

Vestibology in Padua before Arslan

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Introduction

Talking about Vestibology at the University of Padua necessarily means referring to the eminent figure of Prof Michele Arslan (1904-1988).

His decades-long activity as a Clinician and Scientist at the Direction of the Otorhinolaryngoiatric Clinic of the University of Padua, has certainly left an indelible mark on the history of the Faculty of Medicine of the University of Padua and the entire University, as well as leaving a mark on clinical and scientific research in the field of Neuro-otology in the world.

Prof Arslan has made important contributions in the field of Meniere's disease, the analysis and characterization of pathologies of the vestibular system and, finally, in the field of vestibular physiology and pathophysiology. He also founded a School of fellows who, continuing on the main path traced by the Mentor, deepened his studies and opened others of great importance.

The University of Padua is one of the oldest universities in the world. In 2022 it celebrated the 800th anniversary of its foundation (1222), and, in this more than a hundred years of history, a fundamental role has been played by the Medical School, which has contributed significantly to the fame that the University of Padua still enjoys in the world today.

Therefore, considering this more than a hundred years of history of the Paduan Medical School, it seemed interesting to investigate whether before Prof Arslan, there were

scholars of the University who were interested in the vestibular system.

Padua and the anatomy of the vestibular system

Undoubtedly one of the leading figures in the history of the University of Padua was that of the anatomist Andreas Vesalius (1514-64). Vesalius radically and modernly changed the anatomical study by putting the direct observation and dissection of cadavers in the foreground, and the experience that derives from it (Porzionato A, Macchi V, Stecco C, et al (2012) The Anatomical School of Padua. *Anat Rec: Adv Integr Anat Evol Biol* 295:902-916. <https://doi.org/10.1002/ar.22460>).

Vesalius was the first to depict the *malleus* and the *incus* in *De humani corporis fabrica libri septem* (Basel, 1543). Three years after his pupil Giovanni Filippo Ingrassia (1510-80), three discovered the stirrup in Naples.

During his period in Padua (1537-1544), Vesalius, in addition to making the observations that would later be part of his famous book, founded a School whose students brought to Italy and abroad the new experimental approach of studying anatomy developed in Padua (e.g. John Caius in Cambridge) or continued his studies in the University of Padua. One of his pupils, among the latter, Gabriele Falloppio who held the chair of Anatomy and Surgery from 1551 until his death in 1562 (Porzionato et al., 2012).

With Falloppio (1523-1562) we find the first mention of the vestibular system by a scholar of the University of Padua. In his work *Observationes Anatomicae* (1561) he describes in detail the petromastoid part of the temporal bone, giving its internal structures the names that are still used today:

.... Secunda cavita illa est, quae labyrinthus potest appellari, in radice petrosi processus insculpta. Ab haec tres cuniculi oriuntur et in eandem redeunt circulares penitus, a quibus nomen accepit ipsa cavitas. Quorum unum est inferior....

Fallopius however describes the bone structure of the labyrinth. Giulio Casserio (1561-1616), a pupil of Fallopius successor at the University of Padua, Girolamo Fabrici d'Acquapendente (1533-1619), and later, together with the latter, Professor of Anatomy, Surgery and Physiology at the same University, describes (*De vocis auditusque organis historia anatomica*, 1601) for the first time the membranous labyrinth, studied in pike. The membranous labyrinth of man was instead described for the first time by Cecilio Folli (Follius) (1614-1682), a Venetian physician and anatomist in the *Nova auris internae delineatio* published in 1639 in Venice.

The study of the vestibular system moves to other locations than Padua

After the anatomical observations of Falloppio and Casserio, in the following two centuries, despite the discovery of the endolymphatic fluid by Domenico Cotugno (1736-1822) in Naples (1760) and of the vestibular ganglion by Antonio Scarpa (1752-1832) in Pavia (1789), the function of the vestibular system in general still remains unknown and, in particular, its study involves other sites than Padua.

In this period dominated the idea that the function of the vestibular labyrinth was linked to the auditory function and in particular to the ability to identify the direction from which sounds originated. Supporters of this theory were, among others, Antonio Valsalva (1666-1723) and Joseph G. Du Verney (1684-1730).

In 1830 the French physiologist Jean Pierre Flourens (1794-1867) made a series of experiments in the pigeon that refuted the theory of the *auditory function* of the vestibular system. After the selective section of the semicircular

canals, easily accessible in this animal, he observed involuntary movements of the head in the plane of the dissected semicircular canal describing them:

... Il n'est pas moins surprenant de voir des parties qui, par leur position meme dans l'oreille, semblaient ne devoir jouer qu'un role special et bornè à l'audition, avoir une influence si marquée sur les mouvements ; Il ne l'est pas moins enfin de voir chacun de ces parties determiner un ordre ou une direction de mouvements si parfaitement conformes a sa propre direction.

D'un autre cotè, bien que le phenomènes qu'amene la section des canaux semi-circulaires aient une analogie très marquée avec le phenomènes du cervelet, ces deux ordres de phenomènes n'en sont pas moins distincts.

Flourens also observed that *...le mouvement de la tete s'accompagnait toujours d'une agitation très vive des yeux*, the vestibulo-ocular nystagmus consequent to the injury.

In the same years (1820-27) another famous physiologist, the Czech Jan Evangelista Purkinje (1787-1869), studying vertiginous patients, observed the presence of nystagmic eye movements in them, associating them with vertigo. However, he did not perceive the possible relationship of these symptoms and signs with Flourens' observations and therefore with vestibular function (Purkinje 1825)

It was Prospere Meniere (1799-1862) who came to this association by presenting to the Academie Imperiale de Medecine a controversial clinical case characterized by hearing disorders accompanied by vertigo (Meniere 1861). In the following years, in Strasbourg, a city that was then located in Germany, Friedrich Goltz (1834-1902) and his pupil Ernest Julius Richard Ewald (1855-1921) proposed the model that links the function of semicircular canals to the perception of rotational movements of the head and nystagmus as a physiological response to rotation (Ewald 1892). Only with the studies that earned Robert Barany the Nobel Prize the function of semicircular canals was definitively clarified (Barany 1907).

The return of the study of the vestibular system to Padua

In the second half of the 19th century, the vestibular system was studied again in Padua, at the Institute of Physiology.

In 1866, Filippo Lussana (1820-1897), a patriot imprisoned in Lombardy-Veneto (just annexed to the Kingdom of Italy), was called as Professor of Physiology in Padua, in place of Maximilian Von Vintschgau, physiologist of the Viennese school, who had to leave the Institute following the annexation. Lussana had been a pupil of Bartolomeo Panizza (1785-1867) in Pavia, where he had been interested in the functions of brain areas, with a series of observations among which those concerning the suppression of the articulation of the word and the lack of the concept of words, published in 1850, ten years before Broca's classic work (1861).

In 1871, Lussana published "*Physiology of the Encephalic Nerve Centres*", a monograph in which years of observations made after selective lesions of the nervous system were collected.

When he discusses the function of the semicircular canals and their afferent, he quotes Flourens:

"As an appendix to the physiological deductions on the encephalic innervations, which govern the different orders of bodily movements, it is useful to treat of those singular locomotive disturbances, which Flourens first verified to occur following the section of the different semicircular canals." The section of the horizontal canals (writes the illustrious experimenter) is followed by a horizontal movement, and the section of the vertical canals by a vertical movement of the head. Moreover, the section of the horizontal canal is followed by a turning of the animal above itself; that of the posterior canal by a tumble movement backwards; and that of the anterior vertical channel by a tumble movement forward". "If the nerve of the semicircular canals is pursued (reflects the same author) in the encephalon, it is seen that it is always accompanied by the acoustic nerve, with which, however, it is never confused, reaches the encephalon, and there divides again into three branches or nerve bundles. One of these bundles goes to the transverse fibers of the cerebellum or pons of Varolio; the other to the straight fibers of the brain, i.e. to the cerebral peduncles; the third to the posterior fibers of the cerebellum or restiform bodies." ...

Lussana, however, does not share Flourens' conclusions:

"..... Although Flourens, because of the phenomena of dizzying locomotive disturbances described above, wanted to deny the specific auditory faculty to the nerve expansions of the semicircular canals, making them instead as many motor

*centers, nevertheless we still firmly believe that the aforementioned nerve expansions represent nothing but hearing aids, in relation to the direction of sounds. And the sensations of the different directions of sounds, received by the three branches of the semicircular canals, are transformed by the respective cells into progressive, retrograde, transverse movements. It is nothing more than an **auditory vertigo**"*

The idea, as well as originating from what was believed historically (vide supra), was also based on the hypothesis of Johann Heinrich Ferdinand von Autenrieth and taken up by GianBattista Venturi (Venturi 1801). According to this hypothesis, each semicircular channel is a receptor for sound stimuli propagating along a given plane of space. Lussana was further convinced by his observations, as a physician, of patients suffering from Meniere's disease, in whom acoustic disturbances are associated with motor disorders and vertigo (Lussana 1875).

The diatribe between teacher and student

At this point, between 1874 and 1876, a discussion arose within the School of Physiology of Padua on the function of semicircular canals. On the one hand, Lussana supported the idea of an acoustic function of semicircular canals put forward by Autenrieth and on the other his pupil Aristide Stefani (1846-1925), who rejected it. Stefani, who graduated from Padua in 1869, became Lussana's assistant ("*Mr. Doctor Stefani*", cited in the *Physiology of Encephalic Nerve Centres*, as the one who transcribed the observations made in injury experiments into the "*laboratory protocols book*") and then Professor of Physiology in Ferrara from 1872 to 1888, the year in which he returned to Padua to succeed Lussana.

Stefani, basing himself on experiments carried out on the pigeon and interpreting them with the modern observations made by Goltz in Strasbourg, firmly rejects, with the kindness of those times, Lussana's opinion by writing: "*..With all the veneration I profess for my Mentor, I am forced to disagree with him on this subject*" (Stefani 1874). According to Stefani, the ability to evaluate the spatial origin of sound is a "*psychic process*", therefore a central processing of the nervous system. In addition, he is also an attentive clinician, noting that sounds have no effect on the motor

symptoms of pigeons after unilateral lesion of the semicircular canals, and that bilateral lesion of the semicircular canals determines much less motor phenomena than a unilateral lesion. Both observations are in stark contrast with Lussana's hypothesis.

Lussana's response to Stefani's criticism was not long in coming. A year after Stefani's work, Lussana published the work: "*Meniere's disease and auditory vertigo*" (Lussana 1875) where he returned to support the hypothesis of an auditory function of the vestibular system, writing that auditory *vertigo* "is a consequence of *irritative phenomena* that appear after the lesion of the semicircular canals.

"To my physio-pathological opinion of auditory vertigo (both for the lesion of the semicircular canals and for Meniere's disease) my friend Prof. Stefani, in his valuable work read at the Academy of Ferrara, opposed ... that perceiving the direction of sounds is a psychic process and not a simple fact of sensations.... that locomotive disorders are not caused by the impression of sounds... that an illusion about the direction of sounds could not cause disorders of locomotion..."

Lussana repeats the experiments of destruction of semicircular canals and decerebration of the pigeon, agrees with Stefani's observations but reiterates his interpretation

"... For the above reasons, my colleague and friend observes, brainless animals, true that it was the doctrine of Lussana, should not present such disorders once they are operated on in the semicircular canals. And yet the eminent physiologist Stefani undertook an ingenious experimental process to solve the disputed problem: he first removed the cerebral hemispheres in pigeons, and then excised the semicircular canals; and recounting, he first excised the semicircular canals, and then removed the cerebral hemispheres..."

"... Having thus confirmed and completed the experimental results of the trial, which was initiated and carried out by Professor Stefani, I am not, however, on the way to the same deductions but remain firm in believing that the said disorders derive from a disorder of acoustic sensations"

Stefani, always politely replies:

"Only a deep scientific conviction produced by the dispassionate observation of the facts could have made me an opponent on this subject to my venerated teacher Prof. Lussana, to whom I will be bound for the rest of my life by the deepest feelings of gratitude and friendship", and then he wonders decisively why the animal tilts its head in the

opposite direction to the injured side and not from the injured side from which it originates the acoustic alteration supposed by Lussana.

In the end, Stefani closes the dispute with the decisive experiment: the section of the vestibular branch of nerve VIII that induces the appearance of the motor disorders observed in the experiments of lesion of the semicircular canals. A very difficult experiment even today, carried out at the same time by Elias von Cyon in 1876 (Cyon 1876).

Vertigo and nystagmus between the vestibule and cerebellum

Lussana was a scientist and clinician. A scientist impressed by Flourens' experiments, which he repeated in his laboratory while interpreting the results in obstinate antithesis to the French scientist and his pupil Stefani. Clinician for the meticulous analysis of the symptoms of his patients.

In the *Physiology of the Encephalic Nerve Centers* (1871) there is a continuous alternation of experimental and clinical observations, all very precise for each clinical case described. Among these observations is an admirable description of vertigo and vertiginous patients. Although he does not recognize the *vertigo* derived from the lesion of the semicircular canals as *motor*, but *auditory*, and gives the value of *motor* only to that which follows an injury of the cerebellum, Lussana introduces the very modern concept of "perception" of the sensory stimulus when he writes, quoting two professors of the University of Pavia:

"The vertiginous: probe noscit advertitque rotationem illam non esse veram sed apparentem tantummodo (quote from Giovanni Battista Borsieri de Kanilfeld). Extensis brachiis sustentaculum quaerit et forsitan praesentes in auxilium vocat nec ideo conscientiam sui perdit aut ea quae sibi a sensibus externis referantur erronea esse ignorat haud raro majore scilicet vertiginis sub impetu et humi prosternitur aeger quintamen sensibus et motu privatus factorum memoriam amittat (quote from Joseph Frank). Therefore, in order for vertigo to occur, the following two conditions are necessary: 1. disturbance of the muscular and visual senses, 2. preservation of intelligence; or, in other words, anatomical-physiological: 1. lesion of the cerebellum, 2. integrity of the brain. Thus the brain properly so called (intelligence and will and perception) is extraneous to vertigo, indeed it is necessary that the use of the brain be preserved in order that

vertigo may come true. On the other hand, no matter what injury is done to the brain, and even if the whole brain is destroyed, the animals never become dizzying. Indeed, we now add: in order for the animal to suffer from vertigo, it must still have the brain in more or less functional activity: the animal without a brain cannot have vertigo. The dizzying person knows his sensory deception: he knows his mistake, he strives with his intelligence to avert it, he has illusions - but he knows that they are illusions. He has erroneous feelings, but he does not err in judgment. On the other hand, the animal and man, deprived of the functions of the brain (i.e. of intelligence and perception and judgment), no longer know the lie of their dizzying illusions, and are not alarmed by it, they no longer have vertigo. For vertigo means to be disconcerted in voluntarily and intellectually directing one's actions because of the deception of the senses..... Even the psychiatric patient can be dizzying, but provided that and as long as his judgment and his will are altered, but not abolished. But one who is utterly demented cannot be more dizzying, for he, who not only has little or altered will and intelligence, but no longer has any intelligence and no will, can no longer be alarmed by sensory deception."

Also in Stefani's writings, we find a precise description of vertigo and ocular nystagmus following a rotation (Stefani 1920):

"At the beginning of the rotation, with your eyes closed, you have the sensation of turning in the plane and in the direction in which you turn..... When the rotation stops, the sensation of spinning that had disappeared when the rotation speed had become uniform returns; but the rotation seems to be happening in the opposite direction.... The oscillations of the head and eyes occur at the beginning and end of the rotation, like the sensations of turning, and last as long as these last..... Of the two movements of which the oscillation is composed, the one that occurs first, and is produced by the rotational movement, is said to be a reaction; and the other is called nystagmus and is believed to be caused by the previous ocular movement..... The reaction movement is responsible for the sensation of turning the environment that occurs when, once the rotation has ceased, the eyes are opened. This sensation is produced because every displacement of the retina of visual images, which is not the effect of voluntary movements, produces sensations of movement....."

The last sentence is a terrific observation. Decades before Barany observations and the neurophysiologic discovery of motion sensing properties of vertebrate peripheral retina as well invertebrate visual system, Stefani suggests that a passive movement of visual field

on the retina could evoke a motion sensing. However it is the second part of the phrase that it is even more terrific for a neurophysiologist: the observation that motion sensing is not produced when the movement of the visual field on the retina is following a voluntary movement. This is an anticipation of the *Reafferenz prinzip* of Von Holst and Mittaelstedt, in which it is explained how nervous system pre-organizes a copy of the supposed sensory inputs generated by the voluntary movement which will be executed, canceling them from the real sensory inputs generated whenever the voluntary movement is under execution.

Stefani, after the diatribe with the Master, continued his studies on the vestibular system asking himself "...But what is the nerve center, by means of which the excitations that start from the non-acoustic labyrinth are able to realize the observed responses ?....".

His attention focused on the relationship between vestibular receptors and the cerebellum.

In a first series of experiments carried out between 1873 and 1877, he noticed that the motor disturbances induced in pigeons by the lesion of the semicircular canals were similar to those resulting from the removal of the cerebellum. Starting from this observation, he discovered that in the cerebellum of pigeons from which the semicircular canals had been removed, some Purkinje cells undergo degeneration. This allowed him to formulate the hypothesis of a functional correlation between semicircular canals and the cerebellum (Stefani and Weiss 1877). These studies were carried out in collaboration with the Viennese scholar G. Weiss, who brought to Padua the necessary expertise in anatomical microscopy techniques of the nervous system.

Subsequently, as we shall see, this line of research was continued by his pupil Deganello, who in 1899 gave a solid demonstration basis to the initial observation made in 1877 (Deganello 1899).

In a **second** period, from 1878 to 1892, what Stefani defines as his "*doctrine of the cerebellar function*" was progressively formed. Together with Giuseppe Bellonci in 1886 he studied the development of the cerebellar cortex in pigeons in which he noted the relationship between the appearance of postural and locomotor autonomy only when the complete

development of the cerebellar cortex was achieved. Starting from these experiments, Stefani in 1892 commissioned his pupil Lui to *"look for the state of development in which the cerebellar cortex of animals which, like newborn pigeons, do not have the aptitude to stand and walk and the cerebellar cortex of animals that, as soon as they are born, stand and walk" were found at birth.* The research, carried out on numerous and different animals (chickens and sheep that walk as soon as they are born; dogs and cats that, like pigeons, begin to walk and have an upright posture only some time after birth) highlighted that the first group of animals is born with a fully developed cerebellar cortex, while the second group of animals is born with a cerebellar cortex that is not yet fully developed. He continued his studies in humans as well, observing that the complete development of the cerebellar cortex occurs only at the end of the first year of life (Lui 1894). A very important fact also observed by Robert Loewy in Vienna and published in 1910 (Loewy 1910), 16 years after him; this is an example, as well as the one on motor aphasia in Lussana, of how in the world of research it is necessary to publish the results of one's experiments in journals that allow their greater dissemination among scientists.

The studies of Stefani and Weiss and of the pupil Lui were then continued in Padua by Achille Roncato (1887-1963), future first professor of Biological Chemistry at the University of Padua. Roncato, asking himself whether the labyrinth in some way influenced the development of the cerebellar cortex, bilaterally injured the labyrinth in newborn pigeons, observing a slowdown in the development of the cerebellum (Roncato 1914). These results confirmed what Stefani had previously observed (1874) about a rooster *"given to me by the veterinary clinic of Bologna, which presented from birth phenomena typical of labyrinthized pigeons. After killing the rooster, I found both the cerebellum and the semicircular canals atrophic"*.

Stefani then came to identify the cerebellum as the nerve center in which motor responses were carried out through the integration of sensory information. Therefore neither a pure sensory center as his teacher Lussana hypothesized (*muscular sense*) but not even a pure motor center as Luciani hypothesized.

For these pioneering studies on the relationship between the cerebellum and labyrinthine organs, Stefani was awarded the prize of the Accademia dei Lincei in 1903 on the proposal of Luciani himself, with the words *"the special influence of the non-acoustic labyrinth for the normal functionality of the cerebellum brought to light by Stefani and his students is the first truly important fact with which the knowledge of this mysterious organ has been enriched that has fatigued the mind of not a few observers"*

In 1920, by then close to retirement, Stefani summarized his scientific career in a memoir at the Accademia dei Lincei (Stefani 1920). *"In this memoir I propose to summarize and coordinate my and my students' work on the functional relationship between the cerebellum and the non-acoustic labyrinth, the doctrine of which I formulated in 1877."*

In this long and interesting text we find: *"... The doctrine of Goltz which I supported in opposition to my teacher Prof Lussana who had tried to explain the facts demonstrated by Flourens with the doctrine of Autenrieth (1800), admitting that motor disorders, consequent to lesions of the semicircular canals, were phenomena of vertigo produced by noises in different directions, which were produced by irritation of the operated canals, or by the false perception of the direction of sounds that occurred in the environment (Lussana, 1875)..."*. Goltz's experiments date back to 1869. Those of Stefani immediately afterwards considering that he presented them in 1874 also showing some specimens of operated pigeons. In the same years, Breuer (1874), Mach (1875) and Crum Brown (1874), *"simultaneously and independently glimpsed an analogy between the motor phenomena that follow the removal of the semicircular canals and the phenomena of rotatory vertigo demonstrated by Purkinje (Physiologische versuche uber den Schwindel, 1825)..."*

Despite the previous discussion between the two, the memory of the Master, seen as a guide in his scientific path, is striking. Stefani's experimental research on the cerebellum and semicircular canals is motivated by the *"deep impression received, during my fellowship, by the sight of pigeons from which my venerated teacher, Prof. Lussana, removed the organs; and the simultaneity of the research was certainly not extraneous to the intuition of the functional relationship between them, a re-*

relationship that today is generally recognized by physiologists and clinicians”.

A little-known detail of Stefani's interest in vestibular physiology and pathology is that of his collaboration with Agostino Gemelli (1878-1959) when, after Caporetto, he organized, as a medical captain, in the Institute of Physiology of Padua, the Army Laboratory for psychophysiological research that he had founded and directed within the Supreme Command of the Royal Army, whose headquarters had been moved from Udine to Padua. As part of the collaboration, Stefani focused on the “aviators' disease”, disorders related to the excitability of the semicircular canals (see Gemelli A. et al 1920 and Roncato A. 1932).

But the history of Paduan vestibology does not end with Stefani. After the brief inter-

lude of Carlo Foà who left Padua for Milan in 1924, Virgilio Ducceschi (1871-1952), who had trained at Luciani's school and had taught physiology in the faculty of Cordoba in Argentina, was called to the chair of Physiology. Although it was not his primary research topic, Ducceschi kept Stefani's line of research alive and found a young doctor Khayel Michele Arslan as a collaborator. Arslan's research in Ducceschi's laboratory was published in *Valsalva* (Arslan 1931) and in the *Bulletin of Experimental Biology* (Arslan 1933). But Arslan's future was towards the clinic, where he became a professor of OtoRinoLaryngology and a scholar of not only national but international fame.

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