

History of pituitary surgery

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REVIEW

Introduction. We review the history of pituitary surgery from its beginnings in Ancient Egypt to the present day.

Methods. We performed a retrospective, observational review of publications related to the discovery of the pituitary gland as an organ and the evolution of surgical techniques targeting the gland, particularly since the 19th century.

Results. The first transnasal interventions described were performed in Ancient Egypt, as an embalming technique. Aristotle, Galen, and Vesalius described the existence of a “mucus-producing” intracranial gland, the pituitary. The first craniectomies and intracranial procedures were described between 1880 and 1890, and the first transsphenoidal surgery was performed in 1907. The gland’s main hormonal functions were discovered between 1918 and 1944. From 1929 to 1950, transfrontal approaches were used in pituitary surgery. From 1950, the transsphenoidal technique returned, with antibiotics and corticosteroids also being used to reduce rates of surgical complications, enabling gradual advances and eventually the introduction of the neurosurgical microscope. Endoscopic transsphenoidal surgery was first used in 1994. From 1994 to 2020, endoscopic endonasal surgery has been the technique of choice in pituitary surgery.

Discussion. The late 19th century was a key period in the understanding of the pituitary gland and in the development of neurosurgery. In the 20th century, the transfrontal and transsphenoidal approaches used in the early days of pituitary surgery led the way to the perfection of the surgical technique, culminating with today’s endoscopic endonasal surgery. The combination of physiological and surgical understanding of the structure has enabled more precise diagnosis and safer, more effective treatment of patients with pituitary disorders.

KEYWORDS

Transsellar surgery, endoscopic endonasal surgery, transsphenoidal surgery, pituitary, history of the pituitary gland

Introduction

The term “hypophysis” is derived from the Greek *hipos* (under) and *physis* (growth), whereas “pituitary” is derived from the Latin *pituita*. The pituitary is a small endocrine gland measuring 6-8 mm in diameter, located in the sella turcica of the sphenoid bone, in the base of the skull. It is directly connected to the hypothalamus by the pituitary stalk, and plays a crucial hormonal role in internal homeostasis, as part of the hypothalamic-

pituitary axis. Given the importance of the pituitary gland, numerous studies have explored its anatomy and function over the centuries.

The gland is divided into two main parts, the anterior lobe or adenohypophysis (which produces growth hormone, thyroid-stimulating hormone, follicle-stimulating hormone and luteinising hormone, adrenocorticotrophic hormone, and prolactin) and the posterior lobe or neurohypophysis (which produces vasopressin or antidiuretic hormone, and oxytocin).

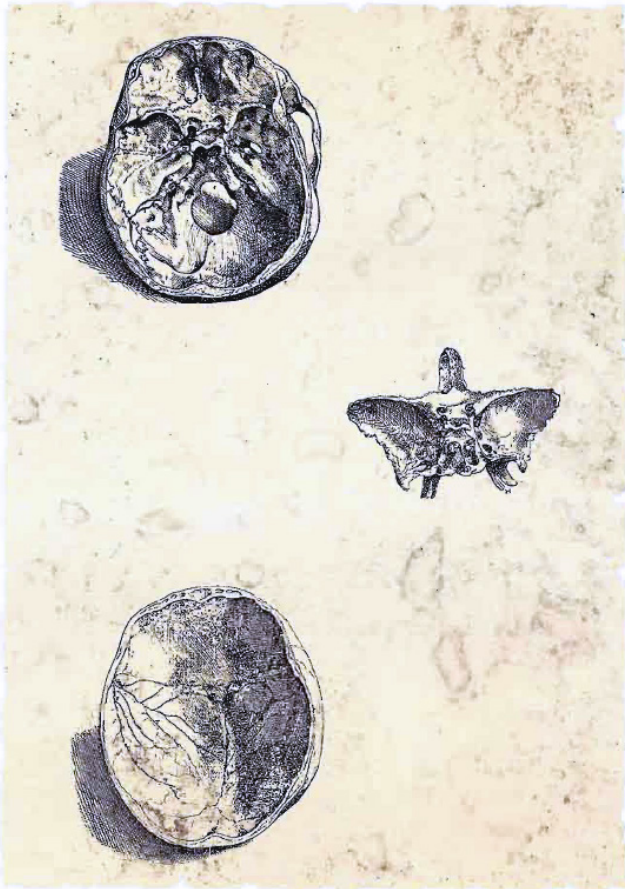


Figure 1. Drawing of the base of the skull. The lower image shows the sphenoid bone. The drawing shows the sphenoid body, with the sella turcica (which contains the pituitary gland). Adapted from an anatomical sheet from *De humani corporis fabrica* (1543) by Andreas Vesalius (Paris: Dacosta; 1980).

Given the close connection between the pituitary gland and the hypothalamus, alterations in either one of these structures promote changes in hormone production, resulting in secondary disorders of the dependent organs. The most frequent intracranial disorders affecting the gland are cysts, empty sella syndrome, tumours, pituitary infarction, and haemorrhages.

Since its discovery, understanding of the anatomy, function, and surgical approaches to the pituitary gland has resulted from a process of evolution, rather than revolution.^{1,2} This evolutionary process is a complex story of innovation and ideological shifts, with periods of extensive animal and surgical experimentation

interspersed with a period of complete rejection of these invasive techniques. This study aims to review the history of pituitary surgery from its beginnings in Ancient Egypt to the present day.

Development

From Ancient Egypt to the nineteenth century: early data on the understanding of the pituitary gland

The ancient Egyptians were one of the first civilisations to thoroughly study and document the anatomy of the human body, and were unarguably the first to use the transnasal route to access the brain. To avoid disfiguring the face of the deceased, the brain was removed through the nose using a curved hook that was inserted through a sphenoidal breach into the base of the skull during the process of mummification. The study of different mummies has provided evidence on the methods used.²

There is evidence from pre-Incan cultures of the first craniotomies on the American continent (1200 BCE): tombs with skulls showing lines of bone fractures suggest that the procedures may have been performed on live patients with the aim of “healing.” No clear evidence of intranasal approaches is described.³

Anatomical knowledge is less represented in the scarce historical documentation available from the following centuries. Religious influences stood in the way of anatomical study and medical progress, which were subject to norms and beliefs in all periods. Furthermore, successive wars prevented the conservation of scientific manuscripts and buildings or institutions that might preserve this knowledge during these centuries; therefore, few data are available.

Herodotus of Halicarnassus (484-425 BCE) and Hippocrates of Kos (460-370 BCE), in his work *On head wounds*, had already described the external morphology of the cranium (sutures, thickness, etc). Some documents from the time of Aristotle (384-322 BCE) reflect the belief that nasal mucus was part of the brain and that the nasal fossae provided direct access to the brain. They describe the existence of a “mucus-producing” intracranial gland, the pituitary. Subsequently, Galen of Pergamon (130-200 CE) also studied the morphology of the cranial sutures and described the first cranial anomalies (macrocephaly, microcephaly).

The Renaissance (15th and 16th centuries), a period of cultural revolution, saw great development in painting,

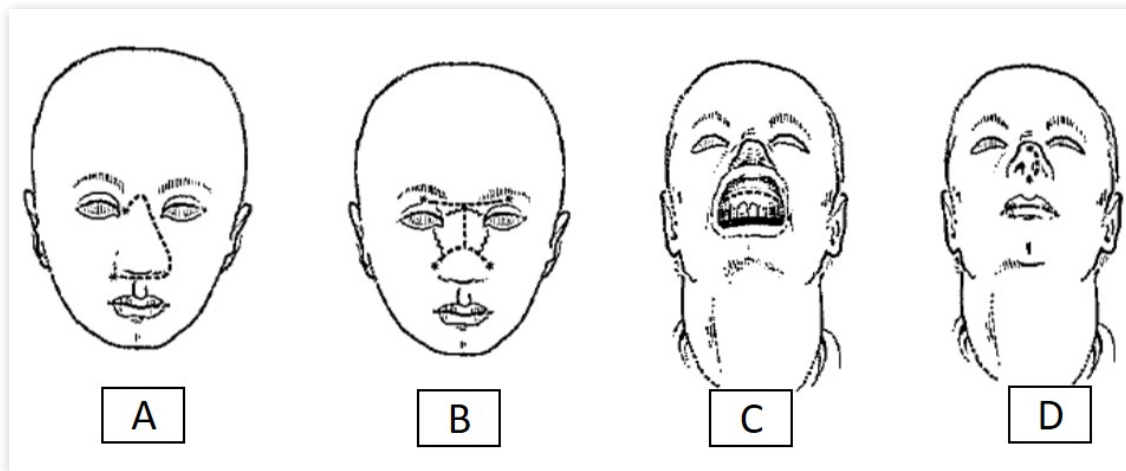


Figure 2. Evolution of different neurosurgeons' incision techniques for transsphenoidal pituitary surgery. A) Schloffer. B) Kocher. C) Halstead and Cushing. D) Hirsch. Adapted from: Welbourn RB. The evolution of transsphenoidal pituitary microsurgery. *Surgery*. 1986;100:1185-90.

sculpture, and the natural and human sciences. Humanism established new concepts of “man” and “world,” placing the focus of art on human beings. Leonardo da Vinci (1452-1519) and Michelangelo (1475-1564) made precise drawings of human bones and muscles, following direct observation. The first human autopsies were conducted in the 15th century, and in the 16th century, after performing numerous dissections, the Belgian anatomist Andreas Vesalius (1514-1564) described the anatomy of the skull in his famous anatomical sheets in *De humani corporis fabrica*.¹ Vesalius believed that nasal mucus was secreted by a gland in the brain, which he (like his predecessors) referred to as the “pituitary” (Figure 1).¹ Vesalius, in his anatomical treatises, and such other Renaissance artists as the Dutch physician Johannes Wier (1515-1588) were pioneers in recognising some signs and symptoms of acromegaly, although the disorder was not well described until several centuries later.

Furthermore, there is evidence that trepanation was performed by the Aztecs in Mexico, and especially by the Inca (1438-1533). Three Spanish surgeons who emigrated to Mexico described the successful use of

trepanation to treat brain trauma in the 16th century: Pedro Arias de Benavides (1521-1570), Alonso López de Hinojosos (1525-1579), and father Agustín Farfán (1532-1604).⁴ However, the evidence on the use of intranasal approaches at this time is unclear.

It was not until 1886 that the neurologist Pierre Marie (1853-1940) assigned the term “acromegaly” to patients with a specific phenotype, for which he gave a full definition, following the early descriptions by Johannes Wier three centuries earlier. Better understanding of this entity subsequently led to the development of pituitary surgery.

The first cranial surgeries were reported in the late 19th century (1870-1880); they were typically performed to treat head trauma, and were carried out by general surgeons or traumatologists. The first craniotomies were described in 1889, performed by the surgeon Henry Beach at Massachusetts General Hospital and the orthopaedic surgeon Edward H. Bradford (1848-1926) at Boston City Hospital. Both patients had brain tumours, and the outcomes were poor.²

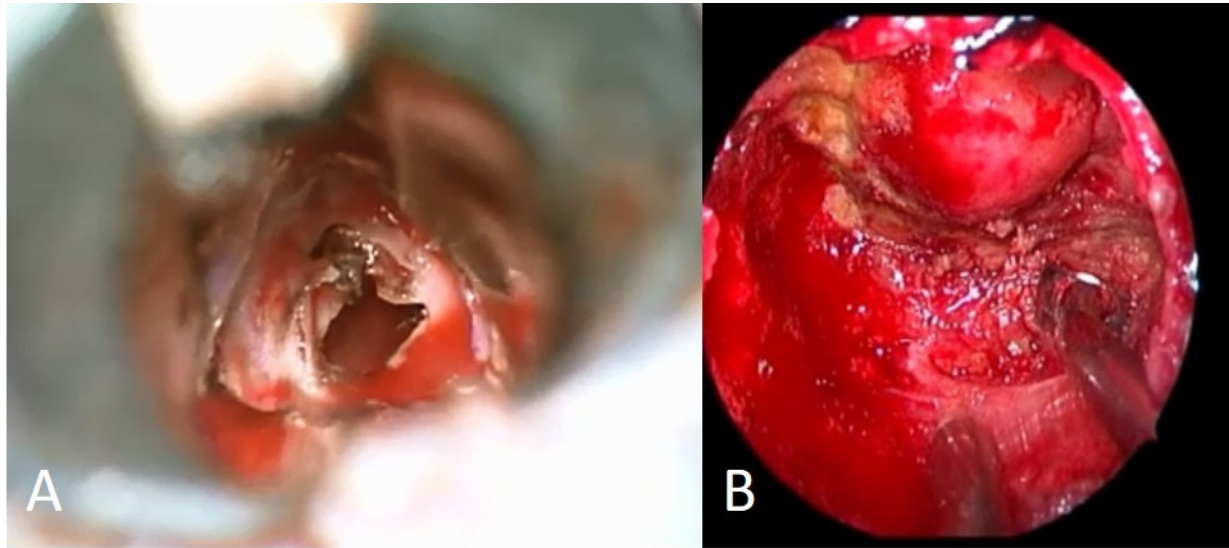


Figure 3. Intraoperative image of the two main approaches for pituitary surgery: microsurgery (A) and endoscopic (B) approaches to treat a pituitary macroadenoma.

Late nineteenth century: early pituitary surgery procedures

The increasing understanding of acromegaly and intracranial tumours led to the development of pituitary surgery.

Transsphenoidal surgery was overlooked until 1894, when an anatomical study by Davide Giordano (1864-1954), head of surgery at Venice Hospital, provided an approach to the sella turcica through an extracranial transsphenoidal approach, after a transfacial exposure.⁵⁻⁷ Based on these observations, the first successful transsphenoidal resection was performed in Vienna in 1907 by Hermann Schloffer (1868-1937), who resected a pituitary tumour in a procedure performed in three phases.⁸ Before Schloffer, pituitary tumours were accessed transcranially, with subfrontal or subtemporal approaches (Figure 2). Sir Victor Horsley (1857-1916) made the first attempt to treat a pituitary lesion with craniotomy. While his first operation was unsuccessful, in 1906 he reported on 10 patients treated with craniotomy.⁸ The English surgeons Richard Caton (1842-1926) and Frank T. Paul (1851-1941) had attempted

to use Horsley's subtemporal approach to remove a pituitary tumour in a patient with acromegaly, but were unsuccessful.⁸ Fedor Krause (1857-1937), in Berlin, reported a successful transfrontal exposure of the optic chiasm in 1902. George Theobald Kiliani (1863-1928) developed a bifrontal intradural approach in cadavers in 1904, hoping to improve the technique.

These approaches were associated with high rates of mortality and morbidity, mainly due to the retraction of the frontal lobes and poor asepsis. Theodor Kocher (1841-1917), mentor to Cushing, modified Schloffer's transsphenoidal approach with submucous resection of the nasal septum, enabling better visualisation (Figure 2). However, it was the Viennese rhinologist Oskar Hirsch (1877-1965) who developed a completely endonasal transseptal transsphenoidal approach, in 1910, based on his mentor Hajek's treatment for sphenoid sinusitis (Figure 2).⁸ The American surgeon Harvey Cushing (1869-1939) subsequently improved the technique, using Kocher's submucous resection of the nasal septum and a nasal speculum (a modified paediatric vaginal speculum).⁷

Albert Halstead (1897-1956) modified the curved incision through the naso-labial junction, suggested by Allen Kanavel (1874-1938).^{5,9,10} He designed a sublabial gingival incision that enabled greater retraction of the cartilage septum, compared to the endonasal approach, achieving better exposure and better aesthetic results.^{5,8,9} Driven by the disappointing results of his transcranial approaches, Harvey Cushing adopted the transsphenoidal approach,¹⁰ initially using Schloffer's procedure (Figure 3). He performed his first transsphenoidal surgery in 1909, in a patient with acromegaly.¹¹ By 1912, he had modified the procedure through a combination of Halstead's sublabial incision and Kocher's submucosal septal dissection,^{8,10} resulting in the procedure followed until very recently by the majority of neurosurgeons. Between 1910 and 1925, Cushing used the sublabial transsphenoidal approach to treat 231 pituitary tumours, with a mortality rate of 5.6%.¹² Cushing was the first to describe Cushing syndrome, in a monograph on pituitary adenoma and excess cortisol levels, published in 1932, although he never operated on any patient to treat the endocrine disorder, focusing instead on the tumour. In 1933, Alfred Pattison (1906-1940) performed the first pituitary surgery on the sella turcica through the implantation of radon seeds. The same year, Howard Christian Naffziger (1884-1961) performed the first partial resection of a pituitary adenoma, improving the symptoms of a patient with Cushing disease.

Alongside the progress in surgical approaches to the pituitary gland, advances were also made in the understanding of its physiology. Through animal studies, the English physiologist Henry Hallett Dale (1875-1968) explained his findings on the effect of pituitary extracts on uterine contraction in cats.¹³ In 1908, Percy Theodore Herring (1872-1967) and Edward Albert Sharpey-Schafer (1850-1935) demonstrated the existence of an antidiuretic substance (later known as antidiuretic hormone) that changed the volume of urine according to the body's needs. In 1922, the American anatomist Herbert Evans (1882-1971) discovered that extracts from the pituitary gland caused growth in rats; the substance, later named growth hormone, was not isolated until 1944, also by Evans.¹⁴ Two gynaecologists, the Israeli Bernhard Zondek (1891-1966) and the German Selmar Aschheim (1878-1965), were able to control sexual development in animals by administering supplements from the anterior

pituitary (gonadotropin); they also developed the first pregnancy test, detecting the hormone in the urine in 1927 (Aschheim-Zondek test).¹⁵

1929, a change of direction: moving away from the transsphenoidal approach

Cushing's great interest in intracranial surgery led him to pursue and develop transcranial approaches to the pituitary gland. As he gained experience and confidence with these procedures, he reduced the mortality rate of the transcranial approach to 4.6%, similar to that of the transsphenoidal approach.¹⁶ By the late 1920s, Cushing had treated numerous patients with suprasellar tumours, especially meningiomas and craniopharyngiomas, with a transfrontal approach; this allowed him to verify the diagnosis of the suprasellar tumour and to perform more extensive resection and better decompression of the optic chiasm. The transcranial approach also avoided the dreaded complications of meningitis and systemic infection, the most common causes of death associated with the transsphenoidal approach. By 1929, Cushing had practically abandoned the transsphenoidal approach, performing pituitary surgery exclusively via the transfrontal route.¹⁶ As was to be expected, the majority of the neurosurgical community followed Cushing's example.

Meanwhile, Norman Dott (1897-1973), whom Cushing taught the transsphenoidal approach in 1923 when he was a visiting intern at Peter Bent Brigham Hospital in Boston, returned to Edinburgh and continued to advocate this procedure,¹⁷ designing a speculum with a light at the tip, which provided better visualisation during the operation.¹² This intermediate phase prevented the extinction of the transsphenoidal approach.

Another key factor in the preservation of the technique was the contribution of Hirsch and Hamlin. Oskar Hirsch emigrated to the United States after his expulsion from Austria by the Nazis in 1938, and collaborated with Hannibal Hamlin (1809-1891), a neurosurgeon from Boston. Hirsch and Hamlin extolled the virtues of transsphenoidal surgery and reported excellent long-term results (Figure 2).⁸ However, despite their enthusiasm, the transfrontal approach continued to be the most popular technique throughout the 1950s and 1960s.

In line with the development of the neurosurgical technique, advances were also made in the understanding

of the physiology of the pituitary: in 1947, the Argentine Bernardo Alberto Houssay (1887-1971) won the Nobel Prize in Physiology or Medicine for his discoveries on the influence of the anterior pituitary in the distribution of glucose in the body.

Small series of patients undergoing cranial procedures began to be published in Latin America.⁴ For example, a series was published by Rafael Lavista in Mexico in 1892, although the majority of cases were cysts and trauma treated with craniotomy or trepanation. In 1940, Clemente Robles Castillo (1907-2001), of the neurosurgery department of Hospital General de México, described a surgical procedure to treat chromophobe adenoma of the pituitary.⁴

In Spain, neurosurgery departments began to appear in the first half of the 20th century. The department at Hospital General de Valencia was created in 1931; it was led by professor José Barcia-Goyanes, who employed neurosurgical instruments and methods that were already being used in Europe, with the development of stereotactic surgery and functional neurosurgery.

However, the historic promoter and pioneer of neurosurgery in Spain was professor Sixto Obrador. He began his training as a neurologist at Hospital de Valdecilla, Santander, in 1933. However, given the shortage of neurosurgeons in Spain, he decided to specialise in this field, travelling to Madrid to participate in the Institute of Neurosurgery. Subsequently, he created and reinforced the neurosurgery departments of the La Princesa, La Paz, and Ramón y Cajal hospitals in Madrid. In addition to founding these departments, he drove forward the implementation of the new microsurgery techniques that were being used in Europe, inviting foreign specialists to his centres to instruct his colleagues in these techniques, mainly in the 1960s and 1970s. Having previously been trained in neurology and psychiatry, he always believed in coordinated, multidisciplinary work, and attempted to offer patients the best specialised care.

1950, a new Renaissance: the revival of the transsphenoidal approach

Numerous innovations in the 1950s played an important role in the renewed interest in transsphenoidal surgery. With the appearance of such medications as corticosteroids and antibiotics, the mortality rates and long-term outcomes of pituitary surgery improved

significantly, with decreased incidence of meningitis and bacteraemia.¹⁸ The two figures who led the resurgence of the transsphenoidal approach were Gerard Guiot (1912-1998) and Jules Hardy (1932-). Guiot visited the Scottish surgeon Norman Dott in 1956; after observing the latter's meticulous technique and excellent surgical outcomes, he reintroduced the transsphenoidal approach when he returned to Paris.¹² He also refined his technique and improved its surgical precision with the introduction of intraoperative fluoroscopy to visualise the anatomy of the anterior skull base during the procedure.¹⁶ This enabled him to apply the transsphenoidal approach to treat craniopharyngiomas, clival chordomas, and parasellar lesions, leading to a revival of the transsphenoidal route over the next two decades.^{8,19,20}

The propagation of the transsphenoidal approach in North America began with Hardy, when he returned to Canada. Working under Guiot in Paris, Hardy returned to Montreal and continued using intraoperative fluoroscopic guidance, which enabled him to perform more extensive resections of large suprasellar tumours.¹⁶ He later adopted the routine use of preoperative angiography, polytomography of the sella turcica, and intraoperative air encephalography.⁸

Furthermore, from 1950, the surgical microscope was introduced in such specialties as traumatology, otorhinolaryngology, and neurosurgery. In 1967, Hardy used the surgical microscope in pituitary surgery, and designed his own instrumentation to increase the view of the surgical field.^{5,8}

The microscope and microsurgical technique enabled better safety and more effective resection of tumours of the pituitary gland and in the sellar and parasellar region, with no cases of severe morbidity or mortality in the first 50 patients.¹⁶ A year later, he introduced the concept of microadenoma, a lesion that may cause endocrine abnormalities without clear deformation of the sella turcica.⁵ He performed selective extraction of microadenomas while preserving the function of the gland. In 1971, he gave a more detailed description of the use of surgical microscopes for better lighting, and systematically used intraoperative fluoroscopy to improve the localisation of the tumour and the orientation of his instruments.^{6,10} It was at this time that the concepts of endocrinological pituitary surgery and hormonal control began to be incorporated, rather than simply aiming to reduce the mass effect and preserve vision.¹⁸

The intervention described by Hardy continued to advance, and became the main surgical procedure used by the majority of neurosurgeons to remove pituitary tumours and other sellar lesions until the beginning of the 21st century.^{5,8} Experts performing the procedure report mortality rates below 1%; therefore, it can be considered reasonably safe and highly efficacious.^{8,21}

1990: endoscopic approach to the skull base

Endoscopy was introduced as a diagnostic technique for various diseases in 1865, although it was not until years later when Walter Dandy (1886-1946) attempted to treat hydrocephalus with a rigid endoscope, in 1918; in 1923, he reported the first endoscopy of the third ventricle. While the technique was first introduced nearly a century ago in neurosurgery, it was mainly limited to intraventricular procedures¹⁶; it was not used in pituitary surgery until the mid-1990s. Since then, endoscopic sinus surgery has completely replaced the conventional open surgery techniques used by otorhinolaryngologists to treat nose and sinus conditions.⁸ The excellent visualisation and improved outcomes associated with endoscopy in sinus surgery drove neurosurgeons to explore the technique's potential in transsphenoidal surgery.^{18,22,23}

Microsurgery had certain limitations in terms of illumination and the angle of the visual field, which was more restricted. Initially, the role of endoscopy was to improve this technique, enabling surgeons to view structures lying beyond the line of sight with straight and angled endoscopes (Figure 3).

Previously, angled mirrors had been used to similar ends.^{8,24} Gerard Guiot was the first to report using an endoscope during sublabial transsphenoidal surgery, in 1963, but he aborted the procedure as he was unable to achieve adequate visualisation.¹⁶ In the late 1970s, Michael L.J. Apuzzo (1940-)²⁵ and K.A. Bushe and E. Halves²⁶ reported on the use of endoscopy as a complementary technique in the microscopic resection of pituitary lesions displaying extrasellar invasion. In relation to this point, we should also mention the improvement in neuroimaging techniques, with the creation of the first brain MRI scanners between 1972 and 1974, which greatly contributed to preoperative diagnosis and localisation of lesions and better assessment of complications and sequelae after the procedure.

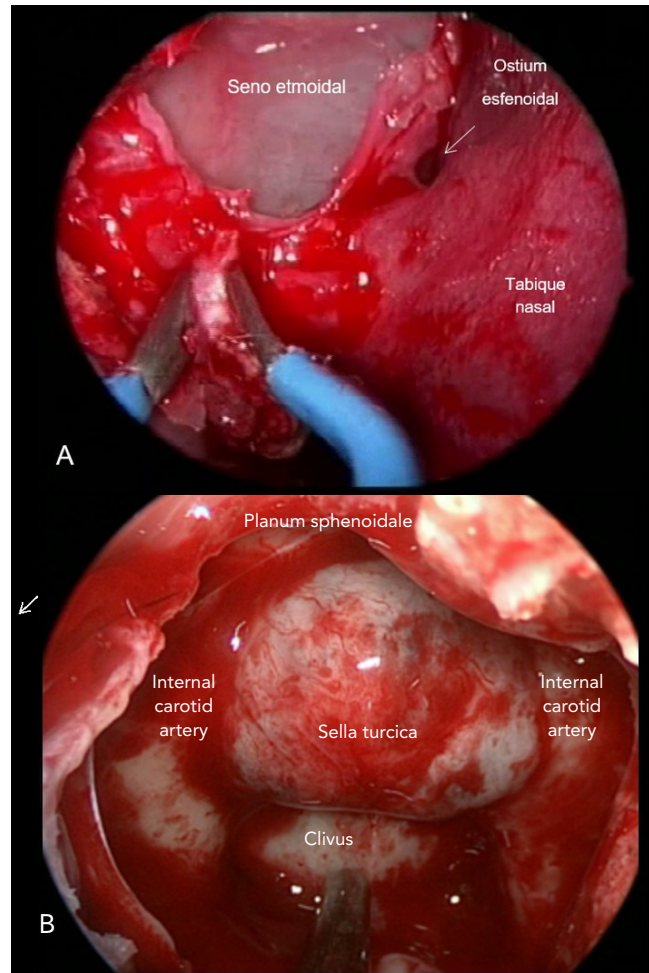


Figure 4. Intraoperative image of the anatomy of the sella turcica: endonasal surgery to remove a pituitary adenoma, performed in 2020. A) Ethmoid sinus (ethmoid sinus, sphenoid ostium, nasal septum). B) Endoscopic image of the sella turcica.

In 1994, the otorhinolaryngologists Ahmed Gamea and Ahmed El-Guindy, and the neurosurgeon Salah Fathi, all from Egypt, reported a series of 10 patients with pituitary adenomas who underwent surgery assisted by endoscopy.²⁷ This technique is known as endoscopy-assisted transsphenoidal surgery. Proponents of the technique went a step further, using the endoscope as the sole visualisation tool for the extraction of pituitary tumours: a purely endoscopic transsphenoidal approach. In 1992, Roger Janowski²⁸ was the first to publish the outcomes of endoscopic procedures in three patients with pituitary adenomas.

However, the turning point came with the work of the neurosurgeon Hae Dong Jho and the otorhinolaryngologist Ricardo Carrau, of the University of Pittsburgh. These physicians made the greatest contribution to the development and popularisation of purely endoscopic endonasal surgery. Their procedure was strictly endonasal, without the use of a transsphenoidal retractor or surgical microscope, and they began applying it to treat pituitary adenoma.^{23,29} In 1997, they published a series of 50 patients undergoing transnasal transsphenoidal surgery for pituitary adenoma.³⁰

Almost simultaneously, Naples had become the centre of the development of endonasal endoscopy in Europe, led by Paolo Cappabianca and Enrico de Divitiis.³¹ They developed a mononostril endoscopic transsphenoidal approach without a speculum, enabling better visualisation of the sella turcica and sphenoid sinus. The technique was also better tolerated by patients, as it was less traumatic, and allowed for subsequent interventions. The authors made a decisive contribution to the development of the technique, even designing specific instrumentation for this approach.³² They also proposed technical improvements³³ and contributed a considerable scientific basis,^{34,35} which would be followed by numerous neurosurgeons worldwide.

Technological improvements in this decade, with the use of flexible, rigid, and semi-rigid endoscopes, intense light sources, and cameras adapted to very thin endoscopes (as small as 1.5 mm), enabled significant advances.

Twenty-first century: pure endoscopic endonasal surgery

In the 21st century, the spread of endoscopic endonasal surgery to approach the sellar region became unstoppable, with development in countless technical areas (smaller, higher-resolution cameras; specifically designed instrumentation; correlation with such advanced neuroimaging techniques as neuronavigation, fMRI, etc) improving the efficacy and minimising the risks of these procedures. This approach provides a closer view of the anatomy and a broader manipulation and visualisation angle, compared to surgery with a microscope, and quicker, more direct access to the sella turcica.

Furthermore, it reduces the duration of the intraoperative period, the risk of diabetes insipidus, and the duration of hospital stays.

It was Amin Kassam, also in Pittsburgh, who made the greatest contribution to the development of the technique in the 2000s, with specific anatomical studies,³⁶⁻³⁹ expanded approaches, haemostasis techniques,⁴¹ techniques for reconstructing the skull base,^{42,43} classifications,⁴⁴ and a long list of scientific contributions.^{44,45}

Given the good outcomes, widespread adoption of the technique soon took place. For instance, in 2002, a Venezuelan study reported 200 cases of endoscopic procedures for different neurosurgical conditions, with pituitary lesions being the largest group of conditions treated (90 cases, 45%)⁴⁶; in Peru, the first endonasal endoscopic procedures were reported in 2008.⁴⁷

Kassam and the Pittsburgh group have had the greatest influence on the development of the technique in Spain, with many neurosurgeons and otorhinolaryngologists having trained with them in the United States (Figure 4).

Conclusion

The late 19th century was a key period in the understanding of the pituitary gland and in the development of neurosurgery. In the 20th century, with the use of corticosteroids and antibiotics, the transfrontal and transsphenoidal approaches used in the early days of pituitary surgery led the way to the perfection of the surgical technique, culminating with today's endoscopic endonasal surgery. The combination of physiological and surgical understanding of the structure has improved the diagnosis and treatment of patients with pituitary disorders.

Conflicts of interest

The authors have no conflicts of interest to declare and have approved the content of the manuscript. This is an original text and has not been submitted for assessment at any other journal or presented at any conference or course. The study is part of Dr Pérez-López's doctoral research. Neither of the authors has received partial or total funding from any pharmaceutical company or any other organisation for this article.

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