Sir Victor Horsley: pioneer craniopharyngioma surgeon

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Sir Victor Horsley (1857–1916) is considered to be the pioneer of pituitary surgery. He is known to have performed the first surgical operation on the pituitary gland in 1889, and in 1906 he stated that he had operated on 10 patients with pituitary tumors. He did not publish the details of these procedures nor did he provide evidence of the pathology of the pituitary lesions operated on. Four of the patients underwent surgery at the National Hospital for Neurology and Neurosurgery (Queen Square, London), and the records of those cases were recently retrieved and analyzed by members of the hospital staff. The remaining cases corresponded to private operations whose records were presumably kept in Horsley’s personal notebooks, most of which have been lost.

In this paper, the authors have investigated the only scientific monograph providing a complete account of the pituitary surgeries that Horsley performed in his private practice, La Patologia Chirurgica dell’Ipofisi (Surgical Pathology of the Hypophysis), written in 1911 by Giovanni Verga, Italian assistant professor of anatomy at the University of Pavia. They have traced the life and work of this little-known physician who contributed to the preservation of Horsley’s legacy in pituitary surgery. Within Verga’s pituitary treatise, a full transcription of Horsley’s notes is provided for 10 pituitary cases, including the patients’ clinical symptoms, surgical techniques employed, intraoperative findings, and the outcome of surgery. The descriptions of the topographical and macroscopic features of two of the lesions correspond unmistakably to the features of craniopharyngiomas, one of the squamous-papillary type and one of the adamantinomatous type. The former lesion was found on necropsy after the patient’s sudden death following a temporal osteoplastic craniectomy. Surgical removal of the lesion in the latter case, with the assumed nature of an adamantinomatous craniopharyngioma, was successful. According to the evidence provided in Giovanni Verga’s monograph, it can be claimed that Sir Victor Horsley was not only the pioneer of pituitary gland surgery but also the pioneer of craniopharyngioma surgery.


KEY WORDS craniopharyngioma; Victor Horsley; Giovanni Verga; temporal craniotomy; history of pituitary surgery; history of pituitary tumors

The decision to do such a difficult operation as pituitary surgery bears the mark of a daredevil venture.

— Herman Schloffer (1868–1937), Austrian surgeon, pioneer of the transsphenoidal approach to the pituitary gland (Beitr Klin Chir 50:767–817, 1906)

Sir Victor Horsley (1857–1916) is considered to be the pioneer of pituitary surgery20,28,52,57 (Fig. 1). In his lecture “On the Technique of Operations on the Central Nervous System,” delivered to the British and Canadian Medical associations in Toronto on August 22, 1906, he claimed to have performed the first pituitary gland operation in 1889, at a time when the functions of the pituitary body had not yet been elucidated.30,31 In the published version of this lecture, Horsley mentioned his surgical experience with pituitary tumors up to that time, encompassing a total of 10 cases.24 However, he did not report the operative details of such procedures, nor did he show evidence of the pathological nature of the pituitary lesions operated upon. Although a few of Horsley’s trainees and colleagues knew about his intention to publish his series of pituitary tumors, the time he spent on his political career and his premature death due to heatstroke during the military campaign in Mesopotamia prevented him from giving a full account of these cases.40 The only mention of verified pituitary tumor operations performed by Horsley at the National Hospital in London was included in the review of the first 500 brain tumors operated on at that institution in the 1900s, published by Tooth in 1912.58 Tooth’s appraisal provides information about neither the results of these procedures nor the microscopic appearances of the tumors.

In 2003, the staff of the Department of Neurosurgery...
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at the National Hospital for Neurology and Neurosurgery (Queen Square, London) analyzed the case books of the neurosurgical operations performed by Horsley at this institution. The records of 4 pituitary tumors operated upon by Horsley between 1904 and 1907 were found. According to the clinical and surgical notes transcribed from Queen Square files, at least 3 of the lesions seemed to correspond to pituitary macroadenomas covered by dura mater of the sellar diaphragm, which had to be scraped out from the sella in small pieces using a sharp spoon. Irrefutably, Horsley can be credited as the pioneer of pituitary adenoma surgery, being the first to successfully remove such a tumor using a transcranial approach.

In addition to his surgical activity at the National Hospital for the Paralyzed and Epileptic, Horsley had a busy private practice. Therefore, some of the 10 pituitary procedures that he reported having performed by 1906 must correspond to private operations. Horsley kept a record of private surgeries in personal pocket notebooks, most of which have, unfortunately, been lost. Yet, there is a man who had access to Horsley’s private notebooks and left a written record of their contents. His name is Giovanni Verga, an Italian surgeon from the University of Pavia, who published in 1911 the first treatise on pituitary surgery: *La Patologia Chirurgica dell’Ipofisi* (Surgical Pathology of the Hypophysis). This monograph, Verga reliably reproduces Horsley’s notes about his series of pituitary surgeries, providing a complete account of both the cases in which surgery was performed at Queen Square and his private cases. Horsley granted permission to Verga to study and publish all his records of pituitary operations. Thanks to Giovanni Verga’s treatise, this invaluable information has not been lost.

In this study we examined the evidence concerning Horsley’s pituitary operations on private patients available in Giovanni Verga’s monograph, *La Patologia Chirurgica dell’Ipofisi* (Surgical Pathology of the Hypophysis). This treatise was retrieved from the National Library of Medicine (National Institutes of Health, Bethesda, Maryland), as were several monographs about pituitary surgery and Horsley’s original articles of interest referenced in the complete list of Horsley’s published articles by Vilenisky et al. Biographical and scientific information about Giovanni Verga was obtained by Paolo Mazzarello from the records of the Historical Archive and the Historical Museum of the Pavia University and from the Archive of the Practitioners of the Province of Pavia.

We present here a detailed description of 2 pituitary tumors that were operated on by Sir Victor Horsley in the 1900s and had distinctive features of craniopharyngiomas (CPs), according to the transcriptions of Horsley’s private notes provided in Verga’s book. These lesions may well be the first documented operations of CPs in the history of neurosurgery. With the information available in Verga’s treatise, part of which is confirmed by additional scientific sources, there is a sufficient amount of evidence to claim that Sir Victor Horsley was not only the pioneer surgeon of pituitary tumors but also the pioneer surgeon of CPs.

**Giovanni Verga and His Report on Horsley’s Pituitary Surgeries**

Giovanni Verga (Fig. 2) was born on July 21, 1879, in Abbiategrasso, a small town about 35 kilometers from Pavia. Abbiategrasso was also the town where Camillo Golgi invented his “black reaction,” the histological staining method that revolutionized research on brain structure. Raised in poverty, Verga enrolled in the University of Pavia School of Medicine, one of the oldest medical schools in Europe, having been established by Holy Roman Emperor Charles IV in 1361. Verga was fortunate to have Camillo Golgi (1843–1926, Nobel Prize winner in 1906 for his invention of the “black reaction”) among his professors. It was Golgi who inspired Verga to pursue an academic and research career in medicine.

Verga was a brilliant student. During the period 1899–1901, he joined as an intern (“allievo interno”) in the laboratory of general pathology and histology headed by Camillo Golgi. Golgi wrote of him that he had “the best attitude for the laboratory research” and that he was “animated by the sacred fire for scientific studies.” Giovanni Verga graduated in medicine on July 7, 1904 (Fig. 3, left), with perfect scores, after having defended a dissertation...
entitled “On traumatic neurosis,” (“Sulle Neurosi Traumatiche,” Tesi di Laurea), prepared under the guidance of Carlo Forlanini. Afterward, Verga joined Golgi’s Institute of General Pathology as a postdoctoral researcher, where he performed studies on experimental surgery of peripheral nerves. Later Verga was nominated assistant at the Institute of Surgical Pathology (1905–1906), where he performed research focused on several topics of general surgery. He later became assistant at the Institute of Human Anatomy (1909–1915) and, finally, assistant professor of human anatomy (1915–1918).

In January 1911, Verga published his monograph, La Patologia Chirurgica dell’Ipofisi (Surgical Pathology of the Hypophysis), a thorough compilation of the existing knowledge of pituitary gland pathology, in which he presented the latest surgical progress on the removal of pituitary tumors, a newly born field of surgery less than a decade old (Fig. 3, right). On April 10, 1911, he successfully defended his dissertation on the surgical pathology of the hypophysis, followed a day after by a lesson on “purulent peritonitis,” to obtain his professional title of “libero docente” or Privatdozent in special demonstrative surgical pathology.

Aside from his academic position as assistant professor of anatomy, Giovanni Verga also worked at the Military Hospital Collegio Borromeo, another institution headed by Camillo Golgi, which was established during the First World War for the treatment of war-related pathologies. In this hospital he performed significant studies on the regeneration of peripheral nerves in humans after surgery (neurorrhaphy). After an abrupt ending of his academic career, due to the fierce competition for university positions among the surgeons of Pavia, Verga left this city and was appointed director of a local sanatorium at Taggia. He died there on May 21, 1923.

We do not know the reasons why Verga became interested in the study of pituitary gland pathology or when he decided to write a monograph analyzing the surgical experiences of individual operations on pituitary tumors recorded in the 1st decade of the 20th century. Certainly, the subject represented a very novel, exciting field to investigate at that time, when transsphenoidal approaches to the pituitary had proved to be a successful route of access to one of the most mysterious and intricately hidden of the ductless glands. Nevertheless, Verga’s main focus was on Horsley’s series of pituitary operations, all performed through a transcranial approach. He even reported that Horsley’s surgical work on the pituitary was his major source of inspiration.

We have been unable to confirm exactly when the meeting between Horsley and Verga took place, nor the way Verga obtained Horsley’s records of pituitary lesion operations. Undeniably, Verga must have had a close personal relationship with Horsley, as evidenced by the last paragraph of the introduction of his monograph. (This paragraph and the other passages from Verga’s monograph that are presented in this paper were all translated from the original Italian by two of the authors [J.M.P. and P.M.]).

With regard to the treatment and symptoms (of pituitary tumors), I largely benefited from clinical cases of pituitary tumors operated on by Sir Victor Horsley in London, some at the National Hospital, some in his private practice, which he has granted me his kind permission to study and publish. This clinical material, formed of no less than twelve unpublished pituitary cases, represents a very interesting and well-documented contribution whose publication, in addition to filling a gap in the field of pituitary surgery, responds to a strongly felt and repeatedly expressed desire by those authors concerning themselves with this topic. To my beloved Prof. Horsley, who, besides providing me such a rich and precious study material, lavished his most courteous hospitality on me, I would like to express publicly my warmest gratitude.

From these words, it can be deduced that Verga traveled to London and met Horsley, at least for a short period, to investigate the records of Horsley’s operations. Whatever the reasons for his interest in pituitary tumors, Giovanni Verga was the only author to whom Horsley gave permission to publish his annotations of private pituitary cases, a fortunate occurrence that has allowed us to identify two of the pioneering surgical operations for the removal of CPs. One of them probably represents the first successful CP surgery ever performed.

Horsley’s Operations on Pituitary Tumors With Distinctive Features of CPs

The topographical extension and anatomical relationships of pituitary tumors operated on by Horsley are described in Verga’s book in all 10 cases. In addition, suc-
cinct information about some gross pathological features of the tumors, such as their appearance, size, shape, consistency, and adherence is also provided. A macroscopic pattern typical of macroadenoma (a large, solid mass with soft consistency, which occupied the whole sella and was enclosed by a relatively intact sellar diaphragm), was observed in 7 of the 10 pituitary lesions. In 2 of these cases, histological confirmation of the adenomatous structure was obtained during autopsy.

The remaining 3 pituitary tumors corresponded to cystic lesions centered either at the sella (Case 3 [III in the original]) or at the infundibulum (Cases 9 [IX] and 10 [X]), the latter showing upward extensions into the third ventricle. One of these infundibular tumors could be analyzed at autopsy after the patient’s sudden death. It was a soft, fluctuant round cystic mass filled with clear fluid. At the base of the cyst, a cauliflower-like epithelial papillary structure protruded into the cyst lumen. This pathological description unmistakably corresponds to the squamous-papillary variant of craniopharyngioma, which was previously reported by some authors, such as Langer, Mott, and Erdheim.15,32,37 Two similar cases would also be found during autopsy and reported in Harvey Cushing’s monograph The Pituitary Body and Its Disorders.34 The last cystic lesion operated on by Horsley was in a young boy; this lesion was formed by a hard, calcified wall and filled with a brownish, chocolate-like fluid, both features typical of an adamantinomatous CP. Moreover, Verga’s book includes a table summarizing the pituitary surgeries reported worldwide up to 1910, in which one of Horsley’s pituitary cases is validated as a “cystic tumor of the hypophysial duct,” the original term used by Erdheim to define CPs.15

Verga’s complete transcription of the clinical and operative notes on the 2 suprasellar cysts with distinctive features of craniopharyngiomas operated on by Horsley is provided below (translated from La Patologia Chirurgica dell’Ipofisi\(^\text{15}\) by J.M.P and P.M.).

[Case] IX
Renny Taillyour, a 51-year-old single woman from London, was referred by Dr. Ferrier to Horsley for the first time on June 8, 1904.

Anamnesis:
The patient had suffered from generalized epileptic seizures and occasional episodes of sleep walking with hallucinations and somnolence. She had once remained in a prolonged hyperthermic and stuporous state for two months. During the previous year she had noticed a progressive impairment of her visual acuity, along with a marked weight gain and pronounced thirst, without glucosuria or albuminuria. She had been examined by Sir William Gowers and Dr. Morton, both of whom had diagnosed the presence of bitemporal hemianopia one year earlier.

Current Status:
She is an obese woman showing an expression of apathy and painful affliction at the same time. She answers direct questions normally, but her spontaneous speech is often confusing and replete with incoherent statements. Sometimes while chatting she suddenly falls asleep and begins to snore. Her left eye is completely blind and her right eye shows a temporal hemianopia.

Surgical Intervention:
The first stage of the operation was the only one performed, on July 21, 1904. It consisted in an osteoplastic temporal craniectomy. Two days later the patient had two generalized epileptic
seizures, dying suddenly during the second one. Until then she had done well, with a normal pulse and body temperature.

Autopsy:
A voluminous cystic tumor was found occupying the area of the infundibulum between the unaffected pituitary gland and the floor of the third ventricle. This large tumor was extending backward, reaching the anterior border of the pons. It had pushed the third ventricle floor upwards and both optic tracts to each side. It had also pushed the pituitary gland downward, against the floor of the sella turcica. The tumor contained a translucent, yellowish fluid. At the inner walls of the cyst some epithelial papillomatous-like vegetations protruding into the cyst lumen were noted.

[Case] X
Wells, a 14-year-old boy from Chicago (private practice). This patient was attended first by Dr. Webster and Dr. Archibald Church in Chicago, the latter publishing part of the case. Horsley attended the patient for the first time on June 12, 1907, when his parents, following the recommendation by Dr. Church to consult the British professor, brought him to London.

Anamnesis:
The boy was healthy until the age of three when he suffered from attacks of whooping cough, some of them involving acute nose bleeding. At the same time, the presence of sugar in his urine was detected. After the whooping cough fits ended, the boy started complaining of recurrent episodes of intense headache, during which he fell into a stuporous state. After these fits, when the boy came around and stood up, his relatives noticed he could not walk properly. Recurrent episodes of headache accompanied with vomiting occurred, most of them ending with profuse nasal hemorrhaging. During one of these fits, at the age of 12, his right side became paralyzed, a hemiparetic state lasting for several days, longer for his right arm. At this time an ophthalmoscopic examination of the boy was done which demonstrated bilateral optic atrophy with traces of preexisting retinal hemorrhages. The boy presented again several fits of transitory hemiparesis and facial central paresis, the former causing him a disturbing ischialgia which led to a secondary spinal scoliosis. The boy always showed an intact mental condition. He presented a notable delay in his sexual development.

Present Examination:
At the time the patient was assessed by Professor Horsley, on June 12, 1907, he showed a curious syndrome, seemingly the result of a complex combination of symptoms: 1. symptoms derived from a hypophyseal tumor; 2. symptoms caused by hydrocephalic distension of the cerebral ventricles; 3. symptoms caused by compression on the cerebellar peduncles.

The most significant symptoms caused by the hypophyseal tumor were: i) Severe visual disturbances observed in the ophthalmoscopic and campimetric exams; he could only perceive light with his left eye, whereas his right eye showed a complete temporal hemianopsia. The funduscope exam evidenced atrophy of both papillae with traces of previous neuritis and neuroretinitis, ii) Absence of sexual development with genitalia of infantile appearance and lack of pubic or axillary hair. iii) Gross alterations of the sella turcica and adjacent regions easily identifiable in the excellent skull x-ray taken by Dr. Worral, which demonstrated significant enlargement and excava- tion of the sella to a volume double those observed in normal individuals, caused by a large oval tumor. The radiograph also very clearly showed opaque suprasellar shadows delimiting the tumor boundaries, which were noticed by Professor Horsley. [Fig. 4] He quickly interpreted these shadows as being caused by calcium spiculae and concretions, as he had seen before while operating on another patient in whom he found a cystic pituitary tumor with a calcified wall (Case IX). With regards to the symptoms related to hydrocephalus, they were revealed by the fits of right hemiparesis, which demonstrated the existence of increased pressure on the left cerebral hemisphere. In addition, the mental status of the patient showed the precocious intelligence characteristic of some hydrocephalic children, but his behavior also showed a certain degree of psychic infantilism. Finally, the compression of the cerebellar peduncles could be diagnosed due to the patient’s mild global ataxia, more evident in the lower limbs when he walked around.

Surgical Procedure:
Performed by Professor Horsley. Chloroform used as anes-thetic.

First stage:
June 23, 1907. A definitive right temporal-parietal craniectomy was performed. Cranium bones are extremely thin. The tense dura mater of a dark bluish color protrudes through the bone opening.

Second stage:
June 27, 1907. At the opening of the dura mater, a notable amount of cerebrospinal fluid is released, allowing the hugely swollen temporal lobe to soften and facilitating the surgeon’s ability to maneuver the lifting of the temporal lobe to access the pituitary gland. Immediately after lifting the temporal sphenoidal lobe, a large cystic tumor is found, with the same appearance as that presumed at diagnosis. It was incised with a scalpel, giving rise to the release of its brownish fluid content. Once the cyst had been drained, the flaps of the dura mater were repositioned and the scalp sutured.

Postoperative Course:
Immediately after the operation, probably in relation to the rapid release of cerebrospinal fluid, the patient shows a peculiar psychic condition: he remained inactive for a short time, making purposeless uncoordinated movements with his arms, but such motor behavior ceased soon. The wound was healed by first intention on the tenth postoperative day, and the patient was able to travel by horse-drawn cart.

His postoperative history was unfortunate. After returning to his home in America, the patient’s convalescence was initially satisfactory. However, drainage of CSF into the subcutaneous space under the temporal scalp flap continued, with develop-

FIG. 4. Lateral skull radiograph obtained by Dr. Worral in Horsley’s Case 10. The radiograph shows the excava tion and significant enlargement of the sella turcica to a volume double that observed in normal individuals, due to a large oval tumor (arrows). In addition, opaque suprasellar shad- ows delimiting the tumor boundaries can be seen. From Verga G. La Patologia Chirurgica dell’Ipofisi. Pavia: Tipografia Cooperativa, 1911.
The Report of Horsley's Pituitary Case 10 by Professor Archibald Church

In 1909, Archibald Church, professor of nervous diseases at Northwestern University Medical School in Chicago, published a particularly original article on pituitary tumors that focused specifically on the clinical and radiological diagnosis of these lesions in patients without symptoms of acromegaly. In this paper, Horsley’s Case 10 listed in Verga’s treatise was also included and described in detail. The patient had been referred to Horsley by Professor Church, who, after a careful examination, presumed he might have a pituitary tumor. Fortunately, this fact allows a comparison between Verga’s account of the case, transcribed from the notes taken by Horsley, and Church’s accurate clinical history as the specialist responsible for the patient. The perfect concordance between both descriptions serves to speak to the reliability of the accounts for the rest of Horsley’s pituitary surgery from his private practice, as described in Verga’s book. A similar degree of agreement can be noted when comparing the details of the clinical reports for Horsley’s 4 pituitary surgery cases from Queen Square (Cases 1–4, Table 1) as presented in Verga’s treatise, with the original files reviewed in 2003 by the staff members of Queen Square.

Some additional, interesting particulars of Horsley’s pituitary Case 10 can be found throughout Church’s narrative. Church described the patient as a 14-year-old boy, who had a very small and frail appearance for his age, reporting that he had been suffering from recurrent headaches in paroxysms associated with vomiting since he was 3 and a half years old. For a few years before being examined by Dr. Church, the boy’s sight had also been worsening slowly. He had been attended for the first time in Chicago in April 1907 by Drs. Archibald Church and J. P. Webster, who noted slight ataxia of the legs, blindness in his right eye, and marked decrease of visual acuity in his left eye to 1/6, in addition to temporal hemianopsia. There was evidence of neuritis, with exudates in both retinas, the discs showing white atrophy. The presumed diagnosis made by Church and Webster, based on the findings of ataxia and optic neuritis, was cerebellar disease, probably a tumor. Given the advanced stage of the patient’s visual deficit and the coincident trip to London scheduled by the patient’s parents, it was Church’s advice to refer the boy to Sir Victor Horsley, with the aim of assessing the advisability of a surgical procedure. Horsley attended the patient and wrote a letter to Church in which he pointed out the clinical and radiological signs that led him to make an accurate topographical diagnosis of the lesion. Horsley wrote:

It appeared to me at first examination that the atrophy (optic) was primary, and that the pigmentary conditions of the fundus were congenital and possibly specific; if the last, then in the third generation. The only positive signs besides the right hemiparesis were the temporal hemianopsia and the disc change. At the same time I was struck by the patient’s attitude and before making a lumbar puncture sent him to my colleague, Dr. Worrall, for a radiogram of the skull base and spine. Here we can see Horsley’s talented clinical reasoning at work. His mastery of the funduscopic examination and thorough knowledge of the focal neurological symptoms allowed him to suspect a common origin for the complex array of symptoms and signs displayed by the boy. This led him to ask for the only available diagnostic proof to check for the presence of a lesion at the skull base, a standard radiograph of the skull. The findings on the radiograph, as suspected by Horsley, were striking and impressed him greatly (Fig. 4):

To our astonishment the photo showed very clearly a pituitary tumor at once and that in its periphery were shadows which I recognized must be calcareous plates in the wall of a cyst, as I had met with this before. The disc condition, the fields and the history were now fully explained.

Once the accurate topographical diagnosis of the lesion had been made, justification for the operation was established. Horsley’s description of the procedure was as follows:

After fully consulting with Dr. Webster, I decided to tap the cyst but not to attempt its removal in view of the boy’s condition. On raising the temporal lobe, by the method I have elsewhere described, the cyst was found. I laid the cyst open by a free incision. It contained about an ounce of brown chocolate-like fluid. The cyst was washed out with sublimate and sponged. Explored with a sharp spoon, the calcareous deposit was felt.

A judicious decision led Horsley to empty the cyst contents rather than attempt the removal of the hard, calcified wall of the cystic tumor, which quite probably was tightly attached not only to the skull base, but also to the vital structures of the brain undersurface and the vessels of the circle of Willis. The calcareous consistency of the cyst wall, the chocolate-like resemblance of its fluid content and the suprasellar position of the mass, occupying the interpeduncular area, were all distinctive features of a CP. The lesion was approached and incised just above the sella turcica, with no mention of a solid mass being observed expanding within the sella. Taking into account the patient’s age, his sequential progression of symptoms, his sexual infantilism, the position of the tumor, and, above all, its cystic nature, with calcified walls and brownish-chocolate-like fluid content, this pituitary tumor must have corresponded with the highest degree of certainty to a CP of the adamantinomatous variant.

The hydrocephalic condition of the patient was resolved, at least temporarily, after release of the cyst contents. The patient’s wound healed well, and 10 days after the operation the boy was allowed to go out for a ride. Regarding the long-term outcome of his procedure, Horsley was especially cautious:

As regards his future, of course, hemorrhagic cysts do not tend to fill again. Therefore, the pressure on the tracts ought to be relieved and the boy’s sight saved. At the same time this is the first cyst (non-suppurative) that I have done and it is not possible to dogmatize on such a subject. If at any time there was evidence of re-established pressure it would be (now) quite
possible to pass an aspirator needle with suitable precautions and very little risk into the cyst.10

Horsley’s genial mind anticipated the major risk of cyst refilling and reappearance of hydrocephalus decades ahead of his time, and he proposed a technical solution consisting of recurrent puncturing and drainage of the cyst using a catheter guided through the subtemporal route. He probably thought that with the aid of x-rays, the location and puncturing of any cystic regrowth could be easily managed. Methods of palliative drainage of recurrent cystic CPs and treatment of associated hydrocephalus would be developed and standardized in the 1940s.55

According to Church, the patient’s health fluctuated from the clinical history and from funduscopic examination—due to the development of a pulsating mass of CSF beneath the wound. The refilling of the cyst with bloody fluid and debris probably prevented CSF from being reabsorbed normally. When the pseudomeningocele became tense, the boy would become stuporous, with intense headache and vomiting. After a few days, his condition would improve, and he would resume his ordinary activities. Regrettably, the patient’s family refused any additional treatment, even a simple lumbar puncture to alleviate the intracranial high pressure, and eventually the boy died 18 months after the operation. No postmortem examination was allowed.

Discussion

Treatment of CPs at the Beginning of the 20th Century: Challenges Overcome by Horsley

With the diagnostic and therapeutic resources available in the 1st decade of the 20th century, Sir Horsley’s achievements are remarkable. The number of patients with pituitary tumors at the time was small, and the recognition of pituitary endocrinological syndromes was still lacking. There was also no blood transfusion, no electrocoagulation, no adequate methods of illumination, no surgical microscope, and no bipolar forceps for pituitary tumor surgery. In addition, Horsley lacked antibiotics, corticoids, and hormone replacement therapy to counteract the certain symptoms derived from hypophyseal insufficiency. Hermann Schloffer (1868–1937), the Austrian surgeon pioneer of the transsphenoidal approach to the pituitary gland, thought that “the decision to do such a difficult operation as pituitary surgery bears the mark of a daredevil venture.”33 Yet, Horsley’s boldness and resoluteness led him to undertake the surgical treatment of pituitary tumors, an entirely new field of surgery. His pioneering role as pituitary surgery bears the mark of a daredevil venture.”33 Yet, Horsley’s boldness and resoluteness led him to undertake the surgical treatment of pituitary tumors, an entirely new field of surgery. His pioneering role was of great importance because of the absence of alternative therapies, as medical treatment consisted of useless administration of iodides, in combination with mercury or not.24,24

Evidence of a pituitary tumor in Horsley’s time came from the clinical history and from funduscopic examination, which in the last decade of the 19th century was a well-established method of assessing the presence of papilledema or optic atrophy.25 Horsley was an expert in the assessment of retinal changes caused by intracranial tumors, and his exceptional acumen in interpreting funduscopic changes is evidenced in his assessment of the patient referred from America by Church to his consult (Case 10). He immediately recognized bilateral optic atrophy as the patient’s fundamental alteration, a sign that led him to
suspect the presence of a pituitary tumor when Church and Webster had instead presumed the diagnosis of a cerebellar tumor.\textsuperscript{10}

The introduction of x-ray technology at the beginning of the 20th century proved an invaluable tool for the diagnosis of pituitary tumors and fostered the development of pituitary surgery.\textsuperscript{14, 46} Plain skull radiographs allowed the confirmation of gross changes in the sella turcica typical of pituitary growths, such as enlargement of the sella and erosion of its floor and clinoid processes. In addition, abnormally dark “shadows” at the suprasellar area were identified when calcifications were present within the tumor, as in the case of craniopharyngiomas and teratomas.\textsuperscript{16} Nevertheless, Horsley could not take advantage of this technique except in one pituitary case, precisely the adamantinomatous CP he operated on successfully (Case 10) (Fig. 4). Such a lack of diagnostic methods gives additional credit to the pituitary surgeries performed by Horsley, which can be considered the only series of pituitary tumors operated on before the x-ray era.

By the year 1907, when Archibald Church contacted Horsley, pituitary surgery was a new field that had been explored only to a limited extent. Only some anecdotal cases of surgical removal of pituitary tumors—either through a transcranial route\textsuperscript{29,36} or by using a transnasal transsphenoidal approach\textsuperscript{61}—had been reported. Mortality rates for transcranial surgery around the pituitary region ranged from 50\% to 80\% in those days.\textsuperscript{45} Archibald Church knew from his own series of pituitary cases in which surgery had necessarily ensued. Bailey and Bremer eventually demonstrated that postoperative deaths in many of Cushing’s pituitary removals through a transpalatal route in cats, but a human pituitary tumor using a subfrontal craniectomy, in 1889 Horsley performed the first recorded approach to the gasserian ganglion.\textsuperscript{24, 26} For Church, the transsphenoidal route represented a less disturbing avenue of approach, save for the problem of infection, than through a lateral aspect of the skull, which necessitates violent handling of the brain. Nevertheless, he made his recommendation to the patient’s parents to visit Horsley in London and consider the option of a transcranial approach, evidence of his confidence in Horsley’s experience with this type of surgery.

**Sir Victor Horsley’s Foundations of Pituitary Surgery**

Horsley’s interest in the pituitary gland started on experimental grounds, at the Brown Institution in London, where he removed the pituitary glands of 2 dogs in 1886.\textsuperscript{22} These seem to have been the first recorded experiments ever done on the pituitary body. The important purpose of these experiments was to confirm the apparently vital role played by the pituitary gland, about which no consensus had yet been achieved. Horsley performed experimental pituitary removals through a transpalatal route in cats, but in the case of dogs and monkeys he used the subtemporal approach. In the paper he wrote with Handelsmann in 1911, he recorded a series of 54 experimental hypophysectomies in all (performed in 20 cats, 21 dogs, and 13 monkeys).\textsuperscript{39} Such extensive practice, in addition to his vast experience on the surgical approach of the gasserian ganglion through the subtemporal extradural approach, the same used by Krause for the treatment of trigeminal neuralgia (Figs. 5 and 6),\textsuperscript{29} gave Horsley the necessary confidence to favor the subtemporal approach over other alternatives to remove pituitary tumors.\textsuperscript{26}

Experimental ablative surgeries of the pituitary showed contradictory results. In some of the experiments the animals succumbed soon after the operation, while others survived for a long time.\textsuperscript{2, 14} Harvey Cushing himself had concluded from his experiments of complete pituitary removal that this gland was absolutely necessary to life, as the animals that had been subjected to this surgery died in a state of lethargy with slow respiration and low temperature, a clinical condition he defined as “cachexia hypophyseopriva.”\textsuperscript{13, 14} The mortal effects of his hypophysectomies, however, were claimed by other authors such as Erdheim and Bailey to be due to injury caused to the basal hypothalamus in the operations.\textsuperscript{2, 16} Horsley likewise criticized Cushing’s conclusions and brought evidence of some animals surviving after complete pituitary gland extirpations to the meeting of the Physiological Society in March 1911.\textsuperscript{27} Unlike Cushing, Horsley did not make an adequate follow-up to record the bodily effects of hypopituitarism.\textsuperscript{27} His animals died naturally several days or weeks after the operation with symptoms of “asthenia,” which Horsley misinterpreted as a natural symptom occurring in animals in captivity, when their deaths were actually due to an adrenal or polyglandular failure, a direct consequence of hypophaesal insufficiency. The important point was that Horsley had proved that the pituitary gland could be removed and that rapid death of the hypophysectomized animals did not necessarily ensue. Bailey and Bremer eventually demonstrated that postoperative deaths in many of Cushing’s experimental hypophysectomies were due to damage to the third ventricle floor.\textsuperscript{2}

According to the report of his 1906 lecture in Toronto, in 1889 Horsley performed the first recorded approach to a human pituitary tumor using a subfrontal craniectomy, although not even a tiny piece of the tumor could be removed.\textsuperscript{23} In the following pituitary operation, performed

![THE OPERATING THEATRE, QUEEN SQUARE, 1906.](image-url)
in 1893 on a 33-year-old acromegalic patient by Dr. Frank Paul in Liverpool, Horsley himself recommended a subtemporal decompression, which was successful and alleviated the patient’s severe headache. In February 1906, in Sheffield, Horsley gave the address “On the diagnosis and surgical treatment of diseases of the pituitary gland,” in which he reported having operated on 9 cases, resulting in 2 deaths, one of these cases representing his initial failed attempt of removal through a subfrontal approach. Howard H. Tooth reviewed the 500 craniotomies performed at Queen Square between 1901 and 1911, reporting only 4 cases of pituitary tumors, the same cases described in detail by Pollock et al. almost a century later. Therefore, several notable pituitary operations are absent from all these records, most significantly 5 of the 9 cases Horsley reported having performed in his address in 1906. These missing records can be explained by the fact that only charity patients were operated on by Horsley at Queen Square, the other procedures were for wealthy patients and physician colleagues performed either at Horsley’s home or at the patients’ homes. These private operations were registered in Horsley’s pocket notebooks, most of which have been lost.

In Verga’s treatise, a total of 12 pituitary interventions performed by Sir Victor Horsley during the 1st decade of the 20th century are reported—4 at Queen Square and 8 in his private practice. An ordered, detailed account of the complete clinical history for each patient is included in Verga’s book, each case being numbered in correlative Roman numerals. No written records in Horsley’s notebooks were available for 2 of the private cases: 1) Horsley’s first attempt to remove a pituitary tumor through a transcortical subfrontal approach in 1889 (involving a patient named Laundy); and 2) Horsley’s last pituitary intervention (involving a patient named Knight), probably performed in 1908 or 1909.94

Horsley’s Strategies and Surgical Nuances for the Treatment of Pituitary Tumors

Upon reading Verga’s transcription of Horsley’s pituitary operations, one cannot avoid the impression that Horsley was a particularly skillful and judicious surgeon. It was the speed of his operating technique that shocked Harvey Cushing during his trip to London in July 1900. Horsley had to act swiftly to limit blood loss and avoid shock, as well as to reduce the rate of postoperative infection. Such rapidity did not appeal to Cushing, who had learned the systematic, meticulous methods of surgical dissection and hemostasis from Halsted, yet Horsley’s most outstanding achievement was obtaining excellent results despite lacking the many aids for this type of operation that we have today. Ernst Sachs, Horsley’s American trainee in neurosurgery, recalled, “Horsley’s opening of the skull was crude but what really counted was his superb knowledge of anatomy and physiology. As soon as the brain was opened his handling of the tissues was exquisite and very delicate.”

Definitive evidence of Horsley’s dexterity is the successful removal and remarkably long postoperative survival of the patient in his pituitary Case 10 after resection of what was in all probability an adamantinomatous CP, one of the most challenging procedures of modern neurosurgery.
route in all his pituitary procedures (Fig. 6). He remarked on the feasibility of obtaining a good exposure and view of the pituitary gland after gentle elevation of the temporal lobe with a spatula and the aid of good illumination (Figs. 7 and 8). His technique involved a 2-staged operation strategy, in which a temporoparietal bone flap was trephined and removed with rongeurs during the first operation and the pituitary lesion was approached and removed in a second procedure, performed usually 4 to 7 days later. The initial temporal craniectomy allowed the patient to recover from heavy blood loss while the elevated intracranial pressure was mitigated in a gradual way.47

Once the area of the sella turcica had been exposed adequately, Horsley incised with a scalpel the lateral surface of the diaphragm sellae, and the mass bulging out from the pituitary fossa was scraped out in small pieces with a sharp spoon. In his 1906 monograph on brain surgery, Horsley described his technique of inserting a small rhinoscopic mirror into the sella turcica to confirm that the entire tumor had been removed. Hot water irrigation was used to control bleeding from smaller vessels, and complete hemostasis was obtained with temporary gauze packs placed in the depths of the subtemporal wound.47

The Problem of Pathological Definition of Pituitary Tumors Around the Turn of the 20th Century

Before Cushing published his monograph on the pituitary body in 1912, great confusion existed as to the nature and proper definition of the different abnormal growths developing within the pituitary gland and its surroundings. Both Harvey Cushing and Giovanni Verga remarked in their works on the great disparity in the nomenclature used to define pituitary lesions.14,59 A careful analysis of the records of pituitary tumors operated on by Horsley at Queen Square reveals an oversimplification of the pathological diagnoses provided, without reporting an accurate histological description of the tissue samples obtained in most cases. This may seem surprising, given the deep interest in pathology Horsley was known to have at the start of his career.53 Horsley’s interest in pituitary tumors may well have been fostered by his collaboration with Sir Rupert William Boyce (1863–1911), assistant professor of pathology at University College of London.48 Boyce shared work with Horsley in the university laboratories until he was appointed as the new chair of pathology at Liverpool in 1894. In 1892, Boyce published his “Textbook of Morbid Histology” (A Textbook of Morbid Histology for Students and Practitioners), a classic treatise on pathology that in essence analyzed and organized the abundant pathological material collected by Professor Horsley.6 In the preface of this work, Horsley remarked on the difficulty of putting forward any division of tumors, given the impossibility of determining the cause and nature of neoplasms.

Interestingly, Boyce was one of the first pathologists to perform a comprehensive review of the pathologies of the pituitary gland, an intriguing subject at the end of the 19th century. In an article published in 1893, Boyce and Beadles analyzed the pituitary bodies in 3000 autopsies on insane individuals and reviewed more than 90 pituitary tumors from the literature.3 This study basically differentiated glandular neoplasms from all the other types of pituitary lesions, including granulomas, abscesses, hematomas, lipomas, teratomas, and tumors of the infundibulum and posterior lobe. Pituitary lesions previously described with the terms adenoma, sarcoma, or carcinoma were now included within the common category of pituitary “strumas,” a term expressing glandular overgrowths reaching striking proportions. However, in the work by Boyce and Beadles, all kind of pituitary cysts were mistakenly included within the category of glandular hypophyseal tumors, an error explained by the structural similarities between the hypophysis and the thyroid gland, the latter frequently showing simple serous and colloid cysts. As a result, papillomatous, ciliated, and stratified epithelial cysts that were derived from Rathke’s pouch were erroneously considered as pituitary hypertrophy variants, when they actually corresponded to CPs and Rathke’s cleft cysts. Such erroneous classifications are evident in the description of a “cystic tumor of the hypophysis cerebri” in Boyce and Beadle’s article (Case 3),

whose wall was partly ossified and filled with a greenish-yellow grumous fluid, both characteristics typical of an adamantinomatous CP, but the tumor was included within the category of glandular hypertrophies of the pituitary.

Accurate differentiation between true adenomas, or pituitary strumas, and other kinds of neoplasms such as sarcomas or carcinomas was simplified enormously after the application of new specific methods for staining pituitary gland cells by Benda in 1900. Pituitary "strumas" were no longer considered sarcomas but true adenomatous benign growths with structural features of the normal anterior lobe. Shortly after, Jakob Erdheim published his original description of hypophyseal duct tumors, a term under which he grouped all epithelial growths that presumably originated from noninvoluted remnants of the craniopharyngeal duct. These lesions had been previously grouped under a vast and confusing list of terms, such as medul lary sarcoma, pituitary carcinoma, ependymal papilloma, cystosarcoma, cholesteatoma, and teratoma. Nevertheless, a mistaken classification of pituitary tumors with topographical and morphological features typical of CP within the group of pituitary "cysts" of a primary glandular nature was a common error in the medical literature between 1890 and 1910, the period in which Horsley performed all his pituitary procedures. In a review of the surgical series of pituitary tumors operated on by authors such as Harvey Cushing, Oskar Hirsch, and Anton von Eiselsberg by 1915, Zacharias Cope evidenced the confusing terminology still employed for "heterogeneous" pituitary tumors other than adenomas, which were classified within multiple categories, such as mixed tumor, endothelioma, teratoma, calcifying chondroma, epithelial cancer, and sarcoma. Seven (11%) of these nonadenomatous lesions proved to have cysts, sometimes filled with a yellow fluid containing cholesterol crystals and epithelial debris. Most, if not all of these 7 cases, may well have corresponded to CPs or Rathke’s cleft cysts. The same vague terminology of “pituitary cysts” was used for some of Horsley’s private cases reported by Verga.

Clinical and Pathological Evidence for a Diagnosis of CP in 2 Pituitary Tumors Operated on by Horsley

Although a comprehensive histological description of the pituitary tumors operated on by Horsley is lacking in Verga’s monograph, the surgical findings and macroscopic features of the tumors allow a fairly accurate estimation of the pathological diagnosis in most of the cases. In particular, the differential diagnosis between “pituitary strumas” (adenohypophyseal hypertrophies caused by enlargement of the anterior lobe) and other types of pituitary tumors can be determined by taking into consideration the topography, shape, consistency, and tissue structure of the mass. In his monumental work on hypophyseal duct tumors in 1904, Erdheim was able to differentiate 2 major pathological variants within this type of tumor (Fig. 9): 1) lesions similar to adamantinomas of the jaw, characterized by strands of a multistratified squamous epithelium with peripheral palisading of nuclei that enclosed sheets of “stellate reticulum” and cysts filled with cell debris and cholesterol particles, and 2) lesions similar to papillomas of the oral mucosa, usually formed of a unilocular cyst, whose inner wall was lined with a squamous epithelium forming wart-like or cauliflower-like excrescences.
These 2 histological variants correspond, respectively, to the adamantinomatous and squamous-papillary CP types recognized currently in the WHO classification.\textsuperscript{51}

The clinical and macroscopic pathological features of Horsley’s pituitary Cases 9 and 10 described in Verga’s monograph are identical to those described by Erdheim for the papillary (Case 9) and adamantinomatous (Case 10) types of CP (Fig. 9). Unaware of this new category of pituitary tumors recognized by Erdheim at the beginning of the 20th century, Horsley was unable to establish an accurate pathological diagnosis for these two suprasellar tumors, which he merely considered “hypophyseal cysts,” in accordance with their cystic structure. Nevertheless, Horsley was probably the first surgeon who recognized the typical suprasellar “shadows” on the skull radiograph of one patient (Case 10) as a sign caused by calcifications within a pituitary tumor different from a struma (an adamantinomatous CP) and the first who used such a neuro-radiological sign to explain the clinical symptoms of the lesion.\textsuperscript{49} Identification of calcifications above a normal-shaped sella turcica in cranial radiographs would mean major progress for the next half a century to accurately diagnose the presence of CPs, especially among children and young patients.\textsuperscript{45,46}

Table I presents the list of the fundamental epidemiological, clinical and pathological features that help to make the macroscopic distinction between hypophyseal macroadenomas and the two CP variants. Macroscopically, adamantinomatous CPs are characterized by their preferential occurrence among children or adolescents, a typical suprasellar topography, a multinodular solid-cystic morphology, a brownish hemorrhagic fluid content, and easily identifiable gross nodular calcifications in skull radiographs.\textsuperscript{\textsuperscript{50,51}} (Fig. 9A). All these characteristics are reported for Horsley’s pituitary Case 10, in contrast to the intrasuprasellar topography and typical homogeneous soft-solid consistency observed in macroadenomas, which are rarely associated with cystic hemorrhagic degeneration and almost never present calcifications. Horsley’s Case 9, investigated during autopsy after the patient’s sudden death, had all the macroscopic features of the squamous-papillary CP type, including its infundibular topography, rounded shape, unilocular cystic consistency and epithelial wart-like papillary projections observed at its inner wall (Fig. 9B). In fact, this lesion is considered a typical hypophyseal duct cyst in the table summarizing the pituitary surgeries reported before 1910 in Verga’s monograph. We can conclude that the evidence supporting the pathological diagnosis of a papillary and an adamantinomatous CP for two of the pituitary tumors operated on by Horsley (Cases 9 [IX] and 10 [X] in Verga’s monograph) is more than sufficient to confirm the correct diagnosis in both lesions. Such evidence serves to defend the pioneering role played by Horsley in the surgical treatment of craniopharyngiomas.

Conclusions

With the information available in Verga’s treatise, part of which is coincident with Church’s report of 1 pituitary tumor operated on by Horsley, there is sufficient evidence to claim that Sir Victor Horsley was not only the pioneer of pituitary tumor surgery but also the pioneer of CP surgery through the transcranial subtemporal approach.

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