Endocrine

MEDICINE GRAND ROUNDS
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DANIEL W. FOSTER, M.D.

CUSHING SYNDROMES

Case Report

MSK is a 30 year old white woman referred from another city for treatment of Cushing syndrome. She states that prior to this illness she had always been healthy. She was not obese as a child and at the time of her marriage in 1973 (age 19) she weighed 102 pounds. In 1977 she began to gain weight rather precipitously. In 1979 she developed high blood pressure. In 1980 because of continued weight gain that appeared to be uncontrollable (about 260 pounds) she had a gastric stapling procedure done in Odessa, Texas. The operation was successful in producing weight loss (137 pounds) but she had continual nausea and vomiting subsequently and in 1983 was told she had abnormal liver function studies (details unknown). The gastric plication was reversed at Texas Tech Medical School (Lubbock) in 1983 with relief of symptoms but regain of weight to 200 pounds.

Despite cessation of nausea she continued to deteriorate and noted profound weakness and loss of energy. Abnormal menstrual periods had been noted with severe dysmenorrhea. (At the time of her surgery in Lubbock she had been told that she had uterine fibroids.) She had also noted increased facial hair. For these reasons she consulted a gynecologist, Dr. P. M. Ranka, in Carlsbad, New Mexico. He suspected that she might have Cushing syndrome and referred her to Dr. Mark Howard, an internist, in that city. He collected a 24 hour urine sample and found values of 21.3 mg for 17 hydroxysteroids and 21.4 mg for 17 ketosteroids, both distinctly elevated. He then did an overnight dexamethasone suppression test with the plasma cortisol the next morning being 6.5 µg/dl. He considered these values highly suggestive of Cushing syndrome and referred the patient to the University of New Mexico for further evaluation and treatment. She was admitted to the Clinical Research Center where the following results were found by Dr. David Schade and the endocrine fellow, Dr. Richard Fedderson:

Date	Dexamethasone	Serum cortisol (AM/PM)	Urine (24 h)		
		(µg/dl)	17 OH (mg)	17 keto (mg)	free cortisol (µg)
4-30-84	0	4/4	5	8	27
5- 1-84	0	11/13	11	15	83
5- 2-84	2	28/36	30	18	1940
5- 3-84	2	38/38	41	22	1824
5- 4-84	8	29/25	15	15	155
5- 5-84	8	11/10	10	-	-

Normal values for the New Mexico lab are: serum cortisol 5-30 µg/dl; 17 OH, 2-8 mg/24 h; 17 keto, 5-15 mg/24 h; free cortisol, 35-120 µg/24 h. A plasma ACTH drawn on 5-3-84 was 98 pg/ml at a time when it should have been completely suppressed. CT scan of the abdomen demonstrated normal adrenal size bilaterally. Contrast studies could not be done because of a history of anaphylactic reaction (rash, bronchospasm, hypotension) during an intravenous pyelogram. The diagnosis of cyclical Cushing syndrome was entertained.

She was discharged to Dr. Howard's care for further study to document cyclicity of her disease. A monumental series of urine collections was then undertaken, all but one of which was judged adequate by measurement of creatinine. The following results were obtained:

Date	17 OH (mg)	free cortisol (μg)
6- 6-84	6	58
6- 7-84	8	78
6- 8-84	28	698
6- 9-84	43	1624
6-10-84	28	419
6-11-84	-------- discarded	---------
6-12-84	3*	20
6-13-84	ND	6
6-14-85	ND	23
6-15-84	10	115
6-16-84	16	337
6-17-84	22	497
6-18-84	14	195
6-19-84	6	50
6-20-84	ND	15

* not detectable

Between February and July menstrual periods began to occur every 2 weeks. Facial and arm hair definitely increased, requiring use of a depilatory. Plasma glucose was never elevated. No back pain was present. She gave the interesting history that she had a cousin 7 feet tall, but no endocrine studies are available.

The patient decided that she wanted treatment in Dallas for personal reasons. On July 31, 1984 I saw her with the following additional history obtained. She was not depressed although she occasionally took Ativan for "sleep." She does not use alcohol, but smokes 2 packs of cigarettes daily. For 3-4 months daily headaches had been noted. There was no diplopia or other visual defects. She had dyspnea on exertion and edema of the legs had been noted for 6-7 months.

On physical examination she was 5'4" tall and weighed 202 pounds. Blood pressure (on 50 mg Lopressor BID) was 120/75. Pulse, respiration and temperature were normal. She had the classic appearance of Cushing syndrome with a round face covered by fine, dark hair. A buffalo hump was noted and there were deep purple striae running vertically over the abdomen. Axillary striae were not present. Supraclavicular fat pads were markedly enlarged. She had dark hair on the arms but pubic hair showed a femine distribution and there was no clitoral enlargement. She did not have acne. There was 2+ edema in the legs to the knee. Muscle weakness was not marked.

CT scan of the pituitary again failed to show an adenoma. Because contrast could not be used we obtained nuclear magnetic resonance imaging of the pituitary and adrenals; both scans were normal.

The patient was admitted to Parkland Memorial Hospital for transsphenoidal hypophysectomy, having chosen this approach after a

thorough discussion of therapeutic options. However, the night before surgery she changed her mind, becoming frightened about "having brain surgery." In consequence, she was started on pituitary radiation combined with o,p'-DDD (mitotane) therapy. She has completed radiation and will be re-evaluated by sequential sampling of 24-hour urinary free cortisol in the coming week.

I. Classification and pathogenesis

The Cushing syndromes represent a constellation of diseases in which there is inappropriate production of adrenocortical steroids to the point of producing signs and symptoms. Four general types are recognized:

(1) Pituitary Cushing syndrome 60-70% 80% adenomas.
(2) Adrenal Cushing syndrome 15%
(3) Ectopic Cushing syndrome 15%
(4) Iatrogenic Cushing syndrome

Pituitary Cushing syndrome has traditionally been called "Cushing's disease," but this term is really not useful and should be abandoned. The molecular pathology underlying these disorders is not known, but the hormonal pathophysiology is reasonably clear. This is outlined schematically in Fig 1.

Figure 1 (ref 1)

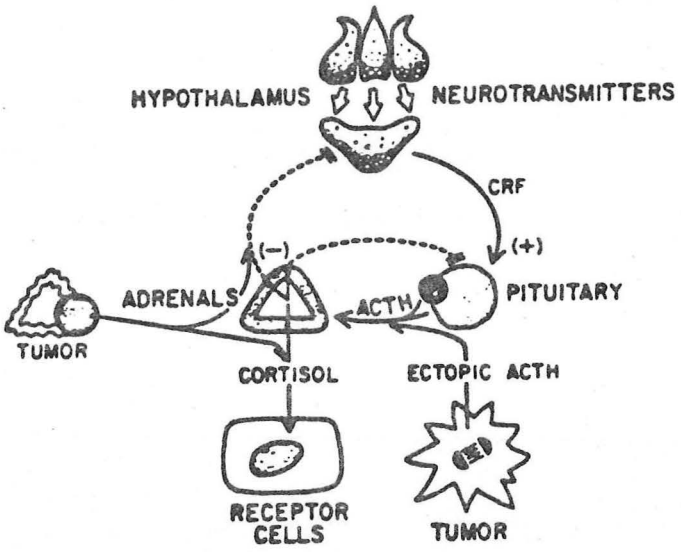

Figure Pathogenesis of the Cushing syndromes. Pituitary adrenocorticotropin (*ACTH*) is normally stimulated (+) by a corticotropin-releasing factor (*CRF*) and suppressed (−) by cortisol action on the hypothalamus and the pituitary. Hypercortisolism may be due to [1] excess pituitary ACTH, usually from a pituitary tumor, [2] ectopic ACTH from a nonpituitary tumor, and [3] excess cortisol produced by an adrenal tumor.

1. Pituitary Cushing syndrome

In pituitary Cushing syndrome there is excessive production of ACTH which results in bilateral adrenal hyperplasia. A significant proportion of cases is associated with microadenomas of the pituitary but in many cases (20-40%) no tumor is apparent (1,2). While ACTH secretion occurs in the face of plasma cortisol concentrations that would ordinarily completely block its release, the pituitary should not be considered autonomous since pharmacologic manipulations designed to alter ACTH secretion in normals can also be shown to work in patients with the syndrome, albeit at higher concentrations (e.g., dexamethasone suppression). Stated simply, the set points regulating the stimulation-inhibition controls are altered but production and release of ACTH are not fixed. It is still not resolved whether the primary defect in pituitary Cushing syndrome resides in that gland or in the hypothalamus (3). It has been reported that patients with this form of the disease have abnormalities usually associated with hypothalamic dysfunction such as altered slow wave sleep and impaired prolactin regulation (4). Moreover, ACTH release can be suppressed by bromocriptine (5) and cyproheptadine (6) which function as dopamine agonist and serotonin inhibitor, respectively. Cases in which combined trophic hormone deficit and prolactin excess accompany bilateral adrenal hyperplasia have also been considered suggestive evidence of hypothalamic involvement (7). Recurrence of overt Cushing syndrome after successful removal of a pituitary microadenoma has been used as an argument for a hypothalamic drive to ACTH production (8). Additional evidence for hypothalamic dysfunction comes from study of patients treated for presumed pituitary Cushing syndrome after adrenalectomy or removal of a pituitary microadenoma. None had Nelson's syndrome. All patients showed an impairment in early (30 minute) ACTH suppression after intravenous cortisol. This defect was reversed by cyproheptadine therapy (9). Attractive as the theory is, it must be considered unproved since increased production of corticotropin-releasing factor (CRF) has never been shown by direct measurement. Increased responsiveness of ACTH release to CRF has been reported (10), suggesting hypersensitivity of the pituitary to the releasing hormone, but this finding is clearly not universal with some patients demonstrating a blunted response (11,12).

A number of attempts have been made to subdivide pituitary Cushing syndrome into subgroups on the basis of response to diagnostic tests. For example, 9 of 23 patients were said to show a paradoxical rise in plasma cortisol after administration of TRH and/or LHRH, a response utilized by the authors to separate them out (13). The argument seems unpersuasive to me. However, it may be that microadenomas originating from the anterior and intermediate lobe of the pituitary behave differently (14). Intermediate lobe tumors, identified by the demonstration of argyrophilic nerve fibers on histologic examination, appeared to be associated with greater resistance to dexamethasone suppression, greater prevalence of hyperprolactinemia, suppression of ACTH and cortisol by bromocriptine and poor response to transsphenoidal hypophysectomy.

2. Adrenal Cushing syndrome

Adrenal Cushing syndrome may be due to a solitary benign adenoma, bilateral macromodular hyperplasia or carcinoma. The hallmark of the primary adrenal form of the disease is suppression of pituitary ACTH release by the autonomous overproduction of cortisol. It is probable that solitary adenomas develop via the same mutations that cause any endocrine tumor to develop. The etiology of bilateral macronodular hyperplasia is less clear. Some investigators believe it actually is a variant of pituitary Cushing syndrome in which the adrenals, rather than becoming diffusely enlarged, develop nodules which eventually become autonomous, suppressing both ACTH and internodular tissue (15,16). Support for this sequence comes from the observation that plasma ACTH levels may be high, normal or suppressed in subjects shown to have macronodular disease by pathological examination of the adrenal glands. Should this interpretation be correct, nodular hyperplasia should be classified as pituitary Cushing syndrome rather than adrenal Cushing syndrome as has been traditional. Micronodular hyperplasia may be an intermediate step in the sequence: diffuse hyperplasia → micronodular hyperplasia → macronodular hyperplasia. It clearly belongs in the pituitary category. The clinical picture, apart from CT scans showing nodules, is not distinguishable in individual patients (16).

Carcinoma of the adrenal is rare (17). It may occur in any age group. About two-thirds of the patients are women. Metastases occur both locally and distally; liver and lung are the most common distal metastatic sites. In addition to the usual clinical features of Cushing syndrome, abdominal pain and a palpable mass are common.

3. Ectopic Cushing syndrome

In ectopic Cushing syndrome bilateral adrenal hyperplasia occurs consequent to production of ACTH by a nonadrenal, nonpituitary tumor (18). The most common cause is oat cell carcinoma of the lung, but essentially any malignancy can dedifferentiate sufficiently to allow ACTH production. Examples include medullary carcinoma of the thyroid, pheochromocytoma, carcinoma of the cervix, carcinoma of the larynx, carcinoma of the ovary, carcinoma of the pancreatic islet, thymoma and carcinoma of the prostate (18-22). Most tumors associated with the ectopic ACTH syndrome also produce CRF (18). The latter conceivably could cause the clinical syndrome by stimulating ACTH release from a normal pituitary (23), but this has never been proven. It is known that some of these tumors in culture produce ACTH and its large precursor, proopiomelanocorticotropin, suggesting that ACTH overproduction *in vivo* is direct and not consequent to CRF.

Although excessive production of ACTH is the usual cause of ectopic Cushing syndrome, this is not always so. For example, one ovarian carcinoma appeared to produce excessive amounts of cortisol rather than ACTH (24).

4. Iatrogenic Cushing syndrome

Excessive ingestion or absorption of steroids used therapeutically may lead to a Cushingoid appearance or frank Cushing syndrome (25-27). It has been suggested that the distinguishing feature of patients with a clinically important response to exogenous steroids

is relative resistance of the hypothalamic-pituitary axis to suppression; i.e., those patients developing a Cushingoid appearance on prednisone would have higher (less suppressed) rates of endogenous hormone production (28).

5. Etiologic distribution

In adults almost all series show two-thirds of cases to have a pituitary origin (1). Of these 60-80% have demonstrable adenomas by CT scan. Ectopic and adrenal causes are generally approximately equal (each about 15% of the total) but in one series of 46 patients only 2 had the ectopic syndrome (29). In the latter, 31 had pituitary Cushing syndrome and 13 the adrenal form. Generally about half of adrenal tumors are adenomas and half carcinomas. Pituitary disease is much more likely to occur in women while most ectopic syndromes are in men (1). In contrast to adults the adrenal syndrome predominates in children; if the onset is before age 15 about two-thirds have adrenal carcinoma (30).

Familial Cushing syndrome is rare in the absence of multiple endocrine neoplasia but does occur with nodular dysplasia (31).

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II. Clinical features

A summary of the clinical features of Cushing syndrome and their frequency is shown in Table 1.

Table 1

Frequency of Clinical Features in Cushing Syndrome

Feature	ref 29 (n=31)	ref 32 (n=450)	ref 33 (n=601)
		%	
Obesity	79	86	88
Moon face	-*	88	75
Weakness	90	67	61
Hypertension	77	-	85
Hirsutism	64	73	65
Menstrual disorders	69	77	60
Bruisability	77	59	42
Purple striae	51	60	-
Edema	48	57	-
Back pain	39	54	40
Psychiatric disorder	48	34	42
Acne	35	54	45
Plethora	84	77	-
Sexual impotence	55	-	-
Buffalo hump	-	54	-
Pathologic fractures	-	38	-
Leg ulcers	-	35	-
Renal stones	-	20	-
Exophthalmos	-	14	-

* frequency of feature not recorded

The classic findings of obesity, plethora, hypertension, hirsutism, weakness and menstrual disorders were present in high and remarkably similar percentages. Nonetheless, considerable variation in clinical presentation may be seen not only between syndromes but in patients with the same etiology. Striae are much more likely to be found in the young while muscle weakness and edema are more common in older patients (29). The classic clinical picture of Cushing's syndrome is rare in the ectopic form being seen in only 7 of 30 patients, and in none of the subjects with bronchogenic carcinoma in one large series (18).

Hypokalemia was present in most patients with ectopic disease at some time during the course but skin pigmentation (23%), edema (30%), muscular weakness (17%), mental symptoms (30%) and hypertension (38%) were much less common than in nonectopic disease. Occasionally patients with Cushing syndrome may present with a single abnormality such as osteopenia (34) or psychiatric disorder (35). The reasons are unknown. Certain differences also exist between spontaneous Cushing syndromes and iatrogenic disease (36). This probably is due to synthetic preparations commonly used therapeutically but it is conceivable that exogenously administered hydrocortisone might also fail to produce the full picture of Cushing syndrome. The usual manifestations of iatrogenic steroid excess are obesity, muscle weakness and mental disorders (1,36). Table 2 compares features of natural and iatrogenic Cushing syndromes.

Table 2 (ref 36)

Natural versus Iatrogenic Cushing Syndromes

1. More common in natural Cushing syndrome
   - hypertension
   - acne
   - menstrual disturbance or impotence
   - hirsutism or virilism
   - striae
   - purpura
   - plethora

2. Virtually unique to iatrogenic Cushing syndrome
   - benign intracranial hypertension
   - glaucoma
   - posterior subcapsular cataract
   - pancreatitis
   - aseptic necrosis of bone
   - panniculitis

3. Nearly equal frequency in both syndromes
   - obesity
   - psychiatric symptoms
   - edema
   - poor wound healing

1. Obesity

The cause of obesity and the central distribution of fat is unknown. Since all acquired obesity tends to be central (in contrast to obesity beginning in childhood which is generalized and involves both trunk and extremities) it is possible that the major cause is simply a cortisol-induced drive to overeat. However, fat cells in the abdomen and those in the thighs are metabolically different and it is also possible that this influences the fat distribution; i.e., fat cell response to cortisol might be different in abdomen and lower extremities (37,38).

2. Hypertension and edema

Hypertension and edema are usually due to hypersecretion of deoxycorticosterone (39,40) which also suppresses plasma renin and lowers serum potassium. Occasionally plasma renin is elevated because glucocorticoids increase concentrations of renin substrate (39). If renin is low it can be assumed that mineralocorticoids are being secreted in sufficient excess to overcome the effect on renin substrate. Aldosterone secretion may be low, normal or high (40,41) as shown in Table 3 ("basal" and "before treatment" simply refers to 2 separate measurements during hospitalization). Hypertension cannot be solely

Table 3 (ref 40)

Table Basal Excretion of Deoxycorticosterone, Aldosterone and Cortisol Before Treatment

		Deoxycorticosterone* (pmol/24 hr)		Aldosterone† (nmol/24 hr)		Urine Free Cortisol‡ (nmol/24 hr)	
Final Diagnosis	Case	Basal	Before Treatment	Basal	Before Treatment	Basal	Before Treatment
Adrenal carcinoma	1	1,485	1,363	33	50	11,669	18,886
	2	1,218	1,375	435	407	268	386
	3	1,875	—	<3	—	1,546	1,595
	4	951	1,472	14	14	19,095	17,242
		1,548		11		18,500	
Adrenal adenoma	5	1,433	318	3	—	424	759
	6	176	—	19	—	308	95
	7	782	679	53	78	397	500
Adrenal hyperplasia	8	251	312	67	53	436	>360
	9	351	—	—	—	688	440
	10	142	136	19	19	>596	>786
	11	1,957	1,248	75	94	1,280	1,580
		2,308		91		1,582	
	12	212	370	6	6	>672	>630
	13	245	255	11	—	454	493
	14	176	—	28	—	588	>442
	15	542	221	36	39	>1,300	>1,000

*Normal range 42-242 pmol/24 hr.
†Normal range 14-55 nmol/24 hr.
‡Normal <270 nmol/24 hr.

due to mineralocorticoid excess since it is seen even in patients with high renin levels and normal values for deoxycorticosterone and aldosterone. Moreover, synthetic glucocorticoids without salt retaining activity can induce hypertension. An intriguing hypothesis is that glucocorticoids enhance vascular responsivity and induce peripheral vascular resistance by inhibiting prostacyclin production (42).

3. Hirsutism, menstrual abnormalities, acne

Hirsutism, menstrual abnormalities and acne in women are due to increased production of adrenal androgens (1,43). The modestly elevated levels of plasma testosterone are suppressed by dexamethasone and stimulated by ACTH in patients with Cushing's syndrome to a much greater extent than in normal women (Table 4). Testosterone levels in

men are low, probably accounting for the loss of libido, impotence and oligospermia that is frequently seen (1,43). The major cause is thought to be a direct effect of cortisol on the testis, but LH and FSH responses to gonadotropin releasing factor (LHRH) are also impaired (44).

Table 4 (data from ref 43)

Plasma Testosterone in Cushing Syndrome

Subjects	Plasma testosterone (ng/dl)			
	basal	Dexamethasone*		
		2 mg	8 mg	16 mg
Women				
Cushing (n=8)	43	37	24	11
Control (n=5)	28	30	30	23
Men				
Cushing (n=4)	320	253	290	117
Control (n=7)	513	522	457	-

*Dexamethasone given for 2 days at indicated dose.

4. Bone disease

Bone disease appears to be most common in children and women over the age of 50. This is probably due to the fact that the initial bone mass is lower in these subsets of patients. Trabecular bone is more sensitive to hormones than cortical bone. This accounts for the fact that pathologic fractures tend to occur in ribs and vertebrae (45). Corticosteroids have two distinct effects on bone. They decrease bone synthesis and increase bone breakdown (45). Diminished synthesis appears to be accomplished by two mechanisms. First, there is a block in conversion of osteoblastic precursors to functioning osteoblasts. Second, there is a direct suppression of the synthesis of bone collagen (46). It is thought that increased osteoclastic activity actually represents a secondary hyperparathyroidism (45,47). Serum parathyroid hormone levels are elevated after glucocorticoid treatment in normal subjects and have also been found elevated in Cushing syndrome (48). The secondary hyperparathyroidism is likely the consequence of diminished intestinal calcium absorption induced by cortisol excess (49). The decreased calcium absorption is probably direct and not the consequence of alterations in vitamin D or its metabolites, although 25-hydroxyvitamin D may be helpful (together with calcium) in preventing the complication (48-50).

5. Skin

The pathogenesis of striae is not well understood. One hypothesis is that adrenal corticosteroids diminish fibroblastic activity such that there is decreased production and poor quality of elastic fibers allowing the skin to thin in broad bands (29). The

violaceous color of the striae results from increased visibility of blood vessels through the thinned skin, together with increased blood flow consequence to edema and plasma volume expansion. It should be noted that purple striae can also be seen in obese subjects who do not have Cushing syndrome (51). Hyperpigmentation does not result from cortisol but is more likely due to ACTH with a variable contribution from β-lipotropin. The idea that β-melanocyte stimulating hormone (β-MSH) was responsible for pigmentation has fallen into disrepute. β-MSH does not circulate freely in plasma; that previously measured was derived artifactually from lipotropin (LPH) during extraction from plasma. LPH is produced from the ACTH/LPH precursor (proopiomelanocorticotropin) shown in Fig 2. β-LPH levels are

Figure 2 (ref 1)

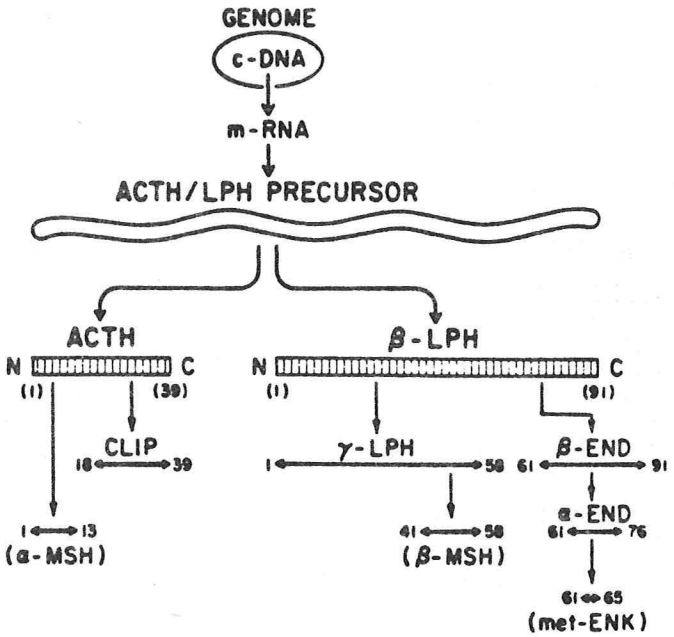

Figure Molecular evolution of adrenocorticotropin (*ACTH*) and other cohormones from a common precursor. LPH = lipotropin, END = endorphin, MSH = melanocyte stimulating hormone, ENK = enkephalin, CLIP = corticotropinlike intermediate lobe peptide.

disproportionately increased relative to ACTH in ectopic Cushing syndrome while in the pituitary form the ratio is reversed. The relationship of β-LPH/ACTH ratios to pigmentation is not known, but β-LPH has only 20% of the melanocyte-stimulating activity of ACTH (1). Acne has already been commented on and is probably the consequence of androgen excess. Acanthosis nigricans may accompany Cushing disease itself and does not suggest the presence of adrenal carcinoma.

6. Muscle weakness

Muscle weakness typically involves proximal muscles, especially the quadriceps femoris. It tends to be symmetrical in distribution and is painless. It is not accompanied by elevated muscle

enzymes. Type 2 muscle fibers (carbohydrate utilizing) are predominantly involved (52). Type 1 fiber diameter also decreases, but this may be due to weakness and disuse from the primary lesion resident in type 2 fibers (53). The mechanism of weakness in the absence of atrophy is unknown although a direct effect of cortisol is thought likely (29). This may be due to a steroid-induced loss of protein but chronic potassium depletion could contribute. The degree of muscle atrophy can apparently be determined by CT scan of the thigh (53). Recovery of fiber size occurs following treatment, but may not be complete. Despite profound disease, muscle enzyme levels in plasma are not elevated (29).

7. Psychiatric abnormalities

The overall incidence of psychiatric abnormalities in Cushing syndrome is about 40% (54), although some have found abnormalities in as many as 80% of patients (55). The abnormalities may be mild or severe (54-58). Table 5 gives a list of the symptoms found in one series of 35 patients (57).

Table 5 (ref 57)

TABLE Frequency of Psychiatric Symptoms in 35 Patients With Cushing's Syndrome

Symptom	%
Increased fatigue	100
Decreased energy	97
Irritability	86
Impaired memory	83
Depressed mood	74
Decreased libido	69
Middle insomnia	69
Anxiety	66
Impaired concentration	66
Crying	63
Restlessness	60
Late insomnia	57
Social withdrawal	46
Hopelessness	43
Guilt	37
Increased appetite	34
Dreams	31
Early insomnia	29
Decreased appetite	20
Thought blocking	17
Speeding thoughts	14
Elation-hyperactivity	11
Slowing thoughts	11
Perceptual distortions	11
Rapid, loud speech	9
Paranoid thoughts	9
Hyperactivity	9
Depersonalization	3
Persistent anhedonia	3
Derealization	3
Decreased fatigue	3
Increased energy	3

The most consistent syndrome consisted of a combination of affective, cognitive and vegetative disturbances. Changes in affect included a depressed mood with frequent crying, while the cognitive abnormalities were usually a decreased ability to concentrate with impairment of memory. Vegetative signs were most often decreased libido and insomnia. Importantly, most psychiatric symptoms disappear with reversal of Cushing syndrome. As noted below, depression may powerfully alter response to dexamethasone. The differential diagnosis between Cushing syndrome and depression thus becomes one of the most difficult problems in medicine.

8. Miscellaneous associations

Cushing syndrome has been associated with a variety of other abnormalities. These will be only briefly commented on. One patient with cyclic hormone production had diabetes insipidus (59). While hyperglycemia is the usual response to cortisol excess, hypoglycemia has occurred with adrenocortical carcinoma (60). The tumor appeared to act like other large solid neoplasms which occasionally cause the plasma glucose to fall to pathologic levels. Galactorrhea with or without amenorrhea is not common but has occurred frequently enough to be more than a chance occurrence (61,62). Galactorrhea may be present in the absence of elevations of prolactin in Cushing syndrome, although prolactin levels are not infrequently high (see below). One patient with a functioning pituitary adenoma and adrenocorticosteroid excess developed pituitary apoplexy with subsequent development of an empty sella (63). Interestingly, Cushing syndrome later reappeared. Spinal compression by epidural fat accumulation has occurred in two patients (64). Diabetic ketoacidosis has been said to occur (8) but the case was not documented.

Opportunistic infections due to steroid-induced suppression of the immune system occurs in Cushing syndrome but only rarely in the pituitary form of the disease (65,66). A high percentage of cases have malignant tumors with ectopic ACTH production (66). The most common infections are cryptococcosis, aspergillosis, nocardiosis and pneumocystosis. Fever is rare. If excess cortisol production is not interrupted rapidly, the chance of recovery is slim. Thromboembolic events have been reported to be increased with Cushing syndrome, but this was not confirmed in one study specifically addressing the question (67).

9. Laboratory abnormalities

A variety of laboratory abnormalities occur in Cushing syndrome, the most consistent of which is hyperglycemia or impaired glucose tolerance (68). Some characteristic changes are shown in Table 6. The hyperglycemic effects are due both to enhanced glucose production and impaired glucose disposal. Although glucocorticoids can alter insulin/insulin receptor interactions, the primary site of the insulin resistance appears to be beyond the insulin receptor (postreceptor resistance) (68a,68b). Plasma glucagon concentrations are also high in Cushing syndrome (68) and contribute to the metabolic abnormalities. Serum triglyceride levels may be grossly elevated. Basal levels of growth hormone, TSH, LH and prolactin are usually normal but the first three do not respond well to stimulatory tests (Table 7) (69).

Table 6 (ref 68)

Table Fasting and 12-hr Mean Hormone and Metabolite Concentrations in Patients With Cushing's Syndrome, Obesity, and Control Subjects

Hormone or Metabolite	Overnight Fast					12-hr Mean				
	Cushing's (n = 6)	Normal Controls (n = 10)	Obese (n = 6)	p_1	p_2	Cushing's (n = 6)	Normal Controls (n = 10)	Obese (n = 6)	p_1	p_2
Glucose (mmole/liter)	5.11 ± 0.26	4.80 ± 0.13	4.79 ± 0.18	NS	NS	5.31 ± 0.39	5.32 ± 0.14	5.41 ± 0.18	<0.01	<0.05
Lactate (mmole/liter)	0.85 ± 0.12	0.68 ± 0.06	0.73 ± 0.08	NS	NS	1.04 ± 0.14	0.72 ± 0.04	0.77 ± 0.07	<0.02	NS
Pyruvate (mmole/liter)	0.105 ± 0.016	0.066 ± 0.004	0.068 ± 0.006	<0.01	<0.05	0.120 ± 0.019	0.070 ± 0.004	0.073 ± 0.006	<0.02	<0.05
Lactate/pyruvate	9.2 ± 0.5	10.3 ± 0.5	10.5 ± 0.5	NS	NS	8.9 ± 0.5	10.2 ± 0.3	10.6 ± 0.4	NS	NS
Alanine (mmole/liter)	0.35 ± 0.05	0.28 ± 0.02	0.25 ± 0.02	NS	NS	0.35 ± 0.03	0.28 ± 0.02	0.29 ± 0.01	NS	NS
3-hydroxybutyrate (mmole/liter)	0.10 ± 0.05	0.05 ± 0.02	0.08 ± 0.03	NS	NS	0.07 ± 0.03	0.05 ± 0.01	0.06 ± 0.02	NS	NS
Acetoacetate (mmole/liter)	0.05 ± 0.02	0.04 ± 0.01	0.04 ± 0.01	NS	NS	0.05 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	NS	NS
Glycerol (mmole/liter)	0.07 ± 0.01	0.07 ± 0.01	0.08 ± 0.01	NS	NS	0.07 ± 0.01	0.06 ± 0.01	0.06 ± 0.02	NS	NS
Nonesterified fatty acids (mmole/liter)	0.66 ± 0.09	0.58 ± 0.03	0.62 ± 0.09	NS	NS	0.51 ± 0.09	0.53 ± 0.04	0.52 ± 0.06	NS	NS
Triglycerides (mmole/liter)	2.15 ± 0.42	0.78 ± 0.20	0.86 ± 0.29	<0.01	<0.05	3.51 ± 1.23	0.89 ± 0.19	0.93 ± 0.23	<0.02	<0.05
Insulin (mU/liter)	12.6 ± 2.2	6.7 ± 0.9	6.7 ± 1.15	<0.01	<0.05	57.3 ± 18.2	19.7 ± 2.5	18.1 ± 4.0	<0.02	<0.05
Glucagon (pmole/liter)	15.7 ± 2.1	11.9 ± 1.0	14.5 ± 0.7	NS	NS	23.2 ± 3.7	12.3 ± 1.5	12.2 ± 2.0	<0.01	<0.02
Growth hormone (μg/liter)	1.0 ± 0.2	3.7 ± 1.6	5.4 ± 2.2	NS	NS	1.2 ± 0.3	2.0 ± 0.5	1.2 ± 0.2	NS	NS
Cortisol (nmole/liter)	559 ± 37	476 ± 42	374 ± 47	NS	<0.01	563 ± 74	276 ± 22	241 ± 32	<0.01	<0.01

Values shown are mean ± SE

12 hr mean for the group is the mean ± SE of the 12-hr average values for each subject.

p_1 is the significance level for differences between Cushing's syndrome and normal controls.

p_2 is the significance level for differences between Cushing's syndrome and obese controls

NS, not significant. Significance calculated as described in the Materials and Methods section.

Table 7 (ref 69)

TABLE Plasma cortisol, GH, TSH, LH, and PRL concentrations in patients with Cushing's disease before operation

Case no.	Cortisol (μg/dl)		GH (ng/ml)		TSH (μU/ml)		LH (mIU/ml)		PRL (ng/ml)	
	Basal	ITT[a]	Basal	ITT[a]	Basal	TRH[a]	Basal	LRH[a]	Basal	TRH[a]
Normal (n = 50)[b]	4.5–24	20–50	<5	10–50	<8	8–52	1–36	52–150	2–20	20–70
1	24	20	1.2	1.1	1	3	12	33	18	36
2	32	27	1.2	1.2	1	1	8	46	8	40
3	28	29	1.0	3.4	1	10	13	62	5	32
4	17	19	1.2	8.0	3	20	14	53	8	27
5	40	34	1.3	4.2	1	1	6	22	7	40
6	21	23	1.0	1.0	1	6	17	92	10	79
7	22	26	1.1	2.1	1	5	10	60	9	38
8	33	35	1.0	1.4	1	2	5	18	6	33
9			2.6	15.0	2	18	15	81	25	50

[a] Peak level after stimulation test.

[b] Ninety-five percent confidence limits of normal controls.

Although often normal, prolactin levels can be elevated (70,71) and, as noted previously, may be sufficient to cause galactorrhea/amenorrhea (61,62). Some patients demonstrate T_4 and T_3 concentrations in plasma that are in the hypothyroid range, the so-called "corticogenic hypothyroidism" (72). TSH levels are low and do not respond to TRF. Although ascribed to a suppressive effect of steroids on TSH release, some or all of the picture could be a variant of the "euthyroid sick" syndrome. Growth failure is common in children with Cushing syndrome but somatomedin levels are normal (73,74). It is therefore probable that the growth deficits are a direct consequence of hypercortisolism rather than a defect in the growth hormone/somatomedin axis. Serum calcium and phosphorus concentrations are normal (75) despite the previously mentioned defect in calcium absorption (Table 8) (49). As noted this is thought to be due to a secondary hyperparathyroidism which contributes to the bone dissolution (45,47,75).

Table 8 (ref 75)

TABLE Laboratory studies in seven patients before and after treatment of ACTH-dependent Cushing's syndrome

Laboratory finding	Normal range	Cushing's syndrome	Remission	*P*
Urinary free cortisol (μg/day)	<100	272 ± 21[a]	28 ± 8[a]	<0.001
Plasma ACTH (pg/ml)	20–100	150 ± 24	49 ± 7	<0.01
Serum creatinine (mg/dl)	0.6–1.4	0.97 ± 0.06	0.91 ± 0.05	NS
Urinary creatinine (mg/day)		1200 ± 102	1104 ± 100	NS
Serum calcium (mg/dl)	8.9–10.1	9.3 ± 0.1	9.4 ± 0.2	NS
Urinary calcium/creatinine (mg/mg)	0.01–0.18	0.23 ± 0.02	0.11 ± 0.02	<0.01
Serum phosphorus (mg/dl)	2.5–4.5	3.1 ± 0.11	4.2 ± 0.20	<0.005
Urinary phosphorus/creatinine (mg/mg)	0.3–0.8	0.74 ± 0.1	0.52 ± 0.1	<0.01
TRP (%)	>86	76 ± 4	89 ± 2	<0.01
Serum iPTH (μleq/ml)	<40	34 ± 5	22 ± 2	<0.05
25OHD (ng/ml)	8–56	18 ± 2	17 ± 2	NS
1,25-$(OH)_2$D (pg/ml)	16–58	44 ± 7	22 ± 3	<0.02

[a] Values given are the mean ± SEM.

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III. Diagnosis

Although Cushing syndromes are relatively rare, the diagnosis is commonly suspected because obesity, hypertension and glucose intolerance are frequently concomitantly present in patients seen in a general medical practice. Since menstrual abnormalities and hirsutism may be also present in such patients, screening for Cushing syndrome is commonly required. Diagnostic workup in suspected Cushing syndrome takes place in two phases. First, one must decide whether the syndrome is present and second one must discern the cause. The latter is crucial since treatment depends on etiology. Several reviews discuss the difficulties in reaching a diagnosis (76-78). Reference 77 is especially valuable. An outline of the overall procedure is shown in Fig 3.

Figure 3 (ref 1)

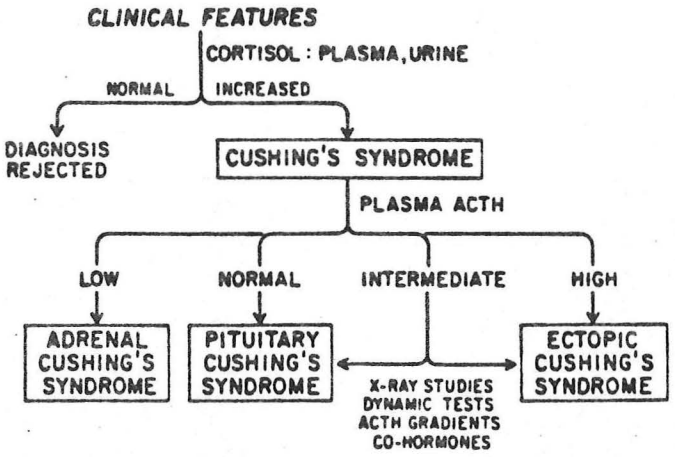

Figure Diagnosis of the Cushing's syndromes. Confirmation requires demonstration of sustained, excessive cortisol production. Differentiation is based on plasma adrenocorticotropin (*ACTH*), although distinction of pituitary from ectopic syndromes often requires additional procedures.

1. Clinical evaluation

The diagnosis of Cushing syndrome requires laboratory testing, but two clues may be helpful from a clinical standpoint. When 70 patients with Cushing syndrome studied over a 30 year period at University College Hospital in London and 711 patients culled from the literature were compared retrospectively with 159 mostly obese subjects who were suspected of having the syndrome but failed documentation by specific testing (79), it was found that bruising (ecchymosis) and myopathy were the primary discriminants of true Cushing syndrome (Table 9) (80).

Table 9 (ref 80)

TABLE DISCRIMINANT INDICES OF CLINICAL FEATURES IN CUSHING'S SYNDROME

Clinical feature	Discriminant index in series	
	Present	Collected
Bruising	10·3	10·5
Myopathy	8·0	7·1
Hypertension	4·4	5·1
Plethora	3·0	3·6
Oedema	2·9	3·3
Hirsutism in women	2·8	2·7
Red striae	2·5	3·1
Menstrual irregularity	1·6	1·6
Truncal obesity	1·6	..
Headaches	1·3	1·1
Acne	0·9	..
Generalised obesity	0·8	..
Impaired glucose tolerance	0·7	0·7

All other features were of lesser value.

2. Diagnostic procedures

The primary screening tests for diagnosis are overnight dexamethasone suppression and measurement of the urinary free cortisol (24 hour sample) (77). Data on the single dose dexamethasone suppression test are shown in Table 10. Most investigators require a value in plasma below 5 $\mu g.dl^{-1}$ after 1 mg of dexamethasone but others consider values of 7 or even 10 $\mu g.dl^{-1}$ as being adequate to rule out Cushing syndrome. Only 3 of 154 patients (1.9%) with Cushing syndrome showed normal suppression. Five of 466 normal controls had abnormal results. The false positive rate in obesity and sick controls was higher (13 and 23%, respectively). Reasons for false positive tests will be considered below.

The upper limit of normal for urinary free cortisol in most labs is about 100 µg/day. Only 3.3% of 479 lean, obese and and chronically ill controls had values above normal while 94.4% of patients with proven Cushing disease had normal levels (i.e., 5.6% false negatives) (Table 10).

Table 10

Urinary Free Cortisol and Overnight Dexamethasone Suppression in Patients with Cushing Syndrome and Control Subjects - Percentage Normal Tests*

	Normal Controls	Obese Controls	Other Controls	Cushing Syndrome
Dexamethasone suppression	461/466 (99%)	151/173 (87%)	246/320 (77%)	3/154 (1.9%)
Free cortisol in urine	261/262 (99%)	99/104 (95%)	103/113 (91%)	14/248 (5.6%)

*Data from literature as recorded in reference 77. Tabulated as total number of patients tested (denominator) and number with normal response (numerator). "Other controls" included patients with acute and chronic illnesses.

Random measurement of plasma cortisol is of little value since normal persons may vary from 3-34 $\mu g.dl^{-1}$ and patients with Cushing syndrome may fall within this range (e.g., current case presentation). Concentrations above 40 $\mu g.dl^{-1}$ in nonstressed persons are distinctly unusual, however. Morning and afternoon plasma values are often obtained looking for lack of diurnal variation, but this test is of relatively little value (76). Cortisol production rates are quite accurate, but are available only in research labs. Urinary 17-hydroxycorticosteroid values are usually elevated in Cushing syndrome but the test is used much less frequently now than in the past since the urinary free cortisol is more accurate. Although 99% of normal controls show 24 levels of 17-hydroxycorticosteroids within the normal range (less than 10-12 mg in most labs), 46 of 173 obese controls (27%) had elevated values suggesting Cushing syndrome. Thirty-four of 311 patients with Cushing syndrome (11%) had normal values (77).

Whenever urine tests are used total creatinine should be measured to aid in evaluating completeness of the collection.

3. Differential diagnosis

The differential diagnosis, once Cushing syndrome has been confirmed, involves both biochemical and radiologic procedures.

a. Biochemical tests. The first test to be obtained is a plasma ACTH. The assay is difficult to do and should be carried out in a research or commercial laboratory that does many determinations. A reliable assay will differentiate adrenal Cushing syndrome from the ectopic or pituitary forms (1,29,77). All patients with pituitary or ectopic forms of the disease have measurable ACTH while adrenal tumors invariably result in suppression of ACTH (Table 11). Some investigators have also felt that plasma ACTH was helpful in separating ectopic from pituitary disease. If one looks at mean values in groups of patients, ACTH levels are low to undetectable (<20 $pg.ml^{-1}$) in adrenal disease, "normal" but inappropriate in pituitary forms (20-120 $pg.ml^{-1}$) and high

in the ectopic category (>200 $pg.ml^{-1}$). In actuality considerable overlap exists in the nonadrenal forms of Cushing syndrome as shown in Table 11.

For measurement of ACTH it is preferable to pool plasma from 3 samples collected 20 minutes apart; plasma cortisol should be measured on the same sample. (Draw blood in a syringe and fill 1/3 of a vacutainer each time. This allows one to avoid centrifuging 3 samples and pooling the plasma; i.e., 1 tube is sent to the lab but that tube contains a mixture of 3 plasma samples collected over 40 minutes.)

Table 11 (ref 77)

Table Plasma ACTH Levels by RIA in Cushing's Syndrome*

Cushing's Disease	Adrenal Tumor	Ectopic ACTH	Normal Range (pg/ml)	Cushing's Disease Range (pg/ml)	Ectopic ACTH Range (pg/ml)	ACTH Assay Sensitivity† (pg/ml)	Reference
7/7	0/3	2/2	20-75	65-400	220-270	20	78, 164
70/70	0/18	81/81	10-80	40-260	90-8000	10	121, 165, 166
22/22	—	29/29	5-112	40-1840	70-3300	5	159, 167
5/5	—	8/8	ND-80	80-800	80-1000	5	158
4/4	0/2	2/2	15-50	178-348	608-690	5	101, 113, 168
—	0/3	—	22-175	—	—	10	169
7/7	0/2	1/1	5-85	85-210	420	5	170
11/11	0/5	5/5	ND-70	30-260	190-1000	15	79
11/11	—	—	ND-60	10-80	—	10	171
12/12	0/8	8/8	5-95	110-400	460-1400	5	172
10/10	—	—	ND-120	30-2600	—	10	161, 173
12/12	—	14/14	10-80	130-650	120-1500	10	129
18/18	0/4	—	20-100	35-345	—	20	35
Total (%) 189/189 (100)	0/45 (0)	150/150 (100)					

*The data in the first three columns are expressed as *n/N* where *n* is the number of patients with the indicated etiology of Cushing's syndrome whose plasma ACTH levels are detectable (equal to or greater than the indicated assay sensitivity), and *N* is the total number of patients. The ranges of plasma ACTH levels for normal subjects and the patients with Cushing's disease and the ectopic ACTH syndrome are presented in the second three columns.

†ACTH assay sensitivity refers to the lowest plasma level of ACTH that can reliably be distinguished from zero. In several of the studies the sensitivity had to be estimated as the lowest recorded normal value.[164,165,172]

A low and high dose dexamethasone suppression test using 2 and 8 mg doses for 48 hours each should also be done. The general rule is that in bilateral adrenal hyperplasia due to hypothalamic-pituitary disease suppression does not occur at 2 mg but does at 8 mg. In adrenal and ectopic syndromes resistance continues at 8 mg. In the 2 mg test urinary free cortisol should be suppressed to 25 µg or less and 17-hydroxycorticosteroids below 4 mg per 24 hours. In the high dose test suppression below 50% of baseline is usually considered to indicate pituitary Cushing syndrome, although some investigators require 40% (32,77). Published experience is summarized in Table 12. Only 2 of 45 patients with Cushing syndrome suppressed on the low dose when urinary free cortisol was the parameter measured (33 of 34 normals did suppress). Using 17-hydroxycorticosteroids 7 of 109 persons with true disease suppressed. With the 8 mg test separation was less than perfect even with urinary free cortisol. Thus 3 of 40 patients with bilateral adrenal hyperplasia did not suppress while 2 of 6 with the ectopic

syndrome did. The take home message is that no single test is 100% accurate for differentiation.

Table 12

Long Dexamethasone Suppression Test

Test	2 mg		8 mg	
	Free Cortisol	17-OHCS	Free Cortisol	17-OH
Non-Cushing control	33/34 (99%)	207/207 (100%)	-	-
Pituitary Cushing	2/45 (4.4%)	7/109 (6.4%)	37/40 (93%)	47/51 (92%)
Adrenal tumor	-	-	0/11 (0%)	1/33 (3%)
Nodular hyperplasia	-	-	4/4 (100%)	1/15 (6.7%)
Ectopic ACTH	-	-	2/6 (33%)	2/14 (14%)

Data from ref 77. Dexamethasone was given as 0.5 mg or 2.0 mg q6h for 48 hours. Tabulated as number showing suppression over the total number tested.

Because collection of urine for 24 hours is cumbersome, even in the hospital, use of plasma (serum) cortisol in conjunction with the long dexamethasone test has been recommended (81). Plasma samples were obtained at 1600 hours on day 1 (baseline), day 3 (2nd day of 2 mg/day) and day 5 (2nd day of 8 mg/day), but it probably would be preferable to take samples on all 5 days. A value greater than 5 µg/dl at 1600 h on the second day was considered nonsuppressed on the low dose schedule while a concentration higher than 10 µg/dl was judged nonsuppressed with the 8 mg test. Serum dehydroepiandrosterone sulfate was also measured; values less than 0.4 µg/ml in the face of nonsuppressibility indicated an adrenal adenoma; similar information was not forthcoming with measurement of 17-ketosteroids (Fig 4).

Figure 4 (ref 81)

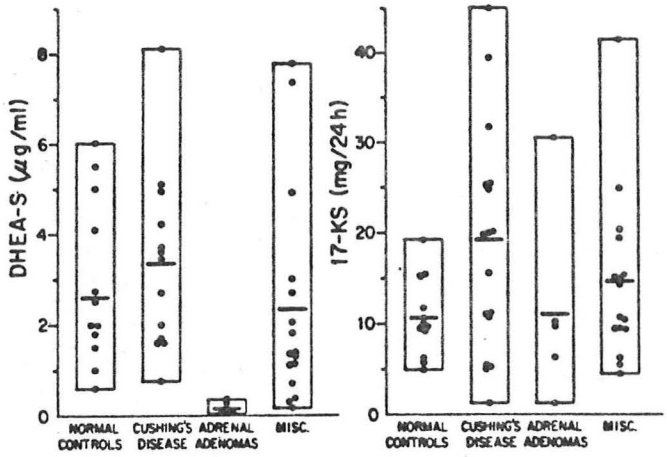

Figure Baseline serum dehydroepiandrosterone sulfate (*DHEA-S*) and urinary 17-ketosteroid (*17-KS*) values in Study A. Patients with nonsuppressible serum cortisol values and a serum DHEA-S value less than 0.4 μg/mL had adrenal adenomas. Note the large overlap of 17-ketosteroid values among different groups.

One report has appeared which claims superiority for the metyrapone test over high dose (8 mg) dexamethasone suppression in differentiating pituitary and adrenal Cushing syndromes (82). In a prospective study of 25 patients the high dose dexamethasone test had a diagnostic accuracy of 81% while the metyrapone test had an accuracy of 100% in differentiating adrenal tumors from pituitary disease. For the test 750 mg of metyrapone is administered every 4 hours beginning at 8:00 a.m. and the serum 11-deoxycortisol value is measured 24 hours later (8:00 a.m. the 2nd day). Inhibition of the 11β-hydroxylase reaction by the drug produces a fall in cortisol and stimulation of ACTH release in normal persons such that the precursor, 11-deoxycortisol rises. All subjects with pituitary Cushing syndrome had 11-deoxycortisol values of 10 μg/dl or greater while patients with adrenal tumors (and the one patient with ectopic disease) had levels below 10 μg/dl (Fig 5).

Figure 5 (ref 82)

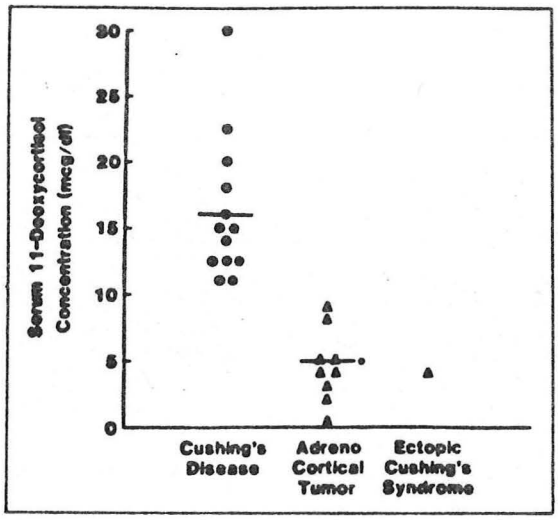

Figure 8 AM serum 11-deoxycortisol measurement following metyrapone testing (750 mg orally every four hours to six doses). The bar (—) represents the mean value. *$p < 0.001$ versus Cushing's disease.

These results suggest that the test may be a valuable addition to the diagnostic tools used in Cushing syndromes, although earlier investigators were less enthusiastic (1,79). While sometimes used, testing by direct administration of ACTH is not reliable and should be abandoned (77).

As mentioned earlier, the administration of corticotropin releasing factor (CRF) has been reported to separate patients with pituitary Cushing syndrome from those with adrenal and ectopic forms (10-12, 83). Patients with pituitary Cushing syndrome tend to show a higher than normal rise of ACTH or cortisol to the releasing factor. However, it is likely that the test will not be definitive (12).

b. Venous sampling. If measurable ACTH is found and there is concern about the possibility of ectopic disease, it is possible in some centers to do selective venous sampling to demonstrate the source of ACTH (84,85). One places the catheter in the inferior petrosal sinus (which receives pituitary hormones from the cavernous sinus) and compares with blood from an antecubital vein. With pituitary Cushing syndrome the ratio in the sinus to peripheral blood is > 2. Samples from jugular bulb or jugular vein do not discriminate.

c. Ultrasound and CT scans. When adrenal Cushing syndrome is present one needs to know whether disease is unilateral or bilateral. Both ultrasound and CT scans of the body are useful (86-91). Nuclear magnetic resonance scanning can also be used to visualize the adrenals. The normal adrenal gland has a linear, triangular or arrowhead appearance (89). Basically any spherical mass is abnormal; convex bulging of the margin of the gland is also suggestive of tumor. In one series of 35 patients with biochemically proven Cushing syndrome and intact adrenals, CT accurately identified 15 adrenal tumors and was able to distinguish between the 10 adenomas and 5 carcinomas (91). It was of interest that 6 of 9 patients with ectopic ACTH had appreciable bilateral enlargement of both adrenals while 9 of 10 subjects with pituitary disease had normal sized glands. (One patient with suspected ectopic disease actually had nodular hyperplasia, accounting for the total of 35 patients.) Adrenal scans may be helpful although results take several days to obtain (92). The most useful agent is 6β-[^{131}I]-iodomethyl-19-norcholesterol (NP-59). Bilateral adrenal hyperplasia and adrenal adenomas are correctly visualized in over 95%. Adrenal carcinomas may not take up the isotope and nonvisualization may result if hyperlipoproteinemia is present (93). Adrenal scans are probably less useful than CT examination.

4. Problems in diagnosis

Overlap between biochemical tests have already been mentioned. Special problems obscuring diagnosis include: drugs, depression, cyclical hormone production, abnormal dexamethasone concentrations and alcoholism (78). A difficult problem is diagnosis in children.

a. Drugs. Estrogens increase cortisol-binding globulin such that total plasma cortisol values are elevated. After an overnight dexamethasone suppression test values > 10 $\mu g.dl^{-1}$ may commonly be found. Spironolactone fluoresces in plasma and interferes with fluorometric assays but not radioimmunoassay as is used at Parkland. Treatment for as short as one day may give values up to 100 $\mu g.dl^{-1}$. Sodium phenytoin enhances dexamethasone metabolism and thus produces nonsuppressibility with overnight and low dose (2 mg) tests.

b. Depression. Endogenous depression is an enormous problem since Cushing syndrome causes depression and depression may induce dexamethasone nonsuppressibility (94). It has been stated that increased cortisol response to hypoglycemia is maintained in depression (though impaired) while cortisol levels are fixed in Cushing syndrome, but significant overlap occurs (32,77,95,96). A very brisk rise in cortisol with hypoglycemia favors depression as a cause of nonsuppressibility but is certainly not absolute.

c. Cyclical hormone production. Hormone production in Cushing syndrome may be cyclical with periods running from 4 to 86 days (78). On occasion much more abrupt cycles - as short as 12 hours - can be seen (97). If a dexamethasone suppression test is done during a down cycle the patient may appear to be suppressible when in fact disease is present. This was the case in the patient presented in these rounds. An illustration is given in Fig 6.

Figure 6 (ref 97)

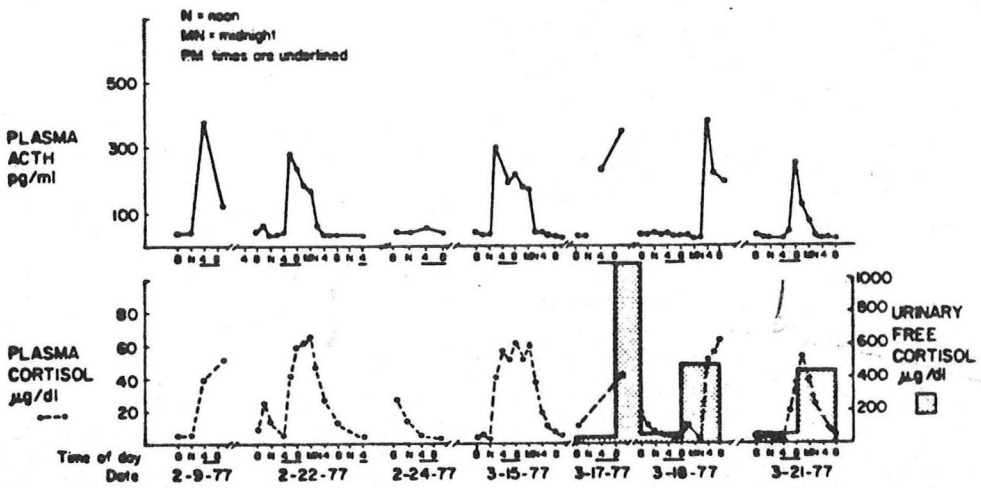

FIG. Pattern of plasma ACTH and cortisol obtained when levels were determined at 2-h intervals for periods of 24 h. Note the close correlation between the peaks of ACTH and cortisol. Urinary free cortisol also shows marked temporal variation.

d. Unusual dexamethasone concentrations in plasma. As noted above, some patients proven to have Cushing syndrome demonstrate normal suppressibility with overnight or low dose dexamethasone suppression test. By measuring plasma dexamethasone levels it was shown that 2 cases of suppressible Cushing syndrome were due to delayed turnover of the steroid such that plasma values were very high (98). The cause of the delayed turnover was not discerned. It is likely that failure of overnight dexamethasone suppression in obesity without Cushing syndrome is due to dilution of dexamethasone in the larger than normal body water pool such that suppressive concentrations are not reached. The fact that most such patients suppress with the 48 hour 2 mg test favors this conclusion (76). The normal relationship between plasma cortisol and dexamethasone is shown in Fig 7.

Figure 7 (ref 98)

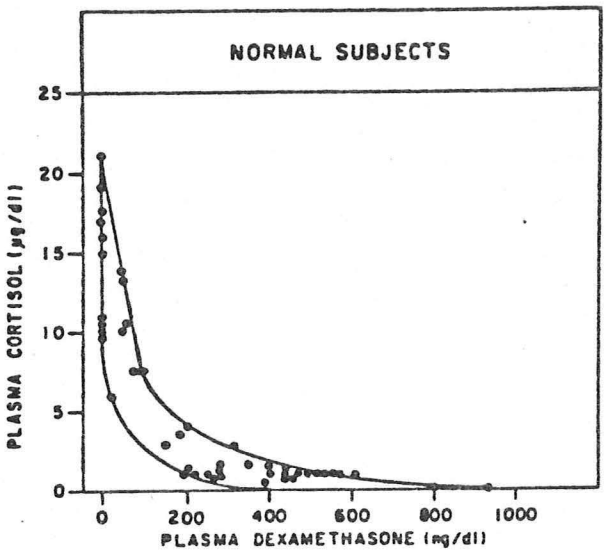

Fig. Eight A.M. plasma Dex and F concentrations after oral Dex administration in normal subjects. The doses were 0.25, 0.5, and 1.0 mg. at midnight and 0.5 and 2.0 mg. every 6 hours for 8 doses.

Concentrations of dexamethasone between 150 and 200 $ng.dl^{-1}$ represent suppressive levels in normals. A patient with pituitary Cushing syndrome has been reported who was insensitive to suppression by dexamethasone despite plasma levels as high as 700 ng/dl (99). The patient did respond to intravenous infusion of hydrocortisone with a fall in ACTH at cortisol concentrations in the physiologic range.

e. Alcoholic pseudo-Cushing syndrome. Several patients have now been reported who have clinical features suggestive of Cushing syndrome (moon face, central obesity, purple striae, hypertension) coupled with high levels of plasma cortisol that are nonsuppressible in the overnight or 2 mg dexamethasone suppression tests (100). Diurnal variation was also lost. In contrast to true Cushing syndrome ACTH, cortisol and growth hormone rose normally with insulin-induced hypoglycemia. As shown in Fig 8, biochemical abnormalities disappear spontaneously in the hospital on withdrawal from alcohol. While the mechanism is unknown, no alcoholic patient should be diagnosed as having adrenal hyperfunction until alcohol has been withdrawn at least 4 weeks. This syndrome has been carefully reviewed (101).

Figure 8 (ref 100)

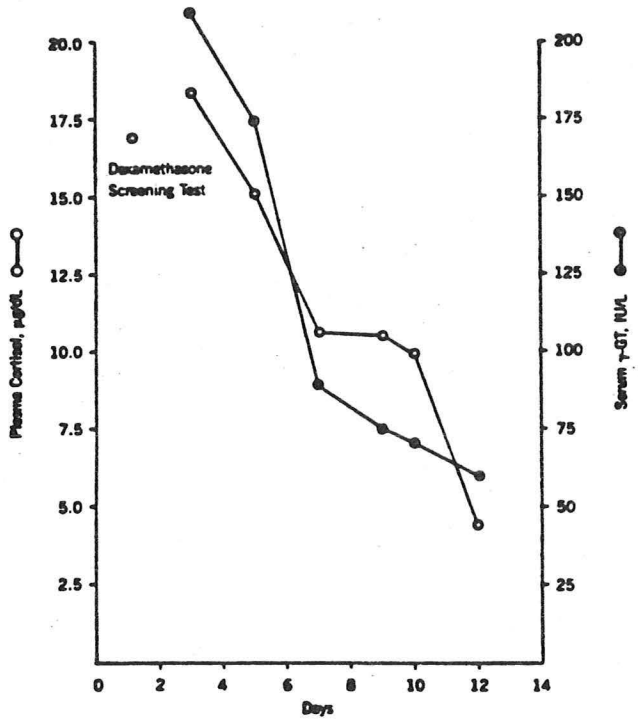

Fig —Course of basal plasma cortisol (at 9 AM) and serum γ-glutamyl transferase (γ-GT) concentrations during hospital admission in patient 1. On first day, plasma cortisol level at 9 AM was insufficiently suppressed in response to oral administration of 1 mg of dexamethasone on previous night at 11 AM.

f. Diagnosis in infants and children. Cushing syndrome may occur as early as 2 months of life (102). The problem is that diagnostic standards have not been well established. Preliminary values in 10 infants under 10 months have been published (102). In older children (>7 years) adult standards have been applied (103) but the validity of this procedure is not known.

5. Conclusion

For the diagnosis of Cushing syndrome I recommend the following sequence:

(1) Overnight dexamethasone suppression test: 1 mg dexamethasone at 2400 with measurement of plasma cortisol at 0800. Normal response < 5 $\mu g/dl^{-1}$; abnormal > 10 $\mu g.dl^{-1}$.
(2) If screening test is positive, measure 24 hour urinary free cortisol: normal value < 100 µg.
(3) If positive, measure basal ACTH levels (0800) and start long dexamethasone suppression test utilizing plasma concentrations at 1600 and 24 h urinary free cortisol.
(4) If patient is nonsuppressible on either the 2 mg or 8 mg dexamethasone test, get CT scan of pituitary and adrenal glands.

(5) Utilize metyrapone test, CRF and insulin-induced hypoglycemia only as adjuncts in difficult cases.
(6) If the patient appears to have Cushing syndrome but initial screening is negative, carry out repetitive tests, including sequential measurements of urinary free cortisol.

A composite picture of the laboratory findings in the various Cushing syndromes is shown in Table 13.

Table 13

The Laboratory Picture in the Cushing Syndromes

Test	Type of Cushing Syndrome		
	Pituitary	Adrenal	Ectopic
Overnight dex	NS	NS	NS
Urinary free cortisol	↑	↑	↑
ACTH	normal	absent or low	high
2 mg dex	NS	NS	NS
8 mg dex	S	NS	NS
Metyrapone	+	-	-
Dehydroepiandrosterone sulfate, plasma	N or ↑	↓	N or ↑
CT scan of adrenals	normal size, symmetrical	asymmetrical, visible tumor	bilateral enlargement

NS = nonsuppressed; S = suppressed; N = normal

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IV. Treatment

The treatment of Cushing syndromes is critical since morbidity and mortality are high. Untreated about 50% of patients die within 5 years (80). The cause of death prior to modern treatment was usually infection, cardiac failure or postoperative complication (134). No current figures on prognosis or cause of death are available. Treatment varies with the cause. Unfortunately it is not always successful.

1. Pituitary Cushing syndrome

a. Transsphenoidal hypophysectomy. For the last several years transsphenoidal hypophysectomy has been the treatment of choice in pituitary Cushing syndrome (104-108). Remission was initially reported in 80-90% of cases but with further experience and prolonged follow-up recurrences or initial failures have received more attention (109). In a survery of 25 academic endocrinologists who had cared for more than 1 patient cure rates ranging from 20-100% and recurrence rates from none to 100% were reported. Since no details were given hardness of the data is suspect; nevertheless, it is clear that initial hopes for universal cure via this procedure have not been sustained. Despite this concern transsphenoidal surgery remains the first line of treatment if an experienced neurosurgical team is available. In 104 patients operated on by Wilson there were four technical failures (110). In the remaining 100 subjects a cure rate of 78% was achieved, this figure increasing to 87% if those with suprasellar extension were excluded. Four of the 78 initial responders have experienced recurrences. Eight-two of the patients had histologically confirmed tumors - 60 microadenomas and 22 macroadenomas. (A summary of the results is shown in Table 14.) Complications in the 100 successful operations were few: myocardial infarction, 2; CSF leak with meningitis, 2; sinusitis, 2; diabetes insipidus, 1; angiographic complication, 1; postoperative visual disturbance, 3.

On the basis of these results the authors recommended transsphenoidal microsurgery in all patients with pituitary Cushing syndrome whether or not a tumor could be demonstrated preoperatively. If no tumor is identified at exploration, a total hypophysectomy is done (110).

Table 14 (ref 110)

Results of transsphenoidal microsurgery in patients with intrasellar tumors and with extrasellar extension

Factor	Intrasellar Tumors		Extrasellar Extension	
	No.	Percent	No.	Percent
no. of patients	71	100	25	100
correction of hypercortisolism	62	87	12	48
selective adenomectomy	55	77	12	48
total hypophysectomy	7	10	0	0
failures	8	11	10*	40
selective adenomectomy	8†	11	9	36
total hypophysectomy	0	0	1‡	4
recurrence	1§	1	3	12
selective adenomectomy	1	1	3‖	12
total hypophysectomy	0	0	0	0

* Includes three patients who underwent debulking procedures only.
† Selective adenomectomy or exploration only.
‡ Incomplete because of posterolateral extrasellar extension.
§ Patient had remission after a second surgical procedure.
‖ All patients with childhood onset.

Radical hypophysectomy has been routinely recommended by other authors on the grounds that permanent cure of Cushing syndrome was more important than the risk of hypopituitarism (111). In 16 consecutive cases 14 successful operations were carried out. Complete clinical and chemical remission was observed in 13 and a partial remission in 1. Hormone replacement therapy was required in 11 subjects. Two patients had diabetes insipidus.

Transsphenoidal surgery has not been utilized extensively in children, but 14 of 15 patients were reported cured in one series (112). Catchup growth was usual if epiphyses had not closed and puberty progressed normally.

All patients should be covered with steroids prior to surgery (110) and replacement hydrocortisone is required for 6-9 months (104,110) because of prolonged suppression of the nonadenomatous pituitary by high levels of circulating cortisol (113). A normal response to a short ACTH test is a good sign that replacement can be withdrawn. The ability to remove hydrocortisone early suggests inadequate surgery or a recurrence.

b. Pituitary radiation. Conventional radiation can cure adult Cushing syndrome but the yield is low: 10 of 51 patients cured and 13 improved in the Vanderbilt series (114). Moreover, the process is slow requiring months to years for full effect. Thus, while relatively safe, the procedure has been largely abandoned as a sole means of therapy. Schteingart and coworkers (115) have combined cobalt irradiation with mitotane (o,p'-DDD) therapy and reported biochemical remission in 29 of 36 patients. Mitotane was given in low doses: 2-4 g daily. Some patients responded early while others were delayed (Fig 9).

Figure 9 (ref 115)

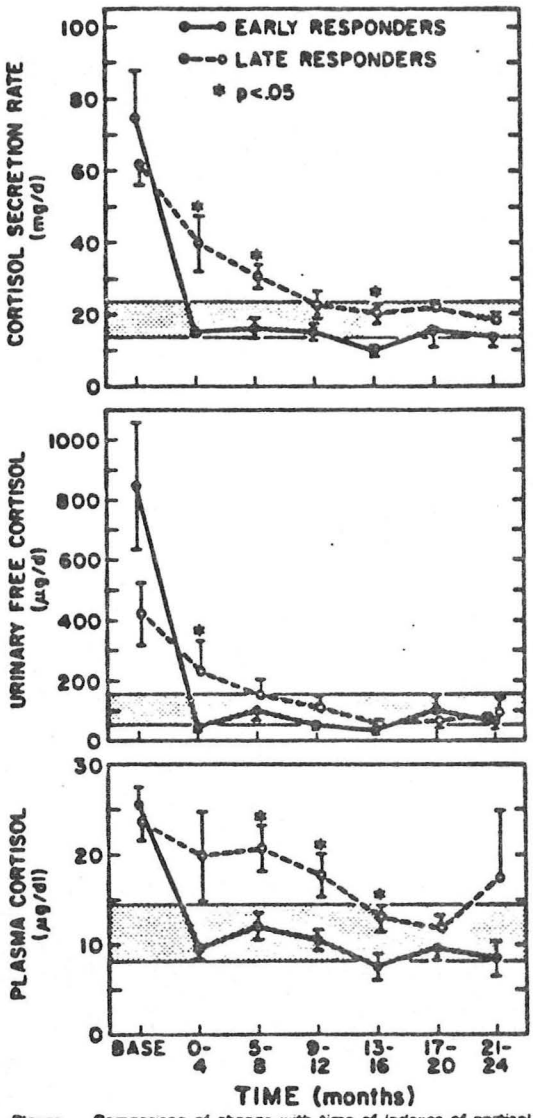

Figure Comparison of change with time of indexes of cortisol secretion (mean ± SEM) in early and late responders. Range of normal values for each test is depicted by the shaded area. Asterisks depict significant differences between early and late responders at each time period.

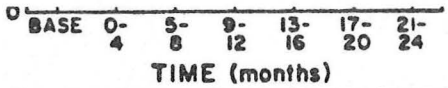

Figure Comparison of change with time of indexes of cortisol secretion (mean ± SEM) in early and late responders. Range of normal values for each test is depicted by the shaded area. Asterisks depict significant differences between early and late responders at each time period.

Lawrence and Linfoot (116) reported their experience with heavy particle radiation in 64 patients but insufficient detail was provided to evaluate the results. In stereotactic radiosurgery the entire radiation

dose is delivered at a single sitting but this procedure is not available in the U.S. (117). In 13 patients a decrease in cortisol excretion was shown, but follow-up was only a few weeks rendering evaluation of the technique impossible.

Children seem to be much more responsive to radiation and may be treated either externally (103) or by implantation of the radioactive isotopes ^{198}Au or ^{90}Y (118). Yttrium 90 has also been used successfully in adults (119). The advantage of radiation is that other pituitary hormones are preserved allowing progression through puberty and subsequent fertility. (See above for normal puberty with transsphenoidal microsurgery in children.) Using conventional cobalt therapy 12 of 15 subjects were cured in the series reported by Jennings and colleagues (103). All 9 subjects had remissions with radioactive implants (118).

Although generally considered safe, external radiation can cause blindness due to optic nerve radiation and late development of sarcomas in radiation portals. An interesting case of radiation failure was due to an ectopically located (sphenoid sinus) pituitary tumor (120).

c. Bilateral adrenalectomy. The standard of treatment only a few years ago, this procedure is now less frequently used. Mortality rates are 4 to 10% (1) and Nelson's syndrome develops in 10-20% of patients. While the latter complication has been claimed to be much more benign than originally supposed (121), some patients have visual loss as tumors enlarge or develop other hormone deficiencies. In addition the pigmentation is cosmetically unattractive. Nelson's syndrome cannot be prevented by radiation of the pituitary prophylactically at the time of surgery (121). It should also be recognized that "total" bilateral adrenalectomy may not cure the patient because of residual adrenal tissue (122).

Some workers have continued to advocate adrenalectomy with autotransplantation of some of the removed gland in children (123,124). I think this is unwise, at least in older children where transsphenoidal surgery can be carried out (112,125).

d. Drugs. In general drugs represent a second line of treatment for Cushing syndrome. They are used to prepare sick patients for surgery or in circumstances where definitive therapy is impossible such as ectopic Cushing syndrome or inoperable adrenal carcinoma (126). They have also been used as adjunctive therapy with pituitary radiation as mentioned above (115). Occasionally combinations of agents are helpful (1). A brief summary of the drugs available follows:

Bromocriptine (Parlodel). This dopamine agonist acts on the central nervous system. Dosage is 10 to 30 mg daily. It is only sporatically effective in pituitary Cushing syndrome (127,128,129).

Cyproheptadine (Periactin). Acts as a serotonin antagonist (6). The usual dose is 24 mg/day. Prolonged remissions have been reported, but they are rare (130).

Metyrapone (Metopirone). Acts on the adrenal to inhibit the 11β-hydroxylation of adrenal steroids (126). The usual dose is 1 to 4 g daily. It is very expensive but can occasionally produce a sustained remission (131).

Aminoglutethimide (Elipten). Blocks the first step in steroid biosynthesis (132). Usual dose 1-2 g daily.

o,p'-DDD (Mitotane, trade name, Lysodren). This drug acts to block steroid synthesis and also is cytotoxic for adrenocortical cells (115,133). The mechanism is not known. The dose varies from 1 to 10 g daily. It is perhaps the best drug for adrenal carcinoma. It can be used in low dosage with radiation as noted above for treatment of noncarcinomatous Cushing syndrome.

Sodium valproate. This drug is an anticonvulsant which acts as a GABA transaminase inhibitor (135). It appears to be quite effective in some patients with pituitary Cushing syndrome, but is not available in the United States. Valproic acid (Depakene) is approved as an anticonvulsant but I have not seen studies with the free acid in Cushing syndrome.

Trilostane (WIN 24,540). This drug acts by blocking 3β-hydroxysteroid dehydrogenase (136). It was originally reported to be helpful in Cushing syndrome, but it now seems clear that it is not useful (137,138).

e. Induced venous infarction. In critical situations it has been possible to infarct the adrenal glands using a venous catheter and dye injection (139).

2. Adrenal Cushing syndrome. Surgery is indicated in essentially all cases. Unilateral tumors, which are much more common than bilateral lesions, require removal only of the involved gland, usually through a flank incision (1). Most patients with adrenal adenoma recover following removal of the tumor (140). If bilateral adrenalectomy for nodular hyperplasia is to be carried out or an operable adrenal carcinoma is present a transfrontal abdominal approach may be preferable.

3. Ectopic Cushing syndrome. If the lesion is benign (thymoma, bronchial adenoma) or the malignancy is resectable, removal provides a cure for the Cushing syndrome. In inoperable cases drug therapy is required.

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