MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

JULY 24, 1975

CUSHING'S SYNDROME:
A CLINICAL AND DIAGNOSTIC PERSPECTIVE

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INTRODUCTION

Approximately four decades have passed since Cushing (1) first drew attention to the clinical syndrome which now bears his name. However, the term Cushing's syndrome should refer to any endogenous form of hypercortisolism, reserving the term Cushing's disease for the most common variety of the disease (i.e. pituitary in origin).

The following classification Table 1 (Slide 1) illustrates the component diseases all of which may produce hypercortisolism.

CUSHING'S SYNDROME

Classification

Adrenal cortex hyperplasia (Cushing's disease)- i.e. pituitary ACTH in origin

Adrenal cortex hyperplasia (Ectopic ACTH syndrome)- i.e. tumor ACTH in origin

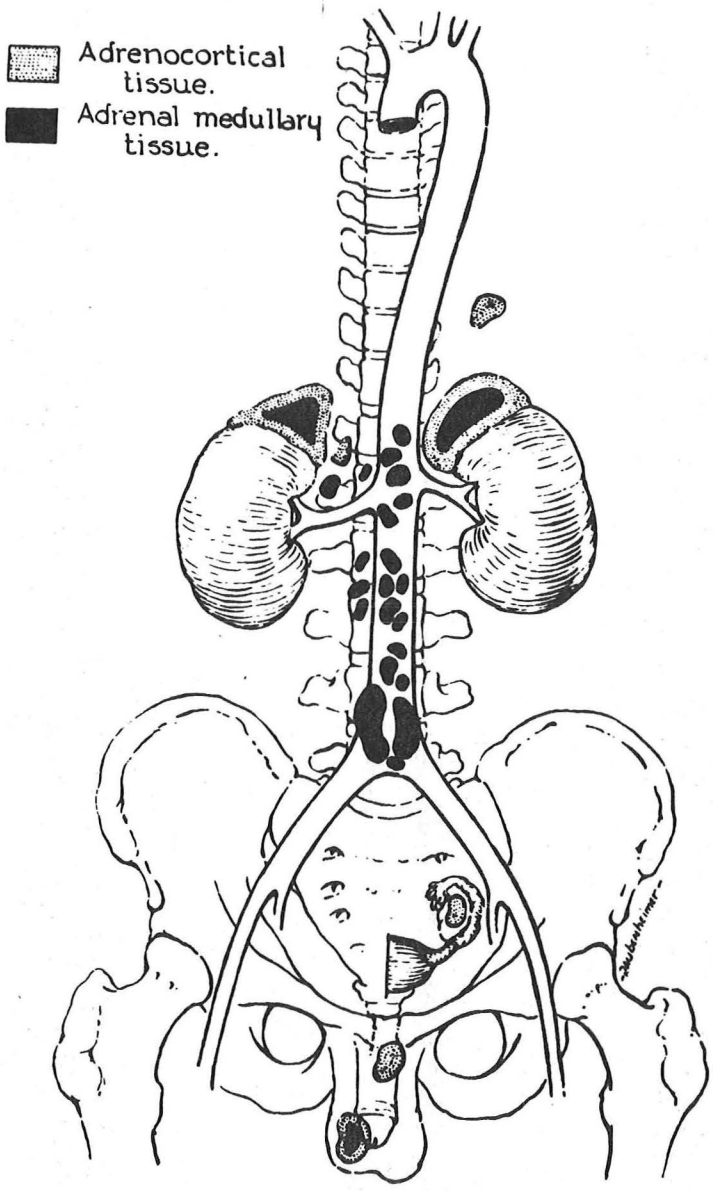
Adrenal cortex adenoma

Adrenal cortex carcinoma

Aberrant adrenal cortex tissue

The most common cause of all, which unfortunately is iatrogenic, will not be discussed. The least common variety of hypercortisolism is related to aberrant adrenocortical tissue. The following diagram Figure 1 (Slide 2)

depicts the spectrum of sites at which adrenocortical tissue has been found in contrast to the more scattered locations documented for adrenomedullary tissue of different embryologic origin.



Patients with Cushing's syndrome, particularly in its florid expression, are easily recognized by the physican who is familiar with the problem. Such patients attract considerable interest because of the myriad physical and metabolic consequences of excess cortisol. However, both the clinical stigmata

and metabolic repercussions of Cushing's syndrome are related to the degree and/or the duration of excessive cortisol secretion. The florid manifestations that are characterized as typical generally do not appear until the late pathogenetic stages of adrenocortical hyperfunction; may be minimal in the early mild case; and may be entirely absent in some patients, especially in those with ectopic hormone production by a malignancy.

Although Cushing's syndrome in any of its forms is uncommon, hypercortisolism is suspected in a relatively large number of patients. Because of the seriousness of the morbidity and mortality rates associated with Cushing's syndrome, a high index of clinical suspicion and effective laboratory screening is essential for early detection.

GENERAL

An analysis of the literature with incorporation of our own experience reveals pertinent biostatistics concerning the etiology, and sex and age distribution of patients with Cushing's syndrome. The etiology and respective incidence is shown in the following Table 2 (Slide 3 & 4).

CUSHING'S SYNDROME

Incidence and Type of Pathology

Author	BAH*	Adenoma	Carcinoma	Ectopic†
Plotz, et al (1952)	58	11	16	?
Poutasse & Higgins (1953)	22	4	2	?
Cope & Raker (1955)	27	12	5	?
Sprague, et al (1956)	69	14	5	?
Roberts & Lattimer (1961)	36	8	5	?
Ross, et al (1966)	45	4	1	?
Neville & Symington (1967)	60	5	7	9
Streeten, et al (1969)	13	2	1	1
Eddy, et al (1973)	11	6	4	3
Total	341	66	46	13
Percentage	73	14	10	3(?)

* = bilaterla adrenal hyperplasia
† = ectopic ACTH syndrome

Approximately 3/4 of all patients with Cushing's syndrome is due to pituitary-dependent bilateral diffuse or adenomatous adrenocortical hyperplasia (i.e. Cushing's disease).

The well known sex distribution in favor of female preponderance is shown in the following Table 3 (Slide 5).

CUSHING'S SYNDROME

Sex Distribution

Author	Males	Females	Total	Percent Female
Cushing (1933)	2	12	14	86
Plotz, et al (1952)	68	121	189	64
Cope & Raker (1956)	10	36	46	78
Sprague, et al (1956)	19	81	100	81
Roberts & Lattimer (1961)	11	38	49	78
Ross, et al (1966)	5	45	50	90
Streeten, et al (1969)	4	13	17	76
Eddy, et al (1973)	10	14	24	58
Total	129	360	489	76

The overall mean incidence of female patients with Cushing's syndrome due to bilateral adrenocortical hyperplasia of pituitary origin is 73%; due to an adenoma is 71.3%; due to a carcinoma is 75%; and, due to "ectopic" malignancy in contrast is only 22%. The more recently published series include a greater number of patients with ectopic ACTH syndrome --- a predominantly male disorder paralleling the incidence of bronchogenic carcinoma. It is probably this fact that is reflected by the slightly less common incidence of females in these more recent reports (7,8). From a clinical point of view the preponderance of female patients with Cushing's syndrome is so striking that when a male patient is encountered with hypercortisolism the likelihood of an ectopic ACTH syndrome is very high.

The age distribution of patients with Cushing's syndrome is shown in the following Table 4 (Slide 6).

CUSHING'S SYNDROME

Age Distribution

Author	Age in Years						
	0-9	10-19	20-29	30-39	40-49	50-59	>60
Plotz, et al (1952)	0	3	14	9	6	1	0
Cope and Raker (1955)	1	4	10	16	9	2	4
Horwith and Stokes (1960)	2	11	12	12	5	2	0
Soffer, et al (1961)	1	8	13	19	5	2	2
Ross, et al (1966)	0	4	9	11	11	11	4
Streeten, et al (1969)	1	2	2	2	3	6	1
Eddy, et al (1973)	0	0	2	4	8	8	2
Total	5	32	71	73	47	32	13
Percentage	2	12	26	27	17	12	4

Again, probably related to the current recognition of ectopic hormone production by malignancy as a cause of hypercortisolism, the age distribution is higher in the more recently published series (6,7,8). The mean age at the time of diagnosis in the earlier (before 1960) series is 31.3 years in contrast to the more current experience of 42.4 years. The overall mean age incidence of patients with Cushing's syndrome due to bilateral adrenocortical hyperplasia of pituitary origin is 39.5 years; due to an adenoma is 43.5 years; due to a carcinoma is 50.5 years; and, due to an "ectopic" malignancy is 55.3 years.

CLINICAL MANIFESTATIONS

The spectrum and incidence of manifestations encountered in patients with Cushing's syndrome is shown in the following Table 5 (Slide 7 & 8).

CUSHING'S SYNDROME

Manifestations

Features	Incidence (Percentage)			
	Ross et al (1966)	Streeten et al (1969	Eddy et al (1973)	Mean
Truneal obesity	94	88	95	92
Moon Facies/Fat pads	84	100	88	91
Hirsutism/Acne	91	85	75	84
Plethora	84	-	79	82
Muscular weakness	79	65	71	72
Hypertension	70	60	63	64
Menstrual changes	76	38	64	59
Striae	52	53	50	52
Backache	50	53	41	48
Bruising/Ecchymoses	36	65	35	45
Mental changes	40	35	50	42
Edema	18	53	20	30
Hyperpigmentation	6	-	8	7
Exophthalmos	2	-	4	3

Very few patients present with all or even a majority of these findings, and some patients (particularly those with the ectopic ACTH syndrome) are strikingly devoid of characteristic clinical features. The higher the physician's index of suspicion and effective screening tests, the earlier in the course of the illness the diagnosis can be established. As one would anticipate, these early, mild cases also manifest less impressive clinical manifestations. Certain clinical features are of particular interest and warrant further discussion.

Obesity. Obesity of truncal or centripedal distribution is the most frequent feature. However, in the milder cases the limb sparing aspects are often minimal. Approximately 35% of the patients showed generalized

obesity of varying degree, but in no instance was the magnitude greater than 40% of their predicted normal weight (i.e. there were no severely obese patients). No correlation was noted between the degree of obesity and the duration of symptoms or the magnitude of cortisol excretion. It has been demonstrated that glucocorticoids have a stimulatory effect upon appetite, and fractional body fat content (45). Cushing (1) stressed the painful and tender nature of the adiposity. This feature however has not been commonly encountered.

Rounded facies/fat pads. Proliferation of localized fat deposits has always been recognized as typical of patients with hypercortisolism. The "moon" facial configuration, enlargement of posterior cervical ("buffalo hump") and supraclavicular fat pads are peculiar to Cushing's syndrome and rank second in overall frequency. The majority of the patients who exhibited localized fat accumulation did so in all three characteristic sites rather than one site or another. This is in contrast to the usual patient with simple obesity. The mechanism by which this unusual fat distribution occurs is unknown. Some evidence (44) has been reported that glucocorticoids promote lipolysis, suppress lipogenesis, and enhance the lipolytic action of catecholamines.

Hirsutism/acne. Hirsutism (i.e. hypertrichosis) of varying degrees is commonly found in the female patients. It is not ordinarily associated with masculinization. If true virilization is present the diagnosis is seldom Cushing's syndrome but rather adrenogenital syndrome or masculinizing tumor. The spectrum of hirsutism in patients with Cushing's syndrome varies from fine, soft lanugo-type to coarse, stiff adult-type hair growth.

Muscular weakness. This complaint (not to be confused with fatigability) is present in about 3/4 of the patients with hypercortisolism. The weakness is invariably related to the proximal musculature of the lower extremities (especially quadriceps femoris) much in the fashion of thyrotoxicosis. It is generally believed that the muscular lesion is related to the excessive corticosteroid production, and indeed a similar myopathy has been reported both in patients and experimental animals receiving large doses of exogenous corticosteroids (13,14). However, unlike iatrogenic and experimental steroid myopathies which resolve spontaneously upon cessation of steroid administration, a persistent myopathy occurs in some patients with Cushing's syndrome despite successful treatment of the primary disorder (15). The sole histologic clue regarding the pathogenesis of the myopathy is the finding of increased intra-fiber fat (15). Hypokalemia, a known cause of myopathy, is an untenuous explanation since it is only demonstrable in a minority of the patients with Cushing's syndrome. Corticosteroid excess per se seems an unlikely explanation since some patients not only continue to have but even develop progressive myopathy once corticosteroid levels have been restored to normal.

A few patients have also been reported to develop myopathy following successful therapy when myopathic symptoms were not a feature of the pre-treatment illness. Finally, some circumstantial evidence exists that steroid myopathy may at least in some instances be due to high circulating ACTH levels. Prineas, et al. (15) have noted an association between steroid myopathy and hyperpigmentation, such as in patients with Nelson's syndrome (16). The fact that we have noted muscular weakness as frequently in patients with hypercortisolism due to autonomous adrenocortical neoplasms (i.e. low circulating ACTH levels) as in patients with Cushing's disease and ectopic ACTH syndrome (i.e. high circulating ACTH levels) mitigates against such a thesis.

Hypertension. Hypertension (blood pressure exceeding 140/90 mm. Hg) occurs in approximately 2/3 of the patients with Cushing's syndrome, 50% of which have diastolic blood pressures greater than 100 mm. Hg. Headaches are a prominent feature in 25% of these patients. Hypertensive retinopathy and/or papilledema are seldom present. Evidence of cardiac decompensation may be present in as high as 30% of these patients and as we will discuss later cardiac failure occupies a prominent position in the list of factors contributing to their natural morbidity and mortality rates. The mechanism of the hypertension is not well understood. Mineralocorticoid levels are usually normal (24) and circulating renin levels are normal except in those few patients with hypertension and hypokalemic alkalosis (25). Elevation of plasma renin substrate has been found which could contribute to excessive angiotensin formation (25) as a potential hypertensive mechanism.

Striae. Violaceous striae are present in about 1/2 of the patients and must be distinguished from the "stretch marks" of simple obesity. The striae associated with hypercortisolism are red to purple, often appear to fluctuate in color from day to day, and are both wider and deeper than those found in obesity. Striae are ordinarily located on the lower and lateral abdomen, but may also occur on the breasts, axillary margins, thighs, calves and shoulders. Stria formation has been attributed to the increased protein catabolic and/or decreased protein anabolic processes (46) shown to occur in experimental animals given glucocorticoids.

Backache. This complaint, present in 1/2 of the patients with Cushing's syndrome, is associated with roentgenographically demonstrable evidence of pathologic fractures and/or demineralization in 80% of these patients. Only an occasional patient reports a reduction in trunk height, however, when the patients with hypercortisolism are systematically measured (6) most reveal a loss of trunk height. And, children with cortisol excess have frequently been shown to have linear skeletal growth retardation (47).

Mental changes. Psychiatric disturbances, varying from emotional lability to frank psychosis, may occur in as high as 1/2 of the patients with hypercortisolism. The most common single complaint is depression which may be profound. Plotz, et al. (2) in their study of the natural history

of Cushing's syndrome reported a 2% incidence of suicide in their mortality rate statistics. A high incidence of cortical atrophy of the cerebral and cerebellar hemispheres revealed by pneumoencephalography has also been reported (17) in patients with hypercortisolism. All 10 of their patients with mental symptoms also had evidence of cortical atrophy, but the severity of symptoms did not correlate well with the degree of cortical atrophy, and a few patients with cortical atrophy did not have psychiatric manifestations. A cause and effect relationship of cortical atrophy to mentation difficulties remains conjectural.

Edema. The presence of ankle and/or facial swelling occurs in about 1/3 of the patients with Cushing's syndrome but has been flagrantly absent from the list of typical manifestations in the past literature. One of our patients in particular presented with the sole complaint of edema unsuccessfully investigated at three previous institutions who was proven to have pituitary-dependent bilateral adrenocortical hyperplasia. Her edema resolved subsequent to successful bilateral adrenalectomy.

Pigmentation. In the more current literature hyperpigmentation occurs on occasion in patients with Cushing's syndrome, but unlike what one would expect, the majority of these patients do not have a demonstrable pituitary adenoma. When hyperpigmentation develops after total adrenalectomy it should arouse suspicion of a pituitary chromophobe adenoma (16). However, in the untreated patient with hypercortisolism the presence of hyperpigmentation is only presumptive evidence of a pituitary tumor. This manifestation may occur in Cushing's disease (with or without a pituitary neoplasm) or more commonly in patients with ectopic ACTH production by a non-endocrine malignancy. Hyperpigmentation is a feature in ectopic ACTH syndrome in as many as 33% of the patients (18,19,20,21), and has been shown to correlate well with immunoreactive β-MSH levels (22). A similar mechanism is a likely explanation for the hyperpigmentation of Cushing's disease and Addision's disease (23) --- both known to be associated with supranormal ACTH secretion. The close relationship of ACTH to β-MSH is not confined to hypercortisolism, but has been reported in situations in which both polypeptide hormones have been measured.

Exophthalmos. Proptosis, sometimes associated with mild chemosis, is reported in the recent literature (6,8) with an approximate frequency of 3%, but has been recognized in the past (2) as frequently as 8%. An occasional patient has a goiter but in general those patients with exophthalmos have not been found to have thyroid enlargement. In the single patient with Cushing's disease with proptosis that we were able to study, thryoid function was normal and suppressed in a normal fashion. Thus, the meager information available tends to incriminate a mechanical process such as localized intraorbital adipose tissue proliferation, a process known to occur in patients with hypercortisolism and alluded to earlier.

ROENTGENOGRAPHIC FEATURES

The radiologic findings and their incidence in patients with Cushing's syndrome are shown in the following Table 6 (Slide 9).

CUSHING'S SYNDROME

Roentgenographic Features

	Incidence (Percentage)			
	Sprague et al (1956)	Ross et al (1966)	Eddy et al (1973)	Mean
Demineralization	40	46	38	41
Pathologic Fractures	20	16	21	19
Renal Calculi	5	16	8	10
Gallstones	?	10	4	7
Sellar Enlargement	6	?	4	5

Demineralization. Radiographically diminished bone density is found in about 40% of the patients. Bachaches occur in about 1/2 of the patients in whom 80% have visible pathologic fractures and/or demineralization. Since approximately 30% bone density change must be present to be detectable by routine x-ray procedures, it is likely that a demineralization process compatible with osteoporosis exists in the majority of patients with hypercortisolism. Certainly, as alluded to earlier, excess glucocorticoids are associated with diminished skeletal mass, backaches and reduction in trunk height in adults (6), and retarded linear growth in children (47).

Renal calculi. The presence of renal stones has been consistently reported in association iwth Cushing's syndrome. The calculi that have been analyzed have been composed of calcium phosphate. Urinary excretion of calcium and phosphate are often elevated in patients with hypercortisolism. Ross, et al. (6) reported a 42% hypercalciuria incidence. Serum calcium and phosphorus levels however are consistently normal (2,6,8), except in the occasional coexistence of hyperparathyroidism (6,26). Hence, the calcium and phosphorus balances are negative in a large number of patients with Cushing's syndrome. The association of a normal calcium concentration and hypercalciuria has been reported with active osteoporosis, the metabolic bone disorder known to occur in hypercortisolism, and the administration of cortisone to normal subjects has been reported to reduce tubular reabsorption of both calcium and phosphate (27).

Parathyroid hyperplasia at autopsy has been reported (36) in 2 of 3 patients with Cushing's syndrome. Recently, it has been shown (35) that exogenous cortisol administration to normal humans increases immunoreactive parathyroid hormone (IR-PTH) levels, and suggest that the decreased bone mass in Cushing's syndrome may be related to cortisol stimulated PTH secretion.

Cholelithiasis has also been found in a significantly higher incidence in patients with Cushing's syndrome (6,8) although most such patients have normal serum cholesterol values. A majority of the patients with gallstones interestingly also have renal calculi (6,8).

Sella turcica. The current literature reveals a 5% incidence of radiologic evidence of sella turcica enlargement at the time of diagnosis despite the fact that bilateral adrenocortical hyperplasia of pituitary origin constitutes the etiology in 3/4 of the cases. The relationship between the adenoma and the hypersecretion of ACTH continues to be controversial --- i.e. is the adenoma (when present) the initiator of the excessive ACTH secretion or is it the result of excessive stimulation by corticotrophin-releasing factor (CRF) of hypothalamic origin. Patients with and without pituitary tumors behave in the same manner with regard to suppressibility of pituitary-adrenal function. Salassa, et al. (28) found a 10% incidence of sellar enlargement (12 patients) either before or after adrenalectomy in 122 patients with pituitary-dependent bilateral adrenocortical hyperplasia. Seven patients (9%) revealed evidence of pituitary tumor prior to, and 2 patients (3%) developed such evidence post-adrenalectomy. It is well recognized that about 10% of the patients develop evidence of pituitary tumors post-adrenalectomy (16,30,32,34), but whether the adrenalectomy has any cause and effect relationship remains conjectural. When the pituitary neoplasm has been examined in these patients, the histology has invariably consisted of chromophobe cells (28) in contrast to the relatively common (3-7%) necropsy finding (29,32,33) of small basophilic neoplasms in patients with Cushing's syndrome. Liddle (30) reported a 13% incidence (6 of 46 patients with Cushing's disease) having sellar enlargement at the time of diagnosis. Thirty-six patients were followed of whom 7 had

total adrenalectomy. Three of the 7 patients subsequently developed pituitary neoplasms (all chromophobe in cell type) and 2 of the 3 patients developed Nelson's syndrome (16). In contrast, none of the remaining 29 patients, all of whom were treated with pituitary irradiation (11 of whom also had total adrenalectomy), developed subsequent sellar enlargement. Their experience suggests that adrenalectomy may provoke pituitary tumor formation or, more likely, enhance the enlargement of a preexisting pituitary tumor which can be prevented by pituitary irradiation. Headaches are manifested in the literature in as many as 40% of the patients with Cushing's syndrome, however, this complaint correlates closely with the presence of hypertension and not with evidence of pituitary disease (2,6,8,9).

ROUTINE LABORATORY FINDINGS

The routine laboratory data and incidence of abnormality in patients with Cushing's syndrome is shown in the following Table 7 (Slide 10 & 11).

CUSHING'S SYNDROME

Routine Laboratory Data

	Incidence (Percentage)			
	Sprague et al (1956)	Ross et al (1966)	Eddy et al (1973)	Mean
Hemoglobin (>18 gm%)	12	2	4	6
RBC count (> 6 million)	12	2	4	6
WBC count (>10,000/mm^3)	?	8	13	10
Lymphocytes (<25%)	81	26	21	43
Eosinophil count (<100/mm^3)	?	74	67	70
Serum electrolytes:				
Sodium (>144 mEq/l)	5	8	13*	9
Potassium (<3.5 mEq/l)	35	4	21*	-20
Bicarbonate (>29 mEq/l)	26	8	25*	20
Fasting glucose (>110 mg%)	57	22	17	32
Abnormal 3-hr OGTT	?	32	29	30

* Malignant lesions only

Hemoglobin, RBC count. The overall hemoglobin and RBC concentrations were elevated in only 6% of the patients. Hence, despite the high incidence of plethora and the inclination towards high packed cell volume, these patients do not commonly become polycythemic by the strict criteria of Fishman (31).

Total and differential WBC count. The total WBC count was elevated in only 10% of the patients, however, lymphopenia occurs more frequently.

Eosinophils. The diagnostic implication of an absolute eosinophil count in patients with Cushing's syndrome was emphasized by Thorn (37) who felt an eosinophil count of less than 50/mm^3 favored the diagnosis. Almost 3/4 of the patients do indeed have eosinophil counts less than 100/mm^3, about 50% of which are less than 50/mm^3 and about 20% of which are less than 10/mm^3. Certainly, an absolute eosinophil count of less than 10/mm^3 strongly favors the diagnosis, however, the information is non-specific (i.e. an eosinophil count of greater than 100/mm^3 does not rule out the diagnosis).

Serum electrolytes. The overall mean serum sodium, potassium and bicarbonate values are abnormal in the minority of the patients with hypercortisolism. In our experience to date only the malignant lesions (especially the ectopic ACTH sydrome) have been associated with hypokalemic alkalosis. This is in striking contrast to the typical textbook description of Cushing's syndrome where hypokalemic alkalosis is represented as a characteristic metabolic event. Hypokalemic alkalosis is rare enough to offer little diagnostic aid, however, its occurence should induce strong suspicion of carcinoma --- either adrenocortical or ectopic in location. The mechanism for the electrolyte disturbance is hence probably related to the magnitude of cortisol (hydrocortisone or compound-F) production. Cortisol, although predominantly a glucocorticoid, has mineralocorticoid activity particularly in higher concentrations. Attempts to measure other known mineralocorticoids (i.e. aldosterone, corticosterone or compound-B, desoxycortisol or compound-S, desoxycorticosterone, etc.) in hypokalemic patients with Cushing's syndrome have revealed no consistent elevation (39,40,41). It is unusual that these ACTH responsive adrenocorticoid compounds (42) are not elevated in those patients with ACTH-dependent hypercortisolism. Whatever the causative agent, the complex of hypertension, hypernatremia and hypokalemic alkalosis is characteristic of mineralocorticoid excess. It has therefore been suggested (43) that an additional adrenal steroid, 18-hydroxy-11-desoxycorticosterone (18-OH DOC), may play an important mineralocorticoid role in man, however, to date this has not been documented.

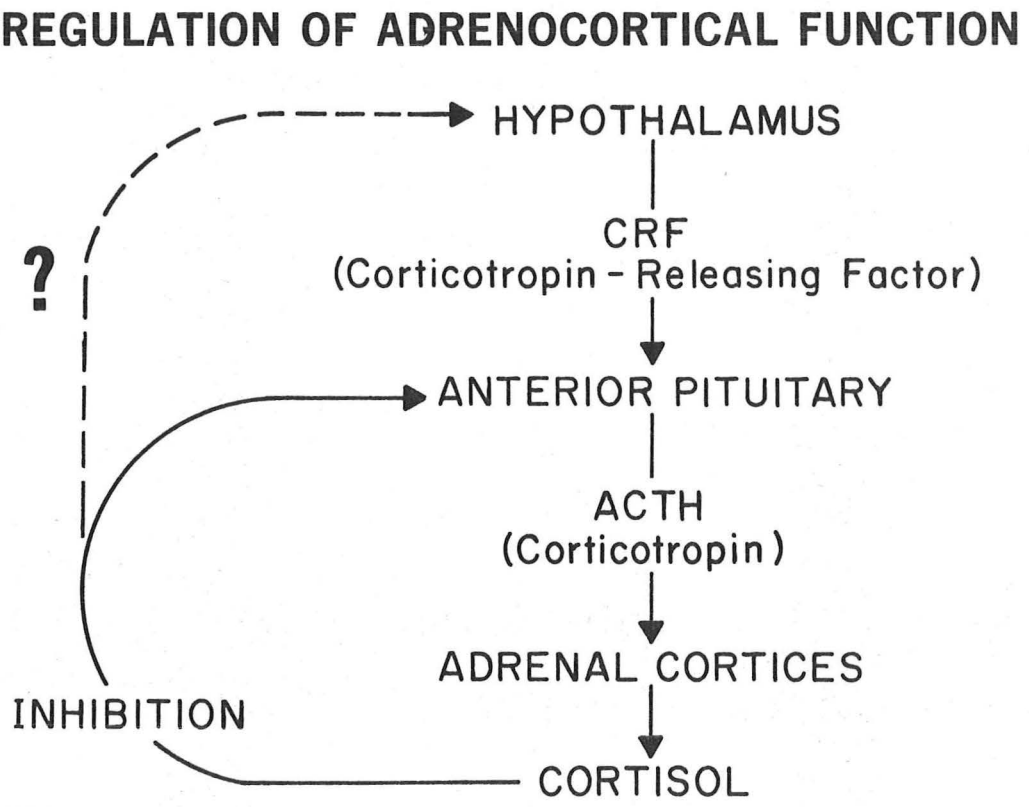
Carbohydrate tolerance. Interestingly, in contrast to the past experience (2,9) where the incidence of carbohydrate intolerance was cited in up to 94% of the patients, only approximately 20% of the patients in the current literature present with an elevated fasting glucose level and only about 30% have abnormal tolerance to glucose challenge. However, the precise incidence of carbohydrate intolerance is difficult to assess since specific

and standardized test procedures and criteria for interpretation of blood glucose concentrations and response to oral glucose challenge has not yet materialized. Many reports in the older literature (2,9,38) state only whether carbohydrate tolerance was impaired or not but fail to discuss the criteria employed. Observations in experimental animals treated with glucocorticoids (48) indicate that the hyperglycemia appears to be a consequence both of increased gluconeogenesis from protein and reduced glucose utilization predominantly by adipose tissue. The myriad effects of glucocorticoids upon body tissues has been recently summarized by Baxter and Forsham (49).

SPECIAL LABORATORY TESTS (Blood Corticoids)

A. Physiology

The normal hypothalamic-hypophyseal-adrenocortical system behaves as a homeostatic unit and is illustrated in the following Figure 2 (Slide 12).



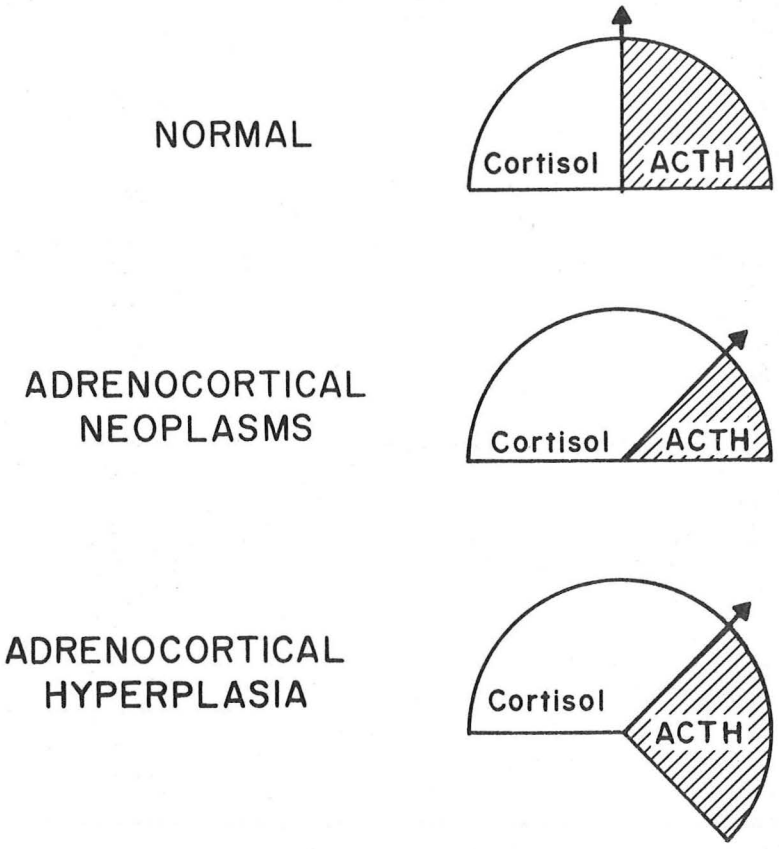
The amount of cortisol secreted is a function of the amount of adrenocorticotrophin (ACTH) reaching the adrenal cortices. And, although other adrenal corticoids are ACTH-responsive, only cortisol in turn regulates "by need" (a negative feedback servo mechanism) the release of ACTH. It is probable that the hypothalamic secretion of corticotropin-releasing factor (CRF) is also similarly controlled, but this will not be a certainty until a specific assay for CRF is developed.

B. Pathophysiology

The following Figure 3 (Slide 13) illustrates the normal cortisol/ACTH relationship versus the pathophysiologic relationship in the two fundamental forms of Cushing's syndrome (i.e. adrenocortical neoplasia and hyperplasia).

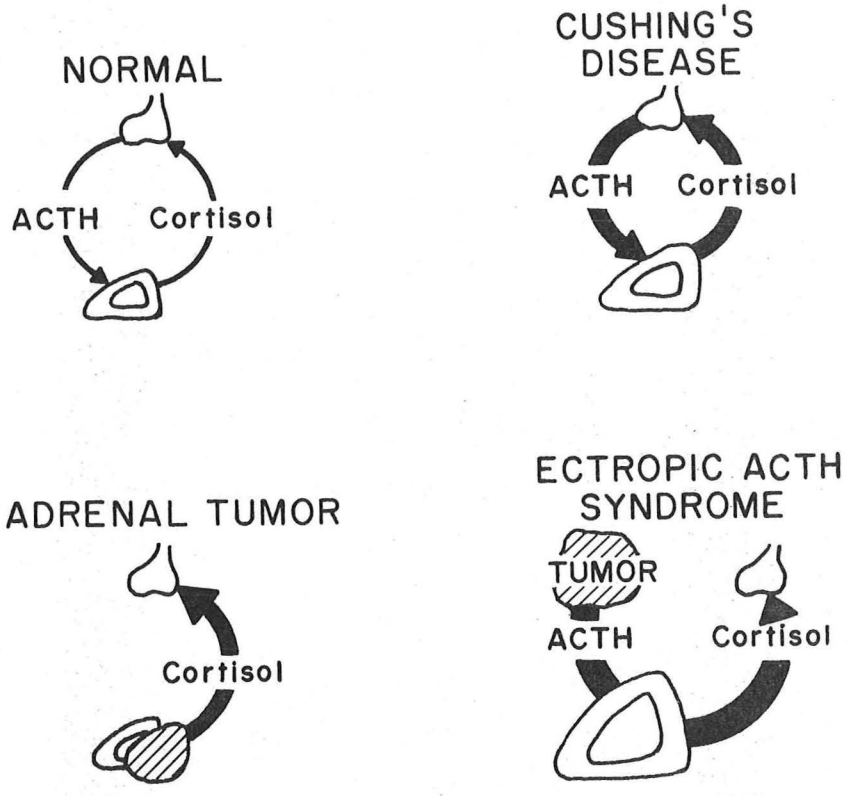
CUSHING'S SYNDROME

CORTISOL-ACTH RELATIONSHIP



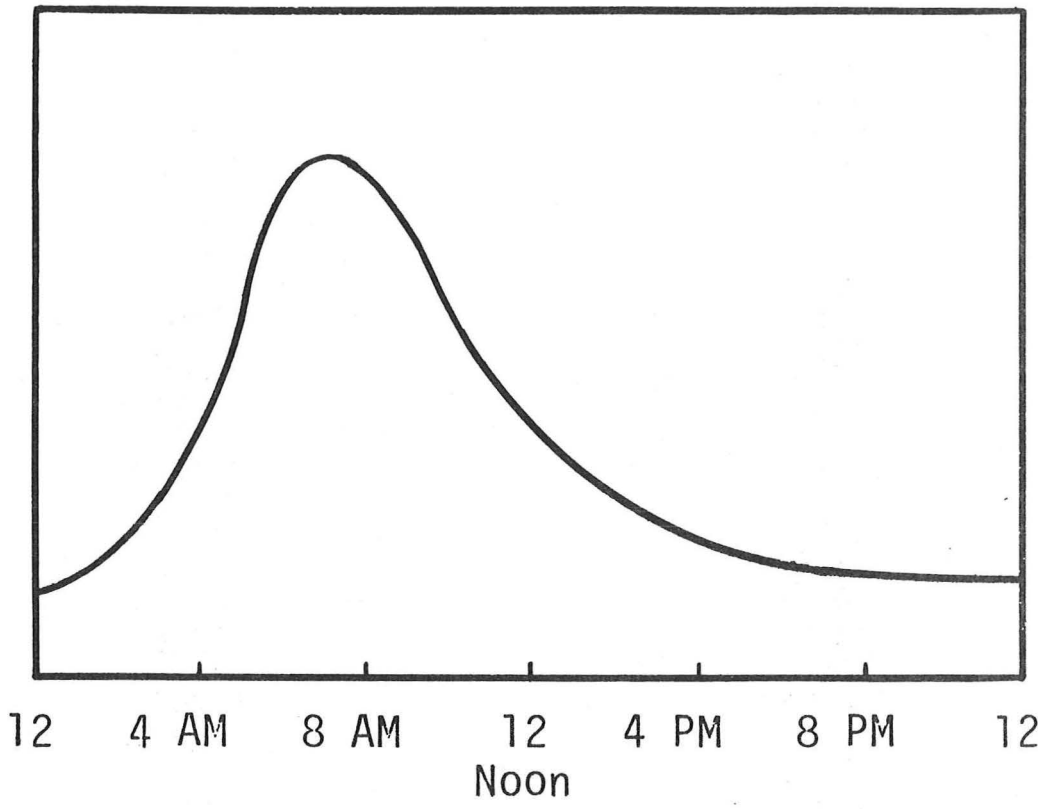
Adrenocortical neoplasia, either benign or malignant, producing Cushing's syndrome represents a primary adrenocortical lesion associated with autonomous production of cortisol (i.e. irregardless of the "need"), and hence suppresses pituitary release of ACTH. In contrast, adrenocortical hyperplasia, whether of pituitary or ectopic ACTH in origin, appears to be merely a normal adrenocortical response to excessive ACTH stimulation (i.e. also irregardless of "need" but appropriate to the magnitude of ACTH production). Hence, the primary defect in the former is inappropriate cortisol production and in the latter is inappropriate ACTH production.

The following Figure 4 (Slide 14) illustrates more explicitly the pathologic cortisol/ACTH relationships in the various forms of hypercortisolism.



C. Circadian Rhythm

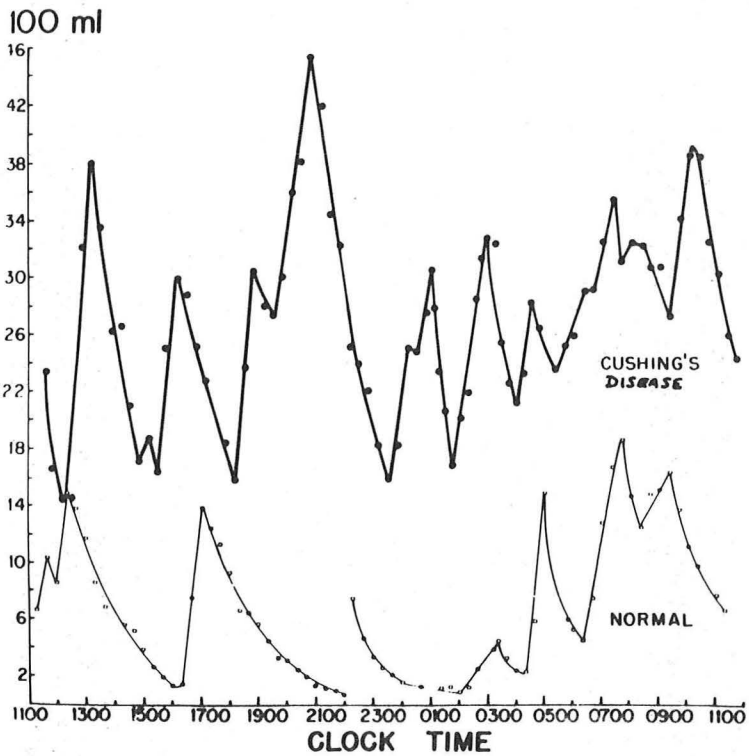
It has been believed for sometime that ACTH/cortisol secretory activity has a circadian rhythm or diurnal variation (50,56). The original concept of this diurnal rhythm is depicted in the following Figure 5 (Slide 15).



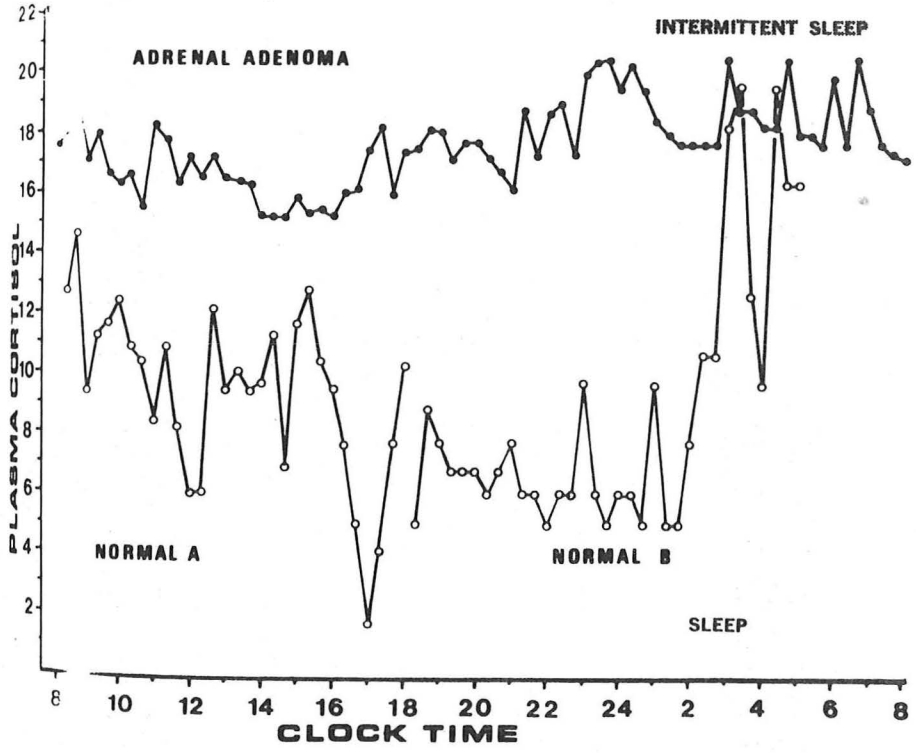
This normal transition from high morning to low evening cortisol levels has been presumed to be a gradual, consistent pattern and formed the basis for the use of 8 AM and 8 PM blood sampling times as a diagnostic test. Patients with Cushing's syndrome indeed tend to lose such a diurnal secretory pattern (51, 52), and the earliest event often is the absence of an evening fall in the blood cortisol concentration (52,53). Unfortunately, some patients with Cushing's syndrome have normal or intermittently high serum corticoid levels (51,54,55); a few such patients may have a reasonably normal appearing diurnal variation (6,53,8); myriad factors may increase blood cortisol concentrations in otherwise

normal people, i.e. obesity (63,8), estrogens (8,57,58,59), emotional and physical stresses (60), nicotine (61), certain drugs (spironolactone); and, finally blood corticoids may be elevated in patients ill with non-endocrine diseases, i.e. infections (62), advanced malignancy (64), congestive heart failure (65), depression (65,66), etc.

Further magnifying the interpretative problems incurred by ad random blood cortisol sampling as a diagnostic aid in patients suspected of hyper-cortisolism is the important report of Hellman, et al. (67). This recent information indicates that cortisol is episodically secreted in varying bursts in normal subjects. Further studies from these investigators utilizing a multiple sampling technique (68) in patients with bilateral adrenocortical hyperplasia, as shown in the following Figure 6 (Slide 16), indicate that such patients also secrete cortisol in spurts but in general at a greater order of magnitude.



Our experience with multiple blood cortisol sampling in such patients is similar, however has revealed considerable overlap between the high values of normal subjects and the low values of patients with Cushing's disease. Hence, the timing of blood cortisol determinations is of paramount importance. Since 15-30 minutes between samples may totally change the titer of cortisol, multiple blood specimens during a single day are necessary in order to obtain a realistic representation of the presence or absence of a circadian rhythm. Tourniaire, et al. (68) have subsequently reported a similar study involving serial plasma cortisol determinations in a patient with hypercortisolism due to an adenoma shown in the following Figure 7 (Slide 17).



The pattern of plasma cortisol values in the patient with the functioning adenoma is typical of patients with solitary adrenocortical neoplasms (benign or malignant) that we have been able to study --- i.e. the magnitude of cortisol production is greater, but (in contrast to the pattern of bilateral hyperplasia shown previously) is devoid of the characteristic large spurts.

The following Table 8 shows our results of plasma cortisol determinations at 8 AM and 8 PM in 24 patients with documented hypercortisolism (8).

Plasma Cortisol (11-OHCS) Base Line and Overnight Suppression with Dexamethasone in 24 Patients with Cushing's Syndrome

Case No.	Adrenal Disease*	11-OHCS (μg/100 ml) Base Line 8 AM	Base Line 8 PM	Dexamethasone† 8 AM
1	BAH	35.0	31.3	8.7
2	BAH	41.9	24.9	11.7
3	BAH	36.6	28.1	6.6
4	BAH	29.7	39.4	19.0
5	Adenoma	42.2	53.0	37.9
6	Adenoma	51.0	38.6	52.5
7	Carcinoma	52.0	59.3	56.0
8	Carcinoma	42.6	50.0	48.2
9	BAH	21.2	15.7	15.5
10	Ectopic	62.2	55.5	70.4
11	Adenoma	54.4	52.9	58.2
12	BAH	29.3	31.4	24.6
13	BAH	40.0	31.6	27.0
14	BAH	34.0	20.5	12.0
15	BAH	31.3	27.2	14.3
16	Ectopic	48.4	41.2	53.5
17	Adenoma	52.2	54.4	50.9
18	Carcinoma	40.0	33.7	44.4
19	BAH	24.4	14.9	10.2
20	Ectopic	80.8	38.9	77.5
21	BAH	39.0	22.5	19.3
22	Carcinoma	92.6	51.9	88.0
23	Adenoma	18.6	16.8	15.7
24	Adenoma	22.0	16.1	16.8
Mean ±SD		42.6 ±17.7	35.4 ±14.3	35.0 ±24.1

* BAH = bilateral adrenal hyperplasia; ectopic = ectopic ACTH-secreting neoplasm.

† Dexamethasone 1 mg given orally at 11 PM the preceding evening.

Four patients (17%) had normal 8 AM and eight patients (33%) had normal 8 PM plasma cortisol concentrations. The majority of the patients with hyperplasia revealed variable 8 AM/8 PM plasma cortisol relationships when repeat blood samples were obtained on consecutive days.

From the same report (8), 15 obese patients without Cushing's syndrome but with "Cushingoid" clinical features were studied by the same protocol. The results are presented in the following Table 9.

Plasma Cortisol (11-OHCS) Base Line and Overnight Suppression with Dexamethasone in 15 Obese Patients with "Cushingoid" Clinical Features

Case No.	11-OHCS (μg/100 ml)		
	Base Line		Dexamethasone*
	8 AM	8 PM	8 AM
25	25.2	14.8	4.5
26	16.7	37.2	7.7
27	31.5	34.3	10.3
28	22.0	15.1	2.1
29	36.3	15.8	1.0
30	29.4	27.1	4.7
31	31.6	17.3	8.5
32	41.8	18.7	10.6
33	35.0	32.0	9.5
34	22.5	37.2	11.2
35	26.0	18.4	6.0
36	19.7	12.7	1.4
37	34.3	20.3	8.6
38	34.6	21.1	3.2
39	38.5	30.0	8.3
Mean	29.7	23.5	6.5
±SD	±7.4	±8.6	±3.5

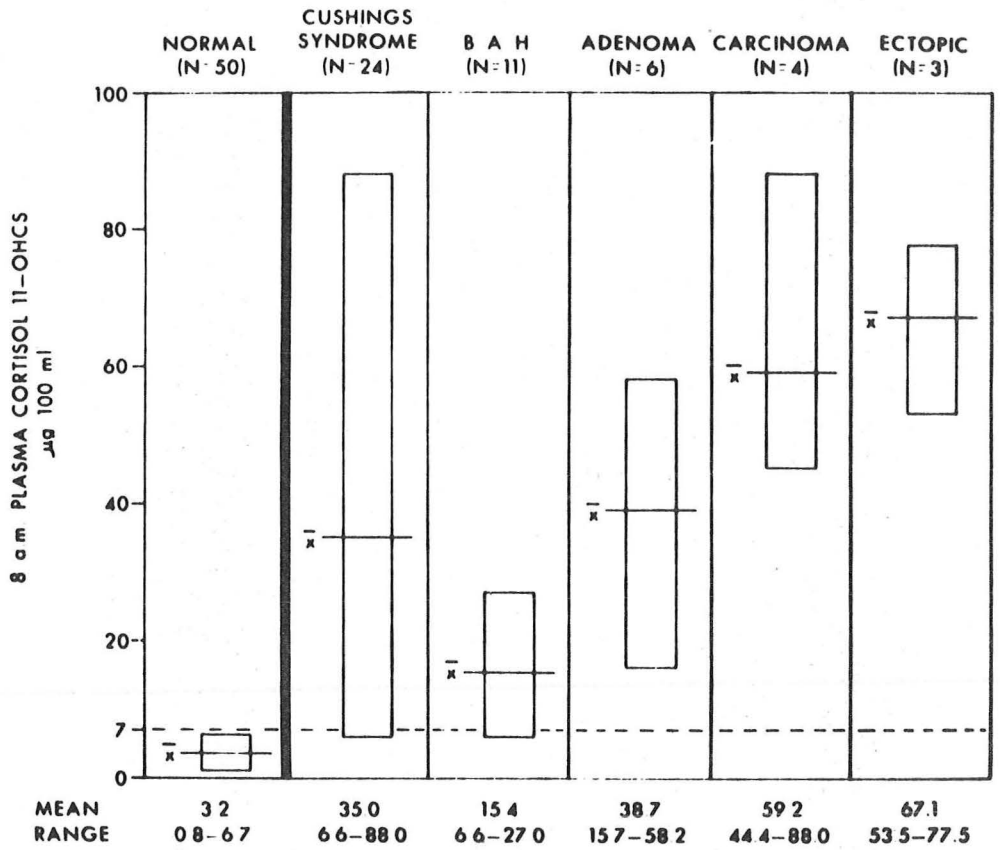
* Dexamethasone 1 mg given orally at 11 PM the preceding evening.

Nine patients (60%) had elevated 8 AM and five patients (33%) had elevated 8 PM plasma cortisol levels. The majority of these obese but otherwise normal people also revealed day to day plasma cortisol fluctuations --- often to the degree of reversal of the previous day's 8 AM/8 PM relationship. The importance of these data is found in the fact that it is from this population of patients with "Cushingoid" features that we as clinicians must decipher the patient with true hypercortisolism.

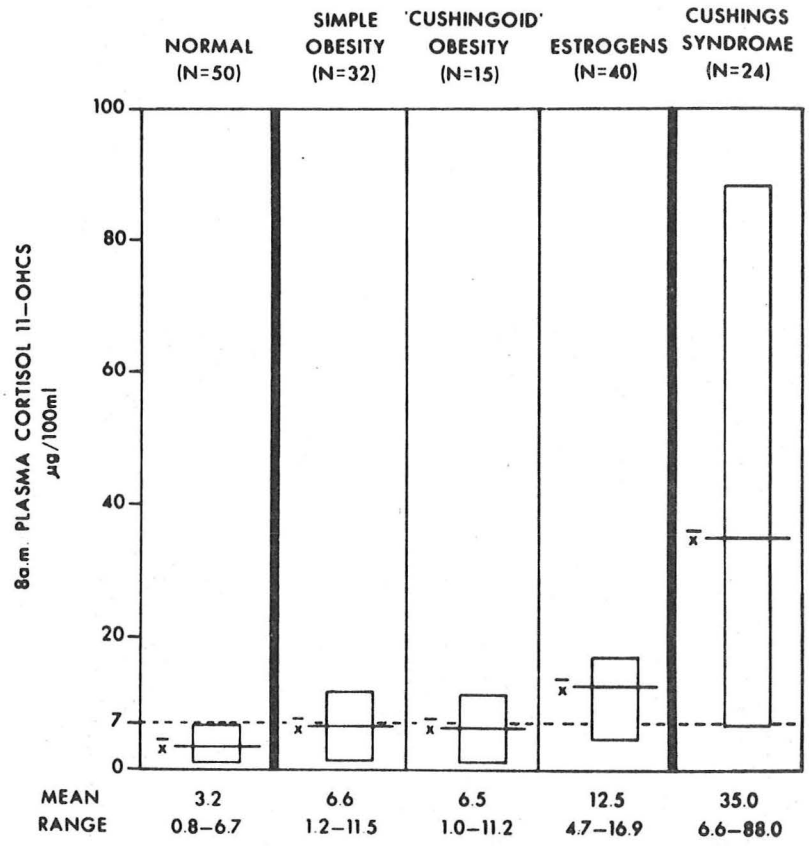
D. Dexamethasone Suppression

Nugent, et al. (70) were the first to propose the use of a single oral dexamethasone suppression test as a rapid screening maneuver for the detection of patients with hypercortisolism. Since then a number of investigators (59, 71, 72) have attempted to standardize the 8 AM plasma corticoid response to overnight dexamethasone suppression utilizing a 1 mg oral dose administered between 11 PM and 12 midnight. However, because of differences in plasma corticoid assay techniques, suppression values have varied in normal subjects between less than 5.0 and less than 11.0 µg/100 ml, and in patients with Cushing's syndrome between less than 13.0 and less than 20.0 µg/100 ml.

The results of the overnight dexamethasone suppression test in our hands (8) as performed in 24 patients with Cushing's syndrome is shown in Table 8. Only one patient had normal suppression as standardized in our laboratory (an 8 AM plasma cortisol of less than 7.0 µg/100 ml). The following Figure 8 (Slide 18) compares the results in graphic form between the patients with Cushing's syndrome and in a control group of 50 normal adults.



The results of the same test procedure in 15 obese patients without Cushing's syndrome but with "Cushingoid" clinical features is shown in Table 9. In eight patients (53%) normal suppression was not achieved. The following Figure 9 (Slide 19) graphically compares these data with those in normal subjects, patients with simple obesity, women taking estrogens, and the patients with Cushing's syndrome.

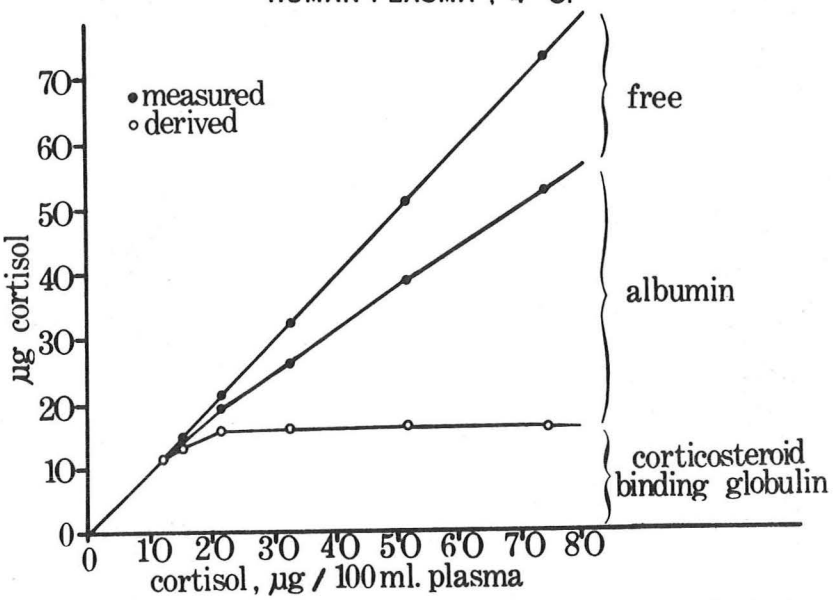


The obese "Cushingoid" patients respond in the same manner to overnight dexamethasone manipulation as do the patients with simple obesity.

Serum or plasma cortisol as it is routinely measured represents total cortisol (i.e. both protein-bound and free fractions). Ninety-five per cent of the total circulating cortisol at normal concentrations is bound to a specific α-globulin (cortisol-binding globulin, CBG or transcortin) (73), the remaining 5% is free (74). The free fraction is the biologically active glucocorticoid secretory product (75,76). As is demonstrated in the following Figure 10

(Slide 20) the free fraction increases disproportionately to the bound component at higher secretory rates (i.e. such as found in patients with Cushing's syndrome).

PHYSICOCHEMICAL STATE OF CORTISOL. NORMAL HUMAN PLASMA, 4°C.



THE PARTITION OF PLASMA CORTISOL BETWEEN UNBOUND, CBG-BOUND AND ALBUMIN-BOUND AT 4°C.

Estrogenic steroids are known to increase CBG or transcortin levels (73, 74) in the same fashion as they do thyroid-binding globulin (TBG). Hence, the total circulating blood cortisol in patients taking estrogen is increased and often fails to suppress normally (Figure 9). Since a large number of women take oral contraceptives, and their plasma protein effects may last as long as 3 months after discontinuance, this further strains the usefulness of the rapid overnight dexamethasone suppression test.

SPECIAL LABORATORY TESTS (Urinary Corticosteroids)

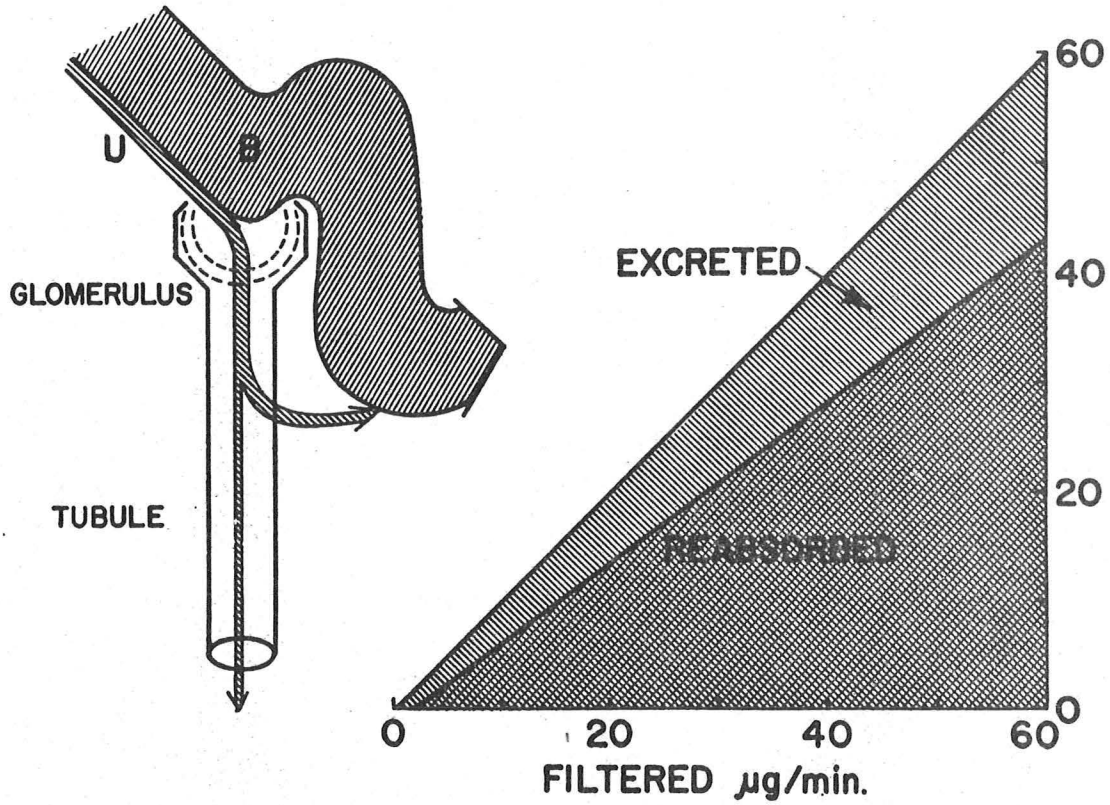
A. Physiology

Traditionally, 17-hydroxycorticosteroid or Porter-Silber chromogens (17-OHCS) and 17-ketogenic or oxogenic steroids (17-KGS) have been the only routine measurements of urinary corticosteroids. Unfortunately, despite the modern availability of more accurate and sensitive assays, many medical centers continue to employ only these colorimetric assays. The following Table 10 compares the specificity of these two assays to detect cortisol with that of assays for "free" cortisol.

CORTICOSTERIOD ASSAY PROCEDURES

Steriod Measured	"Free" Cortisol	Porter-Silber Chromogens (17-OHCS)	17-Ketogenic Steriods (17-KGS)
Cortisol (Compound F)	Yes	Yes	Yes
Corticosterone (Compound B)	Yes	-	-
20-dihydrocortisol	Yes	Yes	Yes
Cortisone (Compound E)	-	Yes	Yes
11- deoxycortisol (Compound S)	-	Yes	Yes
Tetrahydrocortisol	-	Yes	Yes
Tetrahydrocortisone	-	Yes	Yes
Tetrahydro-"S"	-	Yes	Yes
Cortols	-	-	Yes
Cortolones	-	-	Yes
Pregnanetriol	-	-	Yes
17α-hydroxyprogesterone	-	-	Yes
17α-hydroxypregnanolone	-	-	Yes

As is readily discernible, the 17-OHCS assay and in particular the 17-KGS assay measure many non-specific substances other than cortisol, hence their specificity is poor. In contrast, the assays for urinary free cortisol are relatively specific since the amounts of corticosterone and 20-dihydrocortisol are insignificant in man (80). Free cortisol is the only plasma cortisol component appearing in the urine in unaltered form (77). Despite the fact that 90-95% of the filtered free cortisol is reabsorbed (81,77) as depicted in the following Figure 11 (Slide 21), its urinary concentration accurately reflects free cortisol in the blood. With increasing blood concentration a progressively greater proportion of the total circulating cortisol appears in the urine (78,79).



B. Pathophysiology

A number of interpretative problems exist with the use of conventional urinary 17-OHCS or 17-KGS colorimetric assays all in one way or another related to their lack of adequate specificity for cortisol. Both 17-OHCS and 17-KGS levels are known to fluctuate on a day to day basis (6,82,83); they are often spuriously elevated in obese people (58,84,8,85,86); they may be adversely affected by glucosuria (87); and frequently they are poor indices of adrenocortical hyperfunction (6,8,88,58,89). However, the 17-OHCS estimation becomes more accurate and less influenced by obesity when calculated per gram of creatinine excreted (7).

Our experience with urinary assays for 17-OHCS and 17-KGS in 24 patients with Cushing's syndrome (8) is presented in the following Table 11.

Urinary 17-OHCS and 17-KGS Base Line and Suppression with Dexamethasone in 24 Patients with Cushing's Syndrome

Case No.	Sex	Adrenal Disease	Urinary 17-OHCS (mg/24 hr)			Urinary 17-KGS (mg/24 hr)		
			Base Line	Dexamethasone 2 mg/d	Dexamethasone 8 mg/d	Base Line	Dexamethasone 2 mg/d	Dexamethasone 8 mg/d
1	F	BAH	31.4	20.6	9.5	34.0	28.2	11.5
2	F	BAH	35.0	22.9	10.7	38.2	25.0	11.9
3	F	BAH	27.5	19.0	3.2	30.7	24.4	6.5
4	M	BAH	18.3	14.5	8.8	18.8	14.6	5.5
5	M	Adenoma	31.9	32.4	30.5	33.5	32.0	29.8
6	F	Adenoma	41.6	41.0	37.8	37.7	39.1	38.0
7	F	Carcinoma	55.9	57.1	54.2	48.8	46.7	49.5
8	M	Carcinoma	52.6	50.0	55.0	42.0	42.0	43.3
9	F	BAH	5.7	5.5	5.0	10.3	9.0	7.7
10	M	Ectopic	62.0	63.3	61.4	54.5	56.3	51.6
11	M	Adenoma	35.0	34.7	32.9	27.4	26.8	26.6
12	F	BAH	22.2	17.7	6.0	26.5	19.5	8.0
13	M	BAH	26.4	20.8	11.5	28.8	20.1	13.9
14	F	BAH	29.7	19.0	9.9	31.8	20.3	9.2
15	F	BAH	29.2	19.9	7.8	29.5	24.2	12.5
16	M	Ectopic	54.0	55.2	53.4	42.8	43.5	44.0
17	M	Adenoma	27.7	24.4	24.9	19.6	19.2	18.5
18	F	Carcinoma	19.6	20.5	19.1	14.9	16.0	15.3
19	F	BAH	5.1	4.7	4.3	11.1	8.4	7.8
20	M	Ectopic	44.6	42.6	43.0	36.0	36.3	37.5
21	M	BAH	41.1	30.6	18.7	42.2	30.5	17.0
22	F	Carcinoma	71.7	75.0	70.9	60.6	62.1	58.3
23	F	Adenoma	6.0	6.2	5.6	11.5	11.3	10.7
24	F	Adenoma	5.4	4.9	4.8	8.6	8.0	7.7
Mean ±SD			32.5 ±18.2	29.3 ±19.5	24.5 ±21.4	30.8 ±14.1	27.6 ±14.8	22.6 ±16.8

The baseline excretion of 17-OHCS and 17-KGS was normal in four patients (17%). The 17-OHCS and 17-KGS excretion during low (2 mg/day) and high (8 mg/day) dosage dexamethasone administration failed to suppress normally in all 24 patients. Liddle's (38) criteria for normal suppression to low dosage is a 17-OHCS concentration of less than 4.0 mg per 24 hours. Weiss' (90) criteria for normal suppression to low dosage is a 17-KGS level of less than 7.0 mg per 24 hours. These criteria are in close accordance with our own data. The following Figure 12 (Slide 22) illustrates in graphic form the mean ± S.D. baseline and dexamethasone suppression values for 17-OHCS and 17-KGS in these 24 patients with hypercortisolism.

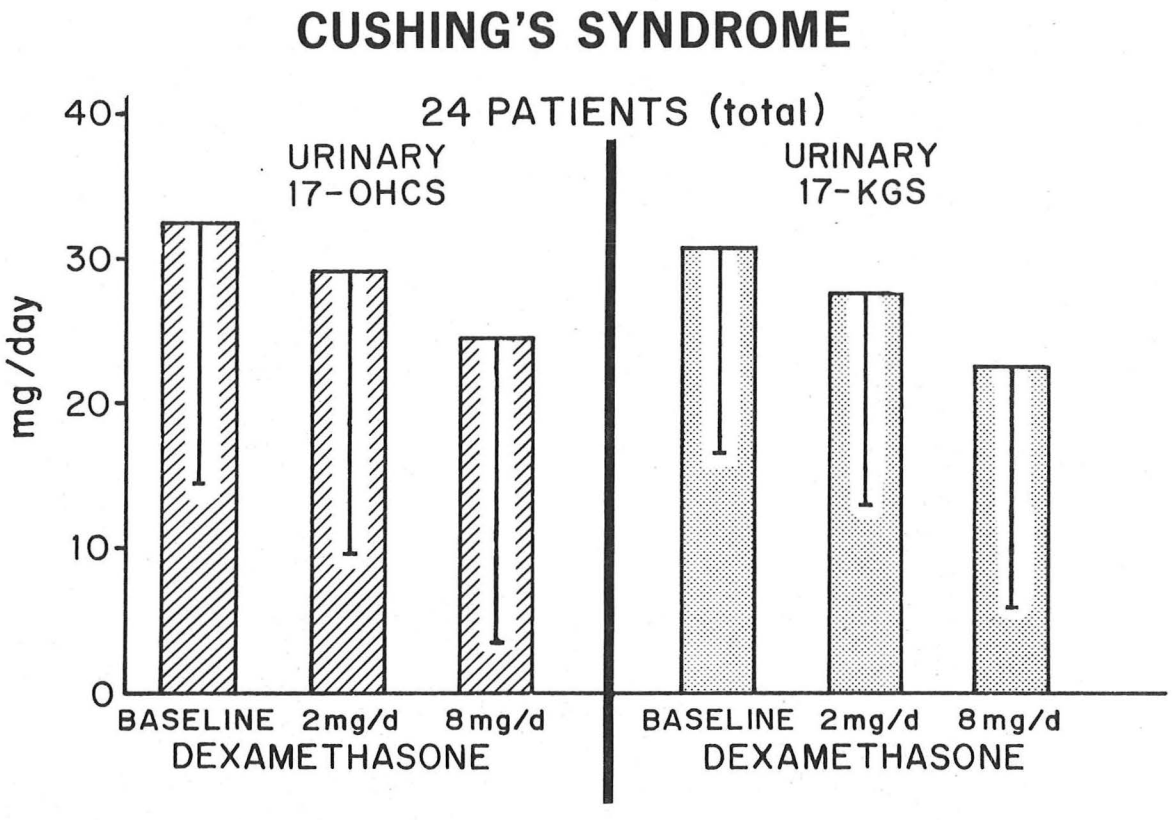
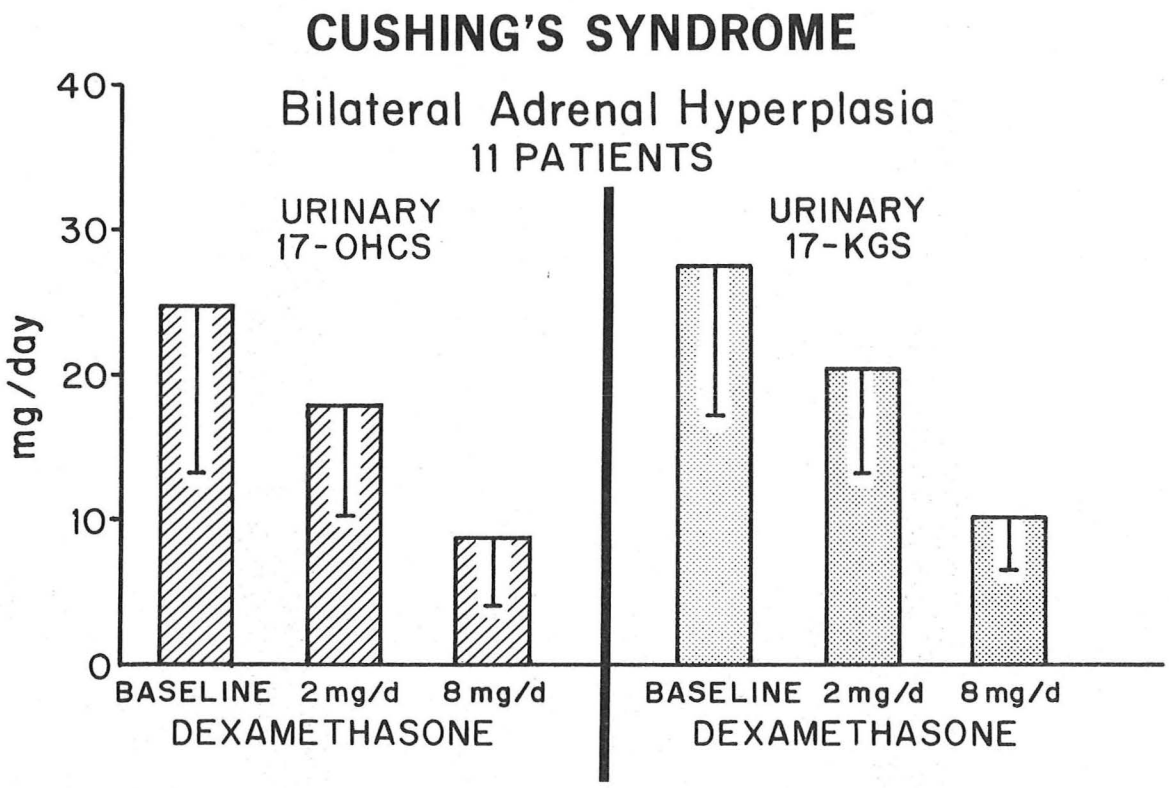


Figure 13 (Slide 23) shows the mean ± S.D. and suppression values for 17-OHCS and 17-KGS in 11 of these patients with bilateral hyperplasia of pituitary origin (Cushing's disease).



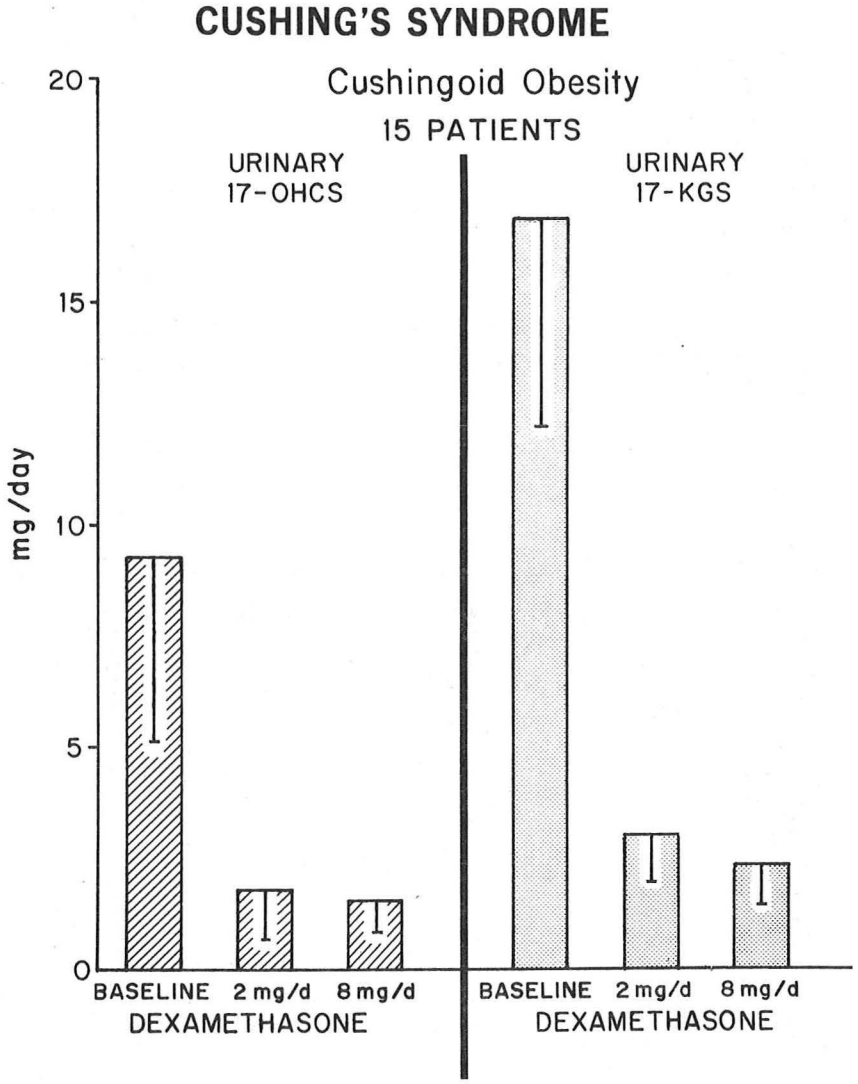
The mean values obtained during high dexamethasone dosage characteristically showed a 65% mean decrease in 17-OHCS and 63% mean decrease in 17-KGS excretion.

From the same report (8), 15 obese patients without Cushing's syndrome but with "Cushingoid" clinical features were studied in an identical manner. The results are presented in the following Table 12.

Urinary 17-OHCS and 17-KGS Base Line and Suppression with Dexamethasone in 15 Obese Female Patients with "Cushingoid" Clinical Features

Case No.	Urinary 17-OHCS (mg/24 hr)			Urinary 17-KGS (mg/24 hr)		
	Base Line	Dexamethasone		Base Line	Dexamethasone	
		2 mg/d	8 mg/d		2 mg/d	8 mg/d
25	9.1	2.0	2.2	15.0	4.0	3.8
26	6.0	1.1	0.8	18.2	2.9	3.0
27	5.4	0.5	0.8	12.1	3.5	3.3
28	16.2	3.2	1.7	23.3	3.8	2.9
29	5.8	1.3	1.5	21.5	2.2	2.5
30	10.0	3.8	2.6	11.5	1.7	0.9
31	13.5	2.4	0.7	13.0	2.4	1.0
32	5.3	1.6	1.0	18.4	4.1	2.2
33	6.0	0.5	0.6	10.8	3.6	1.8
34	15.7	2.1	2.4	20.6	2.6	3.0
35	12.2	0.8	1.0	11.7	1.6	1.2
36	4.9	1.7	0.5	19.0	4.7	2.7
37	4.8	1.0	0.9	16.6	1.7	2.0
38	8.6	2.6	1.2	17.0	2.8	2.3
39	14.6	1.5	0.9	25.3	3.9	3.6
Mean ±SD	9.2 ±4.2	1.7 ±1.0	1.3 ±0.7	16.9 ±4.6	3.0 ±1.0	2.4 ±0.9

The baseline excretion of 17-OHCS was elevated in eight patients (53%), and that of 17-KGS was increased in ten patients (67%). All 15 obese females suppressed normally during dexamethasone administration. The following Figure 14 (Slide 24) graphically illustrates the mean ± S.D. baseline and dexamethasone suppresssion values for 17-OHCS and 17-KGS in these 15 obese patients.

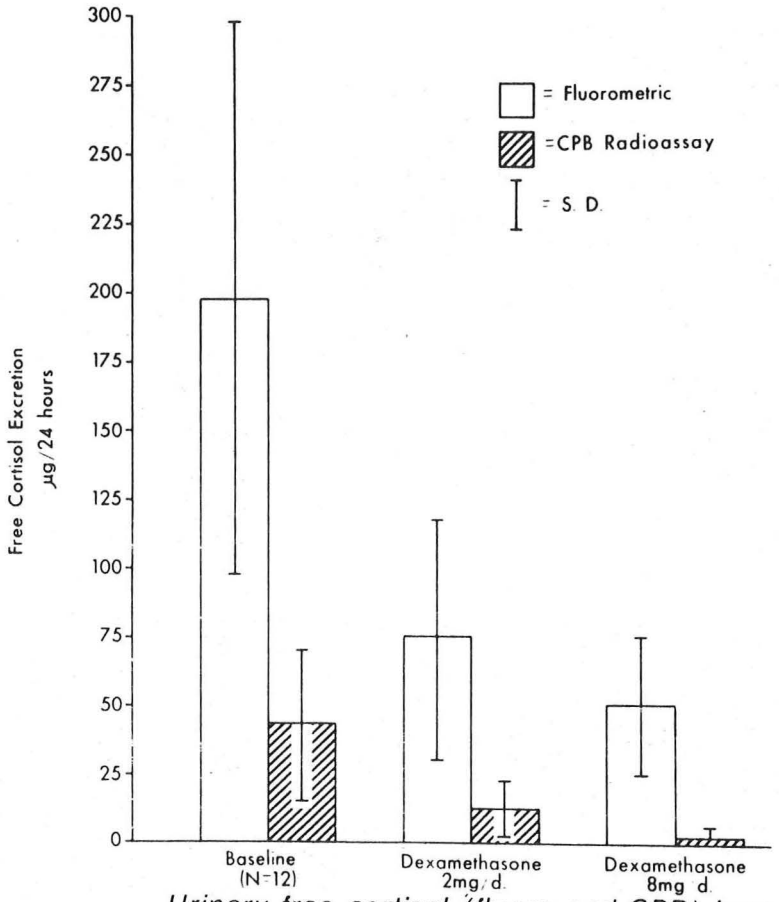


Urinary free cortisol assays by both fluorometric (91) and competitive protein-binding (CPB) radioassay (92,93) methods were also performed on the same urine specimens from these patients (8). The results obtained in the 24 patients with Cushing's syndrome are shown in the following Table 13.

Free Cortisol Excretion Base Line and Suppression with Dexamethasone in 24 Patients with Cushing's Syndrome

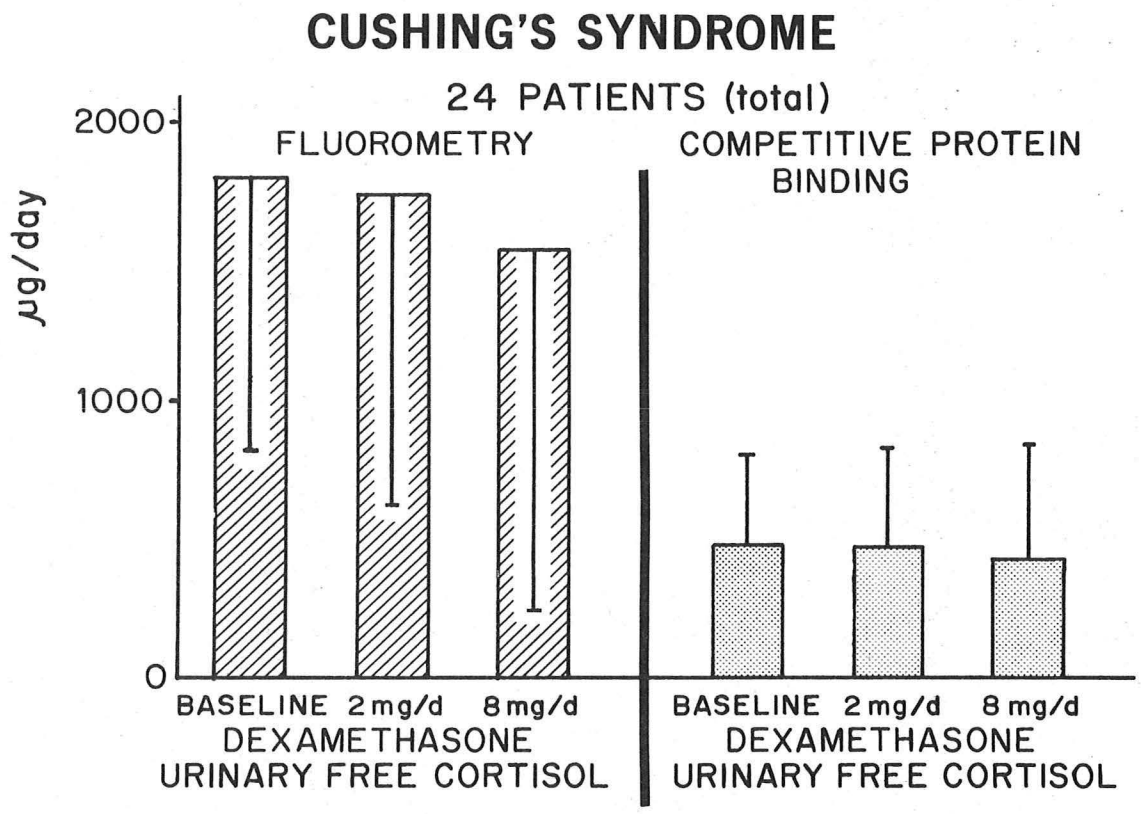
Case No.	Sex	Adrenal Disease	Urinary Free Cortisol (μg/24 hr)					
			Fluoro			CPB		
			Base Line	Dexamethasone		Base Line	Dexamethasone	
				2 mg/d	8 mg/d		2 mg/d	8 mg/d
1	F	BAH	1,359	1,020	611	329	284	155
2	F	BAH	1,512	1,213	623	370	309	168
3	F	BAH	1,216	950	495	319	295	115
4	M	BAH	953	800	534	218	196	127
5	M	Adenoma	1,333	1,361	1,402	313	318	324
6	F	Adenoma	2,224	2,180	1,932	567	562	550
7	F	Carcinoma	2,491	2,845	2,760	629	730	733
8	M	Carcinoma	1,866	1,870	1,854	486	485	477
9	F	BAH	858	717	413	195	166	88
10	M	Ectopic	3,991	4,307	4,584	1,128	1,210	1,300
11	M	Adenoma	1,983	2,016	1,935	515	524	520
12	F	BAH	1,096	882	758	254	206	144
13	M	BAH	1,624	1,431	700	402	339	183
14	F	BAH	1,150	965	513	267	230	117
15	F	BAH	1,327	1,107	588	321	261	135
16	M	Ectopic	4,650	5,009	5,265	1,462	1,613	1,695
17	M	Adenoma	1,400	1,364	1,200	378	359	345
18	F	Carcinoma	1,471	1,523	1,417	363	404	372
19	F	BAH	552	514	443	138	127	92
20	M	Ectopic	3,497	3,655	3,364	1,034	1,140	1,025
21	M	BAH	1,680	1,424	733	400	315	190
22	F	Carcinoma	2,110	2,085	2,238	727	710	746
23	F	Adenoma	1,367	1,241	1,149	349	321	308
24	F	Adenoma	1,344	1,310	1,314	335	330	326
Mean ±SD			1,794 ±988	1,741 ±1,144	1,534 ±1,309	479 ±319	476 ±368	426 ±413

The baseline excretion of free cortisol as assayed by both methods was significantly ($P < 0.001$) elevated, and failed to suppress normally during low and high dosage dexamethasone administration in all 24 patients. The excellent sensitivity of these urinary free cortisol assays is in agreement with other reports (91,92,58,84,94). For comparison purposes, the mean ± S.D. urinary free cortisol values before and during dexamethasone administration in normal subjects (8) is shown in the following Figure 15 (Slide 25).

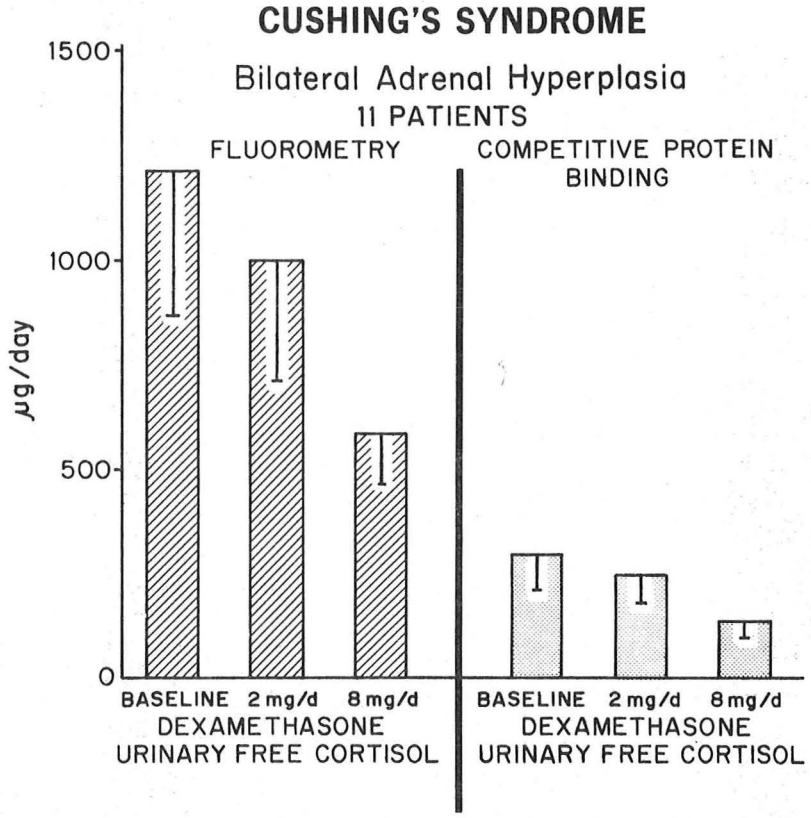


Urinary free cortisol (fluoro and CPB) base line and suppression with dexamethasone in 12 healthy adult volunteers.

In contrast, the following Figure 16 (Slide 26) depicts the mean ± S.D. free cortisol excretion before and during dexamethasone administration in the 24 patients with Cushing's syndrome.



In 11 patients with Cushing's syndrome due to bilateral hyperplasia of pituitary origin (8) the mean ± S.D. concentration of free cortisol in the urine before and during dexamethasone is shown in the following Figure 17 (Slide 27).



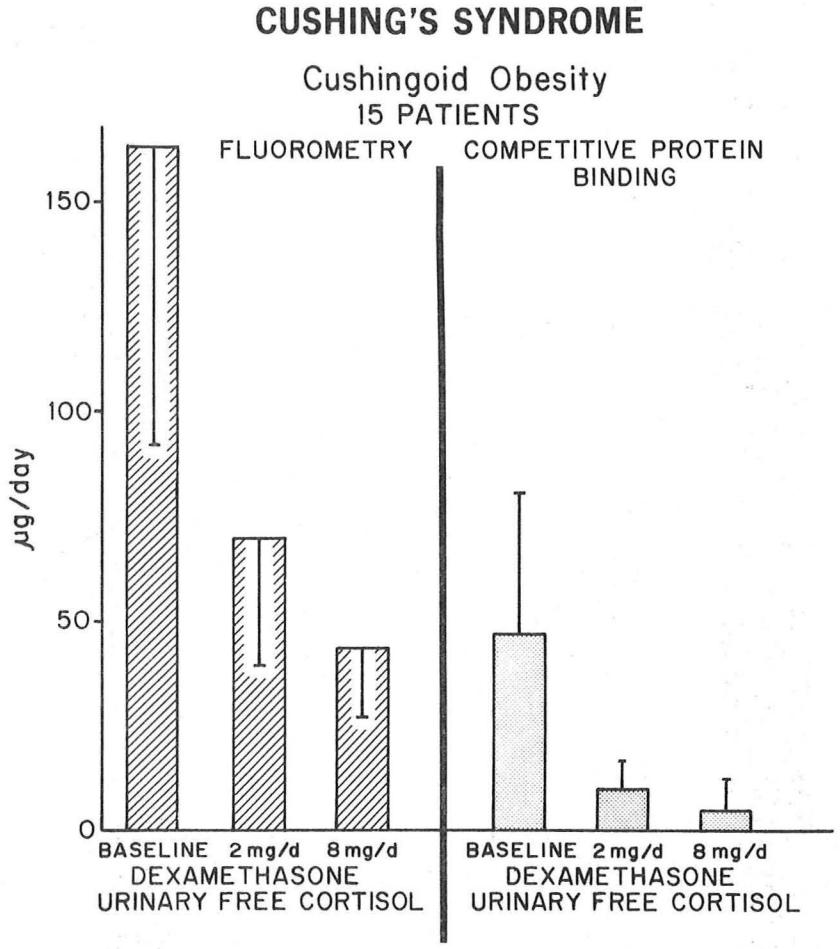
The mean values obtained during high dexamethasone dosage typically revealed a 52 and 53 per cent reduction respectively for the fluorometric and CPB radioassay methods for measuring urinary free cortisol. These data are in accordance with Liddle (38) and Weiss (90) who have demonstrated a greater than 50% reduction in 17-OHCS and 17-KGS respectively in patients with pituitary-dependent hypercortisolism during high dexamethasone dosage.

From the same report (8), 15 obese patients without Cushing's syndrome but with "Cushingoid" clinical features were studied by the same protocol. The results of the urinary free cortisol assays in these patients are shown in the following Table 14.

Free Cortisol Excretion Base Line and Suppression with Dexamethasone in 15 Obese Female Patients with "Cushingoid" Clinical Features

Case No.	Urinary Free Cortisol (μg/24 hr)					
	Fluoro			CPB		
	Base Line	Dexamethasone		Base Line	Dexamethasone	
		2 mg/d	8 mg/d		2 mg/d	8 mg/d
25	170	81.5	51.4	42.2	10.3	<1
26	117	55.3	40.0	27.8	7.7	<1
27	90.5	40.1	32.5	13.5	<1	<1
28	245	111	44.7	93.1	17.5	9.1
29	67.2	34.3	29.1	10.6	<1	<1
30	101	37.0	23.3	17.0	1.3	<1
31	294	128	70.5	102	18.8	6.4
32	214	94.4	45.5	77.5	14.7	5.2
33	105	46.2	34.6	16.4	3.0	<1
34	182	73.7	52.7	50.7	13.5	1.8
35	215	105	62.8	69.6	14.9	3.3
36	84.6	33.4	21.9	12.8	2.2	<1
37	115	45.0	37.2	24.9	5.8	1.5
38	235	87.4	74.0	88.4	19.0	2.7
39	211	79.6	51.6	62.0	11.2	<1
Mean ±SD	163 ±70.4	70.1 ±30.9	44.8 ±15.9	47.2 ±32.6	9.3 ±6.9	2.0 ±2.9

The baseline excretion of free cortisol as well as the free cortisol response to dexamethasone suppression was within normal limits in all 15 patients. The mean ± S.D. urinary free cortisol values before and during dexamethasone administration are illustrated in the following Figure 18 (Slide 28).



The close similarity between the mean free cortisol excretory pattern of these "Cushingoid" obese patients (Figure 18) and the mean excretory pattern of normal subjects (Figure 15) is emphasized by the fact that the measurement of free cortisol in the urine readily separated these patients with "Cushingoid" features from those patients with true Cushing's syndrome. Thus, from a screening point of view, the determination of urinary free cortisol excretion is clearly superior to the conventional urinary 17-OHCS and 17-KGS assays. And, because of the frequency of obesity and interfering estrogenic medications encountered in the fundamentally female patient population to be surveyed for adrenal hypersecretion, free cortisol excretion in the urine functions as a more accurate screening procedure than the blood cortisol overnight dexamethasone suppression test.

All of the urinary corticosteroid assays in response to dexamethasone (6,8,38,90) are equally effective in defining the underlying adrenocortical pathology in the patients with Cushing's syndrome, but only to the point of predicting those patients with pituitary-dependent hyperplasia (Cushing's disease).

Additonal tests, ACTH and metopirone (metyrapone), have at times been utilized in an effort to better define the underlying pituitary-adrenal pathology in patients with Cushing's syndrome. Based upon the concept that ACTH (exogenous stimulation) and metopirone (a form of endogenous ACTH stimulation) stimulate the pituitary-adrenocortical axis at different levels, it has been reported that a normal or exaggerated corticosteroid response to ACTH stimulation is found in patients with pituitary-dependent hyperplasia but only occurs in 50% or less of patients with an adrenal adenoma (30,95,96). However, Weiss, et al. (90) reported that all seven of their patients with hypercortisolism due to an adenoma responded to ACTH stimulation. This variability has led most investigators to conclude, as we have, that the ACTH stimulation test in patients with Cushing's syndrome is too unreliable to be of much diagnostic help (88,6,10). The usefulness of the metopirone test (98) has also been studied in patients with hypercortisolism. It has been reported that patients with Cushing's syndrome due to autonomous tumors (either adenoma or carcinoma) do not show a corticoid response to metopirone (30,38,82), however, Martin, et al. (97) have reported three such patients who did respond to metopirone. And, finally, although most patients with bilateral hyperplasia of pituitary origin do respond to ACTH and metopirone administration, a few such patients have failed to respond (6,82). Hence, in view of the superior reliability of dexamethasone suppression testing and the advent of newer diagnostic techniques (i.e. selective adrenal vein catheterization), the usefulness of the metopirone test in patients with Cushing's syndrome is tenuous.

SPECIAL DIAGNOSTIC PROCEDURES

A number of radiologic approaches have been devised to demonstrate adrenal gland configuration. The following Table 15 (Slide 29) lists these techniques and their varying degree of effectiveness.

CUSHING'S SYNDROME

Radiologic Adrenal Abnormalities

	Incidence (percentage)		
	Plotz et al (1952)	Roberts and Lattimer (1961)	Eddy et al (1973)
IV Pyelogram	-	9	13
Retroperitoneal air insufflation	35	(?) 86	-
selective adrenal angiography*	0	0	88
Selective adrenal angiography and cortisol assay	0	0	100

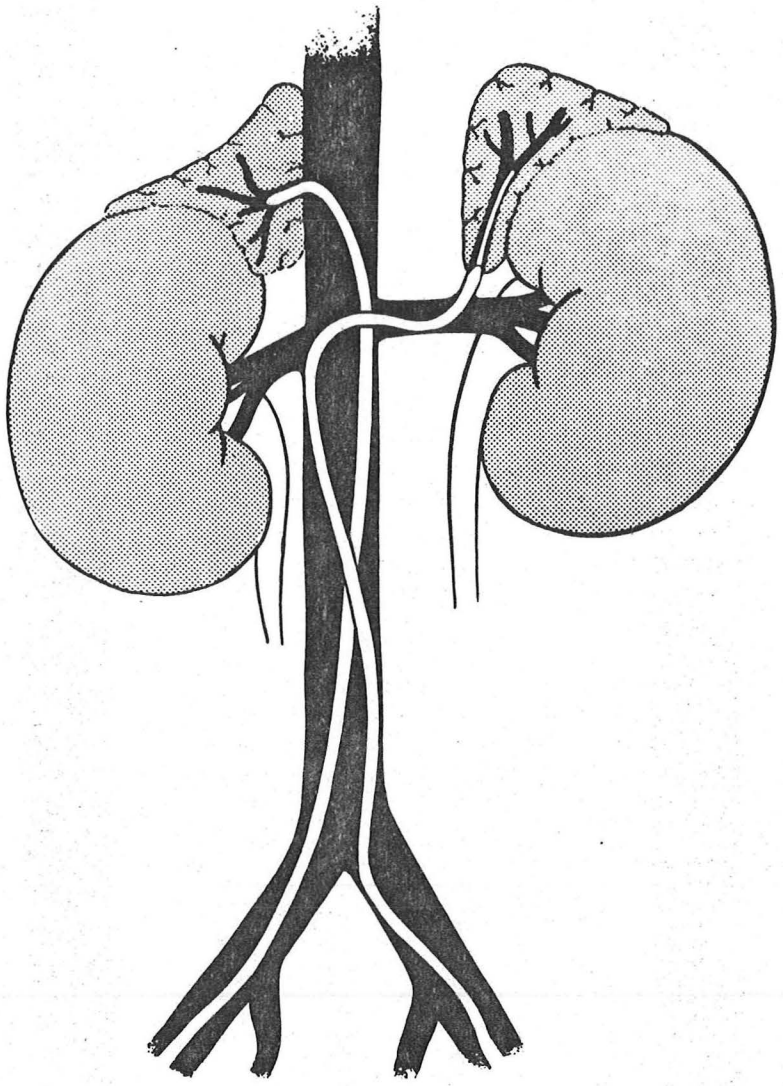
*Performed 3-5 p.m.

Our experience as well as others abdicates intravenous pyelography or excretory urography to little usefulness in the diagnostic armamentarium. Only 3 of our 24 patients (13%) had a correctly predicted adrenal lesion by intravenous pyelography and all three of these patients had relatively large adrenocortical neoplasms. In no instance was bilateral hyperplasia detected despite the fact that three patients with ectopic ACTH syndrome had considerable adrenocortical enlargement, and seven additional patients with adrenal tumors were missed by this technique.

Retroperitoneal or presacral air insufflation is an invasive technique reported with widely variable success (20-80%) which is seldom employed anymore. In contrast, percutaneous selective adrenal vein catheterization, although also invasive, has received a great deal of attention since its technique was originally reported (99). In our hands adrenal venography has been diagnostic in 21 of the 24 patients (88%). If venous effluent was selectively withdrawn

through the indwelling catheter prior to venography and assayed for its cortisol content, then the diagnostic accuracy improved to 100%. The effectiveness of such a combined venographic and assay procedure has been reported by others (100,101,102). The adrenal venous concentration of cortisol fluctuates according to the intrinsic diurnal ACTH/cortisol rhythm, and tends to be rapidly responsive to patient maneuvers as one would expect. Hence, as was recently reportedly (103) wide variations in adrenal effluent cortisol concentrations may be found in patients without adrenal disease. We attempted to minimize these extraneous factors by having the patients quietly immobilized for 45-60 minutes after the catheters were in place and to perform the procedure only in the late afternoon in order to avoid the predominantly morning physiologic cortisol secretory activity.

A diagramatic representation of the adrenal vein catheterization technique is shown in the following Figure 19 (Slide 30).



A venogram (Slide 31) showing a typical adrenocortical tumor, in this case a left suprarenal adenoma, is shown to demonstrate the effectiveness of this procedure.

In our experience adrenal effluent cortisol concentrations obtained by indwelling venous catheters under the standardized conditions mentioned earlier are as shown in the following Table 16 (Slide 32).

CUSHING'S SYNDROME

Selective Adrenal Vein Catheterization*

Serum Cortisol (µg/100 ml)

	Right	Left
Normal	20-50	20-50
Cushing's disease	50-100	50-100
Adrenal tumors	Unilateral	75-300
Ectopic ACTH syndrome	200-500	200-500

* Performed between 3-5 p.m.

Another recent diagnostic development is an adrenal scintiscan procedure utilizing 19-iodocholesterol labeled with radioactive iodine (104,105,106). However, although this technique holds diagnostic promise, it is to date available only on an investigative basis in certain medical centers. We have had only limited experience with this new procedure. Its future diagnostic usefulness remains to be proven.

SUMMARY

We have dwelled at considerable depth on the need for a high clinical index of suspicion; the most sensitive laboratory screening approach; the most accurate assay methods for measuring cortisol production; and, newer techniques for defining the underlying adrenal pathology. The final Table 17 (Slide 33) illustrates the seriousness of Cushing's syndrome and the all important need for early diagnosis.

CUSHING'S SYNDROME

Natural Mortality Rate Factors

	Incidence Percentage Plotz et al Review 1932-1952
Infections	47
Cardiac failure	27
Adrenal carcinoma	15
Cerebrovascular Accident	7
Renal failure	5
Tumor of thymus	5
Pulmonary infarcation	4
Carcinoma of Pancreas	4
GI Hemorrhage	2
Suicide	2

Total Untreated Mortaility Rate (5 yrs): 50%

These data of Plotz, et al. (2) concerning the natural pathogenetic outcome of untreated patients with Cushing's syndrome collected between 1932 and 1952 reflect an impressive 50% mean 5 year survival rate. Almost one half of the mortality was contributed by infectious processess. These data are undoubtedly biased towards infection since the information was accumulated predominantly during the pre-antibiotic era, however, does emphasize the infamously poor wound healing and inability to localize infections in these patients (3,5,9,30). Cardiovascular demise constituted the next most common cause of death (about 1/4 of the patients).

The back portion of this protocol contains five illustrative case reports for your perusal and a list of pertinent references.

FIVE CASE STUDIES (EXAMPLES)

1. A 23 year old white female had oligomenorrhea and rounded facial configuration of 2 months' duration. She manifested no other abnormal physical features. The blood pressure was 128/86 mm of Hg. Routine x-rays (including skull series) were negative. Pertinent laboratory data included: Hgb 13.2 gm%, RBC 4.4 million, WBC 8,600 with 27% lymphocytes, absolute eosinophils 107, electrolytes: sodium 138 mEq/l and potassium 4.1 mEq/l, fasting blood glucose 103 mg%. Serum cortisol (8 AM) 36.6 µg%, 8 PM 28.1 µg% and 8 AM 6.6 µg% following dexamethasone 1.0 mg po at 11 PM. 24-hour urinary corticosteroid data were as follows:

		Dexamethasone	
	Baseline	2 mg/d	8 mg/d
17-KS (mg/d)	13.3	-	-
17-OHCS "	27.5	19.0	3.2
17-KGS "	30.7	24.4	6.5
Free Cortisol (µg/d) (by Fluoro)	1,216.0	950.0	495.0
Free Cortisol " (by CPB)	319.0	295.0	115.0

Selective adrenal vein catheterization was suspicious of bilateral adrenal enlargement. The left and right adrenal venous effluent cortisol concentrations were 70 and 79 µg% respectively.

Pathologic diagnosis: bilateral adrenocortical hyperplasia without tumefaction.

2. A 39 year old white female had insidious onset over 11 months of facial and ankle swelling with associated acneiform eruption, fatigue, backache and muscular weakness. She presented with characteristic "Cushingoid" physical stigmata (e.g. "moon" facies, hirsutism, acne, centripedal obesity, prominent supraclavicular and posterior cervical fat pads, violaceous striae, bruises). The blood pressure was 178/110 mm of Hg. Routine x-rays revealed a negative skull series but generalized bone demineralization. Pertinent laboratory data were: Hgb 16.4 gm%, RBC 5.4 million, WBC 10,300 with 20% lymphocytes, absolute eosinophils 45, electrolytes: sodium 140 mEq/l and potassium 3.9 mEq/l. Fasting blood glucose 118 mg% and 2-hour pc blood glucose 163 mg%. Serum cortisol (8 AM) 34 µg%, 8 PM 20.5 µg% and 8 AM 12 µg% following dexamethasone 1.0 mg po at 11 PM. 24-hour urinary corticosteroid data were as follows:

	Baseline	Dexamethasone 2 mg/d	Dexamethasone 8 mg/d
17-KS (mg/d)	18.6	-	-
17-OHCS "	29.7	19.0	9.9
17-KGS "	31.8	20.3	9.2
Free Cortisol (µg/d) (by Fluoro)	1,150.0	965.0	513.0
Free Cortisol " (by CPB)	267.0	230.0	117.0

Selective adrenal vein catheterization revealed definite bilateral adrenal enlargement. The left and right adrenal venous effluent cortisol concentrations were 82 and 77 µg% respectively.

Pathologic diagnosis: bilateral adrenocortical hyperplasia without tumefaction but with a few microadenomata.

3. A 47 year old white female had polydipsia, polyuria, muscular weakness and personality disturbances of 5 months' duration. She presented with plethora, a tendency towards truncal obesity, and a single stria in the suprapubic region. The blood pressure was 152/94 mm of Hg. Routine x-rays (including skull series) were negative. Pertinent laboratory data were: Hgb 14.9 gm%, RBC 4.9 million, WBC 9,800 with 22% lymphocytes, absolute eosinophils 55, electrolytes: sodium 142 mEq/l and potassium 3.7 mEq/l, fasting blood glucose 132 mg%. A 3-hour oral GTT was abnormal. Serum cortisol (8 AM) 51 µg%, 8 PM 38.6 µg% and 8 AM 52.5 µg% following dexamethasone 1.0 mg po at 11 PM. 24-hour urinary corticosteroid data were as follows:

		Dexamethasone	
	Baseline	2 mg/d	8 mg/d
17-KS (mg/d)	16.4	-	-
17-OHCS "	41.6	41.0	37.8
17-KGS "	37.7	39.1	38.0
Free Cortisol (µg/d) (by Fluoro)	2,224.0	2,180.0	1,932.0
Free Cortisol " (by CPB)	567.0	562.0	550.0

Selective adrenal vein catheterization revealed a vascular and encapsulated 3 x 4 cm left adrenal mass. The left and right adrenal venous effluent cortisol concentrations were 192 and 13 µg% respectively.

Pathologic diagnosis: solitary left adrenocortical adenoma.

4. A 56 year old white male had weight loss of 21 pounds, bruising and plethora of approximately 6 months' duration. He presented with evidence of weight loss, extremity wasting, muscular weakness, and plethoric complexion with facial/chest telangiectasia. The blood pressure was 182/104 mm of Hg. Routine x-rays (including skull series) were normal except for demineralization of the spine and ribs. Pertinent laboratory data were: Hgb 18.3 gm%, RBC 6.1 million, WBC 11,200 with 17% lymphcytes, absolute eosinophils 25, electrolytes: sodium 146 mEq/l and potassium 3.3 mEq/l, fasting blood glucose 126 mg%. A 3-hour oral GTT was abnormal. Serum cortisol (8 AM) 42.6 µg%, 8 PM 50 µg% and 8 AM 48.2 µg% following dexamethasone 1.0 mg po at 11 PM. 24-hour urinary corticosteroid data were as follows:

		Dexamethasone	
	Baseline	2 mg/d	8 mg/d
17-KS (mg/d)	278.0	-	-
17-OHCS "	52.6	50.0	55.0
17-KGS "	42.0	42.0	43.3
Free Cortisol (µg/d) (by Fluoro)	1,866.0	1,870.0	1,854.0
Free Cortisol " (by CPB)	486.0	485.0	477.0

Selective adrenal vein catheterization revealed a large, highly vascularized 8 x 12 cm right adrenal mass. The left and right adrenal venous effluent cortisol concentrations were 9 and 258 µg% respectively.

Pathologic diagnosis: solitary right adrenocorticol grade I adenocarcinoma.

5. A 53 year old white male had weight loss of 36 pounds, weakness, anorexia and dyspnea of approximately 4 months' duration. He presented with evidence of chronic illness, weight loss and predominantly quadriceps femoris muscular weakness but was totally devoid of "Cushingoid" manifestations. The blood pressure was 154/86 mm of Hg. Routine x-rays revealed a left hilar lung mass and pleural effusion. Pertinent laboratory data were: Hgb 14.5 gm%, RBC 4.4 million, WBC 9,800 with 16% lymphocytes, absolute eosinophils 40, electrolytes: sodium 148 mEq/l and potassium 2.9 mEq/l, fasting blood glucose 111 mg%. Serum cortisol (8 AM) 62.2 µg%, 8 PM 55.5 µg% and 8 AM 70.4 µg% following dexamethasone 1.0 mg po at 11 PM. 24-hour urinary corticosteroid data were as follows:

		Dexamethasone	
	Baseline	2 mg/d	8 mg/d
17-KS (mg/d)	21.9	-	-
17-OHCS "	62.0	63.3	61.4
17-KGS "	54.5	56.3	51.6
Free Cortisol (µg/d) (by Fluoro)	3,991.0	4,307.0	4,584.0
Free Cortisol " (by CPB)	1,128.0	1,210.0	1,300.0

Selective adrenal vein catheterization revealed striking bilateral adrenal enlargement. The left and right adrenal venous effluent cortisol concentrations were 386 and 291 µg% respectively.

Pathologic diagnosis: grade III bronchogenic (oat-cell type) carcinoma.

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