Development of intracranial approaches for craniopharyngiomas: an analysis of the first 160 historical procedures

*JOSÉ MARÍA PASCUAL, M.D., Ph.D.,¹ RUTH PRIETO, M.D., Ph.D.,²
INÉS CASTRO-DUFOURNY, M.D.,³ RODRIGO CARRASCO, M.D.,⁴ SEWAN STRAUSS,⁵
AND LAURA BARRIOS, B.S.⁶

¹Department of Neurosurgery, La Princesa University Hospital; ²Department of Neurosurgery, Puerta de Hierro University Hospital; ³Department of Endocrinology, Hospital del Sureste; ⁴Department of Neurosurgery, Ramón y Cajal University Hospital; ⁵Statistics Department, Computing Center, C.S.I.C., Madrid, Spain; and ⁶School of Medicine, Technische Universität, Dresden, Germany

Object. The development of surgical procedures for the removal of craniopharyngiomas (CPs) was greatly influenced by the enormous topographical and morphological heterogeneity displayed by these lesions. In this study the authors reviewed the intracranial approaches designed to treat CPs during the early historical period (1891–1938) with the aim of finding the CP topographical and pathological features that influence patient outcomes.

Methods. The authors conducted a systematic retrospective review of well-described cases of surgically treated CPs in publications from the period 1891–1938. Valuable information regarding the diagnosis of the lesion, type of craniotomy performed, CP topography, and outcome was selected from 418 reports included in medical publications from this period. The type of surgical procedure used, degree of tumor removal, CP position and histological variety, and clinical evidence of postoperative hypothalamic injury were the variables analyzed with the aim of defining their influence on the final patient outcome.

Results. A collection of 160 cases was eligible for analysis. Craniopharyngioma topography was significantly related to the existence of postoperative hypothalamic damage and the degree of tumor removal achieved ($p < 0.001$). The infundibulo-tuberal, or not strictly intraventricular, topography was associated with the highest rate of hypothalamic injury (84%) and impossibility of tumor removal (51%). This topography also showed the worst prognosis ($p = 0.001$). Additional variables correlated with patient outcome were the presence of hypothalamic damage, type of surgical approach used, and degree of tumor removal. Patients having a poor outcome, suffering from permanent coma, or dying after surgery presented with symptoms of hypothalamic injury in 40% of cases ($p < 0.001$). The surgical approach associated with the best outcome was the transsphenoidal (58%), followed by the subfrontal (45%) and the transcallosal (45%). Subtotal resection of the lesion yielded the best postoperative results, with only 17% of patients dying or suffering from a poor outcome, in contrast to the 39% reported for gross-total removal of the lesion ($p = 0.001$).

Conclusions. Two major variables influenced the results of early surgical experience with CPs for the period from 1891 to 1938: 1) the inaccuracy in defining CP topography with the diagnostic methods available at that time; and 2) the ignorance about the risks associated with the dissection of lesions showing tenacious adherence to the hypothalamus. The degree of functional and morphological disturbance of the hypothalamus caused by a CP remains a fundamental variable helping the surgeon to predict the risks associated with the radical excision of the tumor and patient outcome.

(<http://thejns.org/doi/abs/10.3171/2014.2.FOCUS13567>)

KEY WORDS • craniopharyngioma • history pituitary surgery • hypothalamus • pterional approach • third ventricle • transsphenoidal approach

THE history of the development of craniotomies and modern methods to approach the sellar and parasellar areas is invariably linked to the treatment of

craniopharyngiomas (CPs) and the difficulties posed by these lesions. Pioneering surgical approaches and techniques in neurosurgery initially designed with the aim of removing CPs were later used for other pathologies. Craniopharyngiomas remain one of the most challenging intracranial tumors because of the everlasting controversy about the most appropriate therapy for each case. A major reason for this controversy is the enormous variability in

Abbreviations used in this paper: CP = craniopharyngioma; NIH = National Institutes of Health; TSF = transsphenoidal approach; 3D-FIESTA = 3D-fast imaging employing steady-state acquisition.

* Drs. Pascual and Prieto contributed equally to this work.

the topographical location of the tumor, which can affect one to several compartments, from the sella turcica to the third ventricle, as well as its unpredictable degree of adherence. A critical factor influencing patient outcome is the functional impairment and anatomical distortion of the hypothalamus caused by the tumor.

Surgery of the pituitary gland was initially developed to gain access to the sella turcica, with the aim of removing lesions confined to this anatomical osseous compartment. Nevertheless, many of the CPs treated in the early historical period of pituitary surgery were lesions developing primarily at the infundibulo-tuberal area of the third ventricle floor or extending from the sella into the third ventricle. An accurate definition of the CP topographical relationships was impossible at that time given the inadequacy of the available diagnostic methods (radio-graph, ventriculography) for showing the real extension of the tumor. Although patients with large CPs involving the third ventricle usually showed symptoms of hypothalamic derangement, such as increased weight gain, impaired sexual function, abnormal somnolence, unexplained high body temperature, inappropriate emotional responses, and/or defective memory, these disturbances were largely ignored or not linked to the anatomical involvement of the hypothalamus by the lesion. Therefore, initial surgical approaches for CPs were designed with the primary aim of alleviating the high intracranial pressure and visual disturbances associated with the chiasm compression caused by the tumor.

The removal of CP, as compared with macroadenoma, supposed formidable difficulties in the hands of pioneering pituitary surgeons given the CP's hard consistency, multilobulated morphology, and tight adherence to the hypothalamus and surrounding vessels. The different types of transcranial craniotomies and types of transsphenoidal (TSF) approaches used in the first half of the 20th century allowed good excision of the soft upper suprasellar extensions of pituitary macroadenoma. However, the forceful maneuvers necessary to remove CPs tightly adhered to the infundibulo-tuberal area were almost invariably followed by patient death or a prolonged coma state. For this reason, many of these epithelial lesions were erroneously categorized within the group of malignant tumors.

Besides the inadequate methods of illumination, microsurgical instrumentation, and hormone replacement therapies, a major reason for the poor outcomes after the early surgical attempts at CP removal was the absence of a predictive method to categorize the lesion based on its primary location and anatomical distortions of vital structures. This meant that in addition to multiple failed craniotomies, many lesions could not be visualized through a specific approach, as in the case of retrochiasmatic tumors with a large intraventricular extension, or were considered inoperable at that time. Frustrating experiences with the removal of CPs encouraged surgeons to design new methods of approach and surgical techniques to overcome difficulties associated with intricate topographies and tight adhesions of these tumors. Through this process of trial and error, the development of many standard craniotomies currently used in contemporary neurosurgery progressed.

In this study we conducted an extensive retrospective review of the pioneering craniotomies and surgical procedures performed in the first 3 decades of the 20th century for the treatment of CPs. Our analysis focused on the evaluation of CP topographical and pathological features as well as surgical variables having a potential relationship with patient outcome, regardless of the limitations in the diagnostic and therapeutic methods available during that period. We believe that the earliest surgical experiences with CPs provide invaluable lessons to both novice neurosurgeons and current experts in the treatment of these tumors, by showing the avoidable pitfalls related to an inadequate topographical definition of the lesion and surgical strategies leading to hypothalamic injury.

Methods

Database Generation and Case Selection Criteria

We conducted a thorough search of well-detailed cases of surgically treated CPs reported in the scientific literature between the years 1891 and 1938. This survey involved cases presented in both large series and individual reports in official medical journals, as well as in specialized texts and monographs on the field of neurosurgery, published during the last decade of the 19th century and the first half of the 20th century. The initial search comprised all articles shown in the PubMed, MEDLINE, and Scopus databases after entering the keyword "craniopharyngioma." Articles focusing on either the surgical treatment of CPs or the pathological characteristics of this tumor were retrieved. Their reference lists were scrutinized with the aim of selecting older references not included in digital databases. In addition, the IndexCat databases for medical articles published for the historical period in our study were inspected at the National Library of Medicine at the National Institutes of Health (NIH) in Bethesda, Maryland. Articles and monographs of interest selected from our search were retrieved from and reviewed at the following medical libraries: National Library of Medicine, NIH, Bethesda, Maryland; Francis A. Countway Library of Medicine, Harvard School of Medicine, Boston, Massachusetts; Tompkins-McCaw Library of the Health Sciences, Medical College of Virginia, Richmond, Virginia; New York Academy of Medicine Library, New York, New York; Harvey Cushing/John Hay Whitney Medical Library, Yale University, New Haven, Connecticut; Welch Medical Library, Johns Hopkins University, Baltimore, Maryland; The British Library, London, United Kingdom; Complutense Medical School Library, Madrid, Spain; and the medical libraries of La Paz University Hospital, Ramón y Cajal University Hospital, and Gregorio Marañón University Hospital, all in Madrid, Spain.

The database from which the cases of this study were obtained included 418 CPs described or shown in official journals and medical texts published between the years 1890 and 1938. All of these reports provided surgical, neuroradiological, and/or necropsy findings verifying the diagnosis of CP. The criteria for including a case in the cohort of CPs finally analyzed were as follows: 1) The

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diagnosis of CP was confirmed pathologically. 2) For cases in earlier publications, which did not provide histological verification of the lesion, the tumor's macroscopic features corresponded unmistakably to those of CP, that is, a suprasellar-third ventricle multilobulated solid-cystic epithelial tumor with a hard consistency and calcifications filled with a yellowish or brownish chocolate-like fluid containing cholesterol particles. 3) The tumor had been treated surgically, and an at least succinct description of the surgical procedure and operative findings was provided. 4) Information regarding patient outcome was included in the report.

Selection of the Variables Analyzed in the Study

The principal variables considered for each case were as follows: patient sex and age; date the surgical procedures were performed; type of surgical approach used; degree of tumor removal achieved; CP topography, histology, and consistency; postoperative symptoms indicative of hypothalamic injury; final outcome; and duration of follow-up.

Topographical Categorization of CPs Included in Study

Craniopharyngioma location relative to the hypophysis—third ventricle vertical axis was categorized according to the surgical and/or necropsy findings provided in the reports. Five topographical categories of CPs were considered in our analysis: 1) sellar-suprasellar, tumors that occupy both sellar and suprasellar compartments; 2) suprasellar, tumors that occupy only the suprasellar compartment; 3) sellar-suprasellar-third ventricle, tumors that extend from the sellar compartment through the suprasellar cistern to the third ventricle; 4) infundibulo-tuberal, or not strictly intraventricular, tumors that replace the infundibulo-tuberal area of the third ventricle floor and expand at the same time within the third ventricle and the suprasellar cistern (extra-intraventricular tumors); and 5) strictly intraventricular, tumors that occupy only the third ventricle cavity.

Types of Surgical Procedures Performed

Surgical procedures were classified into 6 categories: 1) trepanation or decompressive craniectomy: either exploratory trepanation or any form of decompressive craniectomy; 2) TSF approach: both the superior nasal and the inferior nasal, endonasal, or sublabial routes; 3) subfrontal or subtemporal approach: unilateral or bilateral frontal craniotomy; 4) frontotemporal or pterional approach; 5) transcallosal or frontal transcortical transventricular approach; and 6) other: transparietal, suboccipital, and temporooccipital craniotomies.

Postoperative Hypothalamic Injury and Patient Outcome Assessment

According to the information provided in this case series, the following postoperative symptoms were indicative of hypothalamic injury: emotional and behavioral alterations, memory impairment, body temperature disturbances, diabetes insipidus, autonomic nervous system dysfunction (blood pressure, heart rate, and vasomotor

responses), and consciousness disturbances including abnormal somnolence, lethargy, or permanent coma. Endocrine deficits caused by dysfunction of the different hypothalamus-hypophysis hormone axes were not considered a sign of hypothalamic injury. Patient outcome was classified into 4 categories: 1) good: long-term survival without symptoms of hypothalamic injury; 2) fair: short (days to weeks) or long-term (months to years) survival with symptoms of hypothalamic injury; 3) poor or coma: short-term survival with severe symptoms of hypothalamic injury incompatible with life, including permanent coma; and 4) postoperative death: death occurred within the first 48 hours after surgery.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 21, IBM). Frequencies and descriptive statistics on the various categorical variables under study were obtained. To explore relationships between categorical variables, row $\times$ column frequency tables were constructed. Bilateral correlation between pairs of categorical variables were tested using the asymptotic chi-square test or the Monte Carlo exact test for chi-square in the case of frequency tables containing cells with 0 elements or those in which more than 20% of the cells had fewer than 5 elements. Significance was assumed at a probability value of 0.05.

Results

Epidemiological, Diagnostic, and CP Pathological Features

A collection of 160 CPs surgically treated between 1891 and 1938 was included in this analysis. Table 1 features a summary of data corresponding to the fundamental epidemiological, surgical, and pathological variables selected and analyzed for the 160 CPs.^{1,2,6,7,9–11,13,15–17,19,20,22–25,27,29–32,34–36,40,41,44–52,54–56,64,66,68,69,71,72,74–76,78,82,84,89,92,95,99,100,104,112,115,116,119,123,126,128,129,133–140,142–144} A rather balanced distribution between the sexes was observed, with 55.6% of lesions diagnosed in males and 44.1% in females. Patient ages ranged from 3 to 61 years. The patients were categorized into 4 groups, according to their age: children younger than 10 years old (16), children between 10 and 19 years old (52), young adults between 20 and 39 years old (61), and adults older than 40 years (25; the other 6 patients were described as only “adult” or the sex was unknown). A bimodal age distribution occurred in this patient cohort with two predominant age intervals, one including patients between 10 and 19 years of age and the other including patients between 20 and 40 years old, values similar to those observed in large series of CPs (Fig. 1).

Four major groups of cases could be considered according to the methodology used for tumor diagnosis. In most patients (80.6%) the tumor was diagnosed based on clinical and/or skull radiographic findings. In 24 cases (15%), air ventriculography or iodoventriculography was also used to outline the lesion. In the remaining 7 patients (4.3%) the diagnosis was confirmed at necropsy. To investigate the influence of the different surgical techniques

TABLE 1: Summary of data on early surgical procedures for CPs, 1891–1938*

Case No.	Authors ^(reference) & Year (case no.)	Age (yrs), Sex	Diagnosis	Date of Procedure	Type of Procedure	Degree of Removal	Topography	Pathological Evidence	Outcome & FU
1	Selke ⁴⁷	42, F	clinical-necropsy	1891	exploratory trepanation	none	3V	solid papilloma (A)	postop death
2	Kiliani, 1904	16, M	clinical-necropsy	Dec 12, 1903	FP DC	none	S-SS-TVF	cyst & fluid (A)	postop death
3	Horsley ³⁵ c1	51, F	clinical-necropsy	July 21, 1904	temporal DC	none	TVF-3V	cystic papilloma (A)	seizures/postop death
4	Horsley ³⁵ c2	14, M	clinical + x-ray	June 27, 1907	subtemporal approach	partial	SS-3V	calcified cyst & fluid	CSF leak/death after 18 mos
5	Straussler ¹³⁵	NA	clinical-necropsy	Feb 2, 1907	FT DC	none	NA	hypophyseal duct cyst	good/death after 3 mos
6	von Eiselsberg, 1910 c1	20, M	clinical + x-ray	June 21, 1907	superior nasal TSF	subtotal	S-SS	epithelial cyst & fluid	good/2 yrs
7	von Eiselsberg, 1910 c2	18, F	clinical + x-ray	Dec 18, 1908	superior nasal TSF	partial	S-SS	cyst & chocolate fluid	good/2 yrs
8	Ballance ⁴⁹	35, M	clinical + x-ray	May 9, 1908	transpalate TSF	none	S-SS-3V	malignant sarcoma	carotid laceration/postop death
9	McArthur ¹⁷	11, F	clinical-necropsy	June 8, 1908	FP DC + CSF tapping	none	TVF-3V	adamant CP (A)	postop death at 6 hrs
10	Cushing, 1912 c1	56, F	clinical + x-ray	July 17, 1908	rt temporal DC	partial	SS-IT	probable CP	no improvement/NA
11	Halstead, 1910	39, M	clinical	July 21, 1909	sublabial TSF	subtotal	S-SS	typical CP	good/CSF leak & reop
12	Cushing, 1912 c2	35, M	clinical + x-ray	Oct 12, 1909	superior nasal TSF	partial	S-SS	congenital anlage T	good/death at reop, 1910
13	Pfeiffer, 1910	11, M	clinical-necropsy	Nov 11, 1909	not provided	none	TVF-3V	s-c CP (A)	postop death
14	Mixter & Quackenboss, 1910	27, M	clinical + x-ray	Dec 27, 1909	inferior nasal TSF	subtotal	S-SS	cystic CP	good/CSF leak, 4 mos FU
15	Cushing, 1912 c3	15, F	clinical + x-ray	Apr 21, 1910	sublabial TSF (f)	none	SS-IT	probable CP	good/NA
16	Cushing, 1912 c4	18, F	clinical + x-ray	Nov 26, 1910	rt DTC	none	SS-interpeduncular	probable CP	good/NA
17	Kanavel & Jackson, 1918 c1	18, M	clinical	Feb 21, 1911	inferior nasal TSF	partial	S-SS	probable cystic CP	good/3 yrs
18	Cushing, 1912 c4	adult, M	clinical + x-ray	Nov 21, 1911	sublabial TSF (f)	none	3V	papillary CP (A)	meningitis/death after 13 days
19	Cushing, 1912 c5	adult, NA	clinical + x-ray	Dec 15, 1911	sublabial TSF	cyst drain	SS-interpeduncular	papillary CP (A)	CSF leak/NA
20	Hirsch & Hamlin, 1959 c1	38, F	clinical + x-ray	Sept 15, 1911	endonasal TSF	partial	S-SS-TVF	epithelial cyst & fluid	good/7 yrs
21	Cushing ²⁹ c6	19, M	clinical + x-ray	Jan 4, 19, 1912	1: TSF (f)/2: TSF	partial	S-SS	cystic calcified CP	fair/CSF leak, meningitis
22	Hirsch & Hamlin, 1959 c2	21, F	clinical	Jan 24, 1912	endonasal TSF	subtotal	S-SS	epithelial cyst & fluid	good/25 yrs
23	Frazier, 1913 c1	23, M	clinical + x-ray	July 1912	SF	partial	SS-TVF	pure pituitary cyst	good/NA
24	Hirsch & Hamlin, 1959 c3	46, M	clinical + x-ray	Apr 12, 1913	endonasal TSF	partial	S-SS	solid CP	good/17 yrs
25	Hirsch & Hamlin, 1959 c4	34, F	clinical + x-ray	Nov 28, 1914	endonasal TSF	subtotal	S-SS	epithelial cyst & fluid	good/death at reop (3 mos)
26	Harris & Graham, 1913	38, F	clinical + x-ray	Nov, Jan 1913	2 inferior nasal TSF	partial	IT	probable papillary CP	hypothal injury/death after 1 day

(continued)

TABLE 1: Summary of data on early surgical procedures for CPs, 1891–1938* (continued)

Case No.	Authors ^(reference) & Year (case no.)	Age (yrs), Sex	Diagnosis	Date of Procedure	Type of Procedure	Degree of Removal	Topography	Pathological Evidence	Outcome & FU
27	Husten, 1923 c1	51, F	clinical-necropsy	Sept 8, 1913	superior nasal TSF	partial	S-SS-3V	adamant CP (A)	meningitis/death after 9 days
28	Cushing, 1914 c7	child	clinical + x-ray	1913	1: ST (f)/2: SF	GTR	SS-3V	s-c calcified CP	hypothal injury/death at 2 yrs
29	Cushing, 1914 c8	child	clinical + x-ray	1912–1914	1: ST (f)/2: SF	biopsy	SS-3V	s-c calcified CP	survived reop (6 mos)/NA
30	Cushing, 1914 c9	adult	clinical + x-ray	1912–1914	1: ST (f)/2: SF	partial	SS	cystic CP	survived 3 ops (4 mos)/NA
31	Cushing, 1914 c10	adult	clinical + x-ray	1912–1914	1: ST (f)/2: SF	partial	SS	cystic CP	survived 3 ops (2 mos)/NA
32	Cushing, 1914 c11	adult	clinical + x-ray	1912–1914	SF	partial	SS	cystic CP	survived/NA
33	Kanavel & Jackson, 1918 c2	21, F	clinical	June 27, 1913	inferior nasal TSF	partial	S-SS	probable cystic CP	hyperthermia & postop death
34	Kanavel & Jackson, 1918 c3	18, M	clinical	3 ops, 1914	inferior nasal TSF	partial	S-SS	cystic CP	good, 2 recurrences surgically treated
35	Cope, 1916	21, M	clinical	Feb 1915	SF	partial	SS	cystic CP	good
36	Walton, 1922	14, F	clinical	June 1915	rt SF	partial	S-SS	cystic CP	death after 10 days
37	Heuer, 1920 c1	20, F	clinical + x-ray	May 28, 1914	lt FT	partial	SS-TVF-3V	adamant CP (A)	good/death at reop (3 mos)
38	Cushing ²² c12	30, F	x-ray: large sella	Dec 7, 1915	sublabial TSF	partial	S-SS-temporal	epithelial cyst & fluid	good/death after 3 mos
39	Heuer, 1920 c2	35, M	x-ray: SS calcium	Oct 30, 1915	lt FT	partial	S-SS-TVF	papillary CP (A)	carotid injury/death after 12 days
40	Heuer, 1920 c3	11, F	clinical + x-ray	April 24, 1917	rt FT	GTR	S-SS-TVF	adamant CP (A)	postop death w/ hyperpyrexia
41	Frazier & Alpers, 1934 c2	38, M	x-ray: large sella	Nov 1, 1917	rt SF	GTR	S-SS-3V	papillary CP	hyperthermal/death after 48 hrs
42	Sargent ¹⁰ c1	11, M	x-ray: normal sella	April 3, 1918	suboccipital (f)	none	IT	adamant CP (A)	postop coma/death at 3 wks
43	Frazier & Alpers, 1934 c3	7, M	x-ray: large sella	April 16, 1918	TSF	partial	S-SS	cystic adamant CP	good/reop after 7 yrs
44	Pfeiffer, 1920	17, F	x-ray: eroded sella	Dec 1, 1919	superior nasal TSF	partial	TVF-3V	papillary CP	hypothal injury/death after 2 days
45	Cushing, 1922 c13	15, F	x-ray: SS shadow	April, May 1919	2 SF TLT	GTR	TVF-3V	adamant CP	good/recurrence after 3 yrs/8 yrs
46	Claude & Schœffer, 1921	29, M	clinical	May 6, 1920	rt frontal trepanation	none	TVF-3V	adamant CP (A)	coma/death after 1 day
47	Cushing ⁷ c14	33, M	clinical + x-ray	Nov 6, 1920	sublabial TSF	partial	S-SS-TVF	papillary CP	not provided
48	Vincent, 1931	10, M	x-ray: SS shadow	May 7, 1920	rt FT	subtotal	S-SS-3V	adamant CP	good
49	Sargent ¹⁰ c2	35, F	x-ray: large sella	Feb 28, 1920	rt ST DC (f)	none	S-SS	s-c adamant CP	postop death
50	Sargent ¹⁰ c3	18, F	x-ray: large sella	March 20, 1920	rt FT	partial	S-SS-TVF	calcified CP (A)	postop manic state/death at 2 wks
51	Cushing ⁷ c15	11, M	x-ray: eroded sella	Feb 18, 1921	TSF	partial	S-SS	adamant CP (A)	postop CSF leak/death in days
52	Cushing ⁷ c16	34, M	x-ray: SS shadow	Feb 7, 1921	1: ST (f)/2: SF	subtotal	SS	giant adamant CP	good, visual recovery
53	Frazier & Alpers, 1934 c4	17, M	x-ray: SS shadow	Jan 20, 1921	rt SF	partial	S-SS	s-c adamant CP	good/recurrence & death at 8 yrs
54	Husten, 1923 c2	42, M	clinical	July 27, 1921	bitemporal trepans (f)	none	TVF-3V	papillary CP (A)	postop death
55	Lanman & Smith, 1923	10, F	air-v: 3V defect	July 27, 1921	suboccipital (f)	none	S-SS-TVF	adamant CP (A)	death 1 hr after op

(continued)

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Case No.	Authors ^(reference) & Year (case no.)	Age (yrs), Sex	Diagnosis	Date of Procedure	Type of Procedure	Degree of Removal	Topography	Pathological Evidence	Outcome & FU
56	Sargent ¹⁰ c4	10, M	x-ray: SS shadow	Nov 2, 1921	1: DC/2: SF	partial	S-SS-TVF	s-c adamant CP (A)	coma/death after 24 hrs
57	Frazier & Alpers, 1934 c5	17, M	air-v: 3V defect	Feb 3, 1922	rt temporoccipital (f)	none	TVF-3V	s-c adamant CP	poor, hallucinations/death at 7 wks
58	Cushing ⁶ c17	6, F	x-ray: SS calcium	July 26, 1922	rt SF	partial	SS-TVF-3V	s-c adamant CP	delirium, hyperthermia/death after 3 days
59	Cushing ⁶ c18	14, M	air-v: 3V defect	Aug 12, 1922	1: ST (f)/2: SF TLT	partial	TVF-3V	s-c adamant CP	hypothal injury/death at 3 wks
60	Cushing ⁶ c19	child, F	x-ray: SS shadow	Nov 8, 1922	rt SF	GTR	SS	cystic adamant CP	good/DI & obesity 6 yrs
61	Cushing, 1922 c20	41, F	x-ray: normal sella	1922	ventricular puncture	none	strictly 3V	papillary CP	postop death w/ hyperthermia
62	Orlandi, 1922	27, M	clinical + x-ray	1922	lt DC	none	strictly 3V	s-c papillary CP (A)	death after 2 days
63	Cushing, 1926 c21	23, M	x-ray: SS shadow	August 1922	rt SF	subtotal	S-SS	typical CP	good, resumed growth/4 yrs
64	Sargent ² c5	27, M	x-ray: large sella	Nov 16, 1923	SF (f)	none	IT	cystic CP	death after 2 days
65	Dandy ⁶⁰ c1	35, M	air-v: 3V defect	June 23, 1923	transcallosal	GTR	3V-corpus cal- losum	3V cholesteatoma	postop death
66	Schink, 1925	38, F	x-ray: large sella	Nov 10, 1923	superior nasal TSF	partial	S-SS-3V	epithelial calcified T	fever & death after 6 days
67	Bock, 1924	44, M	x-ray: large sella	1924	TSF	not provided	S-SS	adamant CP (A)	postop death
68	Cushing ⁴⁰ c22	4, M	x-ray: SS shadow	Feb 19, 1924	2 FTV tapping of cyst	cyst drain	SS-3V	s-c adamant CP	death after 48 hrs
69	Cushing ²⁰ c23	20, F	x-ray: SS calcif	Dec 1924	1: SF (f)/2: TC	GTR	TVF-3V	s-c adamant CP	postop coma/death after 24 hrs
70	Bourguet, 1927	17, F	x-ray: eroded sella	Dec 10, 1924	bilat SF	partial	S-SS-3V	cystic CP	good/postop DI, 6 mos
71	Cushing, 1926 c24	60, F	clinical + x-ray	Sept 29, 1925	SF	not provided	not provided	not provided	not provided/NA
72	Cushing ³⁰ c25	26, M	x-ray: large sella	Dec 14, 1925	TSF	partial	S-SS-3V	s-c adamant CP	postop coma/death after 6 wks
73	Frazier & Alpers, 1934 c6	12, M	x-ray: eroded sella	Jan 18, 1924	rt SF	GTR	SS-TVF-3V	cystic adamant CP	poor, blind, lethargy/death at 6 mos
74	Sargent ¹⁰ c6	43, F	x-ray: large sella	July 25, 1924	lt SF	partial	S-SS	s-c CP	good outcome
75	Sargent ²⁵ c7	16, M	x-ray: SS shadow	1925	rt SF	partial	SS	cystic adamant CP	good/death at reop 2 mos
76	Sargent ²⁵ c8	24, F	clinical	1925	rt parietotemporal DC	none	IT	s-c adamant CP (A)	postop coma/death in 1 mo
77	Sargent ^{10,25} c9	60, M	x-ray: large sella	Feb 27, 1925	lt SF	partial	SS-TVF	epithelial cyst & fluid	good/recurrence & death in 1926
78	Sargent ^{10,25} c10	27, F	x-ray: SS shadow	Dec 15, 1925	rt SF	partial	S-SS-TVF	s-c adamant CP	delirium, hyperthermia/death after 12 hrs
79	Frazier & Alpers, 1934 c7	50, F	x-ray: normal sella	Jan 19, 1925	rt SF (f)	none	TVF-3V	papillary CP	death after 2 wks
80	Frazier & Alpers, 1934 c8	15, M	x-ray: SS shadow	Dec 24, 1925	rt SF	partial	SS-TVF-3V	cystic calcified CP	mental disturbances/death at 16 mos
81	Olivecrona ¹³³ c1	6, M	clinical + x-ray	July 8, 1925	rt SF	partial	S-SS	typical CP	poor/recurrence & death at 6 mos
82	Peet, 1927 c1	9, M	x-ray: large sella	Nov 13, 1925	rt FPT	subtotal	S-SS-prechias- matic	s-c adherent adamant CP	good, vision recovery, DI/1 yr

(continued)

TABLE 1: Summary of data on early surgical procedures for CPs, 1891–1938* (continued)

Case No.	Authors(Reference) & Year (case no.)	Age (yrs), Sex	Diagnosis	Date of Procedure	Type of Procedure	Degree of Removal	Topography	Pathological Evidence	Outcome & FU
83	Frazier, 1929 c9	20, M	x-ray: normal sella	March 1926	rt SF	subtotal	SS-TVF-3V	typical CP	good/2 yrs
84	Frazier, 1929 c10	8, F	x-ray: SS shadow	Jan 13, 1926	lt SF	subtotal	S-SS-3V	s-c adamant CP	death 3 wks after op
85	Frazier, 1930 c11	20, M	x-ray: normal sella	May 1, 1926	rt SF	subtotal	IT	cystic CP	good, postop drowsiness/NA
86	Frazier, 1930 c12	33, F	x-ray: normal sella	Dec 20, 1926	rt SF	subtotal	SS-prechias-matic	cystic adamant CP	good, postop drowsiness, DI
87	Grant ⁶⁵	12, F	x-ray: eroded sella	Sept 24, 1926	rt temporal DC	none	SS-TVF-3V	s-c adamant CP	death after 3 mos
88	Peet, 1927 c2	10, F	x-ray: SS shadow	Nov 22, 1926	rt FPT	subtotal	TVF-3V	s-c adamant CP	hypothal injury & death
89	Olivecrona ¹³³ c2	48, M	clinical + x-ray	March 17, 1926	rt SF	partial	not provided	typical CP	good/21 yrs
90	Sargent ¹⁰ c11	21, F	x-ray: normal sella	March 12, 1926	rt SF	partial	S-SS	cystic adamant CP	death 3 days postop
91	Armour ¹⁰	35, F	x-ray: normal sella	June 26, 1926	rt SF (f)	none	TVF-3V	papillary CP	coma & death after 2 mos
92	Hirsch & Hamlin, 1959 c5	14, M	x-ray: calcif sella	Apr 10, 1926	endonasal TSF	partial	S-SS	adamant CP (A)	postop meningitis/death after 12 days
93	Frazier & Alpers, 1934 c13	25, M	air-v: 3V defect	Dec 31, 1926	rt parietal DC	none	SS-TVF-3V	solid adamant CP	death after 12 days
94	Frazier & Alpers, 1934 c14	9, M	x-ray: SS shadow	Apr 27, 1927	rt SF + ON cut	GTR	SS-TVF-3V	adamant CP	hypothal injury & death
95	Peet, 1927 c3	6, F	x-ray: eroded sella	Sept 13, 1927	rt FTP	GTR	S-SS-prechias-matic	s-c adamant CP	good, recovery of vision/NA
96	Olivecrona ¹³³ c3	53, F	clinical + x-ray	Nov 11, 1927	rt SF	partial	not provided	typical CP	poor/recurrence & death at 10 mos
97	Sargent ¹⁰ c12	44, M	x-ray: eroded sella	Feb 9, 1927	rt SF + ON section	partial	tuberal-3V	s-c adamant CP	postop death
98	Sargent ¹⁰ c13	36, M	x-ray: eroded sella	Feb 25, 1927	rt SF (f)	none	tuberal-3V	papillary CP	death after 2 mos
99	Sargent ¹⁰ c14	34, F	x-ray: normal sella	July 1, 1927	rt SF	partial	IT	cystic adamant CP	good/death after 1 yr
100	Sargent ¹⁰ c15	14, M	x-ray: normal sella	Nov 3, 1927	rt SF (f)	none	IT	cystic adamant CP	death postop
101	Sharpe & Sharpe, 1928	12, M	clinical + x-ray	before 1928	rt FP	none	tuberal-3V	cystic adamant CP	shock & postop death
102	Goldstein & Cohn, 1928	15, M	x-ray: normal sella	Jan 22, 1928	DC	none	TVF-3V	cyst adamant CP (A)	postop death
103	Sargent ¹⁰ c16	19, F	x-ray: S shadow	May 11, 1928	rt SF	cyst drain	S-SS	cystic adamant CP	good, obesity/1 yr
104	Sargent ¹⁰ c17	15, M	x-ray: SS shadow	June 29, 1928	rt temporal (f)	none	S-SS	cystic adamant CP	postop death
105	Sargent ¹⁰ c18	52, M	x-ray: large sella	Oct 12, 1928	rt SF	partial	S-SS	solid adamant CP	good/6 mos
106	Sargent ¹⁰ c19	43, M	x-ray: S shadow	Nov 2, 1928	rt SF	partial	S-SS	s-c adamant CP	Korsakoff delirium/recurrence at 5 mos
107	Cushing, 1930 c26	40, F	x-ray: SS shadow	Nov 19, 1928	SF	partial	IT	s-c adherent CP	DI, better vision/death after 2 mos
108	Olivecrona ¹³³ c4	7, F	x-ray: SS shadow	1928	rt SF	partial	SS-TVF-3V	adamant CP (A)	hypothal bleeding & death
109	Frazier & Alpers, 1934 c15	15, M	x-ray: large sella	Nov 9, 1928	rt SF	subtotal	SS-TVF-3V	s-c adamant CP	lethargy, obesity/death at 20 mos

(continued)

TABLE 1: Summary of data on early surgical procedures for CPs, 1891–1938* (continued)

Case No.	Authors ^(reference) & Year (case no.)	Age (yrs), Sex	Diagnosis	Date of Procedure	Type of Procedure	Degree of Removal	Topography	Pathological Evidence	Outcome & FU
110	Hirsch & Hamlin, 1959 c6	46, M	x-ray: normal sella	Dec 15, 1928	1: TSF/2: rt SF (f)	none	tuberal-3V	s-c CP (A)	death 48 hrs after 2nd op
111	Hirsch & Hamlin, 1959 c7	16, M	x-ray: eroded sella	May 30, 1928	endonasal TSF	cyst drain	S-SS	cystic adamant CP	good/8 yrs
112	Hirsch & Hamlin, 1959 c8	19, M	x-ray: normal sella	May 30, 1928	transcranial	cyst drain	SS	adamant CP (A)	postop death
113	Cushing ³⁰ c27	27, F	x-ray: SS shadow	1928	SF	partial	tuberal-3V	s-c CP	coma, hyperthermia/death at 24 hrs
114	Cushing, 1930 c28	46, M	air-v: 3V defect	Nov 5, 1928	SF + split chiasm	subtotal	tuberal-3V	s-c adamant CP (A)	good/recurrence & death at 1 yr
115	Hirsch & Hamlin, 1959 c9	24, M	x-ray: calcified sella	July 16, 1929	2 nasal TSF in 6 mos	partial + lo-cal radium therapy	S-SS	s-c adamant CP	good, vision recovery/6 yrs
116	Olivecrona ¹³³ c5	17, F	clinical + x-ray	July 29, 1929	rt SF	partial	not provided	typical CP	poor/ death after 3-mos recurrence
117	Cushing, 1930 c29	19, F	x-ray: SS shadow	before 1929	SF-TLT	partial	tuberal-3V	cystic adherent CP	DI, better vision/death, high ICP 2 mos
118	Balado & Pardal, 1934 c1	11, M	I-ventr: 3V defect	March 14, 1929	transcallosal (f)	none	TVF-3V	adamant CP (A)	lethargy & death in mos
119	Balado & Pardal, 1934 c2	14, M	I-ventr: 3V defect	Sept 5, 1929	rt SF DC	none	SS	adamant CP (A)	postop death
120	Cushing, 1930 c30	15, F	x-ray: S shadow	May–July 1929	2 SF + split chiasm	GTR	tuberal-3V	cystic CP	good/recurrence & reop
121	Sargent ¹⁰ c20	55, M	x-ray: large sella	Feb 15, 1929	rt SF	partial	S-SS	cystic adamant CP	postop death
122	de Martel, 1930	18, M	x-ray: normal sella	before 1930	2 SF	subtotal	SS	cystic adamant CP	good/NA
123	Frazier & Alpers, 1934 c16	16, M	x-ray: S shadow	June 19, 1930	rt SF	subtotal	S-SS-3V	s-c adamant CP	lethargy/death after 3 mos
124	Olivecrona ¹³³ c6	18, M	clinical + x-ray	June 16, 1930	rt SF	partial	not provided	typical CP	good/23 yrs
125	Olivecrona ¹³³ c7	24, F	clinical + x-ray	Feb 4, 1930	rt SF	partial	not provided	typical CP	poor/recurrence & death at 1 yr
126	Vincent et al., 1931	23, F	x-ray: normal sella	July 25, 1930	rt FT	partial	SS-3V	s-c adamant CP	good/NA
127	Dowman ⁴⁸	30, F	I-ventr: 3V defect	Nov 26, 1930	lt pterional + FTV	cyst drain	3V (A)	papillary CP	hyperthermia, stupor/death at 1 mo
128	Olivecrona ¹³³ c8	19, M	clinical + x-ray	1931	rt SF	partial	not provided	typical CP	good/recurrence after 7 yrs
129	Cardillo, 1933	41, F	x-ray: large sella	April 1931	TSF	partial	S-SS	adamant CP	good/1 yr
130	Cushing ²⁰ c31	23, F	I-ventr: hydroceph	May 7, 1931	rt FTV	GTR	SS-3V	cystic CP	death after 10 days
131	Cushing ²⁰ c32	21, M	I-ventr: 3V defect	July 12, 1931	rt FTV	not provided	tuberal-3V	probable CP	good/NA
132	Frazier & Alpers, 1934 c17	52, M	x-ray: eroded sella	July 29, 1931	rt SF	subtotal	S-SS	cystic mixed CP	good/3 yrs
133	Hirsch & Hamlin, 1959 c10	14, M	x-ray: large sella	July 20, 1931	2 nasal TSF in 6 mos	partial	S	cystic adamant CP	good/25 yrs
134	Fincher, 1934	26, F	I-ventr: 3V defect	March 12, 1932	transparietal transven-tricular	not provided	strictly 3V	papillary	transient hypothal injury

(continued)

Historical surgical procedures for craniopharyngiomas

TABLE 1: Summary of data on early surgical procedures for CPs, 1891–1938* (continued)

Case No.	Authors ^(reference) & Year (case no.)	Age (yrs), Sex	Diagnosis	Date of Procedure	Type of Procedure	Degree of Removal	Topography	Pathological Evidence	Outcome & FU
135	Cushing ²⁰ c33	38, M	I-ventr: 3V defect	April 4, 1932	rt FTV	not provided	SS-3V	adamant CP	good/NA
136	Dandy, 1933 c2	21, F	x-ray: 3V calcif	May 6, 1932	rt FTV	GTR	TVF-3V	adamant CP	good/initial transitory confusion
137	Balado & Parda, 1934 c3	20, M	I-ventr: 3V defect	May 10, 1932	transcallosal	cyst coagul	S-SS-3V	s-c adamant CP	death 17 days after surgery
138	Coleman & Hill, 1934	12, F	clinical + x-ray	Sept 13, 1932	rt pterional	partial	tuberal-chiasmatic	cystic CP (A)	hyperthermia, high ICP, death after 4 mos
139	Masson, 1934	20, F	I-ventr: 3V defect	Oct 15, 1932	rt FTV	total	strictly 3V	papillary cystic CP	transitory irrational behavior
140	Montanini, 1933	19, F	x-ray: eroded sella	1932	rt frontal trepan	none	TVF-3V	adamant CP (A)	coma & postop death
141	Oldberg ¹⁴³ c1	29, M	x-ray: eroded sella	Jan 1933	suboccipital (f)	none	TVF-3V	adamant CP (A)	hyperthermia, coma/death at 3 days
142	Balado & Parda, 1934 c4	34, M	I-ventr: 3V defect	June 1, 1933	transcallosal	cyst drain	TVF-3V	typical adamant (A)	death after 12 hrs
143	Balado & Parda, 1934 c5	7, M	I-ventr: 3V defect	August 10, 1933	transcallosal	cyst drain	SS-3V	cystic CP	good/recurrence & death at 4 mos
144	Dandy ⁴⁰ c3	31, M	x-ray: eroded sella	Jan 1933	rt pterional	subtotal	S-SS-TVF-3V	typical CP	good 3 yrs/death after reop
145	Olivecrona ³³ c9	11, F	clinical + x-ray	Oct 6, 1933	rt SF	partial	not provided	typical CP	poor/death after 3-yr recurrence
146	Puech et al., 1934	22, F	x-ray: eroded sella	Nov 20, 1933	SF	partial	SS-3V	adamant CP	good/1 yr
147	Belloni ⁴⁵	38, F	x-ray: eroded sella	1935	TSF	partial	S-SS	probable adamant CP	good, DI/NA
148	Oldberg ¹⁴³ c2	3, F	x-ray: sellar shadow	Dec 1933	rt frontal tapping	cyst drain	SF-3V	adamant CP (A)	death after 11 days w/ seizures
149	Frazier ¹ c18	39, M	I-ventr: 3V defect	Apr 10, 1934	rt SF (f)	none	strictly 3V	papillary CP (A)	death after 8 days
150	Balado & Parda, 1934 c6	14, F	I-ventr: 3V defect	May 24, 1934	rt ST	partial	S-SS-3V	s-c adamant CP	hyperthermia/death 12 hrs later
151	Dott, 1938 c1	37, M	I-ventr: 3V defect	Jan 1935	1: rt TP DC (f)/2: rt FTV	GTR	TVF-3V	s-c adamant CP	hypothal injury/death at 3 days
152	Salus, 1935	28, F	clinical	Jan 30, 1935	transcallosal tapping	none	TVF-3V	typical CP	death after 4 days
153	Ugelli, 1937 c1	4, M	x-ray: SS calcif	1935	rt & lt pterional	GTR	S-SS-3V	adamant CP (A)	1: good; 2: hyperthermia & death
154	Reymond, 1945	61, F	x-ray: SS calcif	Nov 1936	rt SF	partial	S-SS-3V	adamant CP	good/NA
155	Dott, 1938 c2	24, M	I-ventr: 3V defect	March 1934, 1936	1: rt FTV/2: rt SF + ON cut	subtotal/GTR	TVF-3V	s-c adamant CP	mental disturbance/recurrence 2 yrs
156	Dott, 1938 c3	8, F	x-ray: SS calcif	2 Feb, May 1936	1: rt SF + ON cut/2: rt FTV	subtotal/GTR	TVF-3V	s-c adamant CP	hypothal dysfunction
157	Ugelli, 1937 c2	26, M	x-ray: eroded sella	May 26, 1936	rt pterional	partial	S-SS-3V	adamant CP (A)	hyperthermia & death after 11 days
158	Dott, 1938 c4	37, F	I-ventr: 3V defect	August 1937	rt SF	subtotal	TVF-3V	s-c adamant CP	good, only somnolence
159	Jefferson & Jackson, 1939	51, M	I-ventr: 3V defect	1938	rt FTV	GTR	strictly 3V	papillary CP	good/NA
160	Zeitlin & Oldberg, 1940	21, M	air-v: 3V defect	April 1938	1: SF (f)/2: rt FTV	subtotal	strictly 3V	cystic CP	postop death

* A = autopsy; adamant = adamantinomatous; air-v = air ventriculography; calcif = calcification; coagul = coagulation; DC = decompressive craniectomy; DI = diabetes insipidus; (f) = failed; FP = frontoparietal; FPT = frontoparietotemporal; FTV = frontotemporal; FTV = frontal transventricular approach; FU = follow-up; GTR = gross-total removal; hydroceph = hydrocephalus; hypothal = hypothalamic; I-ventr = icodiventriculography; ICP = intracranial pressure; IT = infundibulo-tuberal; NA = not available; ON = optic nerve; s-c = solid-cystic; SF = subfrontal approach; SS = suprasellar; ST = subtemporal approach; T = tumor; TC = transcallosal approach; TLT = translamina terminalis approach; TP = temporoparietal craniotomy; TVF = third ventricle floor; x-ray = skull x-ray; 1: = first surgical procedure; 2: = second surgical procedure; 3V = third ventricle.

Fig. 1. Histogram of age distribution in 151 cases (age unknown in 9 cases) of CPs surgically treated between 1891 and 1938 for which this information was provided. Frequency indicates the absolute number of patients.

and instruments used during different time periods, we considered 3 distinct intervals: 1) surgeries performed before 1920 (45 cases); 2) surgeries performed in the 1920s (77 cases); and 3) surgeries performed between 1930 and 1938 (38 cases).

Craniopharyngiomas in this cohort were classified into the following categories, according to topographical location: sellar and suprasellar compartments, 22% of tumors (33); exclusively suprasellar location, 10.5% (16); extending from the sella to the third ventricle, 28% (43); infundibulo-tuberal position, 32% (48); and strictly intraventricular, 7% (11). Pathological assignment of the CP to a definite histological type could not be made in 20 of 160 cases. Pathological features characteristic of the adamantinomatous variety were found in 111 cases (79.3%), whereas the pure squamous-papillary variety was reported for 28 cases (20%). Only one case showing mixed features was reported.^{56,117} A pure cystic (50%) or mixed solid-cystic structure (45.5%) was the predominant CP consistency observed in this cohort. Only 4.5% of cases corresponded to pure solid lesions.

Surgical Procedures and Degree of Removal

The CPs included in this series were treated using a wide variety of surgical procedures. Exploratory trepanation or cyst drainage through a bur hole was used in 4 cases. A palliative temporal or hemispheric decompressive craniectomy to alleviate increased intracranial pressure was performed in 12 cases. A TSF approach to the sella turcica through either a superior nasal or inferior endonasal/sublabial route was used in 34 patients. A trans-

cranial subfrontal approach was the most frequently used procedure (68 patients), whereas the pterional approach was performed in 16 cases. Finally, a transventricular approach, either transcallosal or transfrontal, was used in 18 patients (the 8 remaining cases were “other”). All but 5 cases included information regarding the degree of tumor removal. The tumor was not removed in 36 cases. In 78 cases (50%) the tumor was partially removed or biopsied or its fluid content was merely drained. In 22 cases the tumor was subtotally removed, and in the remaining 18 cases (11.6%) gross-total removal was achieved.

Hypothalamic Injury and Patient Outcome

Excluding the 36 patients who died immediately after the surgical procedure, valid information regarding the existence of hypothalamus dysfunction after surgery and/or intraoperative hypothalamic injury was available in 107 cases. The presence of postoperative symptoms related to hypothalamic damage was reported in 58 patients (54%). Postoperative outcome was reported for all but 2 patients. A good outcome was reported in 60 cases (38%). Patients surviving after surgery without disabling complications or severe hypothalamic injury numbered 41 (26%). Fourteen patients remained in a coma or had severe hypothalamic symptoms causing their eventual death. Finally, 36 patients (22.5%) died in the first 48 hours after surgery.

Relationships Between CP Topography or Surgical Procedure and Patient Outcome

Table 2 features a list of bivariate significant relationships between the most important pathological and surgical variables analyzed for the 160 patients. A significant association was observed between patient age and CP histology, with almost all patients younger than 20 years of age showing an adamantinomatous pattern ($p < 0.001$). Among patients 20 years of age or older, two-thirds showed the adamantinomatous pattern and one-third showed the squamous-papillary pattern. Although no significant correlation was found between age and CP topography, note that all 11 tumors with a strictly intraventricular location were found in patients 20 years of age or older.

Variables Related to CP Topography

Craniopharyngioma topography was significantly associated with the occurrence of postoperative hypothalamic damage ($p < 0.001$). Less than 25% of the patients with sellar-suprasellar or suprasellar CPs presented with symptoms of hypothalamic damage after surgery. On the contrary, the rate of hypothalamic injury was the highest among infundibulo-tuberal, or not strictly intraventricular, lesions (84.4%; Fig. 2 upper). Craniopharyngioma topography was also related to the type of surgical approach used ($p < 0.001$). Almost 60% of tumors with a sellar-suprasellar topography were surgically treated via a TSF approach. The subfrontal approach was chosen to remove 75% of the tumors with a purely suprasellar location and approximately 44% of the CPs with either a sellar-suprasellar-third ventricle or an infundibulo-tuberal topography. Finally, 45.5% of the strictly intraventricular cases were surgically treated through a transcallosal or a frontal-transventricular ap-

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TABLE 2: Bivariate relationships between epidemiological, topographical, surgical, and patient outcome categories analyzed for operations for CPs, 1891–1938*

Variable	p Value	Specific Relationships
related to age		
histology	<0.001	highest rate of papillary & mixed tumors in patients w/ age $\geq$ 20 yrs
CP consistency	0.025	highest rate of pure solid tumors in patients w/ age $\geq$ 20 yrs
related to CP topography		
hypothalamic damage	<0.001	highest rate in IT CPs; lowest rate in S-SS & SS CPs
surgical approach	<0.001	highest rate of TSF approach for S-SS CPs; highest rate of TC or transfrontal transventricular approach for strictly intraventricular CPs
degree of tumor removal	<0.001	highest rate of no removal in IT or not strictly intraventricular CPs
histology	<0.001	highest rate of papillary CPs among strictly intraventricular cases
CP consistency	0.009	highest rate of pure solid tumors among strictly intraventricular cases
related to patient outcome		
CP topography	0.001	highest rate of good outcome in S-SS & SS CPs; highest rate of postop death or poor outcome in IT CPs
hypothalamic damage	<0.001	highest rate of good outcome in the absence of hypothalamic damage
surgical approach	0.05	highest rate of good outcome in TSF; highest rate of postop death in trepanation or DC
degree of removal	0.001	highest rate of good outcome in subtotal removal
near significance		
age and CP topography	0.081	all strictly intraventricular CPs in patients w/ age $\geq$ 20 yrs
no significant relationships		
age & outcome	NS	
sex & outcome	NS	
period of time & outcome	NS	
histology & outcome	NS	
consistency & outcome	NS	
age & hypothalamic damage	NS	

* NS = not significant.

proach. The degree of tumor removal also correlated with CP topography ($p < 0.001$). No removal of the tumor was reported for 50% and 60% of infundibulo-tuberal and strictly intraventricular CPs, respectively. A significant correlation between CP topography and histology was found ($p < 0.001$), with 91% of strictly intraventricular cases belonging to the squamous-papillary type. For all other topographical categories, the adamantinomatous pattern was reported in more than 80% of cases. A solid tumor consistency was associated with the strictly intraventricular topography ($p = 0.009$). The pure cystic and solid-cystic consistencies were predominant among the other topographical categories.

Variables Related to Outcome

Craniopharyngioma topography was significantly associated with patient outcome ($p = 0.001$). A good outcome was reported in 64% and 87.5% of the patients with sellar-suprasellar and suprasellar CPs, respectively. On the contrary, only around one-third of the patients with tumors involving the third ventricle had a good outcome (Fig. 2 lower). The worst outcome (postoperative death and irreversible coma [50% of cases]) occurred in the group of infundibulo-tuberal, or not strictly intraventricular, lesions. The presence of hypothalamic damage was

also significantly associated with outcome ($p < 0.001$). Good outcome was reported in almost 90% of the patients without hypothalamic damage, whereas 40% of cases showing hypothalamic injury had a poor outcome or died in the immediate postoperative period.

The type of surgical approach used was associated with outcome ($p = 0.05$). Patients treated through the TSF approach had a good outcome in 58% of cases. In addition, approximately 45% of patients who underwent subfrontal or transcallosal/transventricular procedures showed a good outcome. On the contrary, a majority of trepanations or decompressive craniectomies were associated with a bad prognosis (63%; Fig. 3 upper). Outcome was significantly associated with the degree of tumor removal ($p = 0.001$). Subtotally removed lesions were associated with the best outcome (70%). In contrast, the worst outcome was reported for patients whose tumors were not removed (54%) or for those in whom gross-total removal was achieved (39%; Fig. 3 lower).

Discussion

Diagnosis of CPs in the Early 20th Century

At the beginning of the 20th century neurosurgery

FIG. 2. Bar graphs showing bivariate topographical relationships. **Upper:** Correlation between CP topography and postoperative hypothalamic damage. Less than one-quarter of patients with sellar-suprasellar or suprasellar CPs showed hypothalamic damage. In contrast, more than 60% of the patients with tumors involving third ventricle (sellar-suprasellar-third ventricle [S-SS-3V], infundibulo-tuberal, or strictly intraventricular [IV]) locations suffered from hypothalamic injury. Patients with infundibulo-tuberal CPs showed the highest rate of hypothalamic damage (84%). **Lower:** Correlation between CP topography and patient outcome. More than 60% of patients with sellar-suprasellar or suprasellar CPs showed a good outcome. On the contrary, less than one-third of the patients with tumors involving the third ventricle had a good outcome. Infundibulo-tuberal CPs were associated with the highest rate of postoperative death, close to 40%.

was still in its infancy. Surgical success depended on how quick, simple, and straightforward the operation was, factors directly related to the surgeon's neuroanatomical knowledge and the degree of accuracy in locating the intracranial lesions. Apart from the clinical history, evidence of a pituitary tumor came from funduscopic and campimetric examinations, which in the last decade of the 19th century were established, respectively, as the standard methods of assessing the presence of papilledema or optic atrophy and deficits in the patient's visual fields.⁶⁵ The diagnosis of a pituitary tumor was presumed based on the coexistence of three types of symptoms: 1) recurrent attacks of severe headache and vomiting, suggestive of elevated intracranial pressure caused by a voluminous intracranial mass; 2) rapid, progressive visual loss with a characteristic bitemporal encroachment on the vi-

FIG. 3. Bar graphs showing bivariate patient outcome relationships. **Upper:** Correlation between type of surgical approach used and patient outcome. Simple trepanation and all varieties of decompressive craniectomies (cr.) were associated with the highest rate of postoperative death (56%). On the contrary, the TSF approach was associated with the highest rate of good outcomes, close to 60%. **Lower:** Correlation between degree of tumor removal and patient outcome. The highest rate of postoperative death occurred in patients in whom the tumor was not removed (41%), followed by patients in whom gross-total removal occurred (33%). In contrast, the highest rate of good outcomes was reported for patients in whom the tumor was subtotally removed (70%).

sual fields, a sign of severe compression and distortion of the optic chiasm; and 3) clinical findings of acromegaly or, alternatively, of a sexual infantilism associated with obesity (known as Fröhlich syndrome), both syndromes indicative of a pituitary gland dysfunction caused by the onset of tumor growth.^{5,33,58}

Nevertheless, the lack of knowledge about the physiological roles played by the pituitary gland and the specific symptoms of endocrine deficiencies led clinicians and surgeons to wrongly attribute the symptoms of headache, vomiting, and visual impairment to tumors of a cerebellar origin, as high intracranial pressure was known to severely affect vision. In the case of CPs, this mistake led surgeons to perform craniotomies in the wrong place, especially suboccipital craniotomies, as many patients with CPs showed gait and coordination disturbances similar to those produced by cerebellar tumors.^{10,31,114} The decision to operate on intracranial tumors was extremely risky given the tremendous hazards associated with imprecise

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anesthesia, absence of methods for managing intracranial bleeding, intraoperative brain swelling, and postoperative infection. Clinicians' fear of a patient's probable postoperative death made them wait a long time before deciding to refer the patient to a surgeon to assess the feasibility of operation. Such a delay usually meant irreversible blindness and a comatose condition, consequences of extremely high intracranial pressure. As a consequence, mortality rates of transcranial surgery around the pituitary region ranged between 50% and 80%.

In 1899, Oppenheim described for the first time the bony changes in the sella turcica, which were visible on skull radiographs and were caused by enlargement of the pituitary tumors.¹⁰³ Gross changes in the sella turcica typical of pituitary growths included enlargement of the sella and erosion of its floor and clinoid processes. Harvey Cushing brought one of the first x-ray machines to Johns Hopkins Hospital in Baltimore.⁵⁹ He soon noticed that cystic or solid CPs, lesions initially known as Rathke's cleft or pharyngeal pouch cysts, could be easily identified by the characteristic discrete hyperdense shadows occupying the suprasellar area above the sella turcica, which corresponded to intratumoral calcifications.^{21,31,34} The introduction of cranial radiographs into the diagnostic armamentarium of neurologists and neurosurgeons fostered the development of pituitary surgery, particularly the design of new transcranial approaches for the removal of CPs.^{79,88}

Despite its invaluable utility, the radiographic identification of sellar and suprasellar calcifications favored the generalized, classic assumption that CPs were lesions developing primarily in the sellar and suprasellar areas.¹¹¹ Actually, many pure solid and predominantly cystic CPs in both adult and young patients were lesions occupying the infundibulo-tuberal area and the third ventricle (Fig. 4).^{106–111} Until air ventriculography was developed by Walter Dandy in 1918, a sharp delimitation of the boundaries of the cerebral ventricles was not possible, and the intraventricular extension of CPs was largely ignored (Fig. 5B).³⁹

Foundations of Human Craniotomies for Pituitary Tumors: Experimental Approaches to the Pituitary Gland

The finding of macroadenomas in cadavers with acromegaly marked the beginning of the field of pituitary surgery.^{28,31} Early pituitary surgeons found a decrease in the abnormal swelling in acromegalic patients following the successful surgical removal of the associated adenoma.^{85,132,135} Whether the pituitary gland was essential to the maintenance of life, as asserted by Harvey Cushing, remained unknown, however.^{26,31} Numerous experimental hypophysectomies were performed in a variety of animals during the first decade of the 20th century to answer that question.⁷⁷

In 1886, Sir Victor Horsley was the first author to describe a hypophysectomy in two dogs, who survived without showing any general or neurological symptoms for 5 and 6 months, respectively.^{67,73} He used an intracranial approach through a temporal route, using a technique of "temporal lobe dislocation" to gain access to the hidden pituitary gland. For the next 2 decades, many researchers performed ablative surgeries of the pituitary gland with mixed results; in some of the experiments the

FIG. 4. Illustrations of Selke's case, the first CP to undergo a failed surgical attempt at removal via exploratory trepanation. Notice the solid papillomatous consistency of the lesion and its primary location within the third ventricle. From Dandy: *Benign Tumors in the Third Ventricle of the Brain: Diagnosis and Treatment*. Charles C Thomas, 1933.

animals succumbed soon after the operation, whereas in others they survived for a long time.^{4,26,31,67} Harvey Cushing concluded from his experiments of complete pituitary removal that this gland was absolutely necessary to life, as hypophysectomized animals died in a state of lethargy with slow respiration and low temperatures after progressive weakening and corporal emaciation, a clinical condition he defined as "cachexia hypophyseopriva."^{26,31} However, the selective resection of the pituitary stalk was not followed by death but by a marked polyuria, as well as by a delay in sexual maturity in puppies or atrophy of sexual function in adult animals, symptoms similar to those observed in young human patients with solid-cystic epithelial pituitary tumors expanding outside the sella turcica and involving the third ventricle floor.^{5,58} Based on his experimental results, Cushing, at the 1909 Congress of The American Medical Association, introduced the concepts of "hypopituitarism" and "hyperpituitarism" to classify the different clinical conditions observed among patients with pituitary pathologies.²⁸ In 1912, he published his classic monograph on the pituitary body and its disorders, presenting a list of clinical cases supporting these concepts.³¹

In 1910, Bernhard Aschner (1883–1960) improved the technique for hypophysectomy using a transbuccal approach, which only minimally injured the brain, and he

FIG. 5. **A:** Walter Edward Dandy (1886–1946) introduced ventriculography and pneumoencephalography as routine diagnostic procedures for CPs involving the ventricular system. From Troland et al: *Selected Writings of Walter E. Dandy*. Charles C Thomas, 1957. **B:** Example of a lateral ventriculogram showing the filling defect of the third ventricle, which has been invaded by a tumor. **C:** Lateral skull radiograph of a large intraventricular CP showing the dense linear shadows corresponding to the calcified cystic wall of the lesion at the suprasellar level. **D:** The transcortical-transventricular approach to the tumor used by Dandy. **E:** Diagram showing the position of the tumor and the transcortical approach through one brain hemisphere. Images in panels B–E from Dandy: *Benign Tumors in the Third Ventricle of the Brain: Diagnosis and Treatment*. Charles C Thomas, 1933.

speculated that the same procedure could theoretically be performed in humans.⁴ He described the clinical effects of total hypophysectomy performed in puppies, which consisted of arrested growth, infantilism with genital hypoplasia, and failure of epiphyseal-cleft closure (skeletal infantilism). He claimed, in agreement with other authors such as Jakob Erdheim,⁴⁷ that the mortal effects of Cushing's hypophysectomies were not attributable to the ablation of the pituitary gland but to injury caused to the basal hypothalamus during the operations.⁴ Bailey and Bremer eventually demonstrated that postoperative deaths in many of Cushing's experimental hypophysectomies were caused by damage to the third ventricle floor.⁸

In 1900, Joseph Felix Babinski (1857–1932) was the first author to report the clinical case of an obese young woman with genital hypoplasia, symptoms apparently caused by a solid epithelial tumor infiltrating the infundibulum and third ventricle (Fig. 6A–C).⁵ The following year Alfred Fröhlich (1871–1953) described the clinical course of a young patient with similar symptoms of obesity and sexual underdevelopment in whom a cystic calcified suprasellar lesion was diagnosed and eventually operated on by von Eiselsberg (Fig. 7).^{58,138–140} The reports of this new Babinski–Fröhlich syndrome caused much confusion with regard to the functional role of the pituitary. Neither Babinski nor Fröhlich considered the nature and specific topography of these tumors, which were situated above the pituitary gland and involved the area of the hypothalamus and third ventricle, as the fundamental cause

of their reported syndrome. Both lesions corresponded to adamantinomatous CPs, and in both cases the tumor had severely distorted the third ventricle floor.¹⁰⁸

The Problem of the Pathological Definition of CPs and Their Topographical Variants

Before the publication of Cushing's monograph on the pituitary body, great confusion existed as to the nature and proper definition of the different abnormal growths developing within the pituitary gland and its surroundings.³¹ Many pituitary tumors with topographical and morphological features typical of CPs were included in the group of pituitary "cysts" of a primary glandular nature, a common error in the medical literature of the 1890s and 1900s.¹⁴ A rather arbitrary number of denominations had been used to refer to a group of heterogeneous solid-cystic growths of an epithelial nature developing from the pituitary stalk, the infundibulum, and/or the third ventricle; these included sarcomas, carcinomas, teratomas, cholesteatomas, and papillomas.^{14,98,121} In 1892, Jacques Onanoff, Babinski's student, presented his doctoral work on the pathology of a rare epithelial tumor found at the base of the brain of a young obese woman during autopsy, the same case described by Babinski a few years later (Fig. 6A–C).¹⁰² He was the first author to remark on the similarities between this tumor and ameloblastomas of the jaw. In 1899, Mott and Barratt suggested for the first time that tumors of an epithelial nature developing at the third ventricle floor could originate from

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FIG. 6. **A:** Joseph Babinski (1857–1932), a French neurologist, described the clinical case of a 17-year-old obese girl with amenorrhea, the first report of Fröhlich syndrome. **B:** Pictures of the young girl who died of a third ventricle tumor. **C:** Illustrations of this tumor found at the necropsy by Babinski and described by Onanoff in his Ph.D. thesis. The tumor corresponded to an infundibulo-tuberal CP replacing the third ventricle floor. Images in panels B and C from Babinski: *Rev Neurol* 8:531–533, 1900. **D and E:** Macroscopic and microscopic sagittal images of a tumor, proving its truly intraventricular location. Mott was the first author to relate the origin of this lesion with the implantation of epithelial cells from the mouth migrating into the third ventricle together with Rathke's pouch. Images in panels D and E from Mott et al: *Arch Neurol Path Lab London County Asyl Claybury* 1:417–439, 1900.

epithelial remnants of the mouth outpouching from which the pituitary gland develops (Fig. 6D and E).^{101,122} These epithelial cell nests had first been observed along the pituitary stalk by von Luscha in 1860 (Fig. 8A).¹⁴¹

In a monumental monograph in 1904, the Austrian pathologist Jakob Erdheim gathered the early anatomical evidence about epithelial tumors presumably developing from remnants of the hypophyseal duct, giving the common term of “hypophysengangsgeschwülste” (“hypophyseal duct tumors”) to this new category of lesions (Fig. 8).⁴⁷ Erdheim was able to differentiate two major pathological variants within this tumor type according to their histological arrangements: 1) lesions similar to adamantinomas of the jaw, characterized by strands of a multistratified squamous epithelium with peripheral palisading of the nuclei that enclosed sheets of “stellate reticulum” and cysts filled with cell debris and cholesterol particles (Fig. 8B₁–B₂); and 2) lesions similar to papillomas of the oral mucosa, usually formed by a unilocular cyst whose inner wall was lined with a squamous epithelium forming wart-like or cauliflower-like excrescences (Fig. 4). These two histological variants correspond, respectively, to the adamantinomatous and squamous-papillary CP types recognized in the WHO classification.^{117,125}

Harvey Cushing, with a more practical surgical perspective, differentiated between two major categories of

pituitary lesions on histological as well as developmental grounds: 1) the homoplastic growths of the pituitary body proper, termed “hypertrophies,” “adenomatous enlargements,” or so-called hypophyseal strumas; and 2) the extrapituitary or heteroplastic tumors, which usually arise from some developmental remains of the pharyngeal or infundibular diverticula: the so-called craniopharyngeal duct tumors (Fig. 9A₁).³¹ Nevertheless, he made the same mistake as Victor Horsley and Rupert Boyce in being unable to recognize cystic lesions of the infundibulum and the third ventricle as a special variant of hypophyseal duct-derived tumors, probably because of their atypically high location above the pituitary gland. In his classic monograph *The Pituitary Body and its Disorders*, published in 1912, Cushing described at autopsies two “epithelial cysts” of the third ventricle, which he called “intracystic papillomas,” although they actually corresponded to the squamous-papillary variant of Erdheim’s hypophyseal duct tumors (Figs. 8B₁–B₂ and 9D).³¹ We will see in a following section how the lack of an adequate method of defining the accurate topography of CPs, as well as an inability to recognize symptoms caused by the tumor and/or surgical damage to the hypothalamus, were the two major reasons for Cushing’s early unsuccessful operations on CPs.

In 1916, Zacharias Cope examined the surgical series of 64 pituitary tumors reported on by Cushing (1912–1914), Hirsch (1911), and von Eiselsberg (1910) for

FIG. 7. **A:** Anton Freiherr von Eiselsberg (1860–1939), professor and chairman of surgery at the University of Vienna Medical School and Austrian pioneer of the superior TSF approach to CPs. **B–D:** Surgical steps of Eiselsberg's procedure. Images in panels B and C from von Eiselsberg: *Ann Surg* 52:1–14, 1910 and in panel D from Cope: *Br J Surg* 4:107–144, 1916.

which the microscopic pathological diagnoses had been mentioned.²⁴ Forty-five of the tumors were adenomas. The other lesions were classified in multiple categories, such as endothelioma, teratoma, mixed tumor, calcifying chondroma, epithelial cancer, or sarcoma, evidence of the confusing terminology still used for heterogeneous pituitary tumors during the first 15 years of the 20th century. Of these nonadenomatous lesions, 7 (11%) proved to have cysts, sometimes filled with a yellow fluid containing cholesterol crystals.²⁴ Cope reaffirmed his belief that some of the cysts actually corresponded to the complete degeneration of an anterior lobe adenoma, while microscopic examination of their content merely showed cholesterol crystals and epithelial debris. Most, if not all, 7 of these cases may well have corresponded to CPs or Rathke's cleft cysts. These lesions presented identifiable calcifications on radiography in 85% of cases.⁹⁷ Cushing introduced the term "craniopharyngioma" in 1932 to designate under a single name the heterogeneous group of categories previously used to indicate tumors developing from Rathke's pouch.²⁹

Most of the hypophyseal duct tumors described in Erdheim's seminal paper largely involved the hypothalamus and third ventricle (Fig. 8B₁–B₂). Based on these observations, Erdheim was the first author to point out that the adiposity in Fröhlich syndrome, or dystrophia adiposogenitalis, was caused by tumor infiltration of the third ventricle floor and not by the destruction of the pituitary

gland, a fact confirmed by Bailey 2 decades later.^{8,47} A growing group of specific symptoms caused by CP infiltration and dysfunction of the hypothalamus was properly identified by authors such as Cushing, Bailey, Fulton, Alpers, Riddoch, Dott, and Cairns during the first decades of the 20th century.^{1,8,44,60,61} The most striking clinical alterations were abnormal somnolence and apathy, irregular variations in body temperature, and behavioral and emotional disturbances.^{60,61} The existence of a specific infundibulo-tuberal syndrome associated with CPs, which included all of these symptoms, was articulated by Claude and Lhermitte in 1917.¹⁸

Neurosurgeons operating on CPs that involved the anterior part of the third ventricle soon noticed the frequent hyperthermia and lethargic condition that followed the procedure and suspected that it was related to hypothalamic dysfunction.^{32,71,112} In 1891, Ott was the first author to suggest the participation of the tuber cinereum region in the regulation of body temperature.¹⁰⁵ Emotional alterations caused by hypothalamic disturbances in cases of CPs involving the tuber cinereum and the third ventricle were later documented by Schilder and Weissmann as well as Cushing.^{30,127} Nevertheless, experimental confirmation of the thermoregulatory function of the hypothalamus and its central role in controlling autonomic and emotional responses would not occur until the 1930s.^{30,91} This meant that pioneer pituitary surgeons could not recognize that undue damage to the hypothalamus was the

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FIG. 8. Illustrations of the epithelial cell remnants of the hypophyseal duct, which, according to Jakob Erdheim (1874–1937), were the origin of the group of infundibular tumors later known as CPs. **A:** Midsagittal section through the infundibulum and pituitary gland of a 49-year-old man showing squamous epithelial cell nests (white arrows) within the pars tuberalis. **B₁ and B₂:** Illustrations of the brain under-surface and midsagittal view of an infundibulo-tuberal CP diagnosed in a 16-year-old male who died after a 4-year-history of severe headache, progressive visual deficit, recurrent seizures, and obnubilation followed by bradycardia and respiratory arrest. This adamantinomatous CP was confined to the third ventricle and separated from the suprasellar cistern by the pia mater. From Erdheim: *Sitzungsber Kais Akad Wissen Math Naturw Klin* 113:537–726, 1904.

most significant cause of mortality after radical removal of CPs extending upward into the third ventricle.¹⁰⁸

Early CP Removal Attempts Using the Superior TSF Approach

The significant morbidity and mortality caused by the forceful retraction of the frontal or temporal lobe in early transcranial surgeries of the pituitary gland fostered the development of extracranial basal approaches for pituitary tumors.^{24,74,83,90,94} The shorter distance from the anterior skull base to the sellar floor (55–60 mm), as compared with the distance from the nasal spine to the sella (70–77 mm), initially influenced surgeons' preferential choice of the former.²⁴ Davide Giordano (1864–1954) performed the first anatomical studies in cadavers, proving the feasibility of reaching the pituitary gland via a translabellar-TSF route,³ and his observations led Hermann Schloffer (1868–1937) to perform the first superior transnasal-TSF operation for a pituitary macroadenoma in Innsbruck, Austria, on March 16, 1907.⁹³ The Schloffer procedure was received with enthusiasm, although it revealed the problem of ignoring the accurate topographical diagnosis of the lesion, which could not be properly removed using this route should significant suprasellar and/or third ventricle extensions of the tumor be present. Another major limitation in the early stages of TSF surgery was the inability to perform continuous suction to keep the surgical field free of blood and to prevent blood aspiration.⁸³ The operation was therefore done with the patient's head in a downward position to allow the blood and tumor fragments to run out through the nose.^{139,140}

Only 3 months later, on June 21, 1907, Anton von Eiselsberg (1860–1939), Billroth's successor as professor and chairman of surgery at the University of Vienna Medical School, used the same approach developed by Schloffer to partially remove a pituitary tumor whose clinical and macroscopic features were compatible with a typical CP (Fig. 7).^{113,138} This patient was the same 20-year-old man who 7 years earlier had been reported by Fröhlich as suffering from adiposogenital dystrophy.⁵⁸ von Eiselsberg extended the rhinotomy incision up to the forehead to obtain a wider exposure and remove the vomer, the ethmoid air cells, and all six turbinates, leaving an unsatisfactory cosmetic scar on the patient's face.^{138–140} In 1910, von Eiselsberg spoke before the American Medical Association about his six cases of pituitary tumors, the world's largest experience up to that time, with an operative mortality rate of about 33%.^{139,140} Two of these lesions had macroscopic features typical of adamantinomatous CPs and were successfully removed (Tables 1 and 3). Nevertheless, radical excision of the nasal cavity contents in patients undergoing surgery via the Schloffer-Eiselsberg superior nasal approach caused the loss of normal laminar airflow, excessive dryness of the nasal mucosa, and chronic infection with nasal fetor, serious complications that forced surgeons to swiftly modify the route of access to the sella turcica to an inferior nasal approach.⁸⁷

In 1909, Theodor Kocher (1841–1917) of Berne, Switzerland, improved the transnasal approach by resecting the septum submucosally, with the aim of reducing the risk of postoperative infection and allowing better visualization of the sellar anatomy.^{85,90} For this purpose he used a specially devised nasal speculum that allowed for the surgical displacement of the septal mucosa and turbinates to either side. Using this approach, he removed a pituitary tumor early in 1909. Although the submucosal resection of the septum was a less traumatic technique (almost immediately incorporated by Hirsch, Halstead, Kanavel, Samuel J. Mixer, and Cushing) that spared the frontal, ethmoidal, and maxillary sinuses, Kocher's procedure still involved a complex and disfiguring external nasal incision.

Expansion of the Inferior TSF Approach for the Treatment of CPs

The superior nasal approaches were very quickly replaced by the inferior nasal route, which, in addition to its significantly less unpleasant cosmetic consequences, provided a better view of the suprasellar space given the oblique angle used to approach the floor of the sella turcica (Fig. 7D). von Eiselsberg was the first to announce this change to the American Surgical Association on May 3, 1910, after witnessing the elegant procedure performed by Cushing, which was similar to that by Kanavel and Halstead.¹⁴⁰ In 1909, the young rhinologist Oskar Hirsch (1877–1965) had timidly proposed to the Viennese Medical Society the inferior nasal approach as a method of pituitary tumor removal.^{87,90} From Hajek he had learned about the treatment of purulent sphenoid sinus infections by opening the posterior ethmoid sinus through an endonasal incision, and he had practiced this technique in cadavers. By avoiding the mutilating lateral rhinotomy, Hirsch's en-

FIG. 9. Photograph of Harvey Cushing and examples of CPs he treated via TSF and transcranial approaches. **A₁:** Interpeduncular tumor found at autopsy in a patient with Fröhlich syndrome. Notice the retrochiasmatic, hidden position of this developing infundibulo-tuberal lesion from a subfrontal view. From Cushing: *J Nerv Ment Dis* 33:704–716, 1906. **A₂:** Surgical strategy for chiasm splitting Cushing performed to expose retrochiasmatic CPs through the subfrontal approach. From Cushing: *Arch Ophthalmol (Paris)* 3:505–551, 1930. **B:** The hypothalamic or infundibulo-tuberal topographical type of CP, which frustrated Cushing's surgical attempts at removal through both the TSF and subfrontal approaches. From Cushing: *Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System*. Charles C Thomas, 1932. **C₁–C₂:** Basal and midsagittal view of a solid-cystic infundibulo-tuberal CP primarily developed at the tuber cinereum, which spared the pituitary stalk and pituitary gland and extended into the third ventricle. The tumor was disclosed at the autopsy of a 27-year-old woman who had suffered from symptoms of hypothalamic dysfunction and never regained consciousness after surgery, apparently dying from hyperthermia and cardiac complications. From Cushing: *Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System*. Charles C Thomas, 1932. **D:** An example of a strictly intraventricular CP of the papillary type, the first one identified by Cushing at autopsy. From Cushing: *The Pituitary Body and Its Disorders: Clinical States Produced by Disorders of the Hypophysis Cerebri*. JB Lippincott, 1912.

donasal approach would represent one of the two basic TSF approaches to the pituitary gland performed in the 20th century, the other being the sublabial rhinoseptal approach developed by Kanavel and Cushing.⁹⁴ Hirsch subsequently modified his technique into a single stage and incorporated Kocher's submucous resection of the nasal septum through a median approach instead of a lateral one.⁷² Illumination was provided by a reflective mirrored light commonly used by otolaryngologists.⁶³

Because of his Jewish origins, Hirsch wisely left Austria in 1938 and immigrated to the United States, where he worked in collaboration with the neurosurgeon Hannibal Hamlin at Massachusetts General Hospital in Boston. Despite abandoning the TSF approach in the late 1920s, Hirsch continued to operate using his endonasal method, which he considered appropriate for three groups of cases: 1) predominantly cystic tumors; 2) debilitated elderly patients; 3) largely intrasellar tumors. Hirsch's fundamental surgical philosophy for CPs was to achieve good decompression of the optic apparatus via subtotal resection, as he did not think that the TSF approach could allow for a complete, safe extirpation of the tumor in most cases. Such a strategy allowed him to remove five CPs before 1913, without causing severe hypothalamic complications in the patients, an impressive achievement at that time

(Table 1). In an attempt to prevent the regrowth of residual tumor, he pioneered the use of local irradiation by delivering radium into the subsellar area with a nasopharyngeal applicator secured to the upper teeth and left in situ for a short period of time (Table 3).⁸⁸ (He claimed that “only by this combination of surgery and postoperative radium treatment was it finally possible to achieve lasting results.”) At the end of his career in 1956, Hirsch had treated a total of 413 patients using the combination of the endonasal transseptal approach and the local application of radium, with an overall mortality rate of 5.4%.^{21,72,94}

In 1909, Allen Bucker Kanavel (1874–1938), a young surgeon working at Chicago's Cook County Hospital who had studied surgery in Vienna and had come to know the work of von Eiselsberg, devised a new inferior nasal approach to the pituitary gland to avoid the extremely disfiguring upper nasal method, which was also associated with a high risk of meningitis. He used an infranasal U-shaped skin incision around the lower half junction of the nose to lift it up and expose the entrance to the nasal cavity (Fig. 10).⁸⁰ Although his method required a good source of illumination and long instruments, including a chisel to break the floors of the sphenoid sinus and the sella, Kanavel emphasized that it was associated with less danger of infection since the ethmoid cells were not

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TABLE 3: Fundamental pioneering developments during the early period of surgical treatment of CPs, 1891–1938

Authors ^(reference) & Year	Date of Procedure	Pioneering Advance
Selke ⁴⁷	1891	1st exploratory trepanation for a CP
Horsley ¹³⁵	July 21, 1904	1st DC for a CP
Horsley ¹³⁵	June 27, 1907	1st successful transcranial approach to a CP
von Eiselsberg, 1910	June 21, 1907	1st successful superior TSF approach to a CP
Halstead, 1910	July 21, 1909	1st successful sublabial TSF removal of a verified CP
Mixter & Quackenboss, 1910	Dec 27, 1909	1st successful inferior nasal TSF removal of a CP
Cushing, 1912	Nov 26, 1910	improvement in endocrine symptoms w/ oral administration of pituitary extracts for a CP
Hirsch ⁷²	Sept 15, 1911	successful recovery from mental symptoms & somnolence w/ endonasal TSF approach
Frazier, 1913	July 1912	1st planned transfrontal approach to a CP
Cushing, 1914	1914	1st report of hypothalamic injury as cause of death after removing a CP
Hirsch ⁷²	April 2, 1913	1st use of adjuvant local radium therapy for a CP
Heuer, 1920	May 28, 1914	1st successful pterional partial removal of a CP
Cushing ²²	May 8, 1919	1st successful TLT approach to a retrochiasmatic CP
Vincent ¹³⁶	May 7, 1920	1st successful pterional removal of a CP in France
Lanman & Smith, 1923	July 25, 1921	1st topographical diagnosis of 3V occupation by a CP w/ air-v
Dandy ⁵⁰	June 23, 1923	1st TC to a 3V cholesteatoma
Cushing ²⁰	Dec 1924	1st transcallosal removal of an adamantinomatous CP
Peet, 1927	Nov 22, 1926	1st successful pterional removal of a primary hypothalamic or IT CP
Peet, 1927	Sept 13, 1927	1st successful pterional total removal of a CP
Hirsch ⁷²	May 30, 1928	1st successful transitory recovery from DI w/ rectal implantation of sheep pituitaries
Cushing, 1930	July 1929	1st chiasm splitting for removal of a retrochiasmatic IT CP
Cushing ²⁰	May 7, 1931	1st frontal transcortical transventricular approach to a CP
Dott, 1938	Feb 1934–March 1936	1st combined staged FTV & subfrontal approach for successful removal of a hypothalamic CP

opened.⁸¹ In later procedures he incorporated Hirsch's and Samuel J. Mixter's recommendation to follow a submucosal pathway of dissection along the vomer.⁸² Kanavel openly admitted that he never achieved the low 10% mortality rates reported by Cushing and Hirsch, yet he retired in the early 1930s having performed approximately 25 TSF pituitary operations. Among them were one histologically verified adamantinomatous CP and two additional "pituitary suprasellar cysts" with unmistakable macroscopic features of CPs, surgically treated between 1911 and 1914 (Tables 1 and 3).^{76,82} Two of the patients had a good outcome.

Albert Edward Halstead (1868–1926), who also belonged to the Chicago school of surgery, became familiar with Kanavel's work and modified his approach by performing the incision sublabially, along the mucous border between the upper lip and the gum. With the assistance of Kanavel, Halstead used his new TSF method for the first time on July 21, 1909; this allowed him to drain and curette out a pulsating cystic mass protruding through the sella floor (Fig. 11).^{66,131} The tumor fragments were analyzed by the pathologist and surgeon Dean D. Lewis (1874–1941), who diagnosed an epithelial tumor originating from the craniopharyngeal duct. The procedure was the first operation performed on a histologically verified CP in America.^{43,92} Halstead described his successful operation at the American Surgical Association meeting in 1910, where the topic of pituitary surgery was discussed by Cushing, Kanavel, von Eiselsberg, Dean Lewis, and

Samuel J. Mixter, all pioneers in the surgery of CPs. Halstead showed how his approach yielded better cosmetic results and improved exposure of the operative field. Only 5 months later, on December 29, 1910, William J. Mixter (1880–1958), from the Massachusetts General Hospital, used Halstead's sublabial method to empty a cystic CP, introducing his modification of a submucous septal resection to minimize the danger of infection, with excellent results.⁹⁹ Halstead did not perform any additional TSF approaches to CPs, but his infranasal sublabial incision would become, in Cushing's hands, the standard technique for approaching pituitary adenomas and CPs for the next 2 decades.⁶²

Cushing's Struggle Against CPs: Swing From the TSF to the Transfrontal Approach

Harvey Cushing started pituitary surgery in 1902 at Johns Hopkins Hospital by attempting the removal of pituitary macroadenomas and suprasellar calcified cysts using Horsley's temporal approach in six patients. Nevertheless, he found extreme difficulty in exposing the lesion in all cases because of either an incorrect topographical diagnosis of the lesion or the patient's extremely high intracranial pressure. He was forced to terminate the procedure with a simple decompressive temporal craniectomy in most cases.³¹ Because of such difficulties, Cushing decided to promote the use of the TSF route for the excision of adenomas and CPs presumed to be in patients with an expanded sella turcica. Although Cushing's first

FIG. 10. Surgical steps of Kanavel's procedure for approaching the pituitary gland. From Kanavel: *JAMA* 53:1704–1707, 1909.

TSF approach to the pituitary was done using a modified Schloffer technique in an acromegalic patient on March 26, 1909, he soon incorporated Halstead's and Samuel J. Mixer's modifications of Kanavel's original inferior nasal procedure to approach the pituitary gland.^{31,35} Cushing used his standard sublabial TSF technique with a submucosal septal dissection from 1910 to 1925, a period in which he operated in 231 patients with pituitary tumors, with an extremely low mortality rate of only 5.6%.^{62,83}

In contrast to Hirsch and other pituitary surgeons, Harvey Cushing used endotracheally induced general anesthesia instead of local infiltration with cocaine for his TSF procedures. He first used a headlamp and later a lighted speculum to enhance his vision of the surgical field throughout the entire approach (Fig. 12). In his Weir Mitchell Lecture in 1914, Cushing pointed out the inadequacy of Horsley's subtemporal approach to remove "congenital anlage tumors" (CPs) with an interpeduncular position, wedged between the optic chiasm and the pons and tightly adhered to the third ventricle floor.³⁵ He had attempted to gain access to the interpeduncular and sellar areas by lifting one temporal lobe but had been unable to even expose the lesion in 7 of 8 such tumors, only achieving a partial removal in the remaining case.^{94,114} In 1910, Cushing undertook his first resection of a CP via a TSF approach. He subsequently used this procedure for 14 of 92 CP resections.^{29,114} Disappointing experiences with failed TSF procedures in patients with chiasmatic and/or

Fröhlich syndromes, in whom the sella turcica displayed a normal appearance on skull radiographs, led him to conclude that many CPs developing above the sella and extending into the third ventricle were not lesions accessible through the TSF approach. In fact, vigorous efforts at radical dissection of CPs in such a high location were invariably followed by disastrous symptoms of hypothalamic insufficiency, which were not well known at the time (hyperthermia, bradycardia, low blood pressure, hydroelectrolytic disturbances, and lethargy; Fig. 9C₁–C₂).^{27,29,111} These adverse results led Cushing to progressively discontinue the TSF approach in favor of the subfrontal route, which he considered to provide improved access and superior exposure of the chiasmatic region, especially in the absence of an enlarged sella.^{21,27} Cushing reported on the much lower feasibility of permanently restoring normal visual acuity and fields with the former approach, that is, in only 10% of patients as compared with more than 20% with the latter approach.²⁹ Henderson affirmed Cushing's adoption of the subfrontal route because it allowed better assessment of the optimal release of chiasm compression in patients with macroadenomas causing bitemporal hemianopia.⁷⁰ An additional decisive factor was the lack of an appropriate source of light and proper visualization of the deep surgical field beyond the sella turcica, which was only possible with the introduction of the surgical microscope and the recently implemented use of endoscope-assisted surgery.⁶³ Cushing's preferred transcranial route was Frazier's earlier

FIG. 11. A–C: Illustrations of the successful removal of a CP through a sublabial transseptal TSF approach performed by Albert E. Halstead (1868–1926). D: Patient's picture taken 2 months after the procedure. From Halstead: *Surg Gynecol Obstet* 10:494–502, 1910.

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Fig. 12. Position of the patient (A) and type of incision (B) in the sublabial TSF operation for the removal of pituitary tumors and CPs, which was used by Harvey Cushing (1869–1939) from 1908 to 1929. From Cushing: *JAMA* 63:1515–1525, 1914. Sagittal and frontal pictures of pituitary macroadenoma (C) and CP (D) extending from the sella turcica up to the third ventricle roof after invading the third ventricle. These lesions were found at autopsies after Cushing's failed TSF procedures. Notice how the major extension of the CP (C, S) is above the sellar compartment (I) and the optic nerves (OD, OS). Image in panel C from Cushing: *The Pituitary Body and Its Disorders: Clinical States Produced by Disorders of the Hypophysis Cerebri*. JB Lippincott, 1912. Image in panel D from Cushing: *Intracranial Tumors. Notes Upon a Series of Two Thousand Verified Cases With Surgical Mortality Percentages Pertaining Thereto*. Charles C Thomas, 1932.

transfrontal extradural approach, modified from McArthur's method, but without resection of the supraorbital ridge.^{51,96} Later, Cushing also used Heuer's lateral frontal intradural approach.⁷¹

Cushing decided to definitely abandon the use of the sublabial transsphenoidal TSF approach from 1929 to 1932, a period during which he used almost exclusively the transfrontal craniotomy for the removal of most pituitary lesions, including CPs.¹²⁴ One of the main reasons that he favored the subfrontal route was the frequent finding of suprasellar CPs, when the expected lesion was a soft, subdiaphragmatic macroadenoma. The compact, hard structure and tight adhesions observed for many CPs contributed significantly to Cushing's consideration of these lesions as "the most forbidding of the intracranial tumors."^{21,90,124} A further disadvantage of the TSF approach was the high rate of CP recurrence after the procedure, a factor directly related to frequent extension of the lesion into the infundibulo-tuberal area of the hypothalamus and the third ventricle.¹¹⁸ Reoperations for CP recurrences through previously performed TSF procedures were more difficult and risky than those in cases in which a transcranial approach had been used, given the scarred field and the absence of topographical landmarks.^{29,70} These findings notably contributed to Cushing's final decision to use the transfrontal procedure for accurate diagnosis and better assessment of suprasellar CPs.

Harvey Cushing had the opportunity to study CPs from nonsurgically treated cadavers or failed approaches or partially removed lesions in which significant tumor growth extended into the hypothalamus and the third ventricle (Fig. 9).^{29,30,31,34} Given the position of this subgroup of CPs, the TSF approach had only allowed the removal of a small intrasellar portion of the lesion. In fact, the first suprasellar tumor for which Cushing appreciated the need for transfrontal exploration was the CP. He up-

dated his point of view regarding the value of the TSF approach in an address delivered by Percival Bailey on June 2, 1922, at the III Réunion Neurologique Internationale held in Paris.³⁴ On that occasion, he acknowledged that the TSF approach was suitable for achieving acceptable decompression of the optic chiasm and a remarkable recovery of vision, but he stressed his strong belief that CPs were not suited to TSF operations, which prevented surgeons from appreciating the extent of the intracranial propagation of the tumor.

In September 1929, in his lecture to the International Ophthalmological Congress in Scheveningen, Holland, Cushing discussed his surgical experience with patients presenting with the "chiasmal syndrome," which was characterized by the association of optic atrophy, bitemporal hemianopia, a normal sella on skull radiographs, and mild signs of dyspituitarism.²⁷ Such a syndrome was usually observed among elderly patients in whom a surgical exploration of the sella via the TSF approach revealed a suprasellar lesion, in most cases a CP or a meningioma. Cushing's address concluded with his claim that the differentiation of pure suprasellar lesions such as CPs from outgrowths of originally intrasellar lesions was impossible in all patients affected by chiasmal syndrome.²⁷ This claim was substantiated by E. M. Deery, an assistant in the clinic, in a review of Cushing's series of 225 consecutive transfrontal operations.⁴² In this paper Deery discusses the specific number of diagnostic errors made by Cushing with these "scarcely distinguishable" presentations of the chiasmal syndrome. Overall, a remarkable 32% of diagnostic errors occurred in this cohort of patients, with CPs being mistakenly diagnosed as tumors of another sort 22 of 67 times.⁴² Therefore, Cushing advocated the exploration of the suprasellar area through a transcranial approach to avoid misdiagnosis.

Transfrontal Approaches to CPs: Starting Point of the Dissemination of the Pterional Craniotomy in Neurosurgery

In 1904, Otto Kiliani (1863–1928), professor of clinical surgery at Columbia University in New York, designed a new intradural bilateral subfrontal approach and tested it on cadavers with the aim of operating on a lethargic 16-year-old boy with failing vision and headaches.⁸⁴ The patient eventually died of acute hydrocephalus caused by a large cystic pituitary tumor filled with blood-like fluid. Although the pathological nature of this lesion could not be investigated, its macroscopic features might well have corresponded to those of a CP (Figs. 13 and 14). Kiliani recommended the use of a bifrontal craniotomy as well as ligating and sectioning the falx and anterior longitudinal sinus as the most suitable approach for similar lesions, instead of the small-scale unilateral craniotomy he had performed.⁸⁴ The following year, in 1905, the German pioneer of neurosurgery, Fedor Krause (1857–1937), attempted an extradural subfrontal approach to remove a fibrosarcoma (probable parasellar meningioma) in an obese patient suffering from left-eye blindness and right temporal hemianopia, although the patient eventually died.⁸⁶ Krause would later prefer the superior transnasal-TSF approach described by Schloffer in 1907, and by 1927 Krause considered that the transcranial approach for pituitary tumors was indicated only for primary suprasellar lesions or large intrasellar lesions with a considerable suprasellar component.^{87,88}

For his part, Lewis Linn McArthur (1858–1934), a surgeon from the Chicago school who, like Kanavel and Halstead, had served at the Cook County Hospital, performed the first subfrontal intradural approach to a pituitary tumor in the United States. McArthur was well aware of Church's young Chicago patient who, 1 year ear-

lier in London, had benefited from Horsley's subtemporal approach to drain a cystic pituitary tumor.¹⁷ On March 5, 1908, McArthur proceeded to operate on a similar case by opening a large osteoplastic flap extending from the middle of the eyebrow to the anterior aspect of the ear, followed by intradural elevation of the frontal and temporal lobes.¹³¹ Although McArthur was able to rupture and empty a suprasellar cystic tumor, the patient died the following morning. Despite an unsuccessful initial experience, McArthur performed additional cadaveric work and operated in two additional cases, including a CP (Case 9; Table 1). In a paper from 1912, McArthur explained his modified extradural subfrontal approach in which the frontal lobe covered by dura was retracted upward and the orbital contents were retracted downward to expose the anterior clinoid process and the free ridge of the sphenoid wing. A deep dural incision of 2–3 cm was then made in front of the sella, allowing visualization of the optic chiasm and the pituitary tumor.⁹⁶ McArthur believed that this modification minimized the likelihood of frontal lobe damage associated with retraction maneuvers.

In Philadelphia, Charles H. Frazier (1870–1936) led the transition from the TSF operation to the intracranial subfrontal approach to CPs. His initial technique incorporated a frontal extradural approach similar to McArthur's operation, except that Frazier tried to spare the frontal sinus and resected only part of the orbit (Figs. 14 and 15). Using this technique, Frazier operated on four pituitary tumors between 1912 and 1913 in patients who survived; there was one CP among these tumors (Case 23; Table 1).⁵¹ Frazier then changed his technique to a coronal incision to approach the pituitary from the side, along the wing of the sphenoid rather than from directly in front, to avoid excessive retraction on the frontal lobe.^{54,55} In the case of cystic CPs, Frazier opened the capsule of the le-

Fig. 13. **A:** Otto G. Kiliani (1863–1928), professor of clinical surgery at Columbia University, New York, and pioneer of the bifrontal craniotomy to approach the optic chiasm and tumors developing around the suprasellar area. **B:** Illustration of his proposed surgical method. **C₁** and **C₂**: Views of the base of brain obtained from the autopsy specimen of a cystic tumor at the interpeduncular area, which extended into the third ventricle and whose pathological features were compatible with a CP. Kiliani operated on this lesion on December 12, 1903, but the comatose patient's condition precluded lesion removal. From Kiliani: *Ann Surg* 40:35–43, 1904.

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Fig. 14. Illustration depicting the different craniotomies used to approach CPs. BF = bifrontal (Kiliani, 1904); SF = subfrontal with removal of the supraorbital rim (Frazier, 1913); PT = pterional (Heuer, 1914); ST = subtemporal (Horsley, 1904).

sion and evacuated the contents, then performed a subtotal removal of the capsule except for the portion lying on the floor of the pituitary fossa. Frazier recommended the use of the TSF approach for pituitary lesions largely confined to the sellar compartment in patients with a “sellar headache” and no chiasmal syndrome.⁵⁷ The main reason was the still high mortality associated with transfrontal approaches, approximately 30%, as compared with the extremely low mortality rate of 3.4% for the removal of sellar tumors. He considered the TSF approach to be especially suitable for dealing with cystic lesions.⁵³

In London, Percy Sargent (1873–1933) used Frazier’s approach but without the removal of the supraorbital ridge, as Cushing did.^{10,25} Sargent’s bone flap was larger than Frazier’s, but his mortality rate was high, with 9 of 11 surgically treated patients with infundibulo-tuberal CPs dying within hours to days after the operation, most of them with an irreversible, fatal hypothalamic injury.

In 1914, George Heuer (1882–1950), a surgeon at the Johns Hopkins Hospital in Baltimore, devised a more

direct transcranial method of exposing the optic chiasm and the suprasellar area—the frontotemporal intradural or pterional approach.¹² His large osteoplastic frontoparietal craniotomy exposed the chiasm through an oblique trajectory after opening the anterior end of the sylvian fissure by retracting the frontal and temporal lobes (Figs. 14 and 16). It was a technique providing optimal alleviation of brain swelling and less damaging retraction on the frontal lobe during the procedure. Heuer published the details of the procedure in 1920, after serving in France in World War I.⁷¹ The lesions in three of the patients treated using this pioneering type of craniotomy corresponded to verified CPs involving the infundibulo-tuberal area of the third ventricle.⁴⁶ Two of the patients died from intraoperative carotid and hypothalamic injuries, respectively, and the third tumor recurred in the short term. From 1919 on, Frazier began using this oblique pterional approach from the side. Some years later, with improved anesthesia techniques for brain relaxation, Walter Dandy implemented Heuer’s frontotemporal approach using a smaller bone flap centered around the pterion and recommended the aspiration of CSF from the subarachnoid spaces to aid tumor exposure.³⁷ In 1932, Dandy stated that the frontotemporal craniotomy was an adequate approach for CPs.³⁸ In some cases, if the tumor was too large, the lateral ventricle was punctured to relieve pressure, and one optic nerve could be transected after elevating and lifting the frontal lobe backward. Sometimes the frontal lobe had to be resected to expose the tumor. Dandy’s philosophy was to remove the entire tumor, but such a procedure carried a high risk of mortality, and recurrences were not uncommon.

Diagnosis of Intraventricular CPs and the Development of Transventricular Methods of Approach

Traditionally, CPs have been widely regarded as having a primary sellar or suprasellar location, and yet a large proportion of these tumors involve the third ventricle at the time of diagnosis. Some lesions push the third ventricle upwards until it is obliterated, while others invade the third ventricle cavity after breaking through its floor. Nevertheless, many CPs develop as true hypothalamic and/or third ventricle lesions.^{106–111} The crudeness of the diagnostic tools available during the first half of the 20th century, in addition to the lack of microsurgical instruments, made the surgical outcomes for the subgroup

Fig. 15. Illustrations of the transfrontal operation described by Charles H. Frazier (1870–1936) in 1913. The frontal bone flap included a portion of the roof of the orbit. The frontal lobe was retracted extradurally, and a small deep incision in front of the sphenoidal wing was made to expose the optic nerve (o.n.) and the pituitary body. From Frazier: *Ann Surg* 57:145–150, 1913.

FIG. 16. Surgical stages of the pterional or frontotemporal craniotomy designed by George Julius Heuer (1882–1950) to approach CPs involving the optic chiasm. **A:** Outline of scalp and bone flap. **B:** Technique of exposing the chiasmal region by separating the frontal lobe from the temporal lobe. **C:** Detail of the exposure of the intrasellar compartment achieved through this approach. From Heuer: *Arch Surg* 1:368–381, 1920.

of intraventricular CPs much worse than those observed for other pituitary lesions.^{108,118} The introduction of diagnostic techniques that improved definition of the tumor's topography and extension, such as iodoventriculography and air encephalography, led to the recognition of predominant intraventricular extensions for most suprasellar CPs causing a chiasmal syndrome.³⁹ The use of innovative surgical procedures to approach the intraventricular extension of pituitary tumors, extending beyond the sella turcica, were refined thanks to such novel methods of diagnosis.

The spreading use of radiography as a routine tool for the diagnosis of intracranial masses contributed greatly to the classic erroneous assumption of CPs as lesions developing primarily in the sellar or suprasellar areas.¹¹¹ Most cystic or solid lesions initially known as Rathke's cleft or pharyngeal pouch cysts could be easily identified by their characteristic discrete hyperdense shadows occupying the ill-defined suprasellar area and corresponding to intratumoral calcifications. Nevertheless, other solid, cauliflower-like lesions corresponding to the squamous-papillary CP type did not show suprasellar calcifications that facilitated their diagnosis using plain cranial radiographs. The new diagnostic method of air ventriculography, developed by Walter Dandy in 1918, displayed sharp delineation of the boundaries of the cerebral ventricles, allowing the diagnosis of intraventricular masses (Fig. 5).³⁹ In the case of CPs, however, a true occupation of the third ventricle cavity could hardly be distinguished from an obliteration of the cavity caused by a suprasellar mass pushing the third ventricle floor upwards.¹¹¹

Cushing's preferred technique for removing CPs was the transfrontal approach, in which removal of the mass was usually preceded by the puncture and evacuation of its cystic portion through the lamina terminalis by using a short, narrow needle (Fig. 9A₂).²⁷ The use of the translamina terminalis approach provided a significantly better view of the basal retrochiasmatic portion of CPs, permitting safer tumor dissection and a more favorable prognosis.¹¹¹ Nevertheless, the most challenging part of the procedure was removing the tumor's solid portion, hidden from the subfrontal view and tightly adhered to the walls and floor of the third ventricle.^{108,120,130} Cushing

envisioned a possible solution for this problem during an operation for one such retrochiasmatic CP in April 1919, which involved sagittally splitting the optic chiasm, an injury without serious consequences in patients already suffering from bitemporal hemianopia (Fig. 9A₂).^{22,27} This was one of the first attempts at removing a portion of a CP through the lamina terminalis.¹¹¹ The chiasm-splitting technique allowed Cushing and his assistants to observe the actual position of many CPs, which were centered at the level of “what must have been the base of the third ventricle,” with their largest portion usually occupying the third ventricle cavity. A similar topography was observed by Cushing in most CPs disclosed following autopsies in nonsurgically treated patients who had died of hypothalamic dysfunction (Fig. 9).^{22,29–31}

Although Walter Dandy has been traditionally credited as the pioneer surgeon of the third ventricle,³⁶ Harvey Cushing was able to remove complex lesions hidden within the third ventricle with results similar to those reported by Dandy, an impressive achievement considering that he lacked modern microsurgical technology. Between 1924 and 1932, four intraventricular CPs were operated on by Cushing, and these cases probably represent some of the first CPs with such a topography that were surgically treated through a direct approach to the third ventricle (Cases 69, 130, 131, and 135; Tables 1 and 3).²⁰ Despite Cushing's intense intellectual dedication to CPs, his surgical results were particularly disappointing for this particularly challenging subgroup of lesions because of the serious hypothalamic disturbances that invariably followed the attempts at radical removal of tumors tightly attached to the walls and floor of the third ventricle.²⁰

Cushing's classic monograph on the pituitary gland, *The Pituitary Body and Its Disorders*, features two instances of epithelial cysts wholly within the third ventricle, which were identified on the necropsy studies of nonsurgically treated patients (Fig. 9D). Cushing coined the term “papillary infundibular cyst” to denote this type of lesion, the same described by Jakob Erdheim in 1904 (Fig. 8). Cushing cited the “admirable” monograph by Erdheim in his treatise, but he apparently did not link his own observations with those of Erdheim.¹¹¹ Lesions showing this topography characteristically affect adults

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in whom several unusual mental alterations, such as dementia-like behavior, are observed, in addition to severe memory defects, gait disturbances, and other specific hypothalamic disorders.^{107–109} Approximately 50% of these lesions correspond to the squamous-papillary variety.

Air ventriculography and iodoventriculography were hazardous and time-consuming methods. Cushing was at first reluctant to use ventriculography, a fact that helps to explain the high number of palliative subtemporal decompressions and failed suboccipital explorations he performed in patients with CPs and other pituitary tumors during the first half of the 1920s.^{6,7,22,29,31} Evidence of these misdiagnoses is provided in some of the intraventricular tumor cases reported in the review by Fulton and Bailey, most of them surgically addressed by Cushing during the 2nd decade of the 20th century.⁶⁰ As a result, the concept of a broadly suprasellar topography for CPs was favored.

From the late 1920s on, ventriculography turned out to be the diagnostic method routinely used by Cushing.²⁰ Based on the findings of air ventriculography, Cushing attempted radical removal of predominantly or strictly third ventricle CPs using either the transcortical-transventricular or the transcallosal routes. The absence of a good illumination source and, most importantly, the lack of microsurgical equipment precluded Cushing from attempting the dissection of CPs from the walls and floor of the third ventricle, the site where the tightest tumor adhesions were found. He tried instead to remove the mass through the foramen of Monro by grasping the tumor capsule and pulling it out blindly, as illustrated in his sketches of the operative stages.^{20,22} Regrettably, the use of this technique was followed, in many cases, by irreversible damage to the hypothalamic nuclei and the death of the patient within a few days of the surgical procedure (Cases 69 and 130; Table 1).

Strategies for Removing CPs With Major Hypothalamic Involvement: Bailey's and Dott's Experiences

Cushing did not succeed in his attempts to achieve complete, safe removal of intraventricular CPs, yet his experience definitely influenced the procedures used by the following generation of surgeons who had moved to Peter

Bent Brigham Hospital to be trained in the new field of neurosurgery. Norman McOmish Dott (1897–1973) was probably the man who most successfully adapted the lessons taught by Cushing. He was awarded a Rockefeller fellowship and spent half a year on Cushing's service from November 1923 to June 1924 at the Brigham Hospital. Dott learned sublabial TSF operations from Cushing and continued to use them at the Royal Infirmary of Edinburgh.⁹⁰ He believed that the TSF approach was the best surgical option for pituitary tumors without suprasellar extension and/or optic chiasm compression. Like Cushing, Dott believed that it was essential to determine preoperatively whether the tumor was an adenoma or another parhypophyseal lesion, since suprasellar tumors should be operated on from above the sella. Dott also designed an illuminated nasal speculum to improve visualization of the deep surgical field around the pituitary area.

Norman Dott differentiated between hypophyseal epidermoid lesions (CPs) having a suprasellar position, which push the hypothalamus upward as they enlarge, and the lesions actually originating in the substance of the third ventricle floor, which expand at the very center of the hypothalamus (Fig. 17). Dott's outstanding paper, published in 1938, on the surgical aspects of the hypothalamus showed that the successful removal of masses originating primarily within the hypothalamus was possible by using staged combined approaches, a strategy more than half a century ahead of its time.⁴⁴ He used the transcortical-transventricular approach to remove the usually cystic intraventricular component of the lesion and a basal approach to dissect the solid part embedded within the third ventricle floor and the hypothalamus (Fig. 17C). Because of the fixed position of the optic chiasm, preventing the direct view of the cleavage plane for dissection, he chose to sever and lift the most affected optic nerve and in this way open a free corridor to the mass.^{44,111} The resemblance between this technique and the one performed by Harvey Cushing is obvious.

The concept that hypophyseal duct tumors should be considered hypothalamus-centered lesions developing a major extension into the third ventricle was transmitted not only to British trainees but also to important Ameri-

Fig. 17. A and B: Illustrations of a hypothalamic solid-cystic CP (infundibulo-tuberal, or not strictly intraventricular, type) successfully removed by Norman M. Dott (1897–1973) in 1934 by using a combined staged frontal-transventricular and subfrontal approach. **C:** Depiction of the first surgical stage consisting of a frontal-transcortical-transventricular approach to remove the intraventricular cystic portion of the lesion. From Dott: *The Hypothalamus*. Oliver and Boyd, 1934.

FIG. 18. Midsagittal tumor sections from autopsy specimens showing the four major topographical types of CPs. Drawings for each topographical category are shown in the right column. **A:** A cystic CP with a pseudointraventricular topography. Notice how the lesion is pushing the intact third ventricle floor upwards. From Cushing: *The Pituitary Body and Its Disorders: Clinical States Produced by Disorders of the Hypophysis Cerebri*. JB Lippincott, 1912. **B:** A solid-cystic CP with secondary invasion of the third ventricle. Notice the disruption of the third ventricle floor by the tumor, which is developing from the sella turcica. From Cushing: *Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System*. Charles C Thomas, 1934. **C:** A cystic papillary CP with an infundibulo-tuberal, or not strictly intraventricular, topography. Notice the replacement of the third ventricle floor by the tumor, which preferentially expands within the third ventricle. From Cushing: *Rev Neurol* 38:779–808, 1922. **D:** A cystic papillary CP with a strictly intraventricular position. Notice the anatomical integrity of the third ventricle floor under the lesion. From Cushing: *The Pituitary Body and Its Disorders: Clinical States Produced by Disorders of the Hypophysis Cerebri*. JB Lippincott, 1912.

can neurosurgeons who were trained by Harvey Cushing during the 3rd decade of the 20th century. Percival Bailey (1892–1973), a long-term Cushing assistant at Peter Bent Brigham Hospital, who helped him to develop the field of neuropathology, had numerous publications on CPs in which a major concept inherited from Cushing's observations was affirmed—the concept that CPs are true hypothalamic rather than suprasellar lesions.^{6–8} Bailey also took a special interest in the hypersomnolence and other symptoms related to hypothalamic dysfunction presumably caused by lesions developing within the third ventricle, such as the cerebellar-like disturbances that were particularly frequent in cases diagnosed in adults.⁶ In an excellent and exhaustive monograph created in collaboration with the physiologist John Farquhar Fulton (1899–1960), a close friend and the biographer of Harvey Cushing, Bailey provided evidence of the relationship between symptoms such as adiposity, gait ataxia, body temperature dysregulation, and mental or emotional alterations and the dysfunction of definite nuclei or pathways within the hypothalamus caused by the expansion of third ventricle masses.⁶¹

Conclusions

The development of craniotomies and surgical approaches for the treatment of CPs was chiefly influenced by the extremely wide topographical and morphological variability displayed by these lesions (Fig. 18).^{109,120,130} Two major variables marked the early surgical experiences with CPs during the 1900–1938 period: 1) absence of preoperative knowledge about the real extension of the lesion, and 2) ignorance about the risks associated with attempts at total removal of lesions showing tenacious adhesions to the hypothalamus. Both variables are also the major determinants of tumor resectability and patient outcome today. Nowadays these variables can be accurately assessed, respectively, with the use of high-resolution, heavily T2-weighted/3D-FIESTA MRI sequences and surgical exploration of the cleavage plane between the tumor and the third ventricle floor using the endoscope-assisted expanded TSF approach. The CP's degree of adherence to the hypothalamus was the highest for lesions primarily developing at the infundibulo-tuberal area and for those extending into the third ventricle. By widening the access to the parapituitary area and improving the view of the tumor-hypothalamus interface, pioneers of pituitary surgery, such as Cushing, Peet, Heuer, and Dott, spared vital hypothalamic nuclei and successfully removed CPs. The use of the subfrontal approach in combination with chiasm-splitting or optic nerve-cutting techniques, in addition to the translamina terminalis and transcallosal approaches, represented significant advances for the safe excision of challenging infundibulo-tuberal and intraventricular CPs. Early pituitary surgeons' judicious decisions to restrict the degree of removal to the intra- and suprasellar component of the tumor and to debulk only the central component of the solid and/or cystic mass was associated with the best results in terms of useful patient survival when corticoid and hormone replacement therapies were lacking. These lessons remain valid

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today, when the pendulum between radical and conservative removal of CPs continues to swing.

Acknowledgments

We especially thank Crystal Smith, Reference Librarian of the Department of History of Medicine at the National Library of Medicine, National Institutes of Health, Bethesda, Maryland, for her kind assistance during the process of searching and retrieving articles and monographs used in this study. We are also indebted to Lucretia MacLure and all the staff at the Francis Countway Medical Library at Harvard Medical School, Boston, Massachusetts, for their invaluable help in obtaining some of the original research material used for this study. Finally, we are grateful to George Hamilton for his critical review of the language and style of the manuscript.

Disclosure

The authors report no conflict of interest concerning the material or methods used in this study or the findings described in this paper. This study was supported by the Sixto Obrador Award from the Spanish Society of Neurosurgery (SENEC), granted to the best national research study of neurosurgery in 2013. The contents are the sole responsibility of the authors and do not necessarily represent the official views of the Fund Board.

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

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Manuscript submitted December 15, 2013.

Accepted February 12, 2014.

Please include this information when citing this paper: DOI: 10.3171/2014.2.FOCUS13567.

Address correspondence to: José María Pascual, M.D., Ph.D., Department of Neurosurgery, La Princesa University Hospital, C/ Diego de León 62, Madrid 28006, Spain. email: jmpasncj@hotmail.com.