Cushing's Disease Today

Late Follow-up of 17 Adrenalectomy Patients with Emphasis on Eight with Adrenal Autotransplants

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Cushing's disease has come full cycle. As originally asserted more than 50 years ago, modern diagnostic techniques now demonstrate an adrenocorticotropic hormone (ACTH) secreting pituitary adenoma in approximately 80% of such patients. At this historical juncture, we report a long-term follow-up of our 17 patients who underwent adrenalectomy (8) or later adrenalectomy plus adrenal autotransplantation (9) between 1955 and 1976. Two patients died soon after surgery and five others died later of "natural" causes. Four others moved away but were stable when last contacted. Of the six patients who remain available for current follow-up, three have undergone hypophyseal surgery. Another patient has evidence of pituitary enlargement, and the remaining two are yet to undergo computerized tomography (CT) scan. Four illustrative cases are reviewed in some detail. One case presented with Nelson's syndrome and acute onset blindness. The second represented multiple endocrine adenomatosis with hyperparathyroidism in addition to Cushing's disease. The third exhibited Cushing's syndrome from the autotransplants, finally cured by hypophysectomy. The fourth exhibited huge ACTH levels from a large pituitary adenoma that could not be totally resected and recurrent Cushing's syndrome associated with large autotransplant "adenomas." The initial surgical treatment of choice is pituitary adenectomy. Bilateral adrenalectomy will remain useful where curative pituitary surgery is not feasible. Neither pituitary irradiation nor medical therapy has been truly effective in our patients. Adrenal autotransplants survive, to some extent, in virtually all patients. However, the degree of function is variable, and the full function may not be achieved for many months or even years. Functioning autotransplants have not prevented Nelson's syndrome, and they would appear to offer little practical benefit at this time.

HARVEY CUSHING described in 1932 the clinical syndrome produced by hypercortisolism, which came to bear his name.[1,2] He suggested that the characteristic clinical findings were related to the presence of a basophilic adenoma of the pituitary, which he demonstrated at postmortem on several occasions. Clearly, the most direct surgical management would have been excision of the pituitary tumor, but the diagnostic and technical difficulties attending hypophysectomy were formidable. Therefore, radical subtotal resection of the target organs, the adrenals, became the treatment of choice for many years. As the years passed, there remained considerable doubt in many instances that a pituitary tumor even existed. Subtotal adrenalectomy was the surgical treatment of choice prior to the general availability of cortisone and other effective synthetic adrenocortical replacement therapy. Thereafter, total intraabdominal adrenalectomy with permanent replacement therapy was usually elected.

To avoid the need for such lifelong replacement therapy, we[3–5] and others[6–9] began, in the early 1960s, to explore the benefit of autotransplanting portions of the excised adrenals to some readily accessible subcutaneous site, usually the right sartorius muscle in our patients. Should Cushing's syndrome recur, the transplanted tissue could be partially excised under local anesthesia. Additional clinical objectives were to reduce the risk of late Nelson's syndrome[10] (large pituitary chromophobe tumor then commonly believed to be secondary to adrenalectomy) and the marked skin pigmentation that at times followed adrenalectomy.

Meanwhile, modern refinements in the classical transsphenoidal approach to the pituitary gland, along with the advent of microsurgery and spectacular progress in radiologic imaging techniques, gave rise to renewed interest in hypophysectomy.[11–15] In addition, improved

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Presented at the 96th Annual Meeting of the Southern Surgical Association, Palm Beach, Florida, December 3–5, 1984.

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Submitted for publication: December 18, 1984.

function tests could afford more precise analysis of adrenal and pituitary function and dysfunction. There is now promise that highly selective bilateral petrosal sinus venous sampling for (ACTH) concentrations may afford enhanced precision in lateralizing the tumor within the anterior pituitary lobe itself.[16] Positive results afford additional protection against pituitary surgery when the excessive ACTH arises not from the pituitary but from an ectopic source, such as a lung malignancy.

The surgical management of Cushing's disease stands at an historical crossroads. Total adrenalectomy for Cushing's disease may well be replaced by hypophyseal surgery in most patients. The purpose of this report is to present a brief survey of 17 patients who underwent bilateral adrenalectomy between 1955 and 1976. Eight had subtotal adrenalectomy, and nine had total adrenalectomy with adrenal autotransplantation to the thigh. The principal focus of this discussion will be directed to the adrenal autotransplants—including adrenal tissue survival, its function, late pigmentation of both the patient's skin and the transplants, Nelson's syndrome, and the questionable value of such adrenal autotransplants in the future. Four illustrative case reports will emphasize special considerations.

Results

Two of the 17 patients died soon after surgery, one early on from renal failure secondary to massive intraoperative hemorrhage from the inferior vena cava and the other from postoperative intraabdominal sepsis in the most severely Cushingoid and bedridden patient in the experience of the senior author. Six patients remain alive, seven have died (mostly from "natural" causes), and four have moved away and been lost to follow-up though they were alive and stable when last contacted.

Adrenal Autotransplant Patients§

Adrenal transplantation to the right upper thigh, most often using thin slices introduced into pockets made in sartorius muscle,[3,5] was performed in nine patients, of whom six are still alive. The three known deaths were in a 28-year-old woman who died of cardiac arrhythmia 12 years after adrenalectomy, a patient who died years later of a stroke at age 68, and the extremely Cushingoid female cited above who eventually died of intraabdominal sepsis following operation.

The transplanted tissue was biopsied under local anesthesia in virtually all patients, usually at about 3 months. There was histological evidence of at least minimal survival in every instance. However, the *degree* of survival varied widely, from minimal clumps of apparently viable adrenal cortical cells, at times scattered throughout areas of adrenal necrosis and fibrosis, to almost complete survival of the adrenal tissue as transplanted. Interestingly, one patient, whose transplants exhibited minimal and indeed questionable survival when biopsied 5 months postadrenalectomy, developed recurrent Cushing's syndrome 9 years later, associated with marked growth of the transplanted tissue (Case 4). A second patient developed marked enlargement of the transplants and recurrent Cushing's syndrome at 7 years (Case 3).

The degree of functional activity and support exhibited by the transplants in each patient generally correlated well with the histological evidence of graft survival and growth. Corticosteroid replacement therapy was eventually stopped completely in some patients—for recurrent Cushing's syndrome in two (Cases 3 and 4), but in the majority, some replacement was usually required. In fact, in some patients many months and even *years* elapsed before the transplanted slices of adrenal tissue had achieved sufficient new (parasitic) blood supply to provide truly meaningful function. Thus, in the presence of continued stimulus by excessive plasma ACTH levels derived from an enlarging pituitary corticotroph tumor, recurrent Cushing's syndrome may occur years later. In both our patients who developed recurrent Cushing's disease with marked enlargement of the transplants, the now rounded slices of transplanted tissue ("adenomas") had taken on a darkly pigmented color; this was in sharp contrast to the characteristic vivid yellow adrenal cortical color exhibited by fully viable transplants exposed for biopsy at only several months post-transplant.

Late Postadrenalectomy Hypophysectomy

Three of the six patients available for current late follow-up eventually underwent hypophysectomy. A fourth now has CT scan evidence of pituitary gland enlargement, but significant visual field impairment has not occurred, and thus far she has declined further studies and possible surgical intervention. One nontransplant patient underwent "emergency" hypophysectomy when she developed sudden rapid onset blindness due to hemorrhage into the pituitary tumor 15 years following radical subtotal adrenalectomy; removal of the large "chromophobe" tumor compressing the optic chiasma was followed by a return of vision to almost normal. Of the other two hypophysectomy patients, both of whom developed recurrent Cushing's syndrome from the adrenal autotransplants, one had a large chromophobe tumor that was incompletely excised because it extended beyond the confines of the sella turcica (Case 4). The other patient's recurrent Cushing's syndrome at 7 years

§ A preliminary report of results in these patients was published earlier.[3]

postadrenalectomy and transplantation was reversed by removal of the now nodular transplants (Case 3). However, when Cushing's syndrome developed a third time, she underwent removal of the anterior pituitary lobe and was cured of Cushing's syndrome. There was the possibility that residual transplant nodules remaining in the thigh had once again caused Cushing's syndrome for the third time. Unfortunately, the precise *number* of adrenal slices transplanted in each patient had not been recorded, since the surgeon did not anticipate that the complete excision of the transplanted adrenal tissue would ever become necessary. Other possible causes of the persisting hypercortisolism exhibited by both these patients with recurrent Cushing's syndrome, even after all detectable transplants had been excised from the thigh, could be unresected remnants of adrenal tissue in the abdomen at the usual adrenal sites, or ectopic adrenal rests.

Four Special Case Reports

Case 1

Acute onset blindness due to Nelson's syndrome: hypophysectomy with recovery. A 31-year-old white woman initially had a good result from pituitary irradiation for her Cushing's disease. However, in 1960, she had a recurrence of Cushingoid features and underwent subtotal adrenalectomy with good results. She did well on low-dose steroid replacement until 1976, 16 years postadrenalectomy, at which time she presented with acute onset blindness. She underwent craniotomy and was found to have a large, extensive pituitary tumor that had hemorrhaged massively. Total hypophysectomy was performed and the patient had return of vision almost to normal. She remains well on full pituitary replacement medication.

Case 2

Cushing's disease: part of multiple endocrine adenomatosis. A 16-year-old white girl was admitted to University Hospital in 1963 with acute onset of a florid Cushing's syndrome. Prior to surgery, she developed pseudotumor cerebri with severely increased cerebrospinal fluid pressure and coma, requiring tracheal entubation and assisted pulmonary ventilation for some days. After recovery she underwent bilateral total adrenalectomy with transplantation of a several-gram single mass of each adrenal to the sartorius muscle of the corresponding thigh on June 4, 1963. Biopsy of the transplant on each side on October 14, 1963, under the same general anesthetic used to perform cystogastrostomy for internal drainage of a large pancreatic pseudocyst, revealed remarkable mass survival of typical yellowish "adrenal tissue with focal areas of necrosis but approximately two-thirds appears viable."

Following this, steroid replacement therapy was gradually discontinued by the patient herself. Unhappily, the sometimes bizarre mental behavior, which she was reported to have exhibited prior to her original hospitalization for Cushing's disease, continued after eucortisolism had been restored. Primary hyperparathyroidism with marked hyperplastic enlargement of all four parathyroid glands was diagnosed in 1972, and three glands and part of the fourth were excised, with relief of the hypercalcemia. A large distal gastric ulcer developed in 1972. After several months of medical management without improvement, a bilateral truncal vagotomy and distal Billroth hemigastrectomy was performed. Incidentally, the site at which the pancreatic cystogastrostomy had been performed 11 years previously was virtually undetectable. Serum gastrin levels were normal.

The patient died abruptly at age 28 in 1975. She had just been talking normally with her husband, and death was believed possibly due to sudden cardiac arrhythmia, a known complication of a drug she was taking under psychiatric therapy. Autopsy was not requested by the coroner. Cushing's syndrome had not recurred.

Comment

This patient's case emphasizes that Cushing's disease may represent only one manifestation of a multiple endocrine adenomatosis. Such patients should be studied for hyperactivity of other endocrine glands as well as the adrenals. Secondly, this patient was fully supported by the excellent survival of her adrenal transplants to the thigh. Thirdly, both before and after adrenalectomy, she exhibited abnormal personality traits and behavior.

Case 3[3]

Cushing's disease twice recurrent (from adrenocortical transplants) with eventual hypophysectomy. A 32-year-old white woman underwent total intraabdominal adrenalectomy and transplantation of multiple adrenal slices to the right sartorius muscle on July 30, 1970. Function of the transplants was not formally assessed until 1977, when she developed recurrent Cushing's syndrome. Biopsy revealed hyperplasia of all eight transplant nodules ("adenomas") that were found. Unfortunately, no record had been made of how many adrenal slices had been transplanted in 1970. The hypercortisolism and the clinical features of Cushing's syndrome were abolished, but she continued to require no adrenocortical substitution therapy, and plasma and urinary cortisol values were at normal levels.

By 1978, however, she had again begun to gain weight and by the 1980s she clearly had developed Cushing's syndrome for the third time. Her endocrinologist at our institution had taken a position elsewhere, and she was referred by her local physician to Vanderbilt University Hospital for hypophysectomy in 1984, following appropriate diagnostic studies there. A pituitary microadenoma could not be identified at transsphenoidal surgery, and thus anterior hypophysectomy was done. After surgery, ACTH levels were undetectable and did not respond to corticotropin-releasing hormone, although they had done so before surgery.[17] All clinical signs of Cushing's syndrome are now absent, and her postoperative diabetes insipidus has virtually subsided.

Comment

The patient developed Cushing's syndrome three times, originally from her native orthotopic adrenal glands and next from the adrenal transplants to the thigh. The second episode occurred 7 years after transplantation. The hypercortisolism causing the third episode (about 7 years after excision of most of the detect-

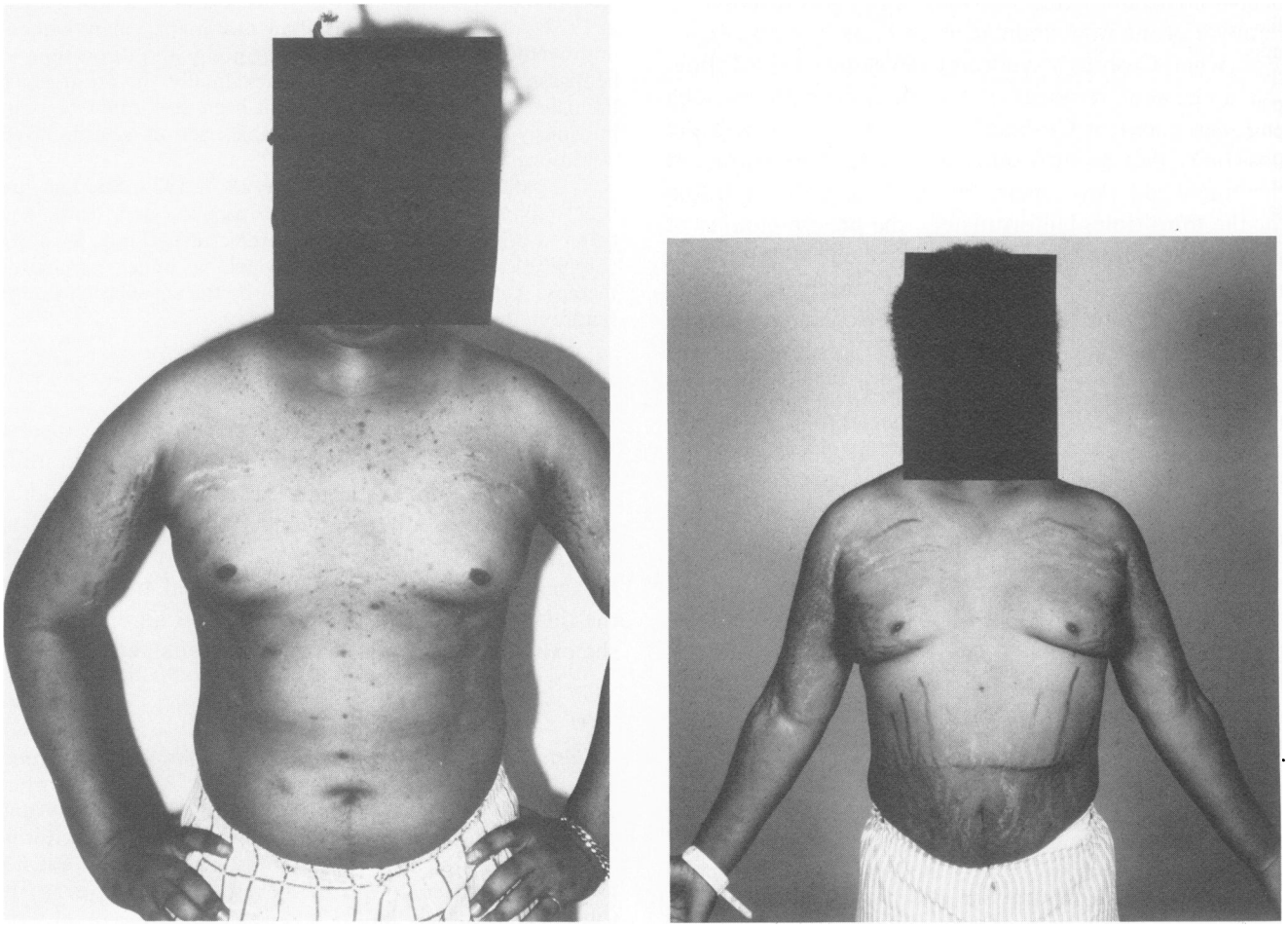

FIG. 1. V.D., Case 4: Cushing's syndrome secondary to ACTH-producing pituitary tumor. *Left,* onset of Cushing's disease at age 16. *Right,* recurrent Cushing's syndrome at age 26. Enlarged adrenal autotransplants to thigh.

able transplants to the thigh and 14 years after adrenalectomy in 1970) could have been due to unexcised transplants, incomplete adrenalectomy in 1970, or to an adrenal rest. It is hoped that this patient will represent one of the approximately 80% of Cushing's disease patients cured by pituitary surgery with excision of hyperfunctioning pituitary tissue.

Case 4

Pituitary corticotroph tumor and "Nelson's syndrome." Recurrent Cushing's syndrome from adrenal transplants. Failure of incomplete hypophysectomy to control extreme plasma ACTH levels. A black teenage football player developed classic Cushing's disease in 1975 at age 16 (Fig. 1). He underwent bilateral total adrenalectomy with adrenal autotransplantation. There was complete resolution of Cushing's syndrome with a fall in the serum cortisol levels. The transplants were biopsied 5 months after surgery and were noted to be minimally and, indeed, questionably viable, with much atrophy and fibrosis. The patient required adrenocortical replacement therapy and did well initially. The serum ACTH level remained substantially elevated, but this was believed then to reflect inadequate adrenocortical replacement therapy. In 1976, 1 year following surgery, the serum ACTH level was more markedly elevated (800 pg/ml, normal < 100; Fig. 2) and skin hyperpigmentation was observed. The sella turcica was not enlarged on plain skull films. Seven years later, however, (8 years after adrenalectomy) sella enlargement and erosion were discovered on skull films and the serum ACTH level was 2850. The patient underwent transsphenoidal hypophysectomy in March, 1983, with removal of a large corticotroph adenoma. The serum ACTH level fell from 11,250 before surgery to a low of 360 after surgery. However, only 8 months following transsphenoidal surgery there was an exacerbation of Cushing's syndrome with elevated serum ACTH and cortisol levels (Fig. 3) and a weight gain of almost 30 pounds. While no C-T evidence of pituitary tumor recurrence was noted, it was considered probable that additional unresected tumor resided outside the eroded sella. The serum ACTH level was 3500 pg/ml in August 1984 with an A.M. cortisol of 36 mcg/dl. A trial of sodium valproate therapy did not suppress the Cushing's syndrome and bromocriptine therapy was begun. Both these agents are believed to diminish production and release of corticotrophin-releasing factor (CRF) by the hypothalamus, but neither drug had much beneficial effect on this patient's Cushing's syndrome.

Meanwhile, it was obvious that the hypercortisolism causing the Cushing's syndrome had to derive from functioning adrenocortical tissue—whether from residual adrenal tissue left in the abdomen, from an adrenal rest, or from the tissue transplanted to the right thigh 9 years previously in 1975. This last possibility seemed unlikely, since biopsy 5 months after transplantation had revealed minimal, if any, survival of the transplanted adrenal slices. However, reexploration of the right sartorius muscle under local anesthesia, on October 31, 1984, disclosed not only survival but nodular hyperplasia of all seven transplants that were found (Fig. 4). Electron microscopy exhibited few secretory granules in the clearly viable adrenocortical cells. The serum free cortisol level promptly declined following removal of the transplants—but not to normal. Thus, we are now faced with the certainty that functioning adrenocortical tissue remains unexcised, somewhere. Unfortunately, the hyperfunctioning residual elements of the ACTH-producing tumor also persist, and radiation therapy is to be administered to the pituitary area.

Comment

This patient's case shows that, while hypophyseal surgery for excision of the usually present anterior pituitary corticotroph tumor can be definitive therapy for Cushing's disease for many or most cases, pituitary surgery is not invariably successful. Under this circumstance, ablation of all functioning adrenocortical tissue

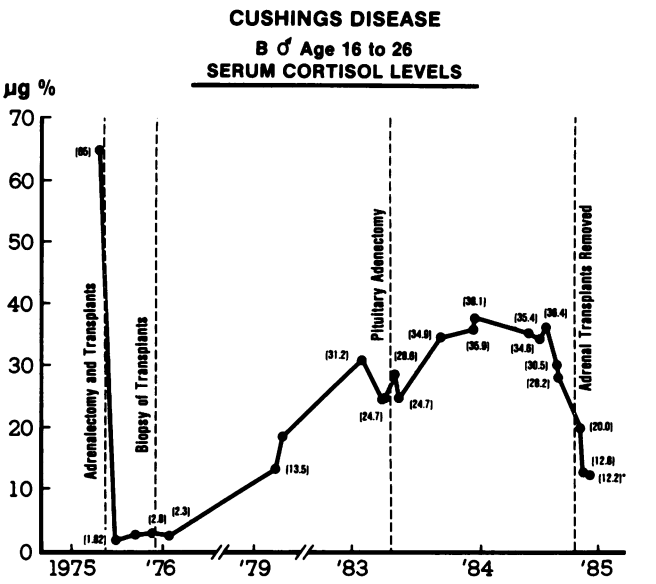

FIG. 3. Note that the serum cortisol level fell to a very low 1.82 mcg% after adrenalectomy in 1975. It gradually rose again under the intense ACTH stimulus from the pituitary tumor. It fell from 36 to 12 after removal of seven transplant nodules in October 1984. Even so, definite cortisol production continues from adrenal tissue somewhere—whether from transplants not excised, or from an adrenal remnant in the abdomen, or from an ectopic adrenal rest.

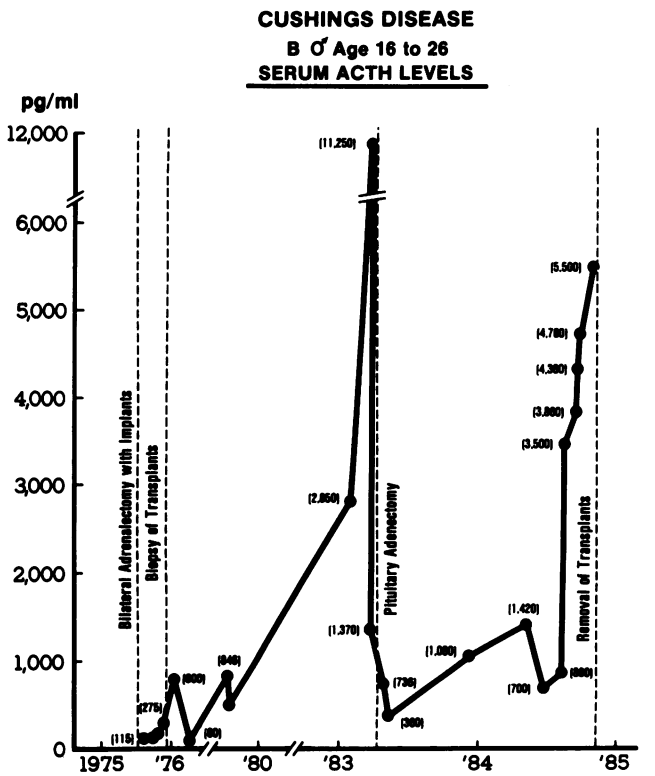

FIG. 2. Note extremely high plasma ACTH level of 11,250 picograms/ml prior to removal of pituitary tumor (incompletely) in 1983 (normal >100 pg/ml). It then fell to 360 but had risen again to 5500 in late 1984.

may be required. The next diagnostic step planned, to locate the residual functioning adrenocortical cortisol-producing tissue, is a scintiscan using administered radioactive cholesterol.

Discussion

Our series of 17 patients with Cushing's disease, while not large, has bridged an important era in the surgery for this disorder. The evolution in our clinic has progressed from subtotal adrenalectomy (removal of all the right adrenal and all but a small nubbin of tissue attached to the central adrenal vein on the left); to total intraabdominal adrenalectomy with adrenal autotransplantation to the thigh; to hypophysectomy under appropriate diagnostic, technical, and otherwise feasible circumstances. Much has been learned, but much room for improvement in diagnostic and therapeutic management remains.

Differential Diagnosis of Cushing's Syndrome

The differential diagnosis of Cushing's syndrome, which may be due to any one of numerous possible causes, as opposed to excessive ACTH secretion by the anterior pituitary itself, has become fairly well-standardized. This has resulted from the increased sophistication of tests of plasma and urinary cortisol levels, plasma ACTH levels, and dexamethasone suppression tests—

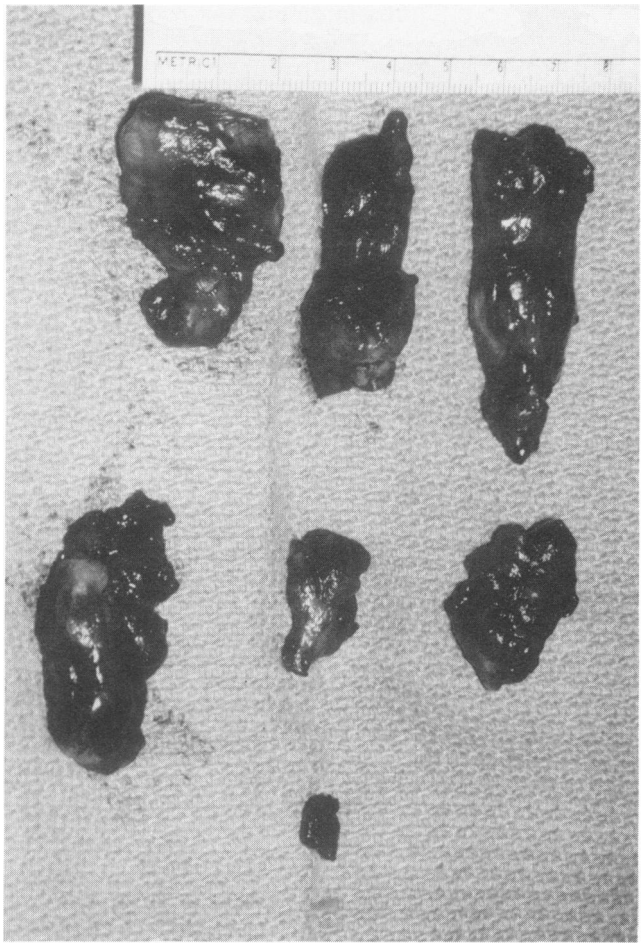

FIG. 4. V.D., Case 4: Seven "adenomatous" transplant nodules excised from the right thigh. These rounded transplants were originally thin slices of adrenal tissue.

plus the remarkable progress made in a variety of radiologic imaging techniques and selective catheterizations relative to both the pituitary and the adrenals. However, false positive and false negative roentgenological and biochemical errors in diagnosis will occasionally occur. When no pituitary microadenoma can be demonstrated on sophisticated radiologic imaging and selective catheterizations, while the hormonal work-up fully supports Cushing's disease, the increasing practice is to remove the anterior lobe of the pituitary. Although no microadenoma may be found even after the most careful pathological examination, such a patient will usually be cured of the clinical features of Cushing's syndrome. Under these circumstances, might there not have been pituitary hyperplasia or indeed hyperfunction of the cytologically normal appearing pituitary as reflected in an excessive number of intracellular secretory granules as seen on electron microscopy? Of course, every effort must be made to exclude some ectopic source of the excessive ACTH.

Management of Cushing's Disease

Nonoperative treatment. The major measures used in an effort to avoid operative intervention are pituitary irradiation, by various source modalities, and drugs. In our experience, pituitary irradiation has almost never effected permanent cure in adults, though the results in children have been considerably better. Several drugs (bromocriptine, sodium valproate, cyproheptadine) have been used in the effort to suppress the production of CRF in the hypothalamus, but beneficial results have been limited thus far.

Drugs targeted against the adrenal cortices themselves have included adrenocorticolytic agents such as o, p-, DDD, but with quite unpredictable results. In some patients, the administration of aminoglutethamide, which blocks the first chemical step after cholesterol (in producing cortisol), has been helpful in controlling the clinical features of Cushing's syndrome despite continued markedly increased plasma ACTH levels. It has been suggested that this drug be used for a period of time prior to hypophysectomy or adrenalectomy, to permit improvement in the patient's general metabolic condition and thus reduce the risk of operation.

By and large, nonoperative management of the adult patient with Cushing's disease is commonly unsatisfactory. Surgery is required to ablate hyperfunctioning endocrine tissue which, if not adequately managed, will prove fatal in the course of time.

Surgical treatment. Appropriate pituitary gland surgery can now be expected usually to produce "cure" of Cushing's disease. That is, the clinical features and the excessive ACTH and cortisol levels can be abolished in approximately 80 per cent of such patients. There will long remain a place for selective adrenalectomy, however. This operation would be elected when the community did not afford the diagnostic and surgical resources for pituitary surgery or when the entire ACTH-secreting tumor could not be removed, or when the patient simply declined pituitary surgery in favor of adrenalectomy.

Corticotroph cell (ACTH-producing) adenomas comprise approximately 20 per cent of pituitary tumors. These tumors were formerly called basophil tumors. Prolactinomas, which produce galactorrhea, account for 50 per cent of pituitary tumors, and somatotroph cell adenomas (formerly termed acidophil adenomas, sometimes causing giantism) 25 per cent.

The so-called chromophobe adenoma, until recently considered a nonsecreting common pituitary adenoma, has, with the advent of electron microscopy and the demonstration of intracellular secretory granules, been found to secrete prolactin in about one-half the cases and growth hormone (GH) and ACTH in others.

Adrenal autotransplantation. It has been well-docu-

mented in a number of clinics that adrenal autotransplants commonly survive.[6,18–24] However, there is also general acknowledgement that the incidence and especially the degree of autotransplant survival is highly variable among patients so treated. It has been found that apparently minimal or even questionable survival of the adrenal implants, as seen on early biopsy, may be followed years later by such growth as to produce (or be associated with) recurrent Cushing's syndrome[19,22,23] (Cases 3 and 4).

The basic question is that of whether adrenal autotransplantation has a useful role in the management of Cushing's disease at this time. We conclude that it does not. Again, it did provide variable and, in some patients, more than adequate adrenocortical activity over time. However, the almost always present pituitary tumor remained active and produced Nelson's syndrome and increased skin pigmentation in some patients.

Conclusion

The senior author has long been impressed that the vast majority of patients with Cushing's disease are female (15 of our 17 patients). Moreover, an impressive number of our patients presented with psychiatric disturbances. At first thought one might conclude that the state of hypercortisolism had produced the personality changes. However, a number of our patients continued to exhibit disturbed personalities after the hypercortisolism had been abolished by adrenalectomy.

It could be that the persisting pituitary tumor, still present and functioning postadrenalectomy, could in some hormonal way have sustained the abnormal psychic state. But what caused the pituitary tumor, the excessive amounts of CRF, originally? It has been shown in animals that long-sustained excessive endocrine stimulation of the endocrine target organ can lead to hyperplasia, then nodularity in some, and later autonomous functioning adenomas in a few. Could excessive CRF produce first a localized pituitary hyperplasia, then an adenoma?

To return to the possibility of excessive stimulus to the hypothalamus to produce more CRF. We have seen that most Cushing's disease patients are female, and it has been demonstrated that the two halves of the cerebral cortex, connected by the corpus callosum, develop functionally somewhat differently in boys and girls. Indeed, in rat and mice experiments it would appear that cerebral cortex qualities can be altered during growth with appropriate sex hormonal stimulation. Incidentally, a number of our female patients had been under severe emotional stress prior to the appearance of clinical evidence of Cushing's syndrome.

Sperry,[25] in delivering his Nobel Prize acceptance speech (the award having been given for his work involving the functions of the right and left cortical hemispheres of the brain), noted that psychologic interbrain relationships might result in endocrine gland pathology. His conclusions were derived from detailed studies of patients who had undergone division of the corpus callosum for intractable epilepsy and from similar experiments in animals.

If the fundamental genesis of Cushing's disease is a sex-linked genetic trait, however mediated from the cerebral cortex to the hypothalamus, some of the many unknown features of this complex neuroendocrine disorder might be better explained.

Acknowledgement

The authors wish to thank Dr. Andrew D. Parent for his suggestions regarding pituitary surgery for Cushing's disease.

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Discussion

DR. H. WILLIAM SCOTT, JR. (Nashville, Tennessee): Dr. Crosby, I apologize for getting up again. I have enjoyed Dr. Hardy's provocative presentation. I would like to show just a few slides, please.

(Slide) Another picture of Dr. Cushing as Surgeon-in-Chief at Brigham Hospital in the 1920s. (Slide) This is the article that was published in the Bulletin of the Johns Hopkins Hospital in 1932 on Cushing's observations in the eight patients whom he reported. (Slide) This is his first patient, seen at the Hopkins Hospital in 1910, and she evoked the classic description of the disease, and which I would recommend that all of you read. It probably has never been improved on by anyone since Harvey Cushing described it in 1932. Four out of the eight patients that he studied had adenomas of the anterior lobe of hypophysis. Four others had collections of basophils which possibly were microadenomas. He called this pituitary basophilism.

(Slide) I think it is very, very interesting that the wheel has come full circle, and Dr. Cushing's ideas about pituitary Cushing's have been proven to be correct.

Why at Vanderbilt, where Dr. Grant Liddle saw so many patients in the last 30 years with Cushing's disease, did we do no more adrenalectomies than the 29 that were presented to you 8 years ago at this meeting here in Palm Beach? Well, it was because both Grant Liddle and our surgical group felt very strongly that Cushing had to be right about the pathogenesis of Cushing's disease as a pituitary syndrome, and we did not want to compound the felony of doing a removal bilaterally of both adrenal glands for a primary pituitary disorder.

Dr. Hardy's experience with subtotal adrenalectomy has not been very good, because of hyperplasia of the remaining segment of adrenal that was left with that operation and the recurrence rate of Cushing's. Total adrenalectomy in our medical center has been done only in patients who were failures of pituitary irradiation, and who did not get responses, at least with a mild degree of improvement, with that modality of treatment. This small group of patients represented people with recurrence of Cushing's after pituitary irradiation or such severe Cushing's that Dr. Liddle did not think they could be permitted to go the 6 months that it takes for irradiation to make a change in Cushing's disease in the 20 or 30% of patients in whom it may be effective.

(Slide) The results in this group of patients were not all good. We had one death; and here is the follow-up as it was 8 years ago in 28 patients. There was one death within 3 months. There was one recent patient; and then 26 patients had been followed up to over 20-odd years, with Cushing's cured in 24. Only one patient got Nelson's syndrome out of that group, the only one who had not had pituitary irradiation.

Cushing's seemed to be cured, but recurred in two patients, and one of these got radiation therapy, which did not do the trick, and then later had hypophysectomy, which did do the trick. Another one that recurred was sent to the Massachusetts General Hospital in Boston for Proton beam therapy, and got a good result.

One does not always get good results, even with total adrenalectomy, and we do not have an explanation as to why these two patients did not get initially good results.

(Slide) Lastly, the transsphenoidal pituitary operative approach to Cushing's began at Vanderbilt about 8 or 9 years ago, in the hands of Dr. Cully Cobb of our neurosurgical service, and he has now treated 39 patients with Cushing's disease in this way. Hypercortisolism has been corrected in 34 of the group, but in five hypercortisolism persisted, and these have been subsequently submitted to total adrenalectomy.

I certainly enjoyed this presentation of Dr. Hardy's, but I still do not quite understand why he did not look at the record of the past in subtotal adrenalectomy and realize that these adrenal transplants were going to undergo bombardment by ACTH and continue to have hyperplasia, with recurrent Cushing's disease. Why did not all of them get recurrent Cushing's, Dr. Hardy, or did they?

DR. JONATHAN A. VAN HEERDEN (Rochester, Minnesota): Rather than apologize for being up here twice in a row, I will blame Dr. Hardy for this. He was kind enough to call last week and ask me to present some data from our neurosurgeons regarding the results of transsphenoidal hypophysectomy for Cushing's disease.

(Slide) I am indebted to my colleague, Dr. Edward Laws, for the next three slides. It should be remembered that if one looks at 100 cases of Cushing's syndrome, Cushing's disease is by far the most common: adrenocortical adenomas, carcinomas, and the ectopic sources count for a small percentage.

(Slide) During the period 1972 to 1983, our neurosurgical colleagues have had a large experience with transsphenoidal hypophysectomy for pituitary adenoma. Cushing's disease accounted for 112 of these patients: acromegaly, prolactin adenomas, the Nelson Sulassa syndrome, and the null cell adenomas, which are basically the nonfunctioning pituitary adenomas, comprised 270 patients.

(Slide) If one looks at Cushing's syndrome (216 patients), one finds that Cushing's disease accounted for 149 unilateral cortical ademonas; 21, bilateral non-ACTH-dependent hyperplasia; 6, adrenal carcinoma in 10; ectopic ACTH syndrome in 25; and probable Cushing's syndrome in five.

I think the point that Dr. Laws wanted me to make—and I am happy to make on the next slide (slide)—is that the treatment of choice of Cushing's disease today is transsphenoidal hypophysectomy. This can be done with excellent results, as evidenced by this slide on these 216-odd patients, in which the operative mortality and morbidity is essentially zero, a few patients have transient diabetes insipidus, and one patient had partial anterior pituitary deficiency.

DR. SAMUEL A. WELLS, JR. (St. Louis, Missouri): I very much enjoyed Dr. Hardy's paper. I also enjoyed Dr. Scott's paper. These senior authors have made substantial contributions to surgical endocrinology.

Harvey Cushing was totally accurate in his hypothesis that in most patients with tumorous hypercortisolemia the disease begins in the pituitary gland. The therapy of the disease therefore usually falls in the province of the neurosurgeon.

The key to the diagnosis is now directed at defining the pathophysiologic derangement. I would like to touch on one point that Dr. Hardy mentioned.

(Slide) This is the scanning electron micrograph of the pituitary gland from the posterior view, showing the two lateral aspects of the