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# Cushing's Syndrome Origins: A Case Report

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## Abstract

**Background:** Harvey Williams Cushing (1869-1939) was known for describing, at the beginning of the 20th century, a syndrome characterized by central obesity, hypertension, proximal muscle weakness, diabetes mellitus, hirsutism, thin skin, and ecchymosis. He observed that this condition could be associated with both adrenal tumors and pituitary adenomas, thus laying the foundations for the recognition of endogenous hypercortisolism (EH). Hypercortisolism caused by a cortisol-hypersecreting adrenal tumor is one of the few serious endocrine-metabolic diseases that can be completely cured by surgical removal of the adrenal tumor. We present a female patient with ACTH-independent hypercortisolism who underwent left adrenalectomy and was found to have a hypersecreting cortical adenoma.
**Objectives:** To develop a historical account of the life of Harvey Williams Cushing and of adrenocorticotropic hormone (ACTH)-independent EH.
**Methods:** A retrospective, multicenter study was performed.
**Results:** A systematic search was conducted in MEDLINE, Cochrane, PubMed, and Google Scholar from 2005 to 2025, yielding 1,990 results, of which 68 studies were included.
**Conclusion:** Historical perspective and learning from the lessons of the past are essential for current medical practice. Cushing's syndrome is undoubtedly a paradigm of polymathy, with great contributions to modern medicine. A clinical case is presented with a diagnosis of ACTH-independent hypercortisolism, which, after surgical removal, achieved complete reversal of hypercortisolism. ACTH-independent Cushing's syndrome is a rare disease whose timely diagnosis is important to reduce the risk of cardiovascular and endocrine-metabolic complications.

**Keywords:** Hypercortisolism; Adrenalectomy; Cushing's syndrome; Cortisol; ACTH; adrenal gland

## Introduction

Harvey Cushing (1869) (Figure 1) was an American neurosurgeon considered the founder of modern neurosurgery. He trained at Yale College from 1887 to 1891, entered Harvard Medical School in 1891, and graduated as a Doctor of Medicine in 1895. He joined

Johns Hopkins in 1896, where he worked under the mentorship of William Halsted and developed pioneering surgical techniques, including the introduction of blood pressure monitoring and the use of intraoperative X-rays [1]. Cushing performed over 2,000 brain tumor operations, dramatically reducing surgical mortality and training a generation of leaders in neurosurgery. Furthermore, he was a prolific author and won the Pulitzer Prize for his biography of Sir William Osler. His interest in the pituitary gland and pituitary tumors led him to describe multiple syndromes and neurological phenomena, such as the Cushing reflex and Cushing's ulcer, as well as the creation of the Cushing Brain Tumor Registry, laying the foundations for modern neuro-oncological research [2]. Cushing's connection to the disease that bears his name is direct and fundamental. At the beginning of the 20th century, Cushing described a syndrome characterized by central obesity, hypertension, proximal muscle weakness, diabetes mellitus, hirsutism, thin skin, and ecchymosis, which he initially called "pluriglandular syndrome." He observed that this condition could be associated with both adrenal tumors and pituitary adenomas, and he postulated the existence of a relationship between the pituitary gland and the adrenal cortex. In 1912, he published his monograph The Pituitary Body and Its Disorders, where he detailed clinical cases and pathological correlations, laying the groundwork for the recognition of endogenous hypercortisolism secondary to pituitary adenomas, which was later termed Cushing's disease. His work was key to differentiating between Cushing's syndrome (hypercortisolism of any etiology) and Cushing's disease (hypercortisolism secondary to an ACTH-producing pituitary adenoma) [1].

Cushing's syndrome is currently defined as a prolonged increase in plasma cortisol levels that is not due to a physiological etiology. While the most frequent cause of Cushing's syndrome is the use of exogenous steroids, the estimated incidence of Cushing's syndrome due to endogenous cortisol overproduction ranges from 2 to 8 per million people per year. Cushing's syndrome is associated with hyperglycemia, protein catabolism, immunosuppression, hypertension, weight gain, neurocognitive changes, and mood disorders. When the disease has an endogenous origin, the most frequent etiology is an ACTH-producing pituitary adenoma (ACTH-dependent Cushing's), which accounts for approximately 80-85% of cases. ACTH-dependent Cushing's due to ectopic hormone production occurs in 5% of cases, while ACTH-independent Cushing's represents between 6% and 15% of cases [3]. We present a clinical case of a female patient with ACTH-independent endogenous hypercortisolism, whose initial clinical suspicion was based on findings such as secondary amenorrhea, weight gain, hirsutism, violaceous striae on the abdominal wall, episodes of dysthymia, depression, hyperglycemia, and centripetal obesity, along with increased cortisol in blood and urine and a contrast-enhanced tomography describing a space-occupying lesion in the left adrenal gland.

## Case Presentation

A 38-year-old female patient reported the onset of her illness in October 2018, characterized by a six-month history of amenorrhea, weight gain of over 30 kg, hirsutism, violaceous striae on the abdominal wall, and episodes of dysthymia. She was evaluated by the endocrinology service, which ordered an abdominal and pelvic CT scan and laboratory tests that revealed abnormal levels of basal cortisol, urinary free cortisol, and ACTH (Figure 2). She was diagnosed with a functioning left adrenal adenoma (ACTH-independent hypercortisolism) and was referred to general surgery. In 2020, a left adrenalectomy was performed, but the pathology report concluded that no adrenal gland was identified in the tissue examined. Given the persistence of symptoms for 4 years and an associated increase in volume in the left flank (incisional hernia/eventration), the patient presented to our institution, where she was evaluated and scheduled for surgery. A contrast-enhanced CT scan of the abdomen and pelvis revealed a well-defined, rounded, hypodense left adrenal gland in the fatty range (5 HU) with peripheral calcification. This lesion enhanced homogeneously in the venous phase after contrast administration, showing an absolute washout percentage of 41% and measuring 2.94 x 2.89 x 3.28 cm. additionally, a musculoaponeurotic defect was evident in the midline and left flank, through which the descending colon, small bowel loops, and left ureter protruded. The abdominal cavity volume (ACV) and hernial sac volume (HSV) were calculated as follows: ACV: 0.52 x 11.82 x 24.87 x 35.8 = 5,495.5; HSV: 0.52 x 16.1 x 14.6 x 13.6 = 1,662.3; resulting in a Tanaka index of 30% (Figure 3). Laboratory studies (Figure 2) reported elevated serum cortisol and urinary free cortisol, with the rest of the paraclinical tests within normal limits. On physical examination, the patient was in fair general condition. Clinical findings included violaceous striae on the upper and lower extremities and the anterior and lateral abdominal wall, as well as facial plethora. The abdomen was globular due to adipose tissue, showing centripetal obesity and a hypertrophic scar in the left lumbar region with a volume increase of approximately 15x20 cm, which was reducible and slightly painful, without color changes. In the midline, a reducible, non-painful supraumbilical abdominal wall defect of approximately 5 cm was evident without color changes. Bowel sounds were present with adequate intensity and frequency. The rest of the abdomen was soft, non-tender to superficial and deep palpation, and without signs of peritoneal irritation (Figure 4).

## Treatment Performed

The patient was taken to the operating room for a supraumbilical exploratory laparotomy and a left transabdominal adrenalectomy.

The surgical findings were: a 5 cm supraumbilical midline defect with protrusion of bowel loops; a 15 cm aponeurotic defect in the left lumbar region with protrusion of the descending colon and small bowel loops; the left kidney presented multiple firm and loose adhesions to the spleen, abdominal wall, and the adrenal tumor; the adrenal tumor measured approximately 4 x 5 cm with firm and loose adhesions to the left diaphragmatic crus, spleen, and parietal peritoneum (Figure 5). The specimen was sent for pathological analysis, which concluded: Cortical adrenal adenoma. Tumor size: 3.3 × 3.3 × 2.5 cm. No capsular or vascular infiltration was observed. Non-neoplastic adrenal parenchyma showed no evidence of neoplastic infiltration, and the suprarenal vein was also free of neoplastic infiltration and completely resected.

In the immediate postoperative period, the patient was transferred to the intensive care unit (ICU) and presented with hypotension requiring vasopressors. Serum cortisol levels were 3 µg/dL (reference range: 5-15 µg/dL). A diagnosis of adrenal shock (crisis) was made, requiring corticosteroid dose adjustment with a hydrocortisone regimen of 100 mg every 4 hours for 24 hours. After 48 hours, a gradual taper to 80 mg of hydrocortisone every 6 hours was initiated. The patient achieved hemodynamic stability without vasopressor support, and cortisol levels stabilized at 69 µg/dL. The patient was extubated 72 hours after intravenous steroid rescue without immediate or delayed complications. The patient was discharged from the ICU with adequate clinical progress and subsequently discharged from the hospital with outpatient management in conjunction with the endocrinology service.

## Methods

A retrospective, multicenter study was conducted through a systematic search in MEDLINE, Embase, Cochrane, PubMed, and Google Scholar, in both Spanish and English, from 2005 to 2025. The search terms used were "Cushing's syndrome", "Harvey W. Cushing", "ACTH-independent endogenous hypercortisolism", and "Surgery, case reports". The search was limited to published articles, yielding 1,990 results. After reviewing titles, abstracts, and keywords, 1,922 articles did not meet the inclusion criteria or met the exclusion criteria.

**Inclusion criteria:** Studies in English and Spanish describing historical aspects of Harvey W. Cushing and clinical case reports with diagnoses of ACTH-independent endogenous hypercortisolism indicated for and cured by surgical removal of an adrenal adenoma.

**Exclusion criteria:** Studies that did not describe historical aspects of Harvey W. Cushing were excluded. Studies and case reports that did not incorporate surgical removal or surgery as the first-line treatment were also excluded.

## Results

Sixty-eight studies were included, of which 22 performed a literature review regarding historical aspects and 46 corresponded to case reports.

***Figure 1:*** *Harvey W. Cushing, pencil drawing by John Singer Sargent in 1916.*

| **Cortisol basal (2 /7 /2019)** | **37,7 ug//dl VN:5-26** |
|---|---|
| Cortisol libre urinario (2 /7 /2019) | 1.037 VN: 4,0 a 176,0 ug/24h |
| ACTH (2 /7 /2019) | 13.4 VN: menor a 20 pgr/ml |
| Cortisol sérico (10 /6 /2025) | 16,2 ug//dl VN:5/15 ug/dl |
| Cortisol libre urinario (10 /6 /2025) | 220 ug/24h VN: 4,0 a 176,0 ug/24h |

***Figure 2:*** *Laboratory table.*

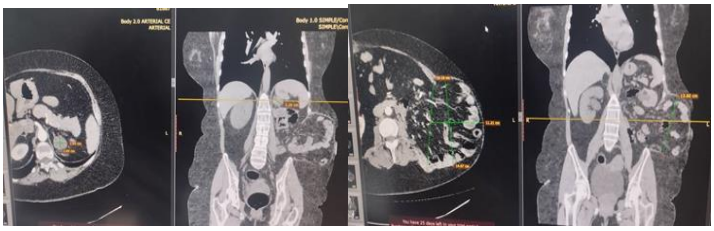

***Figure 3:*** *Contrast-enhanced abdominal and pelvic CT scan showing a left nodular lesion near the left crus of the diaphragm: A. Axial. B. Coronal. C. Abdominal wall aponeurotic defect.*

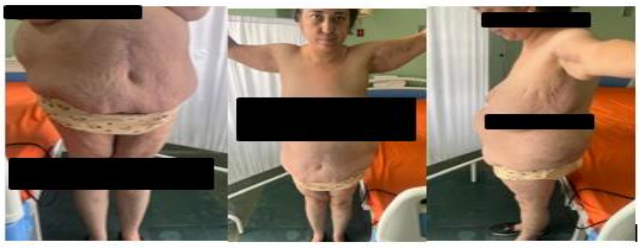

***Figure 4:*** *Clinical manifestations: violaceous striae on extremities and abdominal wall, facial plethora, centripetal obesity*

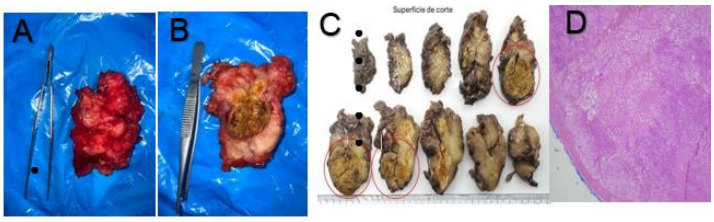


***Figure 5:*** *Left transabdominal adrenalectomy: A. Surgical specimen. B. Specimen cross-section. C. Macroscopic pathology of the left adrenal gland with adenoma in the upper pole. D. Microscopic view of the neoplastic lesion (benign).*

## Development and Discussion

Harvey Williams Cushing was born in Cleveland, Ohio, on April 8, 1869, into a family where his father and grandfather were physicians. His mother was Betsey Maria Williams and his father was Henry Kirke Cushing. He attended Central High School, graduating in 1887; this school focused on both manual and intellectual training. He then entered Yale University for his undergraduate studies and began to take an interest in medicine. In 1891, he was admitted to Harvard Medical School and in 1895 completed his internship at Massachusetts General Hospital. He graduated with honors (cum laude) in Medicine in 1895. After graduation, he moved to Baltimore and joined Johns Hopkins Hospital, which had been founded in 1889 following the model of leading German clinics [4]. There, he began his professional life (18961912), working and training as a surgeon alongside William Halsted and Sir William Osler, who became his mentors and friends especially Osler, who awakened his passion for medical history [5]. Initially, he operated in all surgical areas, but after procedures to alleviate trigeminal neuralgia, he shifted his focus to the nervous system. His advancements in brain surgery were remarkable, and he soon began operating on the skull base and the pituitary gland. In 1897, driven by his interest in the nervous system and its neurosurgical problems, he founded an experimental neurosurgery laboratory: the Hunterian Laboratory of Johns Hopkins Hospital, of which he was the first director [4].

Motivated by the developments in nervous system surgery across the Atlantic, Cushing traveled to Europe in 1900, where Victor Horsley, considered England's first neurosurgeon, became his mentor [6]. Later, he moved to Bern, the capital of Switzerland, where he worked alongside Emil Theodor Kocher (Nobel Prize in Medicine, 1909) and Hugo Kroenke (1839–1914). During this period, he dedicated himself intensely to physiology, conducting experimental research on systolic blood pressure and intracranial pressure. He described the "Cushing reflex" as the relationship between vascular and intracranial pressure. His European journey continued to France, where he observed the techniques of French surgeons treating nervous system lesions. Finally, he returned to England and reinforced his neurology knowledge alongside Charles Sherrington, known for his contributions to the study of nervous system diseases [5]. Upon returning from Europe in 1903, he was appointed associate professor of surgery and diligently continued his surgical interventions on the central nervous system with favorable results. Finally, in 1904, a position was created in Baltimore to treat patients with nervous system lesions requiring surgical treatment. This historical moment is considered crucial in Cushing's life and in the consolidation of neurosurgery, as it was then that "surgery of the nervous system" became properly known as "neurosurgery." He thus provided the name for the nascent specialty to which he would dedicate the rest of his life [4]. That same year (1904), he delivered the lecture "The Special Field of Neurological Surgery" to the Cleveland Academy of Medicine, and in 1906, he published "Surgery of the Head," part of William Williams' encyclopedic text Keen's Surgery, Its Principles and Practice. Years later, "Surgery of the Head" was published in Spain with significant success. By 1910, his surgical success was evident: he had reduced mortality to 13% in 250 patients with brain tumors, a result far superior to the 50% achieved by others [7].

Eight years after dedicating himself solely to nervous system pathologies, he founded the first neurosurgery service in the U.S. in 1912, establishing principles for surgical technique and careful tissue manipulation. Also in 1912, Cushing published his book The Pituitary Body and Its Disorders: Clinical States Produced by Disorders of the Hypophysis, explaining everything related to the disease that bears his name. The text was widely promoted and sold worldwide, catapulting him to the top of the scientific community of his time [6]. During World War I, Cushing led a surgical team for three months at a French military hospital near Paris, treating traumatic brain injuries from gunshot wounds. In 1919, he returned to the United States and, in 1923, received the Distinguished Service Medal. His wartime experience led to several papers, the most important being a detailed study of brain injuries that comprised an entire issue of the British Journal of Surgery in 1918 [5]. Thanks to his extensive experience, he made a wide variety of contributions that remain relevant today, producing approximately 24 books and 658 scientific articles [5]. After Sir William Osler's death, he spent the years from 1920 to 1924 writing his biography as a tribute. The work was critically acclaimed and won the Pulitzer Prize for Literature in 1926. He also authored biographies of other medical figures such as Vesalius and Galvani [7]. Cushing's connection to the disease that bears his name is direct. In the early 20th century, he described the syndrome (obesity, hypertension, muscle weakness, etc.) he initially called "pluriglandular syndrome." He observed its association with both adrenal and pituitary tumors and postulated the pituitary-adrenal cortex relationship. In his 1912 monograph, he detailed clinical cases and pathological correlations, laying the groundwork for the recognition of endogenous hypercortisolism secondary to pituitary adenomas (Cushing's disease). His work was key to differentiating

between Cushing's syndrome (any etiology) and Cushing's disease (ACTH-producing pituitary adenoma) [2].

### Currently, endogenous hypercortisolism is classified into two main groups

- **ACTH-dependent hypercortisolism:** Primarily Cushing's disease due to an ACTH-producing pituitary adenoma and, less frequently, ectopic ACTH secretion.
- **ACTH-independent hypercortisolism:** Autonomous cortisol production by adrenal tumors (adenomas, carcinomas, or macronodular hyperplasia) without ACTH stimulation [8].

Elevated cortisol causes hyperglycemia, abnormal protein catabolism, immunosuppression, neurocognitive changes, bone disorders like osteoporosis, and mood disorders like depression. Weight gain, hypertension, and hypokalemia are common nonspecific features. Propensity for bruising, violaceous striae, and facial plethora are more specific features of Cushing's syndrome, many of which were present in the described case. Among endogenous cases, Cushing's disease accounts for 80-85%, ACTH-independent adrenal production for 6-15%, and ectopic secretion for 6-10%. Unilateral adrenal adenoma or carcinoma and bilateral hyperplasia are the most common causes of ACTH independent production. In suspected cases, exogenous glucocorticoid use must be ruled out before diagnostic testing [9]. Diagnosis requires biochemical testing to determine the cause of excess cortisol. Treatment is specific to the etiology; incorrect diagnosis can lead to inappropriate medical or surgical intervention [2]. Diagnostic tests include 24-hour urinary free cortisol, the overnight 1-mg dexamethasone suppression test, and late-night salivary cortisol measurement. In patients with an adrenal adenoma, dexamethasone suppression is the preferred initial test. A random elevated cortisol level raises suspicion. In patients with high clinical probability, two different tests demonstrating elevated levels can establish the diagnosis, as in our patient. Conversely, two normal results generally exclude the syndrome [10]. Transsphenoidal pituitary surgery is the primary therapy for Cushing's disease. Laparoscopic adrenalectomy is the established treatment for Cushing's syndrome induced by a benign unilateral lesion (adenoma) and is associated with low morbidity (3-7%) and mortality (0.5%). However, it requires perioperative and postoperative glucocorticoid replacement due to central adrenal suppression, which manifests as hypotension and circulatory shock. In the immediate postoperative period, our patient presented with distributive shock (adrenal crisis), requiring vasopressors and high-dose intravenous steroids. An open approach via midline laparotomy was chosen due to significant abdominal wall defects and multiple adhesions [2].

## Conclusion

Cushing's relationship to the disease that bears his name is fundamental. Morbidity from endogenous Cushing's syndrome includes cardiovascular complications, diabetes, obesity, myopathy, infections, and neuropsychiatric disorders. Early diagnosis and treatment are crucial, as untreated disease is associated with increased mortality [2]. A clinical case is presented in which a left transabdominal adrenalectomy was performed for an adrenal cortical adenoma. Strict monitoring of cortisol and vital signs was maintained with oral steroid supplementation. A favorable response was observed one month after surgery, achieving a complete cure through the surgical removal of the adrenal adenoma.

### Conflict of Interest

The authors declare no conflict of interest.

### Informed Consent

Informed consent was obtained from all participants.

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