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Cushing Syndrome

Current Concepts of Diagnosis and Therapy

DAVID M. COOK, MD, and JOHN W. KENDALL, MD, *Portland, Oregon,* and RICHARD JORDAN, MD, *Lackland AFB, Texas*

A variety of diagnostic advances including radioimmunoassay of adrenocorticotropic hormone (ACTH) have increased the number of methods for laboratory investigation of Cushing syndrome. However, experience with these procedures has led to a recognition of their limitations. We have developed an algorithm which incorporates these newer techniques and minimizes the number of procedures required to diagnose the various causes of Cushing syndrome. At present, we recommend pituitary surgical operations for pituitary-dependent Cushing syndrome because we believe this disease is caused by the development of a pituitary ACTH-secreting tumor.*

SEVERAL NEW DEVELOPMENTS in our approach to the diagnosis and treatment of cortisol excess combine to make a review of this subject timely. New variants of hypercortisolism including periodic rhythmic secretion of adrenocorticotropic hormone (ACTH) and an array of extrapituitary sources of ACTH have necessitated revisions of the algorithm for diagnostic evaluation of patients in whom Cushing syndrome* is suspected. The increasing availability of plasma ACTH assays for both "big" and "little" forms of the hormone raises questions as to the pragmatic application of plasma ACTH determinations in the differential diagnosis of various manifestations of the Cushing syndrome. Finally, a recent flurry of interest in pharmacological and microsurgical treatments of Cushing disease has stimulated reappraisals of the choices of therapy for pituitary-dependent hypercortisolism.

From the Department of Medicine, University of Oregon Health Sciences Center, Portland (Dr. Cook); Portland Veterans Administration Medical Center (Dr. Kendall), and the United States Air Force Medical Center, Lackland AFB, Texas (Dr. Jordan).

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Reprint requests to: David M. Cook, MD, Dept. of Medicine, University of Oregon Health Sciences Center, Portland, OR 97201.

*The WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore, Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

Pathophysiologic Classification

The various known causes of Cushing syndrome are listed in Table 1. Undoubtedly, the most common cause of Cushing syndrome is the use of exogenous glucocorticoids for a variety of disorders. We will not discuss the presentation of this syndrome except to say that it does not differ basically from other causes of endogenous hypercortisolism.

Clinical features depend on the steroids being produced. Adrenal adenomas frequently present with florid Cushing syndrome. Often the adenomas produce few if any steroids other than cortisol. The result of this relatively pure cortisol secretion is considerable depletion of protein. Often patients with pure cortisol-secreting adrenal adenomas will lack signs of concomitant androgen secretion such as hirsutism, acne formation and

ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
17-KS = 17-ketosteroids
17-OHCS = 17-hydroxycorticosteroids

oily skin. Lack of adrenal androgen secretion, which appears to attenuate cortisol effects, leads to a syndrome of pronounced glucocorticoid effects. Standard tests may show only modestly elevated indices of cortisol secretion in some patients with adrenal adenoma, which provide a clue to the pathogenesis. Frequently, urinary 17-ketosteroids (17-KS) determinations are within normal range, suggesting that few adrenal androgens are being secreted.

In sharp contrast to patients with adrenal adenoma, those with adrenal carcinomas often produce biologically active steroids other than cortisol. Most commonly these steroids are androgens, but excess estrogens and mineralocorticoids have been reported.[1] It is not unusual for adrenal cancers to produce weak adrenal androgens in great quantities. If urinary 17-ketosteroids are greater than 100 mg per 24 hours in the presence of Cushing syndrome, the cause is most probably cancer of the adrenal glands.

Spontaneous clinical remissions of adrenal adenomas,[2] but not carcinomas, have been reported. However, the possibility of periodic secretion cannot be excluded in such cases.

Endogenous hypercortisolism is most often caused by excess pituitary ACTH secretion. We prefer the designation used by Tyler and West,[3] pituitary-dependent Cushing syndrome, because it encompasses a variety of possible etiologic mechanisms mediated by pituitary ACTH. Central nervous system causes have been suggested by indirect lines of evidence. One such experiment involves use of cyproheptadine, a serotonin antagonist, to treat pituitary-dependent Cushing syndrome. Successful therapy with this agent, as reported in some studies,[4] would suggest that interruption of abnormal central nervous system stimulation of the pituitary is all that is necessary to control abnormal ACTH secretion. Other investigators,[5] however, have not found this form of therapy effective.

The most compelling reason to implicate a central nervous system cause is the absence of a pituitary tumor in about 20 percent of cases of pituitary-dependent Cushing disease. Most pathologic studies, however, occurred before knowledge of the *ectopic* ACTH syndrome,[6] and many such cases described without evidence of a pituitary tumor could have represented examples of this syndrome. Besides the possibility of a mistaken pathologic diagnosis due to ectopic sources of ACTH, is the fact that small microadenomata can cause Cushing disease. Such tiny tumors might be easily overlooked at autopsy. Recently, a microadenoma in an *empty sella* has been described as a cause of this disorder.[7] In clinical situations where a pituitary tumor and ectopic ACTH secretion have been reasonably excluded, a central nervous system cause is suggested.

TABLE 1.—*Causes of Cushing Syndrome*

Exogenous steroid administration
Pituitary-dependent Cushing syndrome
Without demonstrable tumor
With demonstrable tumor
Multinodular adrenal hyperplasia
Adrenocortical tumors
Adenoma
Carcinoma
Ectopic ACTH-producing tumors

ACTH = adrenocorticotropic hormone

On the other hand, pituitary-dependent Cushing disease has been cured by removal of a pituitary adenoma;[8] the subsequent recovery of normal pituitary-adrenal function provides strong evidence that the central nervous system did not cause the disease. At this time, multiple causes of pituitary-dependent Cushing syndrome remain possible and await further studies. Interestingly, although Harvey Cushing is often quoted as suggesting that pituitary tumor is the cause of the disease named after him, he speculated cautiously because in only six of his eight cases was a tumor identified.[9]

Nodular hyperplasia of both adrenal glands is a rare cause of Cushing syndrome. These patients have substantially enlarged adrenal glands which usually respond to ACTH but do not usually respond to metyrapone or dexamethasone suppression. Hidai and co-workers[10] have observed a patient with nodular hyperplasia, in whom the total weight of both adrenal glands was 161 grams. We have observed a previously unreported patient with the same condition whose combined adrenal glands weighed 229 grams. These patients had ACTH detectable in plasma when untreated, and ACTH plasma concentrations greater that normal after bilateral adrenalectomy and replacement cortisol therapy.[10] Data from these

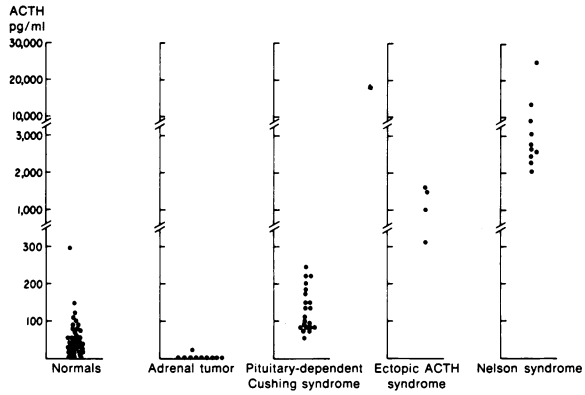

Figure 1.—Plasma ACTH concentrations of patients with various disorders affecting ACTH secretion. (ACTH= adrenocorticotropic hormone)

cases suggest a dual control mechanism: first, a source of excess ACTH which orginates from the pituitary and leads to adrenal hyperplasia. Later, some areas of hyperplastic adrenal tissue become autonomous. Such a pathogenesis would lead to nonsuppressibility and account for supraphysiologic ACTH concentrations in patients who are receiving replacement cortisol after adrenalectomy.

There are innumerable types of nonpituitary tumors that secrete ACTH and cause the ectopic ACTH syndrome. Carcinoma of the lung is, by far, the most frequent source, followed by cancer of the pancreas and thymus.[11] Most tumors that secrete ectopic ACTH do so with apparent absolute autonomy; however, a few tumors such as thymus and bronchial carcinoids have been suppressible with dexamethasone.[12,13] The ACTH molecule secreted by nonpituitary sources appears to be identical to the authentic 39 amino acid pituitary ACTH. One group,[14] however, has reported a thymic tumor with an abnormal ACTH molecule, apparently made up of the 2-38 amino acid sequence. Others have suggested that "big" ACTH may be a circulating marker for ectopic sources of ACTH.[15] Because the larger ACTH molecule is far less active biologically than the usual 1-39 smaller molecule, it may circulate in high concentrations without producing clinical signs or symptoms. Sampling "big" ACTH at regular intervals in patients at high risk for the development of a malignant condition (such as heavy smokers in whom cancer of the lung might occur), may help to detect tumors in an early stage of development. Further experience with large ACTH molecules is necessary before a routine assay in the blood can have wider applications than use in research studies.

Finally, there are recent reports of large amounts of ACTH present in nontumorous lung tissue taken from sites remote from the tumors in patients with lung cancer, suggesting the possibility that the ectopic ACTH syndrome may not be a simple disorder of tumor hormone production.

Plasma ACTH Determinations

Several commercial laboratories now offer the plasma ACTH radioimmunoassay. It is not generally available in clinical pathology laboratories, though some university centers carry out the test on a research basis. Sufficient information has been accumulated to outline general rules regarding the clinical application of plasma ACTH determinations:

(1) *Two or more samples should be obtained to estimate the mean plasma ACTH.* The diurnal variation of plasma ACTH, its short half-life in plasma and the fact that it is secreted in pulsatile bursts[16] contribute to its widely and rapidly varying concentrations in plasma. Occasionally, ACTH may be undetectable in a single specimen from a normal person as well. Thus, in distinguishing normal from low levels, multiple specimens are helpful.

(2) *Plasma ACTH determinations are not useful in distinguishing normal subjects from those suspected of having pituitary-dependent Cushing disease.* Several groups have found that the mean value of random plasma ACTH concentrations in untreated pituitary-dependent Cushing disease is about 100 pg per ml.[17,18] This value overlaps the upper end of the normal range precluding the use of the determination as a screening tool (Figure 1).

(3) *Plasma ACTH determinations appear to be useful in distinguishing adrenal tumor-dependent versus ACTH-dependent hypercortisolism.* ACTH is rarely detectable in multiple specimens from patients with adrenal tumor-dependent disease and almost always detectable in specimens from persons with ACTH-dependent disease. Furthermore, *resting* plasma ACTH values in excess of 500 pg per ml in untreated patients with hypercortisolism are highly suggestive of the ectopic ACTH syndrome.[1,17]

(4) *Care in collection and preservation of plasma specimens is important.* ACTH bioactivity disappears promptly from plasma at room temperature due to enzymatic degradation of the hormone.[19] While immunoreactivity necessary for the radioimmunoassay is hardier than bioactivity, it

TABLE 2.—*Shortcomings of Methods of Estimating Cortisol*

Methods	*Sources of Error, Variability or Nonspecificity*
Plasma cortisol by radioimmunoassay	Diurnal variation. Episodic variation due to pulsatile secretion. Binding protein (transcortin) variations.
Plasma cortisol by fluorescence	Shortcomings listed above plus interfering substances, especially spironolactone (Aldactone). Many fluorescent steroids.
Urinary 17-OHCS (Porter-Silber)	Collection errors. Interfering substances.
Urinary 17-ketogenic steroids	Less specific than 17-OHCS.
Urinary 17-ketosteroids (17-KS)	Nonspecific. Only 5 percent of cortisol is excreted as 17-KS.
Urinary "free" cortisol	Suboptimal specificity. Also measures 11-deoxycortisol and other corticosteroids. Not well standardized.

17-OHCS = 17-hydroxycorticosteroids

too will disappear after several hours at room temperature. Accordingly, collection and refrigeration of blood and the prompt separation of plasma is essential for obtaining valid results. Furthermore, ACTH is readily adsorbed to glass. While the protein content of plasma helps prevent such adsorption it is wise to use plastic containers for collection and shipping of specimens.

(5) *"Big" ACTH determinations and lipotropins.* Evidence exists that ACTH is a portion of a precursor molecule consisting of approximately 260 amino acids referred to as "big" ACTH. Lipotropin is considered a part of this precursor molecule as well.[20] Plasma ACTH levels determined by radioimmunoassay in the ectopic ACTH syndrome are generally higher than in pituitary-dependent Cushing syndrome.[21,22] The lack of substantially elevated cortisol production in association with these extremely high plasma ACTH determinations in the ectopic syndrome suggest secretion of an intact precursor molecule without biological activity. Chromatographic studies have supported this idea.[21,22]

Lipotropin secretion seems to parallel ACTH secretion, which is consistent with the concept of a common precursor molecule.[23] So far, no pattern of ACTH, "big" ACTH or lipotropin secretion has allowed separation of the ectopic ACTH syndrome from pituitary-dependent Cushing syndrome. Further experience with specific assays for ACTH, lipotropin and intact precursor molecules in the future may permit distinguishing the ectopic syndrome from pituitary-dependent Cushing disease.

Measurements of Cortisol

Knowledge that cortisol secretion varies episodically as well as diurnally has served to reinforce the opinion that quantitative clinical estimates of cortisol secretion are best made by measuring cortisol from its metabolites in 24-hour urine collections rather than in random specimens of plasma. Several methods appear to have stood the test of time, and no one seems clearly better than the others, either on a theoretical or practical basis. Table 2 lists available tests requiring 24-hour collection and tabulates the normal excretion values. Some investigators have advocated expression of cortisol values as a function of creatinine excretion or surface area, but we have not found this to be particularly helpful because we place more diagnostic emphasis on suppression or stimulatory manipulations of cortisol excretion rather than on basal values per se. For example, urinary 17-hydroxycorticosteroid (17-OHCS) excretion of 12 mg per 24 hours is a slightly elevated value. Whether or not that basal value exceeds normal limits for a patient is not as important as whether or not the value remains stable for several days.

While the urinary 17-hydroxycorticoid test and the measurement of 17-ketogenic steroids and urinary 17-ketosteroids all reflect excretion of cortisol metabolites, urinary 17-OHCS determinations permit the most specific measurement. Approximately 25 percent to 33 percent of cortisol is excreted as a urinary 17-OHCS in normal subjects, while only 20 percent of 17-ketogenic steroids are derived from cortisol and only 5 percent of cortisol metabolites are 17-ketosteroids. Conversely, only the major steroids cortisol and Compound S metabolites contribute to the 17-OHCS, while numerous other steroids contribute to both 17-ketosteroid and 17-ketogenic determinations.[24]

Urinary Free Cortisol

Free cortisol is commonly understood to represent unmetabolized and unconjugated cortisol. Approximately 0.2 percent of cortisol secreted by adrenal glands is excreted in this form. Urinary

free cortisol appears to be of greatest value as a screening test for hypercortisolism.[25] Two prior shortcomings have limited its wider application. First, the test is not well standardized and considerable overlap of values exists in published reports between suspected and proved cases of Cushing syndrome. Second, the test is relatively nonspecific because reported methods also detect compound S, corticosterone and sometimes progesterone.

Diagnosis of Cushing Syndrome

Referral for diagnostic evaluation of possible Cushing syndrome is generally made because of physical stigmata suggesting hypercortisolism, elevated 24-hour urinary 17-hydroxycorticosteroid excretion, elevated urinary free cortisol concentration or abnormal overnight dexamethasone suppression test. We continue to use overnight dexamethasone suppression as a screening test rather than as part of the definitive diagnostic evaluation. False-positive results (8 AM plasma cortisol of greater than 5 μg per dl after receiving 1 mg of dexamethasone at midnight) can misidentify normal, obese persons as having Cushing syndrome[26] if such testing is substituted for standard low-dose dexamethasone suppression (0.5 mg given every six hours for two days.)[26]

As a practical approach, patients with suspected Cushing syndrome are given the standard low-dose dexamethasone test on an outpatient basis and, if positive, are admitted to the hospital for further testing. Duplicate aliquots of all specimens are stored in a refrigerator on the ward in the event that any are mishandled or lost. To measure basal urinary 17-OHCS and 17-ketosteroids (17-KS), urine specimens are collected on days 1 and 2. Urinary 17-OHCS determinations alone are done during the remainder of the testing period. Metyrapone, 750 mg every four hours in six dosages is administered on day 3. The maximum rise of the urinary 17-OHCS in response to metyrapone is somewhat unpredictable and can occur during either the day of or the day after administration of metyrapone; therefore, no manipulations are done on day 4. Dexamethasone, 0.5 mg every six hours (low dose) is given on days 5 and 6, followed by 2 mg every six hours (high dose) on days 7 and 8.

An algorithm of our diagnostic approach to Cushing syndrome and its interpretation are given in Figure 2. The literature reflects some confusion about interpretation of the low-dose dexamethasone test. As Liddle originally described, values of urinary 17-hydroxycorticosteroids fall to less than 3 mg per 24 hours on the second day of administration of dexamethasone (0.5 mg every six hours).[27] Values above this level are strongly suggestive of Cushing syndrome if the urine collection was accurate and if the patient is not tak-

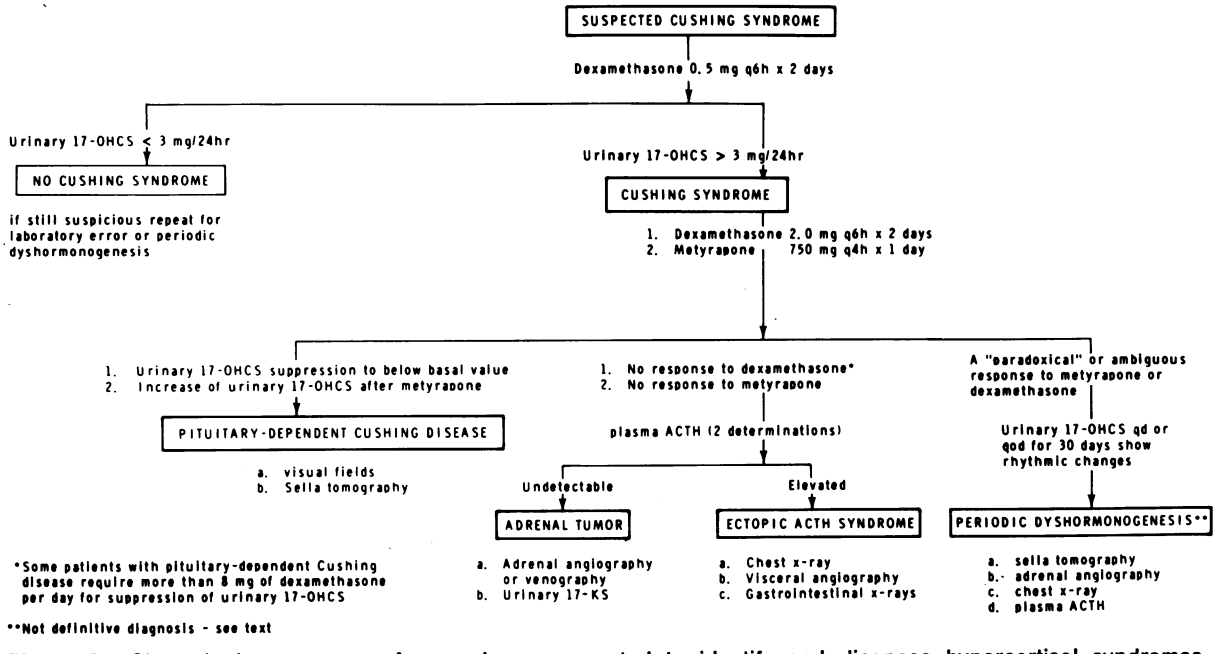

Figure 2.—Chronologic sequence of procedures suggested to identify and diagnose hypercortisol syndromes. (ACTH=adrenocorticotropic hormone; 17-KS=17-ketosteroids; 17-OHCS=17-hydroxycorticosteroids)

ing other drugs that might alter cortisol or dexamethasone metabolism.

Table 3 shows suppression test results in a patient with classic features of Cushing disease. The initial test results were interpreted as "normal in an obese patient." Two years later the test results were obviously abnormal. It is probable that the initial suppression values were also abnormal, but not properly interpreted. Suppression of the urinary 17-OHCS to less than 3 mg during low-dose dexamethasone testing is within normal limits, and is strong evidence against the presence of Cushing syndrome. Lack of a normal response usually confirms the diagnosis of Cushing syndrome but does not distinguish between various causes. With high-dose dexamethasone administration the urinary 17-OHCS will usually suppress to less than half the basal values in pituitary-dependent Cushing syndrome. This reflects a disordered cortisol feedback in which ACTH secretion remains responsive to the suppressive effects of cortisol although higher circulating concentrations are required. Occasionally, a more pronounced feedback abnormality is seen in patients with pituitary-dependent Cushing syndrome in whom no suppression of the urinary 17-OHCS to standard high-dose dexamethasone testing is observed. A fall of the urinary 17-OHCS will occur however, if very large dosages of dexamethasone (8 mg every six hours) are used (Table 4). Such responses seem to indicate that a wide variation in degree of feedback abnormality exists in pituitary-dependent Cushing syndrome.

Metyrapone administration results in a significant increase of the urinary 17-OHCS in pituitary-dependent Cushing syndrome. This agent is primarily an 11β-hydroxylase inhibitor and causes an increase of plasma 11-desoxycortisol levels with a fall of the plasma cortisol concentration. A lowering of the cortisol levels coupled with the negligible ACTH-suppressive activity of 11-desoxycortisol results in increased ACTH secretion. Because 11-desoxycortisol is metabolized to a 17-OHCS, urinary 17-OHCS increases (Figure 3). Routine use of metyrapone is valuable for confirmation of pituitary-dependent Cushing syndrome, especially in patients with resistance to high-dose dexamethasone.

Patients with pituitary-dependent Cushing syndrome should be evaluated for a pituitary tumor with sellar tomography. These findings are usually negative in an untreated case. If a pituitary tumor is present, tests to exclude the possibility of suprasellar extension should be done because knowledge of this complication's presence is critical for selection of an appropriate treatment modality.[28] Findings on visual field examination and pneumoencephalography as well as an elevated cerebrospinal fluid (CSF) ACTH concentra-

TABLE 3.—*Results of Urinary 17-OHCS Suppression Tests in a Patient With Classic Features of Cushing Syndrome*

Date	*Drug Dosage*	*Urinary 17-OHCS (mg/24 hrs)*
1962	None	16
1962	Second day of dexamethasone 0.5 mg every six hours	7
1964	None	21
1964	Second day of dexamethasone 0.5 mg every six hours	13
1965	None	25
1965	Second day of dexamethasone 0.5 mg every six hours (low dose)	19
1965	Second day of dexamethasone 2.0 mg every six hours (high dose)	8

17-OHCS = 17-hydroxycorticosteroids

TABLE 4.—*Response of Urinary 17-OHCS to Large-Dose Drug Therapy in a Patient With Pituitary-Dependent Cushing Syndrome*

Day	*Drug Dosage*	*Plasma ACTH (pg/ml)*	*Plasma Cortisol (μg %)*	*Urinary 17-OHCS (mg/24 hrs)*
1	None	150	38	29
2	Metyrapone	248	24	48
3	None	176	32	44
4	Dexamethasone (2 mg per day)	170	26	41
5	Dexamethasone (2 mg per day)	105	26	42
6	Dexamethasone (8 mg per day)	86	19	23
7	Dexamethasone (8 mg per day)	116	10	26
8	Dexamethasone (32 mg per day)	43	21	23
9	Dexamethasone (32 mg per day)	<30	4.9	10
10	ACTH infusion (50 units per day)	...	...	199

ACTH = adrenocorticotropic hormone
17-OHCS = 17-hydroxycorticosteroids

tion are all valuable indicators of suprasellar extension. An elevated cerebrospinal fluid ACTH concentration with suprasellar extension presumably results because the tumor invades the subarachnoid space and releases hormone directly into CSF. Patients with ACTH-secreting tumors without suprasellar extension have cerebrospinal fluid ACTH levels less than 200 pg per ml despite striking elevation of the plasma ACTH concentration (up to 6,000 pg per ml).[28,29]

Computerized axial tomographic (CAT) scanning is a relatively new tool and, therefore, extensive experience in its use has not been generated. In a recent study,[30] CAT scanning detected all 17 pituitary tumors greater than 1.5 cm in size, three of five between 1.5 and 0.5 cm and none less than 0.5 cm. This experience coupled with our own suggests that small pituitary tumors with minimal suprasellar extension can be more accurately identified by pneumoencephalography than by CAT scanning.

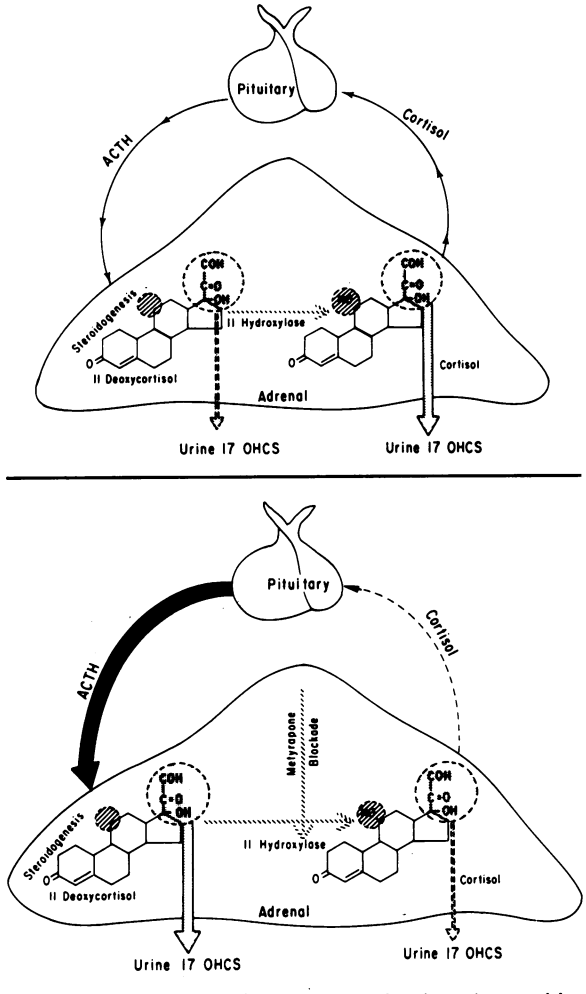

Figure 3.—Metyrapone blockade of adrenal steroidogenesis **(top)**. Because the urinary 17-OHCS test does not discriminate between the precursor to cortisol (11-desoxycortisol) and cortisol, a rise of urinary steroids indicates an intact pituitary adrenal axis **(bottom)**.

Characteristically, patients with a cortisol-secreting adrenal tumor or ectopic ACTH secretion show no change of the urinary 17-OHCS during either low- or high-dose dexamethasone suppression or with metyrapone stimulation. This would be expected because the hypercortisolism is not dependent upon pituitary ACTH secretion. Neither of these maneuvers, therefore, can distinguish patients with ectopic ACTH secretion from those with adrenal tumors. Occasionally, however, the urinary 17-OHCS will fall after metyrapone administration in cases of adrenal tumor. The paradoxical response is probably explained by the dual sites of inhibition of adrenal steroidogenesis exhibited by metyrapone.[31] This drug blocks not only 11β-hydroxylation but also cholesterol cleavage in the *absence* of ACTH. With ACTH present the block of cholesterol cleavage induced by metyrapone is overcome; however, the 11β-hydroxylation block remains.[31] Thus, in states of hypercortisolism without circulating ACTH (adrenal tumors) a block early in steroidogenesis, such as cholesterol cleavage, would cause a fall of urinary 17-OHCS. Additionally, routine measurement of urinary 17-OHCS detects cortisol metabolites more effectively than 11-desoxycortisol metabolites.

More reliably, patients with ectopic ACTH secretion and adrenal tumors can be distinguished from those with pituitary-dependent Cushing disease by measurement of plasma ACTH concentration. Figure 1 shows ACTH concentrations in patients with Cushing syndrome who were evaluated at the University of Oregon Health Sciences Center. Plasma ACTH is almost always undetectable in patients with adrenal tumors. However, one patient with a surgically documented cortisol-secreting adrenal adenoma had low but definitely measurable ACTH in plasma. We have no explanation for this observation. In contrast, patients with ectopic ACTH secretion have plasma ACTH levels that are elevated, often exceeding 1,000 pg per ml. In pituitary-dependent Cushing syndrome the plasma ACTH is usually at or somewhat above the upper limits of normal (110 pg per ml). The highest levels of ACTH that we have observed are in patients with Nelson syndrome. In this condition deep pigmentation with substantially elevated plasma ACTH levels develop after bilateral adre-

nalectomy for pituitary-dependent Cushing syndrome. In most of these patients a large pituitary tumor can be observed. As previously emphasized, at least two plasma ACTH determinations should be done before any diagnostic conclusions are made.

If tests result in undetectable plasma ACTH levels associated with unresponsive urinary 17-OHCS to dexamethasone and metyrapone, or a paradoxical fall of urinary 17-OHCS with administration of metyrapone, a patient has an adrenal tumor. Several varieties of radiologic investigation can then be used for locating the tumor. Large tumors can frequently be detected by intravenous pyelography and tomography. Adrenal venography or selective adrenal arteriography, however, is usually required to find smaller lesions.[32,33] Adrenal scanning with radioiodinated cholesterol can visualize benign adrenal tumors; however, adrenal carcinomas usually cannot be visualized.[34] This noninvasive technique holds promise for the future but is not yet widely available. Differentiation of a benign adenoma from carcinoma can be difficult on the basis of clinical characteristics or radiologic appearance. A basal urinary 17-KS determination, however, of greater than 100 mg is suggestive of a malignant adrenal tumor, and a value greater than 200 mg is pathognomonic for adrenal carcinoma.

Levels of urinary 17-OHCS that are unresponsive to dexamethasone and metyrapone and are accompanied by a high plasma ACTH concentration strongly suggest ectopic ACTH secretion. The most common tumors associated with this syndrome are carcinoma of the lung, pancreatic cancer, thymoma and bronchial adenomas.[11] A careful and exhaustive search using appropriate radiographic studies is indicated in any patient with suspected ectopic ACTH secretion.

A recently described entity is Cushing syndrome with periodic hormonogenesis.[35-38] In this unusual variant, rhythmic fluctuations of ACTH result in a cyclic rise and fall of the urinary 17-OHCS. The causes of the Cushing syndrome in the four previously described cases were a pituitary tumor in two[36,38] and a bronchial adenoma in the other two.[35,37] The durations of the cycles were approximately 7, 11, 18 and 86 days. We recently evaluated a patient with pituitary-dependent Cushing disease and periodic hormonogenesis (Figure 4) and the cycle duration was 7.5 days. Unfortunately, the rapid progression of the patient's disease precluded more extensive studies. It is very likely that the phenomenon of periodic hormonogenesis accounts for earlier reports of paradoxical responses to dexamethasone.[36] If dexamethasone is given during a phase of increasing cortisol secretion, a *paradoxical response* will be observed. In addition, if dexamethasone is given during a period of decreasing cortisol secretion, test results may be misinterpreted as suppression. Metyrapone given either during an ascending or descending phase of the cycle also could result in misleading or confusing laboratory findings. Periodic hormonogenesis can be established only by sequential urine collections.

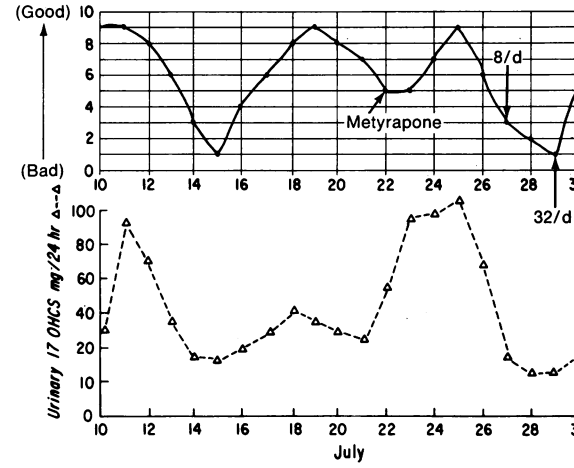

Figure 4.—Fluctuations in sense of well-being correlated with daily urinary 17-OHCS determinations in a 29-year-old man with Cushing syndrome and periodic dyshormonogenesis. (Top graph was constructed by the patient who, at the time, was unaware of urinary steroid values.)

Several other unusual situations can cause confusion in the diagnosis of Cushing syndrome and deserve mention. Suppression of cortisol secretion with higher doses of dexamethasone can occur in patients with ectopic ACTH secretion from a bronchial adenoma.[14] Whether this response is actually due to periodic hormonogenesis is uncertain. Fluctuation of cortisol secretion also occurs in patients with Cushing syndrome and micronodular adrenal hyperplasia, although definitive cyclic variation has not been described.[39] In micronodular hyperplasia there are periods when the urinary 17-OHCS excretion is within normal limits; however, the urinary free cortisol concentration at these times will be elevated.[39] Such patients are usually young and do not have clinical stigmata of Cushing disease. This condition frequently presents as idiopathic osteoporosis. Recently, it

has been recognized that long-term alcohol abuse can produce an excess glucocorticoid appearance associated with abnormal (1 mg dexamethasone at midnight) suppression of plasma cortisol.[40,41] In addition, urinary 17-OHCS excretion can remain abnormally elevated during standard low- and high-dose dexamethasone suppression simulating an adrenal tumor or ectopic ACTH secretion (Jordan, unpublished observations). These abnormalities, however, resolve after withdrawal of alcohol. It is apparent that a history of alcoholism must be sought in a patient with suspected Cushing syndrome if misdiagnosis is to be avoided. Similar resistance to cortisol suppression has been reported in depression which reverts to normal levels after treatment.[42]

Finally, several drugs are capable of affecting the results of a diagnostic evaluation of Cushing syndrome. Diphenylhydantoin is known to accelerate the metabolism of both dexamethasone and metyrapone and this can result in anomalous test results.[43,44] Spironolactone and testosterone can elevate while estrogens can cause spuriously low readings of the urinary 17-OHCS.[45,46] Administration of the following medications also results in alterations of the urinary 17-OHCS: acetazolamide, chloral hydrate, chlorothiazide, chlordiazepoxide, colchicine, dextroamphetamine, digitoxin, digoxin, glutethimide, iodides, meprobamate and oleandomycin.[45,46] A systematic review of drugs affecting pituitary adrenal function tests has been made elsewhere.[47]

Therapy for Cushing Syndrome

Therapy for pituitary-dependent Cushing syndrome remains the most controversial aspect of treatment of hypercortisolemic states. Selection of therapeutic modality has been influenced heavily by local availability of techniques such as neurosurgery or radiation and the fact that no one treatment plan has emerged as uniformly successful. As a result, a plethora of modalities have been used to treat this disorder. The most commonly used therapies have been total bilateral adrenalectomy, conventional or heavy particle pituitary radiation, implantation of radioactive seeds in the anterior pituitary, pharmacologic treatment and, more recently, transsphenoidal surgical procedures to pituitary tumors.

Total bilateral adrenalectomy provides the quickest means of relieving pituitary-dependent hypercortisolism. Some patients, however, cannot tolerate this procedure due to extreme debility associated with the disease or unrelated reasons. Surgical considerations such as severe furunculosis secondary to hypercortisolism, refractory to antibiotic and local therapy, also preclude operation because postoperative wound infection is a concern in these circumstances. An adrenal operation requires, at present, total bilateral adrenalectomy. Previous attempts at partial resection have been unsuccessful because there is at least a 30 percent recurrence rate[48,49] of hypercortisolism. To avoid replacement corticosteroid therapy necessitated by total bilateral adrenalectomy, adrenal autotransplants have been attempted.[50,51] However, we are not aware of any reported successes with this procedure of placing small pieces of adrenal gland into muscle or fat. The use of finely diced pieces of tissue such as has been used for parathyroid autotransplantation of hyperplastic tissue[52] has not been attempted with adrenal tissue.

Patients who receive bilateral adrenalectomy as therapy for Cushing disease are not cured of the pituitary component of the disease. Nelson and colleagues first described[53] the syndrome which bears his name in which hyperpigmentation and a pituitary tumor developed after bilateral adrenalectomy for Cushing syndrome. The condition has been called Nelson syndrome, and its incidence is estimated at 8 percent[54] following bilateral adrenelectomy. Our experience, contrary to that of Moore and co-workers,[54] is that these tumors are particularly aggressive, subject to spontaneous infarction and frequently necessitate a combination of therapeutic approaches such as both pituitary surgical procedures and irradiation to achieve control.[18] The thrust of initial therapy, then, should be twofold—cure the hypercortisolism and prevent or control other deleterious effects of a probable pituitary tumor. We believe that all patients with pituitary-dependent Cushing disease should be treated as if they were harboring a pituitary tumor. Our studies of pituitary ACTH secretion before and after bilateral adrenalectomy support this idea.[18]

We have found that ACTH secretory dynamics are qualitatively similar before adrenal operations and after development of a definite pituitary tumor (Nelson syndrome). Suppression of ACTH by dexamethasone changes quantitatively (1) when observed before any therapy, (2) after bilateral adrenalectomy without evidence of a pituitary tumor or (3) in the presence of evidence of a pituitary tumor. This situation suggests a con-

tinuum rather than a change of the underlying pathology. Because we know that a pituitary tumor exists in the context of Nelson syndrome, we have reasoned that one must exist before any therapy of pituitary-dependent Cushing disease. Also supporting this idea are isolated reports of cure of Cushing disease by pituitary adenomectomy where normal pituitary adrenal dynamics return after pituitary operations.[4,7,8] For this and other reasons primary therapy often has been directed at the pituitary. Conventional pituitary radiation controls the hypercortisolism in approximately a third to a half of patients,[55] but does not seem to completely protect against the development of pituitary tumors.[54,56] Particle irradiation, however, is associated with approximately 33 percent incidence of hypopituitarism.[57,58] Radioactive yttrium or gold implantation has similar drawbacks to particle therapy in that control of hypercortisolism and tumor progression can be achieved but at the expense of a high incidence of hypopituitarism[59] and the risk of CSF rhinorrhea. The use of cyproheptadine, a serotonergic antagonist, has recently been used in treating Cushing disease. Although initially successful in some cases,[4,60] it has not been so in others.[5,61,62] The reasons for lack of universal success with this agent remain unclear. Of course, it could be possible that patients with pituitary-dependent Cushing syndrome represent a heterogeneous group of disorders, ranging from pituitary tumor to a predominantly central nervous system abnormality. Those with a predominant CNS component may be more responsive to serotonin antagonists.

It should be noted that once cyproheptadine therapy was discontinued cortisol secretion resumed at pretreatment levels in those cases where control was possible with this drug. Therefore, it should not be considered definitive therapy. Other pharmacologic agents have been tried but have serious shortcomings. The adrenocorticolytic drug (o,p'DDD or, written in full, 1-dichloro-2-[O-chlorophenyl]-2-[p-chlorophenyl]-ethane) is slow in onset, irreversibly destroys adrenocortical reserve and is poorly tolerated by the gastrointestinal tract.[63,64] Inhibition of cortisol secretion by aminoglutethimide therapy often results in exaggerated endogenous ACTH production (Cook, unpublished data) which overcomes the effect on steroidogenesis and restores cortisol secretion to pretreatment levels. Cortisol hypersecretion has been controlled with aminoglutethimide or metyrapone, or both, during or after pituitary irradiation but before full radiation effects have occurred.

Pituitary surgical procedures have been used in a surprisingly small number of cases. Hardy[65] found a small pituitary tumor in each of 10 patients. Eight of the 10 were cured, one improved and one remained unchanged. Our experience with three cases is contrary to Hardy's. In all three patients the disease persisted after transsphenoidal pituitary operations. Tyrrell and colleagues[66] have attempted transsphenoidal adenomectomy in 20 patients. In two the procedure was terminated because of large dural venous sinuses of the anterior sella. Of the remaining 18, only one did not have a pituitary tumor at the time of the operation. Sixteen of the 17 who had recognizable tumors at that time had glucocorticoids in the normal or subnormal range postoperatively. Similar transsphenoid surgical success has been reported by Schnall and associates[67] and Salassa and co-workers.[68] However, greater experience is needed with this method before it can be widely recommended. Our present therapy recommendations depend upon availability of skilled neurosurgeons and the urgency of relieving hypercortisolism. If urgency and certainty are required, bilateral adrenalectomy is still advocated. If an operation is required and skilled neurosurgeons are available pituitary adenomectomy is suggested. If the urgency is not great, we favor particle irradiation therapy if suprasellar extension does not exist. If suprasellar extension exists, then a pituitary operation is suggested followed by particle irradiation if a cure is not achieved by the surgical procedure.

The therapy for Cushing syndrome associated with adrenal adenoma is obvious. Surgical removal of the adenoma with retention of the remaining contralateral adrenal gland is the therapy of choice. The same can be said for adrenal carcinoma although, because of frequent recurrence or lack of initial surgical cure, chemotherapy is an important adjunct of the therapy.

Aminoglutethimide and o,p'DDD have been used singly or in combination. At present, there is no way to predict which agent is preferable. Frequently, o,p'DDD is not tolerated by patients because of gastrointestinal side effects of nausea and diarrhea. Although steroid values were reduced in 69 percent of 138 patients with carcinoma of the adrenal cortex, Hutter and Kayhoe were not able to show any prolongation of life in patients receiving o,p'DDD therapy.[69,70] Amino-

glutethimide has no adrenolytic properties and provides only occasional symptomatic relief.[71]

Summary

Recent advances in our understanding of the causes of hypercortisolism have been reviewed. An algorithm for differentiating these mechanisms has been proposed using techniques which have been described recently, especially quantitative plasma ACTH measurement. Interpretation of diagnostic tests requires a knowledge of their limitations. Treating patients with pituitary-dependent Cushing syndrome remains controversial —especially because the pathogenesis of this syndrome remains to be defined.

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