

SPECIAL ARTICLE

Cushing's syndrome — 1988

LESLIE R. SHEELER, MD, FACP

■ Despite major advances in laboratory methods, radiology, and neurosurgery, the evaluation and therapy of Cushing's syndrome remains a major challenge to clinicians. In a substantial percentage of the patients with Cushing's syndrome, laboratory and radiologic studies yield data that are confusing or misleading. This paper reviews the various disorders that comprise Cushing's syndrome and addresses some of the problems in diagnosis and therapy.

□ INDEX TERM: CUSHING'S SYNDROME □ CLEVE CLIN J MED 1988; 55:329-337

SINCE Dr. McCullagh's excellent review of Cushing's syndrome, first printed in 1961 and reprinted in this issue of the *Cleveland Clinic Journal of Medicine*, major advances in radiology, laboratory methods, and neurosurgery have modified the diagnostic and therapeutic approaches to this disorder. Some of the features that were disturbing to Dr. McCullagh, such as the normal adrenocorticotrophic hormone (ACTH) levels found in Cushing's disease or the general problem of ectopic ACTH syndrome, have been clarified and better documented. The problem with Cushing's syndrome has been that as soon as one puzzle or problem is solved, a new difficulty arises.

PATHOGENESIS

It is convenient to classify Cushing's syndrome into six major types (*Table 1*). Adrenal tumors causing Cushing's syndrome constitute about 20% of cases. Benign adrenal tumors causing Cushing's syndrome produce predominantly glucocorticoids; androgen and mineralocorticoid production are rare.¹ In adrenal cancers causing Cushing's syndrome, frequently all three classes of adre-

nal steroids are present at high levels.² ACTH levels are suppressed. Following successful removal of an adrenal tumor causing Cushing's syndrome, the remaining adrenal gland and the hypothalamic-pituitary-adrenal axis may remain suppressed for six to 12 months.

Dr. McCullagh was well aware of the existence of a corticotropin-releasing factor (CRF). After decades of study, the structure of CRF was finally deciphered.³ Publications rapidly followed indicating that CRF might be useful to differentiate ectopic ACTH syndrome from pituitary Cushing's syndrome.^{4,5} Subsequently, Howlett and Rees⁶ wrote of a number of exceptions to this ability to differentiate the two ACTH-dependent forms of Cushing's syndrome. A few cases of ectopic production of CRF causing Cushing's syndrome have been reported.^{7,8} The tumors producing the CRF were a bronchial carcinoid and a medullary carcinoma of the thyroid.

Dr. McCullagh's observation that ACTH levels are generally normal in pituitary-dependent Cushing's syndrome has been repeatedly substantiated using radioimmunoassay (RIA) techniques to measure ACTH.^{1,4,5} The conventional explanation for the normal levels is that for the high level of cortisol production, the ACTH levels are inappropriately high. It is now clear that pituitary Cushing's syndrome is due primarily to ACTH-producing pituitary adenomas, many of them quite small (1 to 5 mm). The more fundamental question of whether these tumors are caused by an excess of hypothalamic

Department of Endocrinology, The Cleveland Clinic Foundation.
Submitted for publication June 1987; accepted Oct 1987.
Editor's note: See also McCullagh (pp 339-356).

CRF remains unanswerable. Once the patients are cured after removal of the tumor, the overwhelming majority remain cured for up to seven years.⁹ This suggests, but does not prove, that hypothalamic CRF excess may not cause the ACTH-producing pituitary adenomas.

A small percentage of patients with pituitary-dependent Cushing's syndrome appear to have corticotroph-cell hyperplasia rather than a distinct corticotroph-cell adenoma.¹⁰ It is possible that in this subset of patients either eutopic (hypothalamic) or ectopic (outside the hypothalamus) CRF excess causes the excessive production of ACTH.

Ectopic ACTH syndrome has become much better understood since Dr. McCullagh's paper was published. About half of the cases arise from tumors within the chest, including oat-cell carcinomas, carcinoids, and thymomas. Other reported tumor types include medullary carcinomas of the thyroid, islet-cell tumors, pheo-

chromocytomas, and prostate carcinomas. Classically, these patients present with weakness, weight loss, and hypokalemia. Clinical features of Cushing's syndrome range from absent to profound. ACTH levels and steroid measurements are usually quite high.

Thus for most varieties of Cushing's syndrome, a reasonably simple pathogenesis has been outlined. Most cases are due to ACTH either from the pituitary gland or, less commonly, tumors in other organs.¹ When ACTH mediates the Cushing's syndrome, both adrenal glands become hypertrophic and secrete excessive amounts of cortisol, as well as androgens and mineralocorticoids. Primary adrenal tumors account for most of the remaining cases.

Macroadenomatous hyperplasia is classified somewhere between ordinary Cushing's disease and benign adrenal adenomas. Some authors regard this entity as simply an extension of pituitary Cushing's syndrome.^{11,12} Although this may be the case, test results of at least some affected patients are similar to those of patients with adrenal adenomas. Table 2 shows data relating to two patients with adenomatous hyperplasia. Both patients underwent bilateral adrenalectomy. Except for the measurable ACTH levels, the data could have indicated the presence of adrenal adenoma. Computed tomographic (CT) imaging of the adrenal glands showed enormous bilateral adrenal enlargement, suggesting the diagnosis of bilateral macronodular hyperplasia. In both cases, the pathologic examination confirmed macronodular adrenal hyperplasia. Also, the total weight of the adrenal gland had increased enormously (85 g in the first patient and 116 g in the second [normal, approximately 3-4.5 g per adrenal gland]). Are cases like these two somewhat analogous to hyperthyroidism in an adenomatous goiter?

TABLE 1
ETIOLOGY OF CUSHING'S SYNDROME

Pituitary (Cushing's disease)
ACTH-producing pituitary adenoma
Corticotroph-cell hyperplasia
Ectopic ACTH
Ectopic CRF
Adenomatous hyperplasia
Micronodular
Macronodular
Adrenal adenoma
Adrenal carcinoma

TABLE 2
TWO PATIENTS WITH ADENOMATOUS HYPERPLASIA

	Baseline	Day 1*	Day 2*	Day 3†	Day 4†
Patient 1					
Plasma cortisol (µg/dL)	34	28	27		
Urine-free cortisol (µg/24 h)	311, 515, 250	330		311	422
Urine 17-OH (mg/24 h)	13	11.7	18.6	13.5	9.8
Plasma ACTH (pg/mL)	51, 87	58	51		85
Urine 17-OH (metyrapone)‡	9.6, 7.3	5.4‡	8.9‡	6.6§	
Patient 2					
Plasma cortisol (µg/dL)	23, 27	21	28	25.5	26.5
Urine-free cortisol (µg/24 h)	288	155	220		274
Urine 17-OH (mg/24 h)	11.0	5.6	6.8	19.4	9.9
Plasma ACTH (pg/mL)	38				

* Dexamethasone (0.5 mg every 6 hours for 48 hours)

† Dexamethasone (2.0 mg every 6 hours for 48 hours)

‡ Metyrapone (750 mg every 4 hours for 48 hours)

§ 24 hours after last dose of metyrapone

TABLE 3
SIGNS AND SYMPTOMS IN BENIGN CUSHING'S SYNDROME
(35 WOMEN, 1 MAN)

Finding	Number (%)
Round face	31/36 (86)
Proximal weakness	30/36 (83)
Amenorrhea/oligomenorrhea	19/25 (76)*
Truncal weight gain	29/36 (80)
Hirsutism	28/35 (80)
Plethora	26/36 (72)
Thin skin	26/36 (72)
Psychiatric symptoms	26/36 (72)
Frank psychosis	3
Depression	2
Somatization	4
Admitted to psychiatry unit prior to diagnosis	5
Acne	17/36 (47)
Purple striae	15/36 (42)
Edema	5/36 (14)
Bone-related symptoms†	5/36 (8)
Hypertension	
Pituitary Cushing's syndrome	9/28
Adrenal adenoma	5/6
Macronodular adenomatous hyperplasia	2/2

* The other 10 patients were either menopausal or had undergone a hysterectomy previously.

† Many more patients had osteopenia as shown on radiographs; this only includes those with bone pain or fractures as presenting symptoms.

We simply do not have enough data to be certain. The apparently rare disorder called micronodular adrenal hyperplasia, described by Ruder et al,¹³ appears to be a different entity from macronodular adrenal hyperplasia. The overall size of the adrenal gland is normal. The histologic appearance is characterized by nests of hyperplastic adrenal cortical cells, and the surrounding normal adrenal cells appear suppressed. ACTH levels are low. The pathogenesis of this disorder is not well understood.

CLINICAL FEATURES

Dr. McCullagh's paper refers to most of the well-recognized clinical features of Cushing's syndrome. The presence of hypertension and diabetes mellitus, although frequent, are not helpful in the diagnosis of Cushing's syndrome. *Table 3* summarizes the clinical features of the first 36 cases (35 women and one man) of benign Cushing's syndrome (Cushing's disease or benign adrenal adenoma) I have observed. My approach is that patients with the combination of proximal weakness and thin skin, along with any of the additional features listed in

TABLE 4
SCREENING TESTS

Lack of diurnal variation in plasma cortisol ¹
Plasma cortisol ≥ 2.5 μ dL soon after the onset of sleep ¹⁴
24-hour urine assay for free cortisol ¹⁵
24-hour urine assay for 17-hydroxy-corticoids ¹
Overnight DST measuring cortisol at 8 A.M. after giving 1 mg of dexamethasone at 11 P.M. the previous night

TABLE 5
TESTS TO DIFFERENTIATE CUSHING'S DISEASE FROM OTHER VARIETIES OF CUSHING'S SYNDROME

ACTH levels ¹⁶
DSTs
8 mg at midnight ¹⁷
0.6 mg every 6 hours for 48 hours ¹⁸
2.0 mg every 6 hours for 48 hours ¹⁹
Metapyrone tests
750 mg every 4 hours for 48 hours ²⁰
2,000 mg at midnight ²¹
ACTH levels after CRF administration ⁵
Pituitary or adrenal visualization with CT or MRI ²¹
Inferior petrosal sinus sampling for ACTH ²²
Radiological search for a tumor causing ectopic ACTH secretion ²³
Peripheral venous sampling for multiple polypeptide hormones, including calcitonin, vasoactive intestinal polypeptide, gastric inhibitory polypeptide, pancreatic polypeptide, human chorionic gonadotropin, etc. (a positive test implies ectopic ACTH) ²⁴

Table 3, should be considered to have Cushing's syndrome until the diagnosis is incontrovertibly disproved by repeated testing.

LABORATORY TESTS

Dr. McCullagh succinctly summarized the results of laboratory studies available in 1961. Baseline measuring of urinary 17-hydroxycorticoids and remeasuring these levels after manipulations with metyrapone or dexamethasone were the best evaluations. We still rely on the same principle, especially for dexamethasone suppression tests (DSTs), to confirm the diagnosis and differentiate Cushing's disease from the five other forms of Cushing's syndrome. Available tests have proliferated over the years, as shown in *Tables 4* and *5*. Yet correct differentiation of the six varieties of Cushing's syndrome remains difficult; none of these tests approach 100% sensitivity and specificity.^{6,25} Thus the clinician always faces a major dilemma. Therapy is directed to the pituitary gland or adrenal glands, or even elsewhere in the case

A. If clinical findings suggest Cushing's syndrome:

1. Collect a 24-hour urine sample for free cortisol by RIA, or
2. Do an overnight DST

If the result of either is negative, test again (sometimes repeat more than once if a strong clinical suspicion persists)

B. If findings are positive (i.e., cortisol excess is confirmed)

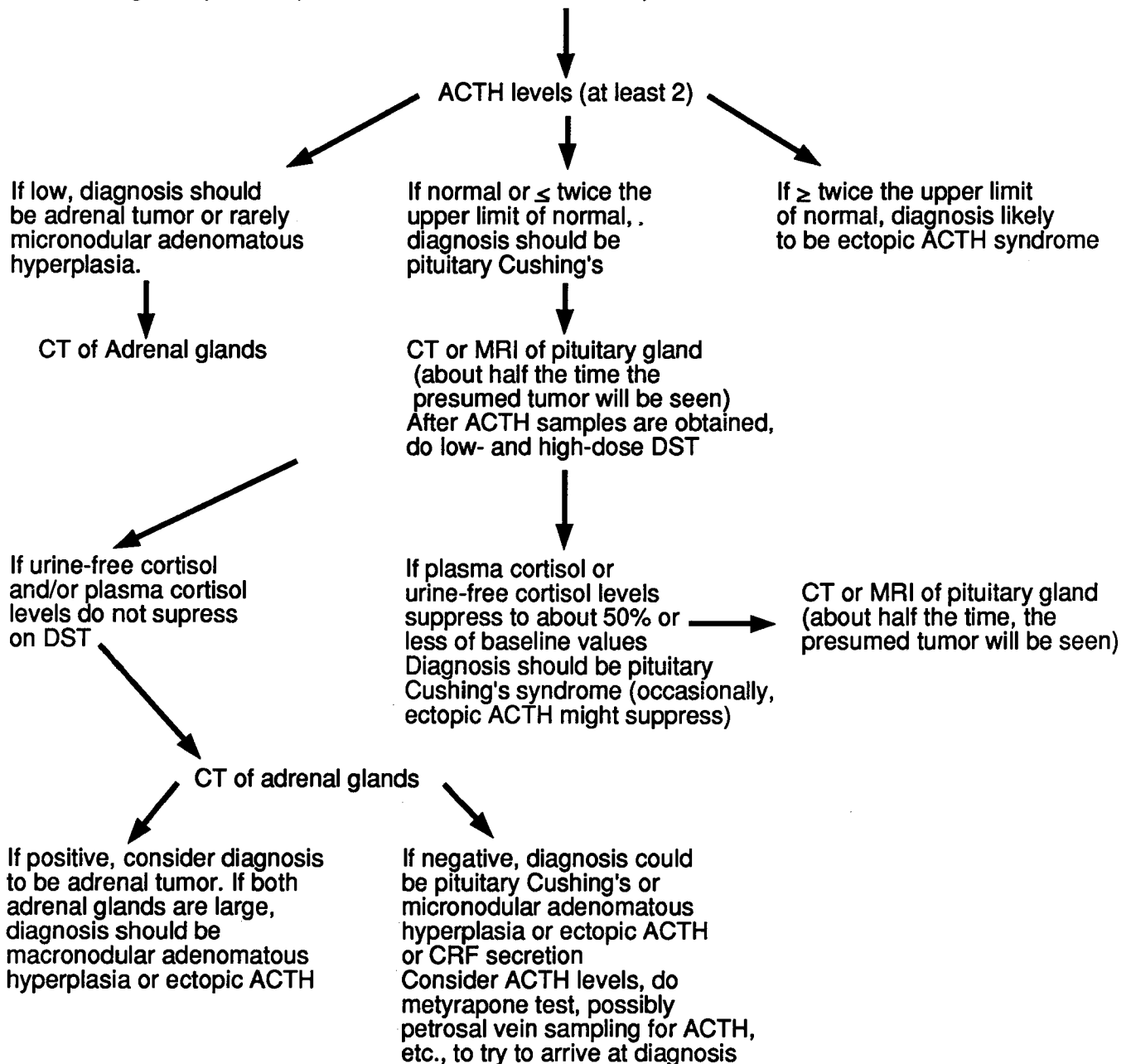


FIGURE 1. Approach to the diagnosis of Cushing's syndrome.

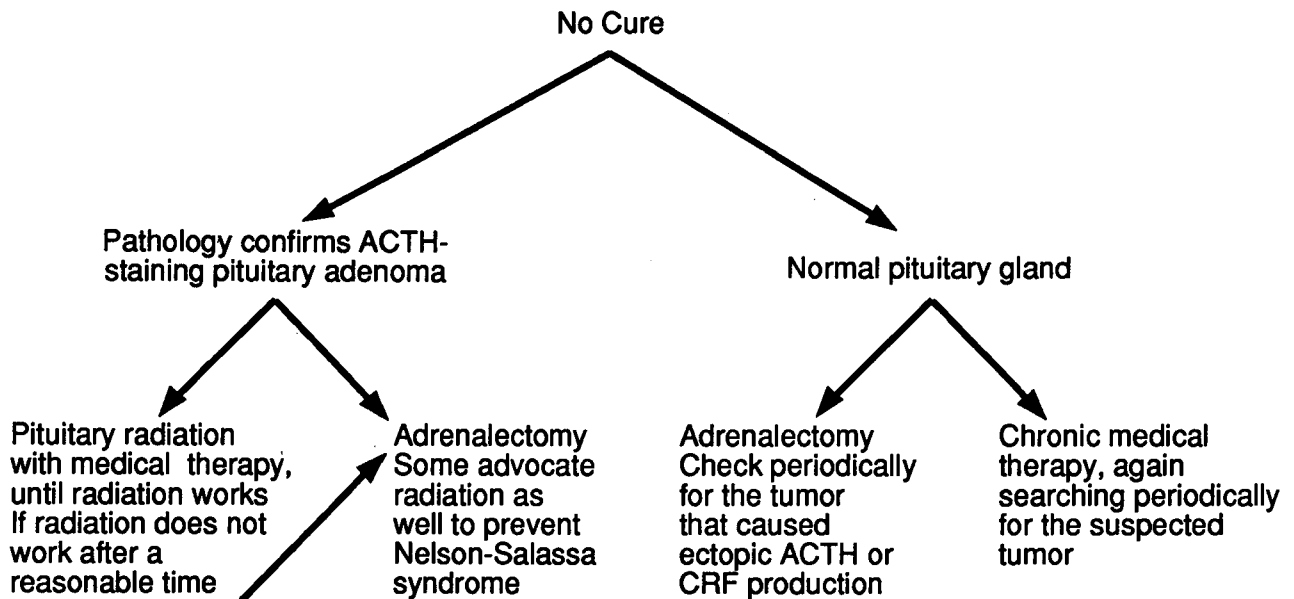


FIGURE 2. Therapeutic options available if transsphenoidal surgery fails to cure a patient.

of ectopic ACTH syndrome, based on imperfect data. Carpenter²¹ estimates that one third of the time (in 250 cases) the data are misleading.

I have had the opportunity to care for 60 persons with Cushing's syndrome. In at least half, test results were confusing or misleading, if the negative pituitary radiologic studies despite later surgical confirmation of a pituitary adenoma, as well as confusing biochemical data, are included. I have found the most straightforward situation to involve primary adrenal tumors. With a reliable ACTH assay (the level is suppressed) and standard DSTs (no suppression), one can determine if an adrenal tumor exists. Either adrenal-sector or abdominal CT scans should then confirm the presence of an adrenal tumor.¹⁰ Every type of Cushing's syndrome, including the type caused by adrenal adenomas, can undergo spontaneous remissions,²⁶⁻²⁹ as Dr. McCullagh was well aware.

The toughest diagnostic problem is to be certain that a patient has pituitary Cushing's syndrome and not ectopic ACTH syndrome, which mimics it.^{30,31} At present, and I suspect for the foreseeable future, a clear solution remains impossible in all cases. One major problem for all clinicians who deal with Cushing's syndrome is the reliability of the ACTH assay, since diagnostic differentiation relies primarily on the evaluation of ACTH levels. During my 11 years in practice at the

Cleveland Clinic, we have had three different RIA assays for ACTH. The first and third have been quite reliable; the second was totally unreliable. Of my first 30 patients with pituitary Cushing's syndrome (proved by pituitary surgery and clinical outcome), six did not show suppression after a large-dose DST and six showed too much suppression after the DST. Thus 40% of the tumors behaved in a "nonclassical" fashion.

My current approach to the diagnosis of Cushing's syndrome is shown (Figure 1), and I believe it can reduce the number of misdiagnoses to an acceptable level. Coates et al³⁰ believe that all cases of apparent pituitary Cushing's syndrome might be unusual presentations of occult ectopic ACTH syndrome. Subsequently, of 71 consecutive patients with ACTH-dependent Cushing's syndrome, they found 10 to have occult ACTH-producing tumors indistinguishable from those in pituitary-dependent Cushing's syndrome. These data correlate well with the experience Bay and I report,³² which shows a 10% to 25% non-cure rate with pituitary surgery for presumed pituitary Cushing's syndrome. One of Coates' colleagues, Dr. Besser, argues that one cannot afford to make a misdiagnosis and direct treatment at the pituitary gland inappropriately (personal communication). Since his approach would involve spending many unnecessary thousands of dollars per patient when most indeed have pituitary Cushing's syndrome, it is more practical and cost effec-

TABLE 6
SUMMARY OF ADDITIONAL DIAGNOSTIC PROBLEMS IN CUSHING'S SYNDROME

Patients who lack the clinical features of Cushing's syndrome, but have high urine-free cortisol levels and/or show poor suppression with dexamethasone, especially shown by overnight DST

1. Classical ectopic ACTH syndrome³³
2. True Cushing's syndrome, other than ectopic ACTH, but with atypical clinical features
3. Depression²⁵
4. Stress
5. Abnormally slow metabolism of dexamethasone²⁵

Patients with clinical features suggesting Cushing's syndrome, but normal urine-free cortisol and/or normal suppressibility as shown by DSTs

1. True Cushing's syndrome, but in remission³⁴
2. True Cushing's syndrome, but diagnosis obscured by abnormally slow metabolism of dexamethasone³⁵
3. Factitious or inadvertent steroid use.³⁴ If topical fluorinated glucocorticoid administration is the cause, urine-free cortisol levels and plasma cortisol levels will be quite low.³⁶

Alcoholism

A small percentage of alcoholics have clinical and biochemical Cushing's syndrome.
Both the clinical and the biochemical changes reverse rapidly with alcohol abstinence.³⁷⁻³⁹

TABLE 7
MEDICAL THERAPY FOR CUSHING'S SYNDROME

Drug	Usual dose	Need to use glucocorticoid with the drug?	Effectiveness	Special comments
Cyproheptadine ⁴⁵	24 mg/d	No	Quite variable	Few patients respond well ^{43,46*}
Trilostane ⁴⁷	200-360 mg/d	No	Generally effective	
Aminoglutethimide ⁴⁸	1-2 g/d	Yes	Usually effective	A skin rash or drowsiness may limit use. Need to use more dexamethasone than one would expect
Metyrapone ^{49,50}	1-2 g/d	No	Usually effective	Least side effects of any of the effective agents
O, P, DDD ⁵¹⁻⁵³	1.5-2 g (much higher dosages for cancer: 8-10 g/d)	Yes	Usually effective	Used mostly for adrenal cancer. ² Can be used for hyperplasia; side effects frequent
Ketoconazole ⁵⁴	400 mg to 1 g/d	No	Usually effective	Newest agent used for medical therapy

* None out of three responded well in my experience.

tive to treat on the basis of the data collected in the approach outlined in *Figure 1*. The patients not cured with pituitary surgery can be dealt with later. Some of the additional problems in the diagnosis are summarized in *Table 6*.

Another technique used in some centers in yet another attempt to obviate this diagnostic dilemma has been to try to prove that the source of ACTH is the

pituitary gland by sampling the inferior petrosal sinuses.⁴⁰ An analysis of some reports and some unpublished information provided by Tyrrell, Arafah, and Orth suggests that even this is not a panacea. There are not enough published data to suggest that routine sampling of the inferior petrosal sinus should become a widely used procedure, especially considering the cost, morbidity, and occasional mortality.



FIGURE 3. Before (left) and one month after (right) treatment with metyrapone (1 g/day) and aminoglutethamide (1 g/day).

TREATMENT

In Dr. McCullagh's time, total or subtotal adrenalectomy was the treatment of choice for ACTH-dependent Cushing's syndrome. The treatment of choice for primary adrenal Cushing's syndrome is still adrenal surgery. Because of lower morbidity and mortality and the feasibility of a high cure rate via transsphenoidal pituitary microsurgery, most centers treating a large number of patients with Cushing's disease have switched to pituitary microsurgery.^{9,10,41,42} Bay and I review our experience with this therapy and compare it with that in other large published series.³²

Since the pituitary adenomas that cause Cushing's syndrome are often too small to be detected with even the most sophisticated neuroradiologic studies, the clinician often must recommend pituitary surgery on the basis of the biochemical data. Yet, as shown previously, ectopic ACTH syndrome can mimic pituitary Cushing's syndrome so closely that even the most experienced clinicians are fooled when they evaluate the biochemical data. Several guidelines may help to solve this problem:

1. Assume that spontaneous hypokalemia in ACTH-dependent Cushing's syndrome indicates ectopic ACTH syndrome.³¹

2. Be very suspicious of cases of ACTH-dependent Cushing's syndrome in males.

3. Look at all the biochemical data closely. Are the steroid measurements or ACTH levels a bit higher than with usual Cushing's disease? Does the DST show less suppression than usually occurs with Cushing's disease? If so, at least consider whether to test again or search for another source of the ACTH.

Daughaday⁴³ succinctly summarized the reasons for the switch from bilateral adrenalectomy to pituitary microsurgery for pituitary-dependent Cushing's syndrome. However, besides lack of cure because of incorrect diagnosis, there may be initial failure because the pituitary tumor is invasive and thus not completely resectable.¹⁰ Late recurrences after an initial cure also have been reported.^{10,41,42,44}

To date there is not enough published information to allow the clinician to recommend a therapy confidently if transsphenoidal microsurgery fails. Some available

options are outlined (Figure 2).

The therapeutic options are similar for patients initially diagnosed as having ectopic ACTH syndrome. At the Cleveland Clinic, we have attempted (without success) to destroy the adrenal glands using adrenal vein injection for a patient in whom, it was ultimately found, a medullary carcinoma of the thyroid was causing the Cushing's syndrome.

Some drugs available to Dr. McCullagh are still in use today as therapy for Cushing's syndrome. Table 7 lists the medications available in the United States. Cyproheptadine, which is effective in a small subgroup of patients, reduces ACTH secretion. All of the other drugs listed block cortisol synthesis at some step in the synthetic pathway. The dramatic clinical improvement that can occur after four to eight weeks of successful treatment is impressive (Figure 3).⁵⁴ Treating more than a dozen patients medically has convinced me that problems such as overblockade, underblockade, and patients who fail to return for continued treatment make chronic therapy too difficult to use. Consequently, I usually reserve medical therapy for the most ill patients prior to adrenalectomy or for patients with ectopic ACTH syndrome.⁵⁵

Is there a role for radiation therapy as the primary method of treatment of pituitary Cushing's syndrome in 1988? Previously published reports^{1,10,33} showing a 15% to

20% cure rate have been discouraging. The results for children are much more hopeful.⁵⁶ Still, the late effects of this therapy (such as memory loss, decline in other cognitive functions, appearance of hypopituitarism) have not been assessed long enough to determine whether such treatment is preferable to pituitary surgery for children with Cushing's disease.⁵⁷

In the future, new tests will undoubtedly be developed that fail to eliminate many of the problems discussed here. Perhaps the neuroendocrine factors that lead to Cushing's disease will be better understood.^{43,58} Therapy for Cushing's disease might be improved if a reliable antagonist for ACTH secretion, such as a polypeptide or small neurotransmitter-type molecule, could be developed.⁵⁸ During the past 50 years, therapy has been directed to the pituitary gland (Cushing's original idea), the adrenal glands (1930s to mid 1970s), and the pituitary gland again (mid 1970s to the present); it would not be surprising to see the cycle shift back to treating the adrenal glands some time in the future.

Department of Endocrinology
The Cleveland Clinic Foundation
One Clinic Center
9500 Euclid Avenue
Cleveland, Ohio 44195

REFERENCES

- Gold EM. The Cushing syndromes: changing views of diagnosis and treatment. *Ann Intern Med* 1979; **90**:829-844.
- Bertagna C, Orth DN. Clinical and laboratory findings and results of therapy in 58 patients with adrenocortical tumors admitted to a single medical center (1951 to 1978)(review). *Am J Med* 1981; **71**:855-875.
- Vale W, Spiess J, Rivier C, Rivier J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and β -endorphin. *Science* 1981; **213**:1394-1397.
- Hermus ARMM, Pieters GFFM, Pesman GJ, Smals AGH, Benraad TJ, Kloppenborg PWC. Responsivity of adrenocorticotropin to corticotropin-releasing hormone and lack of suppressibility by dexamethasone are related phenomena in Cushing's disease. *J Clin Endocrinol Metab* 1986; **62**:634-639.
- Nieman LK, Chrousos GP, Oldfield EH, Avgerinos PC, Cutler GB Jr, Loriaux DL. The ovine corticotropin-releasing hormone stimulation test and the dexamethasone suppression test in the differential diagnosis of Cushing's syndrome. *Ann Intern Med* 1986; **105**:862-867.
- Howlett TA, Rees LH. Is it possible to diagnose pituitary-dependent Cushing's disease? (review). *Ann Clin Biochem* 1985; **22**:550-558.
- Belsky JL, Cuello B, Swanson LW, Simmons DM, Jarrett RM, Braza F. Cushing's syndrome due to ectopic production of corticotropin-releasing factor. *J Clin Endocrinol Metab* 1985; **60**:496-500.
- Schteingart DE, Lloyd RV, Akil H, et al. Cushing's syndrome secondary to ectopic corticotropin-releasing hormone-adrenocorticotropin secretion. *J Clin Endocrinol Metab* 1986; **63**:770-775.
- Boggan JE, Tyrell JB, Wilson CB. Transsphenoidal microsurgical management of Cushing's disease. *J Neurosurg* 1983; **59**:195-200.
- Carpenter PC. Cushing's syndrome: update of diagnosis and management. *Mayo Clin Proc* 1986; **61**:49-58.
- Aron DC, Findling JW, Fitzgerald PA, et al. Pituitary ACTH dependency of nodular adrenal hyperplasia in Cushing's syndrome. *Am J Med* 1981; **71**:302-306.
- Smals AGH, Pieters GFFM, van Haelst UJG, Kloppenborg PWC. Macronodular adrenocortical hyperplasia in long-standing Cushing's disease. *J Clin Endocrinol Metab* 1984; **58**:25-31.
- Ruder NJ, Loriaux DL, Lipsett MB. Severe osteopenia in young adults associated with Cushing's syndrome due to micronodular adrenal disease. *J Clin Endocrinol Metab* 1974; **39**:1138-1147.
- Crapo L. Cushing's syndrome: a review of diagnostic tests. *Metabolism* 1979; **28**:955-977.
- Eddy RL, Jones AL, Gilliland PF, Ibarra JD Jr, Thompson JQ, McMurry JF Jr. Cushing's syndrome: a prospective study of diagnostic methods. *Am J Med* 1973; **55**:621-630.
- Tyrell JB, Brooks RM, Fitzgerald PA, Cofoid PB, Forsham PH, Wilson CB. Cushing's disease: selective transphenoidal resection of pituitary microadenomas. *N Engl J Med* 1978; **298**:753-758.
- Tyrell JB, Findling JW, Aron DC, Fitzgerald PA, Forsham PH. An overnight high-dose dexamethasone suppression test for rapid differential diagnosis of Cushing's syndrome. *Ann Intern Med* 1986; **104**:180-186.
- Nolan PM, Sheeler LR, Hahn JE, Hardy RW Jr. Therapeutic problems with transsphenoidal pituitary surgery for Cushing's disease. *Cleve Clin Q Med* 1982; **49**:199-207.
- Ashcraft MW, Van Herel AJ, Vener SL, Geffner DL. Serum cortisol

- levels in Cushing's syndrome after low- and high-dose dexamethasone suppression. *Ann Intern Med* 1982; **97**:21–26.
20. Sindler BH, Griffing GT, Melby JC. The superiority of the metyrapone test versus the high-dose dexamethasone test in the differential diagnosis of Cushing's syndrome. *Am J Med* 1983; **74**:657–662.
 21. Carpenter PC. Cushing's syndrome: update of diagnosis and management. *Mayo Clin Proc* 1986; **61**:49–58.
 22. Oldfield EH, Chrousos GP, Schulte HM, et al. Preoperative lateralization of ACTH-secreting pituitary microadenomas by bilateral and simultaneous inferior petrosal venous sinus sampling. *N Engl J Med* 1985; **312**:100–103.
 23. White FE, White MC, Drury PL, Kelsey Fry I, Besser GM. Value of computed tomography of the abdomen and chest in investigation of Cushing's syndrome. *Br Med J* 1982; **284**:771–774.
 24. Coates PJ, Doniach I, Howlett TA, Rees LH, Besser GM. Immunocytochemical study of 18 tumours causing ectopic Cushing's syndrome. *J Clin Pathol* 1986; **39**:955–960.
 25. Aron DC, Tyrrell JB, Fitzgerald PA, Findling JW, Forsham PH. Cushing's syndrome: problems in diagnosis. *Medicine* 1981; **60**:25–35.
 26. Brown RD, Van Loon GR, Orth DN, Liddle GW. Cushing's disease and periodic hormonogenesis: one explanation for paradoxical response to dexamethasone. *J Clin Endocrinol Metab* 1973; **36**:445–451.
 27. Kammer H, Barter M. Spontaneous remission of Cushing's disease: a case report and review of the literature. *Am J Med* 1979; **67**:519–522.
 28. Sakiyama R, Ashcraft MW, Van Herle AJ. Cyclic Cushing's syndrome. *Am J Med* 1984; **77**:944–946.
 29. Vagnucci AH, Evans E. Cushing's disease with intermittent hypercortisolism. *Am J Med* 1986; **80**:83–88.
 30. Coates PJ, Doniach I, Howlett TA, Rees LH, Besser GM. Immunocytochemical study of 18 tumours causing ectopic Cushing's syndrome. *J Clin Pathol* 1986; **39**:955–960.
 31. Findling JW, Tyrrell JB. Occult ectopic secretion of corticotropin. *Arch Intern Med* 1986; **146**:929–933.
 32. Bay JW, Sheeler LR. Transsphenoidal surgery for Cushing's syndrome: Cleveland Clinic experience. *Cleve Clin J Med* 1988; **55**:000–000.
 33. Aron DC, Findling JW, Fitzgerald PA, Forsham PH, Wilson CB, Tyrrell JB. Cushing's syndrome: problems in management. *Endocr Rev* 1982; **3**:229–244.
 34. Atkinson AB, Kennedy AL, Carson DJ, Hadden DR, Weaver JA, Sheridan B. Five cases of cyclical Cushing's syndrome. *Br Med J* 1985; **291**:1453–1457.
 35. Kapcala LP, Hamilton SM, Meikle AW. Cushing's disease with "normal suppression" due to decreased dexamethasone clearance. *Arch Intern Med* 1984; **144**:636–637.
 36. Kimmerle R, Rolla AR. Iatrogenic Cushing's syndrome due to dexamethasone nasal drops. *Am J Med* 1985; **79**:535–537.
 37. Smals AGH, Njo KT, Knoben JM, Ruland CM, Kloppenborg PWC. Alcohol-induced cushingoid syndrome. *J R Coll Physicians* 1977; **12**:36–41.
 38. Rees LH, Besser GM, Jeffcoate WJ, Goldie DJ, Marks V. Alcohol-induced pseudo-Cushing's syndrome. *Lancet* 1977; **1**:726–728.
 39. Kapcala LP. Alcohol-induced pseudo-Cushing's syndrome mimicking Cushing's disease in a patient with an adrenal mass. *Am J Med* 1987; **82**:849–856.
 40. Oldfield EH, Chrousos GP, Schulte HM, et al. Preoperative lateralization of ACTH-secreting pituitary microadenomas by bilateral and simultaneous inferior petrosal venous sinus sampling. *N Engl J Med* 1985; **312**:100–103.
 41. Nolan PM, Sheeler LR, Hahn JF, Hardy RW Jr. Therapeutic problems with transsphenoidal pituitary surgery for Cushing's disease. *Cleve Clin Q* 1982; **49**:199–207.
 42. Bigos ST, Somma N, Rasio E, et al. Cushing's disease: management by transsphenoidal pituitary microsurgery. *J Clin Endocrinol Metab* 1980; **50**:348–354.
 43. Daughaday WM. Cushing's disease and basophilic microadenomas (editorial). *N Engl J Med* 1984; **310**:919–920.
 44. Pont A, Gutierrez-Hartman A. Cushing's disease: recurrence after a surgically induced remission. *Arch Intern Med* 1979; **139**:938–940.
 45. Krieger DT, Amorosa L, Linick F. Cyproheptadine-induced remission of Cushing's disease. *N Engl J Med* 1975; **293**:893–896.
 46. Tyrrell JB, Brooks RM, Forsham PH. More on cyproheptadine (letter). *N Engl J Med* 1976; **295**:1137–1138.
 47. Komanicky P, Spark RF, Melby JC. Treatment of Cushing's syndrome with trilostane (WIN 24,540), an inhibitor of adrenal steroid biosynthesis. *J Clin Endocrinol Metab* 1978; **47**:1042–1051.
 48. Misbin RI, Canary J, Willard D. Aminoglutethimide in the treatment of Cushing's syndrome. *J Clin Pharmacol* 1976; **16**:645–651.
 49. Jeffcoate WJ, Rees LH, Tomlin S, Jones AE, Edwards CRW, Besser GM. Metyrapone in long-term management of Cushing's disease. *Br Med J* 1977; **2**:215–217.
 50. Dickstein G, Lahav M, Shen-Orr Z, Edoute Y, Barziali D. Primary therapy Cushing's disease with metyrapone. *JAMA* 1986; **255**:1167–1169.
 51. Becker D, Schumacher OP. *o,p'*DDD therapy in invasive adrenocortical carcinoma. *Ann Intern Med* 1975; **82**:677–679.
 52. Luton JP, Mahoudeau JA, Bouchard PH, et al. Treatment of Cushing's disease by *O,p'*DDD: survey of 62 cases. *N Engl J Med* 1979; **300**:459–464.
 53. Schteingart DE, Tsao HS, Taylor CI, McKenzie A, Victoria R, Therrien BA. Sustained remission of Cushing's disease with mitotane and pituitary irradiation. *Ann Intern Med* 1980; **92**:613–619.
 54. Sonino N, Boscaro M, Merola G, Mantero F. Prolonged treatment of Cushing's disease by ketoconazole. *J Clin Endocrinol Metab* 1985; **61**:718–722.
 55. Higgins TL, Calabrese LH, Sheeler LR. Opportunistic infections in patients with ectopic ACTH-secreting tumors. *Cleve Clin Q* 1982; **49**:43–49.
 56. Orth DN, Liddle GW. Results of treatment of 108 patients with Cushing's syndrome. *N Engl J Med* 1971; **285**:243–247.
 57. Jennings AS, Liddle GW, Orth DN. Results of treating childhood Cushing's disease with pituitary irradiation. *N Engl J Med* 1977; **297**:957–962.
 58. Burch WN. Cushing's disease: a review. *Arch Intern Med* 1985; **145**:1106–1111.