MAYO CLINIC

ENDOCRINOLOGY UPDATE

ENDOCRINOLOGY NEWS FROM MAYO CLINIC

volume 2
number 1
2007

Inside This Issue

The "NEAT Defect" in Human Obesity: The Role of Nonexercise Activity Thermogenesis

James A. Levine, MD, PhD

By the law of conservation of energy, body fat increases when energy intake is consistently greater than energy expenditure. Excess body fat and obesity are the result of sustained positive energy balance. James A. Levine, MD, PhD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic Rochester, says: "Since it is now normal to be overweight or obese in America, the urgency to understand why humans are gaining weight has intensified. In the absence of firm data that link increased dietary intake to obesity, the role of energy expenditure in human energy balance has come under greater scrutiny."

There are 3 components of human daily energy expenditure (Figure 1). Basal metabolic rate is the energy required for core body functions and is measured at complete rest without food; it accounts for about 60% of daily energy expenditure in a sedentary person. Body size accounts for nearly all the variability in basal metabolic rate—the bigger a person, the greater his or her basal metabolic rate. The thermic effect of food is the energy expended in response to a meal and is associated with digestion, absorption, and fuel storage. The thermic effect of food accounts for about 10% of daily energy needs and does not vary greatly from person to person. Activity thermogenesis can be subdivided into exercise activity thermogenesis and nonexercise activity thermogenesis (NEAT).

NEAT Varies by 2,000 Calories per Day

For 2 adults of similar size, daily energy expenditure varies by as much as 2,000 calories per day. As noted, basal metabolic rate is largely accounted for by body size, and the thermic effect of food is small. Thus, activity thermogenesis must vary by approximately 2,000 calories per day. Does the variation of 2,000 calories per day in activity thermogenesis occur because of exercise, or is it because of NEAT? Dr Levine explains: "Exercise is defined as 'bodily exertion for the sake of developing and maintaining physical fitness,' for example, participating in a sport or visiting the gym. The vast majority of the world's population do not participate in exercise, as so defined, and for them, exercise activity thermogenesis is zero. Even for the minority of people who do exercise, for most of them, exercise accounts for an energy expenditure of 100 calories per day. Thus, NEAT

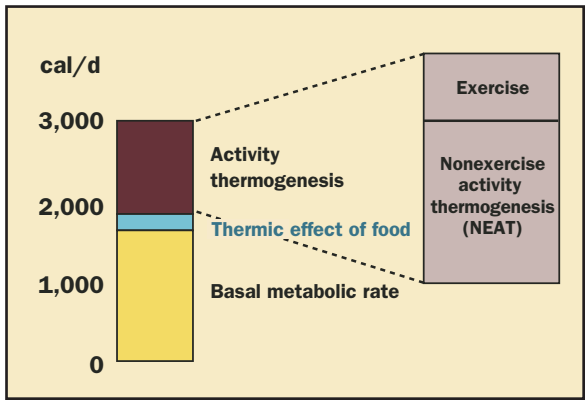


Figure 1. The 3 components of human daily energy expenditure are the basal metabolic rate (about 60% of daily energy expenditure); the thermic effect of food, ie, the energy expended in response to a meal (about 10% of daily energy expenditure); and activity thermogenesis (both exercise and nonexercise activity thermogenesis).

explains why an active person can expend 2,000 calories per day more than an inactive person of the same size. NEAT is the energy expenditure of all physical activities other than volitional sporting-like exercise. NEAT includes all those activities that render us vibrant, unique, and independent beings."

NEAT is expended every day and can most easily be classified as occupational NEAT and leisure NEAT. Occupation is a predominant determinant of NEAT. For an average, nonobese person, occupational NEAT varies, as shown in the Table. Active work can burn 1,000 calories per day more than a sedentary job. Variability in leisure also accounts for substantial variability in NEAT. Depending on one's choice of evening activity, the energy expenditure can range from 30 calories watching TV to 600 calories during more energetic pursuits such as gardening or home repair. Therefore, nonexercise activity varies by as much as 2,000 calories per day because some occupations are far more energy expending than others and because leisure activities range from almost complete rest to those that are highly energized.

NEAT Is Biologically Adjusted to Counterbalance Fat Gain

When 16 lean volunteers were overfed by 1,000 calories per day above their weight maintenance needs, changes in NEAT accounted for the energetic counterresponse to fat gain. Those people who increased their NEAT the most did not gain fat, even with overfeeding. Those who did not increase their NEAT with overfeeding gained the most fat.

Table. Occupational Nonexercise Activity Thermogenesis (NEAT)*

Occupation type	NEAT, cal/d
Chair-bound	300
Seated work (no option of moving)	700
Seated work (discretion and requirement to move)	1,000
Standing work (eg, homemaker, cashier)	1,400
Strenuous work (eg, farming)	2,300

*Data based on a basal metabolic rate of 1,600 cal/d. Adapted from Black AE, Coward WA, Cole TJ, Prentice AM. Human energy expenditure in affluent societies: an analysis of 574 doubly-labelled water measurements. Eur J Clin Nutr. 1996;50:72-92.

NEAT Is Important in Human Obesity

Dr Levine reports: "To examine whether NEAT is important in obesity, we integrated microsensors into undergarments, as shown in Figure 2. These sensors allowed us to quantify body postures and movements, especially walking, every half-second for 10 days. Obese subjects were seated for 2½ hours per day more than lean subjects. The lean sedentary people stood and walked for more than 2 hours per day longer than obese subjects. If the obese subjects were to adopt the same NEAT-o-type as the lean subjects, they might expend an additional 350 calories per day. Thus, NEAT and specifically walking are of substantial energetic importance in obesity."

Dr Levine concludes: "This information collectively demonstrates that there may be a NEAT defect in human obesity and that this effect is underpinned by a profound yet subtle biology. If one is born with the genetic trait to sit, is obesity inevitable? I do not think so, because obesity emerged over the past century and especially the past 20 years, but our genes did not change. Chair-living has proven so enticing that we have forsaken our legs. It is now time to find ways to get us back onto our legs."

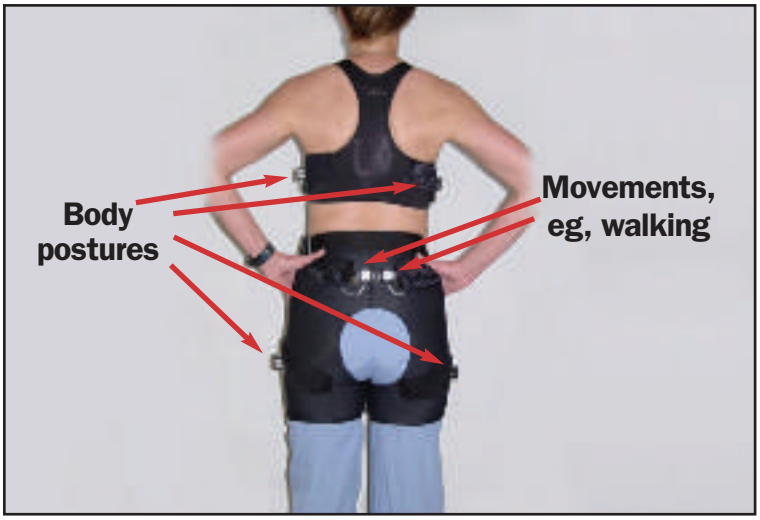


Figure 2. Microsensors embedded in undergarments used to quantify body postures and movements, especially walking, every half-second for 10 days.

Stereotactic Radiosurgery of Growth Hormone-Producing Pituitary Adenomas

Growth hormone (GH)–producing pituitary adenomas account for approximately 20% of all pituitary neoplasms. Todd B. Nippoldt, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic Rochester, says: "Untreated acromegaly is a morbid condition associated with disfigurement and increased mortality. Treatment options include drug therapy, surgical resection, radiotherapy, stereotactic radiosurgery, or a combination of these approaches. The goals of treatment are to achieve normal GH and insulin-like growth factor 1 (IGF-1) concentrations, reverse the signs and symptoms related to GH excess, improve symptoms related to tumor mass effect, and preserve normal pituitary function." Transsphenoidal surgery is generally considered the first-line treatment for acromegalic patients. Surgical resection can normalize hormone levels rapidly for the majority of patients (about 65%). Biochemical remission is achieved less frequently in patients with macroadenomas or in patients whose tumor extends into the cavernous sinus.

Bruce E. Pollock, MD, of the Department of Neurologic Surgery at Mayo Clinic Rochester, explains: "Radiotherapy has long been regarded as a conventional adjuvant to surgical treatment or as primary treatment for inoperable tumors. Despite tumor growth control rates higher than 90% after radiotherapy of GH-producing tumors, the rate of biochemical remission is much lower. Stereotactic radiosurgery has emerged as an effective alternative or adjunct to surgical resection and radiotherapy for patients with pituitary adenomas. Radiosurgery allows the delivery of focused radiation in a single session to the tumor with little radiation exposure to the surrounding normal structures."

Patient Selection

Proper patient selection is the most important factor associated with good outcomes after radiosurgery. Generally, patients with pituitary adenomas with considerable suprasellar extension are typically not considered good candidates for radiosurgery because patients with larger lesions often have visual loss related to mass effect. Although radiosurgery does result in growth control and size reduction in the majority of pituitary adenomas, these effects occur gradually over several years. Therefore, surgical resection is the preferred approach for patients with large pituitary adenomas. Dr Pollock says: "For many patients, complete tumor removal is not possible because the tumor extends into the cavernous sinus. In these patients, radiosurgery can be part of a staged approach with microsurgery. Initially, the tumor is debulked to create a separation between the top surface of the tumor and the optic apparatus, without an attempt at resection of the tumor involving the cranial nerves, major arteries, or dural venous sinuses. Radiosurgery can then be performed for the remaining tumor volume with little risk of cranial nerve deficits. Such multimodality treatment should result in reduced patient morbidity, with long-term tumor control."

Dr Nippoldt notes: "Our center and others have determined that the results of pituitary adenoma radiosurgery are adversely affected by the use of pituitary suppressive medications (bromocriptine, cabergoline, octreotide) at the time of radiosurgery. Consequently, we have patients discontinue these medications at least 8 weeks before radiosurgery."

Radiosurgery With the Gamma Knife

Radiosurgery is performed at Mayo Clinic using the Leksell Gamma Knife (Elekta Instruments, Norcross, Georgia). The Gamma Knife has been used for more than 3 decades to treat more than 350,000 patients worldwide. Radiosurgery is an outpatient procedure, performed with the patient under local anesthesia, and requires virtually no recovery time. After placement of a stereotactic head frame, the patient has an MRI performed for dose-planning purposes (Figure). A dose plan is then created and reviewed by a neurologic surgeon, a radiation oncologist, and a radiation physicist.

Since January 1990, a total of 221 patients with pituitary adenomas have undergone stereotactic

Todd B. Nippoldt, MD, and Bruce E. Pollock, MD

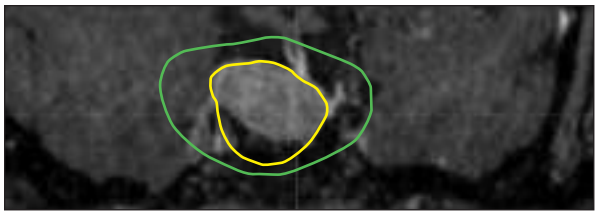


Figure. Postgadolinium coronal MRI of a patient with acromegaly demonstrating the radiation dose plan for radiosurgery. The tumor margin dose (yellow line) receives 20 Gy, whereas the outer green line receives 20% (8 Gy) of the maximum radiation dose (40 Gy). The maximum dose to the adjacent optic nerves is 9.2 Gy.

radiosurgery at Mayo Clinic from a clinical experience that exceeds 3,500 patients. Seventy-four patients (33% of pituitary patients) have had acromegaly. Ninety percent of the patients have undergone prior surgery; 80% had tumors with extension into the cavernous sinus. Dr Pollock notes: "To minimize the incidence of visual deficits after radiosurgery, we limit the radiation dose to the optic nerves to less than 12 Gy. This dose prescription has resulted in visual morbidity of less than 2%. To date, no patient with a GH-producing pituitary has had tumor growth after radiosurgery, with follow-up that now extends beyond 15 years."

Two variables correlate with biochemical remission after radiosurgery in patients with acromegaly (Table). Dr Pollock explains: "First, patients with IGF-1 levels less than 2.25 times the upper limit of normal are almost 3 times more likely to achieve biochemical remission than patients with IGF-1 levels at least 2.25 times the upper limit of normal. Second, patients not taking pituitary suppressive medications for at least 1 month before radiosurgery were more than 4 times more likely to have biochemical remission. The median time to biochemical remission was 3 years, although endocrine normalization has been noted beyond 5 years in some cases. New anterior pituitary deficits occurred in 33% of patients 5 or more years after radiosurgery. The most frequent anterior pituitary deficit was hypogonadism. Biochemical remission is possible in 80% to 90% of properly selected patients with acromegaly."

Table. Results of Radiosurgery for Patients With Acromegaly

Biochemical remission*	Outcome (hazard ratio)
Overall	60% at 5 y
IGF-1 < 2.25 × ULN	79% at 5 y (2.9)
IGF-1 ≥ 2.25 × ULN	29% at 5 y
Off suppressive medications	91% at 5 y (4.2)
On suppressive medications	38% at 5 y
New anterior pituitary deficits	33% at 5 y

IGF-1, insulin-like growth factor 1; ULN, upper limit of normal.

*Biochemical remission was defined as a fasting GH level less than 2 ng/mL and normal age- and sex-adjusted IGF-1 concentration off all suppressive medications.

Pancreatic Islet Autotransplantation: A New Treatment Option for Pancreatogenic Diabetes in Selected Patients Undergoing Pancreatectomy

"Pancreatic islet allotransplantation is rapidly becoming popular for glycemic control in type 1 diabetes," says Yogish C. Kudva, MBBS, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic Rochester, "especially with improved results observed with calcineurin inhibitors instead of corticosteroids for long-term immunosuppression. Several centers in the United States have established islet isolation laboratories and are now offering this treatment for type 1 diabetes."

According to Santhi Swaroop Vege, MD, of the Division of Gastroenterology and Hepatology at Mayo Clinic Rochester: "Total or near-total pancreatectomy is recommended for patients with chronic pancreatitis and narcotic dependence due to intractable pain after medical, endoscopic, and surgical options have been exhausted. Such surgery often results in pancreatogenic diabetes. Distal or extended distal pancreatectomy may result in diabetes in 30% to 45% of patients. The establishment of islet isolation laboratories at tertiary care centers offers islet autotransplantation as an option for these patients."

Evaluation for Pancreas Surgery and Islet Autotransplantation

Mayo Clinic Rochester is currently performing pancreas surgery and islet autotransplantation for a selected group of patients. This is a multidisci-

Table. Characteristics of Patients Eligible for Pancreas Surgery and Subsequent Islet Autotransplantation

Type of disorder	Procedure
Chronic pancreatitis with narcotic-requiring chronic pain in the clinical setting of failed medical, endoscopic, or other surgical treatment options	Total pancreatectomy and islet autotransplantation
Chronic pancreatitis with previous partial pancreatectomy and recurrence of narcotic-requiring pain	Completion pancreatectomy with islet autotransplantation
Prior severe acute pancreatitis complicated by disconnected duct syndrome, requiring removal of substantive portion of the distal isolated pancreas	Resection of disconnected pancreas with islet auto-transplantation
Disabling recurrent acute pancreatitis in the clinical setting of failed medical and endoscopic therapy	Total pancreatectomy and islet autotransplantation

plinary program, with close collaboration among the medical pancreas clinic, pancreas surgeons, the islet isolation laboratory, interventional endoscopy and radiology, diagnostic radiology, and endocrinology (Figure). Characteristics of patients eligible for pancreas surgery and subsequent islet autotransplantation are described in the Table. Such patients may be referred to the Mayo Clinic Medical Pancreas Clinic. The pancreas clinic team identifies appropriate patients in consultation with the pancreas surgeons, endocrinologists, and the islet isolation laboratory.

Process of Islet Autotransplantation

Michael B. Farnell, MD, of the Department of Surgery at Mayo Clinic Rochester, says: "Patients selected for pancreas surgery and islet autotransplantation undergo surgery early in the day. The islet isolation team receives the organ from the operating room and proceeds with isolation in the islet isolation laboratory."

Then, according to Dr Kudva, "The pancreas is perfused with collagenase and cut into several pieces and transferred to a stainless steel chamber containing several hollow stainless steel marbles and a 500-µm mesh screen separating the top and bottom portions of the chamber. Fluid is warmed and maintained at 37°C for the duration of digestion. When appropriate digestion has been observed, enzyme activity is slowed by lowering the temperature and diluting the digest with modified media solution. The tissue digest is collected in conical tubes, centrifuged, and washed. Purification is performed, depending on the volume of the digested tissue."

After the surgical procedure is completed, the patient is managed on the surgical ward until the islet product is ready. An intravenous insulin infusion is started after resection of the pancreas and continued for 3 days. The isolated islets are infused into the portal vein under ultrasonographic guidance by an interventional radiologist with intermittent measurement of portal pressure. Hemostasis is secured with Gelfoam and platinum coils. Ultrasonography is performed within 24 hours to evaluate portal vein anatomy, portal venous flow, and liver parenchyma for any thrombotic complications. Liver function tests are performed periodically to monitor for potential ischemic hepatitis. The hospital stay is not prolonged beyond that usually required for care after

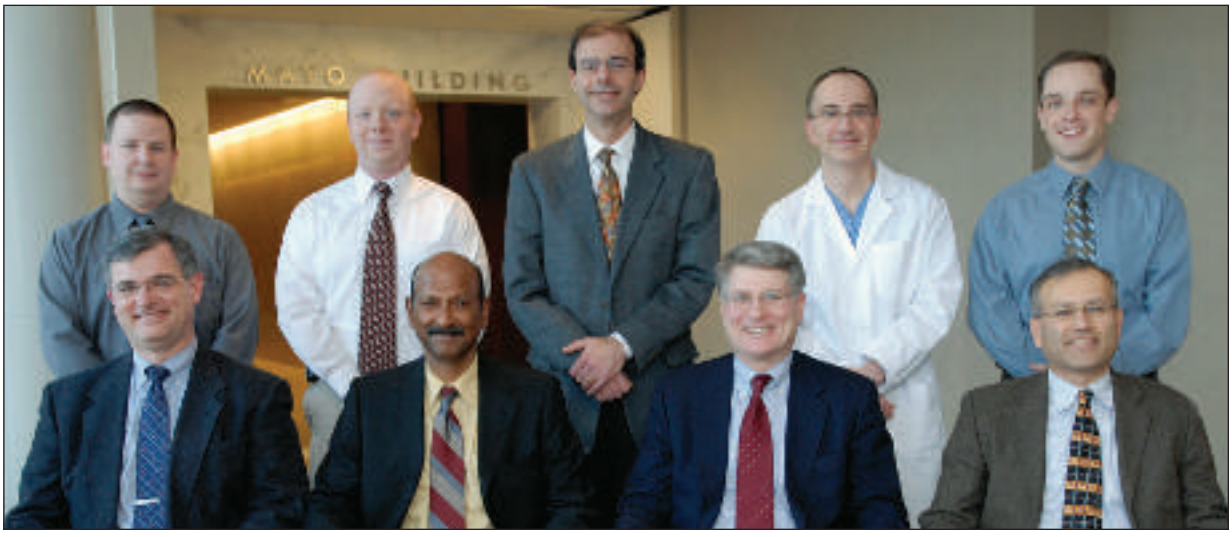


Figure. The islet autotransplantation multidisciplinary team. From left to right, standing: Jarett M. Anderson, Adam S. Armstrong, Mark D. Topazian, MD, Michael J. Levy, MD, and Michael C. Deeds. Seated: Dennis A. Gastineau, MD, S. S. Vege, MD, Michael B. Farnell, MD, and Yogish C. Kudva, MBBS.

pancreas surgery.

Outpatient Management

All recipients of islet autotransplantation are evaluated within a few weeks by the multidisciplinary team. Subsequent follow-up is provided by the medical pancreas clinic and an endocrinologist. All patients are treated with insulin for at least 3 months after autotransplantation.

Results

Dr Vege summarizes: "We have performed this procedure in 4 patients. Disconnected pancreatic duct syndrome requiring extended distal pancreatectomy has not been reported previously as an indication for autotransplantation, and the 2 patients in whom we performed this procedure had resolution of troublesome pancreatic fluid collections and resolution of pain. Three patients had uneventful procedures, but in 1 patient, a perihepatic hematoma developed at the site of the procedure, which required a blood transfusion, but the hematoma resolved without intervention." Dr Kudva notes: "Three patients have sufficient follow-up to comment on resolution of abdominal pain and glycemic status. Abdominal pain resolved in all 3 patients. One of the 3 patients does not require insulin and has normal glucose control. A second patient is well controlled with pharmacotherapy for diabetes without insulin, and the third patient has not completed 3 months since the transplant."

Referral for Pancreas Surgery With Islet Autotransplantation

Referrals for pancreas surgery with islet autotransplantation may be directed to the Mayo Clinic Medical Pancreas Clinic at 507-284-2141 or 507-284-2478.

Research Corner

Detecting Small Pituitary Tumors in Patients With Cushing's Disease: Investigators Pair Hormone Stimulation With MRI Technology

Cushing's disease (CD) is a disorder characterized by hypersecretion of adrenocorticotrophic hormone (ACTH), leading to a potentially life-threatening excess of cortisol. Successful therapy requires removal of an ACTH-producing pituitary tumor. Evaluation and management of patients with this disorder is complicated by the fact that ACTH-producing pituitary tumors are predominantly microadenomas; results of conventional MRI are negative or equivocal in 36% to 63% of cases, and false-positive MRI signs of pituitary microadenoma may be seen in 1% to 10% of normal subjects.

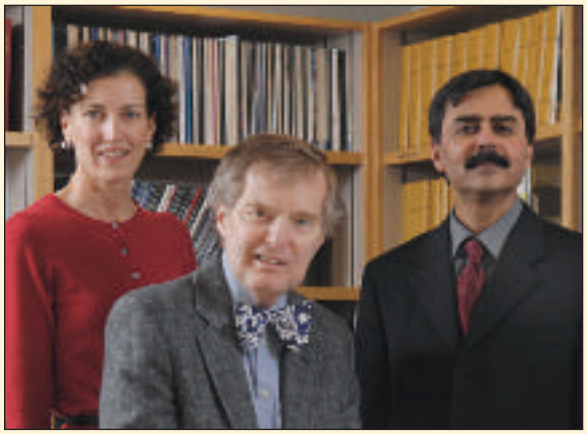
The inability to detect and properly characterize pituitary microadenomas with standard CT and MR imaging has led to the use of invasive inferior petrosal sinus sampling and cavernous sinus sampling to diagnose and localize these tumors. Although these invasive neuroradiologic methods are highly accurate, they are associated with some severe complications, including hypopituitarism, and have not been directly linked to higher cure rates.

Mayo Clinic Rochester endocrinologists and neuroradiologists have launched a study combining state-of-the-art 3-tesla (3T) MRI with adenoma stimulation using corticotropin-releasing hormone (CRH) in an attempt to better detect and characterize ACTH-producing pituitary tumors. The study will compare the sensitivity and specificity of CRH-stimulated 3T MRI with 3T MRI using standard contrast but no hormonal stimulation.

Results of this study might affect how patients with suspected pituitary lesions are managed and might improve the outcome of neurosurgery. Participants will receive an initial endocrine evaluation to confirm their CD diagnosis. They will then have two 3T MRI studies. All study-related examinations and procedures will be provided at no charge to participants.

To refer a patient with ACTH-dependent CD for this research study, please contact Dr Dana Erickson at 507-284-2784.

Recognition



Ann E. Kearns, MD, PhD, received the Outstanding Faculty Award for 2006 from the Mayo School of Continuing Medical Education. Robert A. Rizza, MD, received the Minnesota Diabetes Steering Committee 2006 Bruce Zimmerman Diabetes Award. Sundeep Khosla, MD, received the American Society for Bone and Mineral Research 2006 Frederic C. Bartter Award. Also, B. Lawrence Riggs, Jr, MD (not pictured), received the American Society for Bone and Mineral Research 2006 Gideon A. Rodan Excellence in Mentorship Award.

Hossein Gharib, MD, received the 2006 International Clinician Award of the Italian Association of Clinical Endocrinologists. William F. Young, Jr, MD, received the 2006 American College of Endocrinology Distinction in Clinical Endocrinology Award.

The 2006 Mayo Clinic Department of Medicine Recognition Awards: Steven A. Smith, MD, received the Outstanding Community Involvement Award; Maria L. Collazo-Clavell, MD, received the Laureate Award; and Johannes D. Veldhuis, MD, received the Research Career Achievement Award.

Clive S. Grant, MD, was elected recorder of the Western Surgical Association and is a past president of the American Association of Endocrine Surgeons. Rebecca S. Bahn, MD, was voted president-elect of the American Thyroid Association. Geoffrey B. Thompson, MD, was voted president-elect of the American Association of Endocrine Surgeons.

Education Opportunities

Please call 800-323-2688 or visit www.mayo.edu/cme/endocrinology.html, unless indicated otherwise, for more information about these courses or to register.

Mayo Foundation's 17th Annual Advances and Controversies in Clinical Nutrition, April 13-15, 2007, Hyatt Regency, Savannah, Georgia. This multidisciplinary course will focus on enteral and parenteral nutrition, diabetes, osteoporosis, lipids, and obesity. For more information, phone 800-462-9633 or e-mail cme-jax@mayo.edu.

Mayo Clinic Nutrition in Health and Disease, November 8-9, 2007, Hilton San Francisco Financial District, San Francisco, California. 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.

11th Mayo Clinic Endocrine Course, May 2008, Mallorca, Spain. This course, created for endocrinologists and interested internists and surgeons, will span the full spectrum of endocrinology through short lectures, case-based debates, clinicopathologic sessions, clinical pearls sessions, and small group discussions with experts.

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MC5810-0307

Endocrinology Update

Endocrinology Update
Produced by
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Rochester, MN 55905

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