in bed. **a** The rubber pouch. **b** Hartmann's tube. **c** Politzer's water-filled balloon. From Bárány R: Physiologie und Pathologie des Bogengangapparatus beim Menschen. Leipzig, Deuticke, 1907, fig. 11.

ogy from a vague mental philosophy to an experimental laboratory science, made important observations on the absence of normal vestibular reactions in many deaf mutes. In his 1882 paper in the American Journal of Otology, *The sense of dizziness in deaf mutes,* he wrote: 'The modern theory, that the semicircular canals are unconnected with the sense of hearing, but serve to convey to us the feeling of movement of our head through space, a feeling which, when very intensely excited, passes into that of vertigo or dizziness, is well known. It occurred to me that deaf-mute asylums ought to offer some corroboration of the theory in question, if a true one. Among their inmates must certainly be a considerable number in whom either the labyrinths or the auditory nerves in their totality have been destroyed' [James, 1882]. Of 519 deaf-mutes tested, 186 were found to be 'totally insusceptible of being made dizzy by whirling rapidly round with the head in any position whatever. Nearly 200 students and instructors in Harvard College were examined for purposes of comparison, and but a single one remained exempt from the vertigo'.

The work of Robert Bárány (1876–1936) (fig. 2), a member of Adam Politzer's famous Department of Otology in Vienna, made possible fruitful research on the human vestibular system, as well as clinical evaluation of vestibular function in patients. Starting from his observation that irrigation of the external canal as a treatment for Ménière's disease elicited nystagmus when the water used was either too warm or too cold, he developed his caloric test (fig. 3). For his vestibular contributions, which included the use of the well-known Bárány chair (fig. 4) to produce rotational nystagmus, he was awarded the 1914 Nobel Prize in physiology and medicine. When the award was announced, he was a prisoner of war in Russia, but Swedish diplomacy obtained his release to receive the honor in Stockholm in 1916. He initially returned to Vienna where the award had aroused unfavorable reactions from his detractors, who disputed his right to priority and managed to prevent his appointment to a professorship there. The following year, however, he was appointed professor of otology at Uppsala – appropriate recognition of his historic role as the founder of

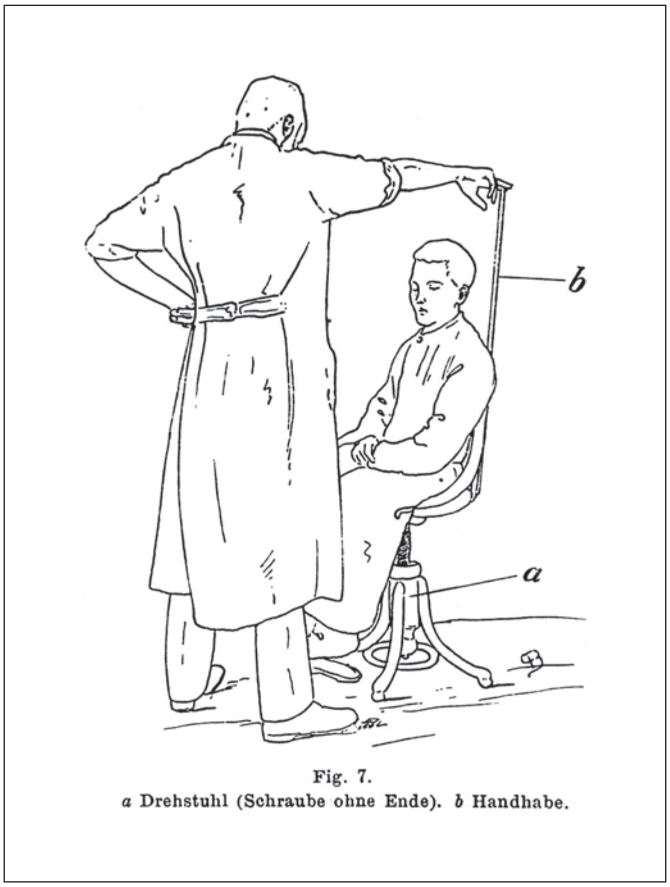

Fig. 4. Bárány's chair. The legend reads: **a** Rotating chair (endless screw). **b** Hand grip. From Bárány R: Physiologie und Pathologie des Bogengangapparatus beim Menschen. Leipzig, Deuticke, 1907, fig. 7.

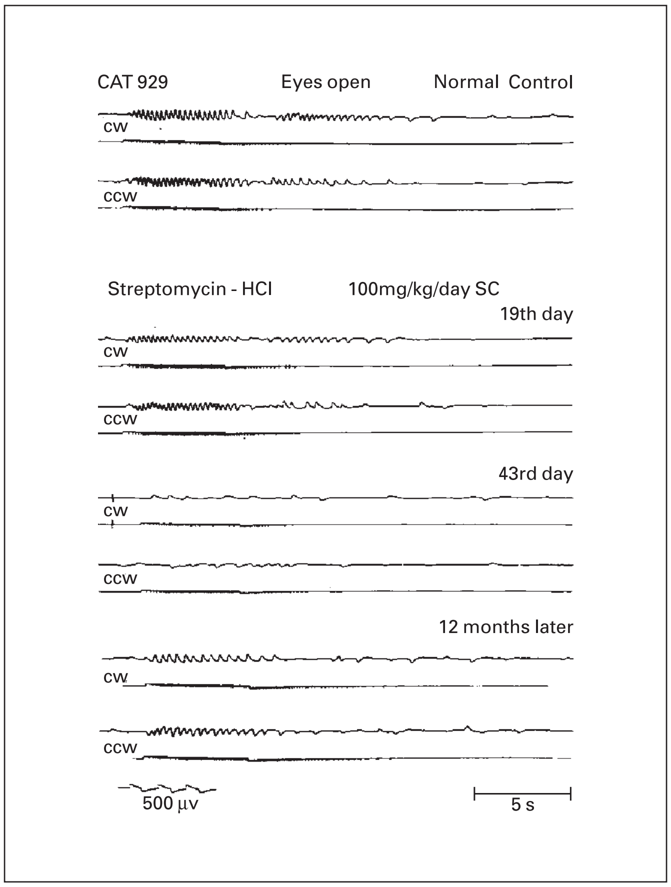

Fig. 6. Nystagmogram of a cat treated with streptomycin. Note the partial recovery after 12 months. From Hawkins JE Jr and Preston RE: Vestibular ototoxicity; in Naunton RF (ed): The Vestibular System. New York, Academic Press, 1975, pp 321–348, with permission from Elsevier.

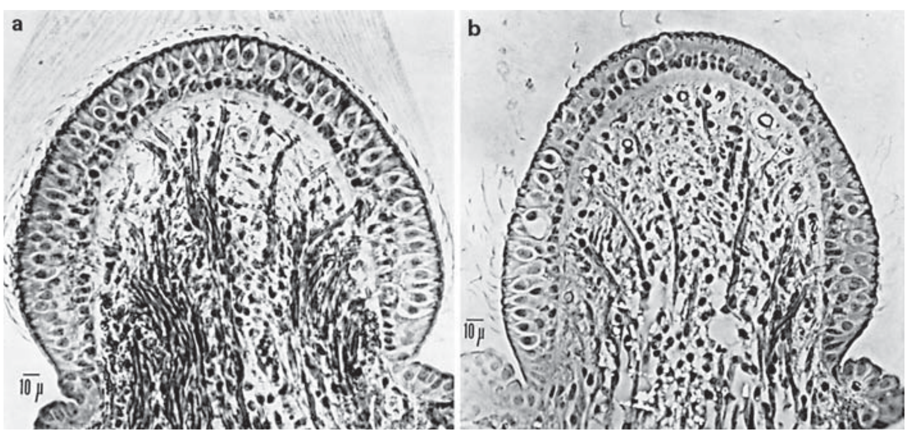

Fig. 5. Cristae ampullaris before (**a**) and after (**b**) treatment with streptomycin. Hair cells have almost completely disappeared. From Hawkins JE Jr and Preston RE: Vestibular ototoxicity; in Naunton RF (ed): The Vestibular System. New York, Academic Press, 1975, pp 321–348, with permission from Elsevier.

otoneurology. Moreover, with his Nobel Prize, the vestibular system had at last achieved full scientific respectability.

Vestibular Renaissance

The initial success of Selman Waksman's streptomycin in the treatment of tuberculosis in the mid-1940s brought with it a strange side-effect: a virtual epidemic of vertigo and ataxia. Some 90% of tuberculous patients who received the antibiotic in early hospital trials suffered from a disturbance of vestibular function. These findings precipitated an intensive research into the side effects of aminoglycoside antibiotics that still occupies us today. Animal experimentation established (and autopsy material from patients confirmed) that the hair cells of the vestibular system were the victims of streptomycin (fig. 5, fig. 6). These observations were extended to other drugs of the aminoglycoside family which either target the vestibular hair cells, the cochlear hair cells or both.

A second boost for vestibular research came with the exploration of space, beginning in earnest in the 1960s with studies of cosmonauts and astronauts in weightlessness on the Voskhod and Gemini missions. The extraterrestrial exploration of the vestibular apparatus continued with animal experiments onboard the space stations.

Finally, just about a decade ago, the long-held dogma that sensory cells in the auditory and vestibular systems do not regenerate, was laid to rest. Hair cells reappeared in vestibular structures after complete destruction by aminoglycoside antibiotics [Forge et al., 1993]. This unexpected capacity for hair cell regeneration in vivo in the mature mammalian inner ear set the stage for the search for the genetic and molecular prerequisites for repair and regeneration of mammalian hair cells.

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