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

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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.

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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 (radiograph, 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 “craniohypophyseal.” 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 included 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
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-tuberol 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 hypophalamus-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 x 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, 1,2,5,7,9–11,13,15–17,19,20, 22–25,27,29–32,34–36,40,41,44–52,54–56,64,66,68,69,71,72,74–76,78,82,84,89,92,95,99,100,104,109,112,115,116,123,126,128,129,133–140,142–144 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*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Authors (reference) &amp; Year</th>
<th>Age (yrs.)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Date of Procedure</th>
<th>Type of Procedure</th>
<th>Degree of Removal</th>
<th>Topography</th>
<th>Pathological Evidence</th>
<th>Outcome &amp; FU</th>
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<tr>
<td>1</td>
<td>Selke47</td>
<td>42</td>
<td>F</td>
<td>clinical-necropsy</td>
<td>1891</td>
<td>exploratory trepanation</td>
<td>none</td>
<td>3V</td>
<td>solid papilloma (A)</td>
<td>postop death</td>
</tr>
<tr>
<td>2</td>
<td>Kiliani, 1904</td>
<td>16</td>
<td>M</td>
<td>clinical-necropsy</td>
<td>Dec 12, 1903</td>
<td>FP DC</td>
<td>none</td>
<td>S-SS-TVF</td>
<td>cyst &amp; fluid (A)</td>
<td>postop death</td>
</tr>
<tr>
<td>3</td>
<td>Horsley135 c1</td>
<td>51</td>
<td>F</td>
<td>clinical-necropsy</td>
<td>July 21, 1904</td>
<td>temporal DC</td>
<td>none</td>
<td>TVF-3V</td>
<td>cystic papilloma (A)</td>
<td>seizures/postop death</td>
</tr>
<tr>
<td>4</td>
<td>Horsley135 c2</td>
<td>14</td>
<td>M</td>
<td>clinical + x-ray</td>
<td>June 27, 1907</td>
<td>subtemporal approach</td>
<td>partial</td>
<td>SS-3V</td>
<td>calcified cyst &amp; fluid</td>
<td>CSF leak/death after 18 mos</td>
</tr>
<tr>
<td>5</td>
<td>Strausser135</td>
<td>NA</td>
<td></td>
<td>clinical-necropsy</td>
<td>Feb 2, 1907</td>
<td>FT DC</td>
<td>none</td>
<td>NA</td>
<td>hypophyseal duct cyst</td>
<td>good/death after 3 mos</td>
</tr>
<tr>
<td>6</td>
<td>von Eiselsberg, 1910 c1</td>
<td>20</td>
<td>M</td>
<td>clinical + x-ray</td>
<td>June 21, 1907</td>
<td>superior nasal</td>
<td>subtotal</td>
<td>S-SS</td>
<td>epithelial cyst &amp; fluid</td>
<td>good/2 yrs</td>
</tr>
<tr>
<td>7</td>
<td>von Eiselsberg, 1910 c2</td>
<td>18</td>
<td>F</td>
<td>clinical + x-ray</td>
<td>Dec 18, 1908</td>
<td>superior nasal</td>
<td>partial</td>
<td>SS-3V</td>
<td>cyst &amp; chocolate fluid</td>
<td>good/2 yrs</td>
</tr>
<tr>
<td>8</td>
<td>Ballance49</td>
<td>35</td>
<td>M</td>
<td>clinical + x-ray</td>
<td>May 9, 1908</td>
<td>transpalate</td>
<td>none</td>
<td>SS-3V</td>
<td>malignant sarcoma</td>
<td>carotid laceration/postop death</td>
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<tr>
<td>9</td>
<td>McArthur17</td>
<td>11</td>
<td>F</td>
<td>clinical-necropsy</td>
<td>June 8, 1908</td>
<td>FP DC + CSF tapping</td>
<td>none</td>
<td>TVF-3V</td>
<td>adamant CP (A)</td>
<td>postop death at 6 hrs</td>
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<tr>
<td>10</td>
<td>Cushing, 1912 c1</td>
<td>56</td>
<td>F</td>
<td>clinical + x-ray</td>
<td>July 17, 1908</td>
<td>rt temporal DC</td>
<td>partial</td>
<td>SS-IT</td>
<td>probable CP</td>
<td>no improvement/NA</td>
</tr>
<tr>
<td>11</td>
<td>Halstead, 1910</td>
<td>39</td>
<td>M</td>
<td>clinical</td>
<td>July 21, 1909</td>
<td>subabial TSF</td>
<td>subtotal</td>
<td>S-SS</td>
<td>typical CP</td>
<td>good/CSF leak &amp; reop</td>
</tr>
<tr>
<td>12</td>
<td>Cushing, 1912 c2</td>
<td>35</td>
<td>M</td>
<td>clinical + x-ray</td>
<td>Oct 12, 1909</td>
<td>superior nasal</td>
<td>partial</td>
<td>S-SS</td>
<td>congenital anlage T</td>
<td>good/death at reop, 1910</td>
</tr>
<tr>
<td>13</td>
<td>Pfeiffer, 1910</td>
<td>11</td>
<td>M</td>
<td>clinical-necropsy</td>
<td>Nov 11, 1909</td>
<td>not provided</td>
<td>none</td>
<td>TFV-3V</td>
<td>s-c CP (A)</td>
<td>postop death</td>
</tr>
<tr>
<td>14</td>
<td>Mixter &amp; Quackenboss, 1910</td>
<td>27</td>
<td>M</td>
<td>clinical + x-ray</td>
<td>Dec 27, 1909</td>
<td>inferior nasal</td>
<td>subtotal</td>
<td>S-SS</td>
<td>cystic CP</td>
<td>good/CSF leak, 4 mos FU</td>
</tr>
<tr>
<td>15</td>
<td>Cushing, 1912 c3</td>
<td>15</td>
<td>F</td>
<td>clinical + x-ray</td>
<td>Apr 21, 1910</td>
<td>subabial TSF (f)</td>
<td>none</td>
<td>SS-IT</td>
<td>probable CP</td>
<td>good/NA</td>
</tr>
<tr>
<td>16</td>
<td>Cushing, 1912 c4</td>
<td>18</td>
<td>F</td>
<td>clinical + x-ray</td>
<td>Nov 26, 1910</td>
<td>rt DTC</td>
<td>none</td>
<td>SS-interpeduncular</td>
<td>probable CP</td>
<td>good/NA</td>
</tr>
<tr>
<td>17</td>
<td>Kanavel &amp; Jackson, 1918 c1</td>
<td>18</td>
<td>M</td>
<td>clinical</td>
<td>Feb 21, 1911</td>
<td>inferior nasal</td>
<td>partial</td>
<td>S-SS</td>
<td>probable cystic CP</td>
<td>good/3 yrs</td>
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<td>18</td>
<td>Cushing, 1912 c4</td>
<td>adult, M</td>
<td></td>
<td>clinical + x-ray</td>
<td>Nov 21, 1911</td>
<td>subabial TSF (f)</td>
<td>none</td>
<td>3V</td>
<td>papillary CP (A)</td>
<td>meningitis/death after 13 days</td>
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<td>19</td>
<td>Cushing, 1912 c5</td>
<td>adult, NA</td>
<td></td>
<td>clinical + x-ray</td>
<td>Dec 15, 1911</td>
<td>subabial TSF</td>
<td>cyst drain</td>
<td>SS-interpeduncular</td>
<td>papillary CP (A)</td>
<td>CSF leak/NA</td>
</tr>
<tr>
<td>20</td>
<td>Hirsch &amp; Hamlin, 1959 c1</td>
<td>38</td>
<td>F</td>
<td>clinical + x-ray</td>
<td>Sept 15, 1911</td>
<td>endonasal TSF</td>
<td>partial</td>
<td>S-SS-TVF</td>
<td>epithelial cyst &amp; fluid</td>
<td>good/7 yrs</td>
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<td>21</td>
<td>Cushing39 c6</td>
<td>19</td>
<td>M</td>
<td>clinical + x-ray</td>
<td>Jan 4, 19, 1912</td>
<td>1: TSF (f)/2: TSF</td>
<td>partial</td>
<td>SS-SS</td>
<td>cystic calcified CP</td>
<td>fair/CSF leak, meningitis</td>
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<td>22</td>
<td>Hirsch &amp; Hamlin, 1959 c2</td>
<td>21</td>
<td>M</td>
<td>clinical</td>
<td>Jan 24, 1912</td>
<td>endonasal TSF</td>
<td>partial</td>
<td>S-SS</td>
<td>epithelial cyst &amp; fluid</td>
<td>good/25 yrs</td>
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<td>23</td>
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<td>M</td>
<td>clinical + x-ray</td>
<td>July 1912</td>
<td>SF</td>
<td>partial</td>
<td>SS-TVF</td>
<td>pure pituitary cyst</td>
<td>good/NA</td>
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<tr>
<td>24</td>
<td>Hirsch &amp; Hamlin, 1959 c3</td>
<td>46</td>
<td>M</td>
<td>clinical + x-ray</td>
<td>Apr 12, 1913</td>
<td>endonasal TSF</td>
<td>partial</td>
<td>S-SS</td>
<td>solid CP</td>
<td>good/17 yrs</td>
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<tr>
<td>25</td>
<td>Hirsch &amp; Hamlin, 1959 c4</td>
<td>34</td>
<td>F</td>
<td>clinical + x-ray</td>
<td>Nov 28, 1914</td>
<td>endonasal TSF</td>
<td>subtotal</td>
<td>S-SS</td>
<td>epithelial cyst &amp; fluid</td>
<td>good/death at reop (3 mos)</td>
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<td>26</td>
<td>Harris &amp; Graham, 1913</td>
<td>38</td>
<td>F</td>
<td>clinical + x-ray</td>
<td>Nov, Jan 1913</td>
<td>2 inferior nasal TSF</td>
<td>partial</td>
<td>IT</td>
<td>probable papillary CP</td>
<td>hypothal injury/death after 1 day</td>
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(continued)
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<tr>
<th>Case No.</th>
<th>Authors (reference) &amp; Year</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Date of Procedure</th>
<th>Type of Procedure</th>
<th>Degree of Removal</th>
<th>Topography</th>
<th>Pathological Evidence</th>
<th>Outcome &amp; FU</th>
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<td>27</td>
<td>Husten, 1923 c1</td>
<td>51, F</td>
<td>clinical-necropsy</td>
<td>Sept 8, 1913</td>
<td>superior nasal TSF</td>
<td>partial</td>
<td>S-SS-3V</td>
<td>adamant CP (A)</td>
<td>meningitis/death after 9 days</td>
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<tr>
<td>28</td>
<td>Cushing, 1914 c7</td>
<td>child</td>
<td>clinical + x-ray</td>
<td>1913</td>
<td>1: ST (f)/2: SF</td>
<td>GTR</td>
<td>SS-3V</td>
<td>s-c calcified CP</td>
<td>hypothal injury/death at 2 yrs</td>
<td></td>
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<td>Cushing, 1914 c8</td>
<td>child</td>
<td>clinical + x-ray</td>
<td>1912–1914</td>
<td>1: ST (f)/2: SF</td>
<td>biopsy</td>
<td>SS-3V</td>
<td>s-c calcified CP</td>
<td>survived reop (6 mos)/NA</td>
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<td>adult</td>
<td>clinical + x-ray</td>
<td>1912–1914</td>
<td>1: ST (f)/2: SF</td>
<td>partial</td>
<td>SS</td>
<td>cystic CP</td>
<td>survived 3 ops (4 mos)/NA</td>
<td></td>
</tr>
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<td>31</td>
<td>Cushing, 1914 c10</td>
<td>adult</td>
<td>clinical + x-ray</td>
<td>1912–1914</td>
<td>1: ST (f)/2: SF</td>
<td>partial</td>
<td>SS</td>
<td>cystic CP</td>
<td>survived 3 ops (2 mos)/NA</td>
<td></td>
</tr>
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<td>32</td>
<td>Cushing, 1914 c11</td>
<td>adult</td>
<td>clinical + x-ray</td>
<td>1912–1914</td>
<td>SF</td>
<td>partial</td>
<td>SS</td>
<td>cystic CP</td>
<td>survived/NA</td>
<td></td>
</tr>
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<td>33</td>
<td>Kanavel &amp; Jackson, 1918 c2</td>
<td>21, F</td>
<td>clinical</td>
<td>June 27, 1913</td>
<td>inferior nasal TSF</td>
<td>partial</td>
<td>S-SS</td>
<td>probable cystic CP</td>
<td>hyperthermia &amp; postop death</td>
<td></td>
</tr>
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<td>34</td>
<td>Kanavel &amp; Jackson, 1918 c3</td>
<td>18, M</td>
<td>clinical</td>
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<td>inferior nasal TSF</td>
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<td>cystic CP</td>
<td>good, 2 recurrences surgically treated</td>
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<td>35</td>
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<td>21, M</td>
<td>clinical</td>
<td>Feb 1915</td>
<td>SF</td>
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<td>SS</td>
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<td>36</td>
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<td>14, F</td>
<td>clinical</td>
<td>June 1915</td>
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<td>S-SS</td>
<td>cystic CP</td>
<td>death after 10 days</td>
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<tr>
<td>37</td>
<td>Heuer, 1920 c1</td>
<td>20, F</td>
<td>clinical + x-ray</td>
<td>May 28, 1914</td>
<td>lt FT</td>
<td>partial</td>
<td>SS-TVF-3V</td>
<td>adamant CP (A)</td>
<td>good/death at reop (3 mos)</td>
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<td>40</td>
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<td>clinical + x-ray</td>
<td>April 24, 1917</td>
<td>rt FT</td>
<td>GTR</td>
<td>SS-TVF</td>
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<td>postop death w/ hyperpyrexia</td>
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<td>rt SF</td>
<td>GTR</td>
<td>S-SS-3V</td>
<td>papillary CP</td>
<td>hyperthermia/death after 48 hrs</td>
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<td>April 3, 1918</td>
<td>suboccipital (f)</td>
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<td>IT</td>
<td>adamant CP</td>
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<td>April 16, 1918</td>
<td>TSF</td>
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<td>S-SS</td>
<td>cystic adamant CP</td>
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<td>x-ray: eroded sella</td>
<td>Dec 1, 1919</td>
<td>superior nasal TSF</td>
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<td>TVF-3V</td>
<td>papillary CP</td>
<td>hypothal injury/death after 2 days</td>
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<td>x-ray: SS shadow</td>
<td>April, May 1919</td>
<td>2 SF TLT</td>
<td>GTR</td>
<td>TVF-3V</td>
<td>adamant CP</td>
<td>good/recurrence after 3 yrs/8 yrs</td>
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<td>Claude &amp; Schäffer, 1921</td>
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<td>May 6, 1920</td>
<td>rt frontal trepanation</td>
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<td>TVF-3V</td>
<td>adamant CP (A)</td>
<td>coma/death after 1 day</td>
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<td>Nov 6, 1920</td>
<td>sublabial TSF</td>
<td>partial</td>
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<td>papillary CP</td>
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<td>May 7, 1920</td>
<td>rt FT</td>
<td>subtotal</td>
<td>S-SS-3V</td>
<td>adamant CP</td>
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<td>x-ray: large sella</td>
<td>Feb 28, 1920</td>
<td>rt ST DC (f)</td>
<td>none</td>
<td>S-SS</td>
<td>s-c adamant CP</td>
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<td>March 20, 1920</td>
<td>rt FT</td>
<td>partial</td>
<td>S-SS-TVF</td>
<td>calcified CP (A)</td>
<td>postop manic state/death at 2 wks</td>
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<td>partial</td>
<td>S-SS</td>
<td>adamant CP (A)</td>
<td>postop CSF leak/death in days</td>
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<td>Feb 7, 1921</td>
<td>1: ST (f)/2: SF</td>
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<td>SS</td>
<td>giant adamant CP</td>
<td>good, visual recovery</td>
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<td>Frazier &amp; Alpers, 1934 c4</td>
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<td>Jan 20, 1921</td>
<td>rt SF</td>
<td>partial</td>
<td>S-SS</td>
<td>s-c adamant CP</td>
<td>good/recurrence &amp; death at 8 yrs</td>
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<td>54</td>
<td>Husten, 1923 c2</td>
<td>42, M</td>
<td>clinical</td>
<td>July 27, 1921</td>
<td>bitemporal trepans (f)</td>
<td>none</td>
<td>TVF-3V</td>
<td>papillary CP (A)</td>
<td>postop death</td>
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<td>55</td>
<td>Lanman &amp; Smith, 1923</td>
<td>10, F</td>
<td>air-v: 3V defect</td>
<td>July 27, 1921</td>
<td>suboccipital (f)</td>
<td>none</td>
<td>S-SS-TVF</td>
<td>adamant CP (A)</td>
<td>death 1 hr after op</td>
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(continued)
TABLE 1: Summary of data on early surgical procedures for CPs, 1891–1938* (continued)

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<thead>
<tr>
<th>Case No.</th>
<th>Authors (reference) &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Diagnosis</th>
<th>Date of Procedure</th>
<th>Type of Procedure</th>
<th>Degree of Removal</th>
<th>Topography</th>
<th>Pathological Evidence</th>
<th>Outcome &amp; FU</th>
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<td>56</td>
<td>Sargent10 c4</td>
<td>10, M</td>
<td>x-ray: SS shadow</td>
<td>Nov 2, 1921</td>
<td>1: DC/2: SF</td>
<td>partial</td>
<td>S-SS-TVF</td>
<td>s-c adamant CP (A)</td>
<td>coma/death after 24 hrs</td>
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<td>57</td>
<td>Frazier &amp; Alpers, 1934 c5</td>
<td>17, M</td>
<td>air-v: 3V defect</td>
<td>Feb 3, 1922</td>
<td>rt temporoparietal (f)</td>
<td>none</td>
<td>TVF-3V</td>
<td>s-c adamant CP</td>
<td>poor, hallucinations/death at 7 wks</td>
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<td>58</td>
<td>Cushing6 c17</td>
<td>6, F</td>
<td>x-ray: SS calcium</td>
<td>July 26, 1922</td>
<td>rt SF</td>
<td>partial</td>
<td>SS-TVF-3V</td>
<td>s-c adamant CP</td>
<td>delirium, hyperthermia/death after 3 days</td>
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<td>Cushing6 c18</td>
<td>14, M</td>
<td>air-v: 3V defect</td>
<td>Aug 12, 1922</td>
<td>1: ST (f)/2: ST TLT</td>
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<td>TVF-3V</td>
<td>s-c adamant CP</td>
<td>hypothal injury/death at 3 wks</td>
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<td>child, F</td>
<td>x-ray: SS shadow</td>
<td>Nov 8, 1922</td>
<td>rt SF</td>
<td>GTR</td>
<td>SS</td>
<td>cystic adamant CP</td>
<td>good/NI &amp; obesity 6 yrs</td>
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<td>1922</td>
<td>ventricular puncture</td>
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<td>strictly 3V</td>
<td>papillary CP</td>
<td>postop death w/ hyperthermia</td>
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<td>Orlandi, 1922</td>
<td>27, M</td>
<td>clinical + x-ray</td>
<td>1922</td>
<td>lt DC</td>
<td>none</td>
<td>strictly 3V</td>
<td>s-c papillary CP (A)</td>
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<td>Cushing, 1926 c21</td>
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<td>August 1922</td>
<td>rt SF</td>
<td>subtotal</td>
<td>S-SS</td>
<td>typical CP</td>
<td>good, resumed growth/4 yrs</td>
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<td>Sargent2 c5</td>
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<td>SF (f)</td>
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<td>cystic CP</td>
<td>death after 2 days</td>
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<td>Dandy50 c1</td>
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<td>air-v: 3V defect</td>
<td>June 23, 1923</td>
<td>transcallosal GTR</td>
<td>3V-corpus callosum</td>
<td>3V cholesteatoma</td>
<td>postop death</td>
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<td>66</td>
<td>Schink, 1925</td>
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<td>x-ray: large sella</td>
<td>Nov 10, 1923</td>
<td>superior nasal TSF</td>
<td>partial</td>
<td>S-SS-3V</td>
<td>epithelial calcified T</td>
<td>fever &amp; death after 6 days</td>
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<td>67</td>
<td>Bock, 1924</td>
<td>44, M</td>
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<td>1924</td>
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<td>not provided</td>
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<td>adamant CP (A)</td>
<td>postop death</td>
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<td>Cushing10 c22</td>
<td>4, M</td>
<td>x-ray: SS shadow</td>
<td>Feb 19, 1924</td>
<td>2 FTV tapping of cyst</td>
<td>cyst drain</td>
<td>SS-3V</td>
<td>s-c adamant CP</td>
<td>death after 48 hrs</td>
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<td>x-ray: SS calcif</td>
<td>Dec 1924</td>
<td>1: SF (f)/2: TC</td>
<td>GTR</td>
<td>TVF-3V</td>
<td>s-c adamant CP</td>
<td>postop coma/death after 24 hrs</td>
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<td>Bourguet, 1927</td>
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<td>x-ray: eroded sella</td>
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<td>partial</td>
<td>S-SS-3V</td>
<td>cystic CP</td>
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<td>Cushing, 1926 c24</td>
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<td>clinical + x-ray</td>
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<td>SF</td>
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<td>not provided</td>
<td>not provided/NA</td>
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<td>Cushing, 1926 c25</td>
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<td>Dec 14, 1925</td>
<td>TSF</td>
<td>partial</td>
<td>S-SS-3V</td>
<td>s-c adamant CP</td>
<td>postop coma/death after 6 wks</td>
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<td>73</td>
<td>Frazier &amp; Alpers, 1934 c6</td>
<td>12, M</td>
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<td>Jan 18, 1924</td>
<td>rt SF</td>
<td>GTR</td>
<td>SS-TVF-3V</td>
<td>cystic adamant CP</td>
<td>poor, blind, lethargy/death at 6 mos</td>
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<td>74</td>
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<td>x-ray: large sella</td>
<td>July 25, 1924</td>
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<td>S-SS</td>
<td>s-c CP</td>
<td>good outcome</td>
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<td>rt SF</td>
<td>partial</td>
<td>SS</td>
<td>cystic adamant CP</td>
<td>good/death at reop 2 mos</td>
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<td>Sargent10 c8</td>
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<td>rt parietotemporal DC</td>
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<td>s-c adamant CP (A)</td>
<td>postop coma/death in 1 mo</td>
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<td>Feb 27, 1925</td>
<td>lt SF</td>
<td>partial</td>
<td>SS-TVF</td>
<td>epithelial cyst &amp; fluid</td>
<td>good/recurrence &amp; death in 1926</td>
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<td>s-c adamant CP</td>
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<td>rt SF (f)</td>
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<td>TVF-3V</td>
<td>papillary CP</td>
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<td>rt SF</td>
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<td>SS-TVF-3V</td>
<td>calcified CP</td>
<td>meningi disturbances/death at 16 mos</td>
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<td>Olivecrona133 c1</td>
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<td>clinical + x-ray</td>
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<td>rt SF</td>
<td>partial</td>
<td>S-SS</td>
<td>typical CP</td>
<td>poor/recurrence &amp; death at 6 mos</td>
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<td>x-ray: large sella</td>
<td>Nov 13, 1925</td>
<td>rt FPT</td>
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<td>S-SS-prechiasmatic</td>
<td>s-c adherent adamant CP</td>
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(continued)
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<th>Case No.</th>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Diagnosis</th>
<th>Date of Procedure</th>
<th>Type of Procedure</th>
<th>Degree of Removal</th>
<th>Topography</th>
<th>Pathological Evidence</th>
<th>Outcome &amp; FU</th>
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<td>83</td>
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<td>March 1926</td>
<td>rt SF</td>
<td>subtotal</td>
<td>SS-TVF-3V</td>
<td>typical CP</td>
<td>good/2 yrs</td>
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<td>cystic CP</td>
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<td>SS-prechiasmatic</td>
<td>cystic adamant CP</td>
<td>good, postop drowsiness, DI</td>
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<td>S-SS</td>
<td>cystic adamant CP</td>
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<td>Armour10</td>
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<td>TVF-3V</td>
<td>papillary CP</td>
<td>coma &amp; death after 2 mos</td>
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<td>Apr 10, 1926</td>
<td>endonasal TSF</td>
<td>partial</td>
<td>S-SS</td>
<td>adamant CP (A)</td>
<td>postop meningitis/death after 12 days</td>
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<td>9, M</td>
<td>x-ray: SS shadow</td>
<td>Apr 27, 1927</td>
<td>rt SF + ON cut</td>
<td>GTR</td>
<td>SS-TVF-3V</td>
<td>adamant CP</td>
<td>hypothal injury &amp; death</td>
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<tr>
<td>95</td>
<td>Peet, 1927 c3</td>
<td>6, F</td>
<td>x-ray: eroded sella</td>
<td>Sept 13, 1927</td>
<td>rt FTP</td>
<td>GTR</td>
<td>SS-prechiasmatic</td>
<td>s-c adamant CP</td>
<td>good, recovery of vision/NA</td>
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<tr>
<td>96</td>
<td>Olivecrona133 c3</td>
<td>53, F</td>
<td>clinical + x-ray</td>
<td>Nov 11, 1927</td>
<td>rt SF</td>
<td>partial</td>
<td>not provided</td>
<td>typical CP</td>
<td>poor/recurrence &amp; death at 10 mos</td>
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<td>97</td>
<td>Sargent10 c12</td>
<td>44, M</td>
<td>x-ray: eroded sella</td>
<td>Feb 9, 1927</td>
<td>rt SF + ON section</td>
<td>partial</td>
<td>tuberal-3V</td>
<td>s-c adamant CP</td>
<td>postop death</td>
</tr>
<tr>
<td>98</td>
<td>Sargent10 c13</td>
<td>36, M</td>
<td>x-ray: eroded sella</td>
<td>Feb 25, 1927</td>
<td>rt SF (f)</td>
<td>none</td>
<td>tuberal-3V</td>
<td>papillary CP</td>
<td>death after 2 mos</td>
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<tr>
<td>99</td>
<td>Sargent10 c14</td>
<td>34, F</td>
<td>x-ray: normal sella</td>
<td>July 1, 1927</td>
<td>rt SF</td>
<td>partial</td>
<td>IT</td>
<td>cystic adamant CP</td>
<td>good/death after 1 yr</td>
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<td>100</td>
<td>Sargent10 c15</td>
<td>14, M</td>
<td>x-ray: normal sella</td>
<td>Nov 3, 1927</td>
<td>rt SF (f)</td>
<td>none</td>
<td>IT</td>
<td>cystic adamant CP</td>
<td>death postop</td>
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<tr>
<td>101</td>
<td>Sharpe &amp; Sharpe, 1928</td>
<td>12, M</td>
<td>clinical + x-ray</td>
<td>before 1928</td>
<td>rt FP</td>
<td>none</td>
<td>tuberal-3V</td>
<td>cystic adamant CP</td>
<td>shock &amp; postop death</td>
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<td>102</td>
<td>Goldstein &amp; Cohn, 1928</td>
<td>15, M</td>
<td>x-ray: normal sella</td>
<td>Jan 22, 1928</td>
<td>DC</td>
<td>none</td>
<td>TVF-3V</td>
<td>cyst adamant CP (A)</td>
<td>postop death</td>
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<td>19, F</td>
<td>x-ray: S shadow</td>
<td>May 11, 1928</td>
<td>rt SF</td>
<td>cyst drain</td>
<td>S-SS</td>
<td>cystic adamant CP</td>
<td>good, obesity/1 yr</td>
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<td>Sargent10 c17</td>
<td>15, M</td>
<td>x-ray: SS shadow</td>
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<td>none</td>
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<td>cystic adamant CP</td>
<td>postop death</td>
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<td>Sargent10 c18</td>
<td>52, M</td>
<td>x-ray: large sella</td>
<td>Oct 12, 1928</td>
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<td>partial</td>
<td>S-SS</td>
<td>solid adamant CP</td>
<td>good/6 mos</td>
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<td>Sargent10 c19</td>
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<td>Nov 2, 1928</td>
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<td>partial</td>
<td>S-SS</td>
<td>s-c adamant CP</td>
<td>Korsakoff delirium/recurrence at 5 mos</td>
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<td>107</td>
<td>Cushing, 1930 c26</td>
<td>40, F</td>
<td>x-ray: SS shadow</td>
<td>Nov 19, 1928</td>
<td>SF</td>
<td>partial</td>
<td>IT</td>
<td>s-c adherent CP</td>
<td>DI, better vision/death after 2 mos</td>
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<tr>
<td>108</td>
<td>Olivecrona133 c4</td>
<td>7, F</td>
<td>x-ray: SS shadow</td>
<td>1928</td>
<td>rt SF</td>
<td>partial</td>
<td>SS-TVF-3V</td>
<td>adamant CP (A)</td>
<td>hypothal bleeding &amp; death</td>
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<tr>
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<td>Frazier &amp; Alpers, 1934 c15</td>
<td>15, M</td>
<td>x-ray: large sella</td>
<td>Nov 9, 1928</td>
<td>rt SF</td>
<td>subtotal</td>
<td>SS-TVF-3V</td>
<td>s-c adamant CP</td>
<td>lethargy, obesity/death at 20 mos</td>
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TABLE 1: Summary of data on early surgical procedures for CPs, 1891–1938 *(continued)*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Authors (reference) &amp; Year (case no.)</th>
<th>Age (yrs), Sex</th>
<th>Diagnosis</th>
<th>Date of Procedure</th>
<th>Type of Procedure</th>
<th>Degree of Removal</th>
<th>Topography</th>
<th>Pathological Evidence</th>
<th>Outcome &amp; FU</th>
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<tr>
<td>110</td>
<td>Hirsch &amp; Hamlin, 1959 c6</td>
<td>46, M</td>
<td>x-ray: normal sella</td>
<td>Dec 15, 1928</td>
<td>1: TSF/2: rt SF (f)</td>
<td>none</td>
<td>tuberal-3V</td>
<td>s-c CP (A)</td>
<td>death 48 hrs after 2nd op</td>
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<td>111</td>
<td>Hirsch &amp; Hamlin, 1959 c7</td>
<td>16, M</td>
<td>x-ray: eroded sella</td>
<td>May 30, 1928</td>
<td>endonasal TSF</td>
<td>cyst drain</td>
<td>S-SS</td>
<td>cystic adamant CP</td>
<td>good/8 yrs</td>
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<td>112</td>
<td>Hirsch &amp; Hamlin, 1959 c8</td>
<td>19, M</td>
<td>x-ray: normal sella</td>
<td>May 30, 1928</td>
<td>transcranial TSF</td>
<td>cyst drain</td>
<td>SS</td>
<td>adamant CP (A)</td>
<td>postop death</td>
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<tr>
<td>113</td>
<td>Cushing*, c27</td>
<td>27, F</td>
<td>x-ray: SS shadow</td>
<td>1928</td>
<td>SF</td>
<td>partial</td>
<td>tuberal-3V</td>
<td>s-c CP</td>
<td>coma, hyperthermia/death at 24 hrs</td>
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<tr>
<td>114</td>
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<td>46, M</td>
<td>air-v. 3V defect</td>
<td>Nov 5, 1928</td>
<td>SF + split chiasm</td>
<td>partial</td>
<td>tuberal-3V</td>
<td>s-c adamant CP (A)</td>
<td>good, recurrence &amp; death at 1 yr</td>
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<td>Hirsch &amp; Hamlin, 1959 c9</td>
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<td>x-ray: calcified sella</td>
<td>July 16, 1929</td>
<td>2 nasal TSF in 6 mos</td>
<td>partial</td>
<td>tuberal-3V</td>
<td>s-c adamant CP</td>
<td>good, vision recovery/6 yrs</td>
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<td>116</td>
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<td>17, F</td>
<td>clinical + x-ray</td>
<td>July 29, 1929</td>
<td>rt SF</td>
<td>partial</td>
<td>not provided</td>
<td>typical CP</td>
<td>poor/death after 3-mos recurrence</td>
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<tr>
<td>117</td>
<td>Cushing, 1930 c29</td>
<td>19, F</td>
<td>x-ray: SS shadow</td>
<td>before 1929</td>
<td>SF-TLT</td>
<td>partial</td>
<td>tuberal-3V</td>
<td>cystic adherent CP</td>
<td>DI, better vision/death, high ICP 2 mos</td>
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<tr>
<td>118</td>
<td>Balado &amp; Pardal, 1934 c1</td>
<td>11, M</td>
<td>l-ventr: 3V defect</td>
<td>March 14, 1929</td>
<td>transcortical (f)</td>
<td>none</td>
<td>TVF-3V</td>
<td>adamant CP (A)</td>
<td>lethargy &amp; death in mos</td>
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<td>119</td>
<td>Balado &amp; Pardal, 1934 c2</td>
<td>14, M</td>
<td>l-ventr: 3V defect</td>
<td>Sept 5, 1929</td>
<td>rt SF DC</td>
<td>none</td>
<td>SS</td>
<td>adamant CP (A)</td>
<td>postop death</td>
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<td>Cushing, 1930 c30</td>
<td>15, F</td>
<td>x-ray: S shadow</td>
<td>May–July 1929</td>
<td>2 SF + split chiasm</td>
<td>GTR</td>
<td>tuberal-3V</td>
<td>cystic CP</td>
<td>good/recurrence &amp; reop</td>
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<tr>
<td>121</td>
<td>Sargent*, c20</td>
<td>55, M</td>
<td>x-ray: large sella</td>
<td>Feb 15, 1929</td>
<td>rt SF</td>
<td>partial</td>
<td>S-SS</td>
<td>cystic adamant CP</td>
<td>postop death</td>
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<tr>
<td>122</td>
<td>de Martel, 1930</td>
<td>18, M</td>
<td>x-ray: normal sella</td>
<td>before 1930</td>
<td>2 SF</td>
<td>subtotal</td>
<td>SS</td>
<td>cystic CP</td>
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<tr>
<td>123</td>
<td>Frazier &amp; Alpers, 1934 c16</td>
<td>16, M</td>
<td>x-ray: S shadow</td>
<td>June 19, 1930</td>
<td>rt SF</td>
<td>subtotal</td>
<td>S-SS-3V</td>
<td>s-c adamant CP</td>
<td>lethargy/death after 3 mos</td>
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<tr>
<td>124</td>
<td>Olivecrona133 c6</td>
<td>18, M</td>
<td>clinical + x-ray</td>
<td>June 16, 1930</td>
<td>rt SF</td>
<td>partial</td>
<td>not provided</td>
<td>typical CP</td>
<td>good/23 yrs</td>
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<tr>
<td>125</td>
<td>Olivecrona133 c7</td>
<td>24, F</td>
<td>clinical + x-ray</td>
<td>Feb 4, 1930</td>
<td>rt SF</td>
<td>partial</td>
<td>not provided</td>
<td>typical CP</td>
<td>poor/recurrence &amp; death at 1 yr</td>
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<tr>
<td>126</td>
<td>Vincent et al., 1931</td>
<td>23, F</td>
<td>x-ray: normal sella</td>
<td>July 25, 1930</td>
<td>rt FT</td>
<td>partial</td>
<td>SS-3V</td>
<td>s-c adamant CP</td>
<td>good/NA</td>
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<tr>
<td>127</td>
<td>Dowman*</td>
<td>30, F</td>
<td>l-ventr: 3V defect</td>
<td>Nov 26, 1930</td>
<td>lt pterional + FTV</td>
<td>cyst drain</td>
<td>3V (A)</td>
<td>papillary CP</td>
<td>hyperthermia, stupor/death at 1 mo</td>
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<tr>
<td>128</td>
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<td>19, M</td>
<td>clinical + x-ray</td>
<td>1931</td>
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<td>partial</td>
<td>not provided</td>
<td>typical CP</td>
<td>good/recurrence after 7 yrs</td>
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<tr>
<td>129</td>
<td>Cardillo, 1933</td>
<td>41, F</td>
<td>x-ray: large sella</td>
<td>April 1931</td>
<td>TSF</td>
<td>partial</td>
<td>S-SS</td>
<td>adamant CP</td>
<td>good/1 yr</td>
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<td>130</td>
<td>Cushing*, c31</td>
<td>23, F</td>
<td>l-ventr: hydroco. ph</td>
<td>May 7, 1931</td>
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<td>GTR</td>
<td>SS-3V</td>
<td>cystic CP</td>
<td>death after 10 days</td>
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<tr>
<td>131</td>
<td>Cushing*, c32</td>
<td>21, M</td>
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<td>July 12, 1931</td>
<td>rt FTV</td>
<td>not provided</td>
<td>tuberal-3V</td>
<td>probable CP</td>
<td>good/NA</td>
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<td>132</td>
<td>Frazier &amp; Alpers, 1934 c17</td>
<td>52, M</td>
<td>x-ray: eroded sella</td>
<td>July 29, 1931</td>
<td>rt SF</td>
<td>subtotal</td>
<td>S-SS</td>
<td>cystic mixed CP</td>
<td>good/3 yrs</td>
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<td>Hirsch &amp; Hamlin, 1959 c10</td>
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<td>July 20, 1931</td>
<td>2 nasal TSF in 6 mos</td>
<td>partial</td>
<td>S</td>
<td>cystic adamant CP</td>
<td>good/25 yrs</td>
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<td>Fincher, 1934</td>
<td>26, F</td>
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<td>March 12, 1932</td>
<td>transcortical transven-tricular</td>
<td>not provided</td>
<td>strictly 3V</td>
<td>papillary</td>
<td>transient hypothal injury</td>
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*Continued...*
TABLE 1: Summary of data on early surgical procedures for CPs, 1891–1938* (continued)

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<th>Case No.</th>
<th>Authors &amp; Year</th>
<th>Age (yrs)</th>
<th>Diagnosis</th>
<th>Date of Procedure</th>
<th>Type of Procedure</th>
<th>Degree of Removal</th>
<th>Topography</th>
<th>Pathological Evidence</th>
<th>Outcome &amp; FU</th>
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<td>135</td>
<td>Cushing10 c33</td>
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<td>l-ventr: 3V defect</td>
<td>April 4, 1932</td>
<td>rt FTV</td>
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<td>SS-3V</td>
<td>adamant CP</td>
<td>good/NA</td>
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<tr>
<td>136</td>
<td>Dandy, 1933 c2</td>
<td>21, F</td>
<td>x-ray: 3V calcif</td>
<td>May 6, 1932</td>
<td>rt FTV</td>
<td>GTR</td>
<td>TVF-3V</td>
<td>adamant CP</td>
<td>good/initial transitory confusion</td>
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<tr>
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<td>Balado &amp; Pardal, 1934 c3</td>
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<td>l-ventr: 3V defect</td>
<td>May 10, 1932</td>
<td>transcallosal cyst coagul</td>
<td>partial</td>
<td>tuberal-chiasmatic</td>
<td>cystic CP (A)</td>
<td>death 17 days after surgery</td>
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<td>Coleman &amp; Hill, 1934</td>
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<td>clinical + x-ray</td>
<td>Sept 13, 1932</td>
<td>rt pterional</td>
<td>partial</td>
<td>TVF-3V</td>
<td>adamant CP</td>
<td>death after 4 mos</td>
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<tr>
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<td>total</td>
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<td>1933</td>
<td>rt frontal trepan</td>
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<td>coma &amp; postop death</td>
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<td>suboccipital (f)</td>
<td>none</td>
<td>TVF-3V</td>
<td>adamant CP (A)</td>
<td>death after 12 hrs</td>
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<tr>
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<td>l-ventr: 3V defect</td>
<td>June 1, 1933</td>
<td>transcallosal cyst drill</td>
<td>TVF-3V</td>
<td>typical adamant (A)</td>
<td>death after 12 hrs</td>
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<tr>
<td>143</td>
<td>Balado &amp; Pardal, 1934 c5</td>
<td>7, M</td>
<td>l-ventr: 3V defect</td>
<td>August 10, 1933</td>
<td>transcallosal cyst drain</td>
<td>SS-3V</td>
<td>adamant CP</td>
<td>good/recurrence &amp; death at 4 mos</td>
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<td>31, M</td>
<td>x-ray: eroded sella</td>
<td>Jan 1933</td>
<td>rt pterional</td>
<td>subtotal</td>
<td>SS-TVF-3V</td>
<td>typical CP</td>
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<td>rt SF</td>
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<td>typical CP</td>
<td>death after 3 yr recurrence</td>
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<tr>
<td>146</td>
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<td>22, F</td>
<td>x-ray: eroded sella</td>
<td>Nov 20, 1933</td>
<td>SF</td>
<td>partial</td>
<td>SS-3V</td>
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<td>1935</td>
<td>TSF</td>
<td>partial</td>
<td>S-SS</td>
<td>probable adamant CP</td>
<td>death after 11 days w/ seizures</td>
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<td>x-ray: sellar shadow</td>
<td>Dec 1933</td>
<td>rt frontal tapping</td>
<td>cyst drain</td>
<td>SF-3V</td>
<td>adamant CP (A)</td>
<td>death after 12 hrs</td>
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<tr>
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<td>Frazier18 c18</td>
<td>39, M</td>
<td>l-ventr: 3V defect</td>
<td>Apr 10, 1934</td>
<td>rt SF (f)</td>
<td>none</td>
<td>strictly 3V</td>
<td>papillary CP (A)</td>
<td>death after 8 days</td>
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<tr>
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<td>14, F</td>
<td>x-ray: eroded sella</td>
<td>May 24, 1934</td>
<td>rt ST</td>
<td>partial</td>
<td>SS-3V</td>
<td>s-c adamant CP</td>
<td>hypothermia death after 12 hrs</td>
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<td>151</td>
<td>Dott, 1936 c1</td>
<td>37, M</td>
<td>l-ventr: 3V defect</td>
<td>Jan 1935</td>
<td>1: rt TP DC (f)/2: rt FTV</td>
<td>GTR</td>
<td>TVF-3V</td>
<td>s-c adamant CP</td>
<td>death after 4 days</td>
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<tr>
<td>153</td>
<td>Ugelli, 1937 c1</td>
<td>4, M</td>
<td>x-ray: SS calcif</td>
<td>1935</td>
<td>rt &amp; lt pterional</td>
<td>GTR</td>
<td>SS-3V</td>
<td>adamant CP (A)</td>
<td>death after 4 days</td>
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<td>154</td>
<td>Reynolds, 1945</td>
<td>61, F</td>
<td>x-ray: SS calcif</td>
<td>Nov 1936</td>
<td>rt SF</td>
<td>partial</td>
<td>SS-3V</td>
<td>adamant CP</td>
<td>good/NA</td>
</tr>
<tr>
<td>155</td>
<td>Dott, 1938 c2</td>
<td>24, M</td>
<td>l-ventr: 3V defect</td>
<td>March 1934, 1936</td>
<td>1: rt FTV/2: rt SF + ON cut</td>
<td>subtotal/GTR</td>
<td>TVF-3V</td>
<td>s-c adamant CP</td>
<td>mental disturbance/recurrence after 2 yrs</td>
</tr>
<tr>
<td>156</td>
<td>Dott, 1938 c3</td>
<td>8, F</td>
<td>x-ray: SS calcif</td>
<td>2 Feb, May 1936</td>
<td>1: rt SF + ON cut/2: rt FTV</td>
<td>subtotal/GTR</td>
<td>TVF-3V</td>
<td>s-c adamant CP</td>
<td>hypothermia &amp; death</td>
</tr>
<tr>
<td>157</td>
<td>Ugelli, 1937 c2</td>
<td>26, F</td>
<td>x-ray: eroded sella</td>
<td>May 26, 1936</td>
<td>rt pterional</td>
<td>partial</td>
<td>S-SS-3V</td>
<td>adamant CP (A)</td>
<td>death after 11 days</td>
</tr>
<tr>
<td>158</td>
<td>Dott, 1938 c4</td>
<td>37, F</td>
<td>l-ventr: 3V defect</td>
<td>August 1937</td>
<td>subfrontal</td>
<td>TVF-3V</td>
<td>s-c adamant CP</td>
<td>death after 3 yr recurrence</td>
<td></td>
</tr>
<tr>
<td>159</td>
<td>Jefferson &amp; Jackson, 1939</td>
<td>51, M</td>
<td>l-ventr: 3V defect</td>
<td>1938</td>
<td>rt FTV</td>
<td>GTR</td>
<td>strictly 3V</td>
<td>papillary CP</td>
<td>good/NA</td>
</tr>
<tr>
<td>160</td>
<td>Zeilin &amp; Oldberg, 1940</td>
<td>21, M</td>
<td>air-v: 3V defect</td>
<td>April 1938</td>
<td>1: SF (f)/2: rt FTV</td>
<td>subtotal</td>
<td>strictly 3V</td>
<td>cystic CP</td>
<td>postop death</td>
</tr>
</tbody>
</table>

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

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

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

* NS = not significant.

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

Craniothypharyngioma 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
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. 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 visual 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.

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. The decision to operate on intracranial tumors was extremely risky given the tremendous hazards associated with imprecise
that question.77 

mals during the first decade of the 20th century to answer 
tal hypophysectomies were performed in a variety of ani
Hopkins Hospital in Baltimore.59 He soon noticed that cys
Cushing brought one of the first x-ray machines to Johns
la and erosion of its floor and clinoid processes. Harvey
Cal of pituitary growths included enlargement of the sel
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speculated that the same procedure could theoretically be performed in humans. 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, 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.

Bailey and Bremer eventually demonstrated that postoperative deaths in many of Cushing’s experimental hypophysectomies were caused by damage to the third ventricle floor. 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). He was the first author to remark on the similarities between this tumor and ameloblastomas of the jaw. 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). He was the first author to remark on the similarities between this tumor and ameloblastomas of the jaw.

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. 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. 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. 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). 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...
Historical surgical procedures for craniopharyngiomas

epithelial remnants of the mouth outpouching from which the pituitary gland develops (Fig. 6D and E). These epithelial cell nests had first been observed along the pituitary stalk by von Luschka in 1860 (Fig. 8A).

In a monumental monograph in 1904, the Austrian pathologist Jakob Erdheim gathered the early anatomico-clinical evidence about epithelial tumors presumably developing from remnants of the hypophyseal duct, giving the common term of “hypophysenganggeschwülste” (“hypophyseal duct tumors”) to this new category of lesions (Fig. 8). 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.

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. 9A). 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. 8B2–B3; and 9D).

We will see in a following section how the lack of an adequate method of defining the accurate toponography 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...
which the microscopic pathological diagnoses had been mentioned.\textsuperscript{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 cholesterin crystals.\textsuperscript{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 cholesterin 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.\textsuperscript{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.\textsuperscript{29}

Most of the hypophyseal duct tumors described in Erdheim's seminal paper largely involved the hypothalamus and third ventricle (Fig. 8B\textsubscript{1}–B\textsubscript{2}). 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{72,71,112} In 1891, Ott was the first author to suggest the participation of the tuber cinereum region in the regulation of body temperature.\textsuperscript{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.\textsuperscript{90,127} 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.\textsuperscript{30,91} This meant that pioneer pituitary surgeons could not recognize that undue damage to the hypothalamus was the
Historical surgical procedures for craniopharyngiomas

Fig. 8. Illustrations of the epithelial cell remnants of the hypophysseal 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. B and B2: Illustrations of the brain undersurface 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: Sitzungsbd Kais Akad Wissen Math Naturw Klin 113: 537–726, 1904.

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.24,27,83,90,94 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 frontal nasal approach by Davide Giordano (1864–1954) performed the first anatomical studies in cadavers, proving the feasibility of reaching the pituitary gland via a transglabellar-TSF route, 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, 1907.25 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.85 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.13,14

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. 7A,13,18 This patient was the same 20-year-old man who 7 years earlier had been reported by Fröhlich as suffering from adiposogenital dystrophy,28 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 53%.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. Mixter, 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.87,140 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-
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. 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. Illumination was provided by a reflective mirrored light commonly used by otolaryngologists.

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). (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%.

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). 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
opened. In later procedures he incorporated Hirsch’s and Samuel J. Mixter’s recommendation to follow a submucosal pathway of dissection along the vomer. 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 1910 and 1914 (Tables 1 and 3). Two of the patients had macroscopic features of CPs, surgically treated between 1910 and 1914 (Tables 1 and 3).

Samuel J. Mixter, all pioneers in the surgery of CPs. Halsted 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 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. 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

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

<table>
<thead>
<tr>
<th>Authors/Reference &amp; Year</th>
<th>Date of Procedure</th>
<th>Pioneering Advance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selke47</td>
<td>1891</td>
<td>1st exploratory trepanation for a CP</td>
</tr>
<tr>
<td>Horsley136</td>
<td>July 21, 1904</td>
<td>1st DC for a CP</td>
</tr>
<tr>
<td>Horsley136</td>
<td>June 27, 1907</td>
<td>1st successful transcranial approach to a CP</td>
</tr>
<tr>
<td>von Eiselsberg, 1910</td>
<td>June 21, 1907</td>
<td>1st successful superior TSF approach to a CP</td>
</tr>
<tr>
<td>Halstead, 1910</td>
<td>July 21, 1909</td>
<td>1st successful sublabial TSF removal of a verified CP</td>
</tr>
<tr>
<td>Mixter &amp; Quackenboss, 1910</td>
<td>Dec 27, 1909</td>
<td>1st successful inferior nasal TSF removal of a CP</td>
</tr>
<tr>
<td>Cushing, 1912</td>
<td>Nov 26, 1910</td>
<td>Improvement in endocrine symptoms w/ oral administration of pituitary extracts for a CP</td>
</tr>
<tr>
<td>Hirsch72</td>
<td>Sept 15, 1911</td>
<td>Successful recovery from mental symptoms &amp; somnolence w/ endonasal TSF approach</td>
</tr>
<tr>
<td>Frazier, 1913</td>
<td>July 1912</td>
<td>1st planned transfrontal approach to a CP</td>
</tr>
<tr>
<td>Cushing, 1914</td>
<td>1914</td>
<td>1st report of hypothalamic injury as cause of death after removing a CP</td>
</tr>
<tr>
<td>Hirsch72</td>
<td>April 2, 1913</td>
<td>1st use of adjuvant local radium therapy for a CP</td>
</tr>
<tr>
<td>Heuer, 1920</td>
<td>May 28, 1914</td>
<td>1st successful pterional partial removal of a CP</td>
</tr>
<tr>
<td>Cushing20</td>
<td>May 8, 1919</td>
<td>1st successful TLT approach to a retrochiasmatic CP</td>
</tr>
<tr>
<td>Vincent138</td>
<td>May 7, 1920</td>
<td>1st successful pterional removal of a CP in France</td>
</tr>
<tr>
<td>Lanman &amp; Smith, 1923</td>
<td>July 25, 1921</td>
<td>1st topographical diagnosis of 3V occupation by a CP w/ air-v</td>
</tr>
<tr>
<td>Dandy60</td>
<td>June 23, 1923</td>
<td>1st TC to a 3V cholesteatoma</td>
</tr>
<tr>
<td>Cushing25</td>
<td>Dec 1924</td>
<td>1st transcallosal removal of an adamantinomatous CP</td>
</tr>
<tr>
<td>Peet, 1927</td>
<td>Nov 22, 1926</td>
<td>1st successful pterional removal of a primary hypothalamic or IT CP</td>
</tr>
<tr>
<td>Peet, 1927</td>
<td>Sept 13, 1927</td>
<td>1st successful pterional total removal of a CP</td>
</tr>
<tr>
<td>Hirsch72</td>
<td>May 30, 1928</td>
<td>1st successful transitory recovery from DI w/ rectal implantation of sheep pituitaries</td>
</tr>
<tr>
<td>Cushing, 1930</td>
<td>July 1929</td>
<td>1st chiasm splitting for removal of a retrochiasmatic IT CP</td>
</tr>
<tr>
<td>Cushing72</td>
<td>May 7, 1931</td>
<td>1st frontal transcortical transventricular approach to a CP</td>
</tr>
<tr>
<td>Dott, 1938</td>
<td>Feb 1934–March 1936</td>
<td>1st combined staged FTV &amp; subfrontal approach for successful removal of a hypothalamic CP</td>
</tr>
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</table>

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. 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
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. Mixter’s modifications of Kanavel’s original inferior nasal procedure to approach the pituitary gland. 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%. 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. 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. 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. 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. 9C–C). 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 chiasmatric region, especially in the absence of an enlarged sella. 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. 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. 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. Cushing’s preferred transcranial route was Frazier’s earlier approach.
transfrontal extradural approach, modified from McArthur’s method, but without resection of the supraorbital ridge.\textsuperscript{51,96} Later, Cushing also used Heuer’s lateral frontal intradural approach.\textsuperscript{71}

Cushing decided to definitely abandon the use of the sublabial transseptal 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.\textsuperscript{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.”\textsuperscript{51,90,124} 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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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 updated 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.\textsuperscript{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.\textsuperscript{27} Such a syndrome was usually observed among elderly patients in whom a surgical exploration of the sello through 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 earlier 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-
Historical surgical procedures for craniopharyngiomas

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

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.
of intraventricular CPs much worse than those observed for other pituitary lesions.\textsuperscript{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.\textsuperscript{29} 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.\textsuperscript{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).\textsuperscript{20} 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.\textsuperscript{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. 9A\textsubscript{2}).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 9A\textsubscript{2}).\textsuperscript{22,27} This was one of the first attempts at removing a portion of a CP through the lamina terminalis.\textsuperscript{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).\textsuperscript{22,29–31}

Although Walter Dandy has been traditionally credited as the pioneer surgeon of the third ventricle,\textsuperscript{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).\textsuperscript{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.\textsuperscript{20}

Cushing’s classic monograph on the pituitary gland, \textit{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.\textsuperscript{111} Lesions showing this topography characteristically affect adults.
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. 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 subtotal decompressions and failed suboccipital explorations he performed in patients with CPs and other pituitary tumors during the first half of the 1920s. 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. 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. 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 adherences 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. 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. 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 parahypophyseal 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. 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. 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. 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.](Image)
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 hypotalamic rather than suprasellar lesions. 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. 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.

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). 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 adherences 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.

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

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Disclosure

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