# Stereotactic and Functional Neurosurgery





Fall 2007

## AANS/CNS Section on Stereotactic and Functional Neurosurgery and American Society for Stereotactic and Functional Neurosurgery

Editor: Konstantin Slavin, MD

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## From the President



Michael Schulder, MD

With good reason, great enthusiasm is building among neurosurgeons for the surgical treatment of psychiatric disorders. There had been a long history of lesioning for obsessive-compulsive disorder by such pioneers as H.T. Ballantine. The

widespread acceptance of deep brain stimulation as an effective and safe method has fueled the attempt to surgically treat other patients who are severely disabled by psychiatric conditions. The reversibility and adjustability of DBS may make it a preferred treatment for patients with severe obsessive-compulsive disorder. Those with depression refractory to psychotherapy, medications or even to electroconvulsive therapy comprise a large group of people who not only are prevented by their ailment from leading productive lives but are also at significant risk for suicide. Perhaps new discoveries in the pathophysiology of schizophrenia may open up possible surgical solutions for some patients so afflicted.

No doubt most if not all of the ASSFN membership is familiar with the history of what was called "psychosurgery." The abuses of the latter years of this approach, with the "ice-pick" transorbital leucotomies performed by the itinerant Walter Freeman, are well known (the author Jack El-Hai gave an excellent presentation on Freeman at our meeting in June 2006, and will reprise this at the upcoming CNS meeting). Still, when introduced in the 1930s psychosurgery was viewed as a great advance in that era before psychotropic medications, when schizophrenic patients were confined to overcrowded institutions without any thought of treatment at

all. Surgery for the first time gave many people the chance to return to the community without frequent violent behavior. Egas Moniz, the Portuguese neurologist, was awarded the Nobel Prize for his work in promoting psychosurgery (and not for his discovery of cerebral angiography).

We must be careful to temper our excitement with an eye to the past, however. Although a federally appointed commission recommended that select centers continue to do surgery for carefully selected psychiatric patients, it is mainly the overuse of unscientific procedures, inevitably exaggerated by popular culture, that remains in the public consciousness (think the conclusion of "One Flew Over the Cuckoo's Nest"). Nor should we underestimate the abhorrence that most psychiatrists and psychologists feel toward surgery for their patients.

Current neurosurgery for psychiatric disorders can barely be compared to the procedures of the mid-20th century. It is based on a rigorous study of neuroanatomy and physiology, supported by functional neuroimaging, and is being studied in conjunction with colleagues in psychiatry and bioethics. If we let our nonsurgeon partners in this endeavor take the lead and advocate for surgery then we can be sure that the "psychosurgery" will remain in the past while neurosurgery for psychiatric disorders has a bright future of which we will be proud.

Michael Schulder, MD Manhassat, N.Y.



## Gene Transfer Therapy for Parkinson's Disease

#### Paul Larson, MD, and Philip Starr, MD, PhD

Although deep brain stimulation is a widely accepted and highly effective treatment for patients with Parkinson's disease, many would agree that it is not a perfect therapy. DBS is a device-based treatment and thus is dependent on batteries that need replacing and hardware that can fail or cause complication; it requires a significant degree of patient compliance for programming; and it is a symptomatic therapy only (that is, it does not appear to alter disease progression). Many clinicians find the concept of a restorative or replacement therapy for Parkinson's disease attractive, although promising treatments such as cell transplantation have not held up in placebo-controlled, blinded trials. Delivery of exogenous growth factors to the ventricles or deep nuclei via pump systems has been explored but has been complicated by unwanted side effects or has not demonstrated efficacy.

Gene transfer is the newest technique to be explored in the arena of neurorestorative therapies for Parkinson's disease. A viral vector is modified to carry a gene encoding a protein of interest, and this is delivered to a specific brain target by a one-time stereotactic infusion. The gene then integrates into the target region's cells, which start producing the new protein. To date, three gene therapy trials for Parkinson's disease have been completed or are underway. The first, sponsored by Neurologix, used adeno-associated virus, AAV, to transfer a gene encoding glutamic acid decarboxylase, GAD, unilaterally into the subthalamic nucleus using microelectrodeguided localization. The theory is that increasing local production of GAD will decrease subthalamic nucleus overactivity. Twelve patients participated in an open label phase I trial, with the procedures performed by Michael Kaplitt, MD, in New York. No adverse events were seen in this safety and tolerability trial, and a statistically significant improvement in Unified Parkinson's Disease Rating Scale scores contralateral to the treated side at one year (27 percent improvement, p = 0.04) was seen.

The second trial, sponsored initially by Avigen and now by Genzyme, uses AAV to transfer a gene encoding amino acid decarboxylase, AADC, into the postcommissural putamen bilaterally. AADC is an enzyme in the pathway converting peripherally administered levodopa to dopamine, and levels of this enzyme decrease as Parkinson's disease advances. The theory is that the effectiveness of oral levodopa can be increased by raising the level of AADC in the putamen. The open label phase I/II trial, currently under way at our center, involves simultaneous placement of two cannulae in the postcommissural putamen with infusion of the vector via convection enhanced delivery.

The final trial, sponsored by Ceregene, also uses AAV but the gene of interest is not an enzyme. Neurturin, a growth factor that is a member of the GDNF family, has been shown to enhance survival of neurons in a MPTP primate model. Neurturin may promote recovery of neurons that are "sick" and nonfunctional but not yet dead and has the potential of being a disease-modifying therapy. A phase I open label trial with procedures performed at our center (eight patients) and by Roy Bakay, MD, in Chicago (four patients) was completed in 2006. Four needle passes were made to cover both the precommissural and postcommissural putamen bilaterally. The therapy was well tolerated in low dose and high dose cohorts, and both groups when off medication showed a 36 percent improvement in their UPDRS scores. These findings justified a double-blinded, placebo-controlled study that is currently under way at eight centers.

In the current trial, two thirds of patients will receive active therapy, while one third will receive a sham procedure consisting of a skin incision and partial burr hole only. Those who receive the sham procedure will be given the opportunity to receive gene transfer at the end of the trial.

Gene therapy may avoid some of the issues surrounding the possible role of the immune response and issues with graft survival that are major questions surrounding therapies such as cell transplantation. Moreover, it avoids the implanted hardware that DBS or growth factor infusion therapies require. While the preliminary results of gene transfer are promising, great caution must be exercised as the only results available to date are from small, open label trials. While the technique of gene transfer appears to be well tolerated so far, we have all seen promising results from open label trials of other neurorestorative therapies (human fetal cells, porcine fetal cells, intraputaminal GDNF infusion) only to see them show no benefit when studied in a placebo-controlled, double-blinded manner. There is little doubt that these trials will continue to be followed with great interest by the Parkinson's disease community.

Paul Larson, MD Philip Starr, MD, PhD University of California, San Francisco

#### From the Editor

In this issue of *Stereotactic and Functional Neurosurgery News*, we are introducing a new feature: a summary of ongoing research projects in the field of stereotactic and functional neurosurgery. Dr. Sharan's idea of sharing brief summaries of each project appears to be a great opportunity for all of us to



Konstantin Slavin, MD

learn about each others' activities, perhaps creating ways to collaborate in the future. Moreover, it tells us which ideas are already being tested and implemented, perhaps eliminating development of repetitive protocols.

What you see in this issue is a preliminary view; eventually, the names of investigators, study endpoints and other important information may be included. At the same time, the list is by no means complete; it would be wonderful if the readers of this newsletter would share information about their ongoing projects and studies. Dr. Sharan may be contacted directly at ashwini.sharan@jefferson.edu.

I would also like to invite all readers to contribute to our newsletter! This is the forum of ASSFN, and announcements, news and updates and that would be of interest to the society's members are welcomed. Please submit all information to my attention at kslavin@uic.edu.

See you all in Vancouver in June of 2008!

Konstantin Slavin, MD Chicago, Ill.

## Neuromodulation Approaches to Cluster Headache

#### Philip Starr, MD, PhD

Cluster headache, CH, is the most severe of the primary headache disorders. It affects approximately 1 in 1000 persons, and 20 percent of patients are significantly disabled in spite of optimal medical therapy. It is characterized by attacks of excruciating unilateral, periorbital pain, usually with evidence of ipsilateral cranial autonomic disturbance that may include lacrimation, conjunctival injection, ptosis, or meiosis. In the International Headache Society definition, attacks may occur from once every other day to up to eight times a day and last 15–180 minutes. In the episodic form of CH, affecting 80 percent to 90 percent of patients, attacks occur seasonally, with periods of complete remission. In the chronic form, affecting 10 percent to 20 percent of patients, remissions do not occur or last less than one month.

Neurosurgeons are occasionally referred cases of medically intractable CH, but until recently only ablative approaches have been used. Various forms of trigeminal nerve ablation procedures have been performed for CH, with little benefit. Radiosurgery of the sphenopalatine gangion has been reported but its effectiveness in the most severe chronic form of CH has not been established.

Recently, two very different neuromodulatory approaches have shown early success in open label trial designs. The first, introduced in 2001 in Milan, Italy, is ipsilateral chronic deep brain stimulation, DBS, of the posterior hypothalamic region. The procedure was

based on the finding that positron emission tomography, using 15-O-H2O as the tracer, has shown a focal increase in cerebral blood flow in the ipsilateral posterior hypothalamic region during a CH attack. The group originating DBS for CH recently published clinical results on the first 16 patients reporting that 13 are "headache free" or near headache free, although some are still on medication (Leone et al., Neurology 2006;67:15-152). The second neuromodulatory procedure recently introduced for CH is ipsilateral or bilateral occipital nerve stimulation. Although CH pain is not in the occipital nerve distribution, the proposed mechanism for pain relief is modulation of second order brainstem or thalamic neurons which receive common inputs from both occipital and trigeminal distributions. In 2007, two independent reports of eight patients each appeared from England (Burns et al., Lancet 2007;369:1099-1106) and Belgium (Magis et al., Lancet Neurol 2007;6:314–321. Nine of the 16 patients had a substantial (>50 percent) reduction in either pain intensity, frequency or both. Both techniques deserve further investigation, with appropriate control groups and longer follow-up.

Philip Starr, MD, PhD University of California, San Francisco

### Remembering Robert Paul Iacono, MD George Mandybur, MD

Editor's note: Robert Paul Iacono, MD, age 55, died in a plane crash on June 16. According to an obituary published in the June 23 Los Angeles Times, he was flying alone from California to Mississippi when the plane crashed into New Mexico's Sandia Mountains.

I worked with Dr. Iacono between 1991 and 1996 during much of the turmoil that was reported about his time at Loma Linda Medical Center. Having read through many of the news articles that comment on his medical career, I can personally attest that some of the information is incorrect or greatly exaggerated. Be that as it may, I would like to remember Dr. Iacono as a very passionate man who worked endless hours in the pursuit of an improved treatment for Parkinson's disease. He was not only a surgeon but also a compassionate human being trying to help those patients in desperate situations. He studied every facet of the disease and became a self-taught expert in neuroanatomy and neuropharmocology. He believed in treating the whole person, not just a piece of brain.

Born in Southern California outside of Los Angeles, he completed most of his schooling in that area and eventually split his neurosurgery residency between the University of Southern California and Duke University. At Duke he learned functional neurosurgery from Blaine Nashold Jr., MD, who, as many of us would agree, is one of the fathers of modern functional neurosurgery.

Dr. Iacono brought his passion for neurosurgery to the University of Arizona, where he practiced until 1990. He then traveled to learn about posterior ventral pallidotomy from Lauri Laitinen, MD, in Sweden and other functional techniques from Fumio Shima, MD, in Japan. In 1991 Dr. Iacono brought his knowledge to Loma Linda Medical Center, where I first met him.

We could easily discuss Dr. Iacono's years of work doing

pallidotomy procedures and expound on the controversies that followed, but I wish to talk more about his humanistic side. He was a very personal man who took much into his own heart. His introverted nature, though, did not always bide well with others in the profession. He did not mind the extra work he imposed on himself to improve the surgical care of his patients, and he greatly enjoyed helping others in need.

In our early experience with posteriorventral pallidotomy, we began to notice that in some patients the lesioning seemed to be off. This troubled Dr. Iacono, and he ended up discussing the matter with Dr. Nashold. Dr. Nashold's answer to our dilemma was to go back to the gold standard for stereotactic targeting: the ventriculogram. Well, that was easier said than done since no ORs of the day were configured for ventriculography and some of the equipment was hard, if not impossible, to find. We eventually found the necessary hardware and learned how to do very accurate ventriculography. This technique helped us later to describe the inaccuracies within MRI targeting.

This is but a small snippet of what Dr. Iacono did to better his techniques to improve the lives of others. It is unfortunate that many medical professionals shunned him and refused to collaborate, and this may be the fate of personalities in society with tremendous passion for their work. One has only to talk to the many people whom he treated or taught directly. Those are the people who really knew him for who he really was—a passionate pioneer.

He is survived by his lovely wife, Dr. Grace Oh; son, Robert; daughter, Rose; father, Paul E.; and the countless patients and students whom he directly influenced. I and many others will miss him deeply.

George Mandybur, MD Cincinnati, Ohio

## Clinical Trials in Functional Neurosurgery

#### Ashwini D. Sharan, MD, and Steven Falowski, MD

The field of functional neurosurgery is rapidly advancing, and significant research continues to explore both current and expanding indications for neural stimulation. Presently there are a number of protocols under investigation which this article will summarize.

The following listing of study titles and descriptions represents a compilation from searches performed on http://clinicaltrials. gov, a service developed by the National Library of Medicine under the auspices of the U.S. National Institutes of Health that contains regularly updated information about clinical human trials. Searches were performed on this site using the key words deep brain stimulation, DBS; spinal cord stimulation, SCS; Medtronic; Advanced Neuromodulation System; Neuropace; Northstar Neuroscience; Cyberonics; and Advance Bionics.

#### **Pain**

CONCEPT: Crossover Efficacy Pain Trial in Motor Cortex Stimulation for Intractable Neuropathic Pain—Phase III, randomized, double-blind, placebo control study sponsored by Medtronic in Europe to evaluate motor cortex stimulation in the treatment of neuropathic pain for central post-stroke and trigeminal facial pain.

**Spinal Cord Stimulation Efficacy Measures**—Phase I, double-blind, randomized study sponsored by New York Neurosurgery & Neuroscience Associates PLLC and Medtronic Neurological at two centers in New York to evaluate the role of frequency and pulse-width in the efficacy of spinal cord stimulation.

Spinal Cord Stimulation for Painful Diabetic Neuropathy (DPN)—Phase IV, nonrandomized, open label trial sponsored by Advanced Bionics assessing SCS in patients with diabetic peripheral neuropathy.

**Spinal Cord Stimulation for Chronic and Intractable Back Pain**—Phase IV, nonrandomized, open label trial sponsored by Advanced Bionics assessing SCS in patients with chronic and intractable back pain who are not surgical candidates.

Effectiveness of the Precision Spinal Cord Stimulation System With the Artisan Paddle Electrode in Patients With Back or Lower Extremity Pain—Phase IV, nonrandomized, open label trial sponsored by Advanced Bionics assessing SCS and the artisan paddle in patients with failed back surgery syndrome and back and lower extremity pain.

**Efficacy of the SCS System as Salvage Therapy**—Phase IV, nonrandomized, open label trial sponsored by Advanced Bionics assessing SCS in patients who have failed intraspinal infusion pump or other SCS system.

**Effect of Pulse Width with Spinal Cord Stimulation**—Phase IV nonrandomized, open label trial sponsored by Advanced Bionics assessing the effects of varying pulse width in patients with SCS and back pain.

**Spinal Cord Stimulation (SCS) for Neuropathic Pain of Back or Lower Extremity**—Phase IV, nonrandomized, open label trial sponsored by Advanced Bionics assessing SCS at different spinal levels, T7 and T8.

Spinal Cord Stimulation versus Nerve Blocks and Physical Therapy—Phase IV, randomized, open label trial sponsored by Advanced Bionics assessing SCS versus conventional therapy in patients with complex regional pain syndrome.

Changes in Cerebral Blood Flow in Patients Treated With Spinal Cord Stimulation for Low Back and Leg Pain—Phase IV, nonrandomized, open label trial sponsored by Advanced Bionics assessing brain regions which may be activated by SCS.

**Spinal Cord Stimulation (SCS) in Refractory Angina**—Phase III, randomized, single-blind, placebo control trial sponsored by Catholic University of the Sacred Heart on SCS.

The Efficacy of Motor Cortex Stimulation for Pain Control—Rrandomized, double-blind study sponsored by Capital District Health Authority, Canada, on motor cortex stimulation for three chronic pain conditions.

#### **Epilepsy**

STIMEP: Assessment of Subthalamic Nucleus Stimulation in Drug Resistant Epilepsy—Phase II/III, randomized, double-blind controlled trial sponsored by University Hospital, Grenoble Ministry of Health, France, evaluating the effectiveness and the safety of STN deep brain stimulation in drug resistant epilepsy.

Controlled Randomized Stimulation Versus Resection (CoRaStiR)—Prospective randomized study sponsored by University Hospital, Ghent, and Medtronic in Europe to assess neurostimulation in the medial temporal lobe for patients with medically refractory medial temporal lobe epilepsy.

RNS<sup>TM</sup> System Pivotal Clinical Investigation—Phase III randomized, double-blind, placebo controlled study on the efficacy of responsive stimulation for refractory epilepsy.

**Electroencephalography (EEG) and Deep Brain Stimulation (DBS) in Epilepsy**—Nonrandomized study sponsored by Weill Medical College of Cornell University on the effects of DBS on EEG signals in patients with epilepsy undergoing DBS.

#### **Psychiatric**

Deep Brain Stimulation for Treatment Resistant Depression (TRD)—Trial sponsored by Emory University Stanley Medical Research Institute Wooruff Fund on chronic subgenual cingulated white matter using the ANS Totally Implantable Deep Brain Stimulation System for treatment-refractory depression. A similar study under way is sponsored by University Health Network, Toronto, and National Alliance for Research on Schizophrenia and Depression.

Study Comparing Outcomes for Patients with Treatment Resistant Depression Who Receive VNS Therapy at Different Doses—Randomized, double-blind, active control study sponsored by Cyberonics investigating different electrical dosages for patients with treatment-refractory depression.

**Treatment-Resistant Depression Registry**—Registry collecting information on patients with TRD.

Subthalamic Nucleus (STN) Stimulation and Obsessive-Compulsive Disorder (OCD)—Phase I/II, randomized, double-blind, placebo control, crossover assignment study sponsored by Groupe Hospitalier Pitie-Salpetriere DRRC on STN stimulation in patients with severe OCD.

**Deep Brain Stimulation for Treatment-Refractory Major Depression**—Phase I, randomized, double-blind, placebo-controlled study sponsored by University Hospital, Bonn and Medtronic.

## Application for New Membership





#### American Society for Stereotactic and Functional Neurosurgery

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Medical School:			
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Determine and circle your membership category:			
Category Vearly Fee Description			

Category	Yearly Fee	Description
Active	\$325	For practicing neurosurgeons in the United States or Canada who have completed residency/fellowship
Resident/Fellow	\$25	One-time fee (not yearly). For neurosurgical trainees currently in residency or fellowship
Senior	Free	For neurosurgeons who are retired and over 65 years old
Associate	\$50	For non-neurosurgeons

The benefits of Active membership include:

- Membership in the AANS/CNS Section on Stereotactic and Functional
- Membership in the World Society for Stereotactic and Functional Neurosurgery

Reduced fees for the biennial ASSFN meetings

Subscription to the journal Stereotactic and Functional Neurosurgery (including online access)

The benefits of all other membership categories are:

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AANS, 5550 Meadowbrook Drive, Rolling Meadows, IL 60008, and check

There are two ways to become an ASSFN member:

Apply online at www.MyAANS.org (for Active member applications only), or mail this application form and check for appropriate fee (see table above) made out to ASSFN to: ASSFN, c/o AANS, 5550 Meadowbrook Drive, Rolling Meadows, IL 60008. For questions or concerns, contact the current (2006-2008) treasurer, Ali Rezai at rezaia@ccf.org, or the membership chair, Kelly Foote, at foote@neurosurgery.ufl.edu.

#### **Movement Disorders**

The Mood/Cognitive Effects of STN vs. GPi Deep Brain Stimulation in Parkinson's Disease—Randomized, double-blind study sponsored by the National Institute of Neurological Disorders and Stroke.

**Deep Brain Stimulation for Parkinson's Disease Trial**—Randomized, double-blind trial sponsored by the National Institute of Neurological Disorders and Stroke on DBS in the globus pallidus internus and the subthalamic nucleus on patients with Parkinson's disease.

Efficacy and Safety of DBS of the GPi in Patients With Tardive **Dystonia**—European-based, phase II randomized, double-blind, multicenter trial on bilateral pallidal stimulation in tardive dystonia.

Deep Brain Stimulation in Treating Patients With Dystonia— Phase II/III study sponsored by the FDA Office of Orphan Products Development and Mount Sinai School of Medicine.

Weight Changes in Parkinsonian Patients, Treated With Deep Brain Stimulation—Randomized, open label trial sponsored by University Hospital, Bordeaux on weight changes and energy balance on patients with Parkinson's and DBS.

Pallidal Stimulation in Patients with Post-Anoxic and Idiopathic **Dystonia**—Phase II and III studies sponsored by Groupe Hospitalier Pitie-Salpetriere Délégation Régionale à la Recherche Clinique on bilateral pallidal stimulation in patients with postanoxic and idiopathic dystonia.

Double-Blind, Multicenter Study to Assess the Efficacy of Bilateral Pallidal Stimulation in Patients with Medically Refractory Primary Cervical Dystonia—Phase III, randomized, double-blind,

placebo control study sponsored by German Parkinson Study Group, Medtronic and Competence Network on Parkinson's disease on the effects of bilateral pallidal stimulation on patients with refractory cervical dystonia.

DBS for Early Stage Parkinson's Disease—Phase I, randomized, single-blind study sponsored by Vanderbilt University.

Bilateral Internal Pallidum Stimulation in Primary Generalized Dystonia—Phase II/III, randomized, double-blind, placebo control study sponsored by Academisch Medisch Centrum-Universiteit van Amsterdam Princess Beatrix Fund, The Netherlands, on DBS of the globus pallidus internus for primary generalized dystonias.

#### **Spinal Cord Injury**

Spinal Cord Stimulation to Restore Cough—Phase I, nonrandomized study sponsored by the National Institute of Neurological Disorders and Stroke on the effects of SCS on the ability to produce effective cough on patients with spinal cord injury.

#### **Fibromyalgia**

Vagus Nerve Stimulation in Fibromyalgia—Phase II, nonrandomized, open label, uncontrolled study sponsored by University of Medicine and Dentistry New Jersey, National Institute of Neurological Disorders and Stroke and National Institute of Arthritis and Musculoskeletal and Skin Diseases on vagus nerve stimulation device implantation in patients with severe fibromyalgia syndrome.

#### **ASSFN-AANS/CNS Section on Stereotactic and Functional Neurosurgery**

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#### **Upcoming Meetings Calendar**

One of the purposes of this newsletter is to inform all ASSFN members about upcoming meetings and conferences of interest. Meeting organizers are encouraged to contact the newsletter editor, Konstantin Slavin, MD, with information regarding future meetings.

#### 2007 Congress of Neurological Surgeons Annual Meeting

San Diego, Calif. Sept. 15–20, 2007

www.neurosurgeon.org/meetings/2007/index.asp

#### 10th Annual Conference of the Indian Society for Stereotactic and Functional Neurosurgery Kolkata India

Kolkata, India Oct. 26-28, 2007

Contact Prof. G.K. Prusty, stereotaxy2007@gmail.com

#### 8th World Congress of the International Neuromodulation Society and 11th Annual Meeting of the North American Neuromodulation Society

Neuromodulation Society
Neuromodulation: Technology at the Neural Interface
Acapulco, Mexico
Dec. 7–12, 2007
www.neuromodulation.org

#### 7th Annual CyberKnife Users' Meeting

Scottsdale, Ariz. Jan. 23–27, 2008 www.cksociety.org

#### 76th Annual Meeting of the American Association of Neurological Surgeons

Chicago, Ill. April 26–May 1, 2008

www.aans.org/annual/2008/default.asp

#### 14th International Meeting of the Leksell Gamma Knife Society

Quebec City, Canada May 18–22, 2008 www.lgks2008.org

#### Biannual Meeting of the ASSFN

Vancouver, Canada June 1–4, 2008 www.assfn.org

#### 2008 Congress of Neurological Surgeons Annual Meeting

Orlando, Fla. Sept. 20–25, 2008 www.neurosurgeon.org

#### XVIII Congress of the European Society of Stereotactic and Functional Neurosurgery (ESSFN)

Rimini, İtaly Oct. 5–8, 2008 www.essfn.org

## 15th Quadrennial Meeting of the World Society of Stereotactic and Functional Neurosurgery

Toronto, Canada May 24–27, 2009 www.wssfn.org