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THE EARLY HISTORY OF TUBULATION IN NERVE REPAIR

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The first experiments for bridging peripheral nerve gaps using nerve tubulation emerged in the 19th century. Because Gluck (1853–1942) is said to have performed the first animal experiment of nerve tubulation in 1880, it is interesting to explore the background and veracity of this claim. The original documents on nerve tubulation in the 19th century were studied. We conclude that the conduit that was initially used for nerve tubulation was derived from a resorbable decalcified bone tube developed for wound drainage by Neuber (1850–1932) in 1879. Gluck proposed the use of the bone tube as a guided conduit for regenerating nerves in 1881 but stated briefly that his experiments failed because of scar formation. Vanlair (1839–1914) documented the first successful application of nerve tubulation using a bone tube to bridge a 3 cm sciatic nerve defect in a dog in 1882.

Keywords: history, nerve tubulation, nerve surgery, neuber, vanlair, gluck

Bridging peripheral nerve gaps after injury continues to be a major clinical challenge. The use of nerve conduits, or tubulation, for this purpose has evolved to a clinical reality over several decades. However, the concept is not a recent one (Mackinnon and Dellon, 1988; Suematsu, 1989). The theoretical background of nerve tubulation a century ago seems to be similar as today: *“to provide a guiding frame for the divided nerves, on which the newly emerging nerve substance can grow in the shortest way from the central to the peripheral stump without much resistance, and to protect the junction against embedding in callus and scar tissues, and to keep the nerve gap open for regeneration from the central into the peripheral stump”* (Foramitti, 1904).

Nerve tubes are said to have been employed in Europe since the early 1880s. Although several historical papers recently discussed the development of nerve tubulation, hardly anything is known about the first attempts to use conduits in nerve repair. To enhance our knowledge of this interesting period in the development of nerve repair, the original early manuscripts on nerve tubulation were studied and are discussed in the context of the surgical and scientific environment at the end of the 19th century. Moreover, some historical inaccuracies are corrected.

THE SEARCH FOR THE FIRST EXPERIMENTS WITH NERVE TUBULATION

The first experimental use of nerve conduits has been attributed to Themistocles Gluck, who is said to have employed decalcified bone tubes in his animal experiments and to have published his results in 1880 in his

article *“Ueber Neuroplastik auf dem Wege der Transplantation”* (Brunelli et al., 1994; Chiu, 1995; Fields et al., 1989; Mackinnon and Dellon, 1988; Suematsu, 1989; Watchmaker and Mackinnon, 1997). However, it is not clear as to why people refer to this publication, for it lacks any information on nerve tubulation (Gluck, 1880). Instead, Gluck described his use of a nerve xenograft (donor: rabbit; recipient: rooster) to bridge a nerve gap (Gluck, 1880). No other paper written by Gluck on nerve tubulation dated 1880 was found. As a historical footnote, it must be noted that Fields seems to suggest that Velpeau (1795–1867) made an even earlier attempt to use a tube in nerve repair (Fields et al., 1989). Fields refers to Velpeau’s manuscript entitled: *“Leçons orales de clinique chirurgicale”* (Velpeau, 1841). However, Velpeau describes no attempt at nerve tubulation in this work.

Constant Vanlair is considered the next in ranking in 1881 (Fields et al., 1989; Suematsu, 1989). According to Vanlair, it was indeed Gluck who introduced the concept of nerve tubulation. However, Vanlair provided another reference dated 1881 (Vanlair, 1882a, b). In 1881, Gluck published two papers in two different German medical journals. The papers had the same title *“Ueber Transplantation, Regeneration und entzündliche Neubildung”* and should be considered a double publication because they share the same contents about nerve tubulation. Gluck wrote: *“I must mention a few new avenues: after resecting a length of nerve, I sewed a piece of Danish leather between the nerve endings or substituted the leather for a bone drain, pony-tail braided catgut or, at last, pieces of muscle. I hypothesized that regeneration of the central and peripheral parts of the nerve might take place, climbing up the*

scaffold of the implanted foreign body as vine climbing a staff" (Gluck, 1881a, b).

In his 1881 papers, Gluck did not mention how he acquired the idea of nerve tubulation (Gluck, 1881a, b). Vanlair called Gluck's nerve tube a "tube de Neuber", after Gustav Neuber from Germany (Vanlair, 1882a, b). Neuber introduced the use of decalcified bone tubes for wound drainage in the journal in which Gluck published one of his 1881 papers (Neuber, 1879). Although Gluck did not refer to Neuber's work, he was probably inspired by him.

PIONEERS OF NERVE TUBULATION

Gustav Adolf Neuber (1850–1932)

To appreciate how Gluck developed the concept of nerve tubulation, it is important to understand Neuber's decalcified bone tube. Gustav Adolf Neuber (Fig 1) was born in Germany (Plagemann, 2000). As a pharmacist's son he studied medicine and became the clinical assistant to Professor Esmarch at the surgical university clinic in Kiel, Germany. At that time, carbolic acid spray was the standard method to prevent wound infection. Antisepsis became Neuber's outstanding topic in research. He developed a device to sterilise surgical instruments and opened the first antiseptic private hospital in the world with air cleaners, washable furniture and a strict separation between septic and

Fig 1 Gustav Adolf Neuber (1850–1932) introduced the decalcified bone tube for wound drainage in 1879. The so-called "tube de Neuber" will be used for nerve tubulation for the first time in history.

aseptic departments. Emanating from his interest in antiseptic wound treatment, Neuber developed an absorbable decalcified bone tube that could be used as a pipe for wound drainage (Neuber, 1879). Neuber tested several materials for drainage of wound discharge: feather shafts, gold paper, glue, catgut, animal bladders, animal arteries, intestines and tracheas, all of which, according to Neuber, led to unsatisfactory results. Finally he manufactured decalcified bone tubes. The tubes were made from horse and cattle bone, and varied in diameter from 0.5 to 6 mm. The horse or cattle bone was placed in hydrochloric acid solution for 10 hours, then washed out in 5% carbolic acid for a longer time. Finally, the bone tubes were stored in 10% carbolic solution. He used them for drainage in cases of bloody operations of the extremities, extirpation of tumours and after resection of necrotic tissue. Fig 2 shows a schematic representation of Neuber's decalcified bone tube in a cross-section of the neck (Neuber, 1883). However, he did not use the bone tube as a nerve conduit (Neuber, 1879, 1880).

Themistocles Gluck (1853–1942)

Gluck proposed the use of the bone tube as a conduit for regenerating axons in peripheral nerve gaps in 1881 (Gluck, 1881a, b). Gluck (Fig 3) was born in Romania. He was the son of the attending physician to the royal family and studied medicine in Leipzig and Berlin (Eynon-Lewis et al., 1992). He became professor and head of the surgical department at the Emperor Frederick Pediatric Hospital. Gluck made great contributions to many branches of experimental surgery, such as replacing lost tissue by means of transplantation and implantation of organic and inorganic foreign bodies. His early experimental work concerned organ resection and transplantation. He was a pioneer of bone and joint replacement, and performed animal trials with various materials including wood, glass, aluminium, nickel-plated steel, and ivory for the development of shoulder, elbow, hand and knee prostheses. In his entire work, Gluck recognised that experimental surgery on various animal species was the way to achieve decisive progress. In his later years he was honoured for his work, and became "extraordinary professor" and honorary member of the German Surgical Society.

Professor Rudolf Virchow (1821–1902), one of the most famous German doctors of his time, was the founding father of cellular pathology. Gluck believed in Virchow's cellular theory and considered complicated life forms as a result of connected simple vital components of life. In an individual patient, these simple vital components of life are equal to a certain sum of living cells. Gluck was fascinated by the possibility of transplanting the vital component of life to attain complex structures and considered the science of the transplantation a powerful support of the cellular

Fig 2 Schematic representation of Neuber's decalcified bone tube for wound drainage in a cross-section of the neck.

Fig 3 Themistocles Gluck (1853–1942) proposed the use of a bone tube as a conduit for regenerating nerves in peripheral nerve gaps in 1881.

theory. Based on this theory he experimented with bone, muscle, tendon and nerve transplantations.

In 1881, Gluck lectured at the meeting of the Berlin Medical Society and published two articles entitled “about transplantation, regeneration and inflammatory new formation” (Gluck, 1881a, b). Gluck performed experiments in rabbits, chickens and dogs with transplanted pieces of nerve that were kept in phosphoric acid solution or kept at 18 °C in a damp chamber. He stated that: “The longest piece of nerve which was successfully transplanted amounted to about six centimetres.”

Besides several experiments with nerve transplantation, Gluck introduced the idea of nerve tubulation. Figure 4 shows some drawings made by Gluck of his experiments with nerve transplantation and tubulation (Gluck, 1881b). Unfortunately, Gluck did not give a detailed description of his experiments with nerve tubulation or state definitively in which animal the experiments were performed. He only described that “I had the idea that consequently a regeneration of the central and peripheral end could take place and that the each other approaching growing fibres would climb around the implanted foreign bodies like grapes along the vine. Although this hope was not correct, the foreign bodies healed very firmly, and grew together with the perineurium by means of the solid scar connective tissue and finally its fate was sealed by mummification or partial absorption” (Gluck, 1881a, b). So the question remains as to who provided the first detailed description of a successful attempt of nerve tubulation.

Constant Vanlair (1839–1914)

Constant Vanlair (Fig 5) was born in France (De Loo, 1936–1938). He studied medicine and became professor of pathological anatomy and forensic medicine at the University of Liège in Belgium. On this occasion he made a scientific journey to Germany. From 1870 to 1876, he carried out a series of experimental research on the reflexes, and on anatomical and functional regeneration of the spinal cord in frogs and dogs. From 1882 to 1896, Vanlair continued his research on the nervous system and devoted a comprehensive study to the degeneration and regeneration of peripheral nerves.

According to a report from Vanlair in 1882, Gluck interposed a decalcified bone tube between two nerve endings by suturing it with catgut (Vanlair, 1882a, b). Vanlair supposed that Gluck's experiments failed either due to the quality of the animal or to the short interval

Fig 4 Schematic representation of Gluck's early experiments with nerve transplantation and tubulation: (A) pony-tail braided catgut inserted between nerve endings; (B) scarred contraction and connective tissue metamorphosis of a transplanted piece of nerve; (C) neuroma formation of a transplanted piece of nerve; (D) bone drain used for nerve tubulation; (E) mummification and resorption of a transplanted piece of nerve that has been kept in phosphoric acid solution for 36 hours; (F) piece of a sciatic nerve treated with acid.

Fig 5 Constant Vanlair (1839–1914) documented the first successful application of nerve tubulation using a decalcified bone tube to bridge a 3 cm sciatic nerve defect in a dog in 1881–1882.

between the operation and the examination of the nerve (Vanlair, 1882b). Regarding Gluck's idea of nerve tubulation he stated: "It is a discovery of a new process for the surgical treatment of traumatic and neoplastic nerve repair" (Vanlair, 1882b). Vanlair provided the first detailed description of nerve tubulation in two articles published in 1882 (Vanlair, 1882b). Vanlair claimed that he succeeded in bridging a nerve defect by nerve

tubulation using Neuber's decalcified bone tube. Vanlair's comprehensive original papers written in French, in which he described the experiments on nerve tubulation, were translated and analysed (Vanlair, 1882a, b).

On September 30, 1881, Vanlair resected 3 cm of a sciatic nerve of a dog. He used Neuber's decalcified bone drain to bridge the nerve defect. The bone drain was initially preserved in carbolic oil and finally kept for 3 days in an aqueous solution with 5% carbolic acid. Its length was 4 cm, its internal diameter measured 3.5 mm and the wall was 2 mm thick. The lateral part of the tube contained drilled holes on each side. The edges of the tube were blunted to avoid damage to the nerve and the surrounding tissue. The nerve endings were encased in the end of the tube and fixed to the wall of the tube by catgut sutures. Newly formed fibres of both nerve endings were directed parallel to the axis of the tube to eventually achieve regeneration of the nerve. The wounds were sutured and closed with catgut. After the operation the animal was given its freedom. From time to time, the leg of the dog avoided contact with the ground and was completely raised. On the day of operation, complete anaesthesia of the foot and leg was noted; even deep insertion of a needle in the flesh caused no cries of pain, and no voluntary or reflex movement. The sensitivity reappeared at the level of approximately 3 cm above the knee. By October 14, the wounds were almost completely healed. The animal was dragging its leg less and its foot was placed flat on the ground even in ordinary gait. By October 24, the animal regained its gaiety. Even the state of sensitivity and motility were restored. In January 1882 the animal ulcerated the end of its foot. The animal ate as usual and its general health did not suffer from the ulcerated leg. By February 1, 1882, four months after insertion of the nerve tube, the sciatic nerve was extirpated and its macroscopic appearance was studied. Vanlair stated that: "anatomical regeneration of the nerve had been carried out during this lapse of time and a nervous tract linked the

divided ends.” Fig 6 presents macroscopic images of the regenerated sciatic nerve of a dog, using Neuber’s decalcified bone tube, to bridge the nerve defect (Vanlair, 1882a).

Vanlair concluded from his experiments that: “A bone drain can persist during four months in the interior of a body and over time it undergoes an atrophic involution. The atrophic involution of the decalcified bone drain is achieved entirely without intervention of the morphological elements of bone,

such as osteoclasts. Before the complete destruction of the bone, its pre-existent cavities, such as the channels of Havers, are used as guides in the neoplastic formation of nervous tissue. Since the walls of the decalcified bone tube consisted of dead material, which cannot provide the nutrition of the nerve fibres, it should be concluded that it is not organic conditions but mechanical influences that regulate the growth of a nerve. Therefore it is a new and very objective confirmation of the general law established by Ranvier.”

Fig 6 Macroscopic images of a regenerated sciatic nerve of a dog, using Neuber’s decalcified bone tube, to bridge the nerve defect over a period of 4 months by Vanlair in 1881–1882.

DISCUSSION

Most nerve injuries were left untreated until the middle of the 19th century because of the poor outcome of available surgical procedures (Fields et al., 1989). The process of outgrowth of axons from the cell body in regenerating nerves became appreciated through several studies in the same period of time. End-to-end suture of nerve stumps and nerve transplants or grafts predate the experiments with nerve tubulation. However, suture materials frequently lead to damage, foreign body reactions and scarring of the suture line by which axons become disorganised, blocked or entangled into neuromas. From the quest for a sutureless method of nerve anastomosis, nerve tubulation emerged in Europe in the last decades of the 19th century. Nerve tubulation techniques offered the possibility of reducing invasion and scarring of the nerve, and aiding the guidance of growing fibres along appropriate paths by mechanical orientation and confinement, to discourage the formation of neuromas or other functional impairments caused by misdirected axonal growth (Fields et al., 1989). Therefore, the discovery of nerve tubulation seems to be a logical next step in the development of nerve surgery at the end of the 19th century.

Nerve tubes can be used to repair peripheral nerve defects (Meek, 2000). In recent years, artificial materials have been used more frequently in the human body. Non-resorbable materials stay in situ as a foreign body. Therefore, the use of resorbable biomaterials has expanded enormously, and they have been employed in nerve surgery. However, the concept of bridging peripheral nerve gaps by using an absorbable nerve tube had already emerged at the end of the 19th century. Over the past century, different kinds of materials have been used as a tube for repair of a peripheral nerve gap. Nerve tubes made of silk thread bundles, silicone, mesothelial tissue, amniotic membranes, arteries, veins, muscle tissue, perineurium and synthetic microporous material have been used in experimental and clinical trials (Meek and Coert, 2002, 2008). Although the basic principles of nerve tubulation have not changed since Gluck's and Vanlair's early experiments, even 127 years later the length of tube currently available in the market for clinical use has not changed (e.g. 3 cm).

Nerve tubulation is now a well-established method for bridging peripheral nerve gaps. Adaptation of the biomaterials and the wall of the nerve guide, and modifications (e.g. incorporation of stimulating factors for nerve regeneration) in and around the nerve guide (less tissue reaction) are aspects that may improve the performance of nerve tubulation in the future. However, we should not forget the original work of pioneers such as Neuber, Gluck and Vanlair in the development of nerve tubulation in Europe at the end of the 19th century.

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