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Inside This Issue

Multifaceted Ghrelin: Growth Hormone Secretagogue, Appetitive Peptide, and Insulin Suppressor

Growth hormone (GH) production is controlled by an array of hypothalamic peptides, intrapituitary factors, and systemic hormones. Johannes D. Veldhuis, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, explains: "Three peptides are critical players: GH-releasing hormone (GHRH, cloned from a human pancreatic tumor), somatostatin (cloned from sheep hypothalamus), and the GH-releasing peptide (GHRP) ghrelin (cloned from rat stomach). The existence of ghrelin was postulated in 1978 by Cy Bowers at Tulane University; the ghrelin receptor was cloned in 1996 by scientists at Merck laboratories; and the ghrelin gene was isolated in 1999 by Kojima and colleagues in Osaka, Japan." The key features of ghrelin are listed in Table 1.

Johannes D. Veldhuis, MD

Table 1. Key Features of Ghrelin

- **Widely expressed: stomach, brain, pituitary, pancreas**
- **Receptors: nearly ubiquitous**
- **First acylated bioactive peptide identified in mammals**
- **Potent GH secretagogue**
- **50% homology with motilin**
- **Enhances appetite, reduces insulin secretion, and stimulates GI tract motility**

Ghrelin is a 28–amino acid Ser^3-octanoylated peptide expressed ubiquitously, including in hypothalamic neurons, the pituitary gland, stomach and upper gastrointestinal (GI) tract, kidney, and cardiovascular system. The acyl (octanoyl or decanoyl) group is critical for endocrine activity (Figure 1). Dr Veldhuis adds: "A subset of gastric oxyntic cells, originally termed X/a-like cells because of their unknown granule content, are now known to be ghrelin and motilin cosecreting cells. Ghrelin and synthetic GHRPs act via the type Ia secretagogue receptor to stimulate GH secretion by about 2-fold in vitro and 5- to 20-fold in vivo. The multifold-greater in vivo effects reflect ghrelin's stimulation of hypothalamic GHRH release and inhibition of somatostatin action. Ghrelin contributes to fasting GH output in the rodent, since transgenic silencing of the central nervous system ghrelin receptor in the female mouse reduces GH secretion and insulinlike growth factor 1 concentrations, and an antagonist of the ghrelin receptor decreases GH pulse size in the male rat. In humans, mutations of the ghrelin receptor are associated with short stature. Conversely, bolus injection and continuous intravenous infusion of ghrelin or GHRPs stimulate pulsatile GH secretion dose-dependently and synergize markedly with L-arginine or GHRH (Figure 2). Thus, combined ghrelin/L-arginine or

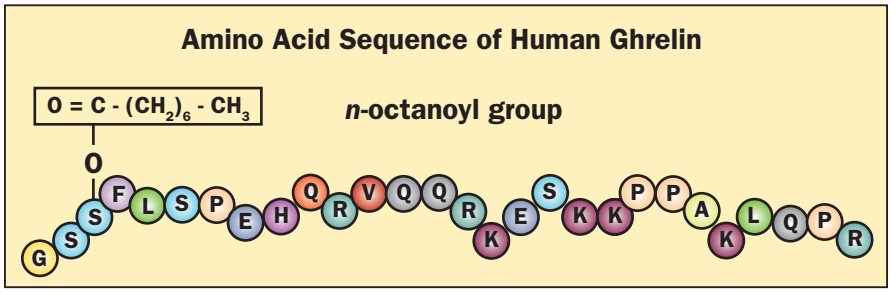


Figure 1. Ghrelin structure. The fatty-acyl moiety esterified to the third serine residue is usually octanoic acid, but may be decanoic or decenoic acid.

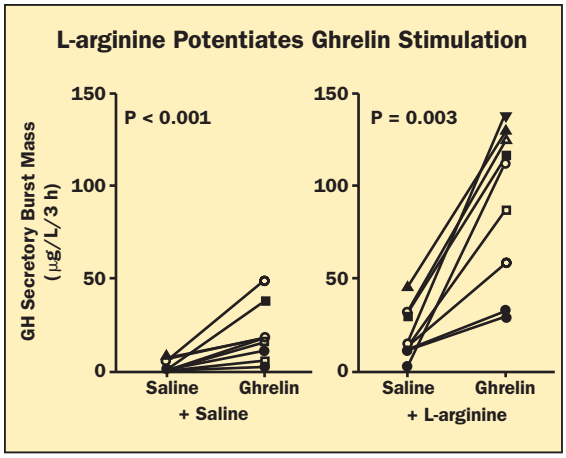


Figure 2. Potentiation of ghrelin-stimulated GH secretion in postmenopausal women by prior L-arginine infusion.

Adapted with permission from J Clin Endocrinol Metab 91:2441-2446, 2006.

Table 2. Potential Applications of Ghrelin Analogs

Ghrelin agonists

- **Increase anabolism in cachectic states (eg, HIV wasting)**
- **Stimulate GI tract motility in patients with motility disorders (eg, gastroparesis, ileus)**
- **Promote appetite in patients with anorexia (eg, anorexia nervosa, chemotherapy)**
- **Increase linear growth in patients with short stature when GHRH is present**
- **Decrease diastolic afterload in patients with heart failure**

Ghrelin antagonists

- **Increase glucose-induced insulin secretion in patients with type 2 diabetes mellitus**

ghrelin/GHRH injection may be useful in evaluating presumptive GH deficiency. Moreover, ghrelin analogs may have utility in the treatment of short stature and GH-deficiency states if GHRH release and somatotrope function are preserved (Table 2)."

Acylated ghrelin is measurable in plasma with suitable N-terminally directed assays. Starvation, fasting between meals, on-going weight loss after gastric-bypass surgery, end-stage liver and kidney disease, malnutrition, and cachexia elevate bioactive ghrelin concentrations. Conversely, nutrient intake (carbohydrate > protein > fat), obesity, hypogonadism, insulin, and somatostatin reduce plasma ghrelin levels. Dr Veldhuis continues: "Ghrelin is the only systemically active appetitive hormone known. Esurient effects can be dissociated from stimulation of GH secretion by using nonpeptidyl ghrelin mimetics. Appetite enhancement is antagonized by inhibitors of neuropeptide Y, agouti-related peptide, and orexin (a peptide that also enhances wakefulness) and potentiated by inhibitors of the anorexigenic peptides, melanocortin or corticotropin-releasing hormone. Given the interlinked and adaptive nature of the anorexigenic/orexigenic neuronal network, it is not yet clear whether ghrelin-receptor agonists will be able to sustain increased food intake in cachetic states, such as AIDS, chronic obstructive pulmonary disease, cancer, and anorexia nervosa (Table 2)."

Ghrelin and GHRPs inhibit insulin secretion acutely. Conversely, ghrelin-receptor blockers enhance insulin secretion and improve glucose control in experimental models of type 2 diabetes mellitus. Intrapancreatic ghrelin is produced in islet epsilon cells, which constitute as much as 10% of the mass of prenatal pancreatic islets. The possibility exists that fetal ghrelin regulates islet replication, since ghrelin is antiapoptic to other cells (eg, cardiomyocytes, endothelia, preadipocytes).

In humans and animals, ghrelin stimulates upper GI tract motility by eliciting a type III migrating motor complex in the stomach and proximal small bowel. Ghrelin analogs are under evaluation as prokinetic agents for treatment of gastroparesis and postoperative ileus.

Dr Veldhuis notes: "Ghrelin also inhibits fat oxidation, induces weight gain, reduces diastolic blood pressure, and increases cardiac output. Thus, other exploratory therapeutic applications of ghrelin include frailty associated with aging and congestive heart failure (Table 2). Despite the potential for diverse therapeutic uses, physiologic regulation of the production and metabolism of the acylated (putatively bioactive) peptide remains poorly understood. Recent cloning of the acyl transferase that octanoylates ghrelin and the deacylase that removes *n*-octanoic acid from ghrelin should lead to better understanding of these points."

High-Value Diabetes Care

In this election year, debate continues about the preferred solution for health care delivery in the United States. Steven A. Smith, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, explains: "There are concerns about the viability of our present system, which has greatly increased the cost burden for our country and has not provided consistent, high-value patient-centered care."

In 2006, the Mayo Clinic National Symposium on Health Care Reform (http://www.mayoclinic.org/healthpolicycenter/2006-symposium.html)

concluded that it was imperative that all people have access to appropriate care and health care insurance and that

- Adequate financial resources exist within the total system to accomplish this task.
- The optimal systems of care, delivery of care, and reimbursement are identified and designed to achieve these results.

Dr Smith continues: "It is well known that diabetes mellitus is a chronic disease that is expensive to treat; however, it is even more expensive not to treat. The population of patients with type 2 diabetes mellitus is growing, and these patients are experiencing increased challenges because of complex treatment regimens and the number of comorbid conditions. Treatment prioritization in these patients is increasingly important to improve the value of the money spent on diabetes care."

Victor M. Montori, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, notes: "It is not possible for us in the health care system to define value for our patients. People should reach their own conclusions about the value we offer by determining how likely it would be for them to be better off if they got our care and what would that take in terms of burden of treatment, the experience of receiving care (including inconvenience and discomfort), and costs."

There has been an increasing emphasis on evaluating provider performance for offering evidence-based care. Dr Smith notes, however: "The performance measures used in such evaluations assume 'one size fits all,' but these measures do not account for changing needs and preferences of patients. Thus, it is often difficult for primary care and specialty clinicians to prioritize interventions for patients with diabetes mellitus when attempting to account for patient preferences and simultaneously responding to external quality measurement requirements (eg, achieving a glycosylated hemoglobin of 7%). Failure to account for patient preferences may be expressed through patients' nonadherence or discontinuation of important medications and nonattendance to scheduled appointments."

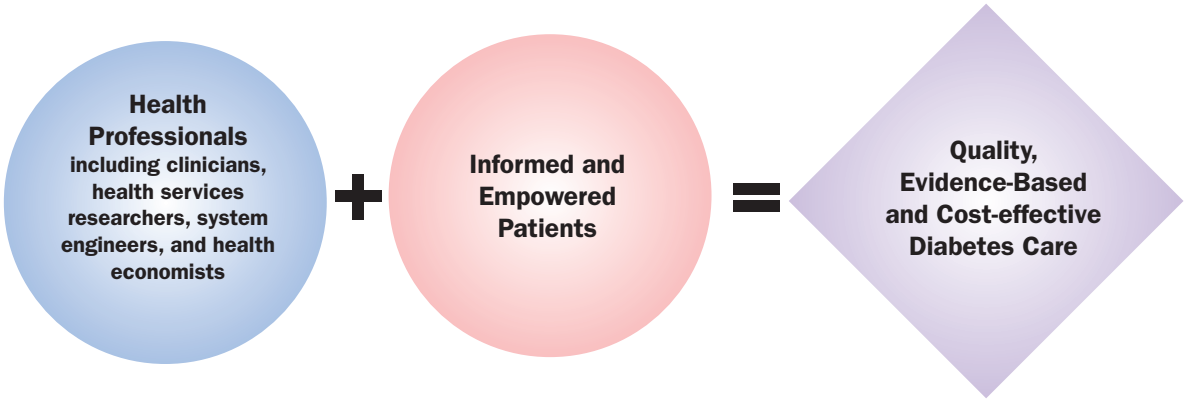
Mayo Clinic in Rochester—in collaboration with North Carolina State University and the University of Colorado—has a dedicated team of clinicians, health services researchers, systems engineers, and health economists who seek to bridge the gaps in the care of people with diabetes mellitus by advancing knowledge about how to optimally treat this disorder over the course of a patient's lifetime.

Victor M. Montori, MD, Steven A. Smith, MD, and Nilay D. Shah, PhD

Nilay D. Shah, PhD, of the Department of Health Care Policy & Research at Mayo Clinic in Rochester, explains: "This strategy considers multiple criteria, including a patient's quality-adjusted lifespan, adherence to treatment, the costs of treatment, and the cost of diabetes-related complications to the health system." These efforts have included the following:

- The development of a natural history model for type 2 diabetes mellitus based on longitudinal analysis of parameters of clinical care and optimization modeling for specific treatment decisions (eg, when to initiate medications to control cholesterol and blood pressure).
- The study of clinician-patient interaction for identification of determinants of treatment choice.
- The development of a model of shared treatment decision making for diabetes and other chronic diseases.
- The design, evaluation, and implementation of decision aids in practice.
- The implementation and evaluation of new models of care (eg, the impact of decision aids, patient-specific tailored evidence-based messages, and telemetric specialty advice for medication management during the clinical encounter).

The collaborators' ultimate goal is to reduce the costs of diabetes care—measured not only in health care dollars but, more importantly, in terms of human suffering and patient outcomes. For example, in October 2007, these investigators reported at the annual meeting of the Society for Medical Decision Making in Pittsburgh, Pennsylvania, the predicted impact on comorbid conditions of the introduction of multiple cholesterol and blood pressure treatments, based on varying national and international practice guidelines. For each of the



therapies commonly considered, these investigators estimated the proportional change in the relevant metabolic factor and time to first cardiovascular event or death from other causes, in relation to total treatment costs. While there did not appear to be differences between these various guidelines for the prediction of cardiovascular death, there were significant differences between the longest and the shortest expected time to first cardiovascular event and the total expected cost of treatment. This observed discrepancy in predicted outcomes suggests that there are potential differences in important patient outcomes, even when adhering to current guidelines.

Dr Smith adds: "We believe that the traditional system of delivery of diabetes care and reimbursement is obsolete and that a new system that fosters collaboration between health professionals, including clinicians, health services researchers, system engineers, and health economists, and informed and empowered patients may provide the best opportunity to deliver evidence-based and cost-effective diabetes care. Regulating an obsolete system will not improve the quality of care and outcomes for people with diabetes.

"Health professionals should be the architects in the care delivery for people with chronic disease such as diabetes. For this to happen, there will need to be a change in national health policy and legislation. If the purpose of a system of delivery of diabetes care is to provide appropriate access to care and decrease bad outcomes—costs in lives, suffering, disability, and health care dollars—then new metrics of productivity and reimbursement will be necessary. This system should provide valid evidence-based diabetes care to all patients with diabetes in the community."

Novel Therapies for Type 2 Diabetes Mellitus

As understanding of the underlying pathophysiology and metabolic abnormalities leading to the development of type 2 diabetes mellitus has increased, novel pharmacologic approaches have been developed to better manage this disease. Roger L. Nelson, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, says: "Since it has been shown that improved glycemic control reduces long-term microvascular complications, more stringent glycemic targets are sought. To achieve these targets, a combination of various agents or classes of drugs has become a necessity in many patients."

Incretin Therapies

Incretins are insulinotropic peptides—secreted by enteroendocrine cells in the gastrointestinal tract in response to a meal—that augment insulin secretion and suppress glucagon secretion. M. Regina Castro, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, explains: "They also slow gastric emptying and suppress appetite by a central hypothalamic effect. Glucagon-like peptide 1 (GLP-1) is the incretin with dominant biological activity. The effects of GLP-1 on glucagon secretion and insulin secretory responses are glucose-dependent, but counterregulatory release of glucagon in response to hypoglycemia is preserved even in the presence of pharmacologic concentrations of GLP-1."

Plasma levels of GLP-1 are low in the fasted state but increase rapidly after eating. However, GLP-1 is inactivated by the enzyme dipeptidyl peptidase IV (DPP IV) within 1 to 2 minutes. The rapid degradation of GLP-1 limits its clinical applicability as a pharmacologic agent.

GLP-1 Analogs

Exenatide (Byetta; Amylin Pharmaceuticals, Inc, San Diego, California) is an injectable GLP-1 agonist that mimics the effects of naturally occurring GLP-1 but is resistant to the action of DPP IV. It was approved by the US Food and Drug Administration (FDA) in April 2005 for use in patients taking metformin, sulfonylureas, or thiazolidinediones who have not achieved glycemic goals. Dr Nelson comments: "Hypoglycemia can occur in patients also taking a sulfonylurea, but reduction in the dose of sulfonylurea reduces potential for hypoglycemia. One of the major advantages of exenatide is its ability to induce weight loss. Recently, the FDA issued a warning after 30 postmarketing reports associated the use of exenatide with development of acute pancreatitis. Therefore, patients taking exenatide who experience symptoms of pancreatitis should discontinue the drug and not restart it, unless an alternative cause for this problem is identified."

Two GLP-1 analogs are currently under investigation in phase 3 clinical trials. Long-acting release (LAR) exenatide shows sustained, dose-dependent glycemic control in animal studies for up to 28 days after a single subcutaneous injection. Preliminary experience with this drug in 45 patients with type 2 diabetes mellitus indicates a much greater reduction in fasting glucose concentration and hemoglobin A_{1c} (HbA_{1c}) after once-weekly administration for 15 weeks, compared with exenatide twice daily. Compared with twice-daily exenatide, LAR exenatide seems to offer a more convenient administration schedule, improved glycemic control, and minimal adverse effects.

Liraglutide (Novo Nordisk US, Princeton, New Jersey) is another GLP-1 analog that is currently under investigation and shows good efficacy and beneficial effects on weight.

DPP IV Inhibitors

Dr Castro explains: "The observation that GLP-1 levels in plasma fall shortly after eating as a result of rapid degradation by DPP IV led to the development of DPP IV inhibitors aimed at prolonging the half-life of endogenous GLP-1. DPP IV inhibitors mimic many of the actions of GLP-1 agonists. These agents reduce serum DPP IV activity by more than 80% after a single oral dose, with some inhibition maintained 24 hours after administration. They differ from GLP-1 receptor agonists in that they are oral medications, are generally weight neutral, and have a lower incidence of gastrointestinal adverse effects—presumably because postprandial levels of GLP-1 seen with DPP IV inhibitors are lower than those seen with GLP-1 analogs. They appear to reduce HbA_{1c} similar to GLP-1 receptor agonists."

M. Regina Castro, MD, and Roger L. Nelson, MD

Sitagliptin (Januvia; Merck & Co, Inc, Whitehouse Station, New Jersey) was approved by the FDA in October 2006 for use either as monotherapy or in combination with metformin or thiazolidinediones. Given as a single daily dose of 100 mg, it has been shown to be well tolerated, without severe hypoglycemia or weight gain. When used in combination with metformin, it resulted in notable reductions in HbA_{1c} (0.5%-1.0%), fasting and postprandial plasma glucose levels, and fasting serum insulin levels.

Dr Castro continues: "More than 5,000 patients are currently enrolled in phase 3 trials involving vildagliptin (Novartis, Basel, Switzerland) in the United States. In the initial studies, vildagliptin has resulted in statistically significant reductions of HbA_{1c}—ranging from 0.5% to 0.9% for 50-mg and 100-mg daily doses, respectively. As with sitagliptin, this agent appears to be weight neutral, well tolerated, and associated with low incidence (<1%) of hypoglycemia. Vildagliptin was recently approved in Europe as add-on therapy for patients who have failed to achieve their glycemic targets on other oral antidiabetic drugs."

Amylin Analog

Pramlintide (Symlin; Amylin Pharmaceuticals, Inc, San Diego, California) is a synthetic analog of amylin, approved by the FDA for use as adjuvant therapy in patients with type 1 and type 2 diabetes mellitus who are treated with insulin. Amylin is a 37–amino acid peptide cosecreted with insulin in response to meal ingestion. It is virtually absent in patients with type 1 diabetes mellitus, but as with insulin, its concentrations may be normal or

increased above normal in patients with type 2 diabetes mellitus. Pramlintide has been modified to prevent formation of amyloid fibrils that occur with native amylin within the pancreatic β-cell. Like exenatide, it decreases appetite, slows gastric emptying, and reduces glucagon secretion. In some patients, pramlintide has been associated with considerable weight loss. It is administered as an additional subcutaneous injection before meals but should never be mixed with insulin. Insulin requirements are usually reduced by 10% to 50%, and postprandial glycemic excursions are reduced as well. Abdominal bloating and nausea are common adverse effects seen with the initiation of treatment and with dose escalation.

Dr Nelson notes: "The initial dose of pramlintide in patients with type 1 diabetes mellitus is 15 mcg administered subcutaneously before each meal, and the dose should be increased gradually up to 30 and 60 mcg, depending on tolerance. For patients with type 2 diabetes mellitus, the starting dose is 60 mcg administered subcutaneously before meals, and the dose may be increased to 120 mcg. Pramlintide is contraindicated in patients with gastroparesis or hypoglycemia unawareness. The mean HbA_{1c} reduction obtained with adjuvant pramlintide is approximately 0.6%."

Conclusions

Dr Castro summarizes: "The costs and benefits of these newer agents should be weighed against the older and much less expensive medications. For example, the daily cost for metformin and the generic sulfonylureas is $0.15 to $0.25 versus $6.00 to $7.50 for the newer agents. In addition, the HbA_{1c}-lowering effect of these new agents is probably less than that of the older agents. It is also important to note that long-term studies specifically evaluating outcomes related to micro- and macrovascular complications with these new agents are not available."

Research Corner

Rituximab in the Treatment of Graves' Ophthalmopathy

Graves' ophthalmopathy (GO), the inflammatory eye disease associated with Graves' hyperthyroidism, is characterized by proptosis, eye pain, periorbital edema, and extraocular muscle dysfunction. The signs and symptoms of GO are detectable in the majority of patients with Graves' disease, with severe and potentially sight-threatening disease being present in 5% of patients. The natural history of GO is one of deterioration during the active phase, followed by gradual improvement over months to years. Some patients experience severe, active disease for several years with significant negative impact on their quality of life. Current therapeutic options—including systemically administered corticosteroids, orbital radiation, and surgery—are of limited efficacy or carry with them serious morbidity. Recent experimental evidence suggests that autoimmunity directed against the thyrotropin receptor (TSHR) and B-cell–produced TSHR autoantibodies are central to the pathophysiology of GO. Based on this work, endocrinologists and ophthalmologists at Mayo Clinic in Rochester are studying the efficacy of rituximab, an anti-CD20 monoclonal antibody that induces transient B-cell depletion and impacts antigen presentation, in the treatment of moderate to severe, active GO.

Thirty patients will be enrolled in a double-blind, randomized, controlled study. Fifteen patients will receive rituximab (1,000 mg administered intravenously twice at a 2-week interval), and 15 patients will receive 2 saline infusions. All patients will return to Mayo Clinic in Rochester 4 additional times during the subsequent year for blood and ocular testing.

Inclusion Criteria: men and women, ages 18 to 75 years, affected by active ophthalmopathy (clinical activity score ≥4) of moderate to severe degree.

Exclusion Criteria: contraindications to therapy with rituximab, including HIV, hepatitis B, hepatitis C, denied consent to HIV or hepatitis testing, inactive or mild GO, absolute neutrophil count less than 1.5×10^9/L, allergy to diphenhydramine.

To refer a patient with GO for this research study, please contact Rebecca S. Bahn, MD, at 507-284-3707, or Marius N. Stan, MD, at 507-284-2463.

Upcoming Education Opportunities

Mayo Clinic Nutrition in Health and Disease, October 9-10, 2008, Chicago, Illinois. This course, designed for physicians, dietitians, nurses, and pharmacists, will provide a full-spectrum, in-depth overview of challenging nutritional issues that clinicians encounter in the ambulatory and hospital settings. For more information about this course, please call 800-323-2688 or visit www.mayo.edu/cme/endocrinology.html.

12th Mayo Clinic Endocrine Course, March 16-20, 2009, on the Big Island of Hawaii. This course, created for endocrinologists and interested internists and surgeons, will present the latest material on the diagnosis and treatment of endocrine disorders. The 5-day course (7:30 AM to 12:30 PM daily) will span the full spectrum of endocrinology. The course will be held at the Hapuna Beach Prince Hotel. Located at the Mauna Kea Resort complex on the Kohala Coast of the Big Island of Hawaii, this spectacular resort is a 30-minute drive from the Keahole-Kona Airport. For more information about this course, please visit http://endocourse.mayo.edu.

Highlights From the 2008 Mayo Clinic Endocrine Course

The 11th Mayo Clinic Endocrine Course—held April 16-19, 2008, Palma de Mallorca, Spain—brought together 392 physicians from 48 countries. Simultaneous Spanish translation was provided. Other unique aspects of the course included short lectures, case-based debates, clinical pearls sessions, computer-based clinicopathologic case presentations, and "case snappers" presented by course attendees. The opening reception was held at Bellver Castle.

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2008 Graduating Endocrine Surgery Fellow

John R. Porterfield, MD (right), and his program director, Clive S. Grant, MD. Dr Porterfield has joined the Department of Surgery at the University of Alabama at Birmingham to build a comprehensive endocrine surgical practice.

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Welcome to the first issue of Physician Update e-mail newsletter. This newsletter will offer access to articles from the Clinical Update print publication, plus other items of general interest to a physician audience.

Patient Care

Inpatient Video-EEG Monitoring for Epilepsy
Continuous video-EEG monitoring (inpatient) helps localize seizure focus, determine seizure type, and quantify the number of seizures in patients with intractable recurrent seizures and those with an unconfirmed seizure diagnosis.

Optimizing the Functional Performance of Cancer Survivors
There is a growing understanding of the importance of exercise and rehabilitation for cancer survivors. Physical Medicine specialists can help patients manage the negative long-term sequelae of cancer and its treatments and obtain a more satisfying, high-quality recovery.

New Endoscopic Treatment for Severe Gastrointestinal Bleeding
Endoscopic ultrasound-guided therapy appears to be a safe and effective treatment for patients with severe gastrointestinal bleeding for whom conventional therapies

Endocrinology Update

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