The past decade has seen a number of remarkable advances in the area of epilepsy research, most notably the identification of specific mutations in genes that appear to be the cause of certain inherited forms of epilepsy. Researchers had long suspected that the genes involved in epilepsy would include those involved in the control of the excitability of brain cells, and this has indeed proved to be the case with the gene mutations discovered thus far – a number of them are so-called “ion channels,” which allow the passage of electrically-charged ions into and out of the cell. However, all of the gene mutations identified to date have been found in a small number of families around the world with relatively rare forms of epilepsy. Yet it is very clear that genetics has a much more widespread influence on epilepsy beyond what is found in these rare families. In addition to seizures being caused by a single gene mutation, scientists know that a combination of more subtle gene mutations in multiple genes is likely the basis for most forms of inherited epilepsy. Also, there are strong reasons to suspect that the ability of anti-seizure medication to control seizures is at least partly determined by genetic causes. For example, certain genes encode proteins that control the rate of metabolism of drugs, and it is well-established that some people have genes that make them “fast metabolizers” while other people are “slow metabolizers.” Other genes are crucial for the transport of drugs into brain cells. These genetic changes could help explain why certain people do or do not respond to anti-seizure medications.

Unraveling the more complex genetics of epilepsy, in particular, in patients with intractable epilepsy represents an enormous challenge, because the questions will only be answered by studying the clinical, laboratory and genetic characteristics of thousands of patients with epilepsy. To meet this challenge, NYU and UCSF have organized a group of epilepsy researchers around the country and initiated “The Epilepsy Phenome/Genome Project” (or EPGP, for short). EPGP brings together 12 prominent epilepsy centers...
From the Director of Research
by Ruben Kuzniecky, M.D.

I am extremely pleased to write to all of our supporters and friends about the exciting epilepsy research program we are building at NYU and many of the other research programs funded by faces as part of our mission of curing epilepsy.

As per the introduction to the newsletter, Dr Lowenstein, from UCSF, and I have devoted the past year to planning and organizing with a group of leading investigators across the U.S. the formation of a consortium to study intractable epilepsy. This effort has been fully supported by faces from onset and with recent faces funding, it is posed to allow the EPGP consortium to finalize a grant application to the NIH this coming spring. We are confident that the EPGP will have a significant impact on our understanding and treatment of epilepsy over the next several decades.

At NYU, the epilepsy research program is expanding and emphasizing two new areas of research. One area is on the imaging aspects of epilepsy. My research over the past 10 years have been devoted to using high field magnets and advanced imaging techniques to unravel the underlying causes of epilepsy. We have begun our collaborative efforts and with external funding have started a number of pilot projects to measure a number of metabolites and neurotransmitters in the brain. Specifically, we are studying if Glutamate, the most important excitatory transmitter in the brain, is abnormally elevated in regions causing seizures. Other imaging projects include measuring GABA or gamma acidic butyric acid, the most abundant inhibitory transmitter in the brain, at seizure onset and using GABA levels as a marker for seizure prognosis. The above research will be complemented by the use of Magnetoencephalography or MEG, a novel development for brain mapping which will be available to NYU researchers next spring. With MEG, tiny magnetic field potentials can be measured with the great advantage of providing the best time resolution of any imaging technique. Combined with MRI and other techniques, MEG can provide a new window into brain function using totally non-invasive techniques. As we go to press, we are starting an NIH sponsored study with Harvard University using MEG, MRI and direct brain recordings in hope of understanding the mechanisms underlying brain function.

The second area is devoted to novel therapeutics or new forms of treatment. As we all know, treatment of epilepsy is primarily based on oral or systemic drug use. All drugs have specific side effects since they have to go through the liver and other organs before reaching the brain. In addition, many drugs that are potentially anticonvulsants may not have the ability to enter the brain. A novel approach is to directly deliver drugs into the brain tissue or the surrounding brain fluid. This method has the potential for minimizing side effects since the amount of drug to be delivered is 1/100 or 1/1000 times smaller than the one needed if taken orally. The other advantage of direct drug

continued on page 7
Neurofeedback for Patients with Epilepsy

Investigators: Melissa Mendez, M.D., Orrin Devinsky, M.D., William Barr, Ph.D., Sidhartha Nadkarni, M.D.

This study is designed to determine whether biofeedback techniques can reduce seizure frequency among individuals with epilepsy. It involves training sessions using “EEG operant conditioning,” which requires participants to observe light and sound images that will appear as “rewards” when the brain’s electrical activity meets certain pre-defined criteria. Seizure activity before, during, and after a period of EEG operant conditioning will be analyzed for significant changes in frequency. Please see the study ad on page 6 for more information.

This study is supported by faces.

Multicenter Study of Epilepsy Surgery – NYU site

Investigators: Steven Pacia, M.D., William Barr, Ph.D., Werner Doyle, M.D.

The purpose of this 10-year longitudinal study is to improve our knowledge about the outcome of surgical treatment of patients with medically uncontrolled seizures as well as quality of life. The study is currently in its sixth year. Patients who have undergone surgery are followed-up over 10 years to determine the efficacy of epilepsy surgery in reducing or eliminating seizures, cognitive and behavioral outcome, including quality of life after surgery.

This study is supported by NIH.

In-Vivo Voltammetry with Microelectrodes for the Detection and Quantification of Neurotransmitters in Epileptogenic Cortex During Epilepsy Surgery

Investigators: Steven Pacia, M.D., Werner Doyle, M.D., Patricia Broderick, Ph.D.

Drs. Doyle and Broderick are conducting this research in patients undergoing epilepsy surgery to learn more about the biochemical profile of brain regions responsible for producing epileptic seizures. This study uses a microelectrode that is placed within the brain that will identify neurotransmitter (specifically norepinephrine, serotonin, and dopamine) concentrations, which are biochemical substances in the brain that allow brain cells to communicate. These neurotransmitters are involved in the spread of seizures throughout the brain.

This study is supported by PACE.
VARETA Localization of Partial Epileptic Seizure Foci with Variable Resolution Electrical Tomography

Investigator: Kenneth Alper, M.D.

The objective of this study is to generate images of partial epileptic seizure foci using Variable Resolution Electrical Tomography (VARETA) with the overall aim of developing this tool as an additional localizing technique which might contribute useful information in planning epilepsy surgery.

This study is supported by faces.

Frequency and Cause of Autism in Tuberous Sclerosis

Investigators: Ruth Nass, M.D, Daniel Miles, M.D., Josiane LaJoie, M.D., Charles Zaroff, Ph.D.

The purpose of this research is to determine how often and why children with Tuberous Sclerosis have neurologic problems that fall on the Autistic Spectrum (varying degrees of problems with language, social interactions, and rigidity or repetitive habits). We are interested in determining whether having an Autistic Spectrum Disorder is related to a medical history of infantile spasms (a seizure disorder in infancy), the gene causing Tuberous Sclerosis, features of tubers (pockets of atypical brain cells) seen on MRI, like location and number, and type of seizure abnormalities on the patient’s EEG. The results of this study may help us determine one of the causes of Autism.

This study is supported by faces.

The Effect of Melatonin in Patients with Intractable Epilepsy

Investigators: Josiane LaJoie, M.D., Daniel Miles, M.D.

Clinical studies have shown melatonin to have anticonvulsant properties and can improve sleep and behavior. This study aims to evaluate the efficacy of adjunctive use of melatonin in epilepsy patients, to establish effective dosing of melatonin, and to evaluate the cognitive and behavioral effects of its use.

This study is supported by faces.

Proliferation Abnormalities in Human Tuberous Sclerosis

Investigator: Ravi Tikoo, M.D.

This research looks at patients undergoing surgery for the treatment of epilepsy and brain tumors. Scientists have learned that many medical problems occur because specific molecules, which are building blocks of the cells that make up the human body, are present in the human body at abnormally high or low levels. The brain tissue removed during surgery will be investigated and levels of specific molecules will be studied. This research is a first step in understanding epilepsy and brain tumors and strives to facilitate the development of new treatments.

This study is supported by faces.
Bioimaging of Epilepsy: NMR Spectroscopy Studies

Investigators: Ruben Kuzniecky, M.D., Julie Pan, M.D., Ph.D., Hoby Hetherington, Ph.D.

The purpose of this study is to better understand the biochemical changes that occur in epilepsy and to evaluate the ability of NMR spectroscopy in determining the location of the seizure focus. NMR spectroscopy uses a strong magnet and radio waves to generate signals that indicate the amount of a variety of important chemical constituents in the body. Alterations in these chemicals provide an indication of metabolic abnormalities that have been linked with the presence of epileptogenic (seizure producing) tissue.

This study is supported by faces and the CURE Foundation.

Neurophysiology of Human Epilepsy and Cognition

Investigators: Orrin Devinsky, M.D., Eric Halgren, Ph.D., Ruben Kuzniecky, M.D., Werner Doyle, M.D.

The purpose of this study is to better understand epilepsy and normal brain function in humans. We are interested in developing better, non-surgical, methods for locating brain activity. The goal of this research is to combine MRI, Magnetoencephalography (M/EEG) and intracranial encephalography (I-EEG) in order to more precisely localize epileptic and normal brain activity.

This study is supported by NIH.

Metabolism of Human Epilepsy

Investigators: Ruben Kuzniecky, M.D., Orrin Devinsky, M.D., Werner Doyle, M.D.

The purpose of this study is to increase our understanding of the metabolic changes that may occur within the ictal/perictal and interictal state. The goal is to study temperature regulation, pH, oxygen utilization in the epileptic focus during different states. This information may permit the development of new treatment strategies for epilepsy.

This study is supported by faces.

The Epilepsy Phenome/Genome Project continued from page 1

throughout the U.S. into a collaboration based on the recognition that no single center can ever hope to study a sufficient number of patients to make the next major breakthrough in epilepsy genetics. Although still in the planning phase, EPGP will create a comprehensive, sophisticated database that contains detailed information on the clinical characteristics of a patient’s seizure disorder (phenome) and information derived from the analysis of a patient’s DNA (genome). By enrolling a large number of patients into EPGP (i.e. an expected 5,000 patients over 5 years), and using state-of-the-art techniques for managing and analyzing huge volumes of data, EPGP will provide the infrastructure for making a number of discoveries that, until now, have been impossible to approach. Some of these will be the identification of gene mutations that cause the more common forms of epilepsy. Others will be identification of genes that cause specific abnormalities in brain development leading to epilepsy. Such discoveries hold the promise of the development of more specific and effective therapies that can be tailored to an individual’s seizure disorder. EPGP will also help identify the gene mutations that explain drug-responsiveness. In the future, such information will enable doctors to predict the likelihood of a medicine working for a given patient.

Recognizing the pivotal importance of this type of large-scale, collaborative research in epilepsy, faces has awarded a grant of $150,000 to help the EPGP team in the planning phase of the project. These funds will be used to design the bioinformatics infrastructure for the study, create and test data collection systems, and support planning conferences by the group so they can prepare a multi-million dollar grant proposal for the National Institutes of Health.
Help Researchers Find New Treatments for Epilepsy: Research Study Participants Needed

“Therapeutic Efficacy of EEG Operant Conditioning in Medically Refractory Epilepsy”

The NYU Comprehensive Epilepsy Center is conducting a study to investigate the therapeutic efficacy of electroencephalograph (EEG) operant conditioning in medically refractory epilepsy. EEG operant conditioning is a non-invasive method of positively reinforcing normal EEG rhythms in the brain. If your seizures have not been controlled by either anti-epileptic drugs (AED’s) or surgical intervention you may be a good candidate for this study. The study entails medical record reviews with a board-certified neurologist, EEG therapy sessions, and follow-up reviews. If you would like to learn more about this study and whether you are a suitable candidate please contact the research coordinator, Anjanette Naga, at 212.263.8325 or via email, anjanette.naga@med.nyu.edu.

Do You Have a Child with Uncontrolled Seizures?

Children with epilepsy between 1 month and 17 years old are needed to participate in a clinical research study involving an investigational use of a marketed drug for epilepsy. All office visits, laboratory tests, study drug and monitoring for seizures related to this study will be provided at no cost to patients. For more information about this study, please contact Maria Hopkins, RN, Clinical Trials Coordinator, NYU Comprehensive Epilepsy Center, at 212.263.8359.

Infantile Spasms Study

The NYU Comprehensive Epilepsy Center seeks to enroll individuals who have been diagnosed with and treated for Infantile Spasms as voluntary participants in a retrospective study on the therapeutic outcome of treating infantile spasms. This study will address the success of treatment based upon choice of therapy as well as comparing the success of treatment of infantile spasms in individuals with Tuberous Sclerosis and those with infantile spasms due to other causes. This study will involve a review of the volunteer’s medical records. Individuals need not be seen or followed at NYU to participate in this study. Ongoing care will be provided by the individual’s own physician.

For more information, or to enroll, please contact study coordinator Nina Ferraris at 212.263.8325 or contact Nina Ferraris and Daniel Miles, M.D. via email at epilepsyresearch@med.nyu.edu.

Participants Needed for Multi-Center Retrospective Study

The NYU Comprehensive Epilepsy Center seeks to enroll individuals with tuberous sclerosis complex (TSC) as voluntary participants in a research study that involves a review of medical records and a phone interview.

Individuals with TSC that have undergone epilepsy surgery are being sought for a research project. This study will review the outcome of patients with regard to seizure control and development. This retrospective study involves the review of the volunteer’s medical records, including physician’s notes, EEG reports, MRI studies, and surgical summaries. No physical examination of the participant is required, but a telephone interview regarding neuropsychological and quality of life issues will take place.

To enroll or to ask any questions regarding the study, please contact study coordinator Nina Ferraris or Daniel Miles, M.D. at epilepsyresearch@med.nyu.edu, or call 212.263.8325 and ask for Nina Ferraris.
delivery is that many potential drugs not used due to systemic toxicity could be used for the treatment of epilepsy. NYU researchers are beginning the planning phase for animal studies devoted at investigating new drug delivery devices and new drugs for epilepsy. This is an exciting development for epilepsy and promises to open a new area of treatment.

One of the most exciting projects now under way is development of a drug delivery system to the central nervous system. This device would have an implanted electrode that could either predict or recognize the occurrence of seizures and then release a drug to this specific area from which seizures arose on a demand basis. The drug would only be released shortly before or during a seizure to either prevent the seizure or stop it from occurring. We are still in the preliminary phase of this project although considerable work has been done in this area, and we are hoping to bring this project to NYU in the near future. If successful, this project could have a great impact on epilepsy therapy and potentially for treatment of other brain disorders.

Finally, faces is devoted to support epilepsy research through collaboration with many other funding agencies. Faces is also one of the principal members in the partnership for pediatric epilepsy research. Together with the Epilepsy Foundation, the American Epilepsy Society, PACE, and several families, the partnership has awarded numerous grants over the past several years to scientists throughout the United States who are dedicated to studying the mechanisms underlying epilepsy and, most importantly, trying to identify avenues for therapeutic advances.

Orrin Devinsky, M.D. is the co-director of the scientific advisory board for the Epilepsy Cure Project. Support from faces has helped to make his time available to spend this leadership role for the Epilepsy Cure Project. With an annual budget exceeding $1.5 million the epilepsy cure project has taken an exciting and active role in identifying and funding translational research opportunities. In doing so, the Epilepsy Cure Project has catalyzed the movement of ideas and research at a basic science level in universities towards real therapeutic advances for people with epilepsy, hopefully in a shorter time frame than might be expected through traditional mechanisms. The Epilepsy Cure Project also has commercialization grants allowing companies to focus their research on epilepsy-related treatments. The Epilepsy Cure Project also sponsors epilepsy.com, an in depth site for information about epilepsy for patients and their families as well as for professionals involved in the care of people with epilepsy. Finally, the Epilepsy Cure Project will also make direct investments into companies with exciting programs for the development of epilepsy therapies.

Magnetic Resonance Spectroscopy in Epilepsy

Using a super powerful magnet (3 times the power of a regular MRI), researchers at the NYU Epilepsy Center are collaborating with physicians at the Albert Einstein School of Medicine to study patients with epilepsy

Magnetic Resonance Spectroscopy at 4 Tesla (Gruss NMR Center, Albert Einstein) in one of our patients with Temporal lobe epilepsy. The purple color coded image shows highly significant increases in the ratio of Creatine/N-acetyl-aspartate from the left and right hippocampal formation. This study is part of Dr. Kuzniecky’s research at NYU.

Questions about research at the NYU Comprehensive Epilepsy Center?

Please email epilepsyresearch@med.nyu.edu for more information regarding any of the research studies mentioned in this special edition of the faces newsletter. The appropriate investigators or research personnel will respond to your email within five business days.
For more information about research at the NYU Comprehensive Epilepsy Center and other epilepsy programs, please go to:

www.nyuepilepsy.org and www.nyufaces.org

Nurses are an integral part of the NYU research team.