

MEDICAL GRAND ROUNDS

March 28, 1963

"ANTERIOR PITUITARY FUNCTION AND DISEASE"

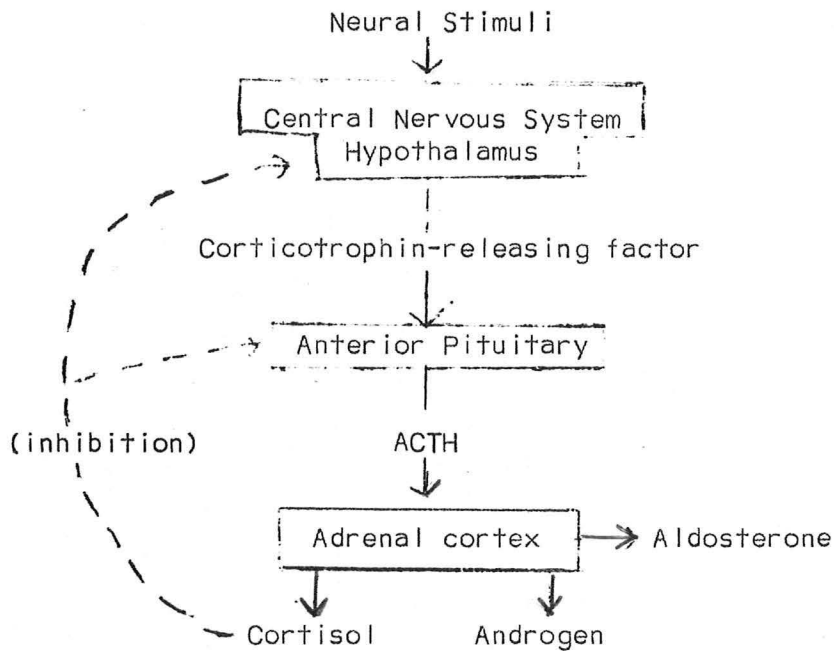


Fig. 1: The control of adrenal cortical function

<u>Control steroid</u> <u>Excretion</u>	<u>Water-load</u>		<u>Metopirone</u>
	<u>Control</u>	<u>After ACTH</u>	
Low	Decreased	Normal	No
Low-normal	Decreased	Normal	No
	Normal	-	Yes
Normal	No		Yes

Fig. 2: Assessment of Pituitary ACTH Secretion

ANTERIOR PITUITARY HORMONES

<u>Hormone</u>	<u>Physiologic actions</u>	<u>Assay</u>	<u>Available form</u>
1. Growth (GH)	<ul style="list-style-type: none"> a. Stimulation of cell growth and division b. Stimulation of protein synthesis with positive nitrogen balance c. Stimulation of cartilaginous bone with positive calcium balance d. Resistance to effects of insulin e. mobilization of fat (?) 	<ul style="list-style-type: none"> a. Immunochemical b. Bioassay c. Hydroxyproline excretion (?) 	Human G.H.
2. Follicle Stimulating (FSH)	<ul style="list-style-type: none"> a. Male: Maturation of germ cells and stimulation of sperm production b. Female: Maturation of follicle for ovulation and estrogen production 	Bioassay	Pregnant mares serum
3. Luteinizing (LH) or interstitial cell stimulating (LCSH)	<ul style="list-style-type: none"> a. Male: Stimulation of androgen production from Leydig cells b. Female: Release of ova, and formation of corpus luteum 	Bioassay	Chorionic gonadotropin
4. Prolactin or luteotropic (LTH)	<ul style="list-style-type: none"> a. "Growth hormone" effects b. Stimulation of progesterone production from corpus luteum c. Stimulation of growth of and milk secretion from the breast 	Bioassay	-
5. Thyroid stimulating (TSH)	<ul style="list-style-type: none"> a. Immediate stimulation of oxygen and glucose utilization by thyroid b. Release of thyroid hormone from colloid c. Stimulation of I uptake and incorporation 	Bioassay	Thyrotropin
6. Adrenocorticotrophic (ACTH)	<ul style="list-style-type: none"> a. Maintenance of anatomical integrity of adrenal b. Stimulation of cortisol and androgen synthesis c. Melanocyte stimulating effect d. Fat mobilizing effect 	Bioassay	ACTH, aqueous or gel
7. Melanocyte-stimulating (MSH)	Scattering of pigment granules within melanocytes	Bioassay	(ACTH)

Hypopituitarism (Simmond's Disease)

I. Etiology

- A. Hypophysectomy and stalk section (3)
 - 1) Carcinoma of breast or prostate.
 - 2) Diabetic retinopathy.
 - 3) Pituitary tumors.
- B. Necrosis, usually Post-partum (Sheehan's) or Diabetic (4)
- C. Traumatic infarction.
- D. Pituitary tumors and cysts (22).
 - 1) Chromophobe adenoma (15).
 - 2) Eosinophilic adenoma (5) ("burnt-out" acromegaly).
 - 3) Craniopharyngioma (1).
- E. Hypothalamic (Suprasellar) tumors.
- F. Infiltrative diseases: granulomas, infections, metastases (1).
- G. Pituitary dwarfism (2).
- H. "Functional"
 - 1) Severe malnutrition.
 - 2) Intestinal malabsorption.
 - 3) Prolonged exogenous corticosteroid therapy.

II. Clinical Features

- A. May be variable, instead of usual progression of gonadal, then thyroidal, then adrenocortical depression.
- B. Combination of myxedema, amenorrhea and a loss of libido strongly suggestive
- C. Etiology Should be Apparent by History or Skull Films For Sellar Size.
- D. Course After Hypophysectomy
 - 1) Adrenal insufficiency apparent within a day.
 - 2) Thyroid insufficiency.
 - a) PBI below 3.5 $\mu\text{g}\%$ often by 1 week.
 - b) Clinical evidence usual after 1 month.
 - c) 10 of 350 patients remained euthyroid
 - 3) Gonadal Insufficiency
 - a) Few "menopausal" symptoms.
 - b) Gonadotropin excretion zero by 3 weeks.
- E. Post-partum necrosis: Failure of lactation and menstruation.

Laboratory Evaluation of Pituitary Function

1. Gonadotropin

- A. Presence of menses best proof of normal function.
- B. Pap smear of vaginal epithelium for estrogen effect (cornification).
- C. Urinary gonadotropin assay (24 hour urine).

- 1) Normal: > 6 mouse units before menopause; >50 after.
- 2) Crude and expensive; may be 0 in normal, menstruating women.

2. Thyroid Stimulating Hormone

- A. No direct assay
- B. Indirect

- 1) BMR
- 2) PBI: normal 4.0 to 8.0 $\mu\text{g}\%$
- 3) RAI uptake (24 hour): normal 15 - 40%

- a) Control value usually 7 - 15% with pituitary insufficiency
- b) Repeat on day after 3 days of exogenous TSH - 10 units I.M. daily.

- (1) Uptake should at least double
- (2) May not increase with long-standing thyroid atrophy.

3. Adrenocorticotropin

- A. Clinical criteria of little value
- B. Control urinary steroid excretion

1) 17-ketosteroid (17-KS)

- a) May be depressed more than 17-HOCS with pituitary hypofunction.
- b) Normal range

- (1) Male: 8 - 22 mg/24 hr.
- (2) Female: 5 - 15 mg/24 hr.

2) 17-hydroxycorticoid (17-HOCS or, preferably, Porter-Silber chromogen).

- a) More meaningful than 17-ketogenic assay (17-KGS).
- b) Normal range

- (1) Male: 3 - 12 mg/24 hr.
- (2) Female: 2 - 10 mg/24 hr.

3) Affected by factors other than pituitary or adrenal dysfunction.

- a) Decreased steroid excretion
 - (1) Liver disease
 - (2) Renal insufficiency.
 - (3) Primary hypothyroidism.

b) Interference with assay techniques

- (1) 17-KS - meprobamate.
- (2) 17-HOCS - ASA, chloral hydrate, chloromycetin.

C. Steroid Excretion After Exogenous ACTH

- 1) Normal response is at least a tripling of 17-HOCS excretion.
- 2) With prolonged depression of adrenal function, prolonged stimulation needed.
 - a) 40 units ACTH gel tid for 3 days, or
 - b) 50 units aqueous ACTH in 500 ml D/W over 8 hours for 2 or 3 days.

D. Water-loading Test (after Oleesky)

- 1) Probably dependent upon direct effect of cortisol on renal tubular cell
- 2) Technique
 - a) Patient fasted overnight, remains in bed except to void.
 - b) Give up to 1,000 ml water orally in 20 minutes.
 - c) Have patient void every 20 minutes for next 2 hours.
 - d) Normal response: urine flow >4 ml/min
 - e) If response subnormal, repeat test after 3 days of ACTH; if response now normal, ACTH deficiency almost certainly exists.

E. Metopirone (SU-4885) Test:

- 1) Indications given in Fig. 2, Page 1
- 2) Mechanism
 - a) Adrenal cortex must be responsive.
 - b) Inhibition of 11-beta-hydroxylase enzyme activity, causing decrease in cortisol synthesis
 - c) Fall in circulating cortisol causes release of ACTH from pituitary via feedback system.
 - d) Increased ACTH stimulates adrenal cortex to synthesize 11-deoxycortisol (11-DO-CS) which is measured in urine
- 3) Technique: Oral test preferred to I.V.
 - a) Collect control 24 hour urine.
 - b) Give 750 mg (3 tablets) Metopirone every 4 hours for 6 doses, starting at 8:00 A.M.
 - c) Collect 24 hour urine on day of and day after Metopirone.
- 4) Interpretation
 - a) Preferable to measure 11-DO-CS alone, instead of all 17-HOCS. This can be done by simple modification of routine 17-HOCS technique.
 - b) Normal response: Increase of 11-DO-CS excretion of 7 mg or more above control excretion.
 - c) Abnormal test reflects deficiency of pituitary ACTH secretion after stimulation of feedback mechanism. This may not, however, mean that ACTH secretion will be deficient in response to stress.

F. Stress Tests (Insulin tolerance or Pyrogen)

- 1) Potentially harmful and unnecessary.
- 2) Not as sensitive as Metopirone.

IV. Therapy

A. Adrenal Corticoids

- 1) Hydrocortisone - 20 to 40 mg in divided dosage.
- 2) Salt-retaining hormones not needed.

B. Thyroid - 1 to 3 grains, after institution of adrenal corticoid replacement therapy

C. Sex Hormones

1) Androgens

- a) Male - 10 to 30 mg methyltestosterone sublingually daily.
- b) Female - 10 mg orally every other day.

2) Estrogens in younger women

- a) 0.1 mg diethylstilbesterol .
- b) May prefer cyclic therapy.

Factors Which Affect the 24-Hour RAI Uptake

- A. Depress.
1. Excess iodine or iodide
 - a. Medications:
 - 1) Vitamins
 - 2) Expectorants
 - 3) Topical Agents: Vioforin, Iodex, Floraquin
 - 4) Miscellaneous: Pathilon, Diodoquin
 - b. X-ray Contrast Media: interfere for at least one month
 - c. Foods: excess intake of fish, cauliflower, cherries
 2. Goitrogenic Foods: Brassica family (cabbage, turnips, etc.)
 3. Antithyroid Drugs
 - a. Thiourea derivatives
 - b. Aromatic compounds
 - 1) Sulfonylureas (mild depression)
 - 2) Para amino salicylic acid (PAS)
 - 3) Resorcinol
 4. Sedatives: Meprobamate (mild), Thiopental
 5. Exogenous Hormones:
 - a. ACTH and cortisone
 - b. Epinephrine (perhaps a factor with extreme agitation)
 - c. Thyroid: may occur with as little as 1 grain of desiccated thyroid for 8 days, and may take 2 - 3 months to disappear
 - d. Sex hormones: oral progestational agents (?)
 6. Miscellaneous Drugs: heavy metals (?), monovalent anions (chlorate, nitrate, thiocyanate), cobalt, phenylbutazone, Vitamin A, salicylates (large doses)
 7. Diseases
 - a. Congestive heart failure
 - b. Renal insufficiency (rarely)
 - c. Subacute thyroiditis (active)
 - d. Klinefelter's Syndrome
 - e. Old age (slight)
- B. Elevate
1. Iodine deficiency
 2. Rebound after withdrawal of antithyroid drugs
 3. Nephrotic syndrome
 4. Subacute thyroiditis (recovery phase), Hashimoto's Disease, non-toxic goiter (very rarely)
- C. No Effect
1. Malabsorption syndrome
 2. Mercurial diuresis
 3. Changes in glomerular filtration
 4. Sedatives: reserpine, pentobarbital.

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