Cushing's Disease: Dilemmas of Diagnosis and Management

M. Saeed-uz-Zafar

Raymond C. Mellinger

Max Wisgerhof

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Determining the cause of Cushing’s disease and correcting the abnormality presents a continuing challenge to the clinician despite remarkable advances in diagnostic and therapeutic techniques. We present seven cases to illustrate 1) the classic disorder cured by pituitary adenomectomy; 2) persistence of the disease after adenomectomy; 3) Cushing’s disease manifesting in the puerperium and remitting with dopamine agonist therapy; 4) a patient whose disease relapsed at least five times during 20 years of treatment by adrenalectomy, pituitary radiation, mitotane, and pituitary adenomectomy; 5) the Nelson syndrome; 6) the ectopic adrenocorticotropic hormone (ACTH) syndrome in a patient with dexamethasone suppressible urinary cortisol who had a pituitary adenoma which stained positively for ACTH but who was not cured by total hypophysectomy; and 7) a patient whose ACTH-secreting tumor proved fatal despite repeated surgical, radiologic, and pharmacologic measures. (Henry Ford Hosp Med J 1991:39:10-17)

Harvey Cushing first described a patient with this disorder in 1912 (1). Twenty years later he reviewed the features of similar reported cases, some of whom were found at autopsy to have basophilic adenomas of the pituitary. He proposed that this pluriglandular disorder resulted from hyperfunction of pituitary basophil adenoma (2). Although understanding of the pathogenesis, diagnosis, and therapy of Cushing’s disease advanced greatly over the next five decades, dilemmas persist. A condition similar to Cushing’s disease can be produced by nodular or neoplastic disease of the adrenal glands as well as by tumors, benign or malignant, arising from either adrenal or pituitary tissue. Development of a reliable adrenocorticotropic hormone (ACTH) assay provides a ready demonstration when the disorder arises from the adrenal glands, for the ACTH levels are very low. However, in the presence of normal or elevated ACTH levels, the clinician is frequently challenged to identify the source of the hormone which is primarily responsible for the syndrome. Despite new techniques to measure pituitary and adrenal hormones and advances in radiological methods to study the two glands, the ultimate cause may defy detection and not be revealed even at autopsy (3). We present the details of seven patients with ACTH-dependent Cushing’s syndrome to illustrate the dilemmas of diagnosis and management encountered in over 150 similar patients treated at this institution in the last five decades.

Classic Cushing’s Disease

Case Report

Over the space of a few years a 75-year-old retired nurse developed facial rounding, centripetal obesity, and multiple ecchymoses. She noticed gradual darkening of her skin, emotional lability, somnolence, and lethargy, but increasing muscle weakness prompted her to seek medical advice. The clinical diagnosis was Cushing’s syndrome. Random plasma cortisol was 797 nmol/L (28.9 µg/dL) and the morning following administration of 1 mg of dexamethasone the level was 830 nmol/L (30.1 µg/dL). Plasma ACTH concentration was 18 pmol/L (81 pg/mL) when cortisol was 847 nmol/L (30.7 µg/dL). Twenty-four hour urinary cortisol was 549 nmol (199 µg). Administration of 8 mg of dexamethasone at night resulted in a decline in plasma cortisol to 143 nmol/L (5.2 µg/dL) and ACTH to less than 2 pmol/L (< 8 pg/mL) the next morning. Although the diagnosis of Cushing’s disease seemed established, computed tomography (CT) of the sella turcica revealed no abnormality. On the strength of the clinical data, transsphenoidal pituitary surgery was recommended and a microadenoma successfully removed. Two days after surgery plasma cortisol was 55 nmol/L (2 µg/dL), and glucocorticoid therapy was required for the subsequent six months of gradual clinical improvement. The removed pituitary tissue stained heavily with ACTH antibody.

Comment

Harvey Cushing noted basophilic pituitary adenomas at autopsy in six of eight patients with this disease and proposed that these tumors were in some fashion the ultimate cause of the hypercortisolism (2). Although the pathogenesis of pituitary ACTH hypersecretion is still incompletely understood, there is no dispute regarding the central role of the pituitary adenoma. The majority of these tumors are small, do not enlarge the sella, and may be difficult to detect before surgery by currently available radiological techniques. Even employing the technique of magnetic resonance imaging (MRI), no more than two-thirds of the tumors can be demonstrated (4-8). Absence of radiologic ev-
Cushing's Disease Persistent After Pituitary Adenomectomy

Case Report
A 30-year-old black female first seen in 1981 had a one-year history of hypertension, diabetes, amenorrhea, and weight gain. She had noticed multiple ecchymoses, increasing pigmentation over her knuckles, and supraclavicular fullness. Blood pressure was 170/100 mm Hg. Plasma cortisol was elevated (966 nmol/L [35 µg/dL]) but urinary cortisol was only 276 nmol/d (100 µg/24 hrs). After transsphenoidal adenomectomy plasma cortisol the morning after administration of 1 mg of dexamethasone was 331 nmol/L (12 µg/dL). The diagnosis of Cushing’s disease was thought likely, but the patient was lost to follow-up for two years. Seen again in 1983 because of increasing muscle weakness, her plasma cortisol was high both in the morning (1,186 nmol/L [43 µg/dL]) and afternoon (1,297 nmol/L [47 µg/dL]). Urinary cortisol had risen to 3,863 nmol/d (1,400 µg/24 hrs) and plasma ACTH was 33 pmol/L (152 pg/mL). CT of the sella was reported as normal. After transsphenoidal adenomectomy plasma cortisol declined to 152 nmol/L (5.5 µg/dL). The postoperative course was complicated by pneumococcal meningitis treated successfully with intravenous penicillin. Subsequently, the plasma cortisol value rose to 497 nmol/L (18 µg/dL) and the patient required no exogenous glucocorticoids. Because the disease was believed not to have been cured, pituitary radiation (5,000 rads) was administered and the patient treated with mitotane. Early in 1984 she discontinued mitotane of her own volition and eight months later afternoon plasma cortisol level was 433 nmol/L (15.7 µg/dL), falling to 69 nmol/L (2.5 µg/dL) the morning after 1 mg of dexamethasone.

Comment
The ability to identify intrasellar microadenomas and the development of microsurgical techniques revived transsphenoidal pituitary surgery. Selective adenomectomy can be performed leaving intact the normal pituitary tissue. Even when a pituitary adenoma is not identified radiologically, if intrasellar ACTH production appears certain, transsphenoidal removal of hyperfunctioning tissue is usually curative (13-17). However, in a substantial number of patients, when intrasellar lesions cannot be identified and totally removed at surgery, ACTH hypersecretion persists. Such cases require subsequent total hypophysectomy, bilateral adrenalectomy, pituitary irradiation, or pharmacologic therapy. In Cushing’s disease the hypercortisolism is the cause of morbidity and prompt correction is necessary. Although bilateral adrenalectomy usually achieves this end, subsequent regrowth of adrenal remnants or the development of pituitary tumors are possible late complications.

In the reported patient transsphenoidal surgery was undertaken despite the absence of radiologic evidence of pituitary neoplasm. Although the surgeon identified a pituitary adenoma at surgery, its removal did not produce a cure and the patient developed pneumococcal meningitis. Ultimately, a combination of mitotane and pituitary irradiation corrected the hypercortisolism. Very possibly, Cushing’s disease in this patient could have been managed primarily with a combination of mitotane and external irradiation. However, reliable criteria are not yet available to select such patients. Review of our total experience with Cushing’s disease suggests that patients whose urinary 17-hydroxycorticosteroid levels fall more than 50% after administration of 8 mg of dexamethasone are likely to respond well to external irradiation.

Pituitary irradiation, once frequently used to treat this disorder, is not often advised as primary therapy. Conventional irradiation involves administration of 4,400 to 5,000 rads but complications increase with doses over 4,800 rads (18,19). Although biochemical and clinical improvement is frequently achieved, the reported cure rate from radiation alone is only 15% to 25% in adults. Significant improvement is said to occur in 80% of children treated (20) and when combined with unilateral adrenalectomy radiation therapy achieves a higher remission rate at all ages (21). Conventional radiation requires about 18 months to attain its maximal effect. With special techniques increased intensity of radiation can be delivered to the pituitary (19). Radioactive gold or yttrium-90 implanted surgically by the transsphenoidal approach produces a remission rate of 65% and an additional 16% of patients are improved (22,23). However, the frequency of operative complications is high and panhypopituitarism is commonly the ultimate result. Heavy particle irradiation is frequently effective but is not widely available (24). Reported side effects include temporary ocular motor disturbance, visual loss, hypopituitarism, and secondary neoplasms (25-27). Heavy particle therapy requires detailed knowledge of the patient’s sellar anatomy to guide the beam correctly, and significant extrasellar extension is a contraindication to its use (24).

Cushing’s Syndrome Developing Postpartum

Case Report
A few days after term delivery, this 33-year-old white woman experienced unexplained rectal hemorrhage. In the following six weeks she experienced emotional lability, hyperkinesia, weakness, polydipsia, and easy bruising. Referred with a diagnosis of fulminant Cushing’s syndrome possibly due to ectopic ACTH production, she was shown to have plasma cortisol as high as 1,545 nmol/L (56 µg/dL) and urinary cortisol of 2,831 nmol/d (1,026 µg/24 hrs) but only minimally elevated ACTH of 21 pmol/L (97 pg/mL). CT revealed pituitary enlargement. After 8 mg of dexamethasone, urinary cortisol rose paradoxically to 6,896 nmol/d (2,500 µg/24 hrs). PENDING ETIOLOGIC DIAGNOSIS, ADMINISTRATION OF AMINOGLUTETHIMIDE LOWERED PLASMA CORTISOL TO 359 nmol/L (13 µg/dL) but was discontinued because of scalp hair loss. Extensive investigation failed to disclose any neoplastic disease, and the pituitary was shown to be undergoing the expected postpartum involution. At this point, therapeutic trial with bromocriptine, 7.5 µg/day, resulted in normalization of plasma cortisol and symptomatic improvement. Inter-
the development of Cushing’s disease postpartum and the prob­
However, these corticotroph cells may proliferate during preg­
years. A detailed case report has been published (28).

Comment
Although pituitary hyperfunction is undoubtedly responsible, this case raises the question of the pathogenetic mechanism for
rapture of the treatment three months later was followed by laboratory and clinical recurrence, so bromocriptine administration was resumed. During prolonged treatment, serum cortisol, ACTH, and urine cortisol levels usually remained at normal concentrations. The patient was symptomatically well except for four transient episodes of weight gain, insomnia, and hyperactivity. During one of these episodes urinary cortisol was elevated, but the episodes resolved without adjustment of the dose of bromocriptine (Fig 1). Treatment was discontinued after 17 months and the patient has remained in remission for more than four years. A detailed case report has been published (28).

Comment
Although pituitary hyperfunction is undoubtedly responsible, this case raises the question of the pathogenetic mechanism for
the development of Cushings disease postpartum and the probable roles played by the anterior and intermediate lobes as well as the hypothalamus (29,30). The intermediate lobe, present in rudimentary form during intrauterine life, involutes after birth. However, these corticotroph cells may proliferate during pregnancy. The cells process the ACTH precursor proopiomelanocortin somewhat differently from the anterior lobe, have few receptors for cortisol, but are inhibited by dopamine. Lambers and associates (31) provided evidence for the hypothesis that in some patients Cushings disease results from overactivity of the intermediate lobe. Histologic studies with argyrophilic staining of removed tissue have been interpreted as revealing neural tis-
sue in six of 15 adenomas. These six subjects had hyperprolacti-
nemia and responded to a single dose of bromocriptine with a decline in prolactin as well as in ACTH levels, but cortisol levels were not suppressed by administration of dexamethasone (30, 31). In the management of Cushings disease, bromocriptine therapy has produced variable results and responses are almost always temporary (32,33). Although the disease results from primary overactivity of the anterior pituitary, a functional abnormality of the hypothalamus may be ultimately responsible in some patients. Such cases may not be cured by transsphenoidal hypophysectomy. A trial of bromocriptine therapy is recommended in selected patients, particularly those with associated hyperprolactinemia, whose cortisol is not suppressed with high-dose dexamethasone, or those whose disease follows preg-
nancy and delivery.

Multiply Recurrent Cushing’s Disease
Case Report
This 25-year-old widow was admitted to the hospital in 1969, following a suicide attempt. Her emotional problems were said to have begun following her husband’s murder three years earlier. Subsequently, she gained weight and developed menstrual irregularities, high blood pressure, and changes in body habitus. Laboratory data were consistent with a diagnosis of Cushings disease and in 1968 bilateral adrenalectomy was performed. Thereafter, she received glucocorticoid replacement therapy but was not clinically improved. One year later, after the suicide gesture, she was referred to us. On admission, she had florid features of Cushings syndrome and the steroid therapy was withdrawn. Plasma cortisol and urinary 17-hydroxycorticoids levels remained well above the normal range. The patient was psychotically depressed and required psychotropic drug therapy. Pituitary radiation was also administered in a dose of 5,000 rads. Very little clinical improvement ensued and plasma and urinary cortisol levels were well above normal a year later. Therapy with mitotane (o,p’-DDD) 2 to 4 g daily was initiated in June 1970.

During the next four years, two remissions, each lasting more than a year, were induced by administration of the drug. During the fourth relapse of the disease, the patient experienced a violent headache and nausea and vomiting which required hospitalization. Cushings disease remitted again, pigmentation subsided, and the gonadotropins and thyroid-stimulating hormone (TSH) became undetectable (34).

For the next 10 years the patient was physically and emotionally stable receiving replacement doses of hydrocortisone, thyroxine, estrogen, and progesterone. However, in April 1988, the hypertcorticism recurred yet again although other pituitary functions remained deficient. After more than a year of variably effective medical management with metyrapone, bromocriptine, and trifluoperazine hydrochloride, the patient agreed to transsphenoidal hypophysectomy. A pituitary adenoma was removed, and postoperatively ACTH was undetectable. The clinical remission still endures, but recent ACTH levels have again been above the normal range. Chronology of this patient’s course is shown in the Table.

Comment
Before steroid replacement therapy became available, subtotal adrenalectomy was the surgical treatment of choice for Cushings disease, but high rates of either persistent and recurrent hypercortisolism or fatal adrenal insufficiency prompted its abandon­ment. Bilateral total adrenalectomy, possible after cortisol
became available for clinical use, corrected the hypercortisolism but necessitated life-long steroid replacement (35,36). Moreover, progressive hyperpigmentation with the development of a persistent hypercortisolism following total adrenalectomy suggests incomplete removal of the adrenal glands. Persistent high ACTH levels stimulate any remaining adrenal tissue and may be sufficient to produce a recurrence of the hypercortisolism (38,39). Remnant adrenal tissue may represent incomplete surgical removal of hyperplastic glands or activation of aberrant adrenal tissue. Accessory and ectopic adrenal cortical tissue has been reported in a number of authors (40-42). Localization of functioning adrenal remnants may be difficult, the most successful method being radioactive iodocholesterol scanning (43-45).

This case of multiply recurrent Cushing's disease illustrates the difficulties of therapy which characterize some patients. Bilateral adrenalectomy and subsequent pituitary radiation failed to produce remission. In our experience either treatment is more likely to fail if there has not been significant suppression of steroid levels after administration of 8 mg of dexamethasone orally. In the reported patient hypercortisolism was repeatedly controlled with mitotane but the remissions were not permanent. The disorder was corrected for 10 years after pituitary apoplexy but ultimately surgical hypophysectomy was required. Removal of the pituitary adenoma initially might well have been the ideal approach although there is early evidence of still another recurrence.

The Nelson Syndrome

Case Report

A 25-year-old white woman was first treated for Cushing's disease in 1953. Adrenal exploration revealed cortical hyperplasia, and she had been treated with pituitary radiation, only 2,000 rads. Clinical remission persisted until 1958 when a suspected relapse was confirmed and she received an additional 1,500 rads. Because remission remained incomplete, bilateral adrenalectomy was performed in 1963. Despite replacement glucocorticoid therapy, the patient became progressively hyperpigmented and in 1967 had transient left third nerve palsy. She received a third course of pituitary irradiation and improved sufficiently to continue with only conventional hydrocortisone therapy. By 1978, hyperpigmentation was intense and ACTH concentration was 1,718 pmol/L (7,800 pg/mL). CT disclosed an intrasellar mass which was removed by the transsphenoidal approach. ACTH level fell to 15 pmol/L (67 pg/mL) postoperatively and the pigmentation diminished. In the next two years ACTH again rose progressively to over 77 pmol/L (> 350 pg/mL) and further pituitary surgery was performed. ACTH concentration has remained normal since 1981.

Comment

In 1958 Nelson and colleagues (46) described a patient with a large pituitary chromophobe adenoma which had developed in the three years after bilateral adrenalectomy for Cushing's disease. The patient had excessive pigmentation, amenorrhea, and visual field impairment. ACTH levels which were markedly elevated did not decline normally after intravenous hydrocortisone administration. The authors proposed that an ACTH-producing tumor had developed in response to the lower cortisol levels produced by bilateral adrenalectomy. Incidence of the Nelson syndrome, diagnosis of which depends upon the criteria employed, ranges between 5% to 78% (47-49). Inclusion of those patients who have hyperpigmentation but no radiographic evidence of a pituitary tumor increases the incidence. The hyperpigmentation and enlarging sellar mass may occur months to years after adrenalectomy and ACTH levels may exceed 3,303 pmol/L (15,000 pg/mL) (37,50).

Previous pituitary irradiation does not prevent occurrence of the Nelson syndrome, contrary to earlier concepts (51,52). Generally, the syndrome has a benign course characterized by hyperpigmentation and slowly progressive changes in the sella turcica. However, some tumors are rapidly progressive, and suprasellar extension compresses the optic nerves (53). Some have even been considered malignant. Pituitary apoplexy occurs with some frequency in these tumors, either spontaneously or in association with manipulative procedures (54).

Development of the Nelson syndrome after bilateral adrenalectomy for Cushing's disease cannot be predicted reliably. About 90% of the large pituitary tumors demonstrated either at the time of diagnosis of Cushing's disease or after adrenalectomy are chromophobe adenomas. An occasional tumor is found to be eosinophilic, but more sophisticated techniques such as electron microscopy and immunohistochemistry confirm that these tumors are composed of corticotroph cells (55).

Results of treatment of the Nelson syndrome, particularly in those patients with large invasive tumors, are disappointing. Conventional irradiation is effective in only a minority. Heavy particle irradiation either with the proton beam or with alpha particles is more effective but cannot be used to treat large tumors with extra sellar extension. Surgery, transsphenoidal or transfrontal, is usually successful, but recurrences are common. Response to administration of cyproheptadine, used in a few cases, is variable and unpredictable. Abandonment of total adrenalectomy as primary therapy for Cushing's disease in favor of transsphenoidal adenomectomy may reduce the frequency of the disorder. Patients who have undergone bilateral adrenalectomy should be monitored regularly by means of plasma ACTH levels, visual field examinations, and MRI of the pituitary.

The described patient developed hyperpigmentation several years after bilateral adrenalectomy. Prior pituitary irradiation


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Fig 2—Pituitary adenoma removed by transsphenoidal hypophysectomy. A) Hematoxylin-eosin stain (× 100). B) Immunoperoxidase stain confirming heavy concentration of ACTH. Removing the adenoma did not lower the plasma ACTH level nor alleviate Cushing's syndrome. After subsequent adrenalectomy, metastatic, ACTH-positive neuroendocrine tumor was demonstrated by liver biopsy.

did not prevent the development of the symptomatic pituitary tumor. Transsphenoidal removal of the pituitary tumor, performed twice, did not completely eliminate ACTH secretion and mild hyperpigmentation persists.

Ectopic ACTH Production of Unknown Source

Case Report

A 23-year-old white woman was admitted to the hospital for management of Cushing's syndrome, symptoms of which had been present for two years. Despite the presence of hypokalemia, hyperglycemia, and high plasma cortisol (1,186 nmol/L [43 µg/dL]), the urinary cortisol level was only slightly above normal (414 nmol/d [150 µg/24 hrs]) and declined to 22 nmol/d (8 µg/24 hrs) after administration of dexamethasone, 2 mg four times a day for two days. Because the patient was taking oral contraceptives to regulate her menses, the hypercortisolemia was considered to be caused by increased cortisol binding globulin. However, a year later when she was not receiving estrogen, plasma cortisol was 828 nmol/L (30 µg/dL) and was not reduced overnight by 1 mg of dexamethasone (910 nmol/L [33 µg/dL]). Moreover, plasma ACTH level was 61 pmol/L (276 pg/mL). Cerebral CT was interpreted as demonstrating an intrasellar mass while chest x-ray was negative. Transsphenoidal hypophysectomy produced no clinical or biochemical improvement although the tissue removed stained heavily for ACTH and the pathologic diagnosis was ACTH-secreting pituitary adenoma (Fig 2). After surgery the ACTH level was 107 pmol/L (485 pg/mL). CT of the chest and abdomen revealed no ectopic source for the ACTH and reexploration of the sella yielded no additional tumor tissue although the pituitary remnant was removed. The patient became progressively worse and was confined to bed with muscle weakness. A few weeks after the second pituitary operation she developed meningitis which responded to antibiotic therapy. Need to correct the progressive illness led to bilateral adrenalectomy with gratifying clinical results. The patient’s strength gradually returned, blood pressure became normal, and she resumed her usual activity. A few months later, however, she developed intense dermal pigmentation (Fig 3), and the ACTH level had risen to 2,202 pmol/L (10,000 pg/mL). Repeat CT of the abdomen now demonstrated a hepatic defect. Tissue obtained by liver biopsy had features of a neuroendocrine tumor and stained intensely for ACTH but not for CRF.

Comment

The most vexing problem facing the clinician is to differentiate excess ACTH of pituitary origin from one of ectopic source. This phenomenon of ectopic ACTH production was one of the
first humoral paraneoplastic syndromes described. In 1928, W. Hurst Brown (56) reported a patient with oat cell carcinoma of the lung who had clinical signs of hypercortisolism and was found to have adrenal hyperplasia. Since then increasing numbers of patients have been reported to have Cushing’s syndrome secondary to extra-endocrine benign or malignant tumors. Clinical manifestations vary. Glucose intolerance is frequent and frank diabetes may occur. Weakness, hypokalemia, and weight loss generally accompany the disorder. However, these features are not unique to the ectopic ACTH syndrome and in some patients the disorder closely mimics Cushing’s disease.

Oat cell carcinoma of the lung is the neoplasm most commonly responsible for this disorder. Other reported tumors include thymoma, carcinoid (thymic, endobronchial, gastric, pancreatic), medullary carcinoma of the thyroid, salivary gland tumors, ovarian cancer, islet cell carcinoma of the pancreas, melanoma, pheochromocytoma, squamous cell carcinoma of the cervix, and carcinoma of the prostate (57-72). Some of these tumors have been reported to produce CRF in addition to ACTH but its biologic significance is not completely understood (73-76).

The hypercortisolism of ectopic ACTH syndrome usually produces significant morbidity such as hyperglycemia, wasting, weakness, and severe electrolyte disturbance. Although treatment which controls hypercortisolism may prolong life, the risk of bilateral adrenalectomy is great for these seriously ill patients, many of whom have malignant tumors. Pharmacologic agents which inhibit adrenal secretion provide useful treatment (77,78).

The reported patient demonstrates several problems in diagnosis and management. The ectopic production of ACTH was not recognized initially, and the location of the primary neoplasm continues to evade us. The undoubted presence of a corticotrophic pituitary adenoma is additionally confounding. The hypercortisolism was not corrected by removal of this adenoma but only by bilateral adrenalectomy. Subsequent generalized hyperpigmentation has been severe.

The Incurable Case

Case Report
A 33-year-old white pipe fitter was seen initially in 1975 with signs and symptoms of Cushing’s syndrome. He was mildly hyperpigmented and his blood pressure was 170/100 mm Hg. Plasma cortisol level was elevated and fell only to 535 nmol/L (19.4 µg/dL) the morning after administration of 1 mg of dexamethasone. Urinary 17-hydroxycorticosteroids were also high and failed to decline after administration of 8 mg of dexamethasone on each of two days (151 µmol/d [54.8 mg/24 hrs]). ACTH level was 73 pmol/L (333 pg/mL). The diagnosis was Cushing’s disease, and 5,000 rads of cobalt radiation were administered to the pituitary area while mitotane (1 to 4 g daily) was taken by mouth. Clinical improvement was not sustained and two years later CT revealed a pituitary mass with suprasellar extension. Transphenoidal hypophysectomy was performed in 1978. Histologic study revealed diffuse fibrosis with degenerative changes of the pituitary but no tumor was found. Nonetheless, after surgery cortisol therapy was required and ACTH remained at undetectable levels for about three years. In 1983 plasma cortisol concentrations rose again to 1,159 nmol/L (42 µg/dL) and mitotane therapy was reinstituted. CT of the sella disclosed a recurrent pituitary mass. Pituitary tissue removed again by the transsphenoidal approach revealed only fibrosis although the patient experienced postoperative failure of both the gonadotropins and TSH. ACTH remained high and the hypercortisolism was controlled with mitotane. Additional radiation was administered but neither cyprophedidine or bromocriptine administration produced any observable effect.

By 1987, ACTH levels consistently exceeded 2,202 pmol/L (10,000 pg/mL), the patient was intensely pigmented, and the pituitary tumor had invaded the cavernous sinus and right orbit. A major but subtotal excision was accomplished transcranially although the ACTH level remained over 1,321 pmol/L (6,000 pg/mL) and mitotane was required to control the adrenal hyperfunction. The pituitary tumor continued to enlarge and the patient died in 1991.

Comment
This case demonstrates that currently available methods to treat Cushing’s disease may be inadequate. This patient underwent “maximum” pituitary irradiation as well as four attempts at surgical removal of the pituitary tumor. He remained uncured. Mitotane administration controlled the glucocorticoid excess, but huge excesses of ACTH were secreted by the devastating intracranial tumor.

In this patient urinary 17-hydroxycorticosteroids were not suppressed by administration of 8 mg of dexamethasone before he had received any therapeutic intervention. In our experience such data suggest a poor prognosis and aggressive surgical treatment should be undertaken at the outset.

Summary
Harvey Cushing’s great contribution at the beginning of this century was to establish the role of pituitary adenoma in the genesis of the disease that bears his name. Although the pituitary adenoma is now clearly understood to be the cause of the classic disorder, variable results of medical, radiologic, and surgical treatment as well as the propensity to recurrence and invasion make management a serious dilemma. Moreover, a clinically similar disorder can be produced not only by hyperfunctioning adrenal neoplasms but also by ACTH produced ectopically in a variety of “nonendocrine” tumors. The true source of ACTH hypersecretion, the incompletely understood involvement of the hypothalamus, and the possible return of pituitary hyperfunction after surgery are considerations which can confound the diagnostician. Despite spectacular radiologic advances, imaging studies can be misleading. We believe that of the currently available diagnostic techniques, the measurement of ACTH gradient in the petrosal sinuses and peripheral vein blood obtained simultaneously after CRH administration is the most reliable means of identifying the source of ACTH excess.

The success of therapy, which at best is unpredictable, depends first of all on accurate diagnosis of the disease. When Cushing’s disease is due to a pituitary adenoma, transsphenoidal adenomectomy is often ideal treatment.

Recurrence of the disease after pituitary adenomectomy may respond to irradiation. Despite a disappointing rate of remission, radiotherapy should not be dismissed as primary therapy, especially in conjunction with medical measures to control adrenal hyperfunction. Neither should medical control of the pituitary...


40. Chaffee WR, Moses AM, Lloyd CW, Rogers LS. Cushing’s syndrome with accessory adrenocortical tissue. JAMA 1963;186:799-801.


