

## Pituitary Causes of Amenorrhea

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*A 32 year old woman stopped her oral contraceptive agent 8 months ago and presents with amenorrhea. A work-up reveals a prolactin level of 32 ng/mL (normal range < 20 ng/mL) and a pituitary MRI with a 1.2 cm sellar mass. What is the differential diagnosis?*

Pituitary causes of amenorrhea should be considered in women with low or normal gonadotropin levels. Pituitary causes of amenorrhea constitute 18% of cases of secondary amenorrhea and 7% of cases of primary amenorrhea (1). Hyperprolactinemia is the most common cause of pituitary amenorrhea, comprising 15% of all cases of secondary amenorrhea and 80% of pituitary cases of secondary amenorrhea (2). This review will highlight potential causes of pituitary amenorrhea.

### HYPERPROLACTINEMIA:

Hyperprolactinemia, the most common cause of pituitary amenorrhea, may be secondary to physiologic or pathophysiologic causes. Importantly, an increased prolactin level due to any cause can result in amenorrhea and subsequent bone loss due to hypoestrogenemia.

### Physiologic Causes of Hyperprolactinemia:

**Pregnancy:** Pregnancy is the most common physiologic cause of hyperprolactinemia. Prolactin levels increase over the course of pregnancy and peak at the time of delivery (3). Prolactin levels may be as high as 600 ng/mL at the time of delivery (3) and therefore any premenopausal woman with hyperprolactinemia should first be evaluated for pregnancy prior to further diagnostic work-up. If a woman does not nurse, prolactin levels typically drop during the first 72 hours postpartum (3).

**Nipple Stimulation:** Suckling may increase serum prolactin levels in nursing women. This rise typically subsides after the first 6 weeks of lactation (3) due to the post-partum drop in estradiol levels and the resultant decrease in lactotroph hyperplasia which leads to smaller increases in prolactin levels post-suckling. In women who are not nursing, breast examination has not been shown to result in significant increases in serum prolactin levels (4).

**Macroprolactinemia:** Macroprolactinemia is typically an asymptomatic condition, although individuals may rarely experience amenorrhea or galactorrhea (5, 6). The predominant form of prolactin in most individuals is a 23 kD form but rare individuals may have a form of prolactin with a higher molecular mass (150 kD) which is cleared from the circulation more slowly (7).

### Medications:

**Psychiatric Medications:** Dopamine suppresses prolactin production; therefore any medication that blocks dopamine receptors may result in a rise in prolactin levels. Typical and atypical antipsychotics are commonly associated with hyperprolactinemia. While the newer atypical agents are thought to lead to less hyperprolactinemia as compared to the older typical agents, risperidone, an atypical antipsychotic agent, has been shown to be associated with significantly greater prolactin levels as compared to the typical antipsychotic, haloperidol (8, 9). The prolactin elevations are not usually greater than 100 ng/mL with antipsychotics, although much higher levels have been reported (9).

Antidepressants are rarely associated with hyperprolactinemia. Selective serotonin reuptake inhibitors (SSRIs), specifically fluoxetine, increase prolactin levels only minimally (10) and less commonly used medications, such as the tricyclics, cause hyperprolactinemia infrequently (9). Similarly, there are only rare case reports of anxiolytics, such as benzodiazepines, causing hyperprolactinemia.

**Other Medications:** Metoclopramide and domperidone are two gastric motility agents which block dopamine receptors and therefore may also increase prolactin levels (9). Serum prolactin levels have been reported to increase 6-fold after oral or IV metoclopramide (11). Methyldopa, an antihypertensive agent which blocks dopamine synthesis (12) and verapamil, a calcium-channel blocker thought to decrease hypothalamic production of dopamine, also may increase prolactin to levels generally less than 50 ng/mL (13, 14).

Estradiol stimulates lactotroph cell proliferation and pharmacologic doses of estradiol have been shown to increase prolactin secretion (15). Supra-physiologic levels of estradiol, as occur with assisted reproductive technologies such as ovulation induction or in vitro fertilization, may cause hyperprolactinemia but the doses of estradiol in oral contraceptive pills do not typically elevate prolactin (9).

### Pathophysiologic Causes:

**Lactotroph Adenoma:** Lactotroph adenomas, also called prolactinomas, are the most common subtype of pituitary adenomas. They are the leading cause of pituitary amenorrhea. In a well-differentiated adenoma, prolactin secretion is proportional to the size of the lesion. This is not the case with poorly differentiated or cystic lactotroph adenomas which may be large but tend to secrete less prolactin than one would expect based on their size.

**Mass Effect:** Dopamine, which is produced in the hypothalamus, suppresses the production of prolactin in the pituitary. Any compression of the stalk which connects the median eminence of the

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hypothalamus to the pituitary gland, for example by a mass or trauma, can disrupt the flow of dopamine into the pituitary gland and result in hyperprolactinemia.

**Chest Wall Injury:** Traumatic injury to the chest wall is another potential cause of hyperprolactinemia (16). Intercostal nerve blockade reduced serum prolactin levels in a patient with hyperprolactinemia after a traumatic burn injury to the chest wall (16) and therefore hyperprolactinemia in this setting is thought to be due to neurogenic stimuli.

**Primary Hypothyroidism:** The hypothalamus secretes thyrotropin releasing hormone which can stimulate pituitary lactotroph cells to secrete prolactin in individuals with primary hypothyroidism (17). Primary hypothyroidism may also lead to significant enlargement of the pituitary gland due to both thyrotroph hyperplasia and possibly lactotroph hyperplasia. Therefore, a TSH should be measured in every patient with hyperprolactinemia to screen for primary hypothyroidism.

**Chronic Renal Failure and Liver Failure:** Chronic renal failure is another cause of hyperprolactinemia. It is thought to be due to both decreased responsiveness of the pituitary to dopamine suppression and decreased prolactin clearance (18). Hyperprolactinemia has also been reported in patients with severe liver disease resulting in hepatic encephalopathy (19).

**OTHER PITUITARY CAUSES OF AMENORRHEA:**

**Non-Lactotroph Adenomas and Sellar Masses:**

Cushing's disease and acromegaly are the result of hyper-functioning pituitary adenomas of the corticotroph and somatotroph cells of the pituitary, respectively, and both are commonly associated with amenorrhea. In Cushing's disease, amenorrhea is typically due to increased circulating androgens produced by the adrenal gland and cortisol can suppress GnRH and therefore LH and FSH pulsatility. In acromegaly, amenorrhea may result from hyperandrogenism, compression of the pituitary gonadotrophs, or hyperprolactinemia — either due to concomitant production of prolactin by the tumor or stalk compression. In men, growth hormone excess has also been shown to have a direct effect on gonadal function (20) and therefore it is possible that this is a potential cause of amenorrhea in women with acromegaly as well.

Any pituitary adenoma, especially those  $\geq 1$  cm in size, as well as any sellar mass, including craniopharyngiomas and meningiomas, may cause amenorrhea due to compression of the pituitary gonadotrophs or stalk compression. Table 1 lists non-adenomatous causes of sellar lesions that may lead to amenorrhea.

**Sheehan's Syndrome:**

During pregnancy, lactotroph cells grow as a result of the increased estrogen levels (21). The increased size of the pituitary can cause compression of the superior hypophyseal artery, from which the pituitary gland receives much of its blood supply, and this compression can make the pituitary gland very sensitive to sudden changes in blood supply or hypotension (22). Cases of massive postpartum hemorrhage may result in ischemic necrosis of the pituitary gland causing postpartum hypopituitarism referred to as Sheehan's syndrome. Sheehan's syndrome is now most commonly seen in developing countries because postpartum hemorrhage is a rare complication of births in the developed world (23, 24).

**Infiltrative and Infectious Causes:**

**Lymphocytic Hypophysitis:** Lymphocytic hypophysitis, an inflammatory condition of the pituitary gland, affects predominantly females (8.5:1) and usually occurs during pregnancy or the postpartum period (25). A case series of 16 histologically-proven cases of lymphocytic hypophysitis found anterior pituitary hypofunction in 63% of the patients and posterior pituitary dysfunction, in the form of diabetes insipidus, in 19% (25). In this series, 3 of the 16 patients died as a result of undiagnosed hypopituitarism and therefore this condition can be lethal if not diagnosed promptly and hormone deficiencies treated (25).

**Hereditary Hemochromatosis:** Hereditary hemochromatosis, a common cause of gonadal insufficiency in men due to excessive iron deposition in either the pituitary gonadotroph cells or the testes, is a rare cause of hypogonadism in women (26). This is likely due to the fact that monthly menstrual bleeding is protective against excessive iron deposition in premenopausal women.

**Other:** Sarcoidosis and tuberculosis are other rare causes of pituitary-associated amenorrhea. In sarcoidosis, amenorrhea is typically the result of granulomatous infiltration of the hypothalamus resulting in decreased gonadotropin releasing hormone synthesis, although granulomas may also infiltrate the pituitary gland result-

**Table 1 Differential Diagnosis for Non-adenomatous Sellar Lesions\*:**

- Craniopharyngioma
- Chordoma
- Ependymoma
- Germ Cell Tumor
- Granular Cell Tumor
- Hemangioma
- Metastatic Disease
- Meningioma
- Primary Lymphoma
- Sarcoma
- Schwannoma
- Vascular Tumor/Aneurysms/AV Fistula of Cavernous Sinus
- Cysts:
  - Rathke's Cleft
  - Arachnoid
  - Dermoid
  - Epidermoid
  - Suprasellar
- Inflammatory/Infectious/Infiltrative Causes:
  - Abscess
  - Fibrous Dysplasia
  - Giant Cell Granuloma
  - Hemochromatosis
  - Hypophysitis
    - Lymphocytic
    - IgG-4-related Disease
    - Ipilimumab-associated
    - Granulomatous
    - Xanthomatous
  - Langerhans Cell Histiocytosis
  - Pituitary Hyperplasia
  - Sarcoidosis
  - Sphenoid Sinusitis

\*Not all cases have been shown to cause amenorrhea

ing in amenorrhea due to destruction of pituitary gonadotroph cells (27). Tuberculous meningitis has also been associated with amenorrhea. A study of 49 patients with a history of tuberculous meningitis in childhood found that 10% developed gonadotropin deficiency (28).

Langerhans cell histiocytosis, a disease in which Langerhans cells inappropriately proliferate and infiltrate various regions of the body including the hypothalamic-pituitary-axis, is a rare cause of pituitary amenorrhea. The most common pituitary dysfunction associated with Langerhans cell histiocytosis is diabetes insipidus, but gonadal dysfunction has also been reported (29).

IgG4-related disease, a newly described inflammatory disease characterized by an infiltrate consisting primarily of IgG4-positive plasma cells (30), has recently been associated with hypopituitarism and hypogonadism (31). Case reports describe improvement with high-dose glucocorticoid treatment (31).

Ipilimumab is an anti-cytotoxic T lymphocyte-associated antigen 4 antibody which is approved for use in metastatic melanoma. Ipilimumab has been associated with hypophysitis-associated panhypopituitarism or hormone deficiencies, including hypogonadism in approximately 4% of patients treated in a phase III trial (32). Careful monitoring of all patients on ipilimumab treatment is recommended to prevent the development of life-threatening panhypopituitarism.

Other infiltrating and infectious diseases may infiltrate the hypothalamic-pituitary axis and result in amenorrhea. Metastatic disease which infiltrates the pituitary gland is also a rare cause of amenorrhea.

## IATROGENIC AND OTHER CAUSES OF PITUITARY-ASSOCIATED AMENORRHEA:

### Surgery:

Based on reports in the literature, surgical treatment of a pituitary adenoma is a rare cause of hypogonadism (33), although the majority of these reports reflect rates of hypopituitarism for individuals undergoing surgery by a dedicated pituitary surgeon. Rates of post-surgical complications are higher in individuals undergoing pituitary surgery by surgeons with lower surgical volumes (34) and therefore the rates of post-surgical hypogonadism are likely higher for patients undergoing surgery by less experienced pituitary surgeons.

### Radiation:

Radiation therapy directed at the hypothalamic-pituitary region is a well-known cause of pituitary dysfunction resulting in amenorrhea (33), as is radiation therapy for non-pituitary brain tumors (35). Rates of hypogonadism approach 50% in individuals treated with radiation alone for pituitary lesions but are higher in individuals who undergo surgery followed by radiation therapy (33).

In individuals who undergo radiation therapy for non-pituitary brain tumors, the development of hypogonadism and hyperprolactinemia is common and has been shown to be associated with the dose of radiation therapy administered (36).

### Traumatic Brain Injury and Subarachnoid Hemorrhage:

Traumatic brain injury and subarachnoid hemorrhage are also potential causes of amenorrhea. Importantly, even individuals with a mild head injury may develop hypogonadism (37) and hypopituitarism may present as far out as 12 months after the initial insult and therefore these patients should be followed carefully and tested for all pituitary deficiencies as other axes may be affected as well (38).

### Genetic:

Mutations in transcription factors involved in the cellular proliferation and differentiation of the pituitary gland may cause anterior pituitary dysfunction and primary amenorrhea. *HESX1*, *GLI2* and *SOX3* mutations are associated with pituitary hormone deficiencies and *SOX2*, *LHX3* and *PROP1* mutations have been associated with gonadotropin deficiency (39). These mutations typically present with other clinical signs which may alert the clinician to the possibility of a genetic etiology. For example, *HESX1* mutations are associated with septo-optic dysplasia and *SOX2* mutations may be associated with sensorineural hearing loss and esophageal atresia. The inheritance pattern of these genes ranges from recessive, dominant, X-linked to de novo (39).

### CONCLUSION:

There are many potential causes of pituitary-associated amenorrhea. A thorough history and physical are invaluable in trimming down the differential diagnosis when evaluating a woman with amenorrhea and hypogonadotropic hypogonadism. Testing for other pituitary deficiencies and MRI imaging of the sellar region are often warranted. The correct diagnosis is important to make because appropriate treatment varies widely depending on the cause.

*The patient in our case had a non-functioning pituitary macroadenoma. Her prolactin level was elevated due to stalk compression. She underwent trans-sphenoidal surgery with complete resection of her lesion. Post-operatively her prolactin level normalized and her menses resumed.*

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# Dyslipidemia in Cushing's Disease (CD)

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## Introduction

Cushing's Disease (CD) - chronic cortisol overproduction by a pituitary corticotroph adenoma - accounts for 70% of cases of endogenous hypercortisolism (1). Relative to control populations, patients with CD face heightened relative risk of cardiovascular disease and all-cause mortality (2). This risk is thought to be driven, in large part, by known CD cardiovascular comorbidities including visceral obesity, hypertension, dysregulated glucose metabolism, and dyslipidemia (3). This review focuses on dyslipidemia in CD with attention to prevalent patterns, pathophysiology, and management strategies.

## Definitions of Dyslipidemia

The definition of dyslipidemia is in flux. Prior to the release of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III in 2001 (4), lipid targets were singular and universally applicable. The new guidelines (4, 5) introduced a paradigm shift, wherein a patient's low-density lipoprotein (LDL) cholesterol goal was dictated by his/her unique, overall cardiovascular risk profile:

For patients with known cardiovascular disease or cardiovascular disease risk equivalents, such as diabetes, an LDL of <100 mg/dl (optional <70 mg/dl) was recommended. For patients with 2+

**"Select medical therapies for CD...may have effects either to promote or ameliorate dyslipidemia."**

cardiovascular risk factors or 0-1 risk factors, LDL goals of <130 mg/dl or <160 mg/dl, respectively, were set. The NCEP ATP III guidelines did not proscribe specific high-density lipoprotein (HDL) or triglyceride targets - only hinting at optimal triglycerides by delineating non-HDL cholesterol goals. Nevertheless, in these guidelines, cut-points for dysregulated HDL and triglycerides can be inferred from metabolic syndrome criteria: HDL <40 mg/dl in men and <50 mg/dl in women, and triglycerides >150 mg/dl among all (4, 5). The complexity of modern dyslipidemia definitions complicates estimation of dyslipidemia prevalence among patients with CD. Patterns of dyslipidemia in CD patients, however, can be discerned from clinical studies describing mean lipid levels in comparison to control groups.

## Average Lipid levels in Active CD

Studies comparing lipid levels in CD patients versus well-matched control subjects suggest an association between CD and dyslipidemia (6-8). Both Faggiano *et al.* and Libe *et al.* reported significantly lower HDL levels in CD patients versus age, sex, and BMI-matched controls ( $39 \pm 3$  vs.  $51 \pm 3$  mg/dl,  $p < 0.05$  and  $23 \pm 2$  vs.  $48 \pm 4$  mg/dl,  $p = 0.005$ , respectively) (6, 8). Giordano *et al.* noted in CD patients significantly higher LDL levels versus similarly matched controls despite 2 of the 14 CD patients being treated with statin therapy ( $131 \pm 12$  vs.  $101 \pm 4$  mg/dL,  $p < 0.01$ ) (7). Of note, CD

patients in these studies had variable levels of obesity and insulin resistance, both of which are known to contribute independently to dyslipidemia (9, 10). For instance, in the study by Faggiano *et al.*, 5 subjects had known diabetes mellitus (6).

## Effect of CD Remission on Lipid Levels

In addition to comparing lipids in active CD patients versus controls, Faggiano, Libe, and Giordano examined lipid levels 1 year after transsphenoidal surgery/CD remission (6-8). A related study by Colao *et al.* compared lipid levels in CD patients 5 years after remission to levels in control subjects (11). Faggiano *et al.* and Libe *et al.* both demonstrated in CD patients significant decreases in LDL levels after remission at 1 year (6, 8). Libe *et al.* additionally showed decreased triglyceride levels and increased HDL levels among CD patients 1 year post transsphenoidal surgery, despite just a modest weight loss of 1.6 kg (8). In contrast to these findings, Giordano *et al.* noted no significant improvement in any lipid parameters among CD patients in remission (7). Colao *et al.* found that patients with CD in remission continued to have significantly lower HDL levels compared to matched control subjects (11), while Giordano *et al.* noted in this group a persistent elevation in LDL levels (7). These discrepant findings likely reflect differences in relevant patient characteristics. Specifically, patient heterogeneity in degree of remission and glucocorticoid replacement, residual obesity and insulin resistance, and co-existence/treatment of secondary hormone deficiencies (e.g. growth hormone deficiency, hypogonadism, hypothyroidism) may underlie mixed results for lipid levels in CD remission.

## Putative Pathophysiology of Dyslipidemia in CD

That select lipid parameters improve upon CD remission does not settle the question of whether hypercortisolism directly promotes dyslipidemia: An alternate explanation is that restoration of normal cortisol levels in CD remission favors weight loss and insulin sensitization, secondarily improving the lipid profile. Nevertheless, accumulating *in vitro*, animal, and human data lends biologic plausibility to a direct link between chronic hypercortisolism and dyslipidemia (12-14).

In peripheral adipose tissue, steroids primarily promote lipolysis and systemic free fatty acid (FFA) release, likely in part through upregulation of hormone sensitive lipase and adipocyte triglyceride lipase (13, 15). Steroids also favor lipolysis and FFA release in the systemic circulation by promoting the activity of lipoprotein lipase. Circulating FFAs are, in turn, taken up by the liver, increasing hepatic triacylglycerol storage and VLDL secretion (12, 13). Steroids are also thought to have a permissive effect on the promotion of peripheral lipolysis by growth hormone (16) and catecholamines (17). In visceral adipose tissue, steroids promote adipogenesis (through preadipocyte differentiation) and, to a lesser degree, concomitant lipolysis (15, 18). Crucial to the effects of chronic hypercortisolemia on lipid metabolism in individual patients are additional factors such as the activity of 11-hydroxysteroid-dehydrogenase type 1 (which catalyzes cortisone to cortisol conversion) (19) and polymorphisms in the glucocorticoid (GR) receptor (20).

### Management of Dyslipidemia in CD

Select medical therapies for CD (potentially employed in cases of failed transsphenoidal surgery) may have effects either to promote or ameliorate dyslipidemia. For instance, the DDT derivative and mitochondrial toxin mitotane increases HMG Co-A reductase activity, prompting marked LDL elevations (21). In contrast, the imidazole derivative and cortisol biosynthesis blocker ketoconazole reduces LDL 29% by inhibiting 14 alpha-demethylation of lanosterol (22). Recent studies have shown that the GR antagonist mifepristone (FDA approved in 2012 for treatment of Cushing's syndrome) and the investigational somatostatin receptor agonist pasireotide have significant effects on lipid levels in CD patients. Specifically, mifepristone decreases HDL cholesterol in CD subjects (23) while pasireotide decreases LDL and triglycerides (24). The mechanistic underpinnings and functional significance of lipid changes in the setting of mifepristone or pasireotide therapy for Cushing's have yet to be elucidated.

There are no dyslipidemia management strategies specific for CD. As in the general population, statins (HMG Co-A reductase inhibitors) are first line therapeutics for LDL lowering (employed in conjunction with lifestyle modification). When initiating statins in CD patients on ketoconazole or mifepristone, one must consider the potential for adverse interactions: ketoconazole by inhibiting hepatic P450 enzymes like CYP3A4 augments serum levels of the commonly prescribed simvastatin, atorvastatin, and lovastatin - increasing the potential for statin myo- or hepato-toxicity. Patients with CD on ketoconazole can more safely take rosuvastatin or pravastatin for LDL lowering, as these agents do not undergo metabolism by CYP 3A4 (25). Mifepristone inhibits CYP 3A as well as CYP2C8/2C9. Based on these properties, respectively, co-administration of mifepristone with simvastatin and/or lovastatin is contraindicated and caution is advised in cases of co-administration with fluvastatin.

### Summary and Directions for Future Research

CD patients are at increased risk of cardiovascular disease and all-cause mortality in part due to cardiovascular comorbidities such as dyslipidemia. That dyslipidemia cut-points vary according to an individual's overall risk profile complicates prevalence estimates of dyslipidemia in CD. Studies comparing average lipid levels in patients with active CD, CD remission and in control subjects suggest the following: in active CD patients versus BMI-matched controls, HDL levels appear to be lower, while LDL levels may be higher. Select lipid parameters appear to improve upon CD remission, but HDL levels remain lower than those seen in controls. *In vitro*, animal, and limited human studies suggest chronic hypercortisolism may directly promote dyslipidemia. Nevertheless, metabolic CD comorbidities such as obesity and insulin resistance may concomitantly, indirectly contribute to dyslipidemia. The primary clinical focus in the treatment of CD is normalizing serum cortisol. At the same time, in an effort to minimize cardiovascular disease risk, clinicians should also carefully screen for and treat dyslipidemia in CD, tailoring a patient's lipid targets to his/her individual risk profile. Note should be made of the potential for CD medical therapies

to worsen (mitotane, mifepristone) or improve (ketoconazole, pasireotide) lipid parameters and of deleterious interactions (ketoconazole, mifepristone) with select statins. Further research is needed to better define the prevalence of dyslipidemia in CD and to fully elucidate ways in which endogenous hypercortisolism dysregulates lipid metabolism.

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# Cushing's Research Presented at The Endocrine Society Annual Meeting 2011

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The first quarter of 2012 marks the eightieth anniversary of the seminal publication by neurosurgeon Harvey Cushing about the syndrome and disease that bear his name (1).

Information about Cushing's Syndrome was highlighted in many sessions at the 93<sup>rd</sup> Annual Meeting of The Endocrine Society ("ENDO"), held in Boston June 4-7, 2011. More than 7,800 scientific attendees from around the world gathered to discuss the latest research in endocrinology. A search of the scientific program of abstracts using the key word "Cushing" yields a remarkable total of sixty-seven original research presentations that were shared in oral or poster presentations over the 4-day meeting on this important topic.

On Saturday June 4, 2011 an entire oral session comprised of six scientific presentations was devoted to the treatment of Cushing's, entitled "Will Medical Management Replace Surgery for Cushing Syndrome?". Some of the talks addressed surgical experience and others focused on medical therapy for Cushing's. Two of the speakers presented the results of large, Phase-3 trials of new medications being tested in Cushing's.

Dr. Maria Fleseriu of the University of Oregon shared the results of one of these clinical trials, in a talk entitled, "Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Refractory Cushing Syndrome: Results from the Study of the Efficacy and Safety of Mifepristone in the Treatment of Endogenous Cushing Syndrome (SEISMIC)" (2). Nineteen medical centers in the United States participated in the trial. Fifty subjects with Cushing's syndrome of all types (Cushing's disease, ectopic ACTH, and adrenal carcinoma) who had failed standard therapy were enrolled. Patients had to have blood sugar abnormalities (glucose intolerance or diabetes) and/or hypertension, because an improvement in these was the "primary endpoint" (key variable being tested) in the study. The medication is a glucocorticoid receptor (GR) antagonist, blocking the action of cortisol in the body, rather than lowering the levels of cortisol. Over the 24 weeks of the trial, 60% of subjects with blood sugar abnormalities and 38% of subjects with hypertension showed an improvement according to predetermined criteria. Common side effects included fatigue, nausea, joint pain, vomiting, headache, swelling, low potassium, increased TSH and changes in the lining of the uterus in women. This medication was subsequently approved by the US FDA in February 2012 for patients with endogenous Cushing's Syndrome who have hyperglycemia and are not candidates for (or did not respond to) surgery.

In the next presentation, trial results for another potential new Cushing's medication were shown in "Pasireotide (SOM230) Demonstrates Efficacy in Patients with Cushing Disease: Results from a Large, Randomized-Dose, Double-Blind, Phase III Study" (3). This study enrolled 162 patients with moderate to severe Cushing's disease based on urine free cortisol (UFC) levels; normalization of UFC with predefined specific criteria was the primary endpoint selected for this study. Patients had persistent/recurrent or newly diagnosed (if they were not considered eligible for surgery) Cushing's disease. It was the largest clinical trial ever conducted in this disorder, and was carried out at 62 medical centers across 18 countries on four continents. The study tested two doses of a somatostatin analogue with receptor specificity targeting the somatostatin receptors on corticotroph adenomas (the pituitary tumors that cause Cushing's disease). Activation of these receptors decreases production of adrenocorticotropic hormone (ACTH) in some patients and the lower ACTH, in turn,

results in lowering of cortisol production from the adrenal glands. About one-quarter of patients treated with the higher dose of the investigational medication achieved a normal urine free cortisol level at 6 and 12 months of treatment. The most common side effects included gastrointestinal symptoms and hyperglycemia which reached the diabetic range in some patients.

As Harvey Cushing himself wrote about the condition 80 years ago, "...those seriously interested in the subject have, step by step, been feeling their way in spite of pitfalls and stumbling blocks innumerable" (1). The next Annual Meeting of The Endocrine Society will be held in Houston June 23-26, 2012, where we expect to hear about further steps being taken to advance our knowledge and treatment options in Cushing's syndrome.

## References

1. Cushing H. 1932; 50(3):137-96.
2. Fleseriu M, et al. J Clin Endocrinol Metab. 2012 Mar 30
3. Colao A, et al. N Engl J Med. 2012; 366:914-24.

## SAVE THE DATE

MASSACHUSETTS GENERAL HOSPITAL AND  
HARVARD MEDICAL SCHOOL CME PRESENT

## CLINICAL ENDOCRINOLOGY: 2013

March 20 – March 24, 2013 (probable dates), The Fairmont  
Copley Plaza, Boston, Massachusetts

For over three decades this course has provided practicing endocrinologists and other healthcare providers with a comprehensive review and update of recent literature in clinical endocrinology. The faculty consists of staff endocrinologists at the Massachusetts General Hospital and Harvard Medical School as well as nationally-renowned guest lecturers, all selected for their teaching and clinical skills. A comprehensive syllabus is provided.

For additional information contact:  
Harvard Medical School Department of  
Continuing Education

By mail: Harvard MED-CME,  
P.O. Box 825, Boston, MA 02117-0825

By telephone: 617-384-8600

Online information about this course can be found  
at: <http://cme.med.harvard.edu>

## RESEARCH STUDIES AVAILABLE

Patients may qualify for research studies in the Neuroendocrine Clinical Center. We are currently accepting the following categories of patients for screening to determine study eligibility. Depending on the study, subjects may receive free testing, medication and/or stipends.

SUBJECTS	STUDIES	CONTACT 617-726-3870
Adults with GHD	<ul style="list-style-type: none"> <li>• Diagnostic testing for GHD</li> </ul>	Karen Pulaski Liebert, RN Beverly M.K. Biller, MD
Adolescent and young adult athletes	<ul style="list-style-type: none"> <li>• Investigating impact of hormonal alterations on menstrual function and bone density</li> </ul>	Madhu Misra, MD Anne Klibanski, MD Kathryn Ackerman, MD
Obese adolescent girls	<ul style="list-style-type: none"> <li>• Investigating impact of growth hormone on body fat distribution and metabolic function</li> </ul>	Madhu Misra, MD Anne Klibanski, MD
Adolescent girls with anorexia nervosa	<ul style="list-style-type: none"> <li>• Investigating the impact of new therapies on bone density</li> </ul>	Madhu Misra, MD Anne Klibanski, MD Kathryn Ackerman, MD Karen K. Miller, MD
Women with anorexia nervosa	<ul style="list-style-type: none"> <li>• New therapies</li> </ul>	Anne Klibanski, MD
Women ages 18-40 with a history of anorexia nervosa	<ul style="list-style-type: none"> <li>• Investigating hormones and brain circuitry involved in appetite</li> </ul>	Elizabeth Lawson, MD Anne Klibanski, MD
Men, ages 18-45	<ul style="list-style-type: none"> <li>• Investigating body weight and GH secretion</li> <li>• GH treatment in abdominal obesity</li> </ul>	Karen K. Miller, MD
Girls and women with current anorexia nervosa or a history of anorexia nervosa, ages 10 and up	<ul style="list-style-type: none"> <li>• Investigating genetics of appetite-regulating and stress hormones</li> </ul>	Elizabeth Lawson, MD Karen K. Miller, MD Anne Klibanski, MD Madhu Misra, MD
Healthy girls and women, ages 10 and up	<ul style="list-style-type: none"> <li>• Investigating genetics of appetite-regulating and stress hormones</li> </ul>	Elizabeth Lawson, MD Karen K. Miller, MD Anne Klibanski, MD Madhu Misra, MD
Healthy normal-weight and obese men	<ul style="list-style-type: none"> <li>• Effect of oxytocin on caloric intake</li> </ul>	Elizabeth Lawson, MD
Obese men	<ul style="list-style-type: none"> <li>• Investigating the effect of growth hormone treatment on skeletal muscle mitochondria</li> </ul>	Hideo Makimura, MD, PhD
Obese men and women	<ul style="list-style-type: none"> <li>• Investigating the effect of acipimox, a medication to decrease free fatty acids, on skeletal muscle mitochondria</li> </ul>	Hideo Makimura, MD, PhD
HIV positive men and women with and without metabolic abnormalities	<ul style="list-style-type: none"> <li>• Assessment of coronary artery atherosclerosis</li> <li>• Growth hormone and growth hormone releasing hormone</li> <li>• Assessment of long-term GHRH</li> <li>• Assessment of menopausal transition</li> <li>• Statin therapy for coronary plaque</li> </ul>	Steven Grinspoon, MD Janet Lo, MD Katie Fitch, FNP, MD Takara Stanley, MD
Adults with moderate-to-severe psoriasis about to be started on etanercept (Enbrel) by their treating dermatologist	<ul style="list-style-type: none"> <li>• Assessment of cardiovascular and metabolic health</li> </ul>	Markella V. Zanni, MD Steven Grinspoon, MD

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## SUPERVISING STAFF

## SERVICES AVAILABLE

### Endocrinology:

Anne Klibanski, MD  
*Chief, Neuroendocrine Unit*  
Beverly M.K. Biller, MD  
Steven K. Grinspoon, MD  
Pouneh K. Fazeli, MD  
Elizabeth A. Lawson, MD  
Hideo Makimura, MD, PhD  
Janet Lo, MD  
Karen K. Miller, MD  
Lisa B. Nachtigall, MD  
Nicholas A. Tritos, MD, DSc  
Markella V. Zanni, MD

### Neurology:

Thomas N. Byrne, MD

### Neurosurgery:

Robert L. Martuza, MD  
*Chief, Neurosurgical Service*  
Brooke Swearingen, MD  
Nicholas T. Zervas, MD

### Radiation Oncology:

Jay S. Loeffler, MD  
*Chief, Radiation Oncology*  
Helen A. Shih, MD

### Psychiatry:

Gregory L. Fricchione, MD  
Hadine Joffe, MD

### Pediatric Endocrinology

Madhusmita Misra, MD, MPH  
Takara L. Stanley, MD

### Facilities

The Neuroendocrine Center is located on the 1st floor (Suite 112) of Zero Emerson Place at the Massachusetts General Hospital. A test center is available for complete outpatient diagnostic testing, including ACTH (Cortrosyn) stimulation; insulin tolerance; oral glucose tolerance and growth hormone stimulation testing. Testing for Cushing's syndrome can also be arranged, including bilateral inferior petrosal sinus ACTH sampling for patients with ACTH-dependent Cushing's syndrome.

### Neuroendocrine Clinical Conference

A weekly interdisciplinary conference is held to discuss new patients referred to the Neuroendocrine Center and to review patient management issues. This multidisciplinary conference is attended by members of the Neuroendocrine, Neurology, Neurosurgery, Psychiatry and Radiation Oncology services. Physicians are welcome to attend and present cases.

### Physicians' Pituitary Information Service

Physicians with questions about pituitary disorders may contact Dr. Biller or Dr. Klibanski at 617-726-3965 within the Boston area or toll free at 888-429-6863, or e-mail to [pituitary.info@partners.org](mailto:pituitary.info@partners.org). The Physicians' Pituitary Information Line has received support from LG Life Sciences and Tercica, Inc. in the form of educational grants.

### Scheduling

Outpatient clinical consultations can be arranged by calling the Neuroendocrine Center Office at 617-726-7948.