The history of pituitary surgery for Cushing disease

Historical vignette

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Although he never performed a pituitary operation for the disease, Harvey Cushing was the first to describe and treat patients with Cushing disease (CD). Other surgeons at the time were reluctant to operate on the pituitary due to the normal sella on skull radiographs in CD and the unclear etiology of the disorder. To better define and understand factors influencing the history of pituitary surgery for CD, the authors analyzed historical texts related to CD biology, diagnosis, and treatment. Cushing’s monograph on basophilic pituitary adenomas and cortisol excess appeared in 1932. One year later in 1933, Alfred Pattison performed the first successful pituitary operation for CD by implanting radon seeds in the sella. Resection of a pituitary adenoma for CD was attempted 1 month later in 1933 by Howard Naffziger, resulting in only transient improvement that corresponded to the lack of tumor in the resected tissue. Soon thereafter, Susman in 1935 and Costello in 1936 described pituitary basophilic adenomas at autopsy in patients without premorbid endocrinopathy. They concluded that the adrenal gland was the cause of CD, which resulted in a 3-decade abandonment of pituitary surgery for CD. Jules Hardy in 1963 used the operating microscope to perform the first selective removal of an adrenocorticotropic hormone (ACTH)–secreting microadenoma, which established a pituitary cause and defined the modern treatment of CD. Subsequent reports by Hardy, Laws, and Wilson resulted in widespread acceptance of pituitary surgery for CD. Initial reluctance to operate on the pituitary for CD was multifaceted and included general uncertainty surrounding the etiology of Cushing syndrome as well as a lack of early surgical success, both due to the small size of ACTH-secreting adenomas. Selective removal of ACTH-secreting adenomas identified the source of CD and ended the delay in acceptance of pituitary surgery for CD.

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Key words • Cushing disease • Harvey Cushing • history • pituitary adenoma • transsphenoidal surgery

In medicine perhaps more than in other walks, discoveries are constantly being re-made and views being readvanced, for knowledge spreads slowly and facts once known and recorded are easily overlooked or forgotten.

Harvey Cushing, “The Cavendish Lecture,” delivered before the West London Medico-Chirurgical Society, June 13, 1922.14

Cushing syndrome is a disorder of hypercortisolism that results in a classic triad of central weight gain, hypertension, and diabetes mellitus, among other symptoms. The endocrinopathy associated with Cushing syndrome underlies the significant morbidity and significantly shortened life span in untreated patients. In most patients, Cushing syndrome arises from ACTH-secreting basophilic pituitary adenomas (CD), which are frequently less than 1 centimeter in diameter. While the current treatment of choice for these lesions is selective adeno-nectomy by transsphenoidal pituitary surgery, the widespread use and acceptance of pituitary surgery for CD was delayed until the latter half of the 20th century for a variety of reasons.

Surgery of the pituitary gland and sella was pioneered by Victor Horsley in 188920 and Fedor Krause in 1905.28 Subsequent to this surgical advance, approaches for pituitary tumors evolved with contributions by many surgeons, including Harvey Cushing, over the following 2 decades. Whereas Cushing described basophilic pituitary adenomas as the cause of the syndrome of cortisol...
Pituitary Surgery for CD

Harvey Cushing (Description of CD)

Harvey Cushing was an early advocate of pituitary surgery and many contemporary pituitary surgeons can trace their professional lineage to him and his trainees. Cushing first attributed the clinical syndrome of cortisol excess to basophilic adenomas of the pituitary gland. Despite the fact that Cushing correctly identified the cause of CD, he never operated on the pituitary gland of a patient with CD. Moreover, he never suggested surgery as potential treatment for the disease.

His only neurosurgical operation on a patient with what we now know as CD was performed on his first and most famous patient with the disease, Minnie G. (a 23-year-old woman). In addition to presenting with the common features of hypercortisolism, Minnie G. presented with persistent nausea, vomiting, headaches, and papilledema. After diagnosing increased intracranial pressure in Minnie G., Cushing performed a subtemporal decompression that relieved her symptoms. Although the surgery was not directed toward the pituitary gland, Cushing attempted to view the region of the sella, without success (because of brain swelling). Shortly afterward, she experienced spontaneous remission of the clinical features of her disorder. Thus, it appears likely that she had pseudotumor cerebri, either because of hypercortisolism or as a result of the remission of hypercortisolism. Though he would later describe 13 additional patients with CD, Cushing did not perform another neurosurgical operation for “pituitary basophilism,” his term for the disorder. Although Cushing did not operate on these patients, he did treat the pituitary gland in 2 of them with external roentgen treatments directed at the pituitary fossa, 1 of whom had an enlarged sella turcica on a plain skull radiograph. Both patients experienced striking improvement of their symptoms and were improved at the last follow-up evaluation.

Alfred Pattison (Sella Radiation Seeds)

Based on Cushing’s encouraging results, one of his pupils, Alfred Pattison (Fig. 1 inset), rationalized the placement of local radiation within the sella of patients with CD. This procedure resulted in the first pituitary operation of any type for CD. Despite the patient’s normal-sized sella turcica, Pattison decided to treat his first patient. In November 1933, he performed a transfrontal operation and placed radon-222 seeds adjacent to the pituitary gland (Fig. 1). The patient experienced significant improvement and was clinically stable 4 years later. Pattison treated a second case using the same approach in May 1936, which also produced clinical improvement.

Similar success with local irradiation was later reported in 1949 by Northfield in 2 patients with CD, although 2 of his other patients died due to postoperative complications (Fig. 2).

Howard Naffziger (Hypophysectomy)

The first attempted resection of a pituitary adenoma in CD took place only 1 month after Pattison’s first use of local pituitary irradiation. In December 1933, Howard Naffziger (Fig. 2 inset), also a Cushing trainee, of the University of California, San Francisco, performed a hypophysectomy in a CD patient with a sella turcica of spherical shape at the upper limit of normal size. The operation was reported by his colleague Hans Lisser 11 years later. During the operation Naffziger performed a subfrontal approach and selectively “…removed about six fragments of pituitary tissue, each about the size of a shoe button.” Histological examination of the resected mass revealed no tumor; several sections were sent to Harvey Cushing, who was also unable to identify a lesion. Although the patient improved over the next year, her condition worsened thereafter. Menses recurred after surgery, which indicated the presence of residual pituitary tissue after incomplete hypophysectomy. It should be noted that at that time knowledge of the regulation of the HPA axis was limited, cortisol would not be discovered until 3 years later, and thus glucocorticoids were not available for replacement therapy had total removal of the pituitary been accomplished.

The next attempt at resection was performed by Pat- tison in October 1935. While in the process of performing a second operation for delivery of local radiation, he instead attempted resection:

Although a supply of radon was at hand the exposure of the sellar diaphragm was so clear that I was decided to make an attempt to remove part of the anterior lobe of the pituitary, in view of the frequency with which basophil adenomas arise in the extreme anterior and superficial parts of the anterior lobe.
Surgical history of Cushing disease

Fig. 2. Illustrations depicting the technique for implantation of radon seeds in the pituitary gland. From Northfield DW, Proc R Soc Med 42:845–853, 1949. In 1935 Howard Naffziger (inset, photograph from 1918) used the same approach in the first attempt to remove a pituitary adenoma in CD.

However, histological analysis of the resected tissue revealed no evidence of adenoma and no change was noted in the patient’s symptoms after surgery. Based on these findings, Pattison and his coauthor concluded that “In view of the doubtful part played by the basophil adenoma in Cushing’s syndrome, it is our opinion that treatment that aims at removing such a tumor is not rational.”

Herbert Olivecrona (Pituitary Electrocoagulation)

No similar pituitary operations were performed until 1951, when Olivecrona and colleagues attempted electrocoagulation of the pituitary gland. The procedure was performed over the course of 2 operations spaced 10 days apart. Despite remission of symptoms through 4.5 years of follow-up, the authors concluded without explanation that “initial treatment in a case of Cushing’s syndrome without adenocortical tumor should, in any event, consist of irradiation of the pituitary region with massive roentgen doses.” Regardless, they operated on a second patient with CD and performed a total hypophysectomy. Again, surgical remission was achieved but their recommendation for resection of pituitary adenomas for CD was tempered by their statement “…hypophysectomy should be considered in those cases in which adenocortical surgery is considered undesirable for various reasons.”

Jules Hardy (Selective Microadenomectomy)

Pituitary surgery continued to evolve through the 1950s with the reintroduction of transsphenoidal surgery by Norman Dott and Gerard Guiot. Clearly, the greatest advance in surgery for CD, though, was the introduction of the operative microscope combined with the transsphenoidal approach by Jules Hardy (Fig. 3 left). He performed the first microsurgical procedure for CD in 1963 (Fig. 3 center), as described below:

As of 1962, I began doing transsphenoidal pituitary tumor surgery only for large tumors in patients with visual difficulties (which I learned from G. Guiot in Paris in 1961) and not for endocrine disorders. The Montreal Cancer Institute was at Notre Dame Hospital and I was referred patients for hypophysectomy in the treatment of advanced metastatic breast cancer. It is during these procedures that I observed occasionally abnormal purple tissue within the normal gland that I removed separately for pathological study—that was a metastasis from the breast cancer. This gave me the idea of selective surgery. I began to look for the normal pituitary within the large adenomas and I rejected the idea that an adenoma was a diffuse hyperplasia of the whole gland. I developed the concept that before a tumor became big it was small—logical, isn’t it? Thus, the term “microadenoma.” But where to find such a lesion? I considered that patients with pituitary hypersecreting disorders and normal size sella turcica must have a microadenoma and that the treatment should be selective microadenomectomy.

In 1963, a 19-year-old patient suffering from CD was referred for hypophysectomy because he also had a left partial III and IV nerve weakness. Skull x-rays revealed that the sella turcica was slightly enlarged and demineralized. On June 5, 1963, I operated on him. At transsphenoidal exploration a pituitary adenoma was carefully removed piecemeal; the normal gland was not removed. Postoperatively, the cranial neuropathy subsided. Due to an erroneous pathological initial diagnosis of a metastasis from a melanoma, he was referred, without my knowledge, to radiotherapy and he received 5500 rads. Eventually, secondary to radiation, he required only cortisone 37.5 mg per day; thyroid-stimulating hormone, human growth hormone, and gonadotropin hormone remained normal. He fathered two children. Now, in 2010 at the age of 66, he is in excellent general condition with normal sexual activity (Fig. 4).

Personal Correspondence to Edward H. Oldfield, on August 17, 2010, from Jules Hardy, Notre Dame Hospital, 1560 Sherbrooke Street East, Montreal, Quebec, H2L 4M1, Canada

Hardy presented the first series of patients with selective adenomectomy for CD when he described remission of the syndrome in 10 cases (3 with prior adrenalectomy) at a conference at the National Institutes of Health in January 1973 that was sponsored by the National Institute of Child Health and Human Development and the National Cancer Institute, and that was attended by a national and international group of endocrinologists and neurosurgeons.

Edward Laws Jr. and Charles Wilson (Widespread Application of Adenomectomy)

Despite the advances in pituitary surgery by Hardy, bilateral adrenalectomy remained the treatment of choice until Hardy, Edward Laws Jr., and Charles Wilson (Fig. 5 left) and Charles Wilson (Fig. 5 right) in 1978 and 1980 published results of successful surgical series in patients with CD. Hardy and Wilson emphasized that an adenoma could usually be
found and selectively removed at surgery even in patients with completely negative pituitary imaging.\textsuperscript{5,42} Publication of these results in widely distributed general medical journals with prominent endocrinologists as coauthors convinced the medical community that basophilic adenomas were, as Cushing had described decades previously, the most common basis of primary hypercortisolism, or CD.

\textbf{Uncertain Etiology of CD}

Much of the delay in acceptance of pituitary surgery for CD can be attributed to uncertainty and misunderstanding surrounding its pathophysiology. During the 1st decade of the 1900s, numerous patients with a distinctive pattern of clinical symptoms began to be reported in conjunction with adrenal tumors.\textsuperscript{19} These patients often had abnormal distribution of fat, hirsutism, hypertension, diabetes, ecchymoses, and amenorrhea or impotence. In December 1910, Cushing observed similar signs and symptoms in Minnie G.\textsuperscript{15} The patient’s combination of both presumed endocrine dysfunction and intracranial symptoms caused Cushing to reason that her disease may have been of pituitary origin and he included her case in his book \textit{The Pituitary Body and Its Disorders}.\textsuperscript{15} Although he noted that patients with adrenal cortical hyperplasia had previously been reported with a similar clinical syndrome, he called it the “polyglandular syndrome” because the functions of the pituitary gland were not fully understood at the time. Because no pituitary surgery was performed and the patient lived longer than Cushing himself, the histology of Minnie G.’s pituitary gland remains unknown. In fact, the patient’s sister refused autopsy when she died in 1958.\textsuperscript{8}

Over time, Cushing consolidated his views of a pituitary etiology for this clinical syndrome with data from Minnie G. and an additional 13 patients in his 1932 publications “The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilia)”\textsuperscript{12} and an addendum published in the \textit{Journal of the American Medical Association}.\textsuperscript{13} In these landmark contributions, he documented the histological analysis of the pituitary from autopsy in 11 of the cases. In 6 cases, basophilic adenomas were evident (Fig. 6 left) and 2 patients improved following external pituitary irradiation.

\textbf{Fig. 3.} Jules Hardy in 1963 (left). The use of the intraoperative microscope for transsphenoidal surgery pioneered by Jules Hardy in 1963 (center) permitted selective adenomectomy and sparing of normal gland (right, upper) and was a critical event in not only establishing treatment of CD, but also was a critical step in establishing pituitary adenomas as the etiology of CD. From Hardy J, \textit{J Neurosurg} 34:582–594, 1971. Hardy successfully conveyed the concept of selective adenomectomy to surgeons and nonsurgeons using these images of the removal of a pimento from an olive (right, lower).

\textbf{Fig. 4.} Photographs of the first patient treated by selective adenomectomy for CD by Jules Hardy. Patient pictured at the time of treatment in 1963 (A), in 1983 (B), and in 2010 (C). Used with permission of the patient.
These contributions resulted in the clinical syndrome being designated Cushing’s syndrome in editorial comments in 1932 shortly after his publication in *The Bulletin of the Johns Hopkins Hospital*.

While Cushing’s findings raised considerable interest in a pituitary source for the syndrome, his proposal was challenged by other clinician-scientists at that time. It is important to recognize that when Cushing made his clinical observations with Minnie G., and even when he published his paper on pituitary basophilism in 1932, the regulation of the pituitary gland by the brain via the pituitary stalk was unknown. Wislocki, who spent 2 years in Cushing’s laboratory in Boston, was the first to describe the venous anatomy of the basal hypothalamus, stalk, and gland in 1936. He proposed that the portal veins of the stalk conveyed chemical signals from the brain to the pituitary gland, rather than the other direction. Moreover, although the functions of the posterior pituitary were just becoming clearer as a result of work by Cushing and others, and it was widely recognized that other types of functional pituitary tumors (such as growth hormone–secreting adenomas) arose in the region of the sella, several of the functions of the anterior pituitary remained unknown or debated.

Shortly after Cushing’s report there was substantial discussion of his proposal of basophilic tumors as a cause for CD in the major medical journals. The growing controversy surrounding a pituitary tumor underlying CD was based on the finding of incidental adenomas of the pituitary gland in autopsy series described by several authors. In 1935, Susman, in a report titled “Adenomata of the pituitary, with special reference to pituitary basophilism of Cushing,” described 23 pituitary adenomas in 22 patients from 260 necropsies. Twenty (87%) of the tumors were purely incidental and had produced no symptoms during life. Eight (35%) of the adenomas were basophilic adenomas. Based on these findings Susman concluded that:

> ...the histological data from this series...give no support to the contentions...of Cushing, that hypersecretion of basophilic cells caused by the presence in the anterior pituitary of a basophilic adenoma or of an area of basophilic hyperplasia will give rise to the syndrome which he has termed ‘pituitary basophilism’. Adenomata as a whole occur in 8 per cent of cases, the basophilic type in 3 per cent, and they are therefore too common to be of any special significance.

In 1936, Costello, as part of his Master’s thesis at the Mayo Clinic, presented a histological analysis of 1000 pituitary glands from autopsy patients without preexisting evidence of pituitary dysfunction. Of 265 incidental tumors found, 72 (27% of adenomas, 7.2% of patients) were basophilic adenomas (Fig. 6 right). Costello termed these tumors “subclinical adenomas” because he concluded that “the majority of adenomas of the anterior pituitary, irrespective of type, are entirely benign and give no recognizable clinical symptoms.” The autopsy reports by Susman and Costello suggested to many that Cushing’s findings of basophilic adenomas in patients with CD were coincidental and that the focus of the etiology of the syndrome should shift to the adrenal glands.

Contemporaneous with these early autopsy findings, plain skull radiographs, which were commonly used in the diagnosis of pituitary tumors until tomography became widely used in the 1970s and 1980s, were nearly always normal (90%) in patients with CD. At that time, expansion of the sella on plain skull radiographs was used to confirm the presence of other types of pituitary tumors (such as nonsecreting tumors, prolactinomas, growth hormone–secreting adenomas, and others) that often presented only when large enough to distort/expand the sella. In contrast, there was no imaging proof of pituitary disease in most patients with CD on plain skull radiographs. Many decades would pass before it was understood that ACTH-secreting tumors are often small (< 10 mm in maximum diameter) when they become clinically significant. In fact, we now know that nearly all ACTH-secreting adenomas are well below the size necessary to expand the sella on plain skull radiographs and many are not detected by our most sophisticated contemporary MR imaging sequences.

Thus, despite Cushing’s findings, the primary treat-
ment for the clinical syndrome remained focused on the adrenal glands. Some clinicians continued to target the pituitary in refractory cases, but many viewed pituitary involvement as a necessary but not essential etiologic factor. The controversy continued through the 1940s and into the early 1950s. Clinicians also were reluctant to divide a single clinical syndrome into more than one distinct disease arising from different organs. Albright summarized this belief:

**Major Premises**

A. Patients with Cushing’s Syndrome presumably have some common denominator in the etiology, as it would be unlikely that two entirely unrelated disorders would produce such a combination of clinical findings.

B. Patients with cancer of the adrenals and Cushing’s Syndrome presumably are suffering from an hyperadrenocorticism of some kind; ergo all patients with Cushing’s Syndrome are suffering from an hyperadrenocorticism.

A critical advance in uncovering the pathophysiology of CD was the discovery of a pituitary hormone that acted on the adrenal glands to stimulate them to make and secrete cortisol. In 1933, Bauer hypothesized that such a hormone existed based on Cushing’s findings. Months later, in 1933, James Collip and coworkers at the University of Alberta identified ACTH. Despite this finding, it would not be until 10 years later that Arthur Jones showed that a corticotrophic factor is elevated in patients with CD. In 1950 Julius Bauer expanded on this biochemical work and eventually distinguished 2 distinct origins of hypercortisolism: “one (primary) produced by functioning tumors of the adrenal cortex and another (secondary) produced by excessive stimulation of the adrenal cortex by a diseased pituitary.” Bauer was also responsible for coining the term “Cushing’s disease” as a term for hypercortisolism specifically due to pituitary dysfunction.

Even after the distinction of 2 sources of hypercortisolism by Bauer had become widely accepted, the basis of the pituitary origin remained clouded, because some scientists with improved knowledge of the HPA axis postulated that hypothalamic dysfunction might be the primary cause of hypercortisolism. This theory was based on the observation by Arnold that hypocortisolism followed irradiation of the hypothalamus of monkeys. He further hypothesized that historical success with irradiation might have been based not on the effects of the therapy on an adenoma of the pituitary gland, but on the presumptive inclusion of the hypothalamus in the treatment field with the larger radiation portals that were initially used. Not only did this hypothesis affect pathobiological thinking about CD at that time, it also had a direct impact on the treatment of CD, as radiotherapy portals were then designed to include the hypothalamus.

Several essential scientific, laboratory, and clinical advances during the late 1940s, as well as the 1950s and 1960s, helped clarify the pituitary origin of CD. These fundamental advances included the isolation and production of cortisol by Kendall and colleagues in 1949, the wide use of serum and urine cortisol measurements developed by Porter and Silber (1954), the development of potent cortisol analogs (dexamethasone) in the mid-1950s, and the ability to accurately measure serum ACTH. Use of these tests and exogenous steroids permitted clinicians to directly test regulation of the normal and abnormal HPA axis. Specifically, Grant Liddle and colleagues performed a series of laboratory and clinical experiments in the 1950s and 1960s, which revealed that while patients with adrenal tumors did not respond to exogenous measures to suppress or stimulate cortisol secretion, patients with adrenal cortical hyperplasia did respond to these measures. For the first time, these findings indicated that differing pathophysiological mechanisms might underlie these 2 pathological entities of the adrenal gland.

Based on his findings in patients with adrenal tumors and hyperplasia, Liddle applied similar endocrinological tools and principles to elucidate sites of dysfunction along the HPA axis in CD. Initially, in his 1969 review “The evolution of Cushing’s syndrome as a clinical entity,” Liddle ascribed the excess ACTH secretion in CD to the pituitary and included the possibility of excess hypothalamic drive of the pituitary, primary pituitary hyperplasia, or an adenoma as possible sources for the increased ACTH. By 1972, he had become convinced that CD was caused primarily by a pituitary adenoma. This evolution in thinking came about, at least in part, by his experience with the special case of a patient described in his 1972 review “Pathogenesis of glucocorticoid disorders”:

A convincing illustration of this fact is found in a case study from the Vanderbilt series. The woman in question was extensively studied prior to and again after a neurosurgical procedure in which a pituitary stalk section was performed and an impervious tantalum plate was installed to separate her hypothalamus from her pituitary gland. All her hormone values prior to the operation were perfectly typical of Cushing’s disease. Plasma ACTH and cortisol concentrations were elevated and lacked a diurnal rhythm. There was partial resistance to dexamethasone-induced suppression of pituitary-adrenal function. The response to metyrapone was vigorous. Within days after pituitary stalk section, it became apparent that this patient’s ACTH and corticosteroid values had not been altered by the procedure. The responses to dexamethasone and metyrapone were the same as in the preoperative period. One might have imagined that the operation had been a technical failure were it not for the fact that the tantalum plate still covered the sella turcica and that hypopituitarism developed with respect to all hormones except ACTH. This woman was ultimately treated for her Cushing’s syndrome by bilateral adrenalectomy. When she died, nine years subsequent to her stalk section, she was found to have a 1 cm chromophobe adenoma of the pituitary. The conclusion seems inescapable that Cushing’s disease in this patient was due to ACTH production by a pituitary adenoma and that this adenoma, in the absence of central nervous system control, functioned in a manner that was perfectly typical of untreated Cushing’s disease.

While these pathophysiological discoveries related to the origin of CD were occurring, it is important to note that by 1973, Hardy had successfully performed selective adenomectomy in 10 patients with CD beginning 10 years earlier, which provided additional direct evidence for the pituitary as the source of CD.

**Discussion**

Pituitary surgery for CD took many years to become
accepted due to several factors. Both the lack of consistency of successful case reports and the protracted debate over the etiology of the disease contributed to the paucity of pituitary surgery to treat CD (Fig. 7). Specifically, uncertainty of an adrenal versus pituitary etiology of CD was the greatest obstacle to the adoption of pituitary surgery in the 1930s through the early 1950s. Despite the fact that several early patients showed marked clinical improvement after treatment directed at the pituitary, many influential physicians were reluctant to accept it as the source of the pathophysiology.\(^1\),\(^2\) However, by the late 1950s, primary and secondary hypercortisolism were well accepted.

Several aspects directly related to pituitary surgery and its development also contributed to its delay in the treatment of CD. Not only were there few successful early surgical cases, but also the cases that were reported were initially forgotten. For example, when Olivecrona's group published their first case from 1951, they indicated that theirs was the first surgery of its kind, failing to recognize the attempts of hypophysectomy by Naffziger and Pattison.\(^2\) Moreover, in addition to lack of recognition of prior reports of pituitary surgery for CD, the results of these early cases were often unconvincing even to the authors of successful cases (see Olivecrona above). Naffziger's initial attempt had only a temporary effect and Pattison's subtotal hypophysectomy was ineffective.\(^3\),\(^2\) Even pituitary irradiation, which provided evidence for directing treatment at the pituitary, bore heterogeneous results.\(^1\),\(^1\)

An additional early deterrent to pituitary surgery was the attendant morbidity of the procedure, limited access to the sella using a transcranial approach, and lack of microscopic magnification for selective adenomectomy. While the transsphenoidal procedure was pioneered as early as 1907 by Schloffer,\(^3\) most surgeons had abandoned the procedure by the 1930s when the first cases of CD were treated by pituitary surgery. The approach of choice to the pituitary region during this era was either transfrontal or subfrontal. These transcranial approaches were substantially more morbid than the transsphenoidal approaches used currently. Moreover, these transcranial approaches posed particular difficulty for the surgeon to access the diaphragma sella and the pituitary beneath it. Finally, before the advent of pituitary microsurgery, selective resection of small tumors was not performed and pituitary surgeons relied on achieving total hypophysectomy to ensure tumor removal. This resulted in total disruption of pituitary hormone production and necessitated lifelong hormone replacement, which did not become available until the 1950s. The introduction of the operative microscope to pituitary surgery and the idea that selective adenomectomy of microadenomas (both concepts introduced by Jules Hardy) made selective tumor resection a possibility and eliminated the need for hormone replacement in most patients.\(^2\),\(^2\)

**Disclosure**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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