



From the Chair
Steven I. Sherman, M.D.



It is a pleasure to introduce this first issue of a new publication from the Department of Endocrine Neoplasia and Hormonal Disorders. Since the creation of the department in 2000, the marked growth and increased breadth of our clinical and research programs has been made possible by an expanded team of clinical faculty and providers: six of our nine faculty physicians and all eight of our mid-level providers have joined us since 2002. Growth has been accompanied by opportunities to develop further areas of specialization and expertise within our field, allowing us to provide the highest levels of expert research-driven care to patients with endocrine tumors as well as to patients with endocrine disorders in the setting of malignant diseases.

In this issue, we highlight one of our very exciting areas of expansion, the research and clinical care for patients with pituitary disease. Drs. Steven Waguespack (Associate Professor) and Jessica Devin (Assistant Professor), along with colleagues in our department as well as Neurosurgery, are championing this program, focusing on the sophisticated endocrinologic evaluation and diagnostic procedures that patients with pituitary tumors often require. For patients with tumors that are all too commonly refractory to traditional medical, surgical, and radiation therapy, they are leading clinical trials for novel therapies to acromegaly and Cushing's disease. The regular multidisciplinary clinical conference that they lead ensures the highest quality of care for our pituitary patients, a hallmark of the M.D. Anderson approach to all patients with neoplastic disease. Those patients successfully treated for their pituitary tumors, however, often are left with the long-term issues related to hypopituitarism, and this is a critically important aspect of the follow-up care and research efforts that our pituitary program is emphasizing.

In future issues of this newsletter, I will have the opportunity to share with you the important developments and opportunities arising in our clinical and research programs. I eagerly look forward to providing updates on our superb thyroid cancer clinical trials, our novel focus on metabolic abnormalities in patients with cancer, and future efforts to improve the endocrine health of cancer survivors. These efforts are all driven by the same underlying mission: to improve the duration and quality of life for cancer patients and survivors by providing the highest quality endocrine care, research that improves our understanding of the biology of disease and develops novel and successful therapies, and training physicians and scientists for the future. In each way, the Department of Endocrine Neoplasia and Hormonal Disorders is Making Cancer History®.

Department of Endocrine Neoplasia & Hormonal Disorders Faculty:

Steven I. Sherman, M.D., Department Chair, Professor & Center Medical Director, Endocrine Center
Naifa L. Busaidy, M.D., Assistant Professor
Gilbert J. Cote, Ph.D., Associate Professor
Jessica K. Devin, M.D., Assistant Professor
Robert F. Gagel, M.D., Professor
Mimi Hu, M.D., Assistant Professor
Camilo Jimenez, M.D., Assistant Professor
Victor R. Lavis, M.D., Professor
Sara Peleg, Ph.D., Associate Professor
Rena Vassilopoulou-Sellin, M.D, Clinical Professor
Steven G. Waguespack, M.D., Associate Professor
Sai Ching Jim Yeung, M.D., Ph.D., Associate Professor

ENDOPERSPECTIVES



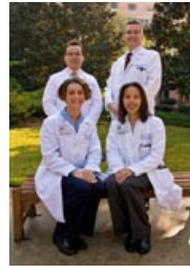
The New Pituitary Tumor Program

We welcome the opportunity to introduce to you in our first departmental newsletter the Pituitary Tumor Program at the University of Texas M. D. Anderson Cancer Center in Houston. We represent a multi-disciplinary team of physicians dedicated to caring for patients with all types of pituitary disorders. We endeavor to provide quality care for patients with newly diagnosed and recurrent pituitary tumors and for those who need long-term follow-up related to their pituitary disorder.

We are composed of endocrinologists knowledgeable in the management of pituitary disease, experienced neurosurgeons, as well as colleagues in the departments of neuro-radiology, neuro-ophthalmology, neuro-pathology and radiation oncology. M. D. Anderson routinely hosts patients who travel remotely, both nationally and internationally. We are well-equipped to provide coordinated, efficient and state-of-the-art care to our patients. We offer detailed outpatient evaluation, including dynamic hormonal testing, pituitary-dedicated MRI imaging, and neuro-ophthalmologic consultation. Our Proton Therapy Center offers patients the most advanced form of targeted radiation therapy to avoid damage to nearby structures. New patients are routinely presented at the monthly Pituitary conference so that an individualized therapeutic plan can be formulated and carried out at M. D. Anderson by a multi-disciplinary team of physicians.

We are committed to educating patients about the management of their pituitary disorder and supporting the physicians who take care of our patients. We pride ourselves on our initiatives to investigate the causes and complications of pituitary disease and on our ability to offer our patients the latest treatments available for their disorder. In this issue you will find an introduction to modern neurosurgical techniques used in the resection of pituitary tumors, as well as an update on the management of Acromegaly and new medical therapies which are currently available in clinical trials at M. D. Anderson to treat this rare pituitary disorder. We invite you to visit our website at: <http://www.mdanderson.org/departments/endocrinology/dlIndex.cfm?pn=7C94FA0E-E9CD-425E-9DE142BFD8CE3805>, where you will find more information about our program, including the faculty and staff, ongoing research protocols, education materials, and the referral process. We look forward to assisting you in the care of our patients with pituitary tumors and their related disorders.

By Jessica K. Devin, MD, and Steven G. Waguespack, MD



Upcoming Events

AACE 17th Annual Meeting & Clinical Congress: The Art & Science of Endocrinology: Focusing on Best Patient Outcomes. May 14-18, 2008. Walt Disney World Dolphin Resort, Orlando FL. <http://www.aace.com/meetings/ams/2008/>

The Endocrine Society (ENDO) Meeting 2008. June 15-18, 2008. San Francisco, CA. <http://www.endo-society.org/educationevents/annual/>

The Bone Disease Program of Texas' 2008 Scientific Retreat & Rolanette and Berdon Lawrence Research Award Competition. April 18, 2008. Marriott Medical Center, Houston, TX. <http://www.mdanderson.org/departments/boneprogram/>

This newsletter was compiled by The University of Texas M.D. Anderson Cancer Center Department of Endocrine Neoplasia & HD.
Unit 435, 1515 Holcombe Blvd., Houston, TX 77030
713-792-2841
713-794-4065 fax

Newsletter Committee:

Steven I. Sherman, MD
Carol Atwood
Steven G. Waguespack, MD
Jessica K. Devin, MD
Mary Jean Klein
Lorraine Medina
Charles Stava

Editors: Charles Stava,

Maggie Newell.

Contributing Writers:

Steven I. Sherman, MD, Jessica K. Devin, MD, Steven G. Waguespack, MD, Ian McCutcheon, MD, and Mary Jean Klein.

Modern Surgical Strategies for Pituitary Tumors

The great majority of patients with a pituitary tumor can safely and successfully be treated by operations that use the nose as a corridor for reaching the tumor. Traditionally this has involved an incision under the upper lip ("sublabial"), and the development of such a corridor between the septum of the nose and its overlying mucosa extending through the sphenoid sinus ("transsphenoidal") to the pituitary tumor. Over the past decade, we have moved increasingly to an "endonasal" transsphenoidal operation, in which the incision is made deep inside the nasal cavity itself. In patients whose anatomy permits an endonasal approach, removal of the tumor can be done with less outwardly visible trauma and a faster healing time, without sacrificing safety or effective removal. Such operations are done with the aid of a surgical microscope and a variety of instruments specially designed for transsphenoidal surgery. As the endoscope allows an angled view into corners of the pituitary region (called the sella) not normally visible with the microscope alone, it is a particularly valuable tool for extending the reach of such surgery. As technology improves, we expect such minimally invasive endoscopic approaches to become our primary way of reaching and removing pituitary tumors.

By Ian McCutcheon, M.D., Dept. of Neurosurgery

Feature Article: Update in Acromegaly

by Steven G. Waguespack, M.D.

Acromegaly is an insidious disease secondary to the chronic hypersecretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1), the predominant GH-dependent protein and mediator of GH action. Acromegaly is a rare disease, with an annual incidence of 3-4/million and a prevalence of 40-70 cases/million. Gigantism refers to growth hormone excess that occurs in children before epiphyseal closure. It is an even rarer entity that is most commonly recognized secondary to dramatic linear growth beyond what is expected for a child's genetic potential.

GH Physiology and Action

GH is a polypeptide hormone that is produced by the somatotroph cells of the anterior pituitary. It has numerous biological effects related to body composition, somatic growth, and intermediary metabolism. Similar to other pituitary hormones, GH is secreted in a pulsatile fashion. This occurs about ten times a day and the greatest pulse amplitudes occur during the nighttime hours. In normal individuals, GH levels are <1ng/ml about 50% of the time. The hypothalamic hormone growth-hormone releasing hormone (GHRH) stimulates GH release and synthesis. GH release is negatively inhibited by somatostatin (SRIF), and it is believed that the interaction of SRIF and GHRH is responsible for the pulsatile secretion of GH.

GH signals through the GH receptor, which is ubiquitous throughout the body but most abundant in the liver, where it acts to produce insulin-like growth factor-1 (IGF-1). Both circulating GH and IGF-1 exert an inhibitory effect on the pituitary somatotroph through a negative feedback mechanism. GH-activated signal transduction occurs only after dimerization of two adjacent GH receptors, which mediates an intracellular phosphorylation cascade involving the Jak/Stat pathway. Although GH can directly have cellular effects, most of its physiologic actions are mediated by IGF-1. Acid labile subunit and IGFBP-3 are other important GH-dependent proteins that circulate with IGF-1 as part of a ternary complex and affect its bioavailability.

Major Actions of GH and IGF-1
– Stimulates linear growth in children
- other roles in bone metabolism
– Increases lipolysis and lipid oxidation
– Stimulates protein synthesis
– Antagonizes insulin action
– Involved in phosphate, sodium, and water retention

Pathogenesis of Acromegaly

Almost all cases of GH excess result from autonomous GH production by a pituitary adenoma. Most (80%) of these tumors are macroadenomas (>1cm in size), reflecting the frequent delay in diagnosis of most cases. Although 60% of these tumors are pure somatotroph tumors, somatotroph/lactotroph tumors are seen in about 25% of cases and mammosomatotroph tumors are identified in another 10% of cases. Plurihormonal adenomas and pituitary carcinomas are less common tumors associated with acromegaly. Acromegaly can be a component of MEN1, the McCune-Albright Syndrome, and the Carney complex. In addition, acromegaly can be an isolated familial occurrence. Recently, mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene have been identified in families with familial somatotropinoma.

Less than 1% of acromegalics have ectopic acromegaly, defined as GH excess that occurs from etiologies other than a GH-secreting intrasellar pituitary tumor. The most frequent cause of ectopic acromegaly is a GHRH-producing carcinoid tumor. The astute clinician should consider ectopic acromegaly in any patient with classic clinical and biochemical features of acromegaly who does not have a clear adenoma identified on imaging studies, or if the imaging study suggests pituitary hyperplasia.

Symptoms of Acromegaly

The diagnosis of acromegaly is usually made 8-9 years after its onset, and the typical patient with GH excess is diagnosed in their early forties. Common symptoms of GH excess are detailed on the following page:

Clinical Sequelae of Acromegaly

- Tumor mass effects	- Goiter/thyroid nodules
• Headaches, visual loss, cranial nerve palsies, hypopituitarism	- Obstructive sleep apnea
- Coarsening of facial features	- Hyperhidrosis, skin oiliness, skin tags
• Frontal bossing/widening of nose	- Hypertension, ventricular hypertrophy, valvular disease
- Prognathism/ tooth separation, malocclusion	- Hypogonadism (low SHBG) and menstrual irregularities
- Macroglossia	- Hyperprolactinemia/galactorrhea
- Deepening of voice	- Insulin resistance and diabetes
- Acral enlargement and skin thickening	- Hypertriglyceridemia
- Depression / loss of self esteem	- Hypercalcuria/Hyperphosphatemia
- Headaches	- Osteoporosis/vertebral fractures
- Arthralgias, joint hypermobility, arthropathy	- Increased colon polyps
• carpal tunnel syndrome	- Increased cancer risk

Diagnosis of Acromegaly

The best screening test for acromegaly is a random IGF-1 level, which is then compared to appropriate age- and sex-matched ranges. A markedly elevated IGF-1 level coupled with the classic clinical signs and symptoms is often sufficient to make the diagnosis. The gold standard for diagnosis is a 75-gram oral glucose tolerance test, during which GH levels are measured every 30 minutes for 2 hours after the oral glucose load. This test will be unreliable in a patient with uncontrolled diabetes mellitus. Unlike normal individuals, patients with acromegaly do not suppress GH release in response to a glucose load. Therefore, failure to suppress GH to levels below 1ng/ml (using ICMA or IRMA) at any point during the test is a positive result. It should be noted that the diagnostic cutoff level may be lowered further in the future, given that most normal individuals will suppress GH to less than 0.3 ng/ml on these highly sensitive assays. Another caveat to remember is that milder cases of acromegaly may have normal responses to an OGTT using the current criteria. Therefore, a normal OGTT does not always preclude a diagnosis of acromegaly. Once the diagnosis of acromegaly is established clinically, the next appropriate step would be to obtain an MRI of the pituitary with and without gadolinium contrast.

Treatment of Acromegaly

In general, acromegalics live 10 years less than the normal population and have a death rate 2-4 times that of normal. Retrospective population based studies have demonstrated that the lowering of GH and IGF-1 levels results in an improvement in morbidity and a normalization of mortality rates. Therefore, it is essential to aggressively treat any patient with a diagnosis of GH excess.

Similar to any patient with a functional pituitary tumor, the goals of therapy are to 1) treat hormone excess, 2) treat mass effects from the tumor, and 3) assess for and treat any coexistent pituitary hormone deficiencies. In general, the biochemical goal in acromegaly is to normalize IGF-1 levels for age and sex, to lower the GH level to <1 ng/ml after glucose suppression, and to maintain random GH levels <2.5 ng/ml. This in turn should lower morbidity and mortality, thereby improving the quality and quantity of life in these patients. Most patients are followed long-term using IGF-1 levels, glucose-suppressed GH levels (which can be complementary to measurement of IGF-1, particularly in terms of prognosis for relapse), and MRI as indicated.

The major treatment modalities used in the management of GH excess include surgery, medical therapy, and radiation. Although surgery remains the cornerstone of acromegaly therapy (particularly in smaller tumors where there is a better chance of cure), primary medical therapy may be beneficial in certain situations, such as in those with unresectable tumors or contraindications to surgery. Although the available data do suggest a comparable efficacy with primary octreotide therapy, it is generally believed that surgical therapy should be undertaken when there is a chance for cure, since medical therapy does not offer that hope. Although surgery is unlikely to cure a patient with an invasive macroadenoma, surgical debulking of a large tumor may be of benefit in the long term medical treatment of the acromegalic patient. The most important consideration in terms of surgical therapy is to refer the patient with acromegaly to a neurosurgeon whose primary focus is on pituitary surgery, since studies have shown that positive patient outcomes directly correlate with pituitary surgery volume. Despite surgery, medical therapy is often needed to control GH and IGF-1 secretion and, in 2008, there are many options from which to choose. (See table). The somatostatin analogs are considered by many to be the initial therapy of choice, and these drugs are particularly considered when significant tumor bulk remains after surgery, since they afford the possibility of tumor shrinkage. In addition to Sandostatin® LAR® (octreotide LAR), there is now a second somatostatin analog available in the United States - Somatuline® Depot (lanreotide)—that is given as a deep subcutaneous injection every 4 weeks. The growth hormone receptor antagonist, Somavert® (pegvisomant), has been FDA approved for the treatment of acromegaly since 2003. It is administered as a once daily subcutaneous injection and is particularly useful in patients who also have diabetes, since it does not negatively impact on insulin secretion like the somatostatin analogs can. On the horizon is a new somatostatin analog, pasireotide, which binds to 4 of the 5 somatostatin receptors and which is currently about to undergo further testing in a phase III clinical trial. An octreotide implant is also under investigation. Finally, radiation still has a role in the treatment algorithm of acromegaly and, outside of surgery, offers the only hope for cure in this debilitating disease. As potentially safer and more precise radiation methods such as proton therapy become more widely used and better studied, radiation may start to play a more prominent role in the upfront treatment of acromegaly.

	Percent of Patients with normalized IGF-1	Possible Adverse Events	Comments
Surgery Transsphenoidal resection	<ul style="list-style-type: none"> • 80% microadenomas • <50% macroadenomas 	<ul style="list-style-type: none"> • CSF leak • Hypopituitarism • Anesthetic risks 	<ul style="list-style-type: none"> • Immediate effect • Definitive therapy • Initial treatment in most cases • Critical to refer to an experienced neurosurgeon
Radiation Conventional radiation	• 30-60%	<ul style="list-style-type: none"> • Hypopituitarism (>50%), visual disturbance, neurological damage, secondary tumors 	<ul style="list-style-type: none"> • 40-50 Gy over 5-6 weeks • Very slow biochemical response (up to 10 yrs) • Reduction in tumor size
Stereotactic radiosurgery	• 30-60%	<ul style="list-style-type: none"> • Same as above • Risks minimized through less exposure of normal tissues to radiation 	<ul style="list-style-type: none"> • Response may be quicker • Best for residual tumor in the cavernous sinus • Fewer data on outcome
Medications Dopamine Agents Bromocriptine	• 10%	<ul style="list-style-type: none"> • GI disturbance, orthostatic hypotension, nasal stuffiness, dry mouth, headaches, drowsiness 	<ul style="list-style-type: none"> • Best for tumors co-secreting prolactin • May have symptomatic response separate from IGF-1 effect • Up to 20mg daily
Cabergoline	• 34%	<ul style="list-style-type: none"> • Same as bromocriptine 	<ul style="list-style-type: none"> • Same as bromocriptine • Less frequent GI side effects • 1-4 mg weekly in divided doses
Somatostatin Analogs			<ul style="list-style-type: none"> • Affinity for somatostatin receptors 2 and 5 • Can cause tumor shrinkage
Octreotide LAR	• 67%	<ul style="list-style-type: none"> • Nausea, malabsorption, diarrhea, gallbladder disease, changes in glucose tolerance 	<ul style="list-style-type: none"> • Deep intramuscular injection • 10-30 mg every 4 weeks
Lanreotide Depot	• 58%	<ul style="list-style-type: none"> • Same as octreotide 	<ul style="list-style-type: none"> • Deep subcutaneous injection • 60-120 mg every 4 weeks
GH receptor antagonists Pegvisomant	• 82%	<ul style="list-style-type: none"> • Elevated LFTS • Theoretic risk of increased tumor size 	<ul style="list-style-type: none"> • Daily self-administered injection • 10-30 mg daily • Must follow IGF-1 levels because GH levels will not be interpretable

Research

The endocrine system is a complex hormonal system. These hormones affect many parts of the human body, and are produced in many locations within the body. With such a broad range of rare diseases, research has taken a new and visionary approach to the field of endocrinology.

There has been a new interest in both the system and in its uncommon diseases in the research arena. Thus, we are currently able to offer new studies in multiple arenas.

The endocrine department at M.D. Anderson Cancer Center has open research stud-

ies in several disease processes some of which are pituitary related. Current studies involve Cushing's disease and Acromegaly. Further information on the studies listed below can be either mailed to you or can be viewed through the attached links.

ACROSTUDY – A Multicenter, Post Marketing Surveillance Study of Somavert Therapy in Patients with Acromegaly in the US and Europe Phase 4 study to follow patients currently being treated with Somavert.
2005-022

A MultiCenter, Open Label Study to Assess the Ability of Subjects with Acromegaly, or their Partners, to Administer Somatuline® Autogel®. This is a study to evaluate self injection with Somatuline® Autogel a recently approved drug for treatment of Acromegaly
2007-0048

New Additions to the Endocrine Faculty Team



Dr. Jessica K. Devin earned her medical degree from Vanderbilt University School of Medicine, where she also earned a Master of Science degree in Clinical Investigation. Dr. Devin completed both her internal medicine residency and endocrinology fellowship at Vanderbilt University Medical Center in the American Board of Internal Medicine Research Pathway. Her clinical interests include pituitary tumors, Cushing's syndrome, hypopituitarism and adrenal disease. Her research interests include cardiovascular risk in hypopituitarism, optimizing the health-related quality of life in patients with pituitary disease, and hypopituitarism as a consequence of cancer-related therapies.

Dr. Mimi Hu is a native of Philadelphia and earned a degree in mechanical engineering from Rice University. She worked in a Houston consulting firm before starting medical school at the University of Texas Houston Health Sciences Center. Following medical school



she went to Baylor College of Medicine for her residency in internal medicine. After staying an additional year as chief medical resident, she started her fellowship in endocrinology there. She spent two years of clinical research at M.D. Anderson under the mentorship of Dr. Robert Gagel. During that time she developed an investigator-initiated study evaluating the efficacy of short-term teriparatide in patients with acute postoperative hypocalcemia, which has recently been activated with plans for patient enrollment in March 2008. Her clinical experience has focused on evaluating and managing patients with metabolic bone diseases, hyperparathyroidism, and thyroid carcinoma (particularly medullary thyroid carcinoma). She joined the faculty at M.D. Anderson on August of 2007.

New Clinical Trial

The Pituitary Tumor Program at M. D. Anderson Cancer Center will soon be opening a new multi-center Phase III clinical trial sponsored by Novartis: "A randomized, double-blind study to assess the safety and efficacy of different dose levels of Pasireotide (SOM230) over a 6 month treatment period in patients with de novo, persistent or recurrent Cushing's disease."

Pasireotide is a novel somatostatin analogue that exhibits a high binding affinity for four of the five known human somatostatin receptors, whereas expression of somatostatin receptors 1, 3 and 5 has been demonstrated in ACTH-secreting pituitary tumors. Pasireotide inhibits the release of ACTH from the tumor and thereby controls hypercortisolemia. The effect on tumor volume remains to be determined. The outcome of the clinical trial may allow pasireotide to become available for medical treatment for patients with Cushing's disease.

Eligibility criteria include:

- Patients (18 years or older) with persistent or recurrent Cushing's disease secondary to an ACTH-secreting pituitary tumor

after surgical resection are eligible to participate.

- Patients with de novo Cushing's disease may be included only if they are not considered surgical candidates.
- Patients must not have received radiation therapy to the pituitary within the last ten years or have a pituitary tumor compressing the optic chiasm.
- Patients who are currently treated with adrenal blocking medications are eligible after a brief wash-out period.
- Additional criteria for participation in the study apply.

Study participants will need to self-administer pasireotide subcutaneously twice daily and participate in 18 study visits at MD Anderson over the course of 14 months. Participants will not be charged for any costs related to the study drug or visits. Patients will have the option to continue to receive therapy with pasireotide after study completion as long as they do not meet any of the criteria for discontinuation of the study or until pasireotide is commercially available or the pasireotide development program is discontinued. Please contact Mary Jean Klein, Manager, Clinical Protocol Administration, at 713-792-2840 for further information.

The University of Texas M.D. Anderson Cancer Center
Department of Endocrine Neoplasia & Hormonal Disorders
Unit 435, P.O. Box 301402
Houston, Texas 77230-1402