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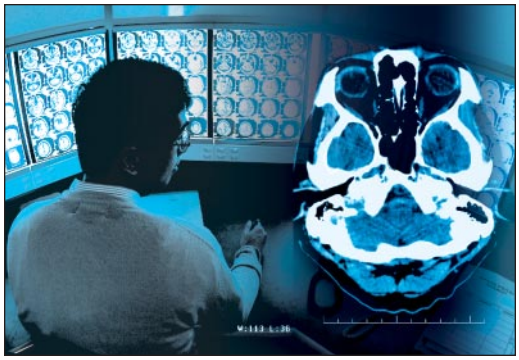
Research Expands Role of Deep Brain Stimulation in Neurologic Disorders



Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital have been among the pioneers in using deep brain stimulation (DBS) in the routine treatment of a growing array of neurologic disorders. DBS was developed initially as a treatment for Parkinson's disease and was approved by the Food and Drug Administration for that purpose in 1997. However, clinical trials of DBS in the treatment of epilepsy are in progress.

"About one third of people with epilepsy do not have their seizures adequately controlled with available therapies. Surgery can be very effective in epilepsy, but you need a highly localized source in an accessible area where the risks of damage to surrounding tissue is low," said Douglas R. Labar, MD, PhD. "The advantage of deep brain stimulation is that it can exert control over seizure activity even when the exact location of the seizure source has not been isolated."

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Centers Advance Management of MS Patients

NewYork-Presbyterian Hospital now has 2 eminent centers for the management of multiple sclerosis (MS). The recently opened Multiple Sclerosis Care and Research Center, NewYork-Presbyterian Hospital/Columbia University Medical Center joins the center of the same name at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, which has been a leader in MS management and clinical research for more than a decade.

"There has been enormous progress, not only in treating the underlying disease process, but also in addressing the complications of MS," noted Brian Apatoff, MD, PhD. "The advantage of a center dedicated to the management of MS is that it can bring together a clinical team that provides patients with the array of services they need to minimize the impact of this disease."

The NewYork-Presbyterian/Weill Cornell center was established in 1993 and has been around long enough to have participated in the Phase III trials that led to approval of key immunomodulatory agents. These therapies have played a critical role in reducing the number of exacerbations in MS, and they may alter the natural history of MS by slowing its progression. The new center at NewYork-Presbyterian/Columbia, which is part of the Neurological Institute of New York, will also conduct clinical

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Continuing Medical Education

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"Brain Attack 2006" course.
November 17, 2006.

NewYork-Presbyterian
The University Hospital of Columbia and Cornell

Groundbreaking Study Reveals Protective Effects of Alcohol Against Stroke

The Northern Manhattan Study, coordinated by Columbia investigators at NewYork-Presbyterian Hospital, has confirmed that moderate alcohol consumption of up to 2 drinks (1 drink was considered to be 4 oz wine, 12 oz beer, or 1.5 oz ethanol) per day reduces the risk of ischemic stroke by approximately one third and also reduces the risk of myocardial infarction and vascular death. The new data are the latest in a series of reports from one of the most important initiatives in the world to evaluate the epidemiology of stroke.

"The Northern Manhattan Study was established in 1990, and it is being conducted in an area of New York in which about half the population is Hispanic, one of the most rapidly growing segments of the population," noted Ralph L. Sacco, MD. "This is an important advantage for evaluating risk factors across racial groups."

Moderate alcohol consumption ... reduces the risk of ischemic stroke by approximately one third.

The Northern Manhattan Study is an outgrowth of the leading role Columbia investigators at NewYork-Presbyterian Hospital have played in the study of stroke. The initiatives support clinical work that makes the Hospital one of the leading treatment centers in the country. The studies led by Dr. Sacco and his colleagues will keep NewYork-Presbyterian at the center of stroke research for the foreseeable future.

The study of alcohol consumption, just published in *Stroke* (2006;37:13-19) by lead author Mitchell S.V. Elkind, MD, evaluated alcohol consumption in 3,176 individuals living in upper Manhattan. None had a history of stroke at enrollment. The mean age of the participants was 69. Slightly more than 60% were women. When stratified by race and ethnicity, about half were Hispanic with the rest divided among non-Hispanic whites and non-Hispanic blacks. Participants who entered the study were interviewed in person about alcohol consumption over the previous year. Most of the population were either nondrinkers (62%) or moderate drinkers (33%), meaning that they had 1 or more drinks per month but 2 or fewer drinks per day. The remaining were intermediate drinkers, meaning they had more than 2 but fewer than 5 drinks daily, or heavy drinkers, who had 5 or more drinks per day.

After adjusting for risk factors, the hazard ratio for ischemic stroke in those who consumed moderate alcohol compared to those who did not drink was 0.67 (95% CI, 0.46-0.99) (see Table). According to Dr. Elkind, a nonlinear risk assessment suggested that the minimum risk for stroke is achieved with 1.2 drinks per day. The presumed protection conferred by alcohol, which has been previously demonstrated for cardiovascular disease, is thought to be partially achieved through an increase in high-density lipoprotein (HDL) levels. It is notable that the protective effect in this study was observed even after adjusting for HDL and was greater against cryptogenic, cardioembolic, and lacunar strokes than against atherothrombotic strokes.

The protective effect of alcohol against stroke has been observed previously, but many of the large epidemiologic studies have been conducted in a primarily white population. The strength of the study is that it provides prospective data on a multi-ethnic population that has been found to have a greater burden of stroke.

In new guidelines for secondary prevention of stroke, for which Dr. Sacco was the lead author, moderate consumption of alcohol, defined as 2 or fewer drinks per day for men and 1 drink per day for women, "may be considered." Despite the benefits of moderate alcohol consumption in the study, caution was expressed about some of the potential adverse consequences of alcohol. The new guidelines are the most comprehensive evidence-based recommendations for the prevention of stroke in survivors of stroke and transient ischemic attack. Besides covering the latest recommendations on risk factor control, interventional procedures,

Table. Risk of Ischemic Stroke Associated With Recent Moderate Alcohol Consumption*

	Adjusted HR (95% CI)†
Age < 70 y	0.81 (0.45–1.46)
Age ≥ 70 y	0.54 (0.33–0.90)
Men	0.76 (0.44–1.32)
Women	0.59 (0.34–1.03)
Hispanic	0.54 (0.29–1.02)
Non-Hispanic Black	0.86 (0.46–1.60)
Non-Hispanic White	0.67 (0.32–1.42)
Nonsmokers	0.51 (0.26–1.00)
Former smokers	0.61 (0.32–1.15)
Current smokers	1.12 (0.55–2.29)

* Referent group is persons who drank no alcohol (<1 drink/mo) in year.

† Adjusted for age (continuous), sex, race–ethnicity, education (high school graduate vs not), hypertension, diabetes mellitus, atrial fibrillation, levels of high-density lipoprotein, and current cigarette smoking.

Source: Elkind MSV, Sciacca R, Boden-Albala B, et al. Moderate alcohol consumption reduces risk of ischemic stroke; the Northern Manhattan Study. *Stroke.* 2006;37:13-19.

anticoagulants, and antiplatelets, they cover a broad spectrum of issues, such as sickle-cell disease, hypercoagulable states, use of anticoagulation after cerebral hemorrhage, and stroke risk in women, particularly in regard to pregnancy and the use of postmenopausal hormones. The new guidelines are jointly sponsored by the American Heart Association and the American Stroke Association and endorsed by the American Academy of Neurology; they were recently published in *Stroke*.

"In those who already consume moderate amounts of alcohol, the data suggest that they should continue because of the likelihood that this will reduce their risk of stroke as well as their risk of cardiovascular disease," Dr. Sacco said. "However, there are risks to alcohol consumption, and I would hesitate to suggest that individuals should start drinking as a risk-reduction strategy."

While Dr. Sacco chaired the panel of experts on stroke from around the world to design these guidelines, it is likely that work at NewYork-Presbyterian/Columbia will contribute data useful for future guidelines. According to Dr. Sacco, ongoing or planned prospective studies include detailed analyses of the role of carotid thickening, periodontal disease, and inflammatory markers on stroke risk. Like the Framingham Heart Study, which has played an increasingly important role in evaluating cardiovascular risk factors as data have accumulated over more than 50 years of research, the already important impact of the Northern Manhattan Study will increase as data accrue over time.

"One of the current projects involves magnetic resonance imaging to evaluate the presence of subclinical brain disease and its subsequent evolution," noted Dr. Sacco. This type of information may ultimately be translated into new strategies for prevention.

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NewYork-Presbyterian Neuroscience

is a publication of the Neuroscience Centers of NewYork-Presbyterian Hospital. The Neuroscience Centers are at the forefront of research and practice in the diagnosis, treatment, and rehabilitation of neurologic disease. The Neuroscience Centers include the Neurological Institute of New York at NewYork-Presbyterian Hospital/Columbia University Medical Center and the Weill Cornell Neuroscience Institute at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, which are respectively affiliated with Columbia University College of Physicians and Surgeons and the Weill Medical College of Cornell University.

Mitochondrial Metabolism: A Potential Source for New Treatments for Neurologic Disorders

Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are studying the potential role of mitochondrial metabolism as a gateway to treatment of major diseases, including neurologic disorders such as Parkinson's, Huntington's, and amyotrophic lateral sclerosis (ALS). Interest in this area has intensified recently as a result of progress in understanding both the underlying physiology of mitochondria and mitochondrial genetics as controlled by mitochondrial DNA (mtDNA).

"So far, very few of the defects are treatable, but there are some promising concepts about what can be done to restore mitochondrial function or treat the effects of dysfunction," noted Darryl C. DeVivo, MD. "I think we are moving in a direction in which we will see some clinical trials provide some positive results."

Some therapies, such as dichloroacetate (DCA) and high doses of antioxidants, including vitamins C and E, have long been used in various mitochondrial diseases, many of which are characterized by elevated lactic acid levels. In general, these therapies have had very limited efficacy, and they do not address the underlying defect. In fact, a recent, rigorous therapeutic trial has shown DCA to be neurotoxic in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes. Any beneficial effect in lowering cerebral lactic acidosis appeared to be overshadowed by damage to peripheral nerves. However, all antioxidants have not been abandoned. For example, coenzyme Q_{10}, a powerful antioxidant and mitochondrial cofactor, is being considered as a possible treatment of several mitochondrial disorders.

Fatty acid oxidation defects are among the most commonly inherited mitochondrial anomalies and therefore are among the targets most actively pursued by investigators. Salvatore DiMauro, MD, is a pioneer in this field. In 1973, he and a team of researchers identified carnitine palmitoyltransferase (CPT) deficiency (now better defined as CPT II deficiency), which is implicated in recurrent muscle breakdowns (episodic myoglobinuria) as well as in childhood encephalopathy with hypoketotic hypoglycemia. Although he has moved on to investigate a much broader group of mitochondrial diseases, Dr. DiMauro's discovery was one of the advances that helped focus clinicians on mitochondrial abnormalities as treatable defects.

> The challenges are faced on every level, from diagnosis to isolation to the development of effective therapies.

Another hereditary disorder of fatty acid oxidation, primary carnitine deficiency, "is one of the major successes in the treatment of mitochondrial disorders," said Dr. DeVivo. "It is an autosomal recessive disorder that is life-threatening but highly treatable. It can be diagnosed with a simple blood carnitine measurement. Patients with an otherwise fatal disease can lead essentially normal lives just by carnitine replacement."

The challenges in mitochondrial disorders are faced on every level, from diagnosis to isolation of the defect (or defects) involved, to the development of effective therapies. Dr. DiMauro and Eric Schon, PhD, co-authored an influential review article 3 years ago on mitochondrial diseases for *The New England Journal of Medicine* (2003;348:2656-2668). Although substantial progress has been made since that review was written, Dr. DiMauro cautioned that treatments for most mitochondrial defects are still waiting for a better understanding of the basic pathogenetic mechanisms, which might reveal targets for therapy. However, it is clear that basic science is providing the foundation for treatment strategies.

One concept with the specific potential to move from basic science to clinical application is treatment of mutant mtDNA. As cells contain thousands of mtDNA molecules, usually wild-type or normal mtDNA coexist with mutant mtDNA, a phenomenon known as *heteroplasmy* (as opposed to *homoplasmy*, meaning that all mtDNAs are identical). Mitochondrial diseases do not appear to be expressed until the mutant mtDNAs reach some critical threshold and produce oxidative dysfunction. Organs most dependent on oxidative metabolism, such as the brain, may require lower levels of mutant mtDNAs before clinical signs of mitochondrial dysfunction manifest. Efforts to reduce the proportion of mutant mtDNAs offer an attractive intervention target.

"We believe that the main goal for treatment of mutant mtDNA is gene shifting," noted Dr. DiMauro. "Although we are in the early years of understanding how this is best accomplished, reasonable strategies have been proposed, such as selective destruction of the mutations by importing restriction enzymes into the mitochondria or replacing a mutant mtDNA-encoded protein with a genetically engineered normal equivalent in the nucleus."

According to M. Flint Beal, MD,

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New Neurology Chief Promises Focus on Technology and Patient-Centered Care

For Matthew E. Fink, MD, returning to NewYork-Presbyterian Hospital is a homecoming. The new Chief, Division of Stroke and Critical Care Neurology, and Vice Chairman for Clinical Services at NewYork-Presbyterian Hospital/Weill Cornell Medical Center—who is also Professor of Clinical Neurology and Neuroscience at Weill Medical College of Cornell University—has in fact returned to the place where, years ago, he began his distinguished career.

Dr. Fink's philosophy now is not very different from his philosophy then—in a nutshell: "Never give up." What is new, however, are the technological advancements that have enabled continued progress and development in neurocritical care and vascular neurology overall. Dr. Fink focuses on the importance of pursuing all reasonable and meaningful treatments for patients, even when others may view a patient's condition as hopeless. He credits multidisciplinary team work—individuals with specialized knowledge working together toward the same goal—as a key to success in the field.

While this philosophy is instrumental in his efforts and plays a large role in directing his vision for the Division of Stroke and Critical Care Neurology, Dr. Fink stresses the value of new technological developments in advancing the field of neuro-critical care and stroke neurology. He cites technological advancements as a key component of the overall improvement in neurological care available to patients, particularly in relation to the intensive care management available to critically ill patients.

Such progress has changed the face of the specialty. Of particular significance are the advances in neurosurgery, neuroimaging, radiosurgery, and endovascular therapy. NewYork-Presbyterian Hospital has been at the forefront of these advancements to date; it is Dr. Fink's hope that, under his tenure, the Hospital will continue to take a leadership role in advancing new diagnostic and therapeutic modalities based on advanced technology.

This emphasis on the overall importance of continuing technological advancement in the field as a means of improving patient care is, of course, consistent with Dr. Fink's forward-thinking approach to medicine generally and neuro-critical care specifically. However, he specifies substantially significant advancements, currently implemented at NewYork-Presbyterian Hospital, as critical to improve patient care.

Dr. Fink reinforces the significance of developing new therapies based on translational research. The Stroke and Critical Care Division is participating in a variety of clinical trials focused on the prevention and treatment of stroke. First, in collaboration with Columbia researchers at NewYork-Presbyterian, Weill Cornell investigators will begin testing the beneficial effects of high-dose statins in the treatment of acute ischemic stroke later this year.

According to Dr. Fink, this research will focus on benefits that are "independent of their lipid-lowering properties," including improvement of endothelial function, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory responses, immunomodulatory actions, regulation of progenitor cells, and stabilization of atherosclerotic plaques.

"We are studying the effects of treatment of acute ischemic stroke after 3 hours, when intravenous TPA is no longer an option," noted Dr. Fink. "Our neuro-critical care team is evaluating the benefits of an oxygen sensor inserted into the brain as a method to maximize blood flow in patients with acute brain ischemia."

Under Dr. Fink's leadership, Weill Cornell researchers will also be involved in studies of the effects of different antiplatelet medications with a new device that measures platelet activity in patients. The goal is to increase understanding of the negative effects of antiplatelet therapy—such as bleeding complications—as well as issues including safety and treatment compliance.

Researchers will also be involved in studies evaluating the benefits of closing a patent foramen ovale (PFO) in patients with migraine as well as cryptogenic stroke. Recent research has indicated that PFO has a causative relationship with embolic ischaemic stroke, migraine with aura, and cerebral and cutaneous decompression disease. While PFO plays a vital role in neurodevelopment in utero, studies have shown it to have no physiologic benefit post utero.

"And we are participating in a trial of a new direct thrombin inhibitor to prevent stroke in patients with atrial fibrillation, as an alternative to warfarin," added Dr. Fink. Based on these initiatives, it is clear that researchers within the Division of Stroke and Critical Care Neurology at NewYork-Presbyterian/Weill Cornell will be involved in several key projects, the hallmark of which will be the almost dogged pursuit of new treatment options for common, yet troublesome, neurologic disorders.

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Multiple Sclerosis

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research. It has already been enlisted to participate in the first large-scale, multicenter study to evaluate a combination of 2 proven immunomodulator therapies. The trial is being funded by the National Institutes of Health.

"The CombiRx study is a Phase III trial evaluating the combination of interferon beta with glatiramer acetate," said Mark Tullman, MD. "These agents have very different mechanisms of action and are modestly effective when used alone. Hopefully, the combination, which was safe in a preliminary study, will turn out to be more protective than either agent used alone."

A variety of other clinical research projects will soon be under way at the new center, including a biomarker study aimed at providing a better understanding of the disease and how it responds to therapy. Along with developing better disease-modifying therapies, Dr. Tullman and his colleagues aim to improve the quality of life of MS patients and help them maintain an optimal level of functioning.

"Although we need to improve our disease-modifying drugs, the currently available therapies have enabled many patients to function at an extremely high level," said Dr. Tullman. "For patients with more disability, a multidisciplinary approach, which often combines physical and occupational therapy with pharmacotherapy, can often alleviate some of the daily symptoms of MS and significantly improve quality of life." Drs. Apatoff and Tullman both believe a comprehensive program is needed because MS is such a variable disease and affects different individuals in a variety of ways.

"We have several members on our team who have been significant innovators in helping patients cope with their complications," added Dr. Apatoff. "Because of the heterogeneity in how this disease advances, each case is different, so we consider the individual needs and solutions that will work best in specific circumstances."

> "The emphasis of our research will be on its potential to improve patient care."
>
> —*Mark Tullman, MD*

According to Dr. Apatoff, the disease-modifying agents have been a significant advance in the control of MS, but they are not a cure; in most patients the disease eventually progresses, gradually limiting daily activities. As MS begins to affect bowel and bladder function, vision, mobility, and other systems, a team of specialists is available to find solutions to help patients maintain their independence and the best possible quality of life.

Patients managed at the centers benefit from both the expertise of a dedicated team and advances that people active in clinical research are in a position to bring. Dr. Tullman and his colleagues have access to advanced magnetic resonance imaging (MRI) systems that are used exclusively for research purposes.

Currently, MRI is the best tool for evaluating MS lesions in the brain and spinal cord and tracking change over time. It is hoped that serial measurements obtained with increasingly sophisticated techniques will provide insight into the pathophysiology of this disease and help monitor response to therapy.

"The emphasis of our research will be on its potential to improve patient care," Dr. Tullman reported.

Dr. Apatoff and his team, meanwhile, are coordinating a broad research program that includes a laboratory of human molecular immunology, where gene expression is being evaluated as a target for disease control, and a laboratory of neurogeneration, which is evaluating the ability of stem cells to repair myelin, the major target of the inflammatory process that characterizes MS.

The mission of the Multiple Sclerosis Center at NewYork-Presbyterian/Weill Cornell has been advanced by a major grant from the Feil Family Foundation. The grant will fund a state-of-the-art patient care facility in the facility's new ambulatory tower. "This exceptional donation has provided an extraordinary infrastructure to ensure that the Hospital continues to play a leading role in defining the best clinical care for patients with MS," Dr. Apatoff said.

"While we look for treatments that can prevent the disease from advancing, the focus at our center has been to keep patients leading active and full lives," he continued. "As the disease advances, this takes a team approach, and this has been a strength of our program."

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Brain Stimulation

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Clinical trials demonstrating the advantages of DBS in epilepsy are proceeding rapidly. One of the techniques that Dr. Labar has been working with is known by its acronym, SANTE (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy). The SANTE device, like other devices used for DBS, consists of an electrode or electrodes implanted into the brain, a pacemaker-like generator implanted elsewhere into the body, often the chest region, and a cable tunneled under the skin and through the neck to connect them.

"The pilot study demonstrated a promising degree of efficacy and safety, setting the stage for the pivotal trial, which is just beginning," Dr. Labar said. "If results are favorable, these devices could be available in about 3 years."

Investigators are also involved in studies of the responsive neurostimulator system (RNS), which has features similar to those of the SANTE instrumentation but is a closed-loop device that responds to seizure activity. Lawrence J. Hirsch, MD, likened the activity of the RNS to that of a cardiac defibrillator programmed to provide shocks only in response to abnormal electrical activity.

"The electrodes are implanted in the brain at the site or sites of seizure onset," he noted. "The device continuously monitors the [electrocardiogram] and responds to abnormal activity by providing an electrical impulse to abort seizures and stop them from spreading."

According to Dr. Hirsch, patients are not even aware that the device is active when it is working optimally. Some patients require hundreds of stimulating impulses per day to control seizure activity. Like the SANTE device, the RNS has demonstrated feasibility and safety in a pilot study. Dr. Hirsch was a co-investigator of a recent open-label, multicenter study in which 47 patients experienced no serious surgical or device-related complications and preliminary evidence of efficacy was observed.

As a result of the favorable preliminary clinical trials, "the pivotal trial with this device is about to begin," noted Dr. Hirsch. "This could be an important advance for individuals with refractory epilepsy who do not respond to current options."

According to Robert R. Goodman, MD, PhD, the principal investigator of the pilot study with the RNS system, studies of DBS at the Hospital have been ongoing for almost a decade. Some of the first procedures to implant DBS devices were performed at NewYork-Presbyterian in 1998, initially in patients with Parkinson's disease. This work provided a basis for the more recent studies in epilepsy, which began in 2004. Dr. Goodman credited Dr. Labar's experiments with vagus nerve stimulation as being an important step forward in applying electrical stimulation to control epilepsy, and he indicated that the development and use of implantable electronic devices to treat epilepsy is critically dependent on a close collaboration of neurologists and neurosurgeons. The neurologists and neurosurgeons, he added, must have a special interest and expertise in dealing with medically refractory epilepsy.

> "Deep brain stimulation… can exert control over seizure activity even when the exact location of the seizure source has not been isolated."
>
> —*Douglas R. Labar, MD*

"The surgical techniques have been quite safe in the pilot studies," said Dr. Goodman. "The electrodes are implanted by discrete burr holes rather than craniotomy, and brain mapping permits placement with relative precision, providing a low risk of complications." He added that the risks in patients with epilepsy may be even lower than in patients with Parkinson's disease because those with epilepsy tend to be younger and healthier at the time of the procedure.

Although the results of Phase III trials are essential to demonstrate that the use of DBS as a routine treatment for refractory epilepsy is viable, the future appears promising. It is anticipated that the next generation of devices will incorporate an increasing degree of sophistication in adjusting to electrical activity in the brain to achieve a very tight control of seizures. In the substantial proportion of patients whose epilepsy is poorly controlled by current treatments, DBS is expected to be a breakthrough technology.

"Epileptic activity can be complicated and difficult to control when there are multiple foci unresponsive to medical therapy," noted Dr. Hirsch. "The DBS system and RNS have the potential to control electrical activity in the brain in order to prevent seizures or to stop them before they can cause symptoms." Although medical therapies and surgery are important options in the right patients, brain stimulation may substantially increase the proportion of patients with epilepsy in whom symptomatic control can be achieved.

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Mitochondrial

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research efforts are under way to better define the role of mitochondrial defects in ALS, Parkinson's, Huntington's, and Alzheimer's. In Huntington's disease, the evaluation of the antioxidant vitamin coenzyme Q_{10} has reached Phase III investigation, while parallel studies into the potential therapeutic effects of Q_{10} in ALS and Parkinson's are being pursued by Petra Kaufmann, MD, MSc, and Dr. Beal, respectively. All of the clinical studies are focused on the premise that defects in mitochondrial function may be addressed by reducing oxidative stress. However, researchers are also pursuing gene therapy, with the hope of curing rather than treating these disorders.

"The mitochondria are the largest source of free radicals identified," explained Dr. Beal. "They cause oxidative stress in a variety of tissues, some of which may be associated with normal physiologic processes such as aging. But defects in mitochondrial metabolism appear to play an important role in the processes that lead to expression of some of the most common neurological disorders, including Alzheimer's."

Although the concept of mitochondrial diseases as treatable disorders is now more than 40 years old, there was a long latent phase in identifying viable clinical approaches. Now, progress in basic research has paved the way for significant clinical advances. New therapeutic approaches will almost certainly evolve over the next few years.

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