MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

November 12, 1964

CUSHING'S SYNDROME vs EXOGENOUS OBESITY

Figure 1. The Pituitary-adrenal System.

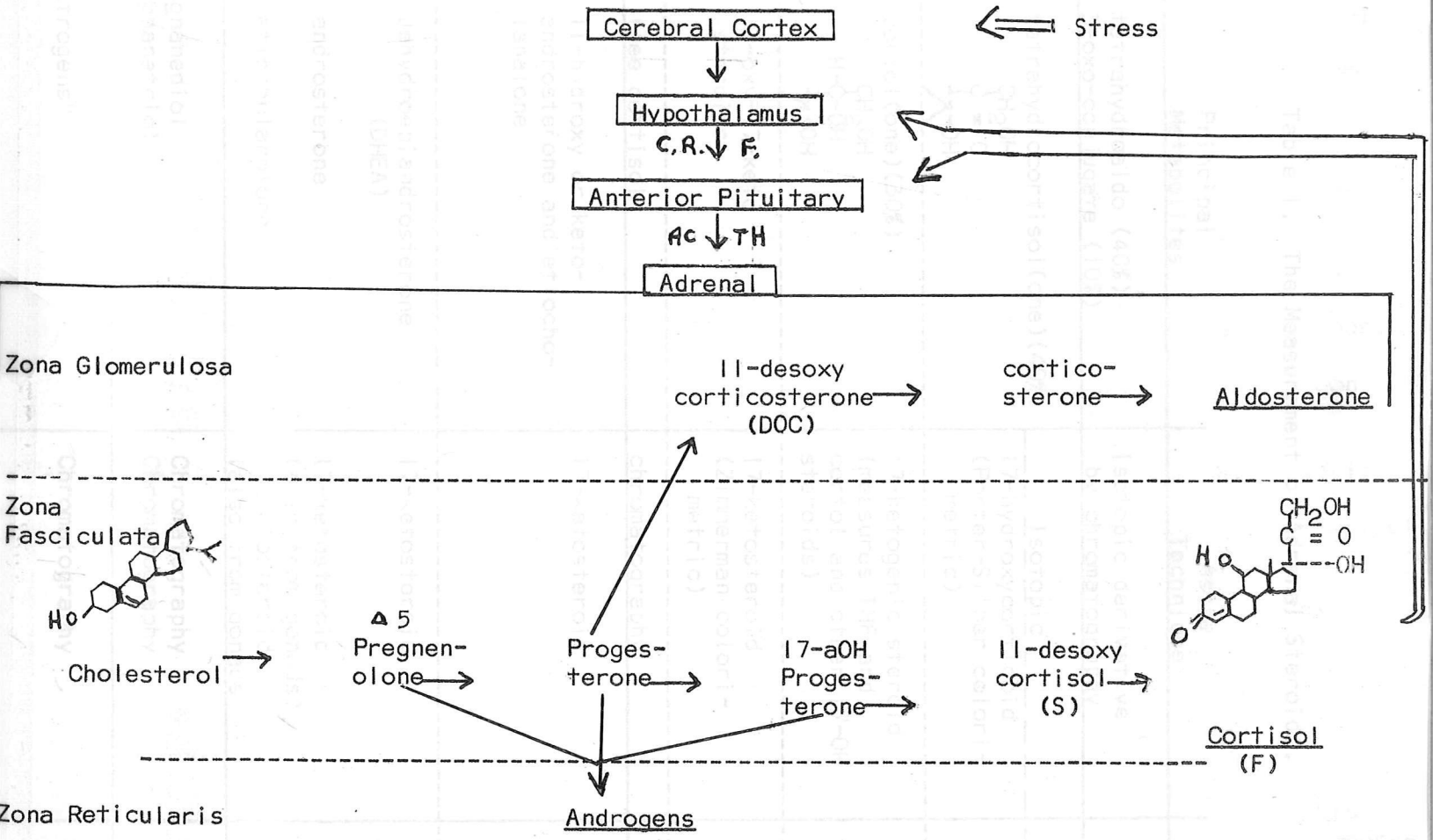
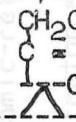
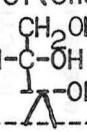


Table I. The Measurement of Adrenal Steroids.

Steroid	Principal Metabolites	Assay Technique	Normal Levels
Mineralocorticoid			
Aldosterone	1) tetrahydroaldo (40%) 2) 3-oxo-conjugate (10%)	Isotopic derivative by chromatography	Secretion rate = 50-200 µg/day Urine excretion = 5-20 µg/day
Glucocorticoid			
Cortisol	1) tetrahydrocortisol(one)(40%) 	Isotopic 17-hydroxycorticoid (Porter-Silber colorimetric)	Secretion rate = 15-25 mg/day Plasma (8 A.M.) = 6-25 µg% (5 P.M.) = 3-15 µg% Urine excretion = 3-12 mg/day
	2) cortol(one)(30%) 	17-ketogenic steroid (measures THF and cortol and other 17-OH steroids)	Urine excretion Female = 5-15 mg/day Male = 8-20 mg/day
	3) 11-oxy-17-keto steroids	17-ketosteroid (Zimmerman colorimetric)	Urine = 1-2 mg/day (See below)
	4) free cortisol	chromatography	Urine = 10-80 µg/day
Androgens 1) 11-OH-andro-stenedione 2) adrenosterone	1) 11-hydroxy or keto-androsterone and etiocholanalone	17-ketosteroid	Urine: Female: 5-15 mg/day Male: 8-22 mg/day
3) dehydroepi-androsterone	2) dehydroepiandrosterone (DHEA)	17-ketosteroid	
4) testosterone	3) androsterone	17-ketosteroid (also from gonads)	
5) androstene-dione	4) etiocholanolone	17-ketosteroid (also from gonads	
Progestins			
Progesterone	Pregnanediol	Chromatography	0-1.5 mg/day(2-7 during luteal
17-OH-proges-terone	Pregnanetriol	Chromatography	0-4 mg/day phase)
Estrogens			
Estradiol 18-OH-estrone	"Estrogens"	Chromatography	Male: 4-25 µg/day Female: 4-60 µg/day

I. The Pathophysiology of Cushing's Syndrome.

A. Definition: A disease manifesting the effects of cortisol excess.

B. The normal pituitary-adrenal relationship (Figure 1).

1. Control of ACTH secretion.

a. Hypothalamic via Corticotrophin Releasing Factor (CRF).

b. Negative feed-back by cortisol.

The concept of hypothalamic control of anterior pituitary function by a neurohumoral mechanism is based mainly on the work of Harris. Attempts to isolate and characterize the ACTH-releasing factor continue.

(1) Harris, G.W. The development of ideas regarding hypothalamic-releasing factors. Metabolism 13:1171, Oct. 1964 (Part 2).
(2) Schally, A.V. and Bowers, C.Y. Corticotrophin-releasing factor and other hypothalamic peptides. Metabolism 13:1190, Oct. 1964 (Part 2).
(3) Porter, J.C. and Rumsfeld, H.W. ACTH-releasing activity of bovine posterior pituitaries. Endocrinology 70:62, Jan. 1962.

The presence of a negative feed-back control by the circulating level of cortisol is certain, but the exact location of the feedback mechanism is uncertain.

(4) Yates, F.E. and Urquhart, J. Control of plasma concentrations of adrenocortical hormones. Physiol. Rev. 42:359, July 1962.
(5) Davidson, J.M. and Feldman, S. Cerebral involvement in the inhibition of ACTH secretion by hydrocortisone. Endocrinology 72:936, June 1963.

The effect of cortisol upon stress-induced release of ACTH (presumably via the hypothalamus) is also unsettled.

(6) Estep, H.W., et al. Pituitary-adrenal dynamics during surgical stress. J. Clin. Endocrinol. 23:419, May 1963.

2. The effects of ACTH upon the adrenal.

a. Pathway of adrenal steroid synthesis.

b. The site and mode of action of ACTH.

The effect of ACTH is almost exclusively upon the synthesis of cortisol, perhaps because it is localized in the zona fasciculata. The mode of action may be through the activation of phosphorylase, supplying TPNH required for enzyme activity.

(7) Dorfman, R.I. Metabolism of adrenal cortical hormones. Lieberman, S. Chemistry of adrenal corticosteroids in The Adrenal Cortex, ed. H.D. Moon, Hoeber, New York, 1961.
(8) Haynes, R.C., Jr. and Berthet, L. Studies on the mechanism of action of the adrenocorticotropic hormone. J. Biol. Chem. 225:115, March 1957.

3. The transport and metabolism of cortisol.

a. The normal diurnal variation in plasma cortisol.

b. The presence of a binding globulin (CBG).

The plasma and urinary concentrations of cortisol show a diurnal variation, which results from variation in the release of ACTH.

(9) Migeon, C.J., et al. The diurnal variation of plasma levels and urinary excretion of

17-hydroxycorticosteroids in normal subjects, night workers and blind subjects. J. Clin. Endocrinol. 16:622, 1956.
(10) Ney, R.L., et al. Correlation of plasma ACTH concentration with adrenocortical response in normal human subjects, surgical patients, and patients with Cushing's disease. J. Clin. Invest. 42:1669, Nov. 1963.
(11) Martin, M.M. and Hellman, D.E. Temporal variation in SU-4885 responsiveness in man: Evidence in support of circadian variation in ACTH secretion. J. Clin. Endocrinol. 24:253, March. 1964.

The presence of a binding protein for cortisol is of physiologic importance and must be considered in evaluating plasma cortisol levels.

(12) Sandberg, A.A. and Slaunwhite, W.R. Transcortin: A corticosteroid-binding protein of plasma. V. In vitro inhibition of cortisol metabolism. J. Clin. Invest. 42:51, Jan. 1963.
(13) Beisel, W.R., et al. Cortisol transport and disappearance. Ann. Int. Med. 60:641, April 1964.

C. The abnormal pituitary-adrenal system in Cushing's Syndrome.

1. Adrenal neoplasia.

   a. Adenoma - 12%.

   b. Carcinoma - 16%.

   c. Adrenal cortical rest tumors in ovary.

2. Excess ACTH with secondary adrenal hyperplasia.

   a. Primary pituitary tumors.

   b. Non-endocrine tumors.

   c. Hypothalamic (?) - 60%.

There is no question about the pathophysiology of adrenal tumors, although rare variations in steroid patterns are noted. Feminizing syndromes may occur with carcinoma.

(14) Kirschner, M.A., et al. Cushing's Syndrome: nodular cortical hyperplasia of adrenal glands with clinical and pathological features suggesting adrenocortical tumor. J. Clin. Endocrinol. 24:947, Oct. 1964.
(15) Lipsett, M.B. and Wilson, H. Adrenocortical cancer: Steroid biosynthesis and metabolism evaluated by urinary metabolites. J. Clin. Endocrinol. 22:906, Sept. 1962.
(16) Stewart, W.K., et al. The feminizing syndrome in male subjects with adrenocortical neoplasms. Am. J. Med. 37:455, Sept. 1964.

Cushing originally proposed that his syndrome was caused by basophil adenomas of the pituitary. There is no question that pituitary tumors may cause some cases.

(17) Cushing, H. The basophil adenomas of the pituitary body and their clinical manifestations. Bull. Johns Hopkins Hosp. 50:137, 1932.

Primary tumors of the pituitary are being recognized with increasing frequency and should be looked for in every patient, particularly those with hyperpigmentation. The possibility that such tumors may only become obvious after total adrenalectomy is strongly suggested. Most are chromophobe, not basophil, in type.

(18) Krieger, D.T., et al. Cushing's Syndrome associated with a suprasellar tumor. Acta endo. 47:185, Oct. 1964.
(19) Decourt, J. Study of hypophysial adenoma with Cushing's Syndrome favoring identification of corticotrophic cells in man. Ann. endocrinol. 24:497, July-Aug. 1963 (From 1964 YearBook of Endocrinology).

(20) Plotz, C.M., et al. The natural history of Cushing's Syndrome. Am. J. Med. 13:597, Nov. 1952.
(21) Nelson, D.H., et al. ACTH-producing pituitary tumors following adrenalectomy for Cushing's Syndrome. Ann. Int. Med. 52:560, March 1960.
(22) Salassa, R.M., et al. Pituitary tumors in patients with Cushing's Syndrome. J. Clin. Endocrinol. 19:1523, Dec. 1959.
(23) Mason, A.S. and Greenbaum, D. Cushing's Syndrome and skin pigmentation. Brit. M.J. 2:445, Aug. 18, 1962.

Case I. Possible Pituitary Tumor.

[redacted]) - Cushing's Syndrome diagnosed in 1951 following a 5-year illness with hypertension, obesity, weakness, fatiguability, backache. Treated with courses of pituitary irradiation in 1951 and subtotal adrenalectomies in 1952. He became Addisonian and was maintained on small doses of cortisone. In 1954, recurrent episodes of ventricular tachycardia secondary to arteriosclerotic heart disease began. By late 1955, he had developed overt Cushing's Syndrome again, with accompanying bronze hyperpigmentation of the skin and purplish pigmentation of the buccal mucosa. Additional irradiation of the pituitary and adrenal areas was administered. Surgery was advised but not performed, primarily because of his precarious cardiac status. Diffuse blurring of vision was noted, but the fundi were clear and the sella was not enlarged in early 1957. He died at home in mid 1958. An autopsy was not performed.

Cushing's Syndrome may appear from the elaboration of ACTH or ACTH-like material from non-endocrine tumors of various sites. A rapid course with death before typical "Cushingoid" features appear, hyperpigmentation and severe hypokalemia and alkalosis and markedly elevated plasma and urinary 17-hydroxycorticoids are frequently noted. The hypokalemia and alkalosis result from the high cortisol levels. Aldosterone production is normal.

(24) Bagshawe, K.D. Hypokalemia, carcinoma and Cushing's Syndrome. Lancet 2:284, Aug. 6, 1960.
(25) Prunty, et al. Adrenocrotical hyperfunction and potassium metabolism in patients with "non-endocrine tumors" and Cushing's Syndrome. J. Clin. Endocrinol. 23:737, Aug. 1963.
(26) Liddle, G.W., et al. Nonpituitary neoplasms and Cushing's Syndrome. Arch. Int. Med. 111:129, April 1963.
(27) Jarrett, L., et al. Characterization by immunofluorescence of an ACTH-like substance in nonpituitary tumors from patients with hyperadrenocorticism. J. Clin. Endocrinol. 24:543, June 1964.

The degree of ACTH stimulation may be so great as to stimulate accessory adrenocortical tissue.

(28) Chaffee, W.R, et al. Cushing's Syndrome with accessory adrenocortical tissue. J.A.M.A. 186:799, Nov. 23, 1963.

Adrenal hyperfunction is common in patients with bronchogenic carcinoma and neoplasia is more common in patients with Cushing's Syndrome.

(29) Hymes, A.C. and Doe, R.P. Adrenal function in cancer of the lung, with and without Cushing's Syndrome. Am. J. Med. 33:398, Sept. 1962.
(30) Werk, E.E. Jr., et al. Further studies of adrenocortical function in patients with carcinoma of the lung. Am. J. Med. 34:192, Feb. 1963.
(31) Riggs, B.L. Jr., and Sprague, R.G. Association of Cushing's Syndrome and neoplastic disease. Arch. Int. Med. 108:85, Dec. 1961.

Case II. Cushing's Syndrome Secondary to Non-endocrine Tumor Production of ACTH.

[redacted] was a 50-year-old [redacted] male who was admitted to [redacted] in [redacted] 1963 for evaluation of a right upper lobe infiltrate. Weight loss for 3 months, marked polyuria with nocturia for 1 1/2 months and weakness for 1 month had been noted.

He was thin and weak. Wasting of the muscles of the shoulders and legs was obvious, but there were no Cushingoid features. Hyperglycemia (130 mg%), hypernatremia (150 mEq/L) and hypokalemia (2.4 mEq/L) were found. Urinary 17-ketosteroids were 33 and 55 mg/24 hours; urinary 17-hydroxycorticoids 43 and 69 mg/24 hours.

The diagnosis of small cell bronchogenic carcinoma was made and the patient expired from pulmonary insufficiency after surgery for a perforated gastric ulcer.

Tumor ACTH, measured by Dr. Liddle, was 0.435 mU/gm.

Case III. Cushing's Syndrome Secondary to Non-endocrine Tumor Production of ACTH. [redacted]) was a 52-year-old [redacted] male, admitted to [redacted] for evaluation of a pulmonary hilar mass, which was shown to be an oat cell carcinoma. Hypokalemia (2.5 mEq/L) persisted despite administration of as much as 120 mEq of KCl daily.

Urinary steroids were: 17-hydroxycorticoids - 60 mg/day, 17-ketosteroids - 50 mg/day, aldosterone - 12.7 µg/day. Urinary 17-HOCS increased from 68 mg/day to 85 mg/day after 50 units of ACTH intravenously.

The exact nature of the defect in the most common form of Cushing's Syndrome, bilateral adrenal hyperplasia, is unsettled but there is considerable evidence favoring a primary pituitary disorder with hypersecretion of ACTH. This in turn may reflect a hypothalamic disorder with excessive secretion of Corticotrophin Releasing Factor.

(32) Liddle, G.W. Tests of pituitary-adrenal suppressibility in the diagnosis of Cushing's Syndrome. J. Clin. Endocrinol. 20:1539, Dec. 1960.
(33) Jailer, J.W., et al. Studies in Cushing's Syndrome. II Adrenal weight-maintaining activity in the plasma of patients with Cushing's Syndrome. J. Clin. Invest. 36:1608, 1957.
(34) Nugent, C.A., et al. A possible explanation for Cushing's Syndrome associated with adrenal hyperplasia. J. Clin. Endocrinol. 20:1259, Sept. 1960.
(35) Davis, B.M.A. Blood corticotrophin in normal adults and in patients with Cushing's Syndrome. Acta endo. 45:55, Jan. 1964.
(10) Ney, et al.
(36) Fujita, T., et al. Clinical applications of urinary ACTH assay. J. Clin. Endocrinol. 23:143, Feb. 1963.
(37) Givens, J.R., et al. Absence of a normal diurnal variation of plasma ACTH in Cushing's disease. Clin. Res. 12:267, April 1964 (Abstract).
(38) Roginsky, M.S., et al. The pituitary-adrenal relationship is abnormal in Cushing's disease, normal in Addison's disease. J. Clin. Invest. 43:1287, June, 1964 (Abstract).

The possibility of a hypothalamic disorder was raised many years ago and supported recently.

(39) Heinbecker, P. The pathogenesis of Cushing's Syndrome. Medicine 23:225, 1944.
(40) Decourt, J. and Bernard-Weil, F. Dynamic investigation of two cases of Cushing's disease with pituitary adenoma by means of test with posterior pituitary extract combined with inhibition by dexamethasone. Presse méd. 72:379, Feb. 8, 1964. (from 1964-65 YearBook of Medicine, p. 659).

There is little evidence that the adrenal response to ACTH is abnormal in bilateral hyperplasia.

(41) Mulrow, P.J. and Cohn, G.L. Corticosteroid release and synthesis in vitro by adrenal slices from patients with Cushing's Syndrome. J. Clin. Invest. 40:1250, July 1961.
(42) Guignard-de Maeyer, J.A., et al. An alteration in cortisol metabolism in patients with Cushing's Syndrome and bilateral adrenal hyperplasia. J. Clin. Endocrinol. 23:127, Dec. 1963.

Table 2. The Effects of Cortisol in Excess as seen in Cushing's Syndrome

Type	Physiologic	Pathologic	Frequency
Carbohydrate	Gluconeogenesis	Abnormal G.T.T.	85%
	Inhibit peripheral utilization of glucose	Hyperglycemia	33%
Protein	Gluconeogenesis	Negative nitrogen balance	
	Increased catabolism	Muscle wasting and weakness	74%
	Decreased anabolism	Thinning of skin (striae)	60%
		Plethora	77%
		Osteoporosis	58%
Fat	Fat deposition	Obesity, moon facies	88%
		Centripetal redistribution	86%
		? Premature atherosclerosis	
Electrolyte	Sodium retention	Hypertension	85%
		Edema	57%
		Hypernatremia	34%
	Potassium secretion	Hypokalemia	15%
		Metabolic alkalosis	70%
	Water diuresis	Polyuria	32%
Cardiovascular	"Permissive" for pressor agents	? Hypertension	85%
Hematologic	Lysis of lymphoid tissue	Lymphopenia	66%
	? Stimulation of marrow	Neutrophilia	50%
	Destruction of eosinophils	Eosinopenia	90%
	Stimulate erythropoiesis	Polycythemia	20%
Mesenchymal	Inhibit fibroblast formation	Delayed wound healing	35%
	Anti-inflammatory action	Reduced resistance to infection	15%
		Masked inflammation	
	Decrease cartilage	Retardation of growth	
Bone	Inhibit osteoblastic activity	Osteoporosis	58%
	Decrease calcium deposition	Renal calculi	20%
Central nervous system	Lower excitation threshold	Psychoneurosis	50%
		Euphoria	46%
	(? Other effects)	Psychosis	5%
		Headache	40%
Gastrointestinal	Increase gastric secretion	Peptic ulcer	
Androgenic	Virilization	Hirsutism	73%
		Acne	54%
		Amenorrhea	77%

D. The clinical features of Cushing's Syndrome (Table 2).

1. Initial signs and symptoms (order of frequency):
amenorrhea, obesity, virilism, moon facies, hypertension, edema, striae.

2. Presenting signs and symptoms (order of frequency):
moon facies, obesity, hypertension, plethora, amenorrhea, fatigue, hirsutism, weakness, striae, easy bruising, osteoporosis, edema, buffalo hump, acne, ecchymoses.

3. Course of the disease if untreated.

a. Spontaneous remission rarely occurs.

b. Cause of death (order of frequency):
infection, cardiac failure, CVA, renal failure.

4. Less common manifestations.

a. Feminization in males (usually with carcinoma).

b. Peripheral neuropathy (Case VI).

c. Pregnancy.

(43) Soffer, L.J., et al. Cushing's Syndrome. Am. J. Med. 30:129, 1961.
(20) Plotz, C.M. et al.
(44) Soffer, L.J., et al. The Human Adrenal Cortex. Lea and Febiger, Philadelphia, 1961.
(45) Kreines, K., et al. Pregnancy in Cushing's Syndrome. J. Clin. Endocrinol. 24:75, Jan.1964.

Although specific laboratory tests are usually needed in one-half the patients suspected of Cushing's Syndrome, the diagnosis can be confirmed or excluded with a high degree of confidence and with an accuracy far greater than that provided by simple steroid screening tests such as single plasma or 24-hour urine 17-hydroxycorticoid determinations.

(46) Nugent, C.A., et al. Probability theory in the diagnosis of Cushing's Syndrome. J. Clin. Endocrinol. 24:621, July 1964.

From their analysis of 211 patients in whom the diagnosis was suspected, the following features were of greatest value in diagnosis.

	With Cushing's	Without Cushing's
Osteoporosis	64%	3%
Weakness (deep knee bend)	65%	7%
Generalized obesity	3%	62%
Ecchymoses	53%	6%
Hypokalemia	25%	4%
Central obesity	90%	29%
Plethora	82%	31%

These features were of less value:

	With Cushing's	Without Cushing's
Acne	52%	24%
Striae	46%	22%
Hypertension (diastolic > 105)	39%	17%
Edema	38%	17%
Leucocytosis	58%	30%
Hirsutism	50%	29%
Oligomenorrhea	72%	51%
Hematocrit > 49	37%	32%
Abnormal GTT	88%	77%
Headaches	41%	37%

Case IV. "Typical" Cushing's Syndrome.

[redacted] is a 23-year-old [redacted] woman, referred to Gyn Clinic for amenorrhea of 8 months duration. She had gained 40 pounds, with an obvious increase in abdominal girth and a "bloated look" to her face. Polyuria, slight facial hirsutism, loss of libido, headaches and easy fatiguability had also been noted.

On admission, she was normotensive, but had a classical Cushingoid appearance with striae over the flanks, axillae, and breasts.

Lab work revealed normal CBC, urine, FBS and serum electrolytes. The oral glucose tolerance test was abnormal. Steroid studies revealed:

Plasma 17-HOCS	0800	1500	After ACTH
(µg%)	24	15	55

Urine 17-HOCS	Control	0.5 Decadron	2.0 Decadron
(mg/day)	11.6-20.8	10.2	8.2

Urine 17-KS = 12.5 mg/day.

Bilateral total adrenalectomies were performed with the removal of hyperplastic glands weighing 7 and 8.5 grams. The patient was discharged on 30 mg cortisol and 0.1 mg Florinef per day. She returned once, feeling weak and nauseated and the dose of cortisol was increased to 40 mg per day. She has not been heard from since.

Case V. "Early" Cushing's Syndrome.

[redacted], a 52-year-old [redacted] male, was admitted to [redacted], because of compression fractures of L-1 and L-3 from severe osteroporosis. He had experienced low back ache for 4 years and weakness in both legs for about 6 months. His arms and legs had become thinner but no other changes in his body features were noted. On admission, the blood pressure was 160/100, the trunk was somewhat obese compared to the extremities and one small striae was found over the lower abdomen.

Lab work revealed normal CBC, urine, serum electrolytes and calcium. Steroid values were:

Plasma 17-HOCS	8 A.M.	4 P.M.
(µg%)	30.1	22.0

Urine 17-HOCS	Control	0.5 Dex	2.0 Dex
(mg/24 hr)	22.5	14.5	4.1
Urine 17-KS	22.7	16.6	9.1

Bilateral total adrenalectomies were performed. The adrenals weighed 7.7 and 10.9 grams and displayed diffuse cortical hyperplasia.

Case VI. Cushing's Syndrome with Diabetes and Peripheral Neuropathy.
[redacted] is a 33-year-old [redacted] woman who rather rapidly developed marked weakness of the right leg in 1960. Diabetes was diagnosed, but the weakness increased and involved the left leg as well. During the next year, classical features of Cushing's Syndrome appeared and the diagnosis was made in [redacted] 1961.

Initial therapy was pituitary irradiation (4,000 r) which was followed by a definite clinical and laboratory remission. However, the features of Cushing's reappeared about 6 months later and bilateral adrenalectomies were performed in late 1963. The adrenals were hyperplastic, microscopically, but weighed only 4.0 grams each. On substitution therapy of 25 mg of cortisol and 0.2 mg of Florinef, she has noted virtually complete disappearance of the stigma of Cushing's Syndrome, improvement of the peripheral neuropathy and return of the blood sugar to normal.

Representative steroid values:

	Urine 17-HOCS (mg/day)			Plasma 17-HOCS (µg%)	
	Control	0.5 Dex	20 Dex	8 A.M.	5 P.M.
[redacted] (before X-ray Rx)	13.6	7.4	3.5	34.0	
[redacted] (3 mos. after X-ray)	7.0			15.2	
[redacted] (6 mos. after X-ray)	14.9			34.3	
[redacted]	14.0			24.1	18.7
	14.5	2.4	0.6		
	14.8	4.7	4.8	32.6	
	15.4	4.5	3.3		

E. Laboratory procedures.

1. Basal studies.

a. Hypokalemia and alkalosis in patients with markedly elevated cortisol levels.

b. Urinary 17-ketosteroids of little value.

c. Urinary 17-hydroxycorticoids best routinely available procedure for confirmation, but

1) Obesity, thyrotoxicosis, drug intake, stress, etc., may give high values.

2) A few patients with Cushing's have normal values.

d. Plasma 17-HOCS.

1) Early A.M. level of little value.

2) Look for persistent "high"value in late afternoon or evening.

e. Urinary free cortisol - more difficult but much more sensitive and specific.

f. Cortisol secretion rates - even more difficult, but the most definitive

2. Stimulation tests.

   a. ACTH - despite "Harvard's" enthusiasm, of limited value in diagnosing the disease or differentiating the type.

   b. Metopirone - a hard way to obtain little information.

3. Suppression tests.

   a. Dexamethasone suppression of urinary 17-HOCS excretion has been well-standardized and found to be of great value.

      1) One and preferably 2 control specimens.

      2) 0.5 mg dexamethasone q 6 h for 2 days.

         a) Normal suppresses to below 2.5 mg/day.

         b) Cushing(any type) does not suppress.

      3) 2.0 mg dexamethasone q 6 h for 2 days.

         a) Adrenal hyperplasia suppresses below 50%.

         b) Adrenal neoplasia will not suppress.

   b. Plasma procedure has not been so well-established but is much simpler, less expensive and time consuming and has given good results.

      1) Control 7 A.M. - 9 A.M. plasma 17-HOCS.

      2) 1.0 mg dexamethasone at 10-11 P.M.

      3) Repeat 7 A.M. - 9 A.M. plasma 17-HOCS the next A.M.

      4) Normal - repeat (after dexamethasone) value below 7 µg%.

Results of urinary and plasma suppression tests on patients "suspected" and "proven" to have Cushing's Syndrome (PMH).

	Urinary 17-HOCS (mg/day)			Plasma 17-HOCS (µg%)	
	Control	0.5 mg dex	2.0 mg dex	Control	After dex
29 "suspected"	1.8-21.1 (above 12 in 4)	0-4.1 (below 2.5 in 26)	1.4-1.7	4.0-24.2	0-21.7 (below 7.0 in 26)
3 "proven"	11.6-14.9	7.4-10.2	3.5-8.2	24.0-31.0	15-18

(47) Ekman, H., et al. Plasma 17-hydroxycorticosteroids in Cushing's Syndrome. J. Clin. Endocrinol. 21:684, June 1961.

(48) Harris, J.J. and Crane, M.G. Urinary cortisol excretion as a test of adrenal cortical function. Metabol. 13:45, Jan. 1964.

(49) Beisel, W.R., et al. Physiology of urinary cortisol excretion. J. Clin. Endocrinol. 24:887, Sept. 1964.

(50) Cope, C.L. and Black, E.G. The reliability of some adrenal function tests. Brit. M.J. 2:1117, Nov. 28, 1959.

(51) James, V.H.T. and Caie, E. Determinations of urinary 17-hydroxycorticosteroids and their relation to cortisol secretion. J. Clin. Endocrinol. 24:180, Feb. 1964.

(32) Liddle, G.W.
(52) Slater, J.D.H., et al. Dexamethasone suppression test in diagnosis of Cushing's Syndrome. Brit. M.J. 1:1584, June 9, 1962.
(53) Brooks, R.V., et al. Appraisal of adrenocortical hyperfunction. Patients with Cushing's Syndrome or "non-endocrine" tumors. J. Clin. Endocrinol. 23:725, Aug. 1963.
(54) Harden, R.M. and Forrest, A.P.M. Cushing's Syndrome with atypical biochemical results. Acta endo. 46:256, June 1964.
(55) Silverman, S.R., et al. Failure of dexamethasone suppression test to indicate bilateral adrenocortical hyperplasia in Cushing's Syndrome. J. Clin. Endocrinol. 23:167, Feb. 1963.
(56) Nugent, C.A. Rate of adrenal cortisol production in response to maximal stimulation with ACTH. J. Clin. Endocrinol. 23:684, July 1963.
(57) Borushek, S. and Gold, J.J. Commonly used medications that interfere with routine endocrine laboratory procedures. Clin. Chem. 10:41, Jan. 1964.

F. Differential Diagnosis.

1. Exogenous obesity.

2. Pregnancy.

3. Androgenic excess.

   a. Acquired adrenogenital syndrome.

   b. Idiopathic hirsutism.

   c. Polycystic ovaries (Stein-Leventhal).

Case VII. Pregnancy with Hirsutism.

[redacted] is a 26-year-old [redacted] woman who was well until about 1 1/2 years before admission, when she began to gain weight (55 pounds in a year) and developed generalized and facial hirsutism. Menses stopped in [redacted] 1962. She was evaluated elsewhere in [redacted] 1962, and found to have urinary 17-ketosteroids of 26.8 mg/day and 17-ketogenic steroids of 47.1 mg/day. A dexamethasone suppression test was done, using 0.75 mg tid for 3 days, with the urine on the third day containing 17-KS = 10.8 mg and 17-ketogenic steroid = 9.2 mg.

She was admitted in [redacted] 1962, and found to have generalized obesity with trunkal predominance, many striae and profuse hirsutism. BP = 120/80.

Lab studies revealed a normal CBC, serum electrolytes and blood sugar. Steroid values were:

Urinary 17-HOCS		Plasma 17-HOCS	
Control	0.5 dex	8 A.M.	5 P.M.
3.5 mg/day	0.7 mg/day	20 µg%	9 µg%

The patient thought she might be pregnant. A KUB revealed a 6-7 month fetus. She delivered uneventfully in Feb. 1963. Thereafter, regular menses returned and the hirsutism was of much lesser degree.

(58) Thomas, J.P. and T.G. Flynn. Adrenal function in normal pregnancy and toxemia. Clin. Sci. 26:69, Feb. 1964.
(59) Poidevin, L.O.S. Striae gravidarum: Their relation to adrenal cortical hyperfunction. Lancet 2:436, Sept. 26, 1959.

Case VIII. Congenital Adrenogenital Syndrome.

[redacted] is a 21-year-old [redacted] woman who had neither menstruated nor developed feminine secondary sexual characteristics. Although "something wrong" was noted at her birth, no medical attention had been sought until her admission here. She had become increasingly hirsute, having to shave every day.

She was short, stocky and covered with hair. No breast development was noted. The clitoris was enlarged, but the internal genitalia, though immature, were normal.

Urinary steroids were 17-ketosteroids of 33 mg/day and pregnanetriol of 25 mg/day. On 30 mg of cortisol daily, these values fell to 7.4 and 2.2 mg respectively. After 2 months on this therapy, menses appeared and breast development began. She left for California and wrote that she was soon to be married.

(60) Brooks, R.V., et al. Post-pubertal adrenal virilism with biochemical disturbance of the congenital type of adrenal hyperplasia. Brit. M.J. 1:1294, April 30, 1960.

Idiopathic hirsutism may represent a mild form of acquired adrenal androgen overactivity.

(61) Lloyd, C.W, et al. Studies of adrenocortical function of women with idiopathic hirsutism: Response to 25 units of ACTH. J. Clin. Endocrinol. 23:413, May 1963.

(62) Kent, J.R., et al. Relation of urinary 17-ketogenic steroids to Porter-Silber chromogens in certain adrenal cortical disorders and "idiopathic" hirsutism. J. Clin. Endocrinol. 23:828, August 1963.

Case IX. Polycystic Ovaries.

[redacted] is a 35-year-old [redacted] woman who was seen by the Ob-Gyn department in 1959 because of secondary amenorrhea. Mild facial hirsutism was noted.

Control 17-ketosteroids and 17-hydroxycorticoids were normal.

Polycystic ovaries were found at abdominal exploration and wedge resections were performed. Post operatively, menses returned and have continued in a regular fashion.

Urinary 17-hydroxycorticoids measured in October 1964, were 9.8 mg/day with a fall to 2,2 mg/day on 0.5 mg of dexamethasone 2 6 h.

Considerable evidence is now available that ovarian androgen production is increased in patients with the polycystic ovary syndrome. Manifestations of androgenic excess are quite variable, but commonly include amenorrhea and hirsutism. Wedge resection of the ovaries is usually successful, presumably by decreasing the mass of androgen-producing tissue. Ovarian suppression by progestin-estrogen medication may be the best therapy unless pregnancy is desired.

(63) Leventhal, M.L. and Scommegna, A. Cause of Stein-Leventhal Syndrome. Am. J. Obstet. Gynec. 87:445, 1963.

(64) Short, R.V. and London, D.R. Defective biosynthesis of ovarian steroids in the Stein-Leventhal syndrome. Brit. M.J. 1:1724, June 17, 1961.

G. Therapy.

1. Bilateral hyperplasia.

a. Surgery.

1) Subtotal: Although still done in Boston, not the preferred approach.

2) Total: Life-long replacement therapy is required thereafter.

b. Pituitary irradiation.

1) External X-ray: With 4,000-4,500 r, 1/3 to 1/2 have remissions.

Soffer suggests unilateral adrenalectomy and X-ray. Proton beam therapy may be even better.

2) Pituitary implantation procedures: Gold - 198.

c. Drugs: Not yet satisfactory.

2. Adenoma - surgery.

3. Carcinoma.

a. Surgery usually too late.

b. Drugs - o,p' - DDD the best, but only palliative at best.

(64) Raker, J.W., et al. Surgical experience with the treatment of hypertension of Cushing's Syndrome. Am. J. Surg. 107:153, Jan. 1964.
(65) Roberts, M.S. and Lattimer, J.K. The surgical treatment of Cushing's Syndrome. J.A.M.A. 175:93, Jan. 14, 1961.
(43) Soffer, et al.
(66) Linfoot, J.A., et al. The alpha particle or proton beam in radiosurgery of the pituitary gland for Cushing's disease. New Eng. J. Med. 269:597, Sept. 19, 1963.
(67) Joplin, G.F., et al. Partial pituitary ablation. Lancet 2:1277, Dec. 9, 1961.
(68) Danowski, T.S., et al. O,p' - DDD therapy in Cushing's Syndrome and in obesity with Cushingoid changes. Am. J. Med. 37:235, Aug. 1964.

II. Exogenous Obesity.

A. Adrenal Function in Obesity.

1. Basal values.

a. Plasma levels are normal.

b. Urinary excretion often increased.

c. Cortisol secretion rates usually increased.

2. Suppression tests usually normal.

Obese individuals usually produce more cortisol and excrete more 17-hydroxycorticoids and 17-ketosteroids. When these values are corrected for body surfaces or expressed as per unit body weight, the levels come closer to the normal, but may still be elevated. Plasma levels, response to ACTH stimulation and suppression by dexamethasone are usually normal. The best way to be certain is to reduce the patient's weight and observe a fall in steroid levels.

(69) Szenas, P. and Pattee, C.J. Studies of adrenocortical function in obesity. J. Clin. Endocrinol. 19:344, Mar. 1959.
(70) Simkin, B. and Arce, R. Steroid excretion in obese patients with colored abdominal striae. New Eng. J. Med. 266:1031, May 17, 1962.
(71) Schteingart, D.E., et al. A comparison of the characteristics of increased adrenocortical function in obesity and in Cushing's Syndrome. Metabol. 12:484, June 1963.
(72) Migeon, C.J., et al. Study of adrenocortical function in obesity. Metabol. 12:718, Aug. 1963.
(73) Gogate, A.N. and Prunty, F.T.G. Adrenal cortical function in "obesity with pink striae" in the young adult. J. Clin. Endocrinol. 23:747, Aug. 1963.
(74) Baird, I.M. Urinary corticosteroid excretion in obese adults. Lancet 2:1022, Nov. 16, 1963.
(75) Dunkelman, S.S., et al. Cortisol metabolism in obesity. J. Clin. Endocrinol. 24:832, Sept. 1964.

(76) Jacobson, G., et al. Importance of body characteristics in the excretion of 17-ketosteroids and 17-ketogenic steroids in obesity. New Eng. J. Med. 271:651, Sept. 24, 1964.

Case X. Exogenous Obesity.

[redacted] is a 50-year-old [redacted] man referred here for evaluation of probable Cushing's Syndrome. During the past year, while remaining home during a lay-off from his job, he gained over 50 pounds and noted increasing weakness, polyuria and occasional pedal edema. His face became round and red. A urinary 17-HOCS (unknown lab) was 53.2 mg/day, a urinary 17-KS was 16 mg/day.

On admission, he was massively and generally obese, but there were no striae seen. BP = 160/100. Muscle strength was normal.

Lab work revealed normal CBC, urine, and electrolytes. The FBS was 154 mg%. Steroid values were 17-KS = 15.4 mg/day and:

Urinary 17-HOCS		Plasma 17-HOCS		
Control	0.5 mg dex	8 A.M.	4 P.M.	After dex
8.6	1.8	21.5	12.7	4.9

B. Therapy of Obesity.

1. Diet.

a. Nibbling - Gordon regimen.

b. Two a day.

2. Starvation.

Total starvation is an effective, and if properly supervised, safe way to lose weight. A sympathetic physician is probably the next best thing.

(77) Gordon, E.S., et al. J.A.M.A. 186:50, 1963.
(78) Seaton, D.A. and Duncan, L.J.P. Treatment of "refractory obesity" with a diet of two meals per day. Lancet 2:612, Sept. 19, 1964.
(79) Bloom, W.L. Fasing as an introduction to the treatment of obesity. Metabol. 8:214, May 1959.
(80) Drenick, E.J., et al. Prolonged starvation as treatment for severe obesity. J.A.M.A. 187:100, 1964.