MEDICAL GRAND ROUNDS

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NEW APPROACHES TO PITUITARY DISEASE

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CASE REPORTS

Hypothalamic Diseases

1. *Precocious puberty:* This boy began secondary sexual development at age 8 and was fully developed by 9. He had multiple cafe-au-lait areas of pigmentation, numerous radiolucent lesions in long bones and progressive visual loss. Optic gliomas were partially removed and the pituitary area irradiated. When last seen at age 15, his vision was grossly intact and he appeared to be well. He represents the fourth known case of Albright's syndrome (polyostotic fibrous dysplasia) in a male.

2. *Deranged wake-sleep pattern:* This 65 year old woman had a surgical hypophysectomy followed by pituitary irradiation for a large chromophobe adenoma. She was overtly hypopituitary before surgery, her hypothyroidism manifested by increased night-time sleep. Post-irradiation and surgery, while on full replacement therapy with cortisol and thyroxine, she has been unable to stay awake during the day or sleep at night despite use of multiple sedatives and attempts to keep her active during the day. Her appetite, body temperature and general status are normal.

Pituitary Diseases

1. *Normal pituitary function:* This 36 year old woman did not re-start menses after her last pregnancy 8 years ago. She developed increasing fatigue and emotional lability. Because of low urinary gonadotropins, the diagnosis of hypopituitarism was made and therapy begun with adrenal steroids, thyroxine, and estrogen. She was admitted for pituitary evaluation 6 weeks after all medications were stopped.

2. *Enlarged sella:* This 42 year old man was found to have an enlarged sella when a skull X-ray was taken after an episode of transient dizziness. Other than for slight loss of libido, he feels well. Physical exam, including visual fields, is negative.

3. *Hypophysectomy, incomplete:* This 37 year old man had a chromophobe adenoma removed by surgical resection in 1962 after sudden loss of vision in one eye. Post-operatively, 3,700 r were delivered to the pituitary area. For 6 years thereafter, he took 20 mg cortisol daily but no other replacement therapy while feeling well, maintaining normal libido and siring two children. For the past 2 years, he took no hormonal therapy.

4. *Empty sella:* This 46 year old woman was found to have an enlarged sella by X-ray in 1969 when being evaluated for headaches and tinnitus. Other than for hypertension and obesity, her physical exam was negative. Pneumo-encephalogram revealed air in the sub-arachnoid space extending well down into the markedly enlarged sella.

5. *Hypopituitarism following trauma:* This 30 year old man sustained a puncture wound into the left eye in an automobile accident. He was transiently unconscious and a craniotomy revealed severance of the left optic nerve. Post-operatively, he developed considerable polyuria and then became volume depleted and hypotensive. After large amounts of intravenous cortisol and fluids, he improved. Thereafter, daily therapy with cortisol, thyroxine and testosterone was begun.

6. *Hypophysectomy, complete:* This 43 year old man had a cryohypophysectomy in April 1971 for control of progressive diabetic retinopathy. While on replacement therapy of cortisone, 30 mg and l-thyroxine 0.2 mg daily, his daily NPH insulin requirement fell from 40 to 12 units.

   He suddenly lost control of his car at 5:30 PM without prior symptoms of hypoglycemia. Despite the stress of considerable trauma, the plasma sugar 30 minutes later was 55 mg%.

7. *Hypopituitarism, post-partum:* This 29 year old woman had profuse bleeding from a placenta praevia at the end of her fourth pregnancy. For the two weeks after an emergency C-section with transfusion of 4 units of blood, she remained weak, failed to lactate and developed nausea and vomiting. Prompt improvement followed adrenal steroid therapy and she was maintained on daily doses of cortisone, 25 mg, Florinef, 0.2 mg and cyclic estrogen therapy.

8. *Galactorrhea:* This 34 year old woman failed to menstruate following an uneventful pregnancy, 3 years ago. Lactation was considered normal in the immediate post-partum interval but continued intermittently thereafter. Though she remained otherwise fairly asymptomatic, she was treated with estrogens, thyroid and intermittent adrenal steroid therapy.

I. Control of Anterior Pituitary Function

As shown in Figure 1, the secretion of pituitary hormones is controlled by 2 basic mechanisms:

1) hypothalamic neurohormones
2) feed-back inhibition by the hormonal products (e.g., thyroxine) of the end organs (e.g., thyroid gland) affected by pituitary trophic hormones (e.g., TSH).

Though the second mechanism may be important in minute-to-minute regulation of pituitary function, the first is much more central to pituitary control. The release of these hypothalamic neurohormones is, in turn, affected by 3 mechanisms:

1) neural stimuli from the c.n.s., probably the mechanism for various circadian rhythms
2) direct feed-back inhibition by pituitary hormones, the short feed-back loop, via the short portal vessels
3) indirect feed-back inhibition, the long feed-back loop, by the hormonal products (cortisol) of the end organs (adrenal cortex) affected by pituitary trophic hormones (ACTH).

The blood supply to the pituitary provides a direct pathway for the hypothalamic neurohormones to reach the gland. (Slide 2)

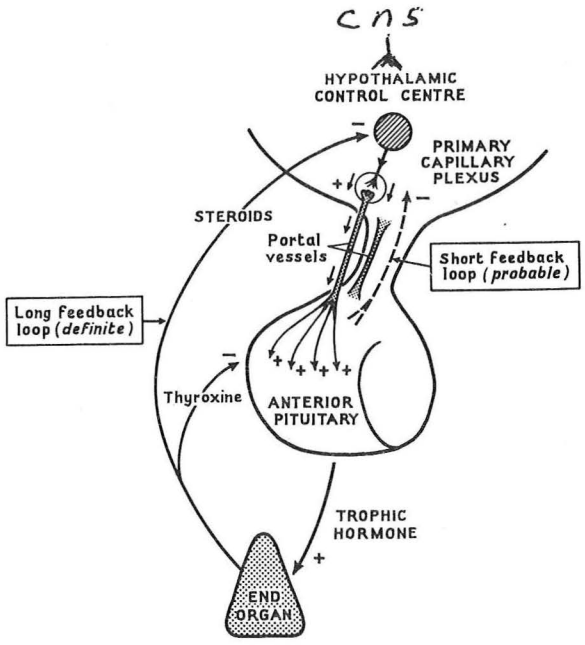


Fig. 1—Control of anterior pituitary function.
Releasing hormones are secreted into the primary capillary plexus of the portal vessels and pass along them to stimulate trophic-hormone release by the cells of the anterior pituitary. Negative feedback occurs from peripheral hormones (long loop) and trophic hormones (short loop) to the hypothalamus.

Hypothalamic Neurohormones
- Corticotropin Releasing Factor
- Growth Hormone Releasing Factor
- Thyrotropin Releasing Factor
- Luteinizing Hormone Releasing Factor
- Follicle Stimulating Hormone Releasing Factor
- Prolactin Inhibiting Factor
- Melanocyte Inhibiting Factor

Anterior Pituitary Hormones
- ACTH
- Growth Hormone
- TSH
- LH
- FSH
- Prolactin
- MSH

(from Catt, K. Lancet 1:827,1970)

TABLE I: Hypothalamic and Pituitary Hormones

Hypothalamic Neurohormone	Structure	Pituitary hormone	Pituitary content (µg)	Secretion rate (µg/day)	Plasma level (ng/ml)
Corticotropin R.F.		ACTH	300	10	0.03
Growth Hormone R.F.	11 amino acids	G.H.	8,500	500	1.0-5.0
Thyrotropin R.F.	Glu-His-Pro	T.S.H.	300	110	1.0-2.0
Luteinizing H.R.F.	9 or 10 amino acids	L.H.	80	30	0.5-1.5
Follicle-stimulating H.R.F.		F.S.H.	35	15	0.5-1.0
Prolactin inhibiting F.		Prolactin			undetectable
Melanocyte inhibiting F.		B-M.S.H.			0.02-0.11

A. Hypothalamic Neurohormones

These are of low molecular weight, from a few 100 to 2,000, and are active in minute concentrations. As shown in Table I, the approximate site of origin within the hypothalamus has been established for most of the neurohormones but the actual structure is known only for G.H.R.F. and T.R.F. The latter has been synthesized and is now available for clinical investigation. Its use will be described.

The effects of higher areas of the central nervous system upon hypothalamic neurohormone secretion are most clearly recognizable in 3 areas: circadian rhythms, reproduction and stress. These interrelations are obviously important for integration of hormonal secretion in meeting internal requirements, such as with prolonged fasting, as well as responses to environmental and emotional stimuli. These latter stimuli, including light and odor, greatly influence reproductive function in many mammals.

The rhythmic release of gonadotropins from the pituitary during the menstrual cycle is apparently due to an intrinsic rhythm of hypothalamic neurohormone secretion, which is present in the female and absent in the male. This difference reflects suppression of an inherent rhythmicity by testicular androgens. Androgen treatment of newborn female rats abolishes the rhythm, leading to tonic rather than cyclic release of gonadotropins, in turn causing infertility and polycystic ovaries similar to the Stein-Leventhal syndrome.

B. Brain Catecholamines and Hypothalamic Neurohormone Secretion

Nor-epinephrine and its precursor, dopamine, are thought to be the neuro-transmitters between the c.n.s. and the hypothalamus, stimulating the hypothalamic cells to secrete their neurohormones. In addition, they may enter the portal circulation with the neurohormones and modify pituitary response to them. The evidence for these actions includes:

1. Localized concentration of catecholamines in the hypothalamic and median eminence areas wherein the portal capillaries arise

2. Injection of norepinephrine into the third ventricle of the rat leads to G.H. release from the pituitary. John Porter has recently found enhanced releasing factor activity in portal venous blood after dopamine and nor-epinephrine injection into the third ventricle

3. Drug alterations of brain catecholamines are associated with altered pituitary

function:

a. l-DOPA, a precursor of dopamine which is able to cross the blood-brain barrier, increases G.H. release

b. Phentolamine, an alpha-adrenergic blocker, suppresses G.H. release

c. Chlorpromazine and other phenothiazines antagonize catecholamine action by either blocking adrenergic receptors or impairing permeability of storage granules. These drugs inhibit G.H. secretion and depresses various hypothalamic functions

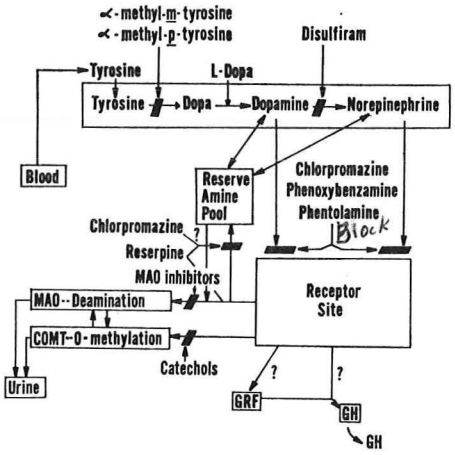


Fig. 2—Metabolic cycle of brain catecholamines, with some drugs that enhance or inhibit their activity.

COMT, catechol-O-methyl transferase; MAO, monoamine oxidase.

A schematic representation of these various drug effects upon brain catecholamines is shown in Figure 2, taken from reference 4.

References

1. Catt, K.J. Pituitary Function. Lancet I:827,April 18,1970.
The second of a series of 8 articles, "ABC of Endocrinology", all of which are clear and concise.

2. Burgus, R. and R. Guillemin Hypothalamic releasing factors. Ann. Rev. Biochem. 39:499,1970.
A good summary of the biochemistry and physiology of releasing factors as of 1970.

3. Frontiers in Neuroendocrinology, 1971, edited by L Martini and W. F. Ganong. Oxford Press, New York, 1971.
The second of a series with excellent reviews of the field. Included are chapters on Brain Monoamines by Anton-Tay and Wurtman, Pituitary blood flow and portal vessels by Porter, Kamberi and Grazia, and Mechanism of action of hypothalamic-hypophyseal stimulating and inhibiting hormones by McCann.

4. Sherman, L. and H. P. Kolodny. The hypothalamus, brain-catecholamines, and drug therapy for gigantism and acromegaly. Lancet I:682,April 3,1971.
An attractive presentation of the experimental evidence favoring the author's clinical use of chlorpromazine and medroxyprogesterone in the therapy of acromegaly.

C. The special case of Prolactin Inhibiting Factor (PIF) and Prolactin

1. PIF

Unlike the other hypothalamic neurohormones, the release of prolactin from the pituitary is normally inhibited by a hypothalamic neurohormone, called PIF. A small polypeptide, PIF is synthesized and secreted from the same area of the hypothalamus as LH-Releasing Factor. The release of prolactin from the pituitary occurs either by suppression of PIF or some interference with its reaching the pituitary, most easily demonstrated by section of the pituitary stalk. Stalk section invariably leads to increased prolactin release and frequently to galactorrhea. Among the inhibitors of PIF (and stimuli of prolactin release) are:

a. Hypothalamic lesions
b. Suckling
c. Estrogen therapy
d. Psychotropic drugs: reserpine, Mellaril, chlorpromazine (now used as a test for prolactin release)

Of both experimental and therapeutic interest is the effect of l-DOPA in inhibiting prolactin secretion, presumably by increasing the production of PIF, in the same manner as shown in Figure 2 for Growth Hormone Releasing Factor.

2. Prolactin

Despite clinical and experimental evidence that it existed as a separate hormone, not until recently was there adequate data to prove that prolactin was indeed distinct from growth hormone. As reviewed in the paper by Sherwood, the evidence is now over-whelming.

Though prolactin has not been completely purified or synthesized, a radioimmunoassay has been described. Its activity in blood can also be measured by a highly sensitive and specific assay involving induction of milk protein synthesis in organ cultures of mouse mammary-glands. (If that sounds difficult, consider that the previously used assay involved growth of the pigeon crop sac.)

Another lactogen, identified during pregnancy, is known to be of placental origin. Human placental lactogen (HPL) is similar to Growth Hormone chemically and in its prolactin activity.

3. Prolactin and galactorrhea

Most instances of galactorrhea can be related to structural or functional inhibition of PIF control upon prolactin release. Though elevated prolactin levels have not been documented in all these conditions, the availability of the new assay procedure should clarify the issue. The major causes of galactorrhea are:

a. Normal puerperium
b. Inhibition of PIF

1) Drugs: In addition to the psychotropics, Aldactone, Aldomet and thiazides.

2) Pituitary stalk section
3) Extra-sellar lesions: craniopharyngioma, post-encephalitis, pinealoma
4) Pseudocyesis

c. Inhibition of PIF or primary hypersecretion of prolactin

1) Pituitary dysfunction

a) Chiari-Frommel: post-partum with amenorrhea
b) del Castillo: with amenorrhea
c) Forbes-Albright: with pituitary tumor

2) Pituitary hyperfunction

a) Primary
(1) Acromegaly
(2) Cushings
b) Secondary
(1) Hypothyroidism
(2) Ovarian failure

d. Placental lactogen

1) Pregnancy
2) Hydatidiform male
3) Chorioepithelioma

e. Stimulation of anterior chest wall: trauma, chest surgery, burns, herpes zoster

References

5. Sherwood, L.M. Human prolactin. New Engl J Med 284:774,Apr.8,1971.

ectopic tumor bronchogenic

6. Turkington, R.W., L.E. Underwood and J.J. VanWyk. Elevated serum prolactin levels after pituitary-stalk section in man. New Engl J Med 285:707,Sept.23,1971.

7. Hwang, P., et al. Biosynthesis of human growth hormone and prolactin by normal pituitary glands and pituitary adenomas. J Clin Endocr 33:873,Nov.1971.

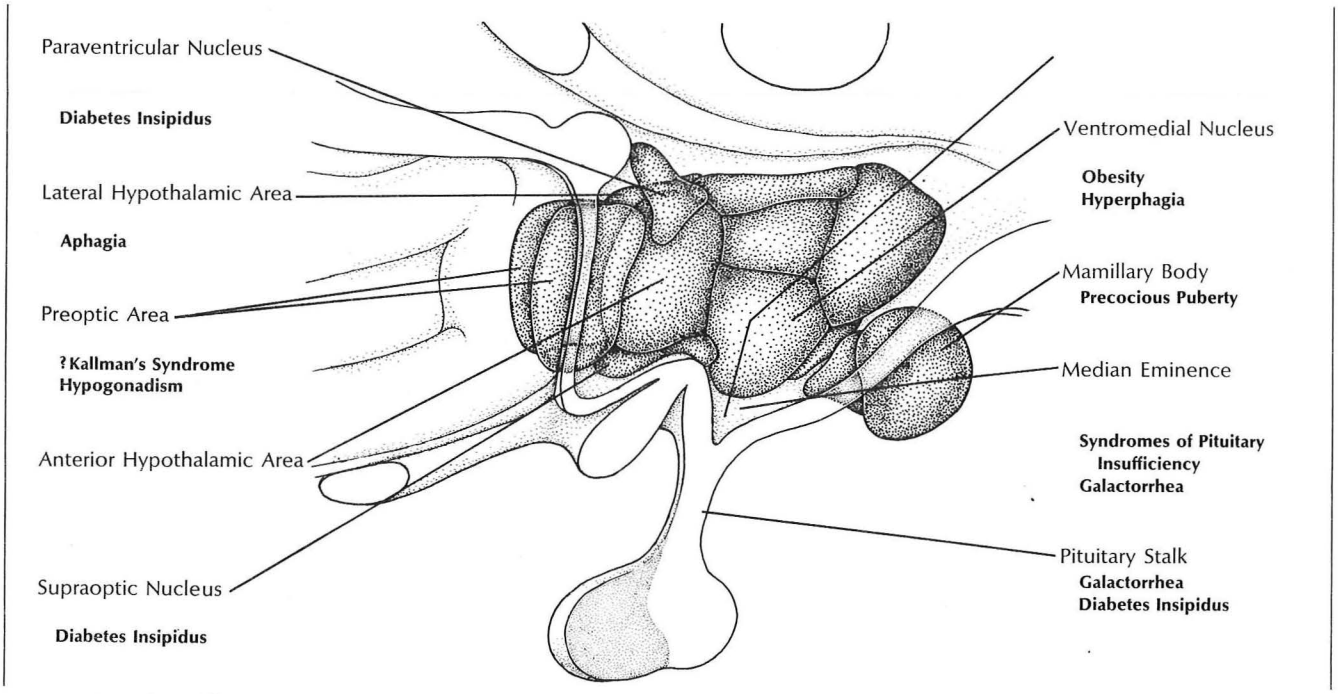
8. Kleinberg, D.L., G.L. Noel and A.G. Frantz. Chlorpromazine stimulation and l-DOPA suppression of plasma prolactin in man. J Clin Endocr 33:1, July 1971.

9. Malarkey, W.B., L.S. Jacobs and W.H. Daughaday. Levodopa suppression of prolactin in nonpuerperal galactorrhea. New Engl J Med 285:1160,Nov.18,1971.

Reference 8 suggests a therapeutic value for l-DOPA in galactorrhea associated with excess prolactin. Turkington, in an abstract at the Central Society meeting in November 1971, found excellent results in 14 patients, but Reference 9 reports minimal therapeutic value despite good suppression of prolactin.

D. Ectopic production of neurohormones

Upton, G.V. and T.T. Amatruda, Jr. Evidence for the presence of tumor peptides with corticotropin-releasing-factor-like activity in the ectopic ACTH syndrome. New Engl J Med 285:419,Aug.19,1971.
This is an intriguing report of the finding of corticotropin-releasing factor-like (CRF) activity in 4 tumors taken from patients with the ectopic ACTH syndrome. The syndrome is usually attributed to the direct synthesis of ACTH from the tumors but in these patients the tumors contained peptides which, when separated from the ACTH present, had no direct adrenal-stimulating activity but did have ACTH-releasing activity. Amino acid analysis indicated that the peptide was different in composition from ACTH.



II. Hypothalamic diseases

The above figure, taken from a paper by D. T. Kriger in Hospital Practice 6:127, November, 1971, demonstrates the probable location of hypothalamic disease associated with certain diseases in man. The types of pathology seen include:

1. Gliomas of the optic nerve
2. Craniopharyngiomas
3. Pinealomas
4. Meningiomas of the sphenoid ridge
5. Sarcoid
6. Aneurysms of the internal carotid

An intriguing possibility is that at least some of the steadily increasing number of isolated pituitary hormone deficiency states being uncovered may result from hypothalamic disease. Only with the availability of the hypothalamic neurohormones for testing, at this moment possible only for Thyrotrophin Releasing Factor, will it be possible to prove this mechanism. The first documented case of hypothalamic hypothyroidism has been reported by Pittman, et al. New Engl J Med 285:844,Oct.7,1971. This 19 year old man had been knocked unconscious at age 12 with subsequent development

of diabetes insipidus. He had overt hypothyroidism with undetectable blood TSH but a normal rise in TSH levels after TRF. Growth hormone responses to arginine and insulin were also deficient. We are currently testing 3 patients with TRF who had previously been diagnosed as having "isolated TSH deficiency."

Other endocrine diseases which seem likely to be secondary to hypothalamic disturbance include:

1. Kallman's syndrome: hypogonadism with low gonadotrophins, anosmia, color blindness and mental deficiency
2. Laurence-Moon-Biedl syndrome: hypogonadism, obesity, mental retardation, retinitis pigmentosa
3. Precocious puberty
4. Diencephalic syndrome of infancy
5. Cerebral gigantism
6. Diabetes insipidus
7. Galactorrhea with or without amenorrhea

It is likely that acromegaly and Cushing's disease may begin as hypothalamic disturbances with either no demonstrable enlargement of the pituitary or eventual formation of adenomas. The responses to hyperglycemia in acromegaly and to dexamethasone in Cushing's suggest that the pituitary is being driven by excessive hypothalamic neurohormone secretion, which will suppress if the long feed-back loop is pushed to a high enough level.

Some recent references to hypothalamic disease include:

10. UCLA Interdepartmental Conference. Trends in clinical neuroendocrinology. Ann Intern Med 73:783,Nov.1970.
Rather loosely constructed and occasionally misleading (e.g., as to feasibility of assays of releasing factors in blood) but contains a good review of the ophthalmologic and radiologic work-up of hypothalamic-pituitary disease.

11. Kahana, L., et al. Endocrine manifestations of intracranial extrasellar lesions. J Clin Endocr 22:304,March,1962.
14 patients with extrasellar lesions whose clinical features simulated primary pituitary disease.

12. Martin, M.M. Coexisting anterior pituitary and neurohypyseal insufficiency. Arch Intern Med 123:409,April,1969.
5 patients with various intra and extra-sellar lesions and evidences of anterior pituitary deficiency. Their hypothalamic involvement became apparent when they developed diabetes insipidus after institution of cortisol therapy.

13. Fox, R.H., et al. Hypothermia in a young man with an anterior hypothalamic lesion. Lancet 2:185,July 25,1970.
Repeated episodes of bizarre behavior, irritability and shivering were associated with hypothermia down to 28.9 degrees C. Tests of body temperature control were abnormal but all other hypothalamic-pituitary functions were intact. Necropsy revealed a localized degenerative lesion in the anterior hypothalamus.

14. Gailani, S.D., et al. Hypopituitarism due to localized hypothalamic lesion. Arch Intern Med 126:284,Aug.1970.
Diabetes insipidus and progressive loss of anterior pituitary function developed in a man with bronchogenic carcinoma. At autopsy, the pituitary was somewhat shrunken

in size but otherwise normal but there were bilateral hemorrhagic lesions in the hypothalamus.

15. Maddy, J.A. and W.W. Winternitz. Hypothalamic syndrome with hypernatremia and muscular paralysis. Amer J Med 51:394,Sept.1971.
A 28 year old obese, sexually immature, partially deaf school teacher developed recurrent episodes of weakness and paralysis during which his serum sodium went as high as 216 mEq/L. Testing revealed insensitivity of osmoreceptors to cellular dehydration and hyperosmolality but no evidence of diabetes insipidus.

16. Sherman, B.M., P. Gorden and G. di Chiro. Postmeningitic selective hypopituitarism with suprasellar calcification. Arch Intern Med 128:600,Oct.1971.
A 17 year old boy had short stature, sexual immaturity and diabetes insipidus. He had tuberculous meningitis at age 3 1/2 and developed polyuria at 10. He had normal Thyroid and adrenal function but deficiencies of gonadotrophin and growth hormone secretion.

III. Evaluation of Anterior Pituitary Function

A. Anatomic

1. Sellar size: Using lateral films taken at a distance of 36 inches, with care taken that the projection is a true lateral, the following measurements have been reported in normals:

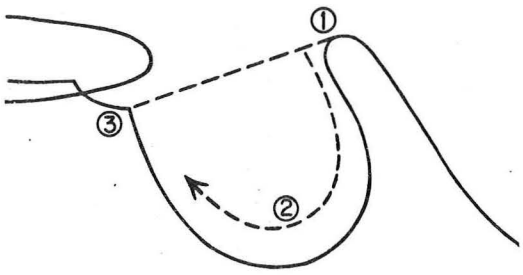


FIGURE 3. Method for measuring lateral area of sella turcica. The contour of the pituitary fossa is traced from the tip of the dorsum sellae [1] clockwise [2] to the tuberculum sellae [3] and then following a straight line back to the point of origin [1]. See Silverman (7) for variations in sellar configuration.

a. Length: distance from tuberculum sellae to the dorsum sellae, in mm.
   1) Males: 13.5 $\pm$ 1.8 (S.D.)
   2) Females: 13.3 $\pm$ 1.4 (S.D.)
b. Depth: distance from line joining above points to the lowest part of the sella
   1) Males: 7.2 $\pm$ 1.2
   2) Females: 7.1 $\pm$ 1.1
c. Lateral area: Using planimetry, Silverman has presented a reproducible method for area, as shown in Figure 3. The mean area is around 100 mm^2 with a SD of about 20.
d. Volume: Di Chiro and Nelson estimated the sellar volume from lateral and P-A views using a formula of 1/2 (width x height x length).

17. Acheson, R.M. Measuring the pituitary fossa from radiographs. Brit J Radiol 29:76,1956.

18. Silverman, F.N. Roentgen standards for size of the pituitary fossa from infancy through adolescence. Amer J Roentgen 78:451,1957.

19. Di Chiro, G. and K.B. Nelson. The volume of the sella turcica. Amer J Roentgen 87:989,1962.

20. Meador, C.K. and J.L. Worrell. The sella turcica in postpartum pituitary necrosis. Ann Intern Med 65:259,Aug.1966.
The sellar size was abnormally small in all 8 white and 2 of 6 black women with Sheehan's syndrome. Whether they shrunk after the postpartum hemorrhage or were small to begin with is unknown.

2. PEG and arteriography are being increasingly used for delineation of extrasellar spread of tumors, the recognition of intracranial aneurysms which may cause hypopituitarism and of the "empty" sella syndrome.

3. Visual disturbances: The presenting symptom in one-half or more of patients with pituitary tumors is ocular. Despite marked defects in visual fields, patients may be unaware of a loss of vision presumably because of the slow, and, usually, symmetrical progress. Diplopia and difficulty in focusing or judging position may be the initial symptom. Though the commonest defect is bitemporal hemianopsia a variety of defects can be found including scotomas, quadratic cuts, etc. Confrontation, best done with a red button, is quite accurate for most purposes. Palsies of cranial nerves 3, 4 and 6 may occasionally be seen. Sudden and total loss of vision may occur with hemorrhage into a tumor.

   Lyle, T.K. and P. Clover. Ocular symptoms and signs in pituitary tumors. Proc Roy Soc Med 54:611,July 1961.

4. Headaches are frequent but variable in nature and location.

B. Functional: The pattern of pituitary insufficiency is occasionally atypical and as adequate testing procedures have become available, more and more isolated and partial deficiencies are being uncovered. As a general rule, patients suspected of pituitary disease should have studies of all 4 trophic hormones which can now be obtained with relative ease and moderate cost. If done with care and planning, a complete workup can be completed in 3 or 4 days. Since various medications affect hormonal levels or assays in various ways, patients should be off all drugs for one month before workup, if possible. As an example, estrogens affect the blood level of growth hormone, cortisol, thyroxine and gonadotropins. Obviously a valid workup cannot be done on a patient taking estrogens.

   The only exception would be in patients given cortisol without proof of need, as after surgical removal of a chromophobe adenoma or treatment of post-partum collapse. Without stopping the cortisol and thereby exposing the patient to the danger of adrenal deficiency, the other trophic hormones can be assayed with accuracy.

The general approach to pituitary function:

21. Dingman, J.F. Pituitary function. New Engl J Med 285:617,Sept.9,1971.
(Much too brief and in-exact for clinical usefulness.)

22. Odell, W.D. Isolated deficiencies of anterior pituitary hormones JAMA 197:1006, Sept.19,1966.

23. Rabkin, M.T. and A.G. Frantz. Hypopituitarism: A study of growth hormone and other endocrine functions. Ann Intern Med 64:1197,June 1966.

Isolated hormone deficiencies: (See Odell above)

24. Martin, J.E., P.C. MacDonald and N.M. Kaplan. Successful pregnancy in a patient with Sheehan's syndrome. New Engl J Med 282:425,Feb.19,1970.
A woman with deficiencies of GH, TSH and ACTH but with enough gonadotropins to become pregnant.

24. Miyai, K., et al. Familial isolated thyrotropin deficiency with cretinism. New Engl J Med 285:1043,Nov.4,1971.
A good example of the value of pituitary testing in diagnosing the cause of hypothyroidism.

Special circumstances wherein pituitary function may be unexpectedly impaired:

1) Post-partum

26. Schneeberg, N.G., W.H. Perloff and S.L. Israel. Incidence of unsuspected "Sheehan's syndrome". JAMA 172:20,Jan.2,1960.

27. Sheehan, H.L. and J.P. Stanfield. The pathogenesis of post-partum necrosis of the anterior lobe of the pituitary gland. Acta Endocr 37:479,1961.

28. Sheehan, H.L. The frequency of post-partum hypopituitarism. J Obstet Gynec Brit Comm 72:103,1965.

The incidence of clinically recognizable hypopituitarism after significant hemorrhage is perhaps 10%, but, since destruction of over 95% of the gland is needed to induce overt panhypopituitarism, the incidence of partial deficiency is probably much higher.

2) Ante-partum in patients with diabetes mellitus

29. Schalch, D.S. and S.Z. Burday. Ante-partum pituitary insufficiency in diabetes mellitus. Ann Intern Med 74:357, March 1971.
Diabetic women are susceptible to pituitary necrosis without apparent cause.

3) Short stature

30. Goodman, H.G., M.M. Grumbach and S.L. Kaplan. Growth and growth hormone. New Engl J Med 278:57,Jan.11,1968.

4) Tall stature

31. Zimmerman, T.S., et al. Hypopituitarism with normal or increased height. Amer J Med 42:146,Jan.1967.
Presumably, growth hormone deficiency was not complete or occurred late.

5) Anemia

32. Pastore, R.A., J.W. Anderson and R.H. Herman. Anterior and posterior hypopituitarism associated with sickle cell trait. Ann Intern Med 71:593,Sept.1969.

33. Rodriquez, J.M. and N.T. Shahid. Erythrocyte 2, 3-diphosphoglycerate in adaptive red-cell-volume deficiency. New Engl J Med 285:479,Aug.26,1971.

The first a report of a rare cause of hypopituitarism,the second a study showing that the anemia of hypopituitarism is associated with no increase in red-cell 2, 3-DPG unlike patients with other types of decreased RBC mass. The decreased RBC mass in hypopituitarism is considered "adaptive" due to decreased tissue O_2 requirement.

6) Post-traumatic

34. Daniel, P.M., et al. Traumatic infarction of the anterior lobe of the pituitary gland. Lancet 2:927,Nov.28,1959.
Unlike our patient, these 5 patients did not sustain puncture wounds but rather transected the pituitary stalk from the force of the injury to the head.

7) Hyponatremia

35. Cooke, C.R., et al. Persistent antidiuresis with hypoaldosteronism and sodium wasting in hypopituitarism. Amer J Med 47:653,Oct.1969.

Hyponatremia in hypopituitarism is usually ascribed to poor renal excretion of water from either increased ADH secretion (Ahmed, et al. J Clin Invest 46:111,1967) or a specific defect in free water formation by a lack of glucocorticoid action on the renal tubule (Kleeman, et al. J Clin Invest 43:1641, 1964).

Salt wastage is not usually observed and aldosterone secretion, though lower than normal, responds appropriately to sodium depletion (Raiti, et al. Johns Hopkins Med J 122:229,1968). However aldosterone secretion may be impaired in some patients perhaps after long standing hypopituitarism with atrophy of the adrenal from the absence of ACTH. This paper suggests that decreased aldosterone levels may also reflect a "physiologic suppression" by volume expansion from water retention induced by excess ADH.

The "empty sella" syndrome

PEG is being done more frequently, in part because of the need for careful delineation of pituitary size before heavy-particle irradiation and cryohypophysectomy. With more PEG's, more instances of the "empty sella" syndrome are being uncovered.

The sella is ordinarily covered by a thick dural membrane, the diaphragm sella, through which the pituitary stalk passes. This opening in the diaphragm sella is usually small and CSF is not found in the sella. But in 20 to 40% of autopsied subjects, defects are present and the sub-arachnoid space, with CSF, extends into the sella. That this holds true in the living is suggested by the occurrence of CSF rhinorrhea in 20% of patients whose sella is punctured from below during transphenoidal hypophysectomy.

The suggested mechanisms for "empty sellas" include:

1) Ballooning by normal or increased CSF pressure through an open diaphragm sella
2) Subarachnoid adhesions which impair CSF drainage around the diaphragm
3) Rupture of intra-sellar cysts arising either from remnants of Rathke's pouch or degeneration of pituitary tumors
4) Post-irradiation or surgery of pituitary tumors

Patients with "empty sellas" have variable degrees of pituitary deficiency. Patients whose enlarged sellas are "empty" should not be treated with radiation or surgery.

36. Caplan, R.H. and G.D. Dobben. Endocrine studies in patients with the "empty sella syndrome". Arch Intern Med 123:611,June 1969.

C. Testing procedures for pituitary function

1. *Growth hormone:* As GH radioimmunoassays have become increasingly available assessment of its secretion has become the most popular test of pituitary function, particularly since the actual trophic hormone and not a product of its action is measured.

   a. Normal basal serum level: 0-4 ng/ml

   b. Stimuli used for clinical testing

      1) Insulin-induced hypoglycemia to a nadir below 50% of the initial plasma glucose is the most potent stimulus and will simultaneously provide a test for ACTH secretion by assays of plasma 17-OHCS.

      2) Arginine infusion, 0.5 Gm/Kgm B.W. over 30 minutes. The response is enhanced in men by prior administration of estrogen (Stilbesterol 2.5 mg bid for 2 days). We now do the insulin-arginine tests sequentially on the same day (technique of Penny, et al.) since about 15% of normals fail to respond to one or the other. (Figure 4, p15)

      3) Glucagon: not adequate

      4) Vasopressin: not adequate

      5) Pyrogen: not adequate

      6) Sleep-induced: a peak in G.H. normally occurs about 1 hour after start of sleep.

      7) l-DOPA: Recently found to induce a rise in G.H. in normals but we have shown it fails to work in obese or hypothyroid patients as well as arginine-insulin

TABLE II: Results of arginine-insulin tests for G.H. and ACTH

	Growth Hormone (ng/ml)			Plasma 17-OHCS (µg%)	
	Control	Arg. peak	Ins. peak	Control	Peak
Normal	1.7	37.6	92.0	12	44
Enlarged sella	1.2		>40.0	18	26
Hypox, incomplete	1.5	4.5	3.0	14	16
Empty sella	4.8	4.4	4.4	18	33
Hypox, complete	2.5	1.6		On cortisol	
Hypopit, post-partum	0.6	1.5		On cortisol	

growth hormone is most common deficiency in pituitary disease

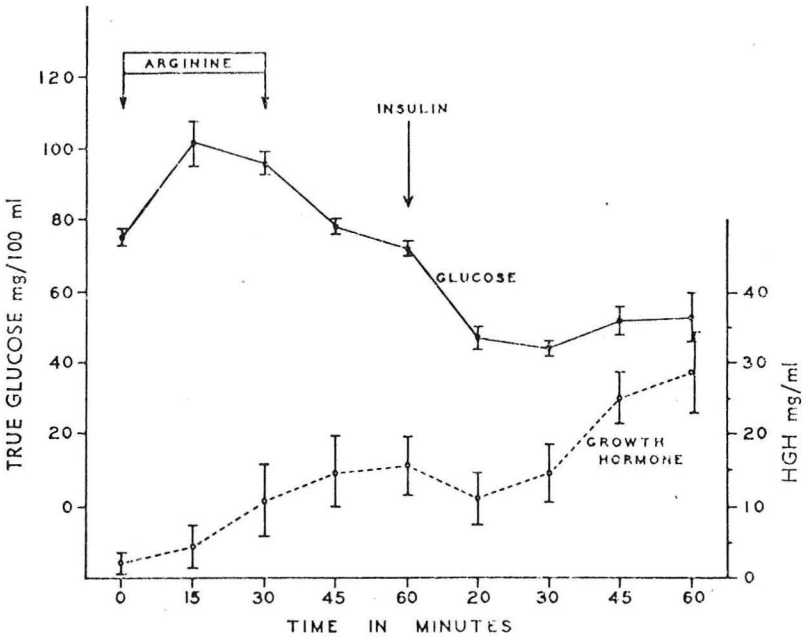


FIG. 4. Mean response ± SEM in 9 adult normals (5 males, 4 females) receiving arginine and insulin tolerance tests sequentially.

c. Factors affecting G.H. secretion

1) Increased by:

a) Fasting
b) Exercise
c) Stress, including emotional
d) Estrogens
e) ACTH

2) Decreased by:

a) Hyperglycemia
b) Hypothyroidism
c) Obesity
d) Progestogens in high doses
e) Corticosteroids

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2. *ACTH:* Assessment of ACTH secretion is indirect since neither an immunoassay for measurement of ACTH in blood nor the specific corticotropin-releasing-factor is presently available. ACTH bioassays and RIA are being used in a few labs but are not generally available. The Metyrapone test works well and has been modified to improve its clinical usefulness. A rise in plasma 17-OHCS of more than 5 µg% during insulin-induced hypoglycemia indicates an intact pituitary-adrenal system but is less sensitive than the Metyrapone test. Patients who fail to respond to these stimuli of endogenous ACTH secretion must be shown to have adrenal responsiveness to exogenous ACTH. Apparently the adrenal may lose this responsiveness after prolonged ACTH deficiency.

   a. Metyrapone test: By causing relatively selective inhibition of the last step in cortisol synthesis, 11-hydroxylation, this drug will lower plasma cortisol levels which in turn provokes the release of ACTH from the pituitary. The ACTH stimulates the adrenal to secrete increased amounts of cortisol precursors, mainly 11-deoxycortisol (11-DOCS or Compound S)

      1) Technique

         a) Standard: 750 mg Metyrapone every 4 hours x 6 doses with assays of urinary total 17-OHCS excretion, or better, 11-DOCS excretion. The rise in 11-DOCS excretion is usually maximal on the day after Metyrapone. A normal response is at least a doubling of total 17-OHCS excretion or a rise in 11-DOCS excretion of more than 7 mg/day. Plasma 11-DOCS can also be measured in 8 AM samples taken just before the start and 4 hours after the last dose

         b) Rapid: 2 or 3 grams of Metyrapone (30mg/Kgm BW) in a single midnight dose with measurement of urinary 11-DOCS excretion for the next 24 hours or, even better, plasma 11-DOCS levels at 8 AM the next morning. To ensure that the Metyrapone has been effective, a fall in plasma cortisol should be shown to accompany the rise in plasma 11-DOCS. (Figure 5, p17)

2) Problems

a) The adrenals of some patients with pituitary insufficiency may lose the capacity to respond to ACTH

b) Estrogen therapy impairs the action of Metyrapone

c) Patients with primary hypothyroidism may show a decreased response, presumably because of delayed action of the Metyrapone

b. ACTH test

1) Technique: A rise in plasma cortisol, measured by a specific competitive-binding assay, 30 or, even better, 60 minutes after a single I.M. dose of aqueous ACTH, 40 units is generally adequate. Even easier is to use synthetic ACTH, giving 0.25 mg I.V. immediately after obtaining the initial blood for cortisol (Figure 6)

2) Problems

a) Patients with hypopituitarism may have a slow or absent response to exogenous ACTH

b) Endogenous pituitary ACTH secretion and the resultant adrenal cortisol response is episodic. Changes in plasma cortisol may reflect these endogenous fluctuations and not just the response to exogenous ACTH

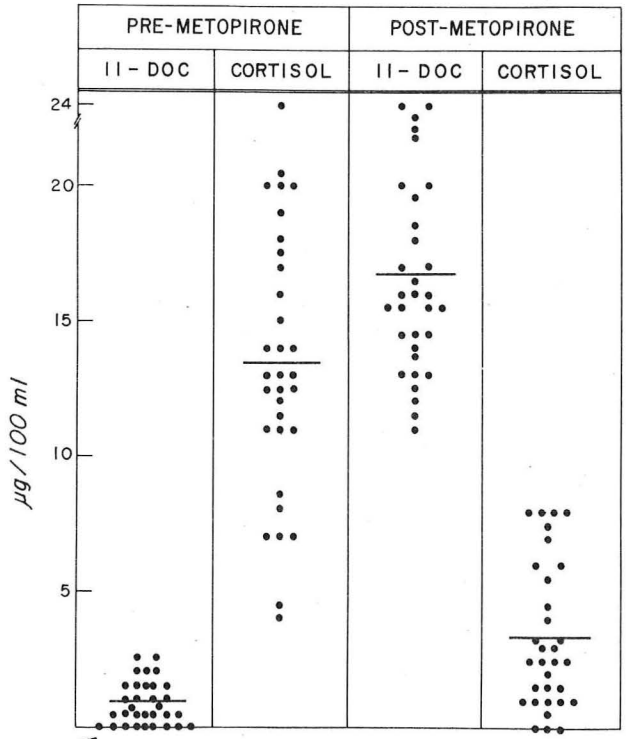
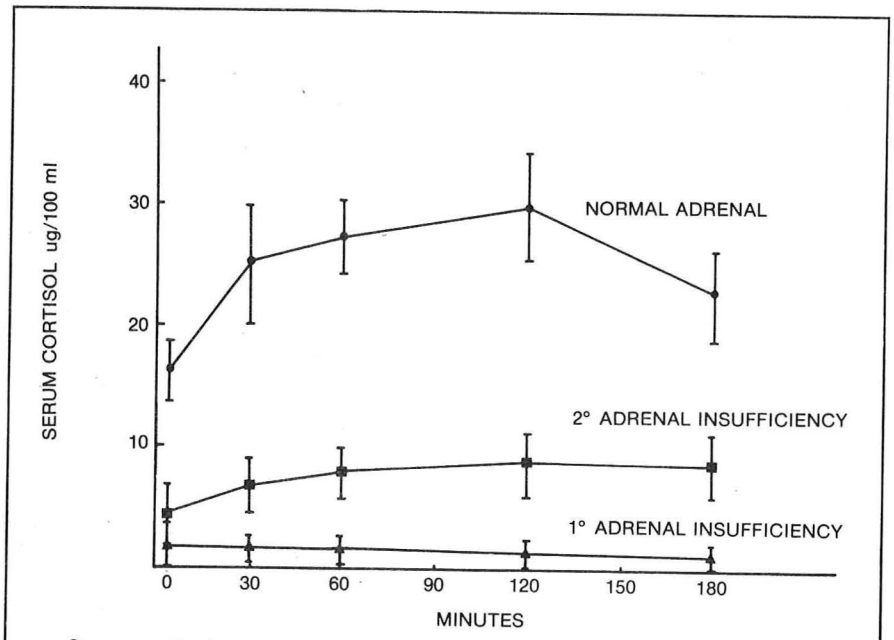


Figure 5. Serum 11-deoxycortisol (*11-DOC*) and cortisol before and after metyrapone (Metopirone®) administration, 750 mg every 4 hours for six doses in normal patients.
(Spark, Ann Intern Med 75:717, 1971)



Serum cortisol response to 0.25 mg of cosyntropin in normal subjects (n = 9), hypopituitarism (n = 8), and Addison's disease (n = 7). P < .01 between all means except zero times in primary and secondary adrenal insufficiency.

Figure 6. Speckart, et al Arch Intern Med 128:761, 1971

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3. *TSH:* The direct assay of the serum TSH response to Thyrotropin Releasing Factor (TRF) or Hormone (TRH) will soon become widely used. Synthetic TRH will be available for general clinical use. For the first time, a direct assessment of the pituitary response to a hypothalamic neurohormone is available. This procedure is particularly needed since no technique is now available to even indirectly assess pituitary TSH release. We have had to depend upon the demonstration of low thyroidal function and a response to exogenous TSH.

   The assay of serum TSH level itself should be of great value in the differential of primary hypothyroidism (with high TSH) and secondary hypothyroidism (with low TSH). (Figure 7)

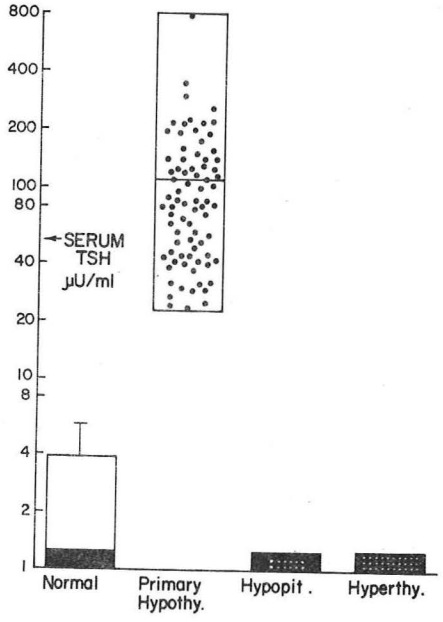

Figure 7. Serum TSH in Normal Subjects (Mean ± SD), 79 Patients with Primary Hypothyroidism, 12 Patients with Hypopituitarism (Hypopit.) and Secondary Hypothyroidism, and 30 Patients with Hyperthyroidism (Hyperthy.).

The dark areas indicate undetectable levels.

Hershman. New Engl J Med. 285: 997, 1971

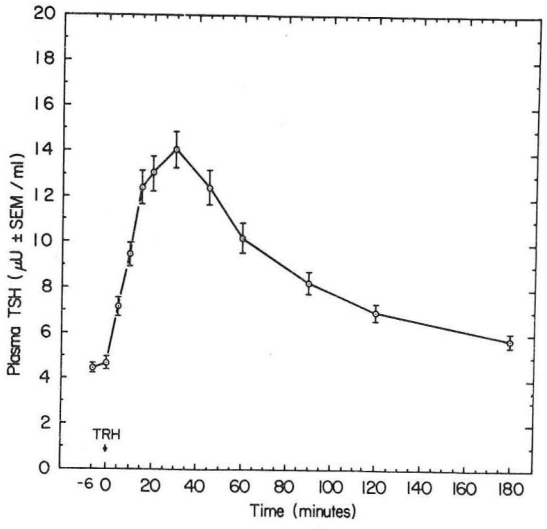

Figure 8. Mean Plasma TSH Responses to Intravenous TRH in 79 Normal Subjects.

The vertical bars represent one standard error of the mean. TSH is shown on the ordinate in microunits per milliliter, and time, in minutes, is indicated on the abscissa.

Anderson, et al New Engl J Med 285:1279, 1971

a. The TRH test for TSH

1) Serum TSH is obtained just before and every 15 minutes for one hour after the rapid injection of 400 µg of TRH

2) The normal response is shown in Figure 8. No significant side effects have been observed. Our initial results are shown in Table III.

TABLE III: TRH tests for TSH secretion

	Basal	15	30	45	60
Normal	1.5	1.5	2.6	8.5	12.5
Hypopit, complete	<1.5	<1.5	<1.5	<1.5	<1.5

b. The radioimmunoassay used for the measurement of TSH levels has not been sensitive enough to differentiate hypopituitary patients from normals. A modification has improved the sensitivity so that the level in enthyroid subjects (<0.4-3.1 µU/ml) can usually be distinguished from that of hyperthyroid patients (undetectable to 1.6). This improvement should allow separation of normals from hypopituitary patients.

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4. *Gonadotropins:* Both LH and FSH can be measured in plasma by radioimmunoassays which are becoming readily available. There is no need any longer to do 24 hour urinary gonadotropin assays.

Through human LH releasing factor has not been isolated or synthesized, purified porcine LH-RF has been shown to be effective in releasing both LH and FSH in normal subjects. In the interim, clomiphene may be useful as a clinical test for LH release, though the only report of its use involved measurements of urinary LH over 14 days.

a. Normal plasma LH levels

1) Children, prepubertal: 2.5-15 mIU/ml
2) Male, adult: 2.5-10
3) Female: Follicular phase: 6-30
Ovulatory phase: 60-120
Luteal phase: 7-10
Postmenopausal: >40

b. The basal LH level should be of value in the recognition of hypopituitarism in the postmenopausal female. In other patients, some stimulus, hopefully the LH-RF, will be required to assess pituitary secretory capacity. Rapid changes in plasma LH, similar to those in plasma ACTH, have been observed.

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TIMETABLE FOR WORKUP OF PITUITARY FUNCTION

DAY 1

1) At 12 midnight, i.e., 8 hours before obtaining the blood listed under 2), start collection of 24 hour urine for 17-OHCS and 11-DOCS.

2) Bloods for T_4 by isotope and T_3 resin uptake (large red top tube), plasma cortisol (small green), 11-DOCS (small green) and LH (small red).

3) Arginine-insulin provocative tests for growth hormone. Keep the patient in basal condition, in bed without food. Place an indwelling catheter for multiple blood sampling and wait at least 30 minutes before starting test. (Multiple venipunctures may stimulate growth hormone levels and interfere with interpretation.)

Time	Blood to be obtained		
	Growth Hormone (small red top)	Blood Sugar (gray top)	Cortisol (green top)
0	✓	✓	✓
	Infuse Arginine, 30 g or 0.5 g/Kg B.W., using a 5% solution, so that 600 ml (1 1/2 units) should be given to most adults. Infuse in 30 minutes.		
30			
60	✓		
90	✓	✓	
	Inject regular insulin 0.1 μ/Kgm B.W. or enough to lower blood sugar to below 50% of the basal level.		
120	✓	✓	
150	✓	✓	✓
180	✓	✓	✓

4) At 12 midnight, end first 24 hour urine collection; give 2-3 g of Metopirone P.O. with milk and small snack. Start collecting the second 24 hour urine for 17-OHCS and 11-DOCS.

DAY 2

1) Get blood for Cortisol and 11-Deoxycortisol at 8 AM.

2) TRH test for TSH: Obtain basal TSH (small red), inject 400 μg TRH and obtain bloods for TSH at 15, 30, 45 and 60 minutes.

3) Complete 24 hour urine for 17-OHCS and 11-DOCS at midnight.

DAY 3

Do 1 hour ACTH test, obtaining blood for cortisol before and 1 hour after 40 units aqueous ACTH I.M. or 0.25 mg synthetic ACTH I.V.