The pituitary gland controls endocrine function and straddles a region between the nose and the brain. Given these features, pituitary tumors are best managed through the coordinated approach by an interdisciplinary surgical and medical team. Mayo Clinic in Minnesota has one of the largest pituitary tumor practices in the world, performing more than 120 pituitary surgeries annually. The team of pituitary experts is anchored by an endocrinologist and includes, as needed, physicians in neuroradiology, neurosurgery, neurology, otorhinolaryngology (ENT), ophthalmology, radiation oncology, and laboratory medicine.

Pituitary tumors are usually benign and nonmetastatic. Often extremely small, they can be either functioning (hormone-producing clinical syndrome) or nonfunctioning (non–hormone-producing or no clinical syndrome). As John L. D. Atkinson, MD, a Mayo Clinic neurosurgeon with expertise in pituitary surgery, explains, patients with functioning tumors producing an excess of such hormones as prolactin, corticotropin (ACTH), thyrotropin, or growth hormone typically experience symptoms and seek medical care. However, not all functioning tumors have clinical sequelae and, like nonfunctioning tumors, they may go undetected unless they are visualized coincidentally on MRI. Some become large enough to compress the optic nerves or the pituitary gland, causing symptoms of visual loss or pituitary failure.

Comprehensive Diagnosis
When a pituitary tumor is suspected, additional tests may include biochemical testing, MRI, ophthalmologic examination, and petrosal sinus sampling. Since it opened in 1976, Mayo's Endocrine Testing Center has conducted more than 145,000 tests and procedures.

MRI is a standard diagnostic technique for pituitary tumors. Mayo has advanced 3-Tesla MRI scanning, which generates the high-resolution images necessary for detecting what are often very small tumors. However, some pituitary tumors, such as those secreting excess ACTH in Cushing disease, may be too small to be detected with radiologic imaging. When laboratory tests indicate excess ACTH production, patients are referred to radiology for petrosal sinus sampling, conducted by injecting corticotropin-releasing hormone through a catheter and measuring the pituitary response. The test cannot only determine if a tumor is present, but can also help identify its location.

Surgical Management
Surgery is the primary means of treating pituitary tumors, and it, too, is a collaborative effort. Surgeons at Mayo Clinic use an endoscopic transnasal approach rather than a sublabial transseptal approach. An ENT surgeon advances a nasal endoscope through the nostril to the anterior wall

Figure. Endoscopic approach through the nose to the sella, which harbors the pituitary gland. The procedure for tumor resection may be then performed as an endoscopic technique or an endoscopic-microscopic combination.
of the sphenoid sinus. The neurosurgeon then uses either an endoscope or an endoscopic-microscopic combination to enter the sella turcica and resect the tumor (Figure). Because the surgery does not require an external incision and resection, it can be accomplished without interfering with other brain structures. Thereby, the duration of the surgery, postsurgical recovery time, and patient postoperative pain is reduced.

Dr. Atkinson notes that unless there are complications, most patients leave the hospital the following day. He goes on to say, “Expected complications may include a spinal fluid leak, which occurs in about 30% of patients. Another might be increased urine output from transient diabetes insipidus, for which there are medications. Serious complications such as stroke, death, and blindness are very rare. It is one of the lowest-risk brain operations we perform, in part because the transnasal approach makes the tumor very accessible.”

After discharge, patients are typically seen the same day by the endocrinologist for medical follow-up. If they remain in the hospital longer than overnight, the endocrinologist does an in-patient consultation. It is very important that the endocrinologist evaluate the patient preoperatively and postoperatively because the function of the gland is so diverse and regulates so many other endocrine organs.

Postoperative management of remaining tumor, depending on its size, location, and other features, may be amenable to radiosurgery with a single-day dosing gamma knife procedure. Other residual or recurrent tumor, depending on size or configuration, may be treated with radiation oncology, observation, or medical therapy, if appropriate.

Dr. Atkinson sums up the team approach at Mayo by noting that the primary objective is to relieve the patient of symptoms through medical management, tumor resection, or irradiation and that it takes a collaborative effort to maintain normal pituitary function. “The advantages of our multispecialty practice,” he says, “are that patients benefit not only from a coordinated care plan, but also from state-of-the-art advances across the spectrum of the disciplines involved—be they improved radiologic and imaging techniques, new endocrine laboratory tests and verification methods, the latest medications, advanced surgical techniques, or innovations in radiation delivery, such as the heavy particle proton beam, soon to be acquired. The needs of the patient come first at Mayo, and this is certainly true in patients with conditions as complex as pituitary disease.”

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**Early Findings From Mayo Clinic’s Population-Based Study on Dementia**

Who will get dementia? Can we cure it? Can we prevent it? Early detection, intervention, and prevention are the motivating forces that drive clinically focused dementia research.

Mayo Clinic’s approach to these research goals is unique in that it is a population-based, prospective (vs retrospective), longitudinal research program in which cognitively healthy elderly individuals are tracked over time to see if they continue to be cognitively healthy or transition to mild cognitive impairment (MCI) or dementia. The behavioral tracking measures are a comprehensive set of published cognitive and neuropsychological instruments. The biologic measures are continually updated as advances in imaging and pathophysiologic testing become available.

The study participants are randomly selected from a community (Olmsted County, Minnesota) in which the medical records linkage system through the Rochester Epidemiology Project links medical record data from Mayo Clinic and almost all other sources of medical care available to the local population. The number of participants in the study is kept to approximately 2,000 active individuals, with new participants added as needed.

The Mayo Clinic Alzheimer’s Disease Research Center (ADRC) is directed by Ronald C. Petersen, MD, PhD, at Mayo Clinic in Minnesota with associate directors Neil R. Graff-Radford, MD, and Steven G. Younkin, MD, PhD, at Mayo Clinic in Florida. The population-based research study is known as the Mayo Clinic Study of Aging (MCSA). Both the center and the study are funded by the National Institute on Aging.
Prevalence of MCI
MCI is often considered an intermediate state between normal cognitive aging and the earliest clinical signs of dementia, particularly Alzheimer's dementia (AD). It can be a challenging diagnosis to make without a careful clinical evaluation because people with MCI are generally able to carry out activities of daily living, and their cognitive impairments may be subtle.

One of the first goals of Mayo's population-based dementia research was to identify the prevalence of MCI (Neurology. 2010;75[10]:889-97). MCI was diagnosed using published criteria and was further characterized as either amnestic (aMCI) or nonamnestic (naMCI). Of the population sample, approximately 75% could be classified as having normal cognitive aging; 15%, MCI; and 10%, dementia (Figure).

The prevalence of MCI increased with age and was greater in men and in individuals with the APOE e3/e4 or e4/e4 genotype. APOE e4 has been associated with an increasing risk of AD. The study also found that aMCI was 2.3 times more common than naMCI, consistent with the prevalence of AD compared with other types of dementia found in other studies. MCI also varied with years of education, with a prevalence of 11% in individuals with greater than 16 years of education and rising to 30.2% in those with fewer than 9 years of education.

In discussing the greater prevalence in men than in women, the researchers noted that further analyses showed it was not due to comorbid conditions. They speculated that men may have an earlier, but more gradual, cognitive decline than women, who may transition later and more rapidly to dementia. This possibility and other questions about the robustness of cognitive health with aging, the transition to MCI, and the transition from MCI to dementia will be addressed as the study continues.

Identification Through Imaging
Braak stages of dementia, considered the gold standard measure of tissue destruction correlated with cognitive decline, can be identified only in postmortem microscopic examination. However, advances in imaging are providing new, noninvasive methods of detecting structural and neurochemical changes consistent with AD and other forms of dementia. Led by Clifford R. Jack Jr, MD, researchers in the Mayo Clinic Center for Advanced Imaging Research are using state-of-the-art, high-resolution imaging technology and generating new algorithms to more precisely interpret neuroimaging on an individual basis.

Among the newest of these algorithms is the Structural Abnormality Index (STAND). Developed by Prashanthi Vemuri, PhD, a senior research fellow in the Center for Advanced Imaging Research, it was found to accurately predict the Braak score from the MRI scans of 101 living patients. The STAND algorithm has also been used as a framework to distinguish AD from frontotemporal dementia and dementia with Lewy bodies, for which it has 75% to 80% accuracy. As Dr Vemuri notes, with further study and refinements, the STAND score could be used not only for detection and differential diagnosis, but also for tracking the efficacy of future medical interventions (NeuroImage. 2008;42[2]:559-67; NeuroImage. 2011;55[2]:522-31).

Prevention: Lifestyle Factors
Neuropsychiatric Condition
Several studies have suggested that depression, apathy, and agitation may predict a transition from MCI to dementia. Yonas E. Geda, MD, a neuropsychiatrist at Mayo Clinic in Minnesota, and his colleagues conducted a prospective study of 358 individuals who had received a diagnosis of MCI in the MCSA. The investigators found a 99% increased risk of dementia in MCI if the person had apathy and a 66% increased risk of dementia if the person showed subtle signs of depression. Dr Geda notes that the results highlight the importance of evaluating neuropsychiatric symptoms in patients with MCI. Future research will address the question of whether treatment for depression or apathy might delay the onset of dementia.

Diet and Nutrition
Diet also may have a role in cognitive decline. Rosebud O. Roberts, MB, ChB, a Mayo Clinic epidemiologist, and her colleagues investigated the association between mono- and polyunsaturated fatty acids and risk of dementia (J Alzheimer’s Disease.

Figure. Prevalence of normal cognitive aging and mild cognitive impairment (MCI) and dementia among participants in the Mayo Clinic Study of Aging. Estimates of MCI and dementia are age- and sex-adjusted to the Olmsted County, Minnesota, population.
DBS at Mayo Clinic: Pediatric Practice and Research Update

Pediatric DBS
Mayo Clinic in Rochester, Minnesota, conducts about 100 deep brain stimulation (DBS) procedures a year. The list of disorders treated includes essential tremor and Parkinson disease, as well as dystonia, chorea, Tourette syndrome, epilepsy, and certain types of centrally mediated neuropathic pain. Four years ago, the DBS practice expanded to include children, as well as adults.

As is true in adults, successful DBS treatment in children depends on careful patient selection, precise neural targeting, and extensive, individualized stimulator programming. At Mayo, an interdisciplinary committee with membership from the departments of neurology, neurosurgery, psychiatry, neuropsychology, pain neurology, nurse programming, and speech pathology reviews every DBS candidate, weighs risk factors against potential benefits, and comes to consensus about disease management.

Kendall H. Lee, MD, PhD, the neurosurgery director of the DBS program at Mayo Clinic in Minnesota, and his colleague, Matt Stead, MD, PhD, a pediatric neurologist, note that the three patients with Tourette syndrome whom they have treated have responded well. The symptoms in one of the patients, who was 19 years old at the time of surgery, all but disappeared after programming adjustments to the DBS stimulator.

DBS for dystonia in children can help eliminate some symptoms. As Dr Stead explains, “It is the best treatment we have to offer for dystonia that is medically refractory. Patients differ in response, but, on average, both adults and children experience about a 50% improvement with DBS.”

Asked about the outcomes for children with chorea, Dr Stead notes that none have had complete symptom remission, but all have had improvement. As an example, he cites a five-year-old child who was nonverbal before surgery and was able to begin speaking after DBS.

Mayo Clinic is one of the few institutions in the world to offer DBS for intractable epilepsy in children. The program’s youngest patient, and the youngest in the world to undergo DBS, was a three-year-old child with Lennox-Gastaut syndrome. “The response was excellent, with marked seizure reduction,” says Dr Lee. Dr Stead adds, “There is no treatment available for this very serious condition, so we were pleased to see how well DBS worked.”

Mechanisms of DBS
Dr Lee is also the director of Mayo’s Neural Engineering Laboratory and a Mayo-based, multi-institutional DBS consortium investigat-
ing the mechanisms of neurostimulation across a spectrum of disorders. In research funded by the National Institutes of Health and benefactor grants, he, Kevin E. Bennett, chair of Mayo’s Division of Engineering, and their colleagues developed the Wireless Instantaneous Neurotransmitter Concentration Sensing System (WINCS), a device that can monitor neurochemical output of targeted brain sites in real time during DBS (Figure 1).

It appears likely that DBS evokes the release of neurochemicals. DBS uses a high-frequency stimulation device applying five to 100 stimulation pulses per second. Traditional chemical detection systems, such as mass spectrometry, are an impractical means of monitoring in vivo chemical changes in the brain during DBS stimulation. WINCS, however, is capable of electrochemical detection using fast-scan cyclic voltammetry and amperometry, sampling a subsecond at a time. Electrochemical monitoring through WINCS during DBS surgery in animals suggests that the positive effects of DBS are based on changes in neural activity and neurochemical transmitters in interconnected structures within a given neural network.

The thalamus, for example, is known to be an effective DBS target for seizure suppression (Figure 2). Dr. Lee and his colleagues have applied high-frequency stimulation (HFS), which mimics DBS, to brain slices from ferrets, monitoring changes with WINCS. They found that HFS suppressed spindle wave oscillations in the nucleus reticularis thalami and in thalamocortical relay neurons in the lateral geniculate nucleus. It also caused elevation in extracellular glutamate levels for many seconds after stimulation. Identification of the prolonged release of glutamate, which decreases neuronal input resistance and abolishes thalamic network oscillatory action in response to HFS, is a step forward in explaining how DBS inhibits seizures and tremor.

WINCS is not just a research tool. The goal is to use WINCS to monitor neurochemical changes during human DBS surgery, to improve target identification and placement precision. In the study cited above, for example, Dr. Lee and his colleagues found that HFS-mediated neurotransmitter release may begin in astrocytes, which may turn out to be an as-yet unappreciated target for DBS stimulation.

**Endarterectomy vs Stenting: Findings From CREST**

For more than 50 years, endarterectomy has been the standard alternative to medical therapy for patients with extracranial carotid stenosis who are in need of revascularization. Carotid stenting, a minimally invasive treatment that was begun less than 20 years ago, has less of a proven track record, in part because it is a newer procedure.

The Carotid Revascularization Endarterectomy vs Stenting Trial (CREST), led by Thomas G. Brott, MD, a neurologist at Mayo Clinic in Florida, was a randomized treatment trial designed to compare the outcomes associated with both procedures. With 2,502 patients from 117 participating institutions in the United States and Canada, it is the largest such study ever conducted.

**CREST Outcomes**

The results of CREST showed that both procedures were associated with similar rates of the outcome measure (Brott et al. *N Engl J Med.* 2010;363[1]:11-32). Configured as a primary composite end point, the outcome measure was ipsilateral stroke, myocardial infarction (MI), or death. Neurologic and cardiac functions were assessed at the periprocedural period (within hours after the procedure and one month later) and at six-month intervals for the four-year duration of the study (Figure).

Study participants were men and women who had been predetermined by vascular experts to need a revascularization procedure. Half were asymptomatic and half were symptomatic. *Symptomatic* was defined as having evidence of a transient ischemic attack, amaurosis fugax, or minor nondisabling stroke involving the carotid artery within 180 days of entering the study.
Eligible patients were randomly assigned to undergo either endarterectomy or stenting.

Overall, in the perioperative period, the rates of stroke, MI, and death were low. The rate of stroke and death was 2.3% with endarterectomy and 4.1% with stenting. The rate of MI was 2.3% in the endarterectomy group and 1.1% in the stenting group. The combined stroke and mortality rates associated with both procedures were “extraordinarily low,” according to Dr Brott, and the outcomes were the best ever reported in a randomized trial that evaluated these outcomes. Of note, physicians participating in CREST had to undergo a credentialing process in which level of experience and rates of complications and death for both endarterectomy and stenting had to meet rigorous study criteria.

**Age-Related Differences**

Because stenting is less invasive than endarterectomy, it might appear to be the better option for older patients, who may be frail and have multiple comorbidities. However, the study found that the opposite was true. Patients older than 70 years had better outcomes with endarterectomy and those younger than 70 years fared marginally better with stenting. These findings could be explained in part by the often deteriorated state of blood vessels in persons older than 70 years. As Dr Brott points out, “Vascular tortuosity and calcification in areas other than the site of the procedure may play a role. In contrast, during endarterectomy, the surgeon interrupts the blood flow below and above the area of narrowing and is not challenged by plaque in other parts of the arterial system.”

Harry J. Cloft, MD, PhD, a neuroradiologist who participated in the study at Mayo Clinic in Minnesota, adds that elderly patients may also be less able than younger patients to form a vascular bypass through collateral circulation in response to a plaque-based occlusion. The researchers are now examining the angigrams of the study population to see if vascular health is associated with poorer outcomes for stenting in patients older than 70 years.

**Ten-Year Follow-up Study Funded**

“All good research leads to more questions,” says Dr Cloft. Bart M. Demaerschalk, MD, a vascular neurologist and CREST site principal investigator at Mayo Clinic in Arizona, notes that although endarterectomy has been shown to reduce stroke risk 10 years postprocedure, a question arising from the CREST results is the long-term durability of stenting. The National Institutes of Health is funding a 10-year follow-up study to compare the long-term outcomes of both procedures, starting this year. The multi-
Research Highlights

**Parkinson Drugs Tied to Impulse Control Problems**
Mayo Clinic researchers reported that dopamine agonists used in treating Parkinson disease result in impulse control disorders in as many as 22% of patients. Their study found that the higher the dose, the greater the likelihood of an impulse control behavior. Mayo Clinic first reported on this topic in 2005. The follow-up study was published online in the February 2011 issue of *Parkinsonism and Related Disorders*. Authors: A. Hassan, J. Bower, N. Kumar, J. Matsumoto, R. Fealey, K. Josephs, and J. E. Ahlskog.

**Cardiac Pacing Helps Epilepsy Patients With Ictal Asystole**
Mayo Clinic researchers found that cardiac pacing may help epilepsy patients with seizure-related falls due to ictal asystole. Researchers identified seven patients who had a diagnosis of ictal asystole and a history of falls associated with it before they underwent cardiac pacing at Mayo Clinic between 1990 and 2004. The researchers found that the rate of injury and falls declined after the patients received their implant. The study was published in the April 2011 issue of *Epilepsia*. Authors: B. Moseley, G. Ghearing, T. Munger, and J. Britton.

**Atrial Fibrillation Increases the Risk of Nonamnestic MCI**
Patients with atrial fibrillation are more likely to have nonamnestic mild cognitive impairment (MCI), report researchers at Mayo Clinic. Their study evaluated 1,450 patients older than 70 years who had a medical history of atrial fibrillation. In general, those with atrial fibrillation had a 1.7% increased risk of nonamnestic MCI. However, in women, this risk was 2.9% greater for patients with atrial fibrillation than for those without it. Atrial fibrillation was not associated with amnestic MCI. This study was presented in April 2011 at the American Academy of Neurology meeting in Hawaii. Authors: R. Roberts, Y. Geda, D. Knopman, R. Cha, V. Pankratz, W. Rocca, and R. Petersen.

**Study Shows Potential to Prevent Hospitalizations in Patients With Brain Tumor**
In a retrospective five-year study, researchers at Mayo Clinic found that common causes of hospitalization for patients with malignant brain tumors, such as seizures, are potentially preventable. Authors of the study reviewed data from a State of California health database and analyzed patients hospitalized for malignant brain tumors from 2003 to 2007. Of the 13,587 hospitalizations identified, seizure was the most common reason for hospitalization, at 18.6%. The researchers concluded that 1) seizure activity is a potentially preventable manifestation of brain tumors and 2) effective treatments to reduce the burden of seizure in this population are needed. This study was presented in April 2011 at the American Academy of Neurology meeting in Hawaii. Authors: D. Johnson and B. O’Neill.

**Tool to Predict Disability Timeline for Patients With Progressive MS**
A new study enabled Mayo Clinic researchers to predict whether patients with progressive multiple sclerosis (MS) will have a faster onset of disability. The study assessed cerebrospinal fluid test results from a sample of 281 patients with progressive MS seen at Mayo Clinic from 2002 to 2007. MS lesions with greater inflammatory activity are more common in secondary progressive MS (SPMS) than in primary progressive MS (PPMS). Therefore, increased intrathecal immunoglobulin G (IgG) synthesis could be more commonly associated with SPMS or single-attack progressive MS than with PPMS. Intrathecal IgG synthesis seems to be associated more commonly with progressive disease preceded by relapses and a faster rate of progression to moderate disability. Increased intrathecal IgG synthesis, but not the presence of oligoclonal bands, could thus be a marker of the inflammatory biology that leads to higher disability levels in progressive MS. The research was presented in April 2011 at the American Academy of Neurology meeting in Hawaii. Authors: J. Tang, D. Crusan, M. Tutuncu, N. Zeid, N. Kale, E. Atkinson, and O. Kantarci.

To read more about Mayo Clinic neurosciences research and patient care, visit www.mayoclinic.org.
Endarterectomy vs Stenting: Findings From CREST

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CREST Effects: Weaving Research Into Clinical Practice

The CREST findings highlight the advantage of treating carotid stenosis with a multidisciplinary team approach in which all options are considered. At Mayo Clinic in Arizona, for example, patients were historically seen by a vascular neurologist, a neurosurgeon, a vascular surgeon, or an endovascular surgical neuroradiologist. Once CREST began, the vascular experts across subspecialties made it mandatory that all patients with carotid stenosis be seen by a member of each subspecialty. The subspecialists then met as a team to assess a patient’s candidacy for CREST.

This practice continues today and includes all patients, regardless of candidacy for CREST. Every patient with carotid stenosis is assessed by a collaborative team that includes a neurologist, a vascular surgeon, or a neurosurgeon and an endovascular surgical neuroradiologist—an approach used at all three Mayo sites. “We rallied around the trial and wove our research into our clinical practice to best serve our patients,” says Dr Demaerschalk. “CREST has shown that both endarterectomy and stenting are safe and effective means of treating carotid artery disease. Patients are well informed before they come to us,” he adds. “They know there are different options, and a team approach removes any perception of potential operator bias.”

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Go to www.mayoclinic.org/publications/medicalprofs-enews.html to sign up for Mayo Clinic’s Physician Update – Neurosciences e-mail newsletter.

Expedited Patient Referrals to Mayo Clinic Departments of Neurology and Neurologic Surgery

While Mayo Clinic welcomes appointment requests for all neurologic and neurosurgical conditions, patients with the following conditions are offered expedited appointments:

1. Cerebral aneurysms
2. Cerebral or spinal arteriovenous malformations
3. Brain, spinal cord, or peripheral nerve tumors
4. Epilepsy with indications for surgery
5. Carotid disease