The endocrinological, radiological, surgical, and pathological experience with 34 consecutive patients operated on for Cushing's disease is presented. Preoperative endocrine evaluation demonstrated that 19 patients had “typical” endocrine patterns for pituitary adrenocorticotropic hormone (ACTH)-dependent hypercortisolism and 11 had “atypical” testing. Pituitary pathology was found in 95% of the patients with typical preoperative endocrine testing but in only 55% of those with atypical testing. Eight of 34 preoperative computerized tomography scans demonstrated tumors, which correlated in all instances with the surgical findings. Microadenomas were removed from 25 patients, 22 of whom achieved postoperative remission of endocrine symptoms. Macroadenomas were found in three patients, only one of whom achieved remission after surgery. One patient had removal of an adenoma in the pharyngeal pituitary, and in another an ectopic lung carcinoid was excised; both of these patients were in postoperative remission. Four patients underwent transsphenoidal exploration but no definitive explanation was found for their hypercortisolism; these patients were not in remission. Immunohistochemical staining was performed on every specimen and all tumors showed excessive ACTH-secreting cells. A new rapid stain of the fibrovascular stroma is described.

Four approaches are presently used in the management of Cushing's syndrome: 1) pituitary surgery; 2) pituitary irradiation; 3) adrenal surgery; and 4) drug therapy. The surgical approach to treating Cushing's syndrome has been significantly improved by the introduction of microsurgical techniques to identify and resect pituitary microadenomas. The rate of complications associated with transsphenoidal microsurgery has been reported to be low, and microadenomectomy promptly reverses Cushing's syndrome in up to 90% of patients. Although the secretion of other tropic hormones is preserved, the secretion of adrenocorticotropic hormone (ACTH) is temporarily lost for 6 to 12 months postoperatively. When the presence of a pituitary adenoma is clearly demonstrated radiographically, a transsphenoidal operation of the pituitary gland is the preferred treatment. In patients in whom there is no radiographic evidence of a pituitary abnormality, surgical exploration may lead to the discovery of a microadenoma or to a total hypophysec- tomy. Since corticotrophic hyperplasia may be the consequence of hyperactivity of the neurohypothalamic mechanism controlling ACTH release, lack of response to surgery or recurrence of Cushing's syndrome can occur postoperatively.

Several reports have described experience obtained with transsphenoidal surgical treatment of Cushing's disease. While pre- and postoperative endocrine data have been available in some of these reports, a comprehensive study correlating the preoperative hormonal and radiographic findings with the operative findings and the postoperative endocrine response has not been published. We report our findings in 34 consecutive patients with the preoperative diagnosis of pituitary ACTH-dependent Cushing's disease treated with exploration of the pituitary gland. All of the patients were operated on by one surgeon (W.F.C.) and all but one were evaluated endocrinologically by a single endocrinologist (D.E.S.). These patients were operated on between 1980 and 1985. Our data correlate the preoperative hormonal and radiographic findings with the intraoperative and
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Clinical Material and Methods

Thirty-four patients, 27 females and seven males, with a mean age of 39 years (range 12 to 71 years), were included in this study. Mean duration of symptoms prior to surgery was 5.5 years (range 6 months to 26 years). As shown in Table 1, the most common clinical signs were obesity and hypertension with striae, hirsutism, easy bruisability, fatigue, and mental status changes (usually depression) being next most common. None of the patients had visual field loss related to the pituitary tumor. Nine of the 34 patients had been treated previously for hypercortisolism: a transsphenoidal subtotal resection of an adenoma in one; cobalt irradiation in four; mitotane treatment in one; and a partial adrenalectomy in one. Of the nine previously treated patients, only three had demonstrated a persistent clinical and biochemical response.

Biochemical endocrine evaluation was carried out preoperatively and repeated within 1 week postoperatively. Preoperative diagnostic evaluation included baseline urinary 17-hydroxycorticosteroids (17-OHCS), 17-ketosteroids (17-KS), cortisol basal levels, cortisol secretion rates, and serum cortisol and plasma ACTH levels. Urinary 17-OHCS were determined by the isotropic dilution method. 

Results

Preoperative Findings

Diagnostic Endocrine Evaluation. For the purpose of evaluating the surgical findings and responses in this series of patients, the endocrine profiles were divided into "typical" or "atypical" categories based on the following criteria. Patients were considered to have "typical" diagnostic criteria for Cushing's disease if they demonstrated elevated urinary 17-OHCS and cortisol basal levels, cortisol secretion rates, and mean cortisol levels; had a positive response to metyrapone (elevated ACTH levels associated with a rise in urinary 17-OHCS); and did not have normal suppression with low-dose dexamethasone but did with high-dose dexamethasone. Patients were considered to have "atypical" diagnostic criteria if they had elevated basal levels but did not respond as described either to metyrapone or to low or high doses of dexamethasone. Of 30 patients in whom a complete set of preoperative data was available, 19 were found to have typical diagnostic criteria whereas 11 had atypical findings. The preoperative values available in these two groups are summarized in Table 2. Although the basal levels appeared higher in...
the atypical group, only the ACTH levels were significantly greater. In four patients there were insufficient endocrine data to allow classification into the typical or atypical category, but they had either a clearly abnormal pituitary CT scan or a previous diagnosis of Cushing’s disease. Prolactin was elevated modestly in one patient at 81 ng/ml, but the growth hormone, TSH, T<sub>4</sub> RIA, and T<sub>3</sub> resin uptake were normal in all patients. Both patients who underwent bilateral simultaneous inferior petrosal sinus sampling demonstrated unilateral gradients, and these correlated well with the operative findings of laterally placed microadenomas.

**Radiographic Evaluation.** Of the 34 patients who underwent high-resolution pituitary CT scans, only six demonstrated focal abnormalities within the pituitary gland consistent with a microadenoma. All six of these patients were found at surgery to have microadenomas, and all tumors corresponded to the location suggested on the scan. Hypodense lesions were noted in three scans (one on the right, one central, one on the left), a hyperdense lesion in one (on the right), and isodense lesions in two (one on the right and one central). Macroadenomas were noted on two additional scans, with one being invasive, involving the left cavernous sinus and carotid artery. All abdominal and lung CT scans as well as adrenal radionuclide scans were normal.

**Operative Findings**

Thirty-three patients underwent transsphenoidal exploration of the intrasellar contents. One additional patient underwent a left subfrontal craniotomy because of radiological evidence of lateral parasellar extension involving the cavernous sinus and carotid artery. At the time of surgery, this patient was found to have an invasive macroadenoma which was nearly totally removed. At surgery, 20 patients were found to have lesions consistent with microadenomas, a diagnosis that was subsequently confirmed by both conventional and immunohistochemical staining. One additional microadenoma (only 3 mm in diameter) was confirmed during pathological examination, but a total hypophysectomy was performed because of inability to identify the tumor during surgery. Eight of the surgically identifiable microadenomas were located to the right, six to the left, and six in the center of the gland. Although many microadenomas were obvious on rather superficial examination of the pituitary, several were deep in the gland and required meticulous and extensive microdissection. In virtually every case, the tumor was whiter and softer than the surrounding normal gland.

In addition to these 21 patients, three other patients were found at surgery to have changes suggestive of microadenomas, with the same soft whitish material being identified and removed. Although the material could not be confirmed pathologically as being adenoma, all three of these patients experienced complete biochemical remission postoperatively. For the purpose of classification, these will be designated as "presumed microadenomas" since clinical and biochemical remission occurred after resection of the lesion. One additional patient was placed in this "presumed microadenoma" group since selective biopsy of a suspicious area brought about complete biochemical remission even though an obvious microadenoma could not be identified. Again, a tumor was not confirmed pathologically in this case. In total, 25 (74%) of 34 patients were found to have microadenomas, 21 of which were proven and four presumed.

Transsphenoidal exploration revealed obvious macroadenomas in two patients. When added to the patient treated by subfrontal craniotomy, this makes a total of three patients (9%) with macroadenomas. Only two of these had convincingly abnormal preoperative CT scans. In the two cases explored transsphenoidally, aggressive tumor resection was undertaken, resulting in a total sellar exenteration in one patient. All of the macroadenomas were confirmed on photomicrographs with standard hematoxylin and eosin (H & E) and immunohistochemical staining.

One of the remaining six patients was suspected of having a discrete abnormal area at surgery, and in fact frozen-section biopsy suggested an adenoma. When a selective resection failed to effect a remission and the permanent sections were negative on pathological examination, a second transsphenoidal approach was made 28 days later and a total intrasellar resection was performed. Once again no adenoma or hyperplasia could be identified on the pathological specimen and, although cortisol levels were reduced, the patient was not in remission.

Three additional patients underwent transsphenoidal exploration with no obvious or suspicious areas of abnormality being identified. Multiple biopsies were performed in two of these (both young women), with negative pathological evaluations and no resultant remissions. Interestingly, both of these patients had atypical preoperative endocrine testing. The third patient with negative findings on surgical exploration was past the childbearing age and, therefore, a total hypophysectomy was attempted, once again with no remission and no pathological identification of tumor or hyperplasia. This patient had a typical preoperative endocrine evaluation, but also exhibited an empty sella on the preoperative CT scan, a finding that was confirmed at surgery. The empty sella condition made it extremely difficult to remove the pituitary tissue completely, since it was very flattened and adherent to the diaphragma sellae. We believe that she does in fact have a pituitary origin for her hypercortisolism, but that the apparently total hypophysectomy may not have been complete due to the technical difficulty related to the empty sella. This brought to a total just four patients in whom the etiology of the hypercortisolism was not confirmed.

The remaining two patients, both with atypical preoperative endocrine testing, were shown to have ectopic sources of ACTH. One of these, who demonstrated no abnormality on transsphenoidal exploration, was found
to have a carcinoid in the lung. The immunohistochemical staining of the lung tumor revealed cells secreting not only ACTH but also corticotropin-releasing factor (CRF), serotonin, chromogranin, and neuron-specific enolase. She was in complete remission after removal of the lung tumor. Interestingly, immunohistochemical staining of the pituitary revealed secondary nodular ACTH-secreting cell hyperplasia. The second case was extraordinarily interesting in that, during transspHENoidal surgery, an 8-mm polyp was noted arising from the mucosa in the anterior portion of the sphenoid sinus. This was well away from the sella and was sent for pathological examination in a routine fashion as a suspected benign mucosal polyp. The pituitary was then carefully explored and no microadenoma could be identified. Biopsies of the pituitary were all diagnosed as negative for adenoma, but the mucosal “polyp” was entirely filled with ACTH-secreting cells and had the classic appearance of a pituitary adenoma. The tumor also stained positively for beta-endorphin and was focally positive for TSH. We believe that this represents an ACTH-secreting adenoma arising within the so-called “ectopic pituitary gland,” or pharyngeal hypophysis. The patient was in complete remission after resection of this tissue. Pharyngeal hypophysis tissue occurs commonly in the general population and has been shown to contain hormone-secreting cells. We therefore believe that this patient had pituitary-dependent Cushing’s disease, but from the pharyngeal pituitary.

One additional surgical observation was made concerning the normal adenohypophysis in the majority of these patients with hypercortisolism. During dissection through the pituitary tissue in a search for a microadenoma, numerous very small areas (< 1 mm in size) of white milky material were encountered. These were found in areas distant from microadenomas as well as in the patients who were discovered to have ectopic sources of ACTH. Numerous attempts to biopsy or aspirate and smear this material have failed to reveal any pathological material. This has only rarely been noted in our experience with other functional or non-functional pituitary adenomas, and may represent some type of change related to chronically high levels of ACTH and cortisol. It is well recognized that there are pathological effects (Crooke’s hyaline changes) of hypercortisolism in the normal adenohypophysis. These small milky areas may be confused with a microadenoma but, although soft, adenomas have always been more substantial than this milky material.

Pathological Findings

In the 21 patients classified above as having microadenomas, the pathological sections of all but three had the classic appearance of pituitary adenomas on H & E and immunohistochemical staining. Each of these stained strongly positive for ACTH-secreting cells with immunohistochemical techniques using the avidin-biotin peroxidase method and antisera from the National Institute for Arthritis, Diabetes, Digestive and Kidney Disease. 13 and 16 of these 18 patients were in remission postoperatively. The remaining three also demonstrated a definite excess of ACTH-secreting cells, but in less typical patterns. The specimens from one child were interpreted immunohistochemically as showing focal hyperplasia, and he is in remission postoperatively. In the remaining two patients, pituitary adenomas were diagnosed on standard H & E staining, but the sections showed multiple foci or micronodules of ACTH-secreting cells on immunohistochemical staining. 12,14 Postoperatively, one was in remission and one was not.

Of the three patients with macroadenomas, two were diagnosed as having a typical adenoma pattern and the other had an adenoma with marked cellular pleomorphism suggesting malignancy. The malignant adenoma appeared in the only patient who had previously undergone pituitary surgery, and the original biopsy specimen obtained 6 years earlier had been diagnosed as a benign adenoma. This patient had also received postoperative irradiation, which may have contributed to the pleomorphism. Immunohistochemically stained sections of the macroadenomas were also all strongly positive for ACTH-secreting cells.

As mentioned above, the tumor from the ectopic pituitary tissue in the sphenoid sinus had the classic appearance of a pituitary adenoma and stained strongly positive for ACTH-secreting cells. The ectopic lung lesion was a carcinoid and stained strongly positive for CRF as well as ACTH.

In 13 of the 34 cases, immunohistochemical staining was carried out for beta-endorphin as well as for ACTH. In each of the cases in which excessive ACTH-secreting cells were identified, staining for cells secreting beta-endorphin was also positive. Sections of these tumors stained negative for growth hormone, prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and TSH.

A 100% correlation existed between finding an adenoma on H & E staining and finding excessive ACTH-secreting cells on immunohistochemical staining. In each case in which an abnormality was noted on H & E staining an abundance of ACTH-secreting cells was identified, and there were no instances in which excessive ACTH-secreting cells were found without an abnormal H & E-stained specimen.

Frozen sections were obtained and reported during all 34 surgical procedures; four of the sections were falsely negative and two were falsely positive. Of the four patients with false-negative sections, three were found to have microadenomas (one of which was only 3 mm in size) and the fourth was the child with focal hyperplasia. One of the false-positive frozen sections misled the surgeon into inadequately exploring the remainder of the pituitary, and when remission was not effected, a second operation was required 4 weeks later to remove the obvious microadenoma from the opposite side of the gland. The other false-positive frozen section led to a selective resection, and no remission

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FIG. 1. Photomicrograph of a specimen of pituitary tissue in which the fibrovascular stroma shows as white on a dark background. The area below the white arrow is normal pituitary (P), showing the typical stromal pattern resembling flattened chicken-wire. The upper half of the field is an ACTH-secreting tumor (T) and demonstrates only islands of fragmented stroma. Rapid stain with fluoresceinated Ricinus communis agglutinin 120 lectin and propidium iodide, x 137.

was achieved; 4 weeks later a total hypophysectomy was carried out, once again without remission.

In an attempt to improve the accuracy of the frozen sections in differentiating between adenoma and normal pituitary, one member of our group (P.E.M.) has developed a rapid stain that takes advantage of the difference in the fibrovascular stromal pattern in these two types of tissue. This stain uses fluoresceinated Ricinus communis agglutinin 120 (RCA 120) lectin, which rapidly binds to the vascular stroma and may be examined within minutes of access to the fresh-frozen surgical specimen. In addition, propidium iodide (PI), which binds nucleic acids and has different excitation and remission spectra than fluoresceinated RCA 120, was used concomitantly to stain the nuclei. Thus, stromal configuration, nuclear morphology, and cell-to-stroma ratio may be used to distinguish adenoma from adenohypophysis. In normal anterior pituitary tissue, the fibrovascular stroma forms a fine interconnecting network around the acini. In pituitary adenomas, this acinar pattern is lost and the stained stromal pattern becomes a collection of disconnected fragments. These different stromal patterns are evident even on very small fragments. This rapid staining was carried out during six surgical procedures in the latter portion of this series. Pituitary adenomas were present in three of these six patients (two microadenomas and one macroadenoma), and all showed the typical pattern of disrupted stroma. Sections from the other three patients, in whom no tumor or hyperplasia was ever identified, showed the normal acinar pattern of fibrovascular stroma. Figure 1 demonstrates both of these stromal patterns on one specimen, since it shows the junction between an adenoma and normal pituitary tissue. The portion of the specimen containing normal pituitary appears like flattened chicken-wire, and that portion containing adenoma shows only isolated islands of stromal tissue. This technique of frozen-section analysis using fluoresceinated RCA 120 and PI has proven useful and will be investigated further in the future.

Complications

There were no deaths and no neurological morbidity related to these surgical procedures. In spite of a total hypophysectomy being carried out in three patients, only one developed permanent diabetes insipidus requiring long-term treatment with desmopressin acetate. In this patient, a portion of the infundibulum was identified in the pathological specimen. Other than the transient suppression of ACTH expected after tumor removal, patients with selective resections have not suffered loss of existing preoperative pituitary function.

Postoperative Findings

Postoperative endocrine evaluation was carried out initially within 1 week after surgery, and selected tests were subsequently repeated as needed. Based on this postoperative endocrine evaluation an opinion was rendered as to whether the patient was in remission (R) or was a surgical failure. We subclassified the patients in remission into those in whom the postoperative cortisol levels were well below the normal range (R₁) and those in whom the cortisol levels had returned to within the normal range (R₂).

Table 3 presents all of the patients and the pathological subgroups relative to the postoperative outcome. Of the 34 patients, 25 (74%) were in postoperative remission as a result of surgery (19 with an R₁ and six with an R₂ remission) and nine were surgical failures. This remission rate includes the patient with the sphenoid pituitary adenoma and the patient with removal of the lung carcinoid. If only the remissions related to intrasellar pituitary surgery are considered, the rate was 68% (23 of 34). Of the 34 patients, 24 had proven pituitary pathology (23 adenomas and one focal hyper-

### Table 3

Comparison of pathological classification and response to surgical treatment

<table>
<thead>
<tr>
<th>Pathology Group</th>
<th>Total Cases</th>
<th>No. in Remission*</th>
<th>Treatment Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>microadenoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>proven</td>
<td>21</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>presumed</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>macroadenoma</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ectopic</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>unknown</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>total</td>
<td>34</td>
<td>25</td>
<td>9</td>
</tr>
</tbody>
</table>

* R₁ = remission with cortisol levels below normal values; R₂ = remission with cortisol levels within normal values.
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Table 4
Operative and postoperative findings in patients relative to preoperative endocrine classification

<table>
<thead>
<tr>
<th>Findings</th>
<th>Typical</th>
<th>Atypical</th>
<th>Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>19</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>proven pituitary pathology</td>
<td>16</td>
<td>84</td>
<td>36 0.01</td>
</tr>
<tr>
<td>proven &amp; presumed pituitary pathology</td>
<td>18</td>
<td>95</td>
<td>65 0.02</td>
</tr>
<tr>
<td>microadenoma</td>
<td>14</td>
<td>74</td>
<td>4 0.36</td>
</tr>
<tr>
<td>presumed microadenoma</td>
<td>2</td>
<td>11</td>
<td>2 0.18</td>
</tr>
<tr>
<td>macroadenoma</td>
<td>2</td>
<td>11</td>
<td>0 0</td>
</tr>
<tr>
<td>ectopic</td>
<td>0</td>
<td>0</td>
<td>2 0.18</td>
</tr>
<tr>
<td>unknown</td>
<td>1</td>
<td>5</td>
<td>3 0.27</td>
</tr>
<tr>
<td>remission with pituitary surgery</td>
<td>13</td>
<td>68</td>
<td>6 0.55</td>
</tr>
<tr>
<td>remission with ectopic surgery</td>
<td>0</td>
<td>0</td>
<td>2 0.18</td>
</tr>
<tr>
<td>total remissions with surgery</td>
<td>13</td>
<td>68</td>
<td>8 0.73</td>
</tr>
</tbody>
</table>

* Fisher's exact test.

Table 5
Mean postoperative endocrine values

<table>
<thead>
<tr>
<th>Endocrine Test</th>
<th>Normal Values</th>
<th>Surgical Remission</th>
<th>Surgical Failure</th>
<th>Significance†</th>
</tr>
</thead>
<tbody>
<tr>
<td>cortisol (µg/dl)</td>
<td>6.5–20.5</td>
<td>4.2 ± 3.9</td>
<td>16.0 ± 4.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>41–68</td>
<td>90.2 ± 114</td>
<td>113.3 ± 73</td>
<td>0.016</td>
</tr>
<tr>
<td>CSR (mg/24 hrs)</td>
<td>12–22</td>
<td>11.6 ± 14.5</td>
<td>55.8 ± 27</td>
<td>0.003</td>
</tr>
<tr>
<td>UFC (µg/24 hrs)</td>
<td>30–130</td>
<td>36.9 ± 46.3</td>
<td>291.5 ± 294</td>
<td>0.0002</td>
</tr>
<tr>
<td>17-OHCS</td>
<td>5–10</td>
<td>2.8 ± 2.1</td>
<td>12.9 ± 8.5</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

* Values are means ± standard deviations. ACTH = adrenocorticotropic hormone; CRS = cortisol secretion rate; UFC = urinary free cortisol; 17-OHCS = urinary 17-hydroxycorticosteroids.
† Wilcoxon rank-sum test.

Plasma), four had presumed microadenomas (remission with selective resection), and two had ectopic tumors, leaving only four patients with an unknown cause for their hypercortisolism.

In the group of 21 pathologically proven microadenomas, 18 patients (86%) were in remission postoperatively. Interestingly, 16 (88%) of these remissions were of the R1 type. Of the 18 tumors that could be classified preoperatively, 14 (78%) had a “typical” endocrine pattern. Of the three patients in this group with surgical failure, one had micronodules of ACTH-secreting cells and in this case tumor tissue was most likely subtotally removed. Another patient underwent two selective resections of adenoma tissue without remission, but a total hypophysectomy was not carried out because of a history of drug addiction and unreliable behavior. The third failure occurred very early in the series and may have represented failure of the surgeon to appreciate the extent of the abnormal tissue.

The patients with “presumed microadenomas” were, by definition of this term, all in remission after a selective resection of abnormal-appearing tissue. It is of interest that three of these remissions were of the R2 type. Preoperative endocrine evaluation showed two to have typical and two atypical diagnostic criteria for Cushing’s disease.

Of the three patients with macroadenomas, only one was in remission postoperatively, and that tumor was of the R2 type. The two patients who were adequately studied preoperatively both showed the typical endocrine pattern for pituitary-origin hypercortisolism. The two patients with ectopic sources of ACTH were both in remission after removal of the neoplastic tissue. Both of these remissions were of the R1 type, and both patients had atypical preoperative endocrine testing. Of the four patients with unknown pathology, none was in remission postoperatively. Three had atypical and one typical preoperative endocrine testing. Two of the patients were young and underwent only biopsies at surgery, and two who were past childbearing age were subjected to attempted total hypophysectomy.

Table 4 is a summary of the findings in the preoperatively determined typical and atypical endocrine classification groups. Of the 19 patients with typical endocrine testing, 84% were proven to have pituitary pathology, as opposed to only 36% of the 11 patients in the atypical group (significance of difference, p = 0.01, Fisher’s exact test). If those with presumed microadenomas are included, the patients with either proven or presumed pathology comprised 95% of the typical group and 55% of the atypical group (significance of difference, p = 0.02). The occurrence of the various pathological subgroups is also given in Table 4, and it is apparent that with typical preoperative endocrine findings a patient is much more likely to have pituitary pathology. The remission rate in the typical group with intrasellar pituitary surgery was 68%, as opposed to 55% in the atypical group (difference not significant, p = 0.35). If the surgical remissions effected in the two patients with ectopic tumors are added to the atypical group, however, the total surgical remission rate in that group is actually 73% (difference not significant, p = 0.57).

Table 5 presents the mean postoperative endocrine values for the group of patients in remission and for the group that failed treatment after surgery. It is clear that the ACTH, urinary free cortisol, and 17-OHCS levels, as well as the cortisol secretion rate, all follow the marked difference in cortisol levels between the two groups (p values significant in all tests).

Discussion

It is important to emphasize that this report examines the surgical treatment and initial endocrine results of 34 consecutive patients believed preoperatively to have pituitary-dependent hypercortisolism, or Cushing’s disease. When the clinical presentation and biochemical
and radiological data suggest the diagnosis of Cushing's disease, surgical pituitary exploration is the treatment of choice. Several factors are paramount in achieving the best possible postoperative results. These include the completeness and accuracy of the preoperative endocrine work-up, the skill and experience of the surgeon, and the quality and completeness of the pathological evaluation. Since the intraoperative surgical judgment is critical in this form of treatment, it is ideal to examine the accumulated experience of a single surgeon. Likewise, since the surgeon is so dependent on the endocrine diagnostic evaluation in determining which patients to explore, it is essential that this evaluation be carried out by an endocrinologist with experience in this disease. This series has been gathered with these characteristics in mind, and consistency of data has been obtained.

The clinical signs and symptoms, preponderance of females (79%), average age (39 years), and length of time between onset of symptoms and diagnosis (5.5 years) were as expected for Cushing's disease.2,3 The incidence of specifically abnormal CT scans was somewhat higher than in previously reported series,1,10 and may reflect the improved resolution of the newer scanners. Of the 24 patients with pathologically proven pituitary adenomas, 33% had positive CT scans, and of the 21 with proven microadenomas, 29% had well-correlated abnormal scans. Although it has been reported that the most common CT abnormality is a focal region of low attenuation,1 the abnormal scans in this series revealed low-density, high-density, or isodense lesions with equal frequency. There were no false-positive CT scans.

The preoperative endocrine evaluation revealed hypercortisolism in all 34 patients and demonstrated the typical pattern of a pituitary origin in 19 cases. The 11 patients with atypical endocrine testing had undergone extensive preoperative evaluation in search of an adrenal or ectopic source (including a thoracotomy in one case), but in no instance was this found and a pituitary origin remained the final preoperative diagnosis.

It is interesting that, of the 19 patients with preoperative endocrine testing typical of Cushing's disease, 95% proved to have tumors of primary pituitary pathology. Microadenomas were proven in 14 and presumed in two, and macroadenomas were proven in two. There were no ectopic tumors. On the other hand, of the 11 patients with atypical testing, only 55% proved to have tumors of a pituitary origin and 18% were ectopic. These data lead us to conclude that in those patients with atypical preoperative endocrine testing and a negative CT scan, additional evaluation is important in reducing the rate of negative explorations. The technique of simultaneous bilateral inferior petrosal sinus sampling for ACTH described by Oldfield, et al.,16 may be of considerable help in these difficult situations. They found a gradient of increased ACTH ipsilateral to a microadenoma in 10 of 10 cases. In three patients the tumor could not be visualized at surgery, but a hemi-resection of the gland on the side of the higher ACTH concentration resulted in remission.

Of the 34 patients explored in this series, microadenomas were identified in 25 and pathologically proven in 21. The existence of microadenomas in the remaining four is substantiated by the fact that all four were in remission with selective micro-resection of the observed tumor. This overall incidence of microadenomas of 74% is comparable to what has been reported previously. Boggan, et al.,1 reported a 64% incidence of microadenomas in their series of 100 cases of Cushing's disease; 60 were pathologically proven tumors and four patients were in remission after selective resection of suspicious-appearing tissue. Salassa, et al.,17 reported a 71% incidence of microadenomas, with 62 proven and eight presumed microadenomas, in 98 surgical explorations. Kuwayama and Kageyama11 found a 76% incidence of microadenomas, with 69 proven and six presumed, in their series of 98 patients. Hardy6 reported finding microadenomas in 73% of 75 patients undergoing surgical exploration.

The incidence of macroadenomas in this series was three (9%) of 34 cases. Boggan, et al.,1 reported a 22% incidence of macroadenomas, Salassa, et al.,17 19%, Kuwayama and Kageyama11 16%, and Hardy6 11%. The true incidence of macroadenomas may be somewhat higher, since the more obvious tumors may not be referred to larger centers for evaluation and treatment.

The fact that two ectopic tumors were ultimately identified and resected in this series of 34 patients reflects the less than precise methods of preoperative evaluation. Although both of these patients had atypical preoperative endocrine testing, one tumor was found to be located within the pharyngeal or ectopic pituitary tissue in the sphenoid sinus. It was fortuitous that this was identified and removed during transthyphoid surgery, since the intrasphenoid tumor was not evident on high-resolution CT scanning. Boggan, et al.,1 reported two ectopic tumors in 100 cases, and Kuwayama and Kageyama11 reported two in 98 cases. Other authors publishing surgical series either did not find ectopic tumors or did not include them along with the primary pituitary tumors.

The specific diagnosis remained unknown in four (12%) of our 34 patients. Atypical testing was found in three of these four, and some of these patients may yet turn out to have ectopic sources of ACTH. Of the 100 cases reported by Boggan, et al.,1 12% remained in this unknown category, as did 9% of the 98 cases of Salassa, et al.,17 and 13% of Hardy's 75 cases.6 Only 7% of the 98 patients of Kuwayama and Kageyama11 remained undiagnosed.

The overall remission rate in our series was 74%. In those patients with proven or presumed microadenomas, the initial postoperative remission rate was 88% (22 of 25). Boggan, et al.,1 obtained remissions in 94% of 64 microadenoma patients, and Salassa, et al.,17
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likewise effected a remission in 94% of 70 patients with microadenomas. Hardy9 achieved remissions in 87% of 55 patients with microadenomas, and Kuwayama and Kageyama11 reported remissions in 96% of 69 patients with microadenomas.

Our remission rate of 33% of three patients with macroadenomas is not meaningful because of the small number of patients. Boggan, et al.,11 reported remissions in 45% of 22 patients with macroadenomas, and Salassa, et al.,17 in 61% of 18 patients with macroadenomas. Hardy9 observed remissions in 63% of eight patients harboring macroadenomas.

Of the 24 patients in this series in whom a specific location of the tumor could be identified, 17 tumors were lateral (nine right and eight left) and seven were central. This 71% incidence of eccentrically placed tumors is in line with the 86% incidence reported by Boggan, et al.,11 and the 79% incidence reported by Kuwayama and Kageyama.11 All of these findings contradict the 6% incidence of eccentric tumors reported by Hardy.9 This apparent contradiction may be a result of differences in definition of “lateral” and “medial,” but it appears that the majority of these tumors do not occur precisely in the midline.

Total hypophysectomies were performed in three patients in this series in situations in which a definite adenoma could not be identified, resulting in remission in one case. Our general approach has been to consider a total resection if the patient is beyond childbearing age and has agreed to this possibility in advance. This procedure is then reserved for those cases with severe Cushing’s disease and typical preoperative endocrinologic testing, in which a definite adenoma cannot be found during surgery. Sometimes it is wise to await postoperative endocrine and pathology reports, then consider reoperation within 4 weeks for a total hypophysectomy if this is indicated. Boggan, et al.,11 encouraged an aggressive approach since they reported seven of 12 patients in remission after total hypophysectomy, but Kuwayama and Kageyama11 supported a more conservative approach as they believed that many of these patients subsequently proved to have ectopic tumors.

Immunohistochemical analysis as well as standard H & E staining were performed on every surgical specimen in this series. Immunohistochemical staining confirmed the presence of excessive ACTH-secreting cells in each case of adenoma diagnosed by H & E staining, but in no case was it alone responsible for the diagnosis. In three macroadenomas unusual ACTH-secreting cell patterns were identified with immunohistochemical staining. Focal hyperplasia was noted in one child, and two adults were found to have multiple micronodules of ACTH-secreting cells. In none of the cases was there an abundance of cells secreting prolactin, growth hormone, TSH, FSH, or LH, but beta-endorphin-secreting cells were present in all nine adenomas in which this stain was used. Although immunohistochemical stains did not add to the diagnostic capability in this series, we believe that this technique is important to better understand the specific cell composition of these tumors.

As pointed out, early frozen-section reports should be interpreted cautiously, and careful inspection of the entire gland should be carried out even in the face of a “positive” frozen-section biopsy. It may be that the rapid-staining technique described above, which uses RCA 120 and PI to determine stromal configuration and nuclear morphology, will improve the diagnostic reliability of the intraoperative pathological evaluation.15

The empty sella syndrome was present in two of our cases and provided a challenging surgical situation in both instances. In one case remission was effected with selective resection, and in the other no remission was obtained in spite of an attempt at total hypophysectomy. In each case the pituitary tissue was extremely adherent to the thin bulging diaphragma sellae. It is important to recognize that, as has been demonstrated with hyperprolactinemia, an empty sella does not preclude the diagnosis of a microadenoma.

The patients with remissions in this series will be carefully observed for signs of recurrence. The patients who did not respond to surgery will continue to be evaluated and treated in an attempt to bring about remission.

References


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