we introduce the new Division of Neuroepidemiology, which brings researchers with over 20 years of experience in the study of the causation, treatment, and outcomes of brain tumors to provide epidemiological expertise to the Department of Neurological Surgery at the University of California, San Francisco.

In May of 2004 the Department of Neurological Surgery at the University of California, San Francisco (UCSF) created the new Division of Neuroepidemiology, to enhance the existing collaborations between the Department of Neurological Surgery and the Department of Epidemiology and Biostatistics and to promote future collaborative projects. Epidemiology—the study of the incidence, distribution, causes, and control of disease in a population—is a valuable counterpart to the clinical and basic science research being performed in the Department of Neurological Surgery. Despite decades of research into the potential causes of brain tumors, there are few known factors predictive of developing this terrible disease. Prior to the advent of new molecular techniques for characterizing tumors, researchers were unable to classify tumors into homogenous groups according to the genetic and epigenetic modifications in the cells that are responsible for tumor formation. Neuroepidemiological studies are currently underway throughout the world to elucidate the many ways in which cells can become malignant. Combining this information with knowledge of environmental exposures, family and personal medical histories, and other factors may help to identify causes of brain tumors. Epidemiological research can also provide insight in the area of brain-tumor treatment. As brain tumors are relatively rare, and tumors that seem histologically identical can exhibit substantial variation in terms of progression, recurrence, and response to therapy, it is often difficult to predict the effectiveness of a specific treatment without large, well-characterized population samples. Specialists in neuroepidemiology provide the expertise needed to examine patterns of disease in the overall population.

Continued on page 2
Brain tumors are increasing in incidence in the United States, and have a huge impact on patients and their families in terms of disability and mortality. An important part of lessening that impact lies in enhancing our understanding of the factors governing the onset and individual response to the disease. Researchers studying all aspects of brain tumors—from genetics and molecular biology to treatment development and clinical trials—benefit from epidemiological studies of the causes and outcomes of brain tumors. The causes of brain tumors remain a mystery. Factors as varied as family history, diet, and environment have been explored, but no definitive causes have been identified. In addition, patients with similar tumors receiving similar treatments can have widely varied outcomes, and the reasons behind such variations are only beginning to be understood. Although the number of patients with brain tumors that might be studied at any one institution is limited, epidemiological studies can pool data from thousands of patients across the nation or the world, providing a view of the “big picture” that would otherwise remain hidden from individual researchers.

There has been a recent push to establish large, nation-wide registries to gather data on patients with brain tumors, in order to provide centralized, extensive, and easily accessible data pools that researchers can use to look for variations in risk factors and in treatment-related outcomes. The Central Brain Tumor Registry of the United States (CBTRUS) is a non-governmental, non-profit corporation that collects and disseminates descriptive statistical data on patients with primary brain tumors. The CBTRUS database currently contains the largest amount of population-based data on the incidence of all types of primary brain and central nervous system tumors in the United States. The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) is a cancer registry that collects and publishes cancer incidence and survival data from 14 population-based cancer registries and 3 supplemental registries, which focus on specific regions within the United States. The Repository of Molecular Brain Neoplasia Data (REMBRANDT) project, a new partnership between the NCI and the National Institute of Neurological Disorders and Stroke, will collect information on both tumor genetics and clinical course for patients throughout the United States, and will allow for large-scale correlative analyses of genetic mutations and outcome.

Here at the University of California, San Francisco, we are pleased to announce the creation of the new Division of Neuroepidemiology within the Department of Neurological Surgery. In addition to participating in ongoing large-scale epidemiological studies and analyses of registry data, (see pages 1 and 3), members of the division will work closely with clinicians and basic scientists in all of the Neurological Surgery Research Centers, to lend their epidemiological expertise to the study of the varied diseases and disorders seen by the Department, from tumors to traumatic brain injury.

Mitchel S. Berger MD
Kathleen M. Plant Distinguished Professor & Chairman

DIVISION OF NEUROEPIDEMIOLOGY
Continued from page 1

Margaret Wrench PhD, one of the two Co-Directors of the new Division, has studied the genetic and molecular epidemiology of glioma since 1991 with her ongoing National Cancer Institute-funded case-control study, Genetic and Molecular Epidemiology of Adult Glioma. John Wiencke PhD, the other Co-Director of the new Division, heads the Molecular Epidemiology Laboratory and has been studying the genetic and molecular epidemiology of various cancers for over 20 years at UCSF. Wrench and Wiencke have complementary skills in population genetics, epidemiology, laboratory genetics, and pathology (see p. 3), and have long worked together on their research projects. When the Department of Neurological Surgery applied for a Brain Tumor Specialized Program of Research Excellence (SPORE) grant, Mitchel Berger MD, Chairman of the Department, asked Wrench to lead one of the four translational research projects. UCSF’s SPORE application was funded, and Wrench and Wiencke began work on the San Francisco Bay Area Adult Glioma Survival Study, in collaboration with Michael Prados MD and other members of the Neuro-Oncology service in the Department of Neurological Surgery. This project facilitated extensive communication between the epidemiologists and the neuro-oncologists, neurosurgeons, and basic scientists in the Department of Neurological Surgery.

Members of the Department saw a very positive contribution from the increased collaboration with the epidemiologists, and thought that research into other diseases and disorders of the central nervous system could benefit from the addition of population-based studies. To expand the epidemiology expertise within the Department, the new Division of Neuroepidemiology was created. Wrench and Wiencke bring their extensive staff including epidemiologists, interviewers, phlebotomists, and laboratory specialists to work in the new Division. With the faculty of the Department, they have begun planning future studies of the epidemiology of traumatic brain injury, back pain, spinal injury, and other conditions commonly treated by the Department of Neurological Surgery. Wrench and Wiencke are also participating in the development of three new multi-center epidemiological studies of brain tumors: a study of meningioma involving 5 research centers in the United States; a Program Project Grant focusing on the epidemiology of brain tumors in children, involving 5 research centers in California; and the Gliogene study, with 11 participating centers in the United States and Europe, which will study families with multiple cases of glioma and conduct genetic linkage studies to identify novel susceptibility genes.

The Department of Neurological Surgery at UCSF is extremely pleased to be making a contribution to the field of neuroepidemiology, and believes that these new studies will provide greater understanding of the causes and outcomes of all-too-often crippling and lethal neurological diseases and disorders.
Population-Based Studies of Brain Tumors

Margaret Wrensch PhD has been investigating the genetic and molecular epidemiology of adult brain cancer for over 20 years. She is currently the Principal Investigator of a population-based case-control study, the San Francisco Bay Area Adult Glioma Study, which has been ongoing since 1991. Thus far, published findings from this study include statistically significant or marginally significant associations of adult-onset glioma with several factors: a family history of brain cancer that is not likely to be due to a single major gene (shown by segregation analyses); lower prevalence of antibodies to the varicella zoster virus; lower history of allergies and lower levels of IgE antibodies; decreased consumption of non-steroidal anti-inflammatory drugs; increased consumption of cured meats in conjunction with decreased consumption of vitamin-C rich fruits and vegetables; decreased consumption of dietary calcium (among female patients); and increased smoking of unfiltered cigarettes. The study has also shown that residential exposure to electromagnetic fields, as gauged by wire codes and spot measurements, up to seven years prior to diagnosis did not differ between adult patients with glioma and control patients. Significant differences between patients and controls with respect to prior head injury or exposure to diagnostic x-rays were not found. Findings from the first genetic analyses of tumor TP53 status have shown that tumors from Caucasians and non-Caucasians significantly differ in frequency of TP53 alterations, an especially interesting finding in light of the fact that Caucasians and non-Caucasians in the San Francisco Bay Area have different incidences of glioma.

In addition to serving as Co-Director of the new Division of Neuroepidemiology in the Department of Neurological Surgery, Wrensch is also the Principal Investigator of one of the four Brain Specialized Program of Research Excellence (SPORE) grant projects ongoing at the University of California, San Francisco—the San Francisco Bay Area Adult Glioma Survival Study. This study is examining the survival of patients with glioma in relationship to several tumor markers that define genetic subtypes of gliomas and are thought to be potentially important prognostic factors.

In ongoing research, Wrensch and colleagues will continue categorization of the molecular pathology of patients’ tumors according to the presence or absence of TP53 modifications and other genetic alterations (such as EGFR and MDM2), in an effort to define subgroups of tumors that are more homogeneous in terms of genetics and outcome. She and her co-investigators will also expand studies of the potential role of immune response mechanisms in carcinogenesis and help researchers discover new ways to improve cancer prevention and therapy. A controversial issue in epidemiology is whether or not the tumors arising in different racial groups have distinct molecular features. Wiencke has proposed and supervised extensive laboratory work on the TP53 gene in adult gliomas—this work was the first to show that race affects the type of TP53 mutations in brain tumors. Over the past 10 years, in addition to his work on brain-tumor genetics, Wiencke has also built a research program that examines the roles of genetics, race, and tobacco use in lung-cancer development.

Molecular Epidemiology of Cancer

John Wiencke PhD received his doctorate in Pathology and Laboratory Medicine from the University of Minnesota, and has been performing research in epidemiology and biostatistics at the University of California, San Francisco (UCSF) since 1986. His primary research goal is to integrate genetics, molecular biology, and population-based studies of cancer. He has been instrumental in developing three large molecular epidemiology studies in Northern California: the San Francisco Bay Area Adult Glioma Study, the San Francisco Bay Area Minority Lung Cancer Study, and the Northern California Childhood Leukemia Study. These studies involve collaborations with the Northern California Cancer Registry, the Kaiser Permanente Division of Research, University of California epidemiologists, and colleagues at the University of California, Berkeley School of Public Health and the State Health Department. In addition to his teaching and research activities at UCSF, Wiencke is a visiting lecturer at the Harvard School of Public Health and has collaborated for many years with researchers there in developing programs to study the molecular epidemiology of tobacco-related cancers and genetic susceptibility to cancer.

The main focus of Wiencke’s research has been racial differences in cancer incidence, which may provide clues to mechanisms of carcinogenesis and help researchers discover new ways to improve cancer prevention and therapy. A controversial issue in epidemiology is whether or not the tumors arising in different racial groups have distinct molecular features. Wiencke has proposed and supervised extensive laboratory work on the TP53 gene in adult gliomas—this work was the first to show that race affects the type of TP53 mutations in brain tumors. Over the past 10 years, in addition to his work on brain-tumor genetics, Wiencke has also built a research program that examines the roles of genetics, race, and tobacco use in lung-cancer development.

As Co-Director of the new Division of Neuroepidemiology in the Department of Neurological Surgery, Wiencke’s future research efforts will focus on the causes of neurological malignancies and on other areas of neurological research related to neurological surgery. He is currently involved in two long-term initiatives to expand studies of the causes of brain tumors: a California-wide Childhood Brain Tumor Study that will include tumor biology, germline genetics, environmental factors, and nutritional epidemiology; and a nation-wide consortium on the molecular epidemiology of meningioma.
The University of California, San Francisco began its Radiosurgery Program in the late 1980s, and installed its first Gamma Knife® (GK) in 1991. The GK is a radiation–therapy device that delivers a single, very finely focused, high dose of radiation precisely to the target abnormality, while causing little or no radiation damage to the surrounding normal tissue. Abnormalities measuring 1.5 inches in maximum diameter or smaller—even abnormalities no larger than a small pebble—are often very responsive to treatment with GK radiosurgery. GK radiosurgery entails very little discomfort, and patients need only a short time to recuperate.

Treatment using the GK is beneficial for many conditions in pediatric patients, particularly brain tumors—such as ependymoma, medulloblastoma, germinoma, and astrocytoma—and vascular malformations. Tumors are usually first treated by surgery. If any residual tumor is found after the operation, the child’s neuro-oncologist may recommend radiosurgery, chemotherapy, or a combination of the two. Radiosurgery offers an advantage over conventional external-beam radiation in that the non-irradiated portion of the brain receives only a very small dose of radiation, reducing the late effects of radiation on the brain. This is particularly important for children, whose rapidly developing brains are vulnerable to radiation damage. For vascular malformations, if part of the lesion remains after surgery, or if the lesion is very deep in the brain, then radio-
surgery can, in most patients, cause obliteration of the lesion. A newer application of radiosurgery is the staged treatment (2-3 separate sessions) of very large vascular malformations that cannot be resected due to high surgical risk. The safety of this technique is improved by the use of functional brain mapping that can help define the target area to avoid functional areas of the brain.

While adult patients most often require only local anesthesia for GK treatment, many aspects of the procedure can be overly uncomfortable or frightening to a child, such as the metal frame that is attached to the patient’s head to allow for precise positioning within the GK unit, or confinement in a small enclosed space for neuroimaging and the radiosurgery treatment itself. Depending on the age of the child, general anesthesia may be used for some or all steps of the treatment. Pediatric anesthesiologists provide the required expertise and are in attendance for every stage of the procedure. Despite the use of general anesthesia, GK radiosurgery is usually an outpatient procedure.

The use and safety of GK radiosurgery for pediatric patients will increase in the future as new research expands the number of conditions that can be treated using the GK, such as epilepsy, and as new imaging tools are developed that can define functionally important regions of the brain.

POPULATION-BASED STUDIES OF BRAIN TUMORS
in the prevention of tumor formation through studies of herpes virus serology and allergies in patients with brain tumors and in controls. These continuing case-control studies will involve collaborations with investigators at the Kaiser Permanente Division of Research in Oakland, California, to obtain tumor specimens and questionnaire information from patients with glioma at the time of diagnosis. Sampling a large number of patients at the time of diagnosis will be especially helpful for distinguishing which genetic polymorphisms are related to causation and which are related to progression and survival.

In addition to her work on brain tumors, Wrench has performed extensive studies of the epidemiology of breast cancer and is co-investigator of a large ongoing population-based study of lung cancer among African-Americans and Latinos in the Bay Area.

DR. WRENCH’S SELECTED PUBLICATIONS


DR. WIENCKE’S SELECTED PUBLICATIONS


The Neuro-Oncology nurses in the Department of Neurological Surgery—Anne Fedoroff RN, Margareta Page RN, MS, and Jane Rabbitt RN—are on the front lines of care for patients with neurological malignancies. The nurses are the first voice on the end of the phone line for patients and physicians calling for information about treatment options and clinical trials. They are also the first health-care professionals in the clinic to interact with new patients, both adults and children, determining what treatment has already been given and what new treatments may be appropriate. They are experts in all aspects of symptom management, in distinguishing tumor-related toxicity from drug-related toxicity, and in the day-to-day evaluation of patients enrolled in clinical trials. Often, they will help a patient through every stage of his or her illness, from diagnosis to end-of-life care.

All three nurses have extensive involvement in the development of new clinical-trial protocols, working closely with the physicians and data managers to produce all the necessary documentation and to determine what measures are necessary for safety monitoring. They are active members of professional organizations such as the Oncology Nursing Society and the American Association of Neurological Nurses, and pride themselves on being aware of national developments in the field. In addition to their commitment to professional nursing groups, they work with the National Brain Tumor Foundation and other non-profit organizations that specialize in patients’ education and community awareness.

Anne Fedoroff RN studied Sociology at the University of California, Santa Cruz. After deciding to pursue a career in nursing, she enrolled at the University of San Francisco, where she received her BSN in 1986. She began working at the University of California, San Francisco (UCSF) in 1986, in the neurology/neurological surgery unit at Long Hospital, where she remained for 11 years. During that time she helped to open a new unit in the hospital, the Neurological Close Observation Unit, where she worked for four years. In 1999 she received the Helen Ripple award for excellence in neuroscience nursing. Fedoroff joined the Neuro-Oncology service in February of 2002. Of special interest to her are the clinical trials and the collaborative effort between members of the Neuro-Oncology Service and the Department of Neurological Surgery that is required for the successful treatment of patients with brain tumors.

Margareta Page RN, MS received her BSN from St. Louis University in 1984. She came to San Francisco and UCSF after a year of working at Washington University in St. Louis as a neurology nurse. She worked as a staff nurse at Long Hospital at UCSF for six years before joining the Neuro-Oncology staff in 1991. While working for the Neuro-Oncology service she obtained a Masters Degree in Neuroscience Nursing at UCSF. Working in Neuro-Oncology allows Page to combine her two favorite specialties: neurological and oncology nursing. Her interests in the field include symptom management and the identification of symptom clusters and their potential impact on patient outcome. Recently, she has been involved with the Advanced Practice Nursing Group of the Oncology Nursing Society, which is working on the Nursing Sensitive Outcomes Project, a project that identifies patient outcomes that are improved as a result of specific evidence-based nursing interventions. Other areas of interest for her include the health and well being of caregivers, and learning more about complementary and alternative therapies being used by cancer patients.

Jane Rabbitt RN received her BSN from Oregon Health Sciences University in Portland, Oregon in 1984. After graduation she moved to San Francisco and began work at UCSF as a clinical nurse in the neurology/neurological surgery unit in the UCSF hospital. After four years, in 1988, she joined the Department of Neurological Surgery as a clinical research nurse in the Neuro-Oncology service. For the last 17 years she has been involved in the design and conduct of clinical trials for patients with brain tumors, and has worked with patients and their families through all stages of their disease. She has also served as a facilitator for a brain-tumor support group in Sonoma County for the last 14 years. She is especially interested in conducting clinical trials and in her relationships with patients and their families.
Christopher P. Ames MD, Assistant Professor of Neurological Surgery, has been awarded a 2005 International Society for the Study of the Lumbar Spine (ISSLS) Prize—formerly known as the Volvo Award—for his paper, “Effect of recombinant human bone morphogenetic protein-2 in an experimental model of spinal fusion in a radiated area.” The research project used an animal model of posterolateral intertransverse process spine fusion after radiation therapy to show that the use of recombinant human bone morphogenetic protein-2, an osteoinductive protein, produced a significantly greater rate of fusion in previously irradiated tissue than the use of an autologous iliac crest bone graft (ICBG), without the morbidity of ICBG harvesting and without the risk of inadvertently using autograft material contaminated by micrometastases. Ames will present his prize-winning paper on May 13 at the 2005 meeting of the ISSLS. More information on the ISSLS Prize can be found at http://www.issls.org/.

Anita Lal PhD, head of the Meningioma Research Laboratory, has received a 2004 Distinguished Scientist Award from the Sontag Foundation for her research project, Notch Signaling in Meningiomas. Lal’s project will focus on the Notch signaling pathway, which is normally only active during embryonic development. Unregulated Notch signaling has been indicated in meningioma formation. Lal will evaluate how Notch pathway components regulate meningioma cell growth in culture and as tumors in mice. She will also test the therapeutic ability of drugs that inhibit Notch signaling, and identify new genes that are downstream targets of Notch signaling in meningiomas. More information on the Sontag Foundation can be found at http://www.sontag-foundation.com/.

Devin K. Binder MD, PhD, chief resident in the Department of Neurological Surgery, has been awarded the 2005 William P Van Wagenen Fellowship from the American Association of Neurological Surgeons. The Fellowship allows the recipient to pursue 12 months of post-resident study in a foreign country. Binder plans to undergo advanced training with Johannes Schramm MD at the University of Bonn, Germany, where a world-class epilepsy research and treatment center has been established. Binder will work directly with Schramm to learn surgical techniques and approaches to epilepsy treatment. He plans to begin his training in July of 2005. More information on the Van Wagenen Fellowship can be found at http://www.aans.org/research/fellowship/aans.asp.

Grant Gauger MD, Clinical Professor of Neurological Surgery, received first prize in the category of Trauma and Critical Care at the 2004 meeting of the American Association of Neurological Surgeons for his paper, Volumetric Proton MR Spectroscopy of Mild Traumatic Brain Injury.

Michael McDermott MD, Professor of Neurological Surgery, has been elected to the position of Secretary-Treasurer of the American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Section on Tumors.

Philip Starr MD, PhD, Associate Professor of Neurological Surgery, has been appointed Secretary-Treasurer of the American Society for Stereotactic and Functional Neurosurgery.

The Department of Neurological Surgery welcomes three new residents into the residency program for 2005: Hansoo Keyoung MD, PhD, Robert Richardson MD, PhD, and Michael Sughrue MD. They will spend the first year of their residency as interns in the Department of Surgery.

The clinical practice of the Department of Neurological Surgery has achieved a 97.3% patient satisfaction rate as measured by Press Ganey Associates, Inc.; this rating is an overall score received in the “Likelihood to Recommend the Practice” category in the patient satisfaction survey.

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Alfredo Quiñones-Hinojosa MD was born in Mexicali, Mexico, and grew up balancing his education and the work required to help support his family. After receiving a BA in Social Sciences and Humanities from the Escuela Normal Urbana Federal Fraternizada, he came to the United States at the age of 19, with only the most basic knowledge of English. While laboring as a farm worker, he learned English, put himself through community college, and eventually transferred to the University of California, Berkeley, where he received a BA in Psychology with Highest Honors. His long-term interest in neuroscience led to his senior thesis at Berkeley, Long-term Pontentiation at the Lateral Perforant Path-Nucleus Accumbens Synapse in the Rat In Vivo.

Quiñones-Hinojosa went on to Harvard Medical School, and continued his neuroscience research with his thesis, Ischemia Studies in the Rabbit Retina In Vitro: Neuprotective by Metabolic Inhibition with Hypothermia, a Pharmacological Cocktail, and Magnesium Plus Mexiletine. He was graduated Cum Laude in 1999. At Harvard, he was involved with the Office of Multicultural Affairs, and helped to coordinate the Hinton-Wright Society and the Summer Biomedical Research Program. These organizations focused on promoting the awareness of diseases that disproportionately affect minorities. For his leadership at Harvard, Quiñones-Hinojosa received the Harvard Medical School Graduation Multiculturalism Award and the Ralph W. Ellison Graduation Award. As a resident in the Department of Neurological Surgery at the University of California, San Francisco, he has continued his commitment to promoting diversity in the medical community, mentoring numerous high school, college, and medical students on a one-on-one basis to help them plan for medical school and residencies.

Last year, Quiñones-Hinojosa obtained a National Research Service Award from the National Institutes of Health under the mentorship of Arturo Alvarez-Buylla PhD. For his research project, he examined the cellular composition of the walls of the human lateral ventricles using immunohistochemistry and electron microscopy in order to elucidate the organization of the adult human subventricular zone—a necessary first step in understanding the cellular proliferation, precursor migration, and neurogenic niche of the largest known adult human germinal region in the adult human brain. Quiñones-Hinojosa plans to pursue a career in academic neurosurgery with an emphasis on the treatment of brain tumors. He is married, and he and his wife Anna have two children, Gabriella (6 years old) and David (3 years old).

### SELECTED PUBLICATIONS


### RESIDENTS’ PUBLICATIONS


— Selected Recent Publications from the Department of Neurological Surgery —


