RECENT ADVANCES IN CLINICAL NEUROENDOCRINOLOGY

Medical Grand Rounds

August 11, 1977

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INTRODUCTION

Recent advances in neuroendocrinology have led to improved methods of diagnosis and treatment of neuroendocrine disorders. These advances include: (1) the structural identification, synthesis and clinical use of three hypothalamic "hypophysiotropic" peptides; (2) the discovery of the pulsatile nature of pituitary and steroid hormone secretion; (3) the use of Bromocryptine for the medical treatment of neuroendocrine disorders; (4) the development of hypocycloidal polytomography and the re-emergence of the transsphenoidal microsurgical technique. This review will attempt to show how these advances have led to improvements in the diagnosis and treatment of neuroendocrine disease.

1. Hypothalamic "Hypophysiotropic" Peptides (HHP)

The HHP are synthesized in the cell bodies of the tuberoinfundibular neurons. They are released at axon terminals which terminate on the capillaries of the portal vessels. These neurosecretory cells have been termed "neuroendocrine transducers" because they convert neural information from the CNS into endocrine messages. These peptides are also found in extrahypothalamic loci and may have additional functions that remain to be elucidated. The HHP bind to specific receptors on their pituitary target cell and exert their effect by activating cyclic AMP. The pituitary hormones and their corresponding hypophysiotropic hormones are shown in Figure 1. The amino acid sequences of the three HHP that have been isolated are shown in Figure 2.

Anterior Pituitary and Hypophysiotrophic Hormones

	Hypophysiotrophic Hormones	
Pituitary Hormone	*Name*	*Structure*
Thyrotropin (TSH)	Thyrotropin-releasing hormone (TRH)	Tripeptide
Adrenocorticotropin (ACTH)	Corticotropin-releasing factor (CRF)	Unknown
Luteinizing hormone (LH)	Luteinizing hormone-releasing hormone (LHRH) or	Decapeptide
Follicle stimulating hormone (FSH)	Gonadotropin-releasing hormone (GNRH)	
Growth hormone (GH)	Growth hormone-releasing factor (GRF)	Unknown
	Growth hormone release-inhibiting hormone* (somatostatin, GIH)	14 Amino acid peptide
Prolactin	Prolactin release-inhibiting factor (PIF)	Unknown
	Prolactin-releasing factor (PRF)†	Unknown

Figure 1

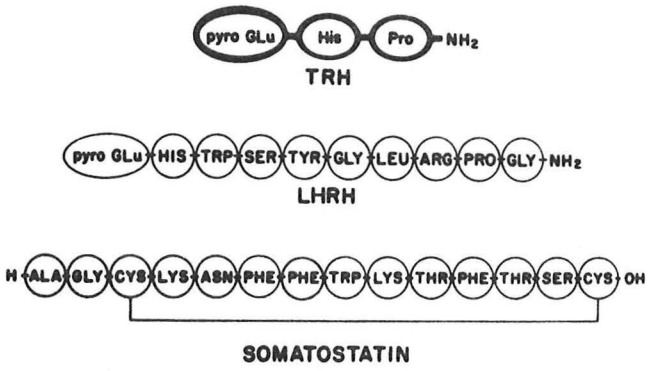

Figure 2

A. Thyrotrophin releasing hormone (TRH)

The intravenous administration of TRH results in the release of both TSH and prolactin (1). The minimum amount of TRH that results in the release of TSH also results in the release of prolactin (Figure 3).

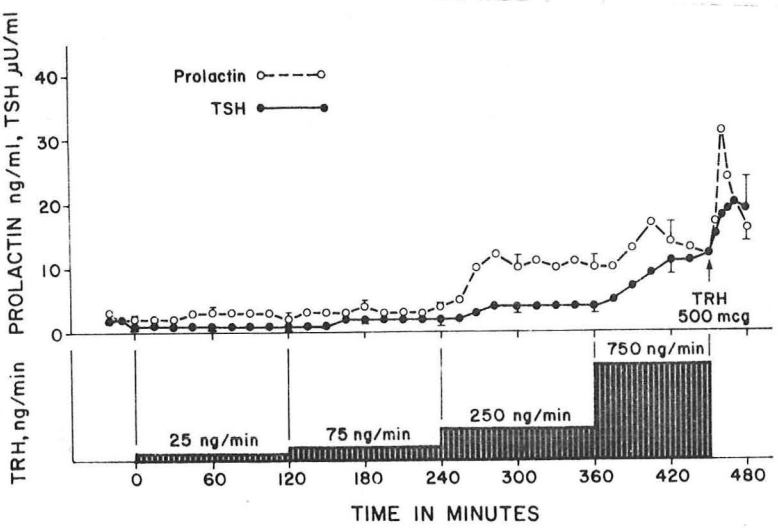

Figure 3

Prolactin and TSH responses to the continuous infusion of TSH followed by a 500µg bolus of TRH in 5 normal men. Vertical lines indicate SEM. (1)

The intravenous administration of TRH results in the rapid release of TSH (2). A maximal response can be obtained with 400µg (Figure 4). The TSH response to TRH usually reflects the existing state of the pituitary thyrotrope. In primary hypothyroidism, basal TSH values are increased and there is an hyperresponse to TRH. In hyperthyroidism, basal TSH levels are usually undetectable and the TSH response to TRH is blunted.

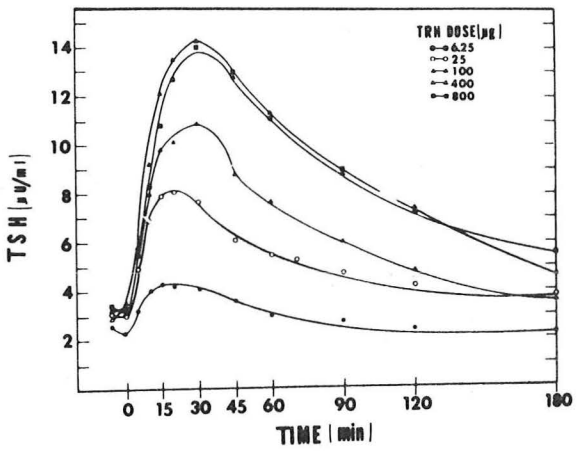

Figure 4

Dose response curve for TRH (2)

The normal TSH increment is between 5-25µU/ml, however, each laboratory should establish its own normal range since the immunoassays and standards used will vary. The peak response occurs between 15 and 45 minutes and a single 30 minute value will often suffice in most clinical situations. The results obtained from a single test should always be interpreted with caution, since the same individual's response can vary as much as 5µU or 65% on different days. In patients suspected of having hypothalamic disease (3), the test should be carried out the complete 3 hours, as these patients show a marked delay in the return of their TSH levels to control values (Figure 5).

In addition, some patients with hypothalamic hypothyroidism may not respond to a single injection of TRH, but will normalize their response after repetitive administration.

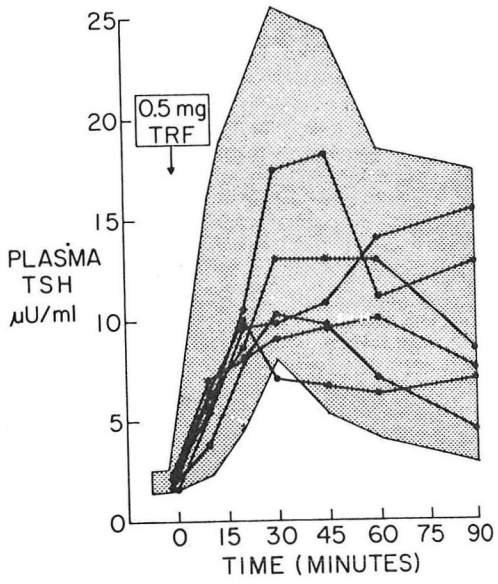

Figure 5

TSH response to TRH in idiopathic panhypopituitarism (5)

Patients with pituitary tumors who are euthyroid will have a normal response to TRH,while those who are hypothyroid will show a blunted response (4,5). In addition, there are several clinical disorders in which TRH elicits the release of growth hormone (Table 1). The mechanism responsible for this loss of specificity is unknown.

TABLE 1

CONDITIONS IN WHICH THYROTROPIN RELEASING HORMONE STIMULATES THE RELEASE OF GROWTH HORMONE

ANOREXIA NERVOSA

DEPRESSION

HYPOTHYROIDISM

PROTEIN CALORIE DEPRIVATION

UREMIA

ACROMEGALY

The prolactin response to TRH is maximal at 100μg. The normal increment is 20-40 ng per ml in men and 30-70 ng per ml in women (6,7). In most circumstances, the prolactin response parallels the TSH, however there have been some exceptions. In patients with isolated TSH deficiency, the prolactin rise is normal while the TSH rise fails to occur (8). Recently, patients with pseudohypoparathyroidism have been shown to have absent prolactin responses to TRH in the presence of normal TSH responses (9). The question of whether TRH is a physiologic prolactin releasing hormone (perhaps one of several) remains unsettled. Clearly, there are physiologic circumstances where the release of TSH occurs without prolactin and prolactin release without concomitant TSH release (Table 2).

TABLE 2

	TSH Release	Prolactin Release
Neonatal period	+	–
Cold exposure	+	–
Hypothyroidism (primary)	+	±
Sleep release	–	+
Pregnancy	–	+
Suckling	–	+

The release of TRH for diagnostic use six months ago has made this the first HHP to be used by the medical community. I have listed some of the possible indications for its use in diagnosis and treatment of thyroid disease.

TABLE 3

Indications for TRH Test

A. Diagnosis
1. Borderline hypothyroidism with high normal or slight elevation of basal TSH.
2. Differentiation of hypothalamic from pituitary hypothyroidism.
3. Borderline cases of hyperthyroidism, T_3 toxicosis and euthyroid Graves' disease.

B. Treatment
1. Adjusting dose of T_4 in patients who require maximal TSH suppression with minimal dose.
2. Assessment of pituitary TSH reserve in patients with pituitary or hypothalamic disease.
3. Testing completeness of suppression in patients with non-toxic goiter.
4. Testing for incipient hypothyroidism in treated hyperthyroid patients.

B. Luteinizing hormone-releasing hormone (LH-RH)

LH-RH stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). It has also been shown to modify sexual behavior by a non-pituitary mechanism (10). At the present time there is no convincing evidence to indicate the existence of a separate FSH releasing hormone. The disparate responses of LH and FSH to LH-RH can be explained by differential sensitivity of LH and FSH to the suppressive effects of gonadal hormones acting at the pituitary level. The LH response reaches a peak at 30 minutes and returns to control values by 3 hours. The FSH response occurs more slowly and is of lesser magnitude than the LH response. The FSH levels also take longer to fall to baseline levels because of the longer half-life of this glycoprotein. Maximal responses are achieved with 10-50μg, but responses that simulate endogenous secretory spikes occur at much lower amounts (11).

Studies utilizing a constant infusion of LH-RH in adults showed that the LH response is biphasic while the FSH response is monophasic (Figures 6 and 7).

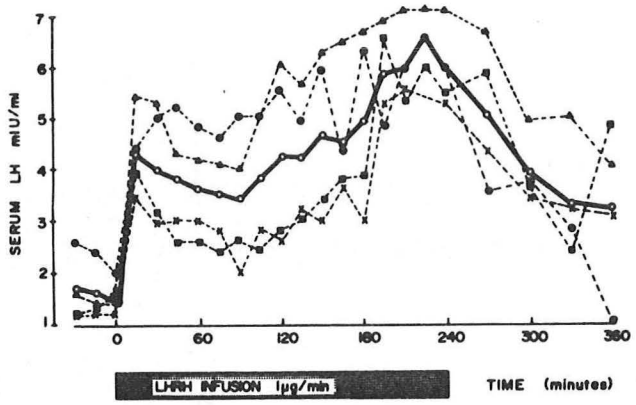

Figure 6

LH response to constant infusion of LH-RH (12)

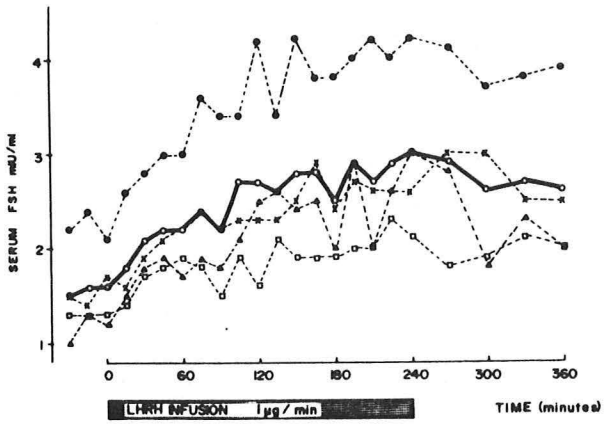

Figure 7

FSH response to constant infusion of LH-RH (12)

The initial phase of the biphasic LH response is believed to represent readily releasable hormone (storage) while the second phase has been felt to represent newly synthesized hormone (12). Since LH and FSH release are almost certainly activated by pulsatile LH-RH release, it is probably more "physiologic" to administer this agent as a bolus or as multiple short pulses, than by a constant infusion.

Studies of LH and FSH responsiveness to LH-RH in children showed an important maturational change as well as a sex difference (Figures 8 and 9). Prepubertal children show minimal LH release which gradually increases as sexual maturation progresses until the maximum response of adulthood is achieved. The FSH response in prepubertal girls is greater than the response in boys during all stages of life (13).

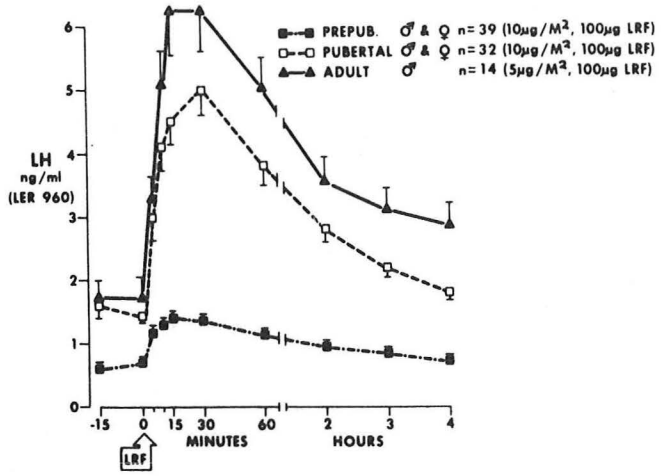

Figure 8

The LH response to LH-RH during puberty (13)

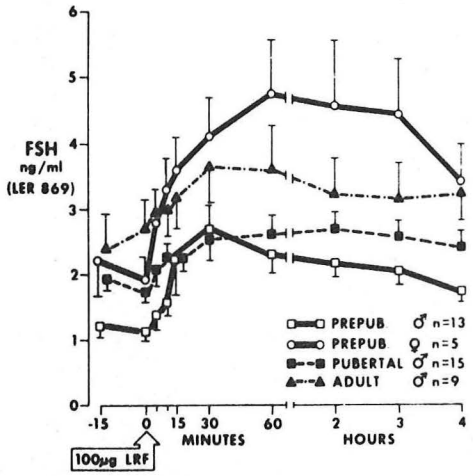

Figure 9

The FSH response to LH-RH during puberty (13)

LH-RH administration to menstruating women showed a change in the LH and FSH responses during different phases of the menstrual cycle (14). The maximum response occurs during the pre-ovulatory phase. This augmentation is in part the result of rising levels of estradiol due to follicular maturation. The repetitive administration of LH-RH has demonstrated a self-priming effect, resulting in greater amounts of LH release with each successive LH-RH pulse. In most clinical situations, the acute response to LH-RH will reflect endogenous LH-RH secretion. There are circumstances where the repetitive administration of LH-RH will be required to release LH and FSH. This has been found in patients with idiopathic hypogonadotropic hypogonadism and anorexia nervosa (15).

The availability of LH-RH for chronic administration will permit the initiation of puberty and spermatogenesis in patients with IHH as well as the induction of ovulation in patients with anorexia nervosa and weight related disorders. Recently, anomalous growth hormone responses after LH-RH have been reported in patients with acromegaly (16). The significance of this aberrant response is not known.

C. Somatostatin (SS or SR-IF)

Studies in humans have shown that this tetradecapeptide is a potent inhibitor of growth hormone release resulting from both pharmacologic and physiologic stimuli (17). In addition, SS can also inhibit the release of gastrin, insulin, glucagon and renin in normal subjects. There has been no convincing evidence that SS affects the release of ACTH, LH, FSH and prolactin in normal subjects. Recently, Tyrrell et al showed that SS inhibits ACTH secretion in patients with Nelson's syndrome (18). Somatostatin has also been shown to inhibit growth hormone secretion in acromegaly (19,20). The effects of SS on arginine and L-Dopa induced growth hormone release are shown in Figures 10 and 11 (21).

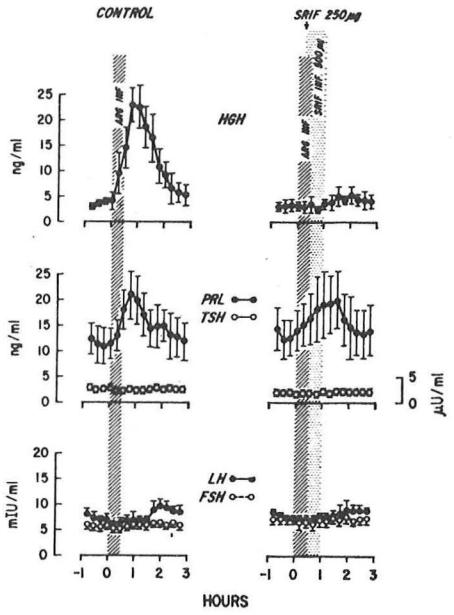

Figure 10

The effect of Somatostatin on Arginine induced growth hormone release (21)

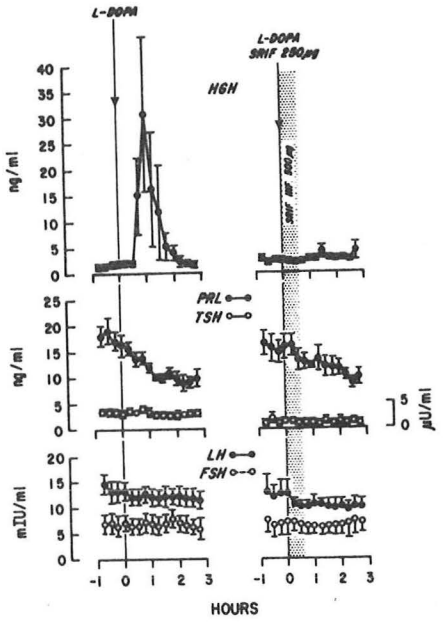

Figure 11

The effect of Somatostatin on L-Dopa induced growth hormone release (21)

II. The Physiologic and Pathophysiologic Control of Prolactin

The development of an homologous radioimmunoassay for the measurement of human prolactin has resulted in major advances in our understanding of its regulation in both normal subjects and hyperprolactinemic patients. Prolactin secretion is markedly augmented during nocturnal sleep and daytime naps (22,23). This augmented release of prolactin during sleep occurs independently of TSH release (Figure 12).

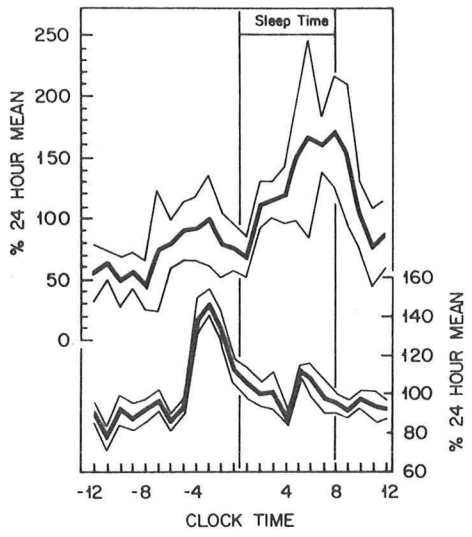

Figure 12

24-hour prolactin and TSH secretory patterns

During pregnancy, prolactin secretion is augmented, but the nychtohemeral rhythm is preserved. Suckling is a potent stimulus for prolactin release and can maintain elevated 24-hour mean prolactin levels for prolonged periods during the late post-partum period. The function of prolactin in non-lactating subjects is unknown. Recently, several groups have suggested that prolactin may stimulate adrenal androgen synthesis. Patients with elevated prolactin levels were shown to have increased plasma dehydroepiandrosterone sulfate levels and elevated urinary DHEA levels (24). These abnormalities return to normal after correction of the hyperprolactinemia .

Prior to the prolactin radioimmunoassay, galactorrhea-amenorrhea syndromes were classified according to the clinical setting in which they occurred and whether or not they were associated with a pituitary tumor (Table 4).

TABLE 4

Galactorrhea-Amenorrhea Syndromes

Syndromes	Definition
Chiari-Frommel	Persistent post-partum galactorrhea-amenorrhea
Argonz-del Castillo	Spontaneous galactorrhea-amenorrhea
Forbes-Albright	Pituitary tumor occurring either post-partum or spontaneously

Hyperprolactinemia can be associated with a failure to initiate puberty, galactorrhea with or without amenorrhea, amenorrhea without galactorrhea, impotence and rarely gynecomastia. The most important pathologic entity is the prolactin secreting pituitary tumor. Approximately 70% of "non-functioning" chromophobic tumors have been shown to be prolactin secreting (25). Hyperprolactinemia is also an important cause of unexplained amenorrhea (26). The differential diagnosis of hyperprolactinemia is listed in Table 5.

TABLE 5

Hyperprolactinemia

A. Physiologic
   1. Pregnancy
   2. Lactation
B. Pharmacologic
   1. Reserpine
   2. Phenothiazine
   3. "Post-Pill"
   4. α-Methyldopa
C. Pathologic
   1. Pituitary microadenoma
   2. Pituitary macroadeoma
   3. Pituitary mammotrophic hyperplasia
   4. Hypothalamic tumor
   5. Hypothyroidism
   6. Acromegaly
   7. Addison's disease
   8. Ectopic ?

A. Diagnosis of Prolactinoma

The persistent unexplained elevation of serum prolactin should alert one to the presence of a prolactinoma. If the plain film of sella turcica is normal, polytomography should be done. The hypocycloidal motion of the Polytome permits tomographic cuts of the sella turcica at 2 mm intervals. Pituitary microadenomas can be detected as "blistering" abnormalities on the lateral tomograms. The finding of a microadenoma radiologically does not predict the true size of the intrasellar lesion. In a recent review of 53 cases of proven pituitary tumors, 50 of 53 showed abnormalities on their lateral tomograms. The frontal tomograms were abnormal in only 20 of the 53 patients. The frontal tomograms were normal in patients with abnormalities in the antero-inferior region of the sella, an area where abnormalities are more readily detected on lateral tomograms. In those patients with localized abnormalities, the anterior region of the sella was affected in 80% of the patients (27).

Recently, McKeel and Jacobs reported 5 patients with hyperprolactinemia that was caused by mammotrophic hyperplasia of the pituitary (28). The hyperplasia of the lactotropes was demonstrated by immunoperoxidase techniques. The incidence of this disorder is not known, but it may be the etiology in patients with persistent hyperprolactinemia in whom a discrete pituitary tumor cannot be found.

B. Treatment of Prolactinomas

1. Surgery

The treatment of prolactin secreting tumors is still an area of controversy. This in part relates to the lack of data relating to the natural history of this disorder. In women with hyperprolactinemia-amenorrhea and a pituitary tumor desirous of fertility, surgical extirpation by an experienced surgeon can be performed relatively easily with little morbidity. Induction of ovulation prior to removal of the tumor is not without risk, since the hormonal milieu associated with pregnancy can result in an increase in tumor size and visual impairement. There have been at least 10 reported cases of progressive, significant visual impairment during pregnancy in patients harboring pituitary tumors. Three of these patients required surgical intervention to prevent blindness. All the patients who developed visual impairment had abnormal sella tomograms prior to the induction of ovulation (29). It seems prudent to treat all patients with prolactin secreting tumors surgically prior to the induction of ovulation. In patients with small pituitary tumors that can be removed easily, ovulatory menstrual cycles will usually return spontaneously.

2. Bromocryptine

The demonstration that dopamine is a potent suppressor of prolactin release has raised the possibility that this monoamine may be P.I.F. (30). Since dopamine restrains prolactin secretion, any drug that de-

creases its effective concentration at the receptor can result in hyperprolactinemia and galactorrhea (Figure 13). The administration of L-Dopa results in the acute lowering of prolactin levels, however, attempts to suppress prolactin for long periods with L-Dopa have been uniformly unsuccessful (31).

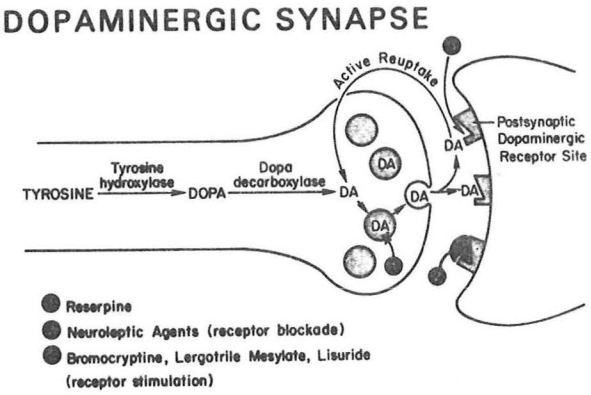

Figure 13

The site of action of drugs that affect the dopaminergic synapse.

The synthesis of the semi-synthetic ergot alkaloid 2 α-bromoergocryptine (Bromocryptine) made available a potent long acting dopamine agonist (Figure 14).

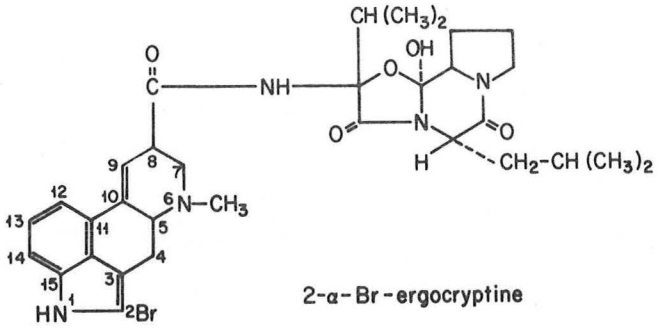

Figure 14

Bromocryptine

This compound activates the post-synaptic receptor and therefore does not require pre-synaptic neurons for conversion as does L-Dopa. This would explain the beneficial effects obtained in patients with Parkinson's disease who no longer respond to L-Dopa. This agent's low toxicity has resulted in a new era of therapy for patients with hyperprolactinemia (32-35). The drug rapidly suppresses elevated prolactin levels irrespective of the etiology and restores fertility in anovulatory women (Figure 15) and potency in men (Figure 16).

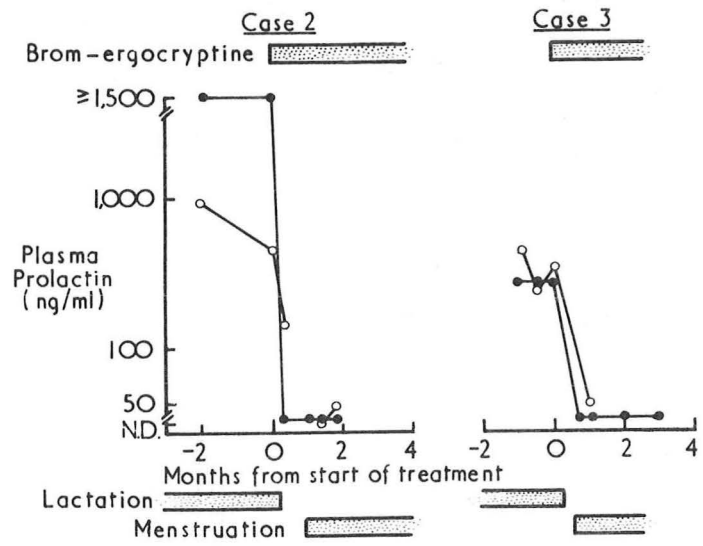

Figure 15

The effect of Bromocryptine in 2 lactating amenorrheic women (32)

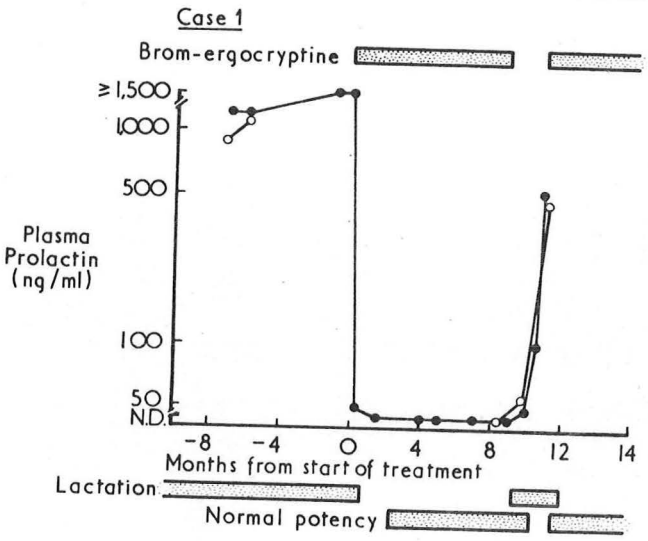

Figure 16

The effect of Bromocryptine in lactating, impotent men (32)

Thus far, 220 babies have been born to mothers who received Bromocryptine for the induction of ovulation and there has been no increased incidence of birth defects. This drug is effective, safe and should be made available in this country within the near future.

3. Etiology of the Prolactinoma

The incidence of prolactin secreting tumors appears to be increasing. Whether this is more apparent than real cannot be answered with certainty. It is clear that the availability of the prolactin radioimmunoassay and the Polytome have brought many more patients to the attention of their physicians. There is also the possibility that there is a real increase in the incidence of this disorder and that it is related in some way to the oral contraceptives. There is no evidence to support this possibility except the frequent occurrence of "post-pill" amenorrhea-galactorrhea and its association with a pituitary tumor.

Recent studies by Frohman and colleagues showed (36) that patients with prolactin secreting tumors had impaired conversion of dopa to dopamine → PIF in the CNS. Whether this is the defect responsible for tumor formation or whether it is secondary to the tumor itself has not been determined, since repeat studies have not been done after extirpation of the tumor. The pituitary and CNS sites of action of Dopa are depicted in Figure 17.

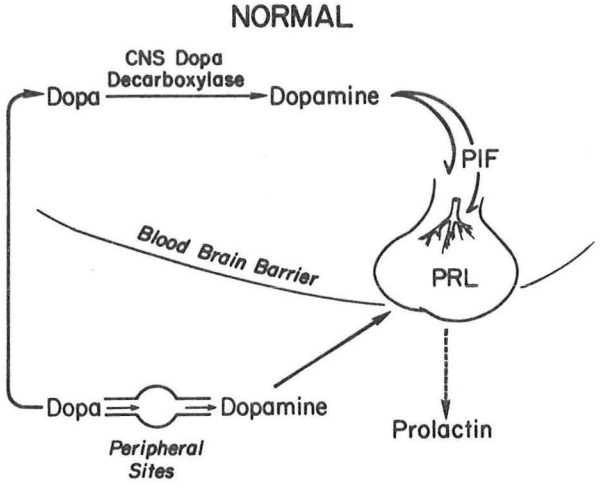

Figure 17

The CNS and pituitary sites of action of Dopa

III. The Regulation of ACTH-Cortisol Secretion

A diurnal variation in ACTH and cortisol had been known for many years. It was not until 1970 that the episodic nature of cortisol secretion was established. Studies in normal subjects showed that the

diurnal variation was the result of a diurnal clustering of discrete secretory episodes. In addition, normal subjects showed a quiescence of secretory activity at the time of lights out (2300-0200 hours). This pattern of cortisol secretion is relatively consistent among normal subjects (Figure 18).

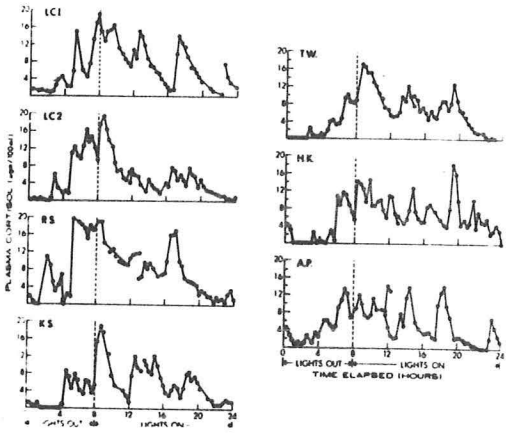

Figure 18

The 24-hour cortisol pattern in 7 normal men (37)

The CNS "program" that controls this circadian variation appears to be in the CNS. Studies in normal and adrenalectomized rats showed a circadian variation of CRF bioactivity in hypothalamic extracts. The extrahypothalamic factors that exert their effect on the hypothalamus have not been delineated. In man, serotonergic mechanisms have been implicated in the control of CRF-ACTH secretion (38). The relatively specific serotonin antagonists metergoline and cyproheptadine have been shown to inhibit ACTH secretion. Inhibitory dopaminergic mechanisms have also been implicated since Bromocryptine can suppress ACTH secretion in Cushing's disease (39).

A. Cushing's Disease (Hypothalamic-Pituitary Hypercortisolism)

Studies of the 24-hour circadian pattern of cortisol secretion in patients with Cushing's disease show a preservation of the episodic pattern, but a loss of the circadian clustering of secretory episodes. In contrast, patients with adrenal adenomas show a relatively constant cortisol level (Figure 19).

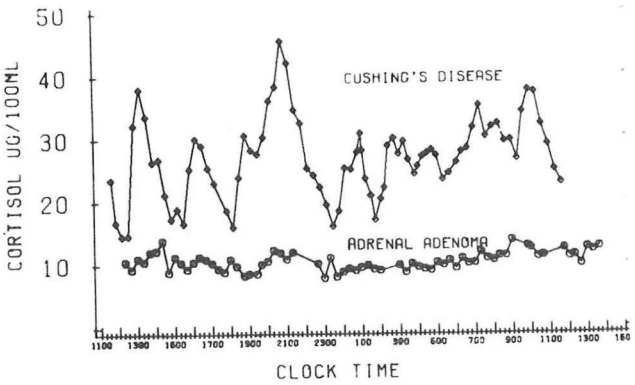

Figure 19

The 24-hour pattern of cortisol in Cushing's disease and Cushing's syndrome (adrenal adenoma)

1. Surgery

The incidence of pituitary ACTH secreting tumors in Cushing's disease is unknown. From early series it was clear that many more pituitary tumors were found post-mortem than were diagnosed clinically. The most extensive recent experience is from the UCSF group (40). They recently reported their experience with 20 patients who underwent transsphenoidal microsurgery for Cushing's disease. In 18 patients who had pituitary surgery (2 were closed because of anterior dural sinus malformations), sixteen had removal of a discrete pituitary tumor. In one patient a total hypophysectomy was performed and discrete adenoma was found anteriorly. Seventeen of the patients had correction of their hypercortisolism. Hardy reported reversal of hypercortisolism in 8 of 10 patients with Cushing's disease after transsphenoidal microsurgery (41). Sixty percent of the patients of both these series had normal polytomography.

Our own experience at Parkland is in agreement with these 2 reports. During the past year, we have studied 4 patients with Cushing's disease. In one, the pituitary tumor was obvious; in 2, the tomograms were non-diagnostic (basophilic adenomas were found in both); and in the 4th patient, the tomograms are abnormal(she is awaiting surgery). An example of the course of one of our patients is described below.

Case #1: L.G. was a 31 year old Latin-American female who was admitted to Parkland Hospital with a history of emotional lability, weight gain, easy bruisability, hypertension and diabetes mellitus.

Physical examination showed a hyperpigmented, plethoric woman who appeared chronically ill. She had hypertension (150/110), centripetal obesity, moon facies, abdominal striae and a buffalo hump. Laboratory evaluation showed:

	17 hydroxycorticosteroids mg/24 hours	17 ketosteroids mg/24 hours	Plasma Cortisol µg/dl
Control	26.2	28.4	15.4
2 mg dex.	22.9	18.9	
2 mg dex.	18.0	17.2	13.0
8 mg dex.	13.9	15.0	
8 mg dex.	7.4	11.8	3.7

The 24-hour circadian pattern of plasma cortisol was characteristic of Cushing's disease and the plasma ACTH was 52 pg/ml. Polytomography of the sella show a suggestive ballooning of the anterior portion. A transsphenoidal adenomectomy was performed on September 23rd and a discrete basophilic adenoma was removed from the inferior surface of the pituitary. The patient had an uneventful post-operative course and was re-studied one week after surgery and found to have no endogenous cortisol. She was gradually tapered off her cortisol replacement over the ensuing 10 months and presently is receiving no replacement therapy. She is menstruating normally, euthyroid and normotensive. Her fasting blood sugar is also normal. A repeat 24-hour study showed a normal cortisol circadian pattern.. This form of therapy has the following advantages and disadvantages (Table 6).

TABLE 6

Advantages of the Transsphenoidal Approach in Cushing's Disease

1. Cure of hypercortisolism
2. Elimination of the possibility of developing Nelson's syndrome
3. Preservation of normal residual pituitary function
4. Absence of the need for cortisol replacement after return of normal circadian cortisol secretory pattern.
5. Low operative morbidity.

Possible Disadvantages of Transsphenoidal Approach in Cushing's Disease

1. If a discrete adenoma is not found, a total hypophysectomy is required (if patient agrees to this prior to surgery).
2. If this is an hypothalamic disease, recurrent Cushing's disease may occur in the future.
3. It may be difficult in some cases to remove all the tumor tissue in which case the disease will remain active.

2. Cyproheptadine

The findings that cyproheptadine inhibits the normal rise in cortisol following hypoglycemia (38) as well as the exaggerated response to metyrapone in carcinoid syndrome (42) led Krieger et al to treat patients with Cushing's disease with this agent (43). These investigators reported lowering of the urinary cortisol and a return of the normal circadian pattern in 3 patients treated with 24 mg of cyproheptadine daily. In addition, she also reported skin lightening and a reduction in ACTH levels in 3 of 4 patients with Nelson's syndrome treated with this agent. Unfortunately, these exciting results have not been widely accepted, as other investigators have not had similar success with this agent. At the present time, there is not sufficient confirmatory data to recommend the use of this drug in patients with Cushing's disease.

3. Bromocryptine

The acute administration of Bromocryptine results in suppression of ACTH levels in Cushing's disease (39). These findings suggest that Cushing's disease may be the result of a deficiency of dopamine in the median eminence. These reports stimulated us to treat a patient with Cushing's disease with a dopamine agonist.

Case #2: A.A. was a 63 year old man who was admitted to Parkland Hospital with severe Cushing's disease associated with a large pituitary tumor. He was markedly wasted, purpuric, hypertensive and his diabetes mellitus was difficult to control. Skull x-rays and a CAT scan showed a large pituitary tumor with suprasellar extension and invasion into the sphenoid sinus. His 24-hour mean ACTH level was 212 pg/ml and his cortisol level was 120µg/dl. In an attempt to improve his clinical state prior to surgery he was treated with a dopamine agonist (Figure 20). After 2 days of treatment, the patient's urinary steroids returned to normal and there was definite clinical improvement. A repeat 24-hour study showed a decrease in his 24-hour mean plasma cortisol to 40µg/dl. Unfortunately, with continued therapy his clinical condition reverted back to the pretreatment state as did his urinary steroids. He underwent a transsphenoidal hypophysectomy with removal of a large pituitary tumor, but expired 2 weeks after surgery of pulmonary complications. Whether the decrease in urinary and plasma steroids was a result of treatment or periodic hormonogenesis cannot be determined. It is clear that additional studies with dopamine agonists should be carried out to determine if these drugs can be used as adjunctive therapy in Cushing's disease.

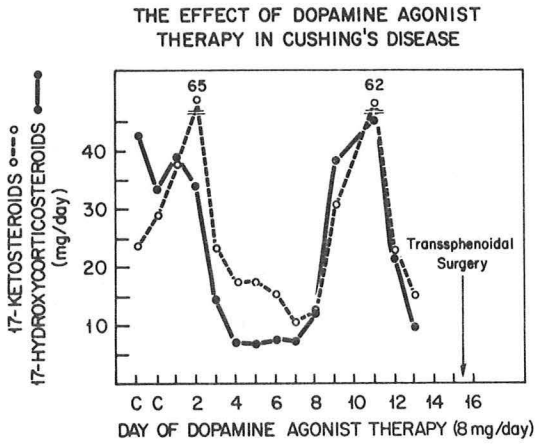

Figure 20

The effect of dopamine agonist therapy in Cushing's disease.

4. Somatostatin

Although somatostatin has no effect on ACTH secretion in normal subjects, Tyrrell et al (18) recently showed that this agent can inhibit ACTH secretion in patients with Nelson's syndrome (Figure 21). In some patients, the suppression of ACTH persisted after the somatostatin infusion was stopped. The availability of a long acting specific somatostatin may be of benefit in patients with this disorder at some time in the future.

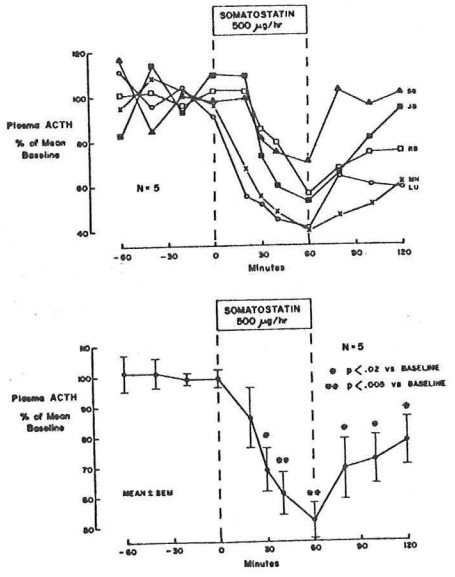

Figure 21

The effect of somatostatin in Nelson's syndrome. (18)

IV. The Regulation of Growth Hormone Secretion

The three major biogenic amines have been shown to participate in the control of growth hormone secretion. Boyd et al (45) showed that L-Dopa is a potent stimulator of growth hormone secretion in Parkinsonian patients (Figure 22). These studies were extended to include normal children and adults and is a standard test for evaluating growth hormone reserve. This effect appears to be mediated via an α-adrenergic mechanism since phentolamine blocks this response. In addition, clonidine an α-adrenergic agonist also stimulates growth hormone release (46). Apomorphine, a specific dopamine agonist also causes the release of growth hormone. β-adrenergic mechanisms inhibit growth hormone release and propranolol has been shown to augment the growth hormone response to glucagon.

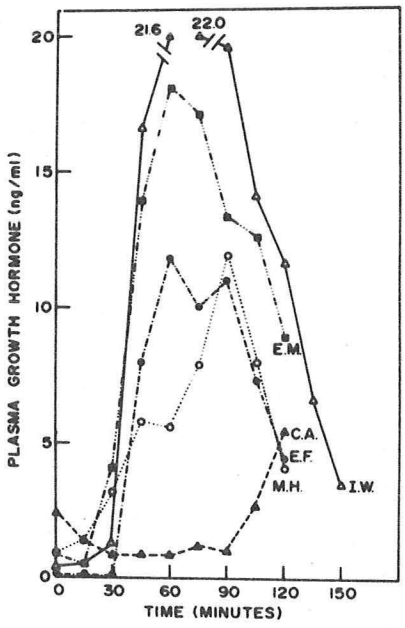

Figure 22

The growth hormone response to L-Dopa (45)

A. Sleep and Growth Hormone Secretion

Takahashi et al (47) measured growth hormone levels during sleep and reported a significant release that lasted 2-4 hours and was associated with slow wave sleep (stages 3 and 4). It was subsequently shown that this release was entrained to sleep and not the time sleep occurred (48). This neurally triggered secretion of growth hormone is not suppressed by hyperglycemia (49) (Figure 23), but is suppressed by somatostatin (50) (Figure 24).

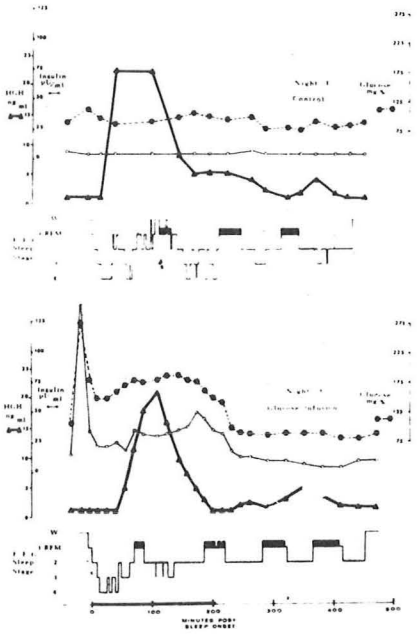

Figure 23

The effect of hyperglycemia on the sleep release of hGH (49)

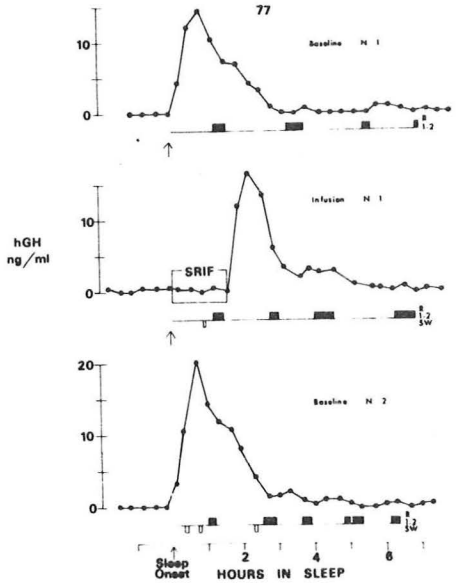

Figure 24

The effect of somatostatin on the sleep release of hGH. (50)

Studies of the 24-hour secretory pattern of growth hormone showed that its secretion pattern is not constant throughout life (51). Prepubertal children and young adults secrete their growth hormone almost exclusively during sleep. During puberty there is a marked augmentation of the amount of growth hormone secreted per secretory episode as well as the frequency of secretory episodes (Figure 25). Studies in elderly individuals showed a loss of the sleep related release (52) as well as a loss of L-Dopa responsiveness. The neurotransmitter control of the sleep related growth hormone release has not been determined. Results of studies utilizing the serotonin antagonist methysergide suggest that serotonergic mechanisms inhibit the release of growth secretion during sleep (53).

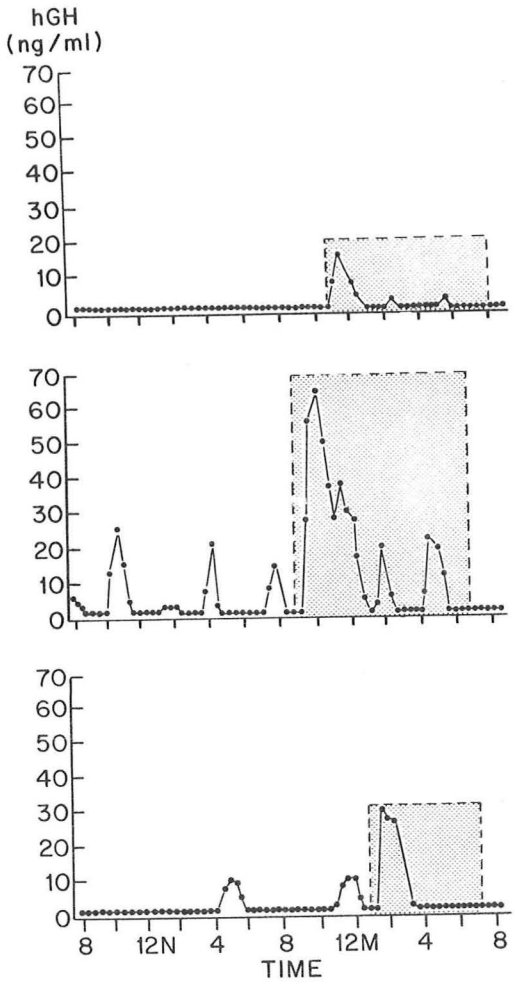

Figure 25

The 24-hour secretion pattern of growth hormone in prepubertal (upper panel), pubertal (middle panel) and young adults (lower panel). The shaded area shows the nocturnal sleep period.

B. Acromegaly

Patients with acromegaly have elevated levels of growth hormone throughout the 24-hour period (54). In addition, there is a loss of the sleep-wake difference characteristic of normal subjects (Figure 26).

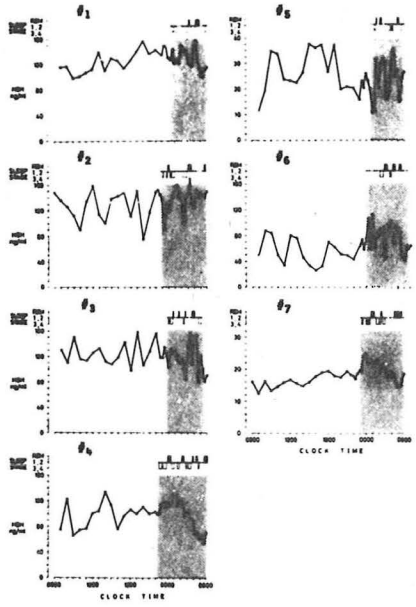

Figure 26

The 24-hour growth hormone levels in 7 patients with acromegaly. (54)

Patients with acromegaly also show paradoxical responses to L-Dopa, apomorphine and glucose, and anomalous responses to TRH and LH-RH. Many of these abnormal responses return to normal after extirpation of the pituitary tumor (55). Because of the suppressive effect of L-Dopa on growth hormone secretion in acromegaly, the effect of Bromocryptine therapy in this disorder was investigated. This drug resulted in a restoration of the normal sleep-wake rhythmicity as well as a lowering of the 24-hour growth hormone levels in most of the patients reported by Chihara et al (54).

1. Surgery

The incidence of pituitary tumors in acromegaly is not known. Since there is no compelling evidence that acromegaly results from hypothalamic dysfunction, a careful search should be made for a microadenoma in cases where the pituitary is grossly normal radiographically. Surgical removal of growth hormone secreting tumors results in a rapid return of growth hormone levels to normal (56,57). This rapid decrease in circulating growth hormone is especially important in patients with cardio-

vascular complications. Although growth hormone secreting tumors are classically eosinophilic, many patients have been shown to have chromophobic tumors by conventional techniques; however, most of these tumors will react with specific growth hormone antisera. In addition, many of these tumors contain both growth hormone and prolactin secretory cells supporting a pituitary origin for this disorder (55). These findings provide an explanation for the frequent occurrence of galactorrhea and hyperprolactinemia in patients with acromegaly. During the past year, we have treated 3 patients with acromegaly by transsphenoidal microsurgery and have had excellent results. All three patients noted an immediate decrease in soft tissue swelling and there was a prompt decrease in growth hormone levels. This form of therapy provides a rapid amelioration of the adverse effects associated with the hypersecretion of hGH.

2. Bromocryptine

The finding that Bromocryptine suppresses the elevated growth hormone levels in acromegaly has led to its use by many investigators abroad. The results of 5 of these studies are summarized below with regard to dose, duration of therapy and the effectiveness in suppressing growth hormone secretion (Table 7, ref. 58-64).

TABLE 7

THE EFFECT OF BROMOCRYPTINE ON ACROMEGALY

Study	Dose (mg)	Duration of Therapy	No. Treated	Success	Failure
1	7.5 - 30	6 mo	12	4	8
2	10	11 mo	13	10	3
3	10	1 mo (acute suppression)	7	7	
		(no acute suppression)	5		5
4	20	2 - 3 mo	11	9	2
5	5 - 10	2 weeks	7	6	1
			55	36 (66%)	19

3. Somatostatin

Although somatostatin can suppress growth hormone hypersecretion in acromegaly, the short half-life of this peptide and its effect on other pituitary, GI and pancreatic hormones limit its potential usefulness in the treatment of acromegaly (62).

V. The Regulation of Gonadotropin Secretion

The measurement of LH and FSH levels at frequent intervals showed that these pituitary hormones were also secreted in a pulsatile manner. Measurement of LH and FSH levels in prepubertal, pubertal and adult subjects showed an ontogenetic change in the pattern of secretion and its relationship to the sleep-wake cycle (63). Early (ages 5-8) prepubertal children show low LH and FSH levels without evidence of pulsatile secretion. At some point in late prepuberty, there is a marked augmentation of LH and FSH secretion that occurs synchronously with sleep (Figure 27).

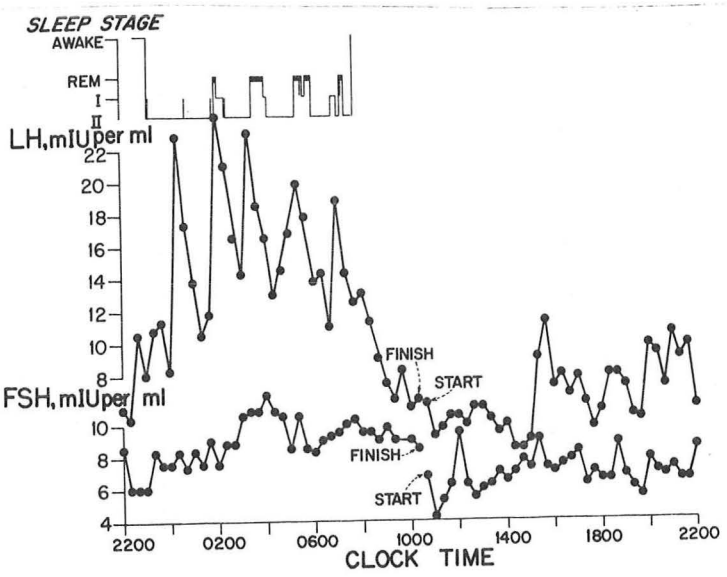

Figure 27

Pulsatile LH and FSH secretion in a normal pubertal girl.

The close relationship between the recurrent non-REM-REM sleep cycle and the recurrent pulses of LH suggest that they may be activated by a common mechanism. Pulsatile LH-RH secretion has been shown to occur in the rat (64) and subhuman primate (65) with radioimmunoassay techniques. Plasma LH-RH bioactive material has also been shown to be pulsatile in humans (66).

The increased secretion of LH and FSH during sleep stimulates testosterone secretion in boys (Figure 28) and estradiol secretion in girls

that results in the development of secondary sexual characteristics (67).

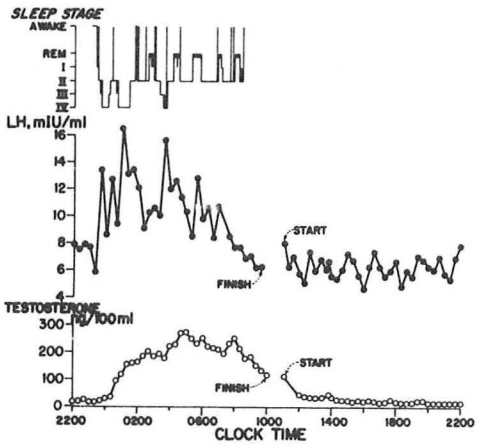

Figure 28

LH and testosterone levels in a normal pubertal boy

After the completion of sexual maturation there is seemingly random pulsatile LH and FSH secretion during the 24-hour period without any relationship to the sleep wake cycle (Figure 29).

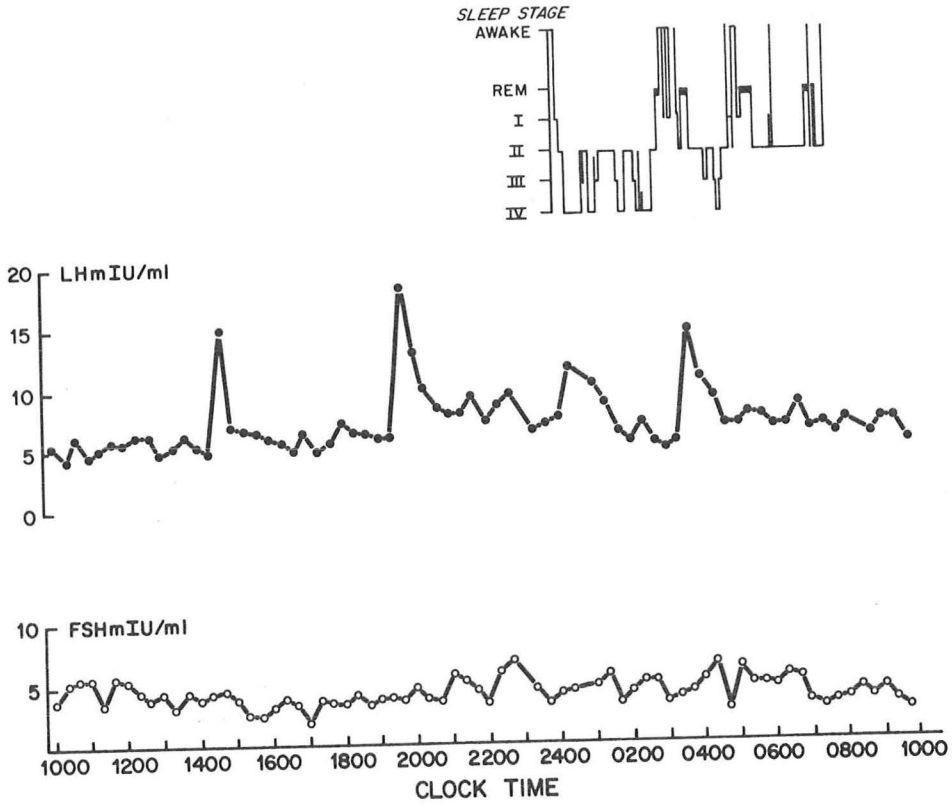

Figure 29

LH and FSH secretion in a normal young adult subject

A. Hypothalamic Disorders of Gonadotropin Secretion

1. Idiopathic Hypogonadotropic Hypogonadism (IHH)

Idiopathic hypogonadotropic hypogonadism is a disorder that manifests itself almost exclusively in males who manifest a defect in the initiation of puberty (68). This disorder is the result of a defect in the synthesis and/or secretion of LH-RH. The administration of LH-RH will result in the secretion of LH and FSH in those patients who fail to show spontaneous pulsatile LH and FSH secretory activity (Figure 30).

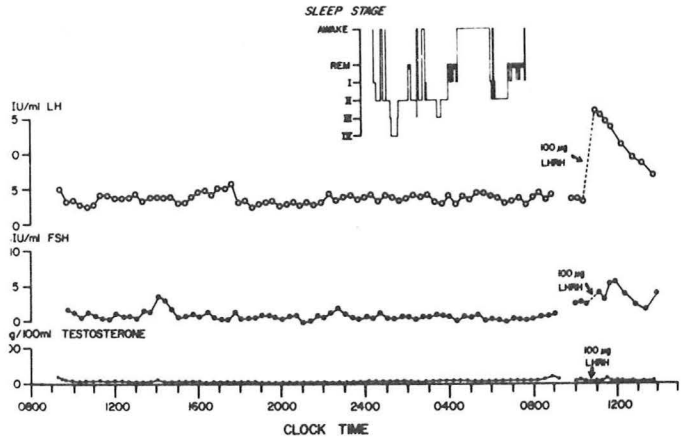

Figure 30

LH, FSH and testosterone levels before and after LH-RH.

These patients often have associated abnormalities that include anosmia, hyposmia, cleft palate, microphallus and cryptorchidism. The microphallus and cryptorchidism are believed to be a manifestation of the inadequate LH-RH activation of pituitary LH secretion during the last trimester. The future availability of LH-RH for chronic use, should enable patients with IHH as well as patients with other forms of hypothalamic hypogonadotropism "physiologic" replacement therapy. This should enable these patients to initiate and complete normal puberty as well as initiate and maintain normal spermatogenesis.

2. Anorexia Nervosa

Recent studies of LH secretory dynamics in patients with anorexia nervosa showed a "regression" or "arrest" of the LH secretory "program" to one that is similar to prepubertal or pubertal children (69). These findings suggested that some factor associated with the loss of body weight concomitantly affected the release of LH-RH. The finding that improved caloric intake and nutritional status resulted in normalization of the LH secretory "program" further supported this view (Figure 31). Since repetitive LH-RH stimulation in patients with anorexia nervosa can result in normalization of pituitary responsiveness to LH-RH and ovulation without any change in body weight, the pituitary and ovarian abnormality must be secondary to chronic LH-RH deficiency. The primary abnormality that results in decreased LH-RH synthesis and release has not been identified. Whether it is an hypothalamic abnormality secondary to the neurochemical concomitants of the psychiatric disorder and/or the severe malnutrition remains to be elucidated. In any event, this disorder provides a model

for the study of factors that may be relevant to the regulation of pulsatile gonadotropin secretion.

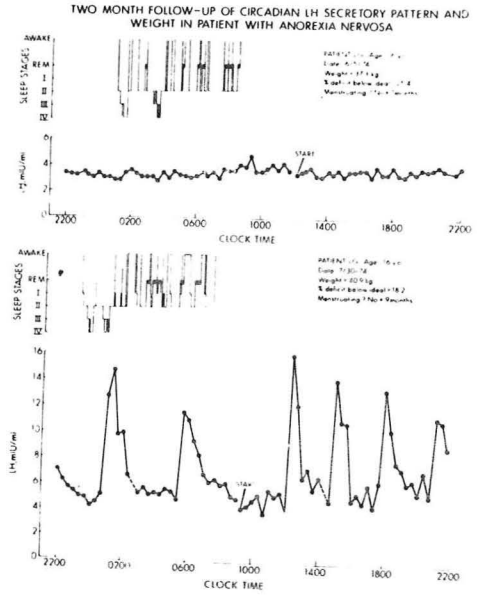

Figure 31

LH secretory pattern during acute phase of anorexia nervosa (upper panel) and after improved caloric intake and weight ain (lower panel).

CONCLUSION

The recent advances in neuroendocrinology have already been translated into improved methods of diagnosis and treatment of neuroendocrine disorders. During the next decade, it is anticipated that (1) progress will be made in the isolation of other hypothalamic "hypophysiotropic" peptides, most important are GRF and CRF; (2) that we will make significant progress in understanding the etiology and the pathogenesis of functioning pituitary tumors; and finally, (3) that medical therapy of neuroendocrine diseases with Bromocryptine, LH-RH and somatostatin analogues will be available to patients who can benefit from them.

REFERENCES

1. Noel, G.L., Dimond, R.C., Wartofsky, L., Earll, J.M., and Frantz, A.G. (1974): Studies of prolactin and TSH secretion by continuous infusion of small amounts of thyrotropin-releasing hormone. J Clin Endocrinol Metab 39:6-17.

2. Snyder, P.J. and Utiger, R.D. (1972): Response to thyrotropin releasing hormone (TRH) in normal man. J Clin Endocrinol Metab 34:380-385.

3. Costom, B.H., Grumbach, M.M. and Kaplan, S.L. (1971): Effect of thyrotropin-releasing factor on serum thyroid-stimulating hormone. J Clin Invest 50:2219-2225.

4. Fleischer, N., Burgus, R., Vale, W., Dunn, T. and Guillemin, R. (1970): Preliminary observations on the effect of synthetic thyrotropin-releasing factor on plasma thyrotropin levels in man. J Clin Endocrinol Metab 31:109-112.

5. Fleischer, N., Lorente, M., Kirkland, J., Kirkland, R., Clayton, G. and Calderon,M. (1972): Synthetic thyrotropin releasing factor as a test of pituitary thyrotropin reserve. J Clin Endocrinol Metab 34:617-624.

6. Jacobs, L.S., Snyder, P.J., Wilber, J.F., Utiger, R.D. and Daughaday, W.H. (1971): Increased serum prolactin after administration of synthetic thyrotropin releasing hormone (TRH) in man. J Clin Endocrinol Metab 33:996-998.

7. Jacobs, L.S., Snyder, P.J., Utiger, R.D. and Daughaday, W.H. (1973): Prolactin response to thyrotropin-releasing hormone in normal subjects. J Clin Endocrinol Metab 36:1069-1073.

8. Miyai, K., Azukizawa, M., and Kumuhara, Y. (1971): Familial isolated thyrotropin deficiency with cretinism. New Engl J Med 285:1043-1048.

9. Carlson, H.E., Breckman, A.S. and Bottazzo, G.F. (1977): Prolactin deficiency in pseudohypoparathyroidism. New Engl J Med 296:140-144.

10. Moss, R., and McCann, S.M. (1973): Induction of mating behavior in rats by luteinizing hormone-releasing factor, Science 181:177-179.

11. Yen, S.S.C., Rebar, R.M., Vanderberg, G., Naftolin, F., Judd, H., Ehara, Y., Ryan, K.J., Rivier, J., Amoss, M., and Guillemin, R. (1973): Clinical studies with synthetic LRF. Hypothalamic Hypophysiotropic Hormones, edited by C. Gual and E. Rosemberg, Excerpta Med., Amersterdam, 217-229.

12. De Kretzer, D.M., Burger, H.G. and Dumpys, R. (1975): Serum LH and FSH response in four hour infusions of luteinizing hormone releasing hormone in normal men, Sertoli cell only syndrome and

Klinefelter's syndrome. J Clin Endocrinol Metab 41:876-886.

13. Grumbach, M.M., Roth, J.C., Kaplan, S.L. and Kelch, R.P. (1974): Control of the Onset of Puberty, ed. Grumbach, Grave and Mayer, 115-166. New York: Wiley, 484 pp.

14. Lasley, B.L., Wang, C.F., and Yen, S.S.C. (1975): The effects of estrogen and progesterone on the functional capacity of the gonadotrophs. J Clin Endocrinol Metab 41:820-826.

15. Yoshimoto, Y., Moridera, K., and Imura, H. (1975): Restoration of normal pituitary gonadotropin reserve by administration of luteinizing hormone-releasing hormone in patients with hypogonadotropic hypogonadism. N Engl J Med 292:242-245.

16. Faglia, G., Beck-Peccoz, P., Travaglini, P., Paracchi, A., Spada, A., and Lewin, A. (1973): Elevations in plasma growth hormone concentration after luteinizing hormone-releasing hormone in patients with active acromegaly. J Clin Endocrinol Metab 37:338-340.

17. Brazeau, P., Vale, W., Burgus, R., Ling, N., Butcher, M., Rivier, J., and Guillemin, R. (1973): Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. Science 179: 77-79.

18. Tyrrell, J.B., Lorenzi, M., Gerich, J.E., and Forsham, P.H. (1975): Inhibition by somatostatin of ACTH secretion in Nelson's syndrome. J Clin Endocrinol Metab 40:1125-1127.

19. Hall, R., Besser, G.M., Schally, A.V., Coy, D.H., Evered, D., Goldie, D.J., Kastin, A.J., McNielly, B.S., Mortimer, C.H., Phenekos, C., Tunbridge, W.M.G., and Weightman, D. (1973): Action of growth hormone-release inhibitory hormone in healthy men and in acromegaly. Lancet 2:581-584.

20. Yen, S.S.C., Siler, T.N., and DeVane, G.W. (1974): Effect of somatostatin in patients with acromegaly. New Engl J Med 290:935-938.

21. Siler, T.N., Vanderberg, G., Yen, S.S.C., Brazeau, P., Vale, W., and Guillemin, R. (1973): Inhibition of growth hormone release in humans by somatostatin. J Clin Endocrinol Metab 37:632-634.

22. Sassin, J.F., Frantz, A.G., Kapen, S., and Weitzman, E.D. (1973): The nocturnal rise of human prolactin is dependent on sleep. J Clin Endocrinol Metab 37:436-440.

23. Sassin, J.F., Frantz, A.G., Weitzman, E.D. and Kapen, S. (1972): Human prolactin: 24-hour pattern with increased release during sleep. Science (Wash. D.C.) 177:1205-1207.

24. Bassi, F., Giusti, G., Borsi, L., Cattaneo, S., Giannotti, P., Forti, G.,

Pazzagli, M., Vigiani, C. and Serio, M. (1977): Plasma androgens in women with hyperprolactinaemic amenorrhea. Clin Endocrinol 6:5-10.

25. Child, D.F., Nader, S., Mashiter, K., Kjeld, M., Banks, L. and Russell Fraser, T., (1975): Prolactin studies in "functionless" pituitary tumours. Br Med J 1:604-606.

26. Franks, S., Nabarro, J.D. (1977): Prevalence and presentation of hyperprolactinemia in patients with "functionless" pituitary tumors. Lancet 1:778-780.

27. Robertson, W.D. and Newton, T.H.: Sellar changes associated with pituitary microadenomas: A tomographic evaluation (to be published).

28. McKeel, D.W. and Jacobs, L.S. Non-adenomatans pituitary mammotroph hyperplasia in patients with pathologic hyperprolactinemia.(1977) Endocrine Society Abstracts, No. 136, p. 124.

29. Editorial. Pituitary tumors and pregnancy (1976). Lancet, p. 404

30. Ben-Jonathan, N., Oliver, C., Mical, R.S., and Porter, J.C. (1976): Hypothalamic secretion of dopamine into hypophyseal portal blood. Fed Proc 35:306.

31. Kleinberg, D.L., Noel, G.L., Frantz, A.G.(1971): Chlorpromazine stimulation and L-Dopa suppression of plasma prolactin in man. J Clin Endocrinol Metab 33:873-876.

32. Thorner, M., McNeilly, A.S., Hagan, C., and Besser, G.M. (1974): Long term treatment of galactorrhea and hypogonadism with bromocryptine. Br Med J (May 25): 419-422.

33. DelPozo, E., Varga, L., Wyss, H., Tolis, G., Friesen, H., Wenner, R., Vetter, L., and Uettwiller, A. (1974): Clinical and hormonal response to bromocryptine (CB-154) in the galactorrhea syndromes. J Clin Endocrinol Metab 39:18-26.

34. Seki, K., Seki, M., and Okumura, T. (1975): Effect of CB-154 (2-Br-α-ergocryptine) on serum follicle stimulating hormone, luteinizing hormone and prolactin in women with the amenorrhea-galactorrhea syndrome. ACTA Endocrinol 79:25-33.

35. Corenblum, B., Webster, B.R., Mortimer, C.B., and Ezrin, C. (1975): Possible anti-tumor effect of 2 bromo-ergocryptine (CB-154)(Sandoz) in 2 patients with large prolactin-secreting pituitary adenomas. Clin Res 23:614A.

36. Fine, S. and Frohman, L.A. (1977): Loss of CNS dopaminergic inhibition of prolactin secretion in patients with hyperprolactinemia-amenorrhea. Clin Res 25:294A

37. Weitzman, E.D., Boyar, R.M., Kapen, S. and Hellman, L. (1975): Recent Prog Horm Res, ed. R.O. Greep, 31:399-441. New York: Academic Press. 631 pp.

38. Plonk J.W., Bivens, C.H., and Feldman, J.M. (1974): Inhibition of hypoglycemia-induced cortisol secretion by the serotonin antagonist cyproheptadine. J Clin Endocrinol Metab 38:836-840.

39. Benker, G., Hackenberg, K., Hamburger, B. and Reinewein, D. (1976): Effects of growth hormone release-inhibiting and bromocryptine (CB-154) in states of abnormal pituitary-adrenal function. Clin Endocrinol 5:187-190.

40. Tyrrell, J.B., Brooks, R.M., Fitzgerald,, P., Cofoid, P.B., Forsham, P.H., and Wilson, C.B. (1977): Pituitary tumors in Cushing's disease: Reversal of hypercortisolism by selective transsphenoidal adenomectomy. Endocrine Society Abstracts, No. 171, p. 142.

41. Hardy, J. (1973): Transsphenoidal surgery of hypersecreting pituitary tumors, Diagnosis and Treatment of Pituitary Tumors (International Congress Series No. 303), Edited by P.O. Kohler, G.T. Ross, Amersterdam Excerpta Medica, pp. 179-194.

42. Plonk, J.W., and Feldman, J.M. (1975): Adrenal function in the carcinoid syndrome. Program of the 57th Meeting of the Endocrine Society, p. 514.

43. Krieger, D.T., Amorosa, L., and Linick, F. (1975): Cyproheptadine-induced remission of Cushing's disease. N Engl J Med 293:893-896.

44. Tyrrell, J.B.,(1976) : Cyproheptadine in Cushing's disease. N Engl J Med 295:1137.

45. Boyd, A.E., III, Spencer, E., Jackson, I.M.D., and Reichlin, S. (1976): Prolactin-releasing factor in porcine hypothalamic extract distinct from TRH. Endocrinology 99:861-871.

46. Lal, S., Tolis, G., Martin, J.B., Brown, G.M., and Guyda, H. (1975): Effect of clonidine on growth hormone, prolactin, luteinizing hormone, follicle-stimulating hormone and thyroid-stimulating hormone in the serum of normal men. J Clin Endocrinol Metab 41:827-832.

47. Takahashi, Y., Kipnis, D.M., and Daughaday, W.H. (1968): Growth hormone secretion during sleep. J Clin Invest 47:2079-2090.

48. Sassin, J.F., Parker, D.C., Mace, J.W., Gotlin, R.W., Johnson, L.C., and Rossman, L.G. (1969): Human growth hormone release: relation to slow-wave sleep and sleep-waking cycles. Science (Wash. D.C.) 165:513-515.

49. Parker, D.C., and Rossman, L.G.(1971): Human growth hormone release in sleep: Non-suppression by acute hyperglycemia. J Clin Endocrinol Metab 32:65-69.

50. Parker, D.C., Rossman, L.G., Siler, T.N., Rivier, J., Yen, S.S.C., and Guillemin, R. (1974): Inhibition of sleep-related peak in physiologic human growth hormone release by somatostatin. J Clin Endocrinol Metab 38:496-499.

51. Finkelstein, J.W., Roffwarg, H.P., Boyar, R.M., Kream, J., and Hellman, L. (1972): Age-related change in the twenty-four hour spontaneous secretion of growth hormone. J Clin Endocrinol Metab 35:665-670.

52. Carlson, H.E., Gillin, J.C., Gorden, P., and Snyder, F. (1972): Absence of sleep-related growth hormone peaks in aged normal subjects and in acromegaly. J Clin Endocrinol Metab 34:1102-1112.

53. Mendelson, W.B., Jacobs, L.S., Reichman, J.D., Othmer, E., Cryer, P.E., Trivedi, B., and Daughaday, W.H. (1975): Methysergide: suppression of sleep-related prolactin secretion and enhancement of sleep-related growth hormone secretion. J Clin Invest 56:690-697.

54. Chihara, K., Kato, Y., Abe, H., Furumoto, M., Maeda, K. (1977): Sleep-related growth hormone release following 2-bromo-alpha-ergocryptine treatment in acromegalic patients. J Clin Endocrinol Metab 44:78-84.

55. Zimmerman, E.A., Defendini, R., Frantz, A.G. (1974): Prolactin and growth hormone in patients with pituitary adenomas: a correlative study of hormone in tumor and plasma by immunoperoxidase technique and radioimmunoassay . J Clin Endocrinol Metab 38:577-585.

56. Williams, R.A., Jacobs, H.S., Kurtz, A.B., Millar, J.G.B., Oakley, N.W., Spathis, G.S., Sulway, M.J., and Naborro, J.D.N.(1975): The treatment of acromegaly with special reference to transsphenoidal hypophysectomy. Q J Med 44:79-98.

57. Atkinson, R.L., Becker, D.P., Martins, A.M., Schaaf, M., Dimond, R.C., Wartofsky, L., and Earll, J.M. (1975): Acromegaly. Treatment by transsphenoidal microsurgery. J Amer Med Assoc 233:1279-1283.

58. Cassar, J., Mashiterk, Joplin, G.F. (1977): Bromocryptine treatment of acromegaly. Metabolism 26:539-546.

59. Sachdev, Y., Gomez-Pan, A., Tunbridge, W.M., Duns, A., Weightman, D.R., Hall, R., Goolamali, S.K. (1975) Bromocryptine therapy in acromegaly. Lancet 2:1164-8.

60. Chiodini, P.G., Liuzzi, A., Bottala, L., Oppizzi, G., Muller, E.E., and Silvestrini, F. (1975): Stable reduction of plasma growth hormone (hGH) levels during chronic administration of 2-Br-alpha-ergocryptine (CB-154) in acromegalic patients. J Clin Endocrinol Metab 40:705-708.

61. Thorner, M.O. , Chait, A.,Aitken, M., Benker, G., Bloom, S.R., Mortimer, C.H., Sanders, P., Stuart Mason, A., and Besser, G.M. (1975): Bromocriptine treatment of acromegaly. Br Med J 1:299-303.

62. Gerich, J.E. (1977): Somatostatin: diabetes and acromegaly. Adv Intern Med 22:251-272.

63. Boyar, R., Finkelstein, J., Roffwarg, H., Kapen, S., Weitzman, E., and Hellman, L. (1972): Synchronization of augmented luteinizing hormone secretion with sleep during puberty. N Engl J Med 287:582-586.

64. Sarkar, D.K., Chiappa, S.A. and Fink, G. (1976): Gonadotropin-releasing hormone surge in pro-oestrous rats. Nature 264:461-63.

65. Carmel, P.W., Araki, S. and Ferin, M. (1976): Pituitary stalk portal blood collection in rhesus monkeys: evidence for pulsatile release of gonadotropin releasing hormone (GRH). Endocrinology 99:243-248.

66. Seyler, L.E. and Reichlin, S. (1973): Luteinizing hormone-releasing factor (LRF) in plasma of postmenopausal women. J Clin Endocrinol Metab 37:197-203.

67. Boyar, R.M., Rosenfeld, R.S., Kapen, S., Finkelstein, J.W., Roffwarg, H.P., Weitzman, E.D., Hellman, L. (1974): Human puberty. Simultaneous augmented secretion of luteinizing hormone and testosterone during sleep. J Clin Invest 54:609-618.

68. Boyar, R.M., Wu, R.H., Kapen, S., Hellman, L., Weitzman, E.D., Finkelstein, J.W. (1976): Clinical and laboratory heterogeneity in idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 43:1268.

69. Boyar, R.M., Katz, J., Finkelstein, J.W., Kapen, W., Weiner, H., Weitzman, E.D., and Hellman, L.(1974): Anorexia nervosa-immaturity of the 24-hour luteinizing hormone secretory pattern. N Engl J Med 291:861-865.