The History of Arachne Through Historic Descriptions of Meningiomas with Hyperostosis: From Prehistory to the Present

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■ BACKGROUND: **Intracranial meningiomas are brain tumors that have probably been known the longest, largely because of the occasional production of grotesque cranial deformities that have attracted the attention and interest of humankind. Because of the tendency of some intracranial meningiomas to cause skull deformation and thickening, these tumors have given rise to various speculations and theories related to their origin, starting in prehistoric times up to the present.**

■ METHODS: **From the Steinheim skull and "pharaonic meningiomas" to the first meningioma monograph and the first explanations of Harvey Cushing regarding the mechanism of hyperostosis, this review aims to weave again the story of Arachne. We identify the main contributors who have tried to understand and explain the tendency of some of these tumors to cause hyperostosis or other skull bone involvements.**

■ CONCLUSIONS: **The contribution of neurosurgeons or pathologists over the centuries is of undeniable importance and is the basis for understanding future molecular mechanisms.**

INTRODUCTION

Meningiomas are brain tumors that have probably been known the longest, largely because of the occasional production of grotesque cranial deformities[1] that have attracted the attention and interest of humankind. Because of the tendency of some intracranial meningiomas to cause skull thickening and deformation, throughout the history of humanity, these tumors have left traces in the form of hyperostosis that gave birth to the early theories related to their origin, starting with the prehistoric period. From an archeological perspective, we may say that meningiomas were primarily identified as a result of changes caused to the ectocranial table,[2] which were true paleopathologic hallmarks of these lesions. From this point of view, 11 intracranial meningiomas with hyperostosis with Paleolithic origins were recorded worldwide (**Table 1**),[3] and the rarity of these tumors may be accounted for by the fact that the mean life expectancy for adults before the end of the medieval period was considered to be <40 years,[13] which meant that these tumors had no time to develop.

The rarity of meningiomas with hyperostosis was also confirmed by Campillo, who, in a study of approximately 3000 ancient skulls in Spain, from the Neolithic period to the late Middle Ages during ≥20 years, found the presence of only 5 lesions that were suspected to be intracranial meningiomas.[14] Also, on the basis of the evidence found, Campillo made a classification into 8 types of bone alteration that can be seen by conventional radiography and by inspection in paleopathology. However, Campillo considered that none of these lesions was pathognomonic to these types of tumors.[14]

Skulls with bone modifications caused by intracranial meningiomas have been found worldwide, in ancient Egypt,[10] in prehistoric America, in the Inca civilization of the Peruvian Andes,[8] and in Germany, and an explanation of their good preservation could be the climate and high lime content of the soil.[5,3]

This review aims to weave again The story of Arachne and of the main contributors from prehistoric times to the present, in their attempt to understand the tendency of some of these tumors to cause skull hyperostosis.

Homo steinheimensis

Of all the skulls with changes caused by meningiomas, the oldest was discovered in 1933 in the city of Steinheiman der Murr in Germany (**Figure 1A**), and it has come to be known in history as the Steinheim skull (**Figure 1B**). It happened to be re-examined some years later, in 2003, at the Eberhard-Karls University of Tubingen by Czarnetzki et al., who showed that the owner of the skull had intracranial meningioma.[5] Moreover, they stratigraphically dated it to 365,000 BC, making it also the earliest record of a *Homo erectus* meningioma.[3,15,16]

The *Homo steinheimensis* fossil (**Figure 1B**) shows some features of the inner cranial table that correspond to a meningioma diagnosis: thinning of the right parietal bone and widened branches of the middle meningeal artery. Furthermore, the investigators found the Pleistocene human to have had a tumor with an

Table 1. Paleopathologic Examples of Meningiomatous Hyperostosis, According to Okonkwo and Laws[3] and Anderson[4]

Location	Date	Gender	Age (years)
Steinheim (Germany)[5]	365,000 BC	F	25–30
Stetten (Germany)[6]	32,500 BC	?	Adult
Chavina (Peru)[7]	Before contact	F	Middle age
Paucarcancha (Peru)[8]	Before contact	M	Elderly
Chicama (Peru)[7]	?	M	Adult
St. Nicholas Island (California, USA)[9]	Before contact	M	Elderly
Helouan (Upper Egypt)[10]	3400 BC (I Dyn)	M	40–60
Meydun (Upper Egypt)[10]	1500 BC (XX Dyn)	M	50–70
Radley (Oxfordshire, United Kingdom)[11]	100 AD (Roman)	F	Adult
Chernovski (Alaska, USA)[12]	1000 AD	M	40
Rochester (Canterbury, United Kingdom)[4]	1400 AD (medieval)	F	35–50

F, female; M, male.

anteroposterior size of 51 mm, a mediolateral size of 43 mm, and a depth of 25 mm; its volume was 29 mL, the size of a mean meningioma diagnosed nowadays.[5,6] In the Pleistocene era, these tumor sizes, in conjunction with the small Steinheim cerebrum of only 1100–1200 mL, smaller than the modern brain of 1300–1800 mL, would have caused continuous headache, significant hemiparesis, and death.[5]

Ancient Egypt and Pharaonic Meningiomas

In the ancient Egyptian medical papyri discovered, there are no indications of head tumors with bone involvement. However, tumors and tumorlike lesions were not uncommon among the Pharaohs' people and they were mentioned especially in the Ebers Papyrus, most probably pointing to alterations of the soft tissue.[17] Discovered in 1862 between the legs of a mummy in the necropolis of Theben, the 20.23 m of the Ebers Papyrus contained medical information, including information about central nervous system conditions.[18,19]

The earliest case of hyperostotic lesion of the skull from ancient Egypt was discovered during the Royal Excavations at Helouan. The skull had a hyperostotic lesion in the right parietal area, which involved both the inner and outer tables, showing the presence of a parasagittal meningioma, and belonged to the First Dynasty of Ancient Egypt (c. 3100–2890 BC).[10,20,21]

A later case from the 20th Dynasty of Ancient Egypt (c. 1186–1069 BC) showed a beautiful specimen of calvarium, with an extensive honeycomb lesion of the right parietal area extending to the left parietal and frontal areas.[10] These Ancient Egyptians, in their attempt to achieve immortality for their Pharaohs and important officials, kept important information about the diseases they experienced throughout their lives,[22] also providing information about "pharaonic meningiomas."

As concerns the treatment of head tumors, Herodotus tells us that in ancient Egypt there were specialists of the head[23,24] and the remedies for these types of tumors included excision with a knife, local paste applications, burning with red-hot irons, spells, or leaving the swelling untreated.[25,26] We have no documentary or physical evidence that in ancient Egypt doctors recognized or treated intracranial meningiomas or other brain tumors.[24]

The oldest record of what could be a meningioma in the existing literature belongs to Felix Platter (1536–1614), professor at the University of Basel in Switzerland. In his book *Platerus Observations in Hominis*, published in 1614,[27,28] Platter described the tumor as follows: "a round fleshy tumor, like an acorn. It was hard and full of holes, and as large as a medium-sized apple. It was covered by its own membrane and entwined with veins. However, it was free of all connections of the matters of the brain so much that when it was removed by hand, it left behind a remarkable cavity."[29,30] Despite the absence of hyperostotic changes, the tumor described by Platter is still a remarkably important finding in the history of meningiomas.

Almost 100 years later (i.e., in 1730), also on the old continent, the German Johann Salzmann (1672–1738) drew the earliest known illustration of an intracranial meningioma with hyperostotic changes[31] (**Figure 2A**). It was a left frontoparietal tumor with intracranial and extracranial components. The case was called "Exostosisseu ex crescentia crania osseospongiosa," and it was reported in *Collegium Naturae Curiosum*,[31] the first medical and natural science journal, and in

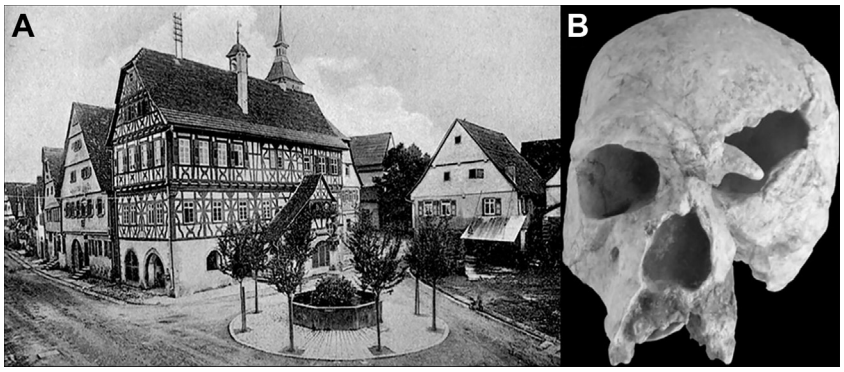

Figure 1. (**A**) Steinheim city center at the time of the discovery of the Steinheim skull. (**B**) Replica of *Homo steinheimensis* skull (adapted, UrmenschmuseumSteinheim) (public domain)

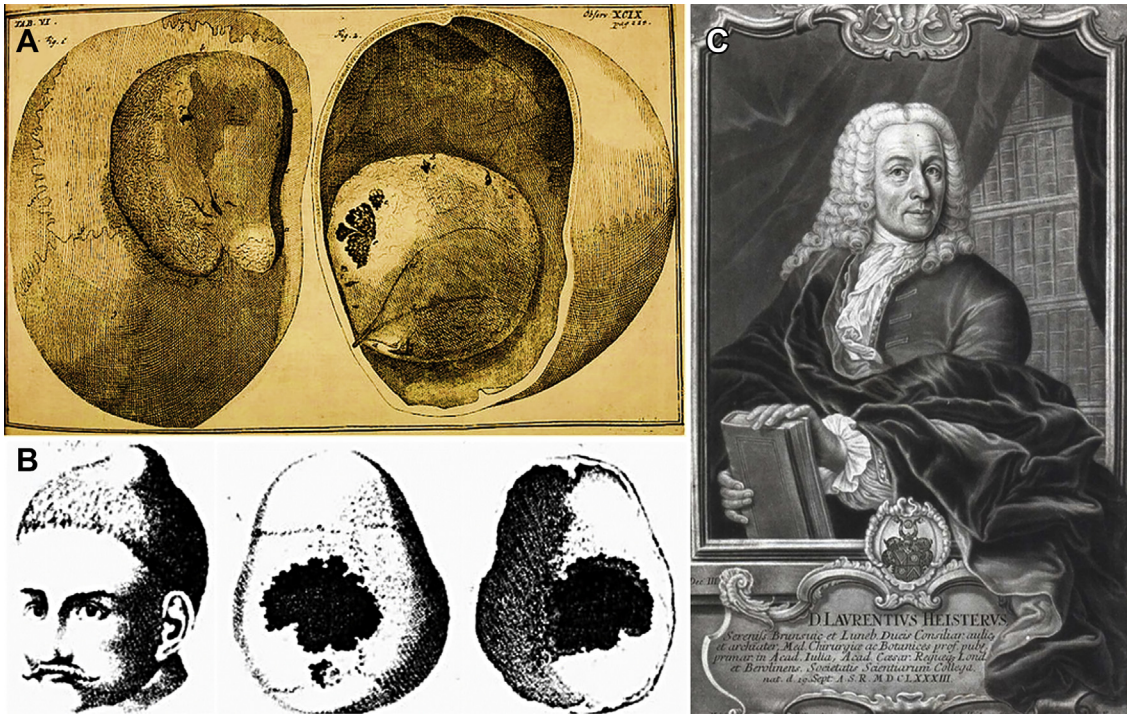

Figure 2. (**A**) Earliest known illustration of a meningioma, reported by Johann Salzmann in 1730, showing both intracranial and extracranial components of the tumor (adapted from Refs.[31,32] and the Biodiversity Heritage Library. Contributed by the National History Museum Library, London, www.biodiversitylibrary.org). (**B**) The Kaufmann-Heister-Crellius case with fungating meningioma (adapted from Refs.[28,33]). (**C**) Laurence Heister (1683–1758) (public domain).

the present-day German Academy of Natural Sciences Leopoldino.[3,34]

Professor of anatomy and pathologic anatomy at the University of Strasbourg, Johann Salzmann was interested in neuropathologic cases, of which he described a few.[35,36] One may notice in Tabula VI (**Figure 2A**), which shows the meningioma, that both intracranial and extracranial components of this tumor are seen. As for the patient's symptoms, they were insidious, lasted for >4 years and were dominated by the intracranial hypertension syndrome. This situation was mainly determined by the intracranial component of the tumor, and Salzmann reconstituted meticulously the course of illness.[35] As Salzmann reported in his article, in March 1727, after he had drunk some water, the 43-year-old man experienced severe abdominal pain, followed by a seizure, and sudden death. Because of this sudden death, he was believed to have been poisoned and a forensic autopsy was performed. During autopsy on the left frontoparietal side of the skull, a large tumor with extra and intracranial components was detected.[35] At the end of the report, Salzmann mentions that the tumor was soft, osseospongious, left an impression on the underlying structures, and displaced the dura and dural blood vessels without infiltrating the brain and without dural involvement.[34,35]

The original report, written in Latin, provides a unique insight into the natural history of an untreated calvarial ectopic meningioma of that time.[32] Although Salzmann does not say anything about tumor histology, in a report published in 2004, Kompanje[34] discusses the possibility that the tumor described by Salzmann may have been osteogenic sarcoma, metastatic carcinoma, Ewing sarcoma, or giant cell tumor. Considering the slow progression of the tumor over at least 4 years, the large size of the tumor with minor and insidious symptoms extending over several years, the extracranial and intracranial components of the tumor, and the compressive effect on the underlying brain, the contemporary investigator is inclined to think it was a slow-growing benign process, most likely a primary extradural meningioma. Moreover, Kompanje considers Salzmann's case as one of the first morbid descriptions of the findings during autopsy of a patient with meningioma ever reported in the scientific literature, and the first reported case of a rare primary extradural calvarial meningioma that provides information on the natural history of the tumor.[34] The next case of calvarial meningioma was reported much later, in 1932, by Bernard J. Alpers and Reed Harrow from the University of Pennsylvania in Philadelphia.[37]

"De Tumore Capitis Fungoso" of a Prussian Soldier and a Spanish Nobleman

Several years after the report of Johann Salzmann's case in *Collegium Naturae Curiosum*, also in Germany, in 1743, in Helmstad, the surgeon and anatomist Laurence Heister (1683–1758) (**Figure 2C**) marked the beginning of the surgical treatment of intracranial meningiomas.[38] One of Dr. Heister's patients was a 34-year-old

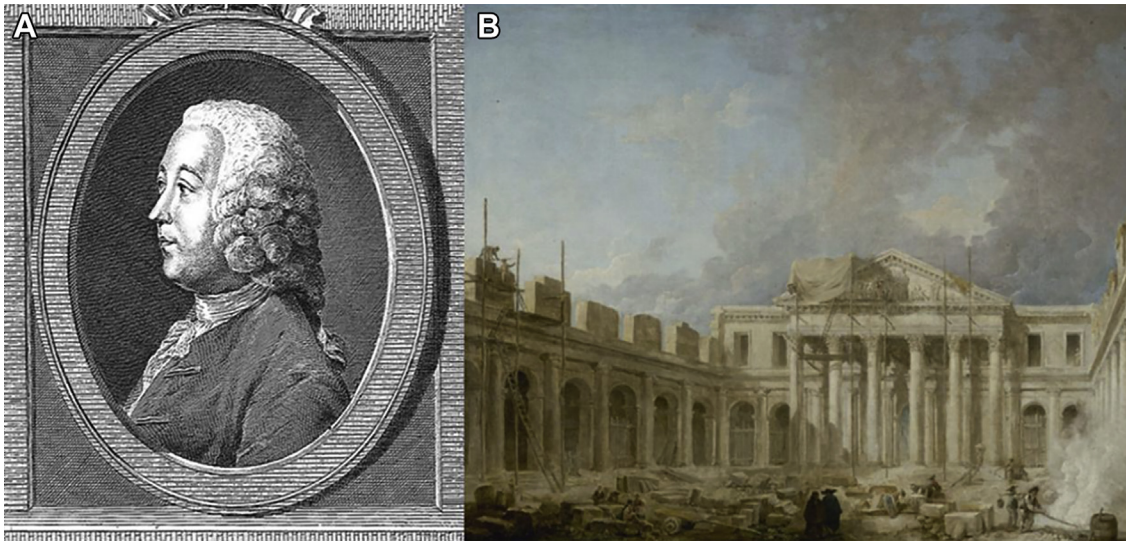

Figure 3. (**A**) Antoine Louis (1723–1792). (**B**) "L'Ecole de Chirurgie en construction" (1733). Académie Royale de Chirurgie. Hubert Robert; Carnavalet Museum, Paris (public domain).

Prussian soldier with an impressively large meningioma, located at the vertex level and having a significant extracranial component (Figure 2B). Heister applied caustic lime to the tumor, but the patient developed a sepsis infection and subsequently died. The autopsy was performed by Johann Friedrich Crellius (1707–1747), who showed the tumor to be "de tumore capitis fungoso."[38,39]

Johann Friedrich Crellius was an anatomy and physiology professor at Wittenberg and later in Helmstedt, paying special attention to pathologic anatomy.[40] He wrote about the Prussian soldier's exostotic meningioma in 1755, in his dissertation thesis, together with Johann Philipp Kaufmann, "De tumore capitis fungoso post cariem crania ex orto." The case was to be later included in the monograph "Mémoire sur les tumeurs fongueuses de la dure-mère," published in 1774 by Antoine Louis.[41]

However, about a century before Heister's surgical treatment, the Italian surgeon and anatomist Marcus Aurelius Severinus (1580–1656), author of *Zootomia* (the first treatise on comparative anatomy) performed the first successful surgical extirpation of a brain tumor, so-called "fungus tumor of the dura madre," probably a meningioma.[42] In his treatise "De Medicina efficaci" (1646), Severinus discussed the operation he performed on the skull of a nobleman of the Spanish court and of the house of the Avalos who had intolerable headaches. The nobleman consented to be subjected to trepanation of his skull, and Severinus found a "fungous excrescence" under the bones. So, he proceeded to destroy the excrescence, providing a definitive cure of the patient's headaches.[43]

First Meningioma Monograph

With the French Enlightenment, the organization of medical sciences in Western Europe started, as a result of intellectual productivity improvement and ever higher academic competition during the reigns of Louis XV and Louis XVI.[38,44] In the final years of the French Enlightenment, the French military surgeon Antoine Louis (1723–1792) (Figure 3A) produced the first documented reference dealing exclusively with meningiomas.[45]

Antoine Louis was the descendant of a family of surgeons and was interested in the surgery of the nervous system,[38] especially of dural tumors, which he called "fongueuses de la dure-mère" (fungoid tumors of the dura mater),[41] being convinced that intracranial meningiomas develop from the dura mater. However, it is not known whether Louis reached this conclusion on the basis of his surgical experience or relying exclusively on autopsy studies.[38,41]

The name suggested by Louis, "fongueuses de la dure-mère," was later to be recognized as the first important attempt to name meningiomas.[3,38] He had his report, "Mémoire sur les tumeurs fongueuses de la dure-mère," published in *Mémoires de l'Académie Royale de Chirurgie* (Figure 3B) in 1774.[38] In this monograph, Louis reported 20 cases, most of which had been gathered in the literature of the latter part of the seventeenth century and the eighteenth century up to the time of publication.[88] He also described and illustrated several cases of skull meningiomas eroding the bone and also having extracranial extension.[41] Louis diagnosed these tumors based primarily on skull deformations, but obviously he also relied on neurologic symptoms such as headache, weakness of the limbs, convulsions, or visual defects.[46] Louis might have included under the term fungal tumors of the dura not only meningiomas but also metastases and syphilitic osteomyelitis.[47]

The treatment of these tumors in Louis' time was the destruction of the tumor by applying caustic solutions (e.g., potash), which was catastrophic in most cases, whereas other medicines, such as rose honey, wine, or herbs, were ineffective. Nevertheless, Antoine Louis recommended the surgical removal of tumors, about which he also wrote an essay in 1774.[46]

The Most Beautiful Illustrations of Meningiomas

Beginning with the early nineteenth century, many doctors, among them Jean Cruveilhier, have attempted to fill the gap that appeared between a developing modern science and an empirical and ageing conception of medicine inherited from antiquity and the Middle Ages.[48] Being a pioneer in pathologic anatomy and general surgery, the Frenchman Jean Cruveilhier (1791–1874) (Figure 4A) also had important contributions to research on cancerous tumors of the meninges.[47] Before him, his fellow countryman Antoine Louis (1723–1792) provided detailed descriptions of what he called the fungal tumors of the dura, which included a variety of pathologic entities such as syphilitic osteomyelitis and metastases and not just meningiomas.[47,50]

Cruveilhier considered meningiomas to be cancerous tumors of the meninges and depending on their origin, he distinguished 2 main types: tumors originating in the external layer of the dura, which tended to grow toward the cranial bone, which they progressively eroded, and tumors arising from the internal layer of the dura, which grew inward and compressed the brain. He also described a third rare type that he believed originated in the arachnoid layer.[47] As for bone involvement, he drew numerous figures in his *L'Anatomie Pathologique du Corps Humain*,[49] perhaps the most beautiful medical book ever printed, illustrated with colored lithographs and made from his extensive collection of specimens as professor of pathology (Figure 4B).[3] The chapter on meningiomas was called "Des Tumeurs Cancereuses des Meninges," reflecting Cruveilhier's belief that meningiomas were malignant tumors.[3]

Because of his encyclopedic descriptive work, Cruveilhier played a major role in the birth of the anatomoclinical method, particularly in neurosurgery and neurology during the nineteenth century, toward evidence-based medicine.[47]

The First Successful Resection of a Meningioma

Starting with the early nineteenth century, in surgery of central nervous system tumors, the Italian school of surgery represented by several Italian surgeons started to advise that intracranial tumors should be completely and promptly removed.[51] Also, newly discovered knowledge in neuroanatomy and neuroscience started to shape the discipline of neurosurgery and neurology in the medical schools and hospitals of Europe.[52,53]

In this regard, the Italian Zanobi Pecchioli (1801–1866) was assigned the important role of having been the first to successfully remove a meningioma.[54] Pecchioli was a Professor of Clinical Surgery and Operative Medicine at Modena and Siena University and, in 1847, he reported his surgical series of 1524 surgeries performed over 16 years, from 1832 to 1847, 16 of which involved skull trepanation.

One of these surgeries was conducted in Siena on July 29, 1835, and it involved the resection of a meningioma.[38,54] Although it was not reported in the literature by Pecchioli, the case was described by the editorial board of the *Nuovo Giornale dei Letterati-Scienze* in 1838.[55] The tumor location was the right sinciput area. It was large, and the entire tumor surface was ulcerated, which was proved by surgery to have originated in the dura mater and to be eroding the skull.[56] The 45-year-old patient had long experienced severe headache that was exacerbated by digital compression of the mass.[38,54] Pecchioli removed the mass with the dural insertion, "thus leaving the underlying arachnoid exposed in two large zones."[56] The tumor was a large ulcerated cranial outgrowth and the extensive postresection area took a long time to heal, with cambric soaked in sweet almond oil, and with the patient needing 4 months to recover.[56] Five years later, in 1840, the description of the surgery was chosen for the competition for the chair of surgery at the University of Paris.[55-57]

Andrea Vaccà Berlinghieri (1772–1826) and Zanobi Pecchioli (1801–1866) suggested several surgical steps to remove "sarcoma" or "fungus" of the dura mater (meningioma), namely craniectomy of bone flap with 5 or 6 burr holes, tumor and dura mater resection using a knife and tying of the cut vessels, and meningeal artery occlusion at the edge of the bone, if damaged during surgery.[51,56,57]

One of the First Attempts at Skull Base Surgery

On November 26, 1841, the Venetian Tito Vanzetti (1809–1888), professor of surgery at Kharkov and surgeon for the Pope, exposed and removed a skull base tumor, which was probably a meningioma.[58] The case was documented 3 years later, in "Quelques observations pratiques recueillies à la

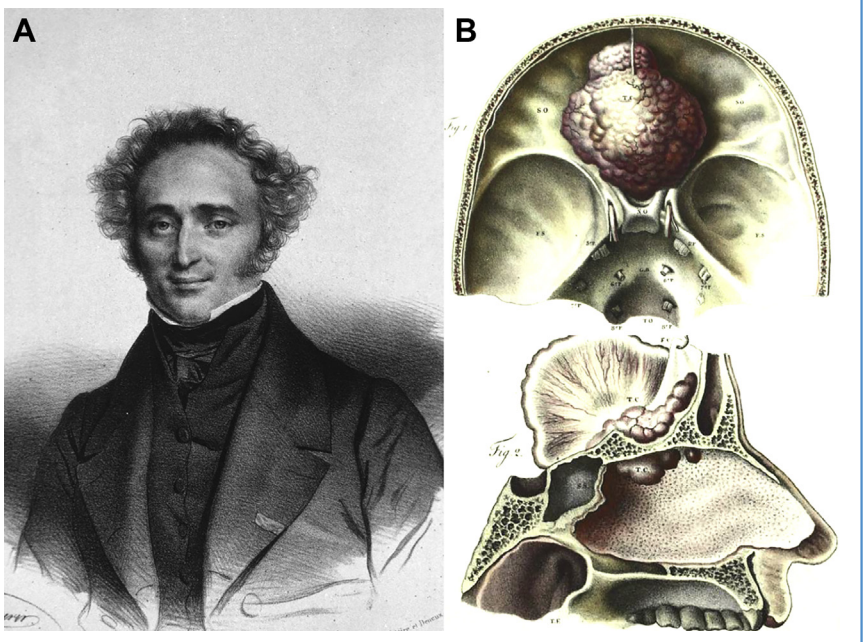

Figure 4. (**A**) Frenchman Jean Cruveilhier (1791–1874). (**B**) Large anterior skull base meningioma invading the cribriform plate (adapted from Refs.[47,49]).

Clinique Chirurgicale de l'Université Impériale de Kharcoff (Russie)"[59,60] and represented "a case of a bone cyst on the right side of the head that had destroyed the base of the skull without affecting cerebral function." The tumor proved to be a solid and massive tumor with intracranial growth, and during the operation, he had to change his original surgical plan for a bone cyst resection, because of the evidence of massive intracranial invasion.[61] Although the patient survived the operation, he died of an infection on the 32nd day and his autopsy confirmed the huge size of the injury and important skull base invasion.[56] Although Vanzetti did not report the histology of the lesion, his operation can certainly be considered one of the first attempts at skull base surgery,[61] which probably involved a meningioma.[58]

"Omnis Cellula e Cellula"

A few years later, in 1864, the renowned German doctor and pathologist Rudolf Ludwig Karl Virchow (1821–1920) (**Figure 5A**) described a psammoma of the dura (meningioma) located at skull base level, overlying an exostosis of the sphenoid bone, which was believed to have developed as a consequence of trauma.[62] According to the figures illustrating this case, the tumor extended behind the crista galli in the midline and the bony exostosis apparently reached a considerable size[37,62] (**Figure 5B**).

Considered by many as the founder of cellular pathology, Rudolf Virchow provided the scientific basis for the modern pathologic study of cancer, also featuring in the history of medicine for his famous "Omnis cellulla e cellula" doctrine (i.e., every cell from a cell).

Meningioma in the Hands of the Modern Brain Surgery Pioneer

Several years later, after Vanzetti's success, in 1881, the Scottish surgeon William Macewen (1848–1924) (**Figure 5C**), reported in *The Lancet* the successful removal of a left frontal meningioma. The case was of a 14-year-old girl with a swelling at the upper and inner part of the left orbital cavity, with occasional frontal headache and miotic left pupil with no response to light.[63] Although the patient had originally come to the doctor for cosmetic deformity, a few days after admission to the Glasgow Royal Infirmary (**Figure 5D**), she experienced seizures that progressed toward secondary generalized seizures and life-threatening status epilepticus.[64,65] The girl was sedated and under antiseptic conditions, her skull was opened off the right front lobe, and the detection of the tumor location was aided by hyperostosis of the skull above the left orbit.[64-66]

In the report in 1881 in *The Lancet*, Macewen described the surgical procedure in detail, but we focused only on the description of the bone infiltration by the tumor: "It was about the size and shape of a kidney-bean [the tumor], its flat surface lying against the roof of the orbit, and extending inwards under the orbital plate of the frontal. It seemed firmly fixed to the periosteum, and it had a fibrous feeling. […]. The bone underneath this little tumour was found to be rough and imparted a softer feeling to the finger than usual. […] The skull was thicker than normal, and attached to the under surface of the disc was a tumour of a gummatous aspect."[29] After the surgery, Macewen noted that "after recovering from the influence of the anaesthetic, the convulsions did not return" and "her intelligence became perfect." Thus, on her discharge from hospital, the patient was in good condition.[29]

At around the same time, in Turin, Italy, in 1883, the Italian surgeon Filippo Giacomo Novaro (1843–1934) operated on a parasagittal frontal hyperostosing meningioma.[67] Just like in Vanzetti's case, the diagnosis was set based on the bone

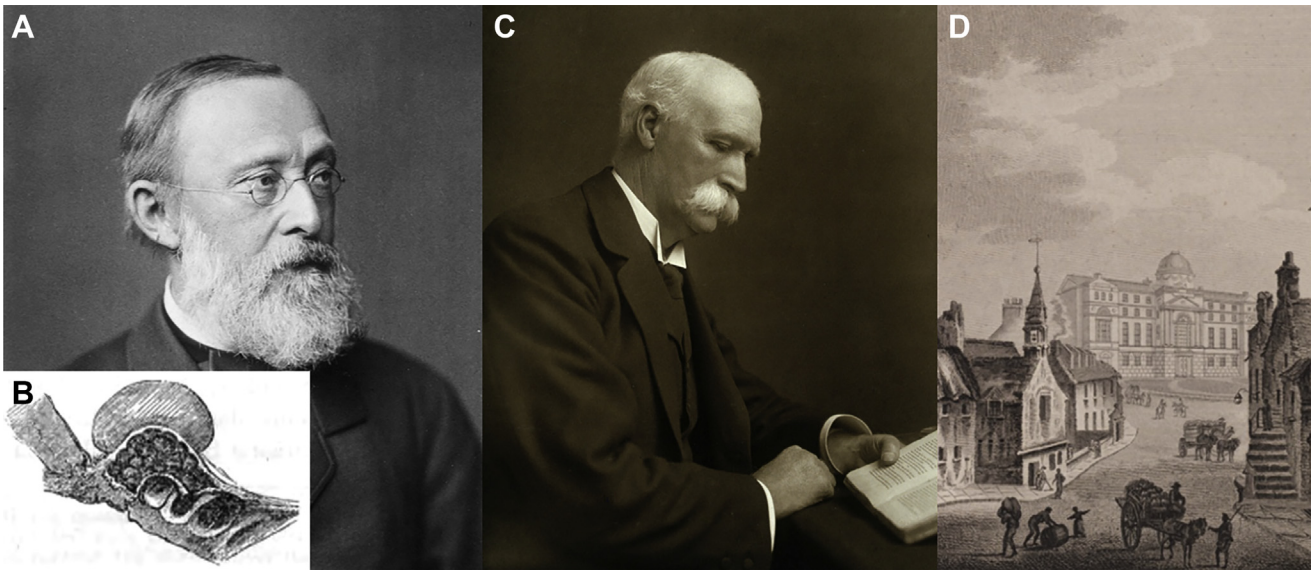

Figure 5. (**A**) Karl Virchow (1821–1920). (**B**) Illustration of Virchow's case of skull base meningioma with exostosis of the sphenoid bone (adapted from Ref.[62]). (**C**) William Macewen (1848–1924). (**D**) Glasgow Royal Infirmary during Macewen's time (in the background of the image) (public domain).

irregularities apparent from the outside, which were associated with epileptic seizures. In this case, Novaro resected the superior sagittal sinus that was infiltrated, but the patient died 1 hour after the surgery[56] as a result of acute anemia caused by a profuse intraoperative hemorrhage from the diploe and superior sagittal sinus.[54]

Hyperostosis in Detail—First Case

In 1899, Spiller reported in detail the first case of meningioma with hyperostosis that enlarged the left side of the head. The case was presented at the meeting of the Section on General Medicine of the College of Physicians of Philadelphia and was subsequently reported together with Stern and Kirkbride, the hospital's pathologist. The abstract of the report published in *The Medical Record*[68] claimed that: "the case was that of a man who, sixteen years previously, had fallen and injured the left side of his head. After eight years a swelling was noticed in this situation, and several years later paresis in the right lower extremity, and later in the right upper extremity also. Headache and vomiting were superadded, speech became paraphasic, and a convulsion occurred. On ophthalmoscopic examination bilateral optic neuritis was found. Operation was decided upon; a segment of greatly thickened and infiltrated bone was removed from the calvarium, and a new growth found in the cortex of the left motor area. Hemorrhage was profuse and death occurred a few hours after the operation from loss of blood and shock. On histologic examination the growth was shown to be an endothelioma [meningioma]."

Spiller drew attention on the contribution of head trauma to the occurrence of hyperostosis, although the belief that intracranial meningiomas were caused by head injuries dates back to the eighteenth century, more precisely to Louis Antoine's time. Spiller also reported 2 cases with previous history of head trauma, arguing that "it is not improbable that these injuries were at least the predisposing cause of the bony proliferation."[69]

During the following years, similar cases were reported by Brissaud and Léreboullet[70] and later by Parhon and Nadjede,[71] who reported in 1905 the case of a 63-year-old patient with bony enlargement and an underlying tumor in the right front lobe, the size of a small orange.

With the development of intracranial radiology initiated by Bollici and Obici in 1897,[33,38] a few years later, in 1902, Pfahler and Mills documented in Philadelphia the first radiologic description of a meningioma with some bone skull changes: "an exposure of four minutes [was] made with a moderately hard vacuum. A negative was obtained which showed good detail of all the structures. A large shadow lying between the coronal suture and the posterior meningeal artery corresponded to the area in which Dr. Mills had located the tumor."[38,72]

Harvey Williams Cushing, the Father of Meningiomas

On the American continent, in 1922, Harvey Cushing (1869—1939) first introduced the term meningioma to describe a group of tumors that arose from the meninges of the brain and clarified the numerous confusions and histopathologic names used before to define this tumor.[73] Cushing also studied hyperostosis related to intracranial meningiomas and reported a series of 20 cases of meningiomas with bony hyperostosis. In every case, Cushing noticed that tumor cells were found in the thickened bone and also pointed out that meningiomas en plaques were more frequently associated with hyperostosis than were meningioma en masse and bony hyperostosis.[73] The term meningioma "en plaque" was introduced by Cushing and his collaborator Eisenhardt to differentiate these meningiomas from the more common form called meningioma "en masse."[33]

Moreover, Cushing believed that the tumor cells were forced into the bone canaliculi by increased intracranial pressure: "under the influence of intracranial pressure, the tumor cells… become crowded into and through the vascular dural spaces, and finally into the canaliculi of the bone. As a consequence, the bone becomes rough, with subsequent osteoblastic proliferation which causes hyperostosis. There can be little doubt that the thickening occurs in this way, but intracranial pressure may have nothing to do with it, in view of the fact that the flat endotheliomas [meningiomas] which do not increase pressure are, as we have seen, those which most often tend to invade the bone."[73]

One of Cushing's most famous patients with intracranial meningioma was General Leonard Wood (1860—1927), chief of Staff of the U.S. Army and a military surgeon himself. Wood had sustained a head injury from a low-lying chandelier in 1898,[3] and several years later he noticed an exostosis, slowly increasing in size, occurring at the site of the previous trauma at the vertex, right in the midline. In 1909, General Wood referred to Cushing, and after a generally failed conservative treatment, Cushing performed 2-stage surgery on him in 1910, at an interval of 4 days apart, and successfully removed the intracranial parasagittal meningioma. A few years later, in 1927, General Wood came again under Cushing's care because of his significantly worsened condition. Although Cushing was able to complete the extirpation of the tumor without any major complications, Wood died only a few hours after the operation as a result of unexpected hemorrhage that broke through into the ventricular system. Saddened, Cushing would confess: "I've never lost a patient after operation that so upset me. It was so near to success. He was a great man."[74]

Mechanism of Hyperostosis

Later after Cushing, Penfield and Phemister showed the frequent bone involvement by meningiomas,[75,76] Phemister asserting that "the new bone is not tumorous in nature, and is merely the ossified stroma of the invading endothelioma".[37,76] At around the same time, in 1927, Grant was the first to successfully remove the frontal hyperostosis of a bilateral parasagittal plaque tumor along with the sinus and the falx.[77-79] At the beginning of the twentieth century, some investigators such as Trossat, Martin, Dechauma, Weiser, Taylor, Kolodny, and Winkelman began to join their predecessors in an attempt to explain the mechanism of hyperostosis in intracranial meningiomas.[37] Thus, the phenomenon of hyperostosis associated with intracranial meningiomas started to be more thoroughly studied and although some investigators suggested that hyperostosis may be a manifestation of tumor invasion,[73,80-87] others concluded that these bony changes represent nothing else but reactionary changes.[88-92] Although some investigators have recently argued that the existence of a neuropeptide

serotonin influences bone metabolism[93-97] or somatostatin receptor 2A expression,[98] the research that has been carried out so far has failed to identify the precise mechanism of hyperostosis and intralesional morphologic changes of the bone associated with meningioma.[98] Thus, the exact molecular and biochemical mechanism of hyperostosis in meningioma remains to be explored.

CONCLUSIONS

Intracranial meningiomas have affected humankind since prehistoric times. Because of the ability of some intracranial meningiomas to develop hyperostosis, which sometimes leads to skull thickening and cranial deformities, they have attracted attention, inspiring humans over centuries to explain their occurrence. Although the molecular mechanisms of hyperostosis related to meningiomas are still unknown, the contribution made by neurosurgeons and pathologists over the centuries have been unarguably of major importance.

REFERENCES

1. Zülch KJ. *Brain Tumors. Their Biology and Pathology*. New York, NY: Springer Science + Business Media; 1957.
2. Brothwell M, Brothwell D. Evidence for ancient meningiomas and a probable case from Medieval Tarbat, Scotland. *Int J Paleopathol*. 2016;13:65-69.
3. Okonkwo DO, Laws ER Jr. Meningiomas: historical perspective. In: Lee JH, ed. *Meningiomas*. London: Springer; 2009.
4. Anderson T. An example of meningiomatous hyperostosis from medieval Rochester. *Med Hist*. 1992;36:207-213.
5. Czarnetzki A, Schwaderer E, Pusch CM. Fossil record of meningioma. *Lancet*. 2003;362:408.
6. Weber J, Spring A, Czarnetzki A. Parasagittales Meningeom bei einem 32.500 Jahrealten Schädel aus dem Südwesten von Deutschland: Neue Erkenntnisseüber den Umgangmit Krankheit in der Altsteinzeit. *Deut Med Wochenschr*. 2002;127:2757-2760.
7. Priola SM, Raffa G, Abbritti RV, et al. The pioneering contribution of Italian surgeons to skull base surgery. *World Neurosurg*. 2014;82:523-528.
8. MacCurdy G. Human skeletal remains from highlands of Peru. *Am J Phys Anthropol*. 1923;6:217-330.
9. Abbott KH, Courville CB. Historical notes on the meningiomas. I. A study of the hyperostosis in prehistoric skulls. *Bull Los Angeles Neurol Soc*. 1939;4:101-113.
10. Rogers L. Meningiomas in Pharaoh's people; hyperostosis in ancient Egyptian skulls. *Br J Surg*. 1949;36:423-424.
11. Brothwell D. The evidence for neoplasm. In: Brothwell D, Sandison AT, eds. *Disease in Antiquity*. Springfield, Illinois: Charles C. Thomas; 1967.
12. Jónsdóttir B, Ortner DJ, Frohlich B. Probable destructive meningioma in an archaeological adult male skull from Alaska. *Am J Phys Anthropol*. 2003;122:232-239.
13. Brothwell D. Paleodemography and earlier British populations. *World Archaeol*. 1972;4:75-87.
14. Campillo D. The possibility of diagnosing meningiomas in palaeopathology. *Int J Osteoarchaeol*. 1991;1:225-230.
15. Wolpoff M. *Paleoanthropology*. Boston, MA: McGraw-Hill; 1999.
16. Ziegler R. Urmenschenfunde in Baden-Württemberg. *Stuttg Beitrg Naturk*. 1999;C44:24-39.
17. Pahl WM, Asaad E, Khattar NY, El-Meligy M. Macroscopic and radiological aspects of tumors of the skull in ancient Egyptians—(Part I). *Hum Evol*. 1987;2:329-363.
18. García-Albea E. Neurology in the medical papyruses of the pharaohs. *Rev Neurol*. 1999;28:430-433.
19. Loriaux DL. Diabetes and the Ebers Papyrus (1552 B.C.E). *The Endocrinologist*. 2006;16:55-56.
20. Hussein K. Quelques specimens de pathologie osseuse chez les anciens Egyptiens. *Bull de l'Inst d'Egypte*. 1951;32:11-17.
21. Hussein K. A description of some bones examined. In: Saad ZY, ed. *Royal Excavations at Saqqara and Helwan, 1941-1945. Suppl. aux Annales du Service des Antiquites d'Egypte*. 3. 1947:257-258.
22. Deeley TJ. A brief history of cancer. *Clin Radiol*. 1983;34:597-608.
23. Herodotus. *Herodotus, Books I—II, with an English translation by A.D. Godley*. Cambridge, MA: Harvard University Press; 1920.
24. York GK, Steinberg DA. Neurology in Ancient Egypt. In: Finger S, Boller F, Tyler KL, eds. *Handbook of Clinical Neurology, Vol. 95. History of Neurology*. Edinburgh, NY: Elsevier; 2010.
25. David AR, Zimmerman MR. Cancer: an old disease, a new disease or something in between? *Nat Rev Cancer*. 2010;10:728-733.
26. David R. The art of healing in ancient Egypt: a scientific reappraisal. *Lancet*. 2008;327:1802-1803.
27. Bir SC, Maiti TK, Bollam P, Nanda A. Felix Platter and a historical perspective of the meningioma. *Clin Neurol Neurosurg*. 2015;134:75-78.
28. Patra DP, Savardekar AR, Dossani RH, Narayan V, Mohammed N, Nanda A. Meningioma: the tumor that taught us neurosurgery. *World Neurosurg*. 2018;118:342-347.
29. Netsky MG, Laprese J. The first account of a meningioma. *Bull Hist Med*. 1956;30:465-468.
30. Plater F. *Observationum in Hominis Affectibus Plerisque Corpori et Amino, Funtionum Laesione, Dolore Aliavemolestia et Vitio Incommendantibus, Libri Tres, Basileae*. Impensis Ludivici Konig; 1614.
31. Salzmann J. Tumor capitis a carne fungosa productus & cum carie crania notabili conjunctus. *Acta Physico-Medica Academiae Caesareae Leopoldino-Carolinae Naturae Curiosum*. 1730;2:225-228 [in Latin].
32. Verhoeven V, Vrints I, De Keyser J, Menovsky T, Thiessen F, Tondu T. A contemporary and a historical patient with an ectopic meningioma [e-pub ahead of print]. *Acta Chir Belg* https://doi.org/10.1080/00015458.2018.1438561. Accessed February 18, 2019.
33. Meningiomas Cushing HEisenhardt L. *Their Classification, Regional Behavior, Life History, and Surgical End Results*. Springfield, IL: Charles C. Thomas; 1938.
34. Kompanje EJ. A patient with a large intra- and extracranial tumor, most probably a primary extradural meningioma, described in 1730. *J Neurooncol*. 2004;67:123-125.
35. Salzmann J. Exostosisseu Ex crescentia Cranii osseospongiosa. *Acta Physico-Medica Academiae Caesareae Leopoldino-Carolinae Naturae Curiosum*. 1730;2:222-225 [in Latin].
36. Salzmann J. Obstipum caput cum ossisoccipitis & superiorum colli vertebrarum carie conjuctum. *Acta Physico-Medica Academiae Caesareae Leopoldino-Carolinae Naturae Curiosum*. 1730;2:219-222 [in Latin].
37. Alpers BJ, Harrow R. Cranial hyperostosis associated with overlying fibroblastoma. *Arch Neurol Psychiatr*. 1932;28:339-356.
38. Al-Rodhan NR, Laws ER Jr. Meningioma: a historical study of the tumor and its surgical management. *Neurosurgery*. 1990;26:832-846 [discussion 846-847].
39. Kaufman J. *Dissertatio de tumore capitis fungoso post cariem crania ex orto*. Helmstad. 1743.
40. Hirsch A. Crell, Johann Friedrich. In: Allgemeine Deutsche Biographie 4 (1876), S. 587, 1876. Available at: https://www.deutsche-biographie.de/sfz27621.html?language=en. Accessed February 18, 2019.
41. Louis A. Mémoire sur les tumeurs fongueuses de la dure-mère. *Mem Acad Roy Chir Paris*. 1774;5:1-59.
42. Reichert FL. The lure of medical history: Marcus Aurelius Severinus (1580-1656): a contemporary of Harvey, and author of the first work on comparative anatomy. *Cal West Med*. 1929;30:183-185.

43. Marcus Aurelius Severinus. Chirurgia quae ad ossa pertinet, cap III, libera I, pars II. In: *De medicina efficaci. Libri III. Sumptibus Joannis Beyeri, Francofurti*. 1646.

44. Garrison FH. *An Introduction to the History of Medicine: with Medical Chronology, Bibliographic Data*. 4th ed. Philadelphia, PA: WB Saunders; 1929.

45. Barthélemy EJ, Sarkiss CA, Lee J, Shrivastava RK. The historical origin of the term "meningioma" and the rise of nationalistic neurosurgery. *J Neurosurg*. 2016;125:1283-1290.

46. Finger S. *Origins of Neuroscience. The History of Explorations into Brain Function*. New York, NY: Oxford University Press; 1994.

47. Berhouma M, Dubourg J, Messerer M. Cruveilhier's legacy to skull base surgery: premise of an evidence-based neuropathology in the 19th century. *Clin Neurol Neurosurg*. 2013;115:702-707.

48. De Saint-Maur PP. The birth of the clinicopathological method in France: the rise of morbid anatomy in France during the first half of the nineteenth century. *Virchows Archiv*. 2012;460: 109-117.

49. Cruveilhier J. *L'Anatomie pathologique du Corps humain*. Paris: J.B. Baillière; 1829.

50. *Académie royale de chirurgie. Mémoires de l'Académie royale de chirurgie. Ménard et Desenne, fils*. 1819.

51. Mastronardi L, Ferrante L. Neurosurgery in Italy: the past, the present, the future. *Neurosurg Rev*. 2009;32:381-386.

52. Smith CMU. Understanding the nervous system in the 18th century. In: Finger S, Boller F, Tyler KL, eds. *Handbook of Clinical Neurology. History of Neurology. Vol. 95*. Amsterdam: Elsevier; 2010.

53. Turliuc MD, Turliuc S, Cucu AI, et al. Through clinical observation: the history of priapism after spinal cord injuries. *World Neurosurg*. 2018;109: 365-371.

54. Paterniti S. Meningiomas surgery in Italy in the nineteenth century: historical review. *Austin Neurosurg Open Access*. 2015;2:1030.

55. Pecchioli Z. Storia di un fungo della duramadre operato coll'estirpazione dal Professore Zanobi Pecchioli. *Nuovo Giornale dei Letterati-Scienze, Pisa*. 1838;36:39-44.

56. Guidetti B, Giuffrè R, Valente V. Italian contribution to the origin of neurosurgery. *Surg Neurol*. 1983;20:335-346.

57. Giuffrè R. Successful radical removal of an intracranial meningioma in 1835 by Professor Pecchioli of Siena. *J Neurosurg*. 1984;60:47-51.

58. Laws ER, Dunn IF. The evolution of surgery—the soul of neurosurgery. In: Cappabianca P, Domenico S, eds. *Meningiomas of the Skull Base*. Stuttgart: Thieme; 2019.

59. Gallassi A. The Italian Tito Vanzetti, surgeon at Kharkov. *Scalpel (Brux)*. 1953;106:1015-1020.

60. Vanzetti T. *Quelques observations pratiques recueillies à la Clinique Chirurgicale de l'Université Impériale de Kharcoff (Russie)*. Paris: Moquet; 1844.

61. Moodie RL. Studies in paleopathology XVIII. Tumors of the head among pre-Columbian Peruvians. *Ann Med Hist*. 1926;8:394-412.

62. Virchow R. *Die krankhaften Geschwülste*. Berlin: A. Hirschwald; 1864.

63. Macewen W. Intra-cranial lesions: illustrating some points in connexion with the localization of cerebral affections and the advantages of antiseptic trephining. *Lancet*. 1881;2:581-583.

64. Kerr PB, Caputy AJ, Horwitz NH. A history of cerebral localization. *Neurosurg Focus*. 2005;18:E1.

65. Macewen W. Intra-cranial lesions. In: Wilkins RH, ed. *Neurosurgical Classics*. New York, NY: Johnson Reprint Corp.; 1965.

66. Finger S, Stone JL. Landmarks of surgical neurology and the interplay of disciplines. In: Finger S, Boller F, Tyler KL, eds. *Handbook of Clinical Neurology. Vol. 95. History of Neurology*. Elsevier; Edinburgh, NY; 2010.

67. Novaro GF. Sulla chirurgia cerebrale. *Bull Sci Med (Bologna)*. 1891;2:63-88.

68. Spiller WG. A case of Jacksonian epilepsy with hemianopsia and monohypertonia, and a case of hemihypertonia post-epileptica. *Trans Coll Phys Phila*. 1899;21:191.

69. Spiller WG. Hemicraniosis and cure of brain tumor by operation. *JAMA*. 1907;49:2059.

70. E. Brissaud and P. Léreboullet. Deux cas d'hémicraniose. *Rev Neurol*. 1903;11:537 [in French].

71. Parhon C, Nadjede G. Sur un nouveau cas d'hémicraniose. *Rev Neurol*. 1905;13:1017 [in French].

72. Mills CK, Pfahler GE. Tumour of the brain localised clinically and by the roentgen rays. *Philadelphia Medical Journal*. 1902;9:268-273.

73. Cushing H. The cranial hyperostoses produced by meningeal endotheliomas. *Arch Neurol Psychiat*. 1922;8:139.

74. Ljunggren B. The case of General Wood. *J Neurosurg*. 1982;56:471-474.

75. Penfield WG. Cranial and intracranial endotheliomata-hemicraniosis. *Surg Gynecol Obstet*. 1923;36: 657-674.

76. Phemister DB. The nature of cranial hyperostosis overlying endothelioma of the meninges. *Arch Surg*. 1923;6:554-572.

77. Black PM. Harvey Cushing at the Peter Bent Brigham Hospital. *Neurosurgery*. 1999;45:990-1001.

78. Laws ER Jr. Neurosurgery's man of the century: Harvey Cushing—the man and his legacy. *Neurosurgery*. 1999;45:977-982.

79. Sampath P, Long DM, Brem H. The Hunterian Neurosurgical Laboratory: the first 100 years of neurosurgical research. *Neurosurgery*. 2000;46: 184-195.

80. Bonnal J, Thibaut A, Brotchi J, Born J. Invading meningiomas of the sphenoid ridge. *J Neurosurg*. 1980;53:587-599.

81. Castellano F, Guidetti B, Olivecrona H. Pterional meningiomas "en plaque. *J Neurosurg*. 1952;9: 188-196.

82. Derome PJ, Guiot G. Bone problems in meningiomas invading the base of the skull. *Clin Neurosurg*. 1978;25:435-451.

83. Echlin F. Cranial osteomas and hyperostosis produced by meningeal fibroblastomas. *Arch Surg*. 1934;28:357-405.

84. Kim KS, Rogers LF, Lee C. The dural lucent sign: characteristic sign of hyperostosing meningioma en plaque. *AJR Am J Roentgenol*. 1983;141:1217-1221.

85. Maroon JC, Kennerdell JS, Vidovich DV, Abla A, Sternau L. Recurrent spheno-orbital meningioma. *J Neurosurg*. 1994;80:202-208.

86. Pieper DR, Al- Mefty O, Hanade Y, Buencher D. Hyperostosis associated with meningioma of the cranial base: secondary changes or tumor invasion. *Neurosurgery*. 1999;44:742-747.

87. Pompili A, Derome PJ, Visot A, Guiot G. Hyperostosing meningiomas of the sphenoid ridge—clinical features, surgical therapy, and long-term observations: review of 49 cases. *Surg Neurol*. 1982; 17:411-416.

88. Freeman H, Forster FM. Bone formation and destruction in hyperostoses associated with meningiomas. *J Neuropathol Exp Neurol*. 1948;7:69-80.

89. Heick A, Mosdal C, Jorgensen K, Klinken L. Localized cranial hyperostosis of meningiomas: a result of neoplastic enzymatic activity? *Acta Neurol Scand*. 1993;87:243-247.

90. Kennedy F. Tumours of the intracranial cavity. In: Nelson T, ed. *Nelson's Loose Leaf Living Medicine*. London: Thomas Nelson and Sons; 1920.

91. Landow H, Kabat EA, Newman W. Distribution of alkaline phosphatase in normal and neoplastic tissues of the nervous system. *Arch Neurol Psychiatry*. 1942;48:518-530.

92. Nasu H. Ferment Histochemischeuntersuchungen an Meningeomen. *Acta Neuropathol (Berl)*. 1964;3: 627-637 [in German].

93. Frost M, Andersen TE, Yadav V, Brixen K, Karsenty G, Kassem M. Patients with high bone-mass phenotype owing to Lrp5-T253I mutation have low plasma levels of serotonin. *J Bone Miner Res*. 2010;25:673-675.

94. Oury F, Karsenty G. Serotonin, two faces of a unique molecule in the regulation of bone mass. *Med Sci (Paris)*. 2010;26:713-718.

95. Oury F, Yadav VK, Wang Y, et al. CREB mediates brain serotonin regulation of bone mass through its expression in ventromedial hypothalamic neurons. *Genes Dev*. 2010;24:2330-2342.

96. Yadav VK, Balaji S, Suresh PS, et al. Pharmacological inhibition of gut derived serotonin synthesis is a potential bone anabolic treatment for osteoporosis. *Nat Med*. 2010;16:308-312.

97. Yadav VK, Ducy P. Lrp5 and bone formation: a serotonin dependent pathway. *Ann NY Acad Sci*. 2010;1192:103-109.

98. Matschke J, Addo J, Bernreuther C, Zustin J. Osseous changes in meningioma en plaque. *Anticancer Res*. 2011;31:591-596.

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