The history of neuro-oncologic surgery

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Abstract

While the first autopsy description of a brain tumour was published in the early 1600s, the first successful surgical treatment of a brain tumour did not take place until over 200 years later by William Macewen, initiating the era of modern neurosurgery. Several advancements had to take place in the late-modern era before this was possible. With the advent of anesthesia, surgeons were able to undertake more complex procedures, fostering the development of the meticulous surgical techniques that characterize the field today. Soon after, the development of aseptic technique pioneered by Joseph Lister began to combat the problem of infection which stifled surgical progress in the centuries before its introduction. Thanks to aseptic techniques, the mortality rate of surgeries showed good improvement and made it safer for patients to go under the knife. One last requirement for brain tumour surgery in an era without modern-day neuroimaging technology was the development of cerebral localization, which guided surgeons to the location of lesions in the brain and informed them of which regions were crucial for quality of life of the patient, and thus to be avoided. Therefore, with these three key developments, modern neurosurgery was able to gain a foothold with the first meningioma resection by Macewen, followed by several others in the decades to come. Progress in brain tumour surgery hit its stride in this era with Harvey Cushing and his introduction of meticulous surgical practices, his revolutionary insight into the importance of adequate intracranial pressure control, and finally the introduction of hemorrhage control through numerous techniques. Legacies of the work of early neurosurgeons can be seen in the 21st century as many of the concepts and techniques remain today, albeit moulded and refined over time.

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Introduction

As one of the world's arguably oldest "surgical speciality," the roots of neurosurgery stretch deep into history beginning in the Neolithic period where ancient practitioners used trephination, or drilling holes to open the human skull. The purposes of this technique are unclear, though it is speculated that it was performed for medical and mystical reasons. Famed physician and historian William Osler (1849-1919) wrote that it "was done for epilepsy, infantile convulsions, headache, and various cerebral diseases believed to be caused by confined demons to whom the hole gave a ready method of escape".[1] There is little mention of brain tumours in ancient literature, though it is likely that some of these trephinations were done on patients with brain tumours as the indications for trephination have many overlaps with symptoms of brain tumours, including seizures, changes in behaviour, and headaches. The existence of tumours in the brain was probably unknown until the first autopsy description of a brain tumour was published in 1614 by Felix Plater (1536-1614), a Swiss physician.[2] In an autopsy performed on a man who "lost his mind," Plater discovered an apple-sized encapsulated intracranial tumour that was compressing the brain – a likely meningioma.[2,3] Surgical treatment of brain tumours would not take place until over 200 years later in 1879 with the first successful removal of a meningioma in a young woman by William Macewen (1848-1924), launching the era of modern neurosurgery. Brain tumour surgeries continued to expand as surgical knowledge and technique improved with time, but it was not until the time of Harvey Cushing (1869-1939) that great strides in brain tumour surgeries were made. Cushing, who is thought to be the father of brain tumour surgery, is credited with ushering in a new mindset and style in neurosurgery that would radically change the practice for years to come. Examination of the history of brain tumour surgery illuminates key aspects of the development of neurosurgery as a specialty. In this article on the history of neuro-oncologic surgery, I will discuss the obstacles preventing successful brain tumour surgeries and the technologies that allowed early neurosurgeons to circumvent these challenges, effectively paving the way for the development of neurosurgery as we know it today.

Anesthesia

In the 19th century, two important developments propelled the surgical field in general into a new era of advancement: anesthesia and asepsis. Without these two discoveries, the ability to open the skull and remove tumours in an effective manner would not be possible. William Morton's (1819-1868) demonstration of the anesthetic effect of ether vapour in 1846 during a neck tumour surgery at Massachusetts General Hospital (Figure 1) was a seminal event in the history of surgical anesthesia as it showed

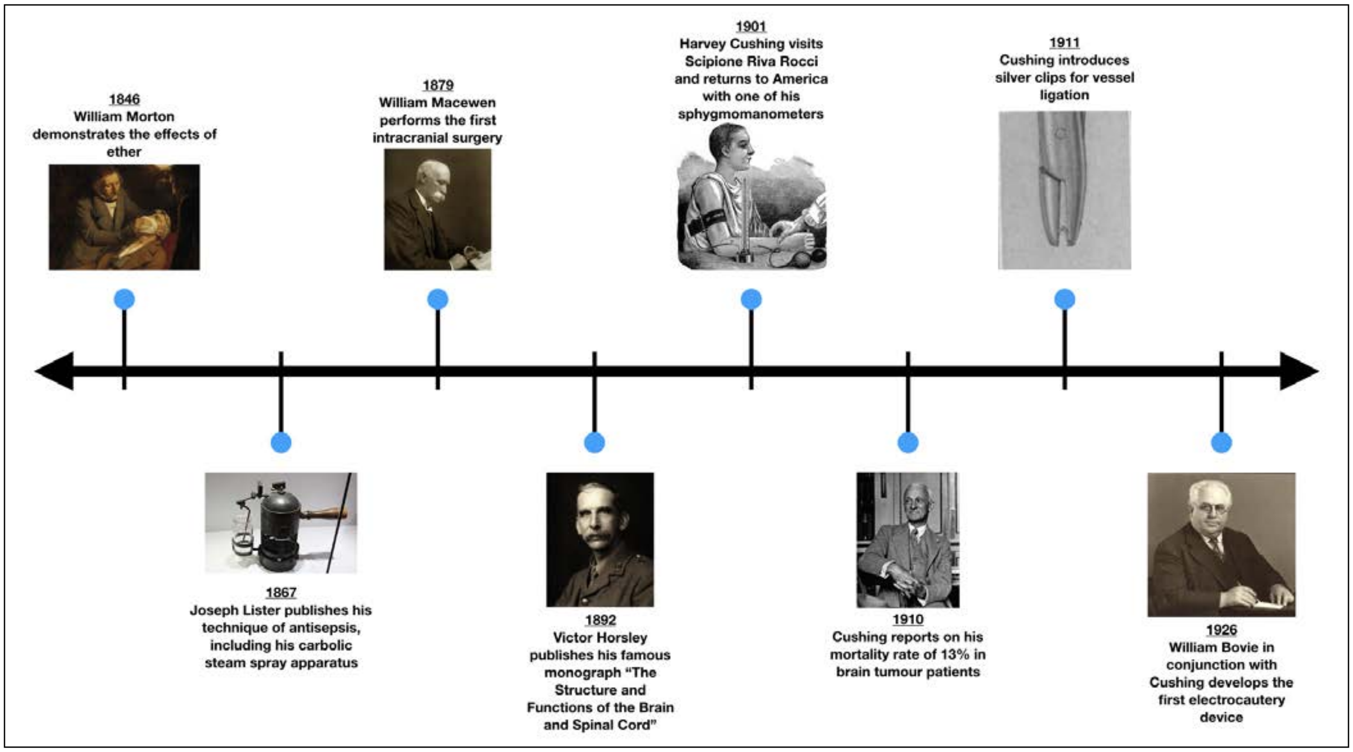

Figure 1. Timeline of seminal events in brain tumour surgery

that anesthesia could be possible and practical.[4] Shortly after, chloroform was introduced by James Simpson (1811-1870) in 1847.[5] Much debate occurred in the neurosurgery sphere in the late 19th century with respect to the merits of ether versus chloroform. Pioneer neurosurgeon Victor Horsley (1857-1916) performed numerous experiments on animals and came to the conclusion that while ether was indeed safer, as it was less toxic to nervous tissue and increased rather than decreased blood pressure, it also caused much "troublesome haemorrhage" and unpleasant post-operative side effects such as headache and vomiting.[6,7] Chloroform, on the other hand, did not aggravate bleeding and had less potent post-operative side effects, but was more dangerous as it affected the respiratory centre in a dose dependent manner. Thus, in light of this, Horsley advocated for using chloroform in carefully regulated doses within precisely tested secure concentrations to avoid respiratory paralysis.[6] However, as evidenced by Harvey Cushing, American surgeons' preferences with regard to anesthetic agents differed from their European counterparts: "In this country [America], where chloroform is doubtless administered less well than ether, the latter is the anaesthetic of choice…"[7] Due to his involvement in an intracranial case using chloroform that tragically turned fatal, Cushing preferred a safer approach and favoured ether over chloroform for this reason, despite being impressed by chloroform's efficacy.[7,8] For Cushing, chloroform should be reserved for multi-staged procedures so as to avoid repeated etherisation and for shorter paediatric cases.[7]

Asepsis

While anesthesia allowed surgeons to operate more deliberately and spared patients great suffering, infection control served as another imposing barrier to neurosurgical progress prior to the 19th century. Elective surgery remained inaccessible since up to 80% of surgeries resulted in hospital gangrene and a mortality rate of nearly 50% for patients undergoing major surgery.[9,10] Louis Pasteur's (1822-1895) work on germ theory in the 1800s deftly overturned the widely-held belief in spontaneous generation and postulated that putrefaction in meat was due to living micro-organisms. Extending off this work, Joseph Lister (1827-1912) used Pasteur's discovery to explain the suppuration of wounds and in 1867 he published his new technique of disinfecting wounds, surgical instruments, and the air surrounding the operating site using a special machine that misted carbolic acid (Figure 1).[11] With this new technique, Lister was able to show in detailed case histories the successful outcomes tied to his new technique; among the few statistics he reports, he demonstrated a drastic reduction of mortality from amputations from 45% to 15%.[12,13] In 1876, Lister toured the United States in order to convince surgeons about surgical antisepsis. In attendance at one conference in Philadelphia was a reputable cranial surgeon, William Keen (1837-1932), who avidly took up Lister's principles and became one of the first surgeons in America to implement them.[14] Improvements on aseptic practices came in the following years with the introduction of heat sterilization of instruments, sterile gowns and caps, surgical masks, and rubber gloves all before the turn of the 20th century. General acceptance and compliance with aseptic principles, on the other hand, would take much longer to permeate the surgical setting.[9]

Cerebral Localization

Though anesthesia and asepsis revolutionized the surgical sphere, there was one missing piece of the puzzle for adequate brain tumour resection: localization of lesions. By understanding the functions of the various parts of the brain, clinicians were able to determine the site of a lesion based on bedside clinical examination. While it was important to know where in the brain to operate, where not in the brain to operate was arguably just as important since surgery in areas such as those responsible for speech and motor function could have catastrophic consequences for the patient. The concept of cerebral localization allowed surgeons to diagnose patients with improved accuracy and kickstarted the field of neurosurgery.[15] Historians have noted that localization served as an "important epistemic break that signals the rise of modern brain surgery".[16] While it was known that the brain was responsible for perceptive, cognitive, and affective processes since Hippocrates, it was not until the 18th and 19th centuries that specific functions of specific parts of the brain began to be discovered.[17] One of the greatest contributors to the field in the late-modern period was John Hughlings Jackson (1835-1911), who is often called the "Father of Neurology." He was known to be meticulously precise in his clinical observations and histories. Until Hughlings Jackson's discovery, the medulla oblongata was thought to be the source of seizures. However, Hughlings Jackson remarked that patients who suffered blunt head trauma often had hemiplegia on the contralateral face and body. Furthermore, if seizures developed in these patients, they would manifest most often on the hemiplegic side of the body.[18] Hughlings Jackson is also well known for his description of seizure patterns where convulsions would start in one part of the body and travel to the next in a sequential and predictable fashion. For example, convulsions might start from the hand, spread to the arm, and then involve the face. Now dubbed the "Jacksonian march," this observation allowed Hughlings Jackson to hypothesize that the cortex was divided into discrete areas that controlled different parts of the body, and that these cortical areas were contralateral to the body part that they controlled.[19] Epileptic activity would move along the cortex and sequentially involve different areas in accordance to a homunculus. Hughlings Jackson's work would set the groundwork for Gustav Fritsch and Edvard Hitzig who later provided evidence of the existence of a motor cortex in dogs in 1870.[20]

Studies of patients with lesions in various regions of the brain would also provide important hypotheses as to the functions associated to those regions. Pioneering work by scientists such as Paul Broca (1824-1880) and Carl Wernicke (1848-1905) on patients with language defects who later had post-mortem autopsies would give us insight into the structural correlates of language processing in the brain.[21] Some scientists went beyond lesion studies and turned to the laboratory to obtain evidence for cerebral localization. David Ferrier (1943-1928), a respected British neurologist, performed experiments on apes, using electrical stimulation on the primate cortex to produce finely detailed cortical maps.[18] Ferrier's work confirmed many hypotheses set forth by Hughlings Jackson. Horsley also performed ablative experiments on the brain and spinal cord of monkeys and finally published his famous monograph "The Structure and Functions of the Brain and Spinal Cord" in 1892 (Figure 1).[22] All of these works on cerebral localization in the 19th and 20th century would prove immensely useful to neurosurgeons as they navigated through the murky waters of the brain.

Thus, the important information gleaned from work from contributors to the field of cerebral localization, combined with the advent of anesthesia and improvement of infection rates via aseptic techniques pioneered by Lister, gave late-modern neurosurgeons bolstered confidence to perform more complex and daring procedures. In 1881, William Macewen reported in The Lancet of a successful operation for a left-frontal meningioma removal in a 14 year old girl – the first intracranial tumour removal in human history (Figure 1).[23] The girl presented to the Glasgow Royal Infirmary with a firm swelling above the left orbit as well as left-sided headaches and a left pupil that was contracted and unresponsive to light. She soon developed right-sided focal seizures that secondarily generalized and then eventually status epilepticus and clinical deterioration. While he was aided by the hyperostosis of the skull just above the left orbit, Macewen was able to localize the tumour by a number of clinical features: the left fixed pupil, the headaches on the left, and the seizures that commenced on the right side. Macewen used the external deformity as a landmark and was able to enter the skull and remove the tumour from the dura. The girl survived the operation and gradually recovered from post-operative hemiplegia and seizures.[18] The girl was engaged in regular employment and would live for 8 more years before passing away due to Bright's disease.[14] Macewen would go on to perform 21 other neurosurgical cases by 1888 with 18 successful recoveries and only 3 deaths. These promising results were attributed by him to "cerebral localization and good aseptic technique".[14] Macewen's seminal surgery would kickstart the era of modern neurosurgery, and soon following were highly publicized brain tumour surgeries by Alexander Bennett (1848-1901) and Rickman Godlee (1849-1925) in London in 1884 and William Keen in America in 1884.[14,16]

Intracranial Pressure

No discussion about the history of brain tumour surgery is complete without mention of one the pioneers of modern neurosurgery: Harvey Cushing. When Cushing began his career at Johns Hopkins in 1901, the mortality rate for intracranial tumour surgeries was a dismal 19-50%, depending on the location of the tumour, according to Ernst von Bergmann.[24] The cause of increased mortality was due to cerebritis and meningitis secondary to brain fungation from high intracranial pressure (ICP).[25] Most people in the late 19th century had only a vague idea of ICP.[26] Cushing set out to Europe in 1900 to conduct an academic Wanderjahr and ended up working in the laboratory of the physiologist Hugo Kronecker (1839-1914) after being introduced by Theodor Kocher (1841-1917). It was in Bern, Switzerland where he started his groundbreaking work on the physiological effects of increased ICP. By manipulating the ICP of small animals using an intracranial bag of mercury while measuring the blood pressure and pulse, Cushing was able to demonstrate a rise in blood pressure and a decrease in pulse with a rise in ICP. He summarized it as such:

> *"As a result of these experiments a simple and definite law may be established, namely, that an increase of intracranial tension occasions a rise of blood pressure which tends to find a level slightly above that of the pressure exerted against the medulla. It is thus seen that there exists a regulatory mechanism on the part of the vaso-motor centre which, with great accuracy, enables the blood pressure to remain at a point just sufficient to prevent the persistence of an anaemic condition of the bulb, demonstrating that the rise is a conservative act and not one such as is consequent upon a mere reflex sensory irritation."*[27]

Today, the triad of hypertension, bradycardia, and irregular breathing – signs of increased ICP – is named "Cushing's triad" in his honour. When Cushing returned to America from his travels in Europe, he began to put into practice the concepts he discovered through his research. Cushing brought with him a device called the Riva-Rocci apparatus, which was an Italian device for measuring blood pressure, and pushed for the measurement of pulse, respiration, and blood pressure intraoperatively (Figure 1). On his reasoning behind measuring the blood pressure, Cushing stated: "Such a record not only furnishes instructive generical data, but often furnishes a means of properly interpreting the effects, whether beneficial or otherwise, of the various operative steps".[28]

Cushing also applied his principles to the treatment of intracranial tumour patients. Recognizing the need to primarily control the ICP in order to avoid high mortality, Cushing planned his operations in stages. When a patient presented with clinical signs of high ICP, including headache, vomiting, and papilledema, Cushing would first perform a decompressive craniectomy in order to relieve high ICP without even trying to localize the tumour – controlling the ICP was paramount.[26,29] Sometimes he even completed two preliminary decompressions before localizing and removing the tumour in a secondary stage. While Cushing was uncertain if this was the right measure at the time, his persistence and ingenuity paid off. In 1910, Cushing reported on 180 tumour patients that he had operated on and claimed a mortality rate of merely 13%, a vast improvement over the near-50% rate at the beginning of his career (Figure 1).[25,30]

Hemorrhage

Once Cushing had a handle on the problem of ICP, he turned to the next great obstacle in brain tumour surgery: bleeding. Neurosurgery is quite different from other fields of surgery by virtue of the material that neurosurgeons work on. While techniques such as sutures and clamps could be used for hemostasis in general surgery, neural tissue is much too delicate for conventional techniques. Accordingly, neurosurgery had to be done slowly and with scrupulous hemostasis. Cushing, who trained under William Halsted (1852-1922), developed a reputation for being a meticulous surgeon like his mentor. Halsted and Cushing were part of a newer generation of surgeons who turned away from the showy, rapid style of surgery that dominated the surgical sphere in the first half of the 19th century.[31] Cushing employed careful surgical procedures which helped with both infection and blood loss. On the importance of careful hemostasis and slow operating, Cushing wrote:

> *"Neighborhood oozing obscures the clear view essential to the safety of such delicate manipulations as are required for the removal of, let us say, a lateral recess tumor or the trigeminal ganglion; whereas a more general loss of blood with the consequent lowering of arterial tension is a cordial invitation to its near relative shock, favors the onset of respiratory paralysis in cases associated with medullary pressure, makes anaesthesia more dangerous, and lowers resistance to infection through secondary anaemia."*[32]

Blood loss was a safety issue for multiple reasons, both intraoperatively for the surgeon to operate and for the stability of the patient. As intracranial procedures became more and more complex, they became lengthier and more tedious due in large part to the fact that hemostasis was very time consuming. The risk of hemorrhage, especially with highly vascular tumours, had the potential to delay surgery to a second or even third stage. Cushing developed a number of technical advancements in order to combat this threatening problem. Cushing employed techniques such as using living tissue from the temporal muscle, pieces of formed blood clots, and small pledgets or gauze attached to a black ligature to encourage hemostasis. In 1911, he introduced silver clips consisting of U-shaped pieces of wire that were held in the jaws of clamps and could be directly applied to blood vessels in delicate regions too awkward for ligation (Figure 1).[32] Finally, in one of his greatest contributions to hemostasis, Cushing, in collaboration with William Bovie (1881-1958), introduced the use of electrocautery in neurosurgery (Figure 1).[33] This technique involves passing a high frequency current to cut and coagulate tissue. While initially met with skepticism from surgeons at the time, the technique was efficacious in stopping bleeding and is still used to this day.[34]

Conclusion

The state of brain tumour surgery is often seen as a proxy of the state of neurosurgery as a whole.[35] Throughout the late-modern period, brain tumour surgery and neurosurgery in general underwent significant overhauls in ideas, styles, and technologies and continued to build upon themselves. With the advent of anesthesia, asepsis, and cerebral localization, early neurosurgeons in the late-modern era were able to begin operating in the brain and attempting to remove tumours. Further improvements in ICP control and hemorrhage were introduced by Harvey Cushing in the early 1900s and progress in neurosurgery hit its stride. Neurosurgery as we know it today is celebrated as a triumph of humanity. The latest data on the outcomes of malignant brain tumours shows an average five-year relative survival rate of 35.8% going up to 74.7% in children due in large part to advances in neurosurgery, chemotherapy, and radiation therapy.[36] This advancement would not have been possible without the contributions of the pioneering scientists and neurosurgeons of the late-modern era. While great advancements have been made in neuro-oncology since Macewen's time, much work remains in neurosurgery to improve outcomes for patients with deadly tumours such as glioblastoma and anaplastic astrocytoma.

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