Harvey Cushing's craniopharyngioma treatment: Part 2. Surgical strategies and results of his pioneering series

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OBJECTIVE Harvey Cushing (1869–1939) developed pioneering surgical techniques for craniopharyngioma (CP) removal. This study exhaustively analyzes the pathological variables and surgical strategies that influenced Cushing's results in his entire series of CP patients.

METHODS The CP records from Cushing's Brain Tumor Registry were carefully reviewed, as were his CP cases published in medical monographs and scientific reports.

RESULTS One hundred twenty-four tumors with characteristics typical of CP comprise Cushing's entire series (CP₁₂₄). Cushing performed 198 surgical procedures in the patients in whom these tumors were treated, with a 23% mortality rate within the first 2 months after surgery. Three periods in Cushing's CP surgical career can be differentiated: an early period (1901–1917, 39 patients) characterized by his use of the transsphenoidal approach and limited cyst drainage procedures, an intermediate period (1919–1925, 42 patients) in which the subfrontal approach was the standard procedure and maximal removal was attempted, and a late period (1926–1932, 43 patients) characterized by the use of air ventriculography for topographical diagnosis and limited resections via a transventricular approach. Among Cushing's CP series were 92 cases that were pathologically verified (CP₉₂). In this subcohort, the unilateral subfrontal approach was predominantly used (72% of cases), followed by the transsphenoidal (15%) and frontal transcortical-transventricular (8%) approaches. Drainage of the CP cystic component or partial excision of the solid component was achieved in 61% of the cases, subtotal removal in 23%, and macroscopic total removal in 10%. Satisfactory outcomes were obtained in 55% of the patients in CP₉₂, whereas poor outcomes and/or death related to hypothalamic injury was observed in 28%. Postoperative symptoms related to hypothalamic dysfunction occurred 53% of the time. The subfrontal approach yielded the highest rates of radical removal ($p < 0.001$) and good outcomes ($p = 0.01$). Partial removals were associated with the highest rates of poor outcomes, including death ($p = 0.009$). Cushing's removal of CPs with a primary infundibulo-tuberal topography or showing third ventricle invasion was associated with the highest rates of hypothalamic injury ($p < 0.001$) and the worst outcomes ($p = 0.009$).

CONCLUSIONS Harvey Cushing's techniques and surgical philosophy varied substantially throughout his career. The experience he gained with this large CP series made him aware of the importance of limiting the extent of tumor removal and leaving untouched the tumor portion strongly adhered to the hypothalamus.

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KEYWORDS craniopharyngioma; Harvey Cushing; history of pituitary surgery; hypothalamus; transsphenoidal approach; subfrontal approach

... disheartening from an operative standpoint, for [craniopharyngiomas] represent one of the most baffling surgical problems.

— Harvey Cushing, 1932⁸

Craniopharyngiomas (CPs) probably represented the greatest surgical challenge Harvey Cushing (1869–1939) faced during his career.³ Despite his revolutionary progress on pituitary tumor treatment, reflected in his first

ABBREVIATIONS BTR = Brain Tumor Registry; CP = craniopharyngioma; CP₉₂ = Cushing's subcohort of 92 pathologically verified CPs; CP₁₂₄ = Cushing's entire series of 124 CPs; DTC = decompressive temporal craniectomy; FTV = frontal transcortical-transventricular; IT = infundibulo-tuberal; SubF = subfrontal; TLT = trans-lamina terminalis; TSF = transsphenoidal; 3V = third ventricle; 3VF = 3V floor.

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masterpiece, *The Pituitary Body and Its Disorders*,⁹ his surgical experiences with CPs proved disheartening time and again.^{7,8} Cushing felt bewildered by his unsuccessful attempts at CP removal; at the same time, however, these difficulties fueled his unwavering commitment to the continued development of new surgical strategies to improve the prognosis of these complex tumors.^{2,19,22} His grueling struggle with CPs in a time before the development of modern diagnostic methods and microsurgical techniques decisively contributed to accelerating the progress of neurosurgery.^{1,3,13}

In Part 2 of our systematic review of Cushing's CP series, we present a comprehensive analysis of the surgical strategies employed for CP excision. Our analysis was centered on the way that Cushing's techniques and surgical philosophy evolved throughout his career. We investigated the specific tumor characteristics and surgical variables that influenced patient outcome, as well as the impact that Cushing's growing surgical experience had on his results.

Methods

Database Generation and Case Selection Criteria

We conducted a thorough search and analysis of a microfilmed copy of Cushing's Brain Tumor Registry (BTR), housed at the Manuscripts and Archives department at Sterling Memorial Library, Yale University, New Haven, Connecticut (Harvey Cushing Papers, boxes 89–107, <http://hdl.handle.net/10079/fa/mssa.ms.0160>), in addition to those cases reported in Cushing's monographs.^{4,7–11} We collected the medical charts of all surgically treated patients with intracranial tumors whose diagnosis was compatible with CP, finding a total of 124 cases that had been treated by Cushing throughout his career (CP₁₂₄), which were included in this analysis. From this cohort, we differentiated a subcohort of 92 CPs that Cushing had pathologically verified (CP₉₂). The differentiation of this verified subset of cases is necessary for a precise, more reliable analysis of the correlations between the tumors' pathological features and the surgical and/or prognostic results in Cushing's series.

Diagnostic and Surgical Variables Analyzed

Table 1 summarizes the most important pathological and surgical data for all 124 patients in Cushing's CP series, ordered chronologically. Table 2 features information on the way each surgical and prognostic variable was categorized and the descriptive statistics for every category within CP₉₂.

Degree of Removal

The degree of tumor removal was classified into five categories, according to Cushing's surgical descriptions and/or anatomical evidence from autopsied brain specimens: 1) none, i.e., the procedure was not intended to or failed to approach or excise any tumor tissue; 2) cyst drainage or biopsy, i.e., only cystic content was emptied or a capsule fragment was obtained for diagnosis; 3) partial, i.e., only a small portion of tumor tissue was removed; 4) subtotal, i.e., at least half the tumor bulk was removed;

and 5) gross total, i.e., macroscopic total removal was performed, as stated by Cushing.

Postoperative Outcome Assessment

Postoperative outcome was classified into five categories: 1) excellent, defined as long-term survival with recovery from preoperative visual/neurological deficits and/or high intracranial pressure; 2) good, defined as long-term survival without new permanent neurological, hypothalamic, or neuropsychological deficits; 3) fair, defined as survival with new, permanent but not disabling neurological, hypophyseal, or hypothalamic deficits, including panhypopituitarism, diabetes insipidus, cerebrospinal fistula, or meningitis; 4) poor, defined as incapacitating symptoms of severe hypothalamic derangement, such as consciousness disturbance, insane behavior, amnesia, cachexia, or hyperthermia; and 5) death, occurring within the first 2 months after surgery.

Statistical Analysis

Statistical analyses were performed using SPSS software (IBM SPSS Statistics for Windows, version 24.0, IBM Corp.). Frequencies and descriptive statistics on the categorical variables under study were obtained. Bilateral correlations between pairs of qualitative variables were tested using the asymptotic chi-square test or the Monte Carlo exact test. Significance was assumed at a probability value less than 0.05.

Results

Cushing's CP Series: Surgical Procedures Employed and Their Complications

Table 1 lists the main surgical procedure employed, the date it was performed, the degree of tumor removal achieved, the occurrence of intraoperative complications, and the postoperative outcome for all patients in CP₁₂₄. Cushing performed a total of 198 surgical procedures. Most patients underwent only one (77 [62%]) or two (29 [23%]) procedures, but six operations, the maximum number, were performed in each of two patients (cases 96 and 97). The types and rates of the different surgical procedures employed in CP₉₂ are shown in Table 2. Within this subcohort, the largest number of cases was operated on in 1921–1929 (55 patients). The surgical approach predominantly utilized was the subfrontal (SubF; 66 patients [72%]), sometimes involving splitting of the optic chiasm or conducting a trans-lamina terminalis (TLT) exploration. In many cases (56 [61%]), drainage of the CP cystic components or only partial removal of its solid portion was achieved. Gross macroscopic removal of the lesion was accomplished in only 10% of patients.

Serious postoperative complications were present in approximately half of the patients in CP₉₂ (47 [51%]). Among the complications present, severe hypothalamic disturbances (malignant hyperthermia, impairment of consciousness, severe electrolyte imbalances), the consequence of traumatic or ischemic injury incurred by the hypothalamus during surgery, were predominant in 17 patients (18%). Additionally, 11 patients postoperatively presented with progressive symptoms of hypothalamic failure, including

TABLE 1. Harvey Cushing's surgically treated CP series: summary of surgical data and patient outcomes

Case No.*	Patient Initials, Yr of Presentation (surgical ID)	Age (yrs), Sex	No. of Proc	Date of Main Proc	Surgical Approach	Degree of Removal	Size (cm)/Hydro	Tumor Adherence	Intraop Complications	Postop Outcome/FU
1	M.D., 1901 (13054)	16, F	3	3-17-1902	Suboccipital	None	4/yes	Tight 3VF	Failed surgery	Death/6 wks
2	A.B.W., 1908 (22665)	56, F	1	7-17-1908	Rt DTC	None	NA/no	NA	None	No Impr/3 yrs
3	Unknown, 1909 (NA)	36, F	1	1909	Rt SubT	None	NA/yes	NA	HICP	No Impr/NA
4	L.T., 1910 (25715)	15, F	1	4-21-1910	TSF (SDC)	None	NA/no	NA	Failed surgery	Fair/1 yr
5	E.D., 1910 (26920)	18, F	1	11-26-1910	Rt DTC	None	NA/yes	NA	None	Death/2 mos (Re)
6	D.M.B., 1911 (28747)	31, M	1	11-21-1911	TSF (SDC)	None	2.5/no	Ses 3VF	Meningitis	Death/12 days
7	W.B.T., 1911 (28818)	48, M	3	12-15-1911	TSF	None	3.5/no	Repl	CSF leak	Death/4 mos (Re)
8	I.B.A., 1911 (29150)	33, M	1	2-7-1912	TSF (SDC)	None	8/yes	Tight All	None	Death/1 wk
9	J.C.A., 1913 (18911)	20, M	4	1-10-1912	TSF	Cyst drain	5/no	Tight sella	None	Good/11 yrs (Re)
10	A.L.R., 1913 (41)	25, F	3	4-1-1913	TSF	None	5/yes	NA	Failed surgery	Fair/1.5 yrs (Re)
11	K.L., 1913 (663)	11, F	2	12-12-1913	Rt SubF & OS	Biopsy	5/yes	Tight 3VF	Intraop bleeding	Fair/10 yrs (Re)
12	O.A.F., 1913 (13-178)	20, M	2	2-13-1913	Rt SubT	None	8/yes	Loose	CSF leak	Fair/8 mos
13	M.N.M., 1913 (75)	58, F	1	4-25-1913	Rt DTC	None	NA/no	NA	None	No Impr/NA
14	J.C.N., 1913 (22-A)	51, F	1	3-6-1913	Rt DTC	None	NA/no	NA	None	Good/15 yrs
15	H.W.F., 1913 (164)	12, M	1	6-9-1913	Rt DTC	None	NA/yes	NA	None	Fair/4 mos
16	A.F.B., 1913 (209)	28, F	1	7-13-1913	Lt DTC	None	NA/no	NA	None	Good/1.5 yrs
17	D.A., 1913 (235)	14, F	3	11-21-1913	Rt SubF	Gross total	7/yes	Ring 3VF	Hypo injury	Death/3 days
18	L.E.M., 1913 (303)	12, M	1	8-22-1913	Rt DTC	None	NA/yes	NA	None	Fair/8 mos (death)
19	E.S., 1913 (1009)	19, F	2	3-24-1914	Rt SubF	None	NA/yes	NA	None	Fair/1 yr
20	B.A., 1913 (538)	51, F	2	11-4-1913	TSF	Biopsy	5/yes	Tight sella	None	Good/3 yrs (death)
21	A.D.S., 1914 (1036)	41, F	4	3-17-1914	Rt SubF	Partial	3.5/yes	Circ 3VF	Hypo injury	Poor/1 mo (death)
22	S.D., 1914 (1033)	30, F	1	3-27-1914	Rt SubF	Cyst drain	4/no	Tight sella	None	Good/16 yrs
23	H.B., 1914 (1291)	19, F	1	5-21-1914	TSF	None	NA/yes	NA	None	Fair/1.5 yrs (death)
24	E.M.S., 1914 (1440)	49, F	1	7-6-1914	Rt DTC	None	NA/yes	NA	None	Good/4 yrs
25	O.M.C., 1914 (1583)	23, F	2	8-8-1914	Lt DTC	None	NA/yes	NA	None	Good/6 yrs (death)
26	L.J.B., 1914 (1629)	27, F	1	8-22-1914	Rt SubF	Cyst drain	NA/yes	NA	Eye protrusion	Good/2 yrs (Re)
27	B.S.L., 1914 (2114)	40, F	1	11-27-1914	TSF	Partial	4/no	Tight sella	None	Good/3 yrs (death)
28	D.C., 1914 (2186)	48, M	1	12-12-1914	TSF	Cyst drain	3/no	NA	None	Good/4 yrs
29	A.L.B., 1914 (2153)	11, F	1	12-15-1914	Rt SubF	Cyst drain	5/yes	Tight 3VF	Eye removed	Fair/6 mos (death)
30	C.K., 1914 (2268)	21, M	1	1-16-1915	Rt DTC	None	NA/yes	NA	None	Good/1 yr (death)
31	H.J.B., 1915 (2323)	15, M	2	1-28-1915	Lt SubF	None	NA/yes	NA	Postop DI	Fair/2 yrs (death)
32	T.L.D., 1915 (3185)	20, M	1	7-21-1915	TSF	Partial	5/yes	NA	None	Good/6 mos (death)
33	H.B., 1915 (3572)	30, M	1	9-28-1915	TSF	Cyst drain	4/yes	Tight sella	None	Good/NA
34	Unknown, 1915 (3883)	30, F	2	12-7-1915	TSF	Partial	6/yes	Tight sella	Meningitis	Poor/3 mos (death)
35	M.C.L., 1916 (4306)	23, F	1	3-4-1916	Lt SubT DTC	None	NA/yes	NA	None	Fair/6 mos (death)
36	M.F.W., 1916 (4487)	31, F	1	4-4-1916	Rt SubF	Partial	4/no	NA	None	Good/6 yrs
37	E.C., 1916 (5617)	8, F	0	—	—	None	NA/yes	NA	Hypo injury	Poor/2 mos (death)
38	M.H.D., 1916 (5839)	20, F	1	12-16-1916	TSF	Cyst drain	5/yes	Tight sella	None	Good/2 yrs
39	L.S., 1917 (6615)	16, F	1	4-18-1917	Rt SubF	Cyst drain	5/yes	NA	None	Fair/3 yrs
40	R.I.R., 1919 (11152)	13, M	1	9-12-1919	Rt SubF	Gross total	4/no	Tight Chi	Hypo injury	Good/12 yrs
41	L.W., 1919 (10067)	15, F	3	5-8-1919	Rt SubF TLT	Subtotal	6/yes	Tight 3VF	None	Good/15 yrs
42	J.P., 1919 (10563)	14, M	4	8-12-1922	Rt SubF TLT	Cyst drain	5/yes	Circ 3VF	Hypo injury	Poor/3 wks (death)
43	F.E., 1919 (10779)	58, F	2	7-18-1919	Rt SubF	Biopsy	4/no	Tight 3VF	Failed surgery	Fair/2 yrs (death)
44	W.C.C., 1919 (11306)	34, M	1	10-23-1919	Rt SubF	Partial	4/no	Tight 3VF	None	Good/7 yrs
45	J.A.P., 1919 (11541)	17, M	1	12-26-1919	Rt SubF	Subtotal	4/no	Tight sella	None	Fair/20 mos (death)
46	J.A.L., 1920 (11764)	30, F	1	1-31-1920	Rt SubF	Cyst drain	5/yes	NA	None	Good/2 yrs (Re)
47	C.L.A., 1920 (12292)	35, F	1	5-9-1920	Rt SubF	Gross total	3/yes	Tight 3VF	None	Good/2 yrs (death)

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Case No.*	Patient Initials, Yr of Presentation (surgical ID)	Age (yrs), Sex	No. of Proc	Date of Main Proc	Surgical Approach	Degree of Removal	Size (cm)/Hydro	Tumor Adherence	Intraop Complications	Postop Outcome/FU
48	M.M.R., 1920 (12502)	18, F	1	6-4-1920	TSF	Cyst drain	3/no	Tight sella	None	Fair/6 yrs
49	J.J.C., 1920 (13110)	12, M	1	9-15-1920	Rt SubF	Cyst drain	5/yes	NA	None	Good/1.5 yrs
50	S.S.N., 1920 (13453)	33, M	1	11-6-1920	TSF	Cyst drain	5/yes	NA	None	Good/14 yrs
51	B.B., 1920 (13553)	25, F	2	12-28-1920	TSF	Subtotal	4/yes	Tight sella	None	Good/6 mos (Re)
52	F.S.D., 1921 (35075)	34, M	3	2-28-1921	Rt SubF	Subtotal	6/yes	Tight 3V	Intraop bleeding	Good/8 yrs (death)
53	H.M.S., 1921 (14011)	11, M	1	2-18-1921	TSF	Partial	5/yes	Tight sella	CSF leak, meningitis	Poor/10 days (death)
54	T.D.L., 1921 (14327)	45, F	1	3-26-1921	Rt SubF	Subtotal	8/yes	Tight 3VF	Hypo injury	Poor/10 days (death)
55	E.P.W., 1921 (14817)	31, F	1	7-15-1921	Rt SubF	Subtotal	3/no	Tight 3VF	None	Good/1.5 yrs (death)
56	M.H.T., 1921 (14996)	57, F	1	8-13-1921	Rt SubF	Subtotal	3/no	Tight Chi	Intraop bleeding	Fair/9 yrs
57	D.E.H., 1921 (17015)	6, F	1	7-26-1922	Rt SubF	Partial	5/yes	Tight 3VF	Hypo injury	Death/3 days
58	J.L.K., 1922 (16147)	15, M	2	3-6-1922	Rt SubF	Subtotal	10/yes	Tight 3VF	Hypo injury	Fair/6 mos (death)
59	G.H.A., 1922 (16889)	21, M	4	7-11-1922	Rt SubF	Partial	10/yes	Tight All	Hypo injury	Death/6 days
60	C.B.H., 1922 (17148)	23, M	1	8-24-1922	Rt SubF	Partial	5/yes	Tight 3VF	None	Good/4 yrs
61	C.B.M., 1922 (17444)	21, M	2	10-28-1922	Rt SubF	None	5/yes	NA	CP not found	Good/2 yrs (death)
62	M.E.K., 1922 (17650)	10, F	2	8-24-1922	Rt SubF	Gross total	4/yes	Tight sella	Postop DI	Good/6 yrs
63	B.A., 1922 (17754)	40, M	2	11-27-1922	Lt SubF	Subtotal	8/yes	Loose	CSF leak	Fair/3 yrs
64	J.A.D., 1922 (17844)	12, M	2	12-11-1922	Rt SubF	Subtotal	3/no	Tight Chi	Breath arrest	Good/11 yrs
65	A.V.F., 1922 (17876)	13, F	1	12-11-1922	Rt SubF	Partial	8/yes	Tight All	Hypo injury	Poor/2 mos (death)
66	P.S., 1922 (19274)	15, M	4	8-4-1923	Rt FTV	Subtotal	8/yes	Ring 3VF	Hypo injury	Death after 1 day
67	W.C.C., 1923 (18658)	25, M	1	5-2-1923	Rt SubF	Partial	3.5/no	Tight 3VF	Intraop bleeding	Good/10 yrs
68	H.V.M., 1923 (18686)	5, M	1	4-30-1923	Rt SubF	Subtotal	3.5/no	Tight sella	Stalk severed	Good/50 yrs
69	J.R., 1923 (18815)	19, F	1	5-19-1923	Rt SubF	Cyst drain	5/no	Tight sella	None	Good/6 yrs
70	F.W.V., 1923 (18827)	43, M	1	6-16-1923	Lt SubF TLT	Partial	2.5/yes	Loose 3V	Postop DI	Good/8 yrs
71	L.M.K., 1923 (20045)	57, F	1	11-22-1923	TSF	Cyst drain	2/no	NA	None	Good/5.5 yrs
72	M.P., 1923 (20411)	18, F	1	1-7-1924	Rt SubF TLT	Partial	4/yes	NA	None	Good/7 yrs (death)
73	K.K.S., 1924 (22493)	19, M	2	10-30-1924	Rt SubF	Gross total	4/yes	Tight 3VF	Intraop bleeding	Good/8 mos (death)
74	T.H.C., 1924 (20737)	5, M	1	2-19-1924	Rt vent puncture	Cyst drain	4/yes	Tight 3V	None	Poor/1 mo (death)
75	A.M., 1924 (20814)	20, F	2	1-20-1925	Transcallosal	Gross total	5/yes	Tight 3V	Hypo injury	Death after 1 day
76	A.G.S., 1924 (22004)	38, M	0	—	—	None	4/yes	Tight 3VF	None	Death after AirV
77	J.C., 1925 (22999)	10, M	2	1-27-1925	Rt SubF	Subtotal	5/yes	Tight 3V	None	Good/10 yrs
78	L.G.B., 1925 (24292)	51, M	2	7-13-1925	Rt SubF	Partial	2/yes	Pedicle 3V	Hypo injury	Death after 1 wk
79	M.T.S., 1925 (31011)	62, F	1	9-29-1925	Rt SubF	Gross total	3.5/no	Tight Chi	Hypo injury	Poor/1 mo (death)
80	L.T., 1925 (28813)	3, F	1	11-17-1925	Rt SubF	Gross total	4/yes	Loose 3VF	None	Good/1 yr (death)
81	H.F.M., 1925 (25383)	26, M	1	12-25-1925	TSF	Partial	4/yes	Tight sella	None	Good/6 wks (death)
82	M.J.R., 1926 (28247)	6, F	4	1-7-1926	Rt SubF TLT	Cyst drain	4/yes	Circ 3VF	Postop DI	Good/2 yrs (death)
83	H.L.R., 1926 (25714)	12, M	1	2-16-1926	Rt SubF	Subtotal	4.5/yes	Tight Chi	Postop DI	Good/6 yrs
84	H.W., 1926 (25886)	17, M	2	3-26-1926	SubF Chi split	Subtotal	4.5/no	Tight 3VF	Heart arrest	Good/3 yrs
85	E.H., 1926 (27320)	8, M	0	—	—	None	4.5/yes	Tight 3VF	—	Fair/1.5 yrs
86	A.C.K., 1926 (26734)	25, M	1	3-20-1930	Rt SubF	Gross total	4/yes	Tight stalk	None	Good/3 yrs
87	J.J.S., 1926 (26200)	10, M	1	5-5-1926	Rt SubF	Partial	5/no	Tight Chi	Heart arrest	Good/5 yrs
88	A.F.M., 1926 (26287)	23, M	1	5-20-1926	Rt SubF	Partial	6/yes	NA	None	Fair/2 yrs
89	H.M.S., 1926 (26470)	62, F	1	6-19-1926	Rt SubF	Partial	3/no	NA	Low BP	Good/2 yrs (death)
90	L.V., 1926 (26753)	36, M	1	7-19-1926	Rt SubF	Subtotal	4/yes	Tight 3VF	Hypo injury	Death after 3 days
91	F.W., 1926 (27041)	27, M	1	8-27-1926	Rt SubF	Partial	3.5/yes	Circ 3VF	Hypo injury	Fair/8 mos (death)
92	J.A.B., 1926 (27398)	30, F	1	11-27-1926	Rt SubF	Partial	7/no	Tight All	Hypo injury	Poor/12 days (death)

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Case No.*	Patient Initials, Yr of Presentation (surgical ID)	Age (yrs), Sex	No. of Proc	Date of Main Proc	Surgical Approach	Degree of Removal	Size (cm)/Hydro	Tumor Adherence	Intraop Complications	Postop Outcome/FU
93	A.Z., 1927 (33831)	32, M	2	12-21-1928	Rt SubF TLT	Partial	3/no	Tight 3VF	Hypo injury	Fair/4 mos (death)
94	M.E.D., 1927 (28383)	8, F	3	3-22-1927	Lt SubF TLT	Partial	3/yes	Tight 3VF	Intraop bleeding	Death after 1 day
95	H.L., 1927 (30302)	13, M	2	12-27-1927	Rt SubF TLT	Partial	6/yes	Tight 3VF	Mental disturbance	Fair/7 yrs
96	E.J., 1927 (29467)	6, M	6	10-26-1927	Lt SubF	Partial	10/yes	Tight All	None	Good/1.5 yrs (death)
97	R.L.J., 1927 (31011)	6, F	6	5-1-1928	Rt SubF	Subtotal	8/yes	Tight 3VF	Hypo injury	Good/3 yrs (death)
98	J.L.B., 1927 (32940)	6, M	3	12-5-1927	Rt SubF	Cyst drain	4.5/yes	NA	Somnolence	Good/3 yrs (death)
99	H.O.C., 1927 (32718)	24, F	2	12-22-1927	Rt SubF	None	3/yes	NA	None	Good/3 yrs
100	E.I.G., 1928 (31094)	20, F	1	4-16-1928	SubF Chi split	Partial	4/no	Tight sella	Intraop pain	Good/3 yrs
101	N.C.S., 1928 (31467)	10, F	1	7-25-1928	Rt SubF	Partial	4/yes	Tight 3VF	None	Good/3 yrs (death)
102	N.F.S., 1928 (31979)	50, F	1	8-16-1928	Rt SubF	Partial	5/yes	Tight Chi	None	Fair/1 yr (death)
103	M.V.O., 1928 (32294)	10, F	1	10-17-1928	Puncture cyst	None	6/yes	NA	—	Fair/1.5 yrs
104	A.B., 1928 (32298)	22, F	1	10-17-1928	Rt SubF	Subtotal	10/yes	Tight 3VF	None	Good/6 mos (death)
105	K.K.S., 1928 (32358)	46, M	1	11-5-1928	SubF Chi split	Partial	4/no	Repl	Intraop bleeding	Poor/1 yr (death)
106	L.R.C., 1928 (32590)	40, F	1	11-19-1928	Rt SubF	Partial	3/no	Tight Chi	Intraop vomiting	Poor/1 mo (death)
107	S.B., 1928 (32718)	30, M	2	12-16-1928	TSF	Cyst drain	4/no	Tight sella	Wound infection	Good/3 yrs
108	M.A.L., 1928 (32851)	9, M	1	12-29-1928	Rt SubF	Partial	5/yes	Tight 3VF	None	Good/1 yr
109	M.V.M., 1929 (33044)	19, F	1	1-15-1929	Rt SubF	Cyst drain	3/yes	Tight 3VF	None	Good/2 mos (death)
110	B.L.E., 1929 (34286)	15, F	2	6-25-1929	Rt SubF	Subtotal	3/no	Tight gland	None	Good/2 yrs (death)
111	M.H., 1929 (35047)	43, F	2	11-1-1929	Rt DTC	None	3/yes	Tight 3VF	CP not found	Poor/17 days (death)
112	N.A.K., 1930 (35581)	16, M	2	5-29-1930	Rt SubF	Partial	3.5/no	Tight sella	None	Good/4 yrs
113	E.M.L., 1930 (35994)	27, F	1	3-18-1930	Rt SubF	Partial	5/yes	Tight 3VF	Hypo injury	Death after 1 day
114	E.J., 1930 (36672)	22, F	0	—	—	None	3/yes	Tight 3VF	Meningitis	Death after 1 wk
115	M.E.P., 1930 (35969)	29, M	2	3-31-1931	Rt FTV	Partial	3/yes	Tight 3VF	CSF leak, meningitis	Fair/10 mos (death)
116	N.E.C., 1931 (38528)	23, F	2	5-7-1931	Rt FTV	Partial	3/yes	Tight 3VF	Hypo injury	Death after 10 days
117	S.G.W., 1931 (38556)	6, M	1	10-4-1931	Rt FTV	Cyst drain	8/yes	Tight 3V	Hypo injury	Death after 3 days
118	C.E.O., 1931 (39201)	70, F	1	7-22-1931	Rt SubF	Gross total	2.5/no	Loose	None	Good/2 yrs
119	M.B., 1931 (39270)	21, F	3	7-12-1931	Rt FTV	Subtotal	2.5/yes	Tight 3V	CSF leak	Good/2 yrs
120	A.C., 1932 (40686)	51, F	1	3-11-1932	Rt SubF	Subtotal	3/no	Tight Chi	Epidural hematoma	Good/1.5 yrs
121	M.E.T., 1932 (40786)	40, F	1	3-24-1932	Rt SubF	Subtotal	3/no	Tight 3VF	Carotid injury	Good/2 yrs (death)
122	M.S.B., 1932 (40859)	38, M	2	4-13-1932	Rt FTV	Gross total	3/yes	Pedicle 3V	None	Good/2.5 yrs
123	M.J.C., 1932 (41028)	17, F	1	4-29-1932	Suboccipital	Cyst drain	7/yes	NA	Failed diagnosis	Good/1.5 yrs (death)
124	I.M.M., 1932 (41416)	56, F	1	7-1-1932	Rt SubF	Partial	4/no	Tight 3V	Intraop bleeding	Good/2 wks

AirV = air ventriculography; All = CP attachment involves all structures, from the sella to the 3V; BP = blood pressure; Chi = optic chiasm; Chi split = optic chiasm splitting; Circ = circumferential type of attachment; CP = craniopharyngioma; CSF = cerebrospinal fluid; DI = diabetes insipidus; DTC = decompressive temporal craniectomy; FTV = frontal transcortical-transventricular approach; FU = follow-up; HICP = high intracranial pressure; Hydro = presence of hydrocephalus; Hypo = hypothalamus; ID = identification; NA = not available; No Impr = no improvement; OS = optic chiasm splitting; Partial = removal of less than 50% of tumor volume; Pedicle = pedicle-like type of attachment; Proc = surgical procedures performed in each patient; Re = recurrence; Repl = CP replacement of 3VF; Ring = ring-like band of CP attachment to the 3VF; SDC = sellar decompression; Ses = sessile type of attachment; SubF = subfrontal approach; SubT = subtemporal approach; Subtotal = removal of at least 50% of tumor volume; TLT = trans-lamina terminalis approach; TSF = transsphenoidal approach; vent = ventricle; 3V = third ventricle; 3VF = third ventricle floor; — = no surgery performed.

* Case numbers in bold indicate a pathologically verified CP.

poikilothermia, hemodynamic instability, mental deterioration, and Addisonian crises, leading to their deaths in a period of less than 2 months. The postoperative infection rate was exceedingly low, only 6.6% (6 of 91 patients).

Cushing's CP Series: Surgical Results and Patient Outcomes

The overall mortality rate within the first 2 months after surgery was 22.5% (28 patients) in CP₁₂₄, including

TABLE 2. Categorization of surgical and outcome variables analyzed in Cushing's CP₉₂ series

Variable	No. of Cases (%)	No. of Cases w/ Valid Data
Surgical variables		
No. of surgical procedures		92
0	1 (1.1%)	
1	55 (59.7%)	
2	22 (23.9%)	
3	7 (7.6%)	
>3	7 (7.6%)	
Anesthesia methods		91
Ether	61 (66%)	
Local novocaine & ether	11 (12%)	
Local novocaine	14 (15%)	
Morphia & novocaine	5 (5.4%)	
Failed initial procedure*	13 (14%)	92
Ventricle tapping	36 (39%)	92
Surgical approach		92
None	1 (1.1%)	
DTC/cyst puncture	3 (3.3%)	
TSF	14 (15.2%)	
SubF	55 (59.8%)	
SubF & TLT/Chi split	11 (11.9%)	
FTV	7 (7.6%)	
Transcallosal	1 (1.1%)	
Degree of removal		92
None	6 (6.5%)	
Cyst drainage/biopsy	20 (21.7%)	
Partial	36 (39.1%)	
Subtotal	21 (22.8%)	
Gross total	9 (9.8%)	
Outcome variables		
Postop outcome		92
Excellent	15 (16.3%)	
Good	36 (39.1%)	
Fair	15 (16.3%)	
Poor	9 (9.8%)	
Death (in 2 wks)	17 (18.5%)	
Visual outcome		83
w/o change	33 (39.8%)	
Better transitory	20 (24.1%)	
Better long-term	24 (28.9%)	
Worsening	6 (7.2%)	
Postop infection	6 (6.6%)	91
Postop complications		92
Not reported	44 (47.8%)	
Hypothalamic (severe)†	20 (21.7%)	
Psychiatric	7 (7.6%)	
Neurological	5 (5.4%)	
CSF leak/meningitis	5 (5.4%)	
Hemorrhagic	5 (5.4%)	
Postop symptoms of hypothalamic dysfunction	48 (52.7%)	91
Postop radiotherapy	6 (6.5%)	92
CP recurrence/regrowth‡	42 (69%)	89

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TABLE 2. Categorization of surgical and outcome variables analyzed in Cushing's CP₉₂ series

Variable	No. of Cases (%)	No. of Cases w/ Valid Data
Postop interval to death		
<3 mos	23 (25.6%)	90
3 mos–1 yr	13 (14.4%)	
>1 to 5 yrs	15 (16.7%)	
>5 yrs	4 (4.4%)	
Alive at last FU	35 (38.9%)	
FU time		
≤1 mo	16 (17.6%)	91
2–6 mos	12 (13.2%)	
>6 mos–1 yr	7 (7.7%)	
>1 to 3 yrs	28 (30.8%)	
>3 to 5 yrs	7 (7.7%)	
>5 to 10 yrs	13 (14.3%)	
>10 yrs	8 (8.8%)	

* Tumor not exposed or found through the intended approach.

† Includes malignant hyperthermia, poikilothermia, hemodynamic instability, consciousness impairment, and severe psychiatric disturbances.

‡ Rate of tumor recurrence calculated for the subgroup of patients surviving the surgical procedure for longer than 2 months (n = 61).

one nonoperated patient who died immediately following diagnostic air ventriculography (case 76; Table 1). Most of the remaining surviving patients had excellent or good outcomes (85%), even though the degree of resection was very limited in the large majority. Accordingly, the rate of tumor recurrence was as high as 69% in the whole series. Visual deficits improved permanently in 29% and transitorily in 24% of the surgically treated patients in CP₉₂. Diabetes insipidus improved in only 9 patients (26.5%), whereas endocrine disturbances remained unchanged after surgery in virtually all cases.

Adequate monitoring of the neuropsychological and psychiatric disturbances, which had hampered quality of life in 57 (45%) of 124 patients before surgery, was only available for 34 patients after surgery, as most of the other patients had died within the first few postoperative days or weeks. In almost half of the survivors (16 patients), these emotional and cognitive alterations markedly improved, at least temporarily, to the point of allowing patients to resume their professional and family responsibilities.

Influence of Surgery-Related Variables on Patient Outcome

Fig. 1 and Table 3 show the significant correlations found for the three fundamental surgical variables (type of approach, degree of removal, and patient outcome) in CP₁₂₄. Cushing achieved the highest rate of radical removal using the SubF approach ($p < 0.001$). By contrast, the transsphenoidal (TSF) approach allowed him to accomplish very limited resections, in most cases only drainage of the intrasellar cystic component. Moreover, in Cushing's hands the SubF approach was associated with the best postoperative outcomes ($p = 0.01$), whereas the highest mortality

FIG. 1. Surgical approach, degree of tumor removal, and surgical outcome in CP₁₂₄. **A:** Correlation between type of surgical approach used and degree of tumor removal. Note that the higher rates of subtotal and total CP removals were achieved with the SubF approach (38%), the SubF approach plus the TLT approach or optic chiasm splitting (SubF + TLT/Chi split; 27%), and the frontal transcortical-transventricular or transcallosal approach (FTV/TC; 50%; $p < 0.001$). **B:** Correlation between type of surgical approach and surgical outcome. The highest death rate occurred with the FTV/TC approach (37.5%), whereas more than 60% of cases treated via the SubF and transsphenoidal (TSF) approaches resulted in excellent or good outcomes ($p = 0.010$). **FIG. 1. (continued)**→

FIG. 1. C: Correlation between degree of tumor removal and surgical outcome. Note that the highest rate of excellent and good outcomes occurred following subtotal (69.5%) or gross-total (80%) removals. In contrast, no deaths were reported following cyst drainage or after biopsy of the lesion ($p < 0.001$). punct. = puncture. Figure is available in color online only.

or severe morbidity was observed for the transventricular methods of approach (frontal-transcortical transventricular [FTV] and transcallosal).

The degree of tumor removal was also significantly correlated to postoperative outcome (Fig. 1C). Counterintuitively, the worst outcomes accumulated among patients undergoing only partial tumor removals ($p = 0.009$). This result should be interpreted in the context that the most troublesome tumors in terms of intricate topography, hard consistency, and strong adherence to the hypothalamus were precisely the CPs for which Cushing cautiously decided to limit the extent of removal. Despite this, even the careful surgical maneuvers employed to partially remove these lesions often caused severe injury to the hypothalamus.

Influence of Tumor Topography on Patient Outcome

A strong relationship between tumor topography and patient outcome was observed in CP₉₂ (Table 3). Fig. 2A shows the highest mortality and severe morbidity rates among patients with CPs developed at the infundibulotuberal (IT) region and sellar/suprasellar tumors invading the third ventricle (3V; $p = 0.009$). Both of these CP topographies were associated with the highest rates of hypothalamic injury related to the surgical procedure ($p < 0.001$; Fig. 2B). It is known that these two topographies present with the most extensive and severe adherence to the hypothalamus, with true replacement of the 3V floor (3VF) in the case of IT CPs ($p < 0.001$; Fig. 2C).^{18,20,28}

Discussion

Cushing's CP Treatment: A Career Divided Into Three Periods

Harvey Cushing's strategies and surgical philosophy for CP removal evolved significantly throughout his career. In accordance with the techniques he employed, three consecutive stages can be differentiated: 1) an early period, between 1901 and 1917, characterized by the generalized use of decompressive craniectomies or the TSF approach, the latter leading to failed or insufficient resections; 2) an intermediate period, between 1919 and 1925, in which the use of the SubF craniectomy became standard; and 3) a late period, between 1926 and 1932, in which specific techniques for the removal of intraventricular tumors were increasingly employed, such as optic chiasm splitting, the TLT approach, and the FTV approach. Fig. 3 shows the overall range of variation in the surgical technique employed, degree of tumor removal achieved, rate of hypothalamic injury, and postoperative outcome across the three surgical periods. The most important correlations between these fundamental surgical variables and the periods in which Cushing's procedures were performed are listed in Table 3.

TABLE 3. Bivariate relationships between surgical/pathological variables and patient outcomes analyzed for Cushing's surgically treated CP series, 1901–1932

Variable	p Value	Influence on Patient Outcome
Related to surgical procedure used (CP ₁₂₄)		
Type of approach & degree of removal	<0.001	Highest rate of gross-total removal w/ SubF
Type of approach & postop hypothalamic injury	<0.001	Highest rate of hypothalamic injury w/ approaches in which dissection maneuvers w/in 3V were done (FTV/TC/TLT approaches)
Type of approach & postop outcome	0.01	Highest rates of excellent/good outcomes w/ SubF & SubF + TLT
Type of approach & postop infections	0.01	Highest rate of postop infections w/ TSF
Degree of removal & postop hypothalamic injury	0.001	Highest number of patients w/ hypothalamic injury after partial removal
Degree of removal & postop outcome	0.009	Highest rates of death/severe morbidity after partial removal
Degree of removal & visual outcome	0.002	Highest rates of short-/long-term visual improvement after cyst drainage & partial tumor removal
Related to period surgical procedure performed (CP ₁₂₄)		
Period of surgery & type of surgical approach	<0.001	Highest rate of TSF in initial period (1901–1917); highest rate of SubF + TLT approach in late period (1926–1932)
Period of surgery & degree of removal	<0.001	Highest rate of gross-total removal in intermediate period (1919–1925)
Period of surgery & postop hypothalamic injury	<0.001	Highest rate of hypothalamic injury in intermediate period (1919–1925)
Period of surgery & surgical outcome	0.015	Excellent/good outcome rates increased linearly over 3 surgical periods; best outcomes reported in late period (1926–1932)
Related to clinical symptoms (CP ₉₂)		
Major syndrome & postop outcome	0.007	Highest rate of poor outcomes/deaths in patients w/ IT/hypothalamic syndrome
Related to CP size (CP ₉₂)		
CP size & interval to death	0.033	Highest long-term survival rate w/ tumors smaller than 4 cm
Related to CP topography (CP ₉₂)		
Postop hypothalamic injury	<0.001	Highest rate of hypothalamic injury in IT & secondary 3V CPs
Postop outcome	0.009	Highest rates of poor outcomes/deaths after removing IT & secondary 3V CPs

FTV = frontal-transcortical transventricular; IT = infundibulo-tuberal; secondary 3V = sellar/suprasellar–secondary intraventricular; SubF = subfrontal; TC = transcallosal; TLT = trans-lamina terminalis.

Cushing's growing awareness about the close relationship between CPs and vital brain structures such as the hypothalamus forced him to abandon the use of the TSF approach as unviable and instead employ the SubF approach as a general rule for CP treatment (Fig. 3A).² Interestingly, once the SubF approach proved useful for achieving radical resections, Cushing reluctantly had to accept the harsh reality that radical removals were associated with much higher rates of severe hypothalamic injury ($p < 0.001$) and poor outcomes ($p = 0.015$). Consequently, his philosophy regarding the optimal degree of resection markedly changed from that in his intermediate period, in which numerous radical resections accumulated, to the late period, characterized by less aggressive procedures associated with much better outcomes (Fig. 3B–D and Table 3).

Cushing's Tentative Initial Methods of CP Removal, 1901–1917

Cushing's promising initial results with CPs were linked to the use of decompressive temporal craniectomy (DTC). By 1905, he had already proved this method to be safe and effective for alleviating, at least temporarily, the symptoms of high intracranial pressure associated with large brain tumors.⁵ His uncertainty about the pathological nature, expected course, and accurate location of CPs

led him to choose DTC in many of the patients he treated between 1901 and 1916.^{7,9,19,22} He performed 15 such procedures in 12 patients, the last one in 1916 (case 35). His DTC technique involved opening the dura mater and closing the temporal muscle over the removed bone flap to prevent brain herniations. He soon acknowledged that this procedure failed to control tumor growth, although, surprisingly, it prolonged survival up to many years in some patients (e.g., cases 14 and 24; Table 1), an effect probably linked to limiting the high intracranial pressure. In fact, half of the DTC patients survived for more than 3 years. These tangible outcomes compared favorably with those obtained for other brain tumors, particularly gliomas.²²

Used in conjunction with DTC, Cushing's sublabial-TSF method was shown to be effective for removing soft pituitary strumas (macroadenomas) confined to the sella turcica (Fig. 4A1).^{9,11,15,25} However, this approach proved inadequate to remove most solid-cystic suprasellar tumors. The majority of these lesions had developed primarily at the infundibulum, above the sella, and extended into the 3V.^{19–22,24} Consequently, Cushing had to endure the discouraging experience, after opening the sella turcica floor, of either finding the intact pituitary gland blocking access to the tumor or exposing an irremovable hard mass tightly adhered to the brain undersurface (Fig. 4A2). Gradually, Cushing acknowledged that the TSF approach was im-

FIG. 2. Influence of CP topography on surgical outcome and pattern of tumor adherence in CP₈₂. **A:** Correlation between CP topography and surgical outcome. The highest rate of excellent and good outcomes occurred among sellar/suprasellar (Sellar-SS; 81%) and pseudointraventricular (SS-Pseudo 3V; 75%) CPs, the two topographies sparing the hypothalamus. In contrast, in almost half of the CP cases with an infundibulo-tuberal (IT) topography (primarily developing within the hypothalamus), the patient had a poor outcome or died following surgery ($p = 0.009$). **B:** Correlation between CP topography and hypothalamic damage. Note that signs indicating hypothalamic damage were observed postoperatively in 90% of IT CPs and in 62% of lesions with a secondary intraventricular (Secondary 3V) topography (hypothalamic encroachment from an original sellar/suprasellar position; $p < 0.001$). **C:** Relationship between CP topography and pattern of tumor adherence. Half of the CPs with a strict intraventricular topography (3V-Strict) had a pedicle attachment to the inner lining of the 3V, whereas more than two-thirds of IT CPs either presented with a strong attachment to the 3V walls or had replaced the 3VF during their growth ($p < 0.001$). Figure is available in color online only.

practical for CP removal and soon rejected it, favoring the transcranial approach instead.^{2,22} In most of his 20 TSF procedures, Cushing only achieved drainage of the CP cystic component or removal of just a small solid portion of the lesion. Even so, merely opening the sellar floor allowed noticeable alleviation of patients' headaches and resulted in long-term survival in 55% of his patients, with a low rate of meningitis and/or CSF leakage (25%). After 1921, Cushing practically abandoned the TSF approach, with only three such procedures being subsequently performed (cases 71, 81, and 107).

Cushing's SubF Approach: His Standard Method for CP Removal, 1919–1925

Cushing's preferred CP removal procedure was the right SubF approach (Fig. 4B1). He used it in a total of 74 patients (60%) in his series. It consisted of a typical C-shaped incision in the forehead, followed by a rectangular bone flap opened above the orbit and extradural elevation of the supraorbital dura mater up to the sphenoid's lesser wing, where a dural incision parallel to the wing was performed to provide access to the optic chiasm. This technique allowed early tapping of the ventricle system with a cannula for effective control of high intracranial pressure due to obstructive hydrocephalus (Fig. 4B2 and B3). The SubF unilateral approach, however, had the shortcoming of limiting the surgeon's view of the retrochiasmatic region, providing insufficient room to reach the IT area, where many of the lesions were centered.^{18,20} Obtaining an optimal view of this area was critical to safely deal with the CP-hypothalamus plane of attachment.²⁸

Cushing's first SubF radical resection was performed in 1913, in the patient D.A. (case 17; Table 1). Along with the tumor bulk, Cushing extirpated part of the circle of

Willis and some of the hypothalamic tissue adhered to the CP capsule, causing profuse intraoperative bleeding and irreversible hypothalamic damage, leading to the death of this 14-year-old girl shortly thereafter (see Fig. 5D in Part 1 for a photograph of this tumor specimen). This traumatic experience had a major impact on Cushing, who still recalled it vividly in the chapter summarizing his CP series, written in 1932.⁷ In a dramatic way, Cushing learned that any forceful, blind manipulation of the retrochiasmatic CP portion strongly attached to the hypothalamus would invariably be followed by a comatose status with uncontrollable hyperthermia and the patient's eventual death.⁸ Henceforth, Cushing's greatest concern was avoiding such a terrible prospect.

An easy way to widen access to the retrochiasmatic CP portion was to sever one optic nerve, usually the one presenting the most severe atrophy, because sacrificing an eye that had been blind for a long period could be accepted without demur. Cushing proceeded with cutting one atrophic optic nerve as early as 1913 (case 11; Table 1), although in this case he could not take advantage of the technique because of intraoperative bleeding, which obliged him to halt the procedure. This maneuver would be used three decades later with outstanding success by his former trainee Norman M. Dott (1897–1973) for the removal of intraventricular CPs adhered to the hypothalamus.²⁶ Still, Cushing always felt reluctant to deliberately cause any injury to nervous structures, even in cases in which they had already been irreversibly damaged by tumor. In 1919, he was able to overcome this problem by approaching the intraventricular solid portion of a CP through the lamina terminalis (case 41), a remarkable experience for him as the spherical lesion could be separated from the 3V walls with relatively little effort, allowing the

FIG. 3. Evolution of surgical strategies and results throughout Cushing's career (CP₁₂₄). **A:** Relationship between surgical periods and surgical approach. Note that the use of DTC and the TSF approach progressively declined from the initial to the final period. In contrast, the FTV/TC and SubF+TLT/Chi split were used increasingly in the late period ($p < 0.001$). **B:** Relationship between Cushing's surgical periods and degree of tumor removal. Note that the highest rate of total removal occurred in the intermediate period (1919–1925, 16.7%), whereas the late period of Cushing's career was characterized by the use of less radical partial or subtotal CP removals ($p < 0.001$). **C:** Correlation between Cushing's surgical period and postoperative hypothalamic damage. Note that the lowest rate of postoperative hypothalamic damage occurred in the initial period (13%), whereas the highest one occurred in the second period (63%; $p < 0.001$), characterized by Cushing's attempts at radical dissection of the CP-hypothalamus cleavage plane. **D:** Relationship between surgical periods and surgical outcome. Note that 87.5% of cases in the second period resulted in a poor outcome or postoperative death, whereas 68% of cases in the last period had an excellent or good outcome ($p = 0.015$), a result related to Cushing's awareness of the vital importance of hypothalamus preservation and the use of less aggressive procedures. Figure is available in color online only.

removal of a large tumor portion without hypothalamic sequelae. Thus, Cushing became the first neurosurgeon to employ the TLT approach for CPs growing within the 3V (Fig. 4C1).^{3,22} He used it in combination with the SubF-transbasal exploration of the chiasmatic cistern on a total of eight occasions (Table 1), most cases corresponding to IT CPs and suprasellar tumors invading the 3V (Fig. 4C2). Unfortunately, Cushing achieved only partial extirpations in these topographical variants, which usually presented dense and extensive adhesions to the hypothalamus, and despite the use of the TLT, he continued to observe early postoperative deaths owing to hypothalamic injury (cases 42 and 94).

In an attempt to minimize hypothalamic damage, in 1930 Cushing utilized the chiasm-splitting technique, which proved quite useful in exposing the circumferential attachment plane between the central part of IT CPs and the hypothalamus (Fig. 4D and E).⁴ Cushing was able to employ it with excellent results in two patients (cases 84

and 100). However, this surgical maneuver did not guarantee a satisfactory outcome, as the death of another adult patient occurred following the attempted removal of a solid IT CP adhered to the hypothalamus (case 105; Table 1).⁸ By this time, Cushing was already aware of the vital role that the hypothalamus played in maintaining homeostasis.¹⁴ New surgical strategies for dealing with intraventricular CPs more effectively had to be developed.¹

Cushing's Exploration of New Transventricular Methods for CP Removal, 1926–1932

By the late 1920s, Cushing openly recognized that strong CP adhesions to the hypothalamus represented a critical problem that prevented him from achieving the successful outcomes he expected following extensive CP resections (Figs. 2C, 3C, and 3D). Therefore, he explored new transventricular techniques to deal more directly with the CP-hypothalamic plane of attachment. His first FTV approach to a CP expanding within the 3V was performed

FIG. 4. Cushing's surgical approaches to CPs. **A1:** Sublabial-TSF approach employed by Cushing from 1908 to 1929 for the removal of pituitary tumors and CPs. From Cushing: *JAMA* 63:1515–1525, 1914. Public domain. **A2:** Cushing's sketches of the intraoperative view obtained with the TSF approach in a CP case (H.B., case 23). **FIG. 4.** (continued)→

FIG. 4. Note how the normal pituitary gland, pushed against the sellar floor by most CPs, is exposed at the opening of the sella floor, hindering access to the tumor. This major shortcoming made Cushing favor the SubF over the TSF approach in the 1920s. **B1:** Cushing's SubF approach to CPs. Notice the wide exposure of this suprasellar prechiasmatic cyst between the stretched optic nerves obtained with this approach (W.C.C., case 44). **B2 and B3:** Cushing's drawings of the CP cystic extensions in a pediatric patient (E.J., case 96). The cysts of this giant, multilobulated CP could be outlined and emptied via the SubF approach. **C1:** Subfrontal approach to a retrochiasmatic CP. Note the prefixed, swollen chiasm and the route employed to gain access to the intraventricular tumor, which protruded through the lamina terminalis and remained tightly attached to the optic chiasm and 3V walls. This patient died without regaining consciousness from cardiac complications due to hypothalamic injury (E.M.L., case 113). **C2:** Cushing's drawings of a tumor found at autopsy. Note the primary IT topography of this lesion, whose solid growth was expanding within the hypothalamus and 3V, above an intact pituitary stalk. From Cushing: *Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System*, Charles C. Thomas, 1932. **D:** Subfrontal TLT approach. This retrochiasmatic, cystic CP expanding within the 3V was emptied and partially removed through the opening of the lamina terminalis, in August 1926 (F.W., case 91). **E:** Subfrontal approach and chiasm splitting for CP removal. This method allowed access to the retrochiasmatic 3V portion of CPs hidden behind the optic chiasm (A.Z., case 93). Panels A2–C1 and D–E reproduced from Cushing's BTR. Public domain. Courtesy of the Manuscript and Archives department of the Sterling Memorial Library, Yale University.

in August 1923, in a 15-year-old boy who had undergone three prior transfrontal evacuations of a huge ventricular cyst, with each evacuation followed by quick refilling of the lesion (case 66; Table 1). With this procedure, Cushing was able to remove the cystic capsule of a grossly calcified suprasellar CP invading the 3V, leaving a free communication between the 3V and the basal suprasellar cistern. However, he acknowledged that the surgical maneuvers employed to free this cyst from the 3V must have caused a good deal of trauma to the hypothalamus. Sadly, Cushing's premonition was confirmed when this patient presented with intractable hyperthermia and died shortly afterward.

In 1925, Cushing attempted his first transcallosal approach to a 3V CP in a 20-year-old woman with an atypical clinical picture dominated by psychiatric disturbances (A.M., case 75; Fig. 5A). Cushing had first tried removing this IT mass through the standard right SubF approach but was unable to attain workable access to the tumor, which was hidden behind a prefixed optic chiasm. Hence, in a second procedure performed 10 months later, in January 1925, Cushing desisted from exploring the chiasm region through the same SubF route and instead transected the corpus callosum through the parasagittal frontal cortex, reaching and emptying a huge cyst in the 3V. At the base of the cyst, a calcareous mass attached to the hypothalamus was also partially extirpated with the aid of rongeurs in what Cushing considered a radical tumor removal, as he observed that the 3V cavity was tumor free afterward. Unfortunately, the patient did not regain consciousness and died on the first postoperative day, suffering from uncontrollable malignant hyperthermia. This failure provided Cushing with the valuable lesson of needing to grasp the actual topographical relationships between CPs invading the 3V and the hypothalamus.^{8,21,26}

During his last 2 years as a practicing neurosurgeon, between March 1931 and April 1932, Cushing employed the FTV to remove intraventricular CPs on five occasions. In each case, he confirmed the intraventricular CP topography using air ventriculography. Despite his excellent view of the CP-3V attachment plane, the postoperative outcome remained appalling in three of these five FTV procedures, with two patients dying in the first postoperative days, showing unmistakable signs of hypothalamic injury (Fig. 5B1 and B2). The strong adherence between the CPs' solid, grossly calcified basal portion and the hypo-

thalamus decisively influenced the poor outcome in these cases.^{18,20,23} The same thing still occurs today despite the use of modern microsurgical techniques.^{21,28} Nevertheless, Cushing ended his career with the report of two successful CP extirpations employing the FTV approach (cases 119 and 122; Table 1). In April 1932, Cushing's destiny with CPs came full circle when he was able to remove, without complication, a squamous-papillary CP in the 3V (case 122; Fig. 5C). This was the very same type of CP he had found during the autopsy of his failed TSF approach in 1911 (case 6; Table 1).¹⁹ This challenging, strictly intraventricular CP could be safely removed from the 3V as it only presented a pedicle attachment to the 3VF, in contrast to the wide band of hypothalamic adhesion present in most IT CPs of the adamantinomatous type.²⁸

Continuing Controversy Over CP Treatment: Lessons Learned From Cushing's Series

A century has passed since Cushing paved the way for CP surgery. Despite the tremendous progress made in diagnostic and surgical methodologies, however, the optimal treatment for these challenging lesions remains controversial.^{12,17,30,32} The debate centers around what is the best surgical strategy, either radical tumor resection or limited debulking plus adjuvant therapy.^{29,31,33,34} Cushing went through the same dilemma, as shown by the continuous evolution of his surgical techniques and philosophy throughout his career. This can be clearly observed when comparing the three periods of CP treatment in his career. Cushing was convinced, as the neurosurgical community is now, that gross-total removal offered the best chance for a CP cure. This is the reason he decided to abandon the TSF approach in favor of the SubF approach. Despite accomplishing radical excision in many cases, however, he was forced to endure the ominous consequences of the hypothalamic injury almost inevitably associated with such procedures. The dissection of CP-hypothalamic adhesions without the aid of microscope magnification definitely influenced Cushing's poor results, as did the lack of corticoids, a critical limitation at the time. Still, none of these medical improvements have allowed neurosurgeons to lower overall rates of serious hypothalamic injury to below 10%–20% nowadays. With great clear-sightedness, Cushing sensed that the reason for the unpredictable outcome among CP patients rested on the morphological het-

FIG. 5. Cushing's transventricular methods of approach to CPs expanding within the 3V. **A:** Cushing's sketches of his first transcallosal procedure for the removal of an IT CP, performed on January 20, 1925 (A.M., case 75). **B1:** Midsagittal brain autopsy specimen showing a strictly intraventricular CP (L.G.B., case 78). This patient underwent two surgical procedures employing the SubF approach, which failed to provide a proper view of the intraventricular mass, which was only emptied and partially removed twice. **B2:** Cushing's drawing showing the IT topography of a CP operated on using a SubF TLT approach in March 1927 (M.E.D., case 94). **C:** Cushing's sketches showing an FTV technique, which he employed in April 1932, to successfully remove a papillary CP from the 3V (M.S.B., case 122). All panels reproduced from Cushing's BTR. Public domain. Courtesy of the Manuscript and Archives department of the Sterling Memorial Library, Yale University.

erogeneity displayed by these lesions. By the end of his career, he recognized that the degree of 3V involvement was a crucial aspect to be assessed preoperatively, and he endeavored to achieve diagnostic accuracy and employed the surgical procedures most suitable for safe removal of the intraventricular component of the lesion.

Our retrospective analysis of Cushing's CP series has shown that tumor topography and, more precisely, the specific type of CP-hypothalamic attachment present in each tumor represent fundamental variables in explaining the reasons for a poor prognosis after radical removal in a subset of patients, both in Cushing's time and today. This concept has been supported by modern MRI studies linking patient outcome with the degree of hypothalamic involvement,^{27,29,34} as well as by anatomical and histological studies demonstrating that the subpial, intra-3VF development of CPs is associated with the highest risk of hypothalamic injury.^{30,34} Harvey Cushing was the first surgeon to demonstrate the feasibility of removing intra-3V CPs by employing direct access to the 3V and careful dissection of the CP-hypothalamus attachment plane through either a TLT or a transcallosal approach. Cushing was far ahead of his time, and his concepts have been validated in the

microsurgical era by the excellent results obtained with proper dissection of the CP attachment to the hypothalamus via the aforementioned transcranial approaches or, more recently, the extended TSF endoscopically assisted approach.^{16,30,35}

Conclusions

Analyzing Cushing's CP series provides invaluable insights into these complex tumors. Harvey Cushing was the first neurosurgeon to face some unavoidable intrinsic challenges related to CPs, which were then, as now, the close anatomical relationship and severe adherence between many of these lesions and the hypothalamus. Cushing's awareness of these facts led him to conclude that the TSF approach was impractical for CP treatment. He eventually decided to employ the SubF approach as it permitted the best control of hydrocephalus, as well as access to the hidden retrochiasmatic tumor portions through the lamina terminalis. Late in his career, Cushing explored new avenues to the 3V through the transcortical and transcallosal routes, which allowed appropriate handling of the intra-3V CP portion to avoid catastrophic hypothalamic injury.

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References

- Cohen-Gadol AA, Geryk B, Binder DK, Tubbs RS: Conquering the third ventricular chamber. **J Neurosurg** **111**:590–599, 2009
- Cohen-Gadol AA, Laws ER, Spencer DD, De Salles AAF: The evolution of Harvey Cushing's surgical approach to pituitary tumors from transsphenoidal to transfrontal. **J Neurosurg** **103**:372–377, 2005
- Cohen-Gadol AA, Spencer DD: **The Legacy of Harvey Cushing. Profiles of Patient Care**. New York: Thieme, 2007, pp 1–93
- Cushing H: The chiasmal syndrome of primary optic atrophy and bitemporal field defects in adults with normal sella turcica. **Arch Ophthalmol (Paris)** **3**:505–551, 1930
- Cushing H: The establishment of cerebral hernia as a decompressive measure for inaccessible brain tumors; with the description of intermuscular methods of making the bone defect in temporal and occipital regions. **Surg Gynecol Obstet** **1**:297–314, 1905
- Cushing H: The hypophysis cerebri: clinical aspects of hyperpituitarism and of hypopituitarism. **JAMA** **53**:249–255, 1909
- Cushing H: **Intracranial Tumors. Notes Upon a Series of Two Thousand Verified Cases With Surgical Mortality Percentages Pertaining Thereto**. Springfield, IL: Charles C. Thomas, 1932, pp 93–98
- Cushing H: **Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System**. Springfield, IL: Charles C. Thomas 1932, pp 43–56
- Cushing H: **The Pituitary Body and Its Disorders**. Philadelphia: JB Lippincott, 1912
- Cushing H: Sexual infantilism with optic atrophy in cases of tumor affecting the hypophysis cerebri. **J Nerv Ment Dis** **33**:704–716, 1906
- Cushing H: The Weir Mitchell Lecture. Surgical experiences with pituitary disorders. **JAMA** **63**:1515–1525, 1914
- Dandurand C, Sepehry AA, Asadi Lari MH, Akagami R, Gooderham P: Adult craniopharyngioma: case series, systematic review and meta-analysis. **Neurosurgery** [pub ahead of print], 2017
- Fulton JF: **Harvey Cushing. A Biography**. Springfield, IL: Charles C. Thomas, 1946
- Fulton JF, Bailey P: Tumors in the region of the third ventricle: their diagnosis and relation to pathological sleep. **J Nerv Mental Dis** **69**:1–25, 145–164, 261–277, 1929
- Henderson WR: The pituitary adenomata. A follow-up study of the surgical results in 338 cases (Dr. Harvey Cushing's series). **Br J Surg** **26**:811–921, 1939
- Kassam AB, Gardner PA, Snyderman CH, Carrau RL, Mintz AH, Prevedello DM: Expanded endonasal approach, a fully endoscopic transnasal approach for the resection of midline suprasellar craniopharyngiomas: a new classification based on the infundibulum. **J Neurosurg** **108**:715–728, 2008
- Müller HL, Merchant TE, Puget S, Martinez-Barbera JP: New outlook on the diagnosis, treatment and follow-up of childhood-onset craniopharyngioma. **Nat Rev Endocrinol** **13**:299–312, 2017
- Pascual JM, Carrasco R, Prieto R, Gonzalez-Llanos F, Alvarez F, Roda JM: Craniopharyngioma classification. **J Neurosurg** **109**:1180–1183, 2008
- Pascual JM, Prieto R: Harvey Cushing and pituitary Case Number 3 (Mary D.): the origin of this most baffling problem in neurosurgery. **Neurosurg Focus** **41**(1):E6, 2016
- Pascual JM, Prieto R, Carrasco R: Infundibulo-tuberal or not strictly intraventricular craniopharyngioma: evidence for a major topographical category. **Acta Neurochir (Wien)** **153**:2403–2426, 2011
- Pascual JM, Prieto R, Carrasco R, Barrios L: Displacement of mammillary bodies by craniopharyngiomas involving the third ventricle: surgical-MRI correlation and use in topographical diagnosis. **J Neurosurg** **119**:381–405, 2013
- Pascual JM, Prieto R, Castro-Dufourny I, Carrasco R, Strauss S, Barrios L: Development of intracranial approaches for craniopharyngiomas: an analysis of the first 160 historical procedures. **Neurosurg Focus** **36**(4):E13, 2014
- Pascual JM, Prieto R, Navas M, Carrasco R: Conquest of third ventricle craniopharyngiomas. **J Neurosurg** **112**:1156–1161, 2010
- Pascual JM, Mongardi L, Prieto R, Castro-Dufourny I, Rosdolsky M, Strauss S, et al: Giovanni Verga (1879–1923), author of a pioneering treatise on pituitary surgery: the foundations of this new field in Europe in the early 1900s. **Neurosurg Rev** **40**:559–575, 2017
- Pendleton C, Adams H, Mathioudakis N, Quiñones-Hinojosa A: Sellar door: Harvey Cushing's entry into the pituitary gland, the unabridged Johns Hopkins experience 1896–1912. **World Neurosurg** **79**:394–403, 2013
- Prieto R, Pascual JM: Norman M. Dott, master of hypothalamic craniopharyngioma surgery: the decisive mentoring of Harvey Cushing and Percival Bailey at Peter Bent Brigham Hospital. **J Neurosurg** **127**:927–940, 2017
- Prieto R, Pascual JM, Rosdolsky M, Barrios L: Preoperative assessment of craniopharyngioma adherence: magnetic resonance imaging findings correlated with the severity of tumor attachment to the hypothalamus. **World Neurosurg** **110**:e404–e426, 2018
- Prieto R, Pascual JM, Rosdolsky M, Castro-Dufourny I, Carrasco R, Strauss S, et al: Craniopharyngioma adherence: a comprehensive topographical categorization and outcome-related risk stratification model based on the methodical examination of 500 tumors. **Neurosurg Focus** **41**(6):E13, 2016
- Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N, et al: Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. **J Neurosurg** **106** (1 Suppl):3–12, 2007
- Qi S, Pan J, Lu Y (eds): **Frontiers of Neurosurgery. Craniopharyngiomas—Classification and Surgical Treatment**. Sharjah, UAE: Bentham Science Publishers, 2017
- Sainte-Rose C, Puget S, Wray A, Zerah M, Grill J, Brauner R, et al: Craniopharyngioma: the pendulum of surgical management. **Childs Nerv Syst** **21**:691–695, 2005
- Shi X, Zhou Z, Wu B, Zhang Y, Qian H, Sun Y, et al: Outcome of radical surgical resection for craniopharyngioma with hypothalamic preservation: a single-center retrospective study of 1054 patients. **World Neurosurg** **102**:167–180, 2017

33. Steňo J, Bízík I, Steňo A, Matejčík V: Craniopharyngiomas in children: how radical should the surgeon be? **Childs Nerv Syst** **27**:41–54, 2011
34. Steňo J, Maláček M, Bízík I: Tumor-third ventricular relationships in supradiaphragmatic craniopharyngiomas: correlation of morphological, magnetic resonance imaging, and operative findings. **Neurosurgery** **54**:1051–1060, 2004
35. Yaşargil MG: Craniopharyngioma, in: **Microneurosurgery. Microneurosurgery of CNS Tumors**. New York: Thieme, 1996, Vol IVB, pp 205–223

Disclosures

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Author Contributions

Conception and design: Prieto, Pascual. Acquisition of data: Prieto, Pascual. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: Prieto, Pascual. Reviewed submitted version of manuscript: Prieto, Pascual. Approved the final version of the manuscript on behalf of all authors: Prieto. Statistical analysis: Barrios.

Supplemental Information

Companion Papers

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