we explore the many options for the treatment of intractable pain offered by the UCSF Department of Neurological Surgery, including spinal and cortical stimulation and implantable drug pumps, for treating diverse conditions such as cancer, trigeminal neuralgia, spinal pain, diabetic neuropathy, and intractable cardiac pain.

Chronic pain is an inescapable accompaniment to many illnesses and post-traumatic conditions. Most patients can be helped with drugs, physical therapy, and other non-invasive treatments, but a small percentage of patients with pain that is refractory to even the best medical management require more aggressive therapy. The Department of Neurological Surgery at the University of California San Francisco (UCSF) offers many treatment options for patients with intractable pain.

Cancer is one of the most common causes of intractable pain affecting patients referred to the Department. Systemic opiates are often given to treat chronic cancer pain, such as pain caused by bone metastases, stomach or pancreatic cancer, lymphoma, or prostate cancer metastatic to the pelvis; but this method of treatment has several drawbacks, among them that patients develop increasing resistance to the drug and are relegated to a poor quality of life.

Interventions for intractable central nervous system pain at UCSF are performed by Nicholas Barbaro MD and Luc Jasmin MD, PhD. A new development in the treatment of intractable cancer pain is the use of intrathecal opiate pumps. A small pump is surgically implanted under the skin and a small catheter extends from the pump to deliver the drug directly to the spinal cord. By bypassing the dura and delivering the opiates directly to receptors in the spinal cord, intraspinal administration uses doses up to one hundred times smaller than doses required in oral administration. This method of delivery provides pain relief with far fewer side effects, allowing Continued on page 2

This lateral x-ray film shows two electrodes placed over the motor cortex to provide stimulation to relieve the patient's central pain syndrome. This was the first time the procedure was performed in this manner—the electrodes sit directly on the cerebral cortex to provide better stimulation, and two electrodes were used to stimulate a larger area of the cortex. After 4 months of stimulation, the pain relief was 100%.
Pain refractory to traditional therapies is undertreated in the United States for many reasons. Some are related to insurance coverage, or to social and legal issues. Others may be related to pharmaceutical and medical issues or factors related to the health care system. But often the reasons have to do with the complex and elusive nature of pain itself. As described in this newsletter, faculty in the Department of Neurological Surgery at UCSF are focusing their clinical and research efforts on demystifying pain and bringing effective pain relief to patients who need it.

Nicholas Barbaro MD is a pain specialist distinguished in the surgical management of trigeminal neuralgia. The trigeminal nerve, the fifth cranial nerve, is the main sensory nerve for the face and the motor nerve governing the jaw. Although trigeminal neuralgia has an annual incidence of only 4 in every 100,000 people, those affected have excruciating pain. The condition may have diverse causes, but vascular compression of the trigeminal nerve often causes the pain. Patients with this form of trigeminal neuralgia who are not responsive to medical management now have two forms of surgical therapy available to them. Microvascular decompression is a highly effective but highly invasive procedure. More recently, Gamma Knife® radiosurgery has afforded a high degree of efficacy, and it is the least invasive surgical option available. To establish the relative merits of these two options, Barbaro is engaged in research to compare the techniques and their results. Luc Jasmin MD, PhD is recognized for his clinical expertise in the use of electrical stimulation to provide relief of spinal pain; the use of implanted cortical electrodes for treating intractable pain syndromes; and the use of intrathecal drug delivery systems to deliver drugs directly to the spinal cord, rather than systemically. In the laboratory, Jasmin is pursuing basic research on the neuroanatomy and neuropharmacology of pain and inflammation. His laboratory findings are being translated into clinical treatment realities. Patients with pain related to osteoporosis and vertebral compression fractures now have available to them two effective and minimally invasive procedures, vertebroplasty and kyphoplasty, which are performed by Philip Weinstein MD and Christopher Ames MD in our Department.

The key to providing every patient with effective pain relief has yet to be discovered, but with thorough evaluations, careful selection, and detailed treatment planning, our faculty work to design a therapeutic course tailored to each specific, individual case, doing everything possible, to see that no patient should have to live with pain.

Several methods of central nervous system (CNS) stimulation can offer relief to patients with many types of intractable pain. One of these procedures is spinal-cord stimulation for leg pain. For spinal-cord stimulation, two small electrodes attached to an implantable power source are placed through the skin and onto the lower spine. The power source is kept externally for testing for a week, and is then implanted under the patient’s skin once the efficacy of the treatment has been confirmed. Spinal-cord stimulation may work by a mechanism called the gate theory, by which the stimulation of innocuous (not pain-causing) nerve fibers blocks the transmission of pain signals. A similar procedure that uses three electrodes placed over the spinal cord may soon be available for treating forms of lower back pain that are not accompanied by leg pain. Spinal-cord stimulation has also been helpful for treating such diverse afflictions as diabetic neuropathy and intractable cardiac pain. Neurosurgeons can place spinal stimulators during an open surgical procedure, which permits the placement of larger, more efficient electrodes than those placed subcutaneously.

Cerebral-cortex stimulation, which is accomplished by placing electrodes directly on the motor cortex, can be of great benefit for patients suffering from central pain. Central pain is caused by a dysfunction in the CNS, often a small stroke to the thalamus that leaves pain over half of the body. Cortical stimulation can also be used for pain related to causes including spinal or cortical injury, trigeminal neuralgia, anesthesia dolorosa, or phantom limb pain, among others.

Patients referred to the Neurosurgery clinic at UCSF may have many other types of pain. Osteoporosis can lead to vertebral compression fractures, especially in the elderly. Two newer, minimally invasive procedures used to treat these fractures are vertebroplasty and kyphoplasty, which are performed by Philip Weinstein MD and Christopher Ames MD in the Department of Neurological Surgery. In vertebroplasty, under radiographic guidance, a cement-like compound is injected into the collapsed vertebra, stabilizing the bone and reducing pain. Kyphoplasty is similar to vertebroplasty except that, for kyphoplasty, balloons are placed percutaneously into the fractured vertebra and are inflated to create a cavity and reduce deformity before the structural compound is injected. These procedures restore stability to the damaged spine and substantially reduce pain.

The Neurosurgery service also treats patients who have trigeminal neuralgia by using the Gamma Knife® in a new non-invasive technique, as well as with the more traditional invasive procedures (see page 3, column 1).

The efficacy of surgical treatment for a variety of pain conditions is now well established for patients who are carefully selected for a treatment specifically proven to help their particular, individual condition. With individualization of treatment and consideration of the unique needs and expectations of each patient, these new forms of treatment have substantially improved the results we are able to provide for patients in pain.
SURGICAL TREATMENT OF TRIGEMINAL NEURALGIA

As the Co-Director of the Department of Neurological Surgery's Functional Neurosurgery program, Nicholas Barbaro MD, Professor and Vice-Chair of Neurological Surgery, has a special interest in surgical pain management, especially the treatment of trigeminal neuralgia. Trigeminal neuralgia, also known as tic douloureux, is one of the most painful conditions a person can suffer. Surgical treatment for trigeminal neuralgia can help many patients whose pain does not respond to traditional forms of medical management.

Barbaro is especially interested in the use of Gamma Knife® radiosurgery to treat trigeminal neuralgia, because it is the least invasive surgical option available to patients. The Gamma Knife (GK) is a device that delivers precise, controlled beams of radiation to targets in the brain and associated nerves, causing enough damage to stop the targeted tissue from growing. For treating trigeminal neuralgia, the GK beams are aimed at a target near the trigeminal nerve root, where the nerve exits the brainstem. GK treatment does not target the root cause of trigeminal neuralgia, but instead damages the trigeminal nerve to "short-circuit" the transmission of pain signals. The procedure requires little or no anesthesia and is performed on an outpatient basis. GK treatment provides significant control or reduction of pain in approximately 80% of patients or more. A drawback is that the patient's response to therapy is usually slower than with other treatments. Patients tend to respond within 4 to 6 weeks after treatment; however, some patients require as long as 3 to 8 months to experience a full response. Barbaro is currently involved in a long-term study of the efficacy of GK radiosurgery for the treatment of trigeminal neuralgia.

In another approach to the treatment of trigeminal neuralgia, Barbaro performs microvascular decompression (MVD) to provide pain relief for patients. This operation, also known as the Janetta procedure, is an open surgical approach in which a small incision is made behind the ear, a small hole is drilled in the skull, and, under microscopic visualization, the trigeminal nerve is exposed. In most cases, there is a blood vessel (usually an artery, but sometimes a vein) compressing the trigeminal nerve. By moving this blood vessel away from the nerve and interposing padding made of Teflon felt, Barbaro eliminates the pressure on the nerve, and the patient nearly always experiences pain relief. Although MVD is the most invasive form of surgery

TREATING NEUROPATHIC PAIN: FROM BENCH TO BEDSIDE

Luc Jasmin MD, PhD, Assistant Professor of Neurological Surgery, specializes both in the surgical treatment of pain and in basic science research on the mechanisms of pain and gene therapy for pain syndromes. While his clinical practice centers on the treatment of pain and spinal disorders, the work in his laboratory focuses on the neuroanatomy and neuropharmacology of pain and inflammation, and on remyelination of the central nervous system (CNS) by Schwann cells.

Clinically, Jasmin has expertise in treating neuropathic pain by using electrical stimulation of the spinal cord. He is also one of the few neurosurgeons who use permanently implanted electrodes placed over the cerebral cortex to manage a number of difficult-to-treat pain syndromes. This technique is used for intractable conditions such as atypical face pain, central pain, and phantom-limb pain. Jasmin also devotes a large portion of his clinical practice to treating cancer pain by using intrathecal delivery systems. These systems most often consist of an implantable infusion pump, with either a fixed or programmable flow rate, connected to a small catheter placed to deliver analgesic drugs directly to pain receptors in the spinal cord. This technique is very efficient at relieving pain and minimizes the side effects often caused by oral drug administration.

Jasmin's laboratory work on cortical modulation of pain behavior has defined a cortical area in the rat brain—the rostral agranular insular cortex—where opioidergic and dopaminergic neurotransmission have a profound effect on pain behavior and on the activation of spinal nociceptive neurons. Imaging studies show that the corresponding area of the brain in humans is also associated with pain perception. Currently, his laboratory is focusing on mechanisms activated by the neurotransmitter gamma-aminobutyric acid (GABA) that are involved in antinociception.

The Jasmin laboratory has also developed rat models of fibromyalgia, a painful disorder that affects 2% of the population. Many different types of physiologic abnormalities have been identified in fibromyalgia and allied conditions, including disturbances in autonomic and neuroendocrine function, in addition to abnormal pain processing. The laboratory is using the rat to model the biochemical anomalies encountered in the CNS of patients who have fibromyalgia—in particular, decreased central noradrenaline and abnormal hypothalamo-pituitary-adrenal axis function.

Continued on page 4
used to treat trigeminal neuralgia, it is also the best procedure for fixing the underlying problem that usually causes trigeminal neuralgia: vascular compression. MVD also causes the least damage to the trigeminal nerve and provides patients, on average, with the longest pain-free periods and the best chance that they will never need pain medication again. MVD, as a stand-alone treatment, has a success rate of approximately 80%.

Barbaro is also highly regarded for his surgical expertise in treating epilepsy and peripheral nerve conditions, including peripheral nerve tumors. In addition to his clinical work, he is an investigator in the Department's Epilepsy Research Laboratory, studying non-synaptic epilepsy mechanisms and synaptic function in human cortical dysplasia.

**DR. BARBARO’S SELECTED PUBLICATIONS**


**DR. JASMIN’S SELECTED PUBLICATIONS**


We are pleased to welcome four new faculty members to the Department.

**Dean Chou MD** has joined the Department as Assistant Clinical Professor. Chou completed his residency at Johns Hopkins University and a fellowship in complex spinal surgery at the Barrow Neurological Institute. His clinical practice includes thoracoscopic, minimally invasive, and open techniques to treat complex spinal disorders. He also has expertise in the treatment of primary and metastatic spinal tumors.

**Graeme Hodgson PhD** has joined the Department as Assistant Professor and a Principal Investigator in the Brain Tumor Research Center. The overarching objective of Hodgson's research program is to combine genomics and biology to efficiently identify and functionally characterize genes that contribute to the development, progression, and maintenance of the cancer phenotype. To date, his research has focused on the development of an array-based comparative genomic hybridization (array CGH) platform and its application to the study of mechanisms of oncogenic cooperation and tumor progression in mouse models of cancer.

**John Wiencke PhD** has joined the Department as Professor and Co-Director of the Department's new Division of Neuroepidemiology. His background is in cyto- and molecular genetics, radiation biology, and molecular epidemiology. His research has been on biomarkers of exposure to chemical toxins and tobacco smoke and on genetic susceptibility to environmental exposures. Wiencke's laboratory will provide support for epidemiological and clinical studies in neuroepidemiology. His laboratory is currently studying molecular subgroups of glioma and aberrant gene methylation.

**Margaret Wrensch PhD** has joined the Department as Professor and Co-Director of the Department's new Division of Neuroepidemiology. Her research has focused on genetic and molecular epidemiology of glioma etiology and prognosis in adults. She is also developing new initiatives in the epidemiology of meningioma and childhood brain tumors with colleagues at UCSF and several other institutions. As Co-Director of the Division of Neuroepidemiology, she will help develop population-science programs for other conditions of interest to the Department.
DIAGNOSING CRANIOSYNOSTOSIS
The final shape of a child’s cranial vault is determined by complex interactions between genetic and developmental factors. Although cranial shape can be affected by suture closure, overall cranial growth is guided mainly by the growth of the brain. A few facts regarding cranial growth and development determine the management of craniosynostosis—the premature closure of one or more cranial sutures. First, the function of the cranial sutures is to provide room for ongoing growth of the calvarium during infancy and childhood. If left untreated, early closure of the sutures causes pronounced changes in the shape of the head that become more prominent during the first few years of life. Second, these characteristic abnormalities in head shape (such as scaphocephaly—a long, narrow head) are usually obvious during a physical examination. When craniosynostosis is suspected but is not the only possible diagnosis, a high-resolution computed tomography (CT) scan with three-dimensional reformatting is the diagnostic test of choice. Third, planning surgical intervention to make the most of the natural processes of rapid bone growth and modeling of the head as the brain grows results in the most favorable cranial shape. For this reason, early detection of craniosynostosis is crucial so that surgical correction can be performed at the most advantageous time, when the child is between four and six months of age.

ISOLATED CRANIOSYNOSTOSIS
Originally, the treatment for single-suture (isolated) craniosynostosis was a surgical procedure to remove the closed suture. Surgeons made no attempt to remodel the cranial vault during this procedure, relying on natural growth of the head to correct the primary deformation. While this approach was successful in some cases, it did not result in entirely acceptable cosmetic results in every case. For this reason, more extensive procedures that combine removal of the closed suture with the reconstruction of segments of the cranial vault have been championed. These complex reconstructive procedures can offer better—often excellent—cosmetic results, but their benefits must be balanced against an increased risk of complications. The safety of these procedures relies on the participation of experienced pediatric anesthesiologists and close cooperation between pediatric neurosurgeons and plastic surgeons who are trained in craniofacial surgery.

Surgeons with the Pediatric Neurosurgical Program at UCSF now have the capability to perform surgery for certain types of craniosynostosis by using minimally invasive endoscopic techniques that help to minimize blood loss during surgery and shorten the time a child must spend in the hospital. These new techniques rely on the use of a molding helmet for several months after the surgical procedure to produce an optimal cosmetic result.

CRANIOFACIAL SYNDROMES
While involvement of a single suture is the most common form of craniosynostosis, multiple-suture closure is much less common. Multiple-suture closure and involvement of sutures at the base of the skull belong to a group of related craniofacial syndromes that often produce a similar physical appearance. These syndromes include Apert’s, Crouzon’s, and Pfeiffer's syndromes. Craniofacial syndromes often require several staged surgical procedures to reconstruct the cranial vault and address a variety of facial anomalies. At UCSF, children who have these syndromes are evaluated and treated in the multidisciplinary Center for Craniofacial Anomalies, a collaborative effort between neurosurgeons, plastic surgeons, maxillofacial surgeons, orthodontists, radiologists, and speech therapists. In general, children with complex craniofacial syndromes initially require cranial vault reconstruction during their first year of life, followed by surgery to bring the midface into a more anterior position. This step has been facilitated by the use of innovative facial distractors that place gradual tension on the facial bones to bring the midface into position.

At UCSF, pediatric neurosurgeons Nalin Gupta MD, PhD and Victor Perry MD—working with craniofacial surgeon William Hoffman MD and orthodontist Karin Vargervik DDS, Director of the Center for Craniofacial Anomalies—are implementing new techniques to treat infants and children who have craniofacial disorders. For more information, contact the UCSF Department of Neurological Surgery at 415-353-7500. The UCSF Center for Craniofacial Anomalies can be reached at 415-476-2271.
The Department of Neurological Surgery has maintained its ranking for 2003 as first in extramural funding by research grants awarded by the National Institutes of Health to departments of neurological surgery throughout the United States.

Mitchel Berger MD, Kathleen M. Plant Distinguished Professor and Chairman of the Department, has been selected to serve as Scientific Program Chair for the 2006 meeting of the American Association of Neurological Surgeons (AANS).

Marlene Burt NP has joined the Department’s Adult Brain Tumor Program as Nurse Practitioner. She takes the place of Heidi Clay RN, MS, CCRN, who is returning to school for post-master’s degree study in the School of Nursing.

Rose Du MD, PhD, Resident in the Department, presented her paper, Comparison of [a] Portable Infrared Pupillometer with Manual Pen Light Pupillary Examination in the Intensive Care Unit, at the 2004 annual meeting of the AANS.

Peter Jun was one of 14 out of 102 Howard Hughes Medical Student Fellows nationwide to be awarded a Howard Hughes Continuing Support Award. Jun is a fourth-year medical student who recently completed his Fellowship in the laboratory of Joseph Costello PhD with his project, Role of Methylation in Meningioma Development and Progression.

Michael McDermott MD, Halperin Endowed Chair in Neurological Surgery, has been elected president of the San Francisco Neurological Society for 2004-2005.

S. Scott Panter PhD, Assistant Professor of Neurological Surgery, has received a grant-in-aid award from the American Heart Association (AHA), which also presented him with the prestigious John Alexander Research award as the top-ranked grant recipient of the AHAs Western States Affiliates.

Guy Rosenthal MD has been appointed Clinical Instructor and Neuroscience Fellow in Neurosurgery at San Francisco General Hospital (SFGH). He will be working on research projects with

Geoffrey Manley MD, PhD, Associate Professor of Neurological Surgery, as well as providing surgical and clinical services to SFGH patients.

In September, Lawrence Pitts MD, Professor of Neurological Surgery, will complete his appointment as Chair of the Statewide Academic Senate for the University of California, which followed his service as the Vice-Chair. During these appointments, he has coordinated faculty efforts in such diverse areas as undergraduate admissions, University budget and advocacy, the Department of Energy National Laboratories, and scholarly communication.

Alfredo Quiñones-Hinojosa MD, Resident in the Department, has been elected to the Alpha Omega Alpha National Medical Honor Society. He also received the AANS 2004 Bittner Award for his paper, Changes in Transcranial Motor Evoked Potentials During Intramedullary Spinal Cord Tumor Resection Predict Severity of Postoperative Motor Deficits. He gave an oral presentation of this work at the 2004 annual meeting of the AANS.

Justin Smith MD, PhD, Resident in the Department, received the Journal of Neuro-Oncology Award given at the 2004 annual meeting of the AANS for his paper, Frame-based Stereotactic Biopsy Remains an Important Diagnostic Tool with Distinct Advantages over Frameless Stereotactic Biopsy.

Philip Starr MD, PhD, Associate Professor of Neurological Surgery, has received the Dystonia “Doctors of Excellence” Award for 2004 from the Dystonia Medical Research Foundation.

Philip Weinstein MD, Professor of Neurological Surgery, was inaugurated as President of the Society of Neurological Surgeons on May 25, 2004.

UCSF Staff Achievement and Recognition (STAR) Awards for 2004 were presented to a number of the Neurosurgery clinic’s outstanding staff and nurses: Dannie Austin, Gilbert Baltazar, Inna Belyaev, Janet Coroo, Melissa DeSuasido, Avelina Gomez, Lisa Hannegan, Diane Holland, Becky Pryce, Erica Terry, Judy Tomsic, Bryan Victoria, and Lori Yee.
Devin K. Binder MD, PhD grew up in Berkeley, California. Early on he thought he might become a musician, playing the violin or piano. He went to Harvard as an undergraduate, where he developed an interest in biology, anthropology, and neuroscience, and he was graduated with a degree in Biological Anthropology in 1991. He then enrolled in the MD/PhD program at Duke University, graduating in 1999. During graduate school, seeing Robert Wilkins MD work with patients in the clinic and operating room kindled a lasting interest in clinical neurosurgery. Throughout his training, Binder has been an avid investigator. As an undergraduate, he studied the brainstem physiology and pharmacology of rapid-eye-movement (REM) and non-REM sleep in the laboratory of J. Allan Hobson MD at Harvard Medical School, leading to his summa cum laude and Hoopes Award-winning undergraduate thesis, Serotonin and Behavioral State. In graduate school, he combined molecular biology with immunohistochemistry and in vivo electrophysiology in an animal model of epilepsy to specifically determine the functional role of brain-derived neurotrophic factor (BDNF) in epileptogenesis. At UCSF, with Mitchel Berger MD, he has reviewed the biology of glioma invasion, the role of lasers in neurosurgery, and gene therapy for gliomas. With Nicholas Barbaro MD, he has studied the epidemiology of auras in patients undergoing temporal lobectomy, reviewed the role for language mapping in temporal resection, reviewed the literature on anterolateral cordotomy, and published Barbaro’s series of primary brachial plexus tumors. With Philip Starr MD, PhD, he has analyzed the factors contributing to the risk of hemorrhage following deep brain stimulation (DBS) surgery for movement disorders. This work in particular was recognized with the American Society for Stereotactic and Functional Neurosurgery Resident Award in 2003. With Geoffrey Manley MD, PhD, he has examined the role of aquaporins (in particular, aquaporin-4) in the susceptibility to seizures in vivo, and has studied the expression of aquaporins in gliomas and meningiomas. With Alan Verkman MD, PhD, he has developed an entirely new fluorescence technique for measuring extracellular space diffusion in vivo and used it to study cytotoxic and vasogenic edema, seizures, and tumor biology.

Binder has presented clinical and research papers at many conferences. He has also served as instructor for the Medical School’s Brain, Mind, and Behavior course. In addition to basic and clinical neuroscience, Binder enjoys wine and food, travel, running, and scuba diving. He plans to pursue a career in the areas of epilepsy and functional neurosurgery.


Du R, Young WL, Lawton M. “Tangential” resection of medial temporal lobe arteriovenous malformations with the orbitozygomatic approach. Neurosurgery 2004;54:45-53. This paper was presented by Du at the 2004 American Association of Neurological Surgeons/Congress of Neurological Surgeons Cerebrovascular Section meeting, as well as at the 2004 American Society of Interventional and Therapeutic Neuroradiology Joint Meeting.


