BRAIN ACTIVITY

ACADEMIC AND RESEARCH NEWS VOLUME 6 NUMBER 1

IN THIS ISSUE . . .

. . . we highlight the UCSF Department of Neurological Surgery's efforts in meningioma research, including clinical and basic science research and collaborative efforts both within the Department and with outside partners. We also introduce the new UCSF Spine Center, a collaboration of Neurological Surgery and Orthopedic Surgery.

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UCSF DEPARTMENT OF NEUROLOGICAL SURGERY TARGETS MENINGIOMAS

Meningiomas are the second most common primary brain tumor after gliomas, accounting for approximately 26% of all cases. Although most meningiomas are benign, recurrence after surgical treatment is not unusual. Standard therapies to date have included reoperation, external radiation therapy, and radiosurgery. Malignant meningiomas, which account for 10% to 15% of meningiomas, have high recurrence and mortality rates within 5 years of diagnosis. No effective treatment is currently available for these malignant tumors.

The UCSF Department of Neurological Surgery is pursuing aggressive clinical and research programs for the treatment of both benign and malignant meningiomas. Michael McDermott MD, Associate Professor of Neurological Surgery, holds the newly established Robert and Ruth Halpern Chair in Meningioma Research and heads the meningioma surgery program. The meningioma surgery team at UCSF also includes Mitchel Berger MD, Sandeep Kunwar MD, and Andrew Parsa MD, PhD. An operation to resect a giant meningioma can require two or three surgeons for a marathon operation taking as long as 8 to 10 hours to complete. Currently, the Department sees 100 to 120 patients with meningiomas each year. Christopher Dowd MD, Randall Higashida MD, and Van Halbach MD from Neuroradiology assist with preoperative angiography and emoblization of some of the very large tumors to reduce blood loss and operative time.

Postoperatively, patients may be referred for additional treatment, most often for radiation therapy: 3D-conformal irradiation, intensity modulated radiation therapy (IMRT), or stereotactic radiation therapy, radiosurgery, or brachytherapy. Patricia Sneed MD, David Larson MD, PhD, and William Wara MD from Radiation Oncology collaborate in the treatment of complex meningiomas.

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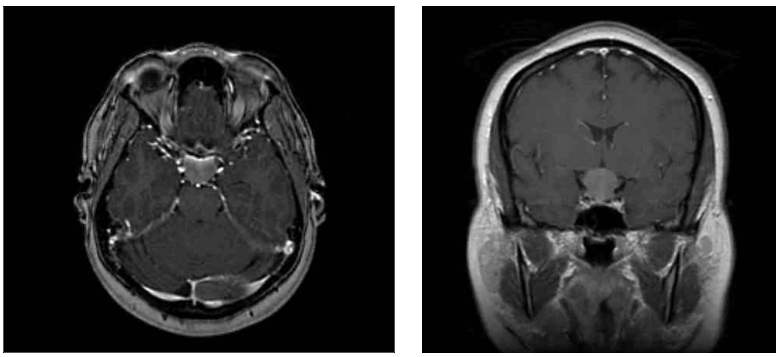
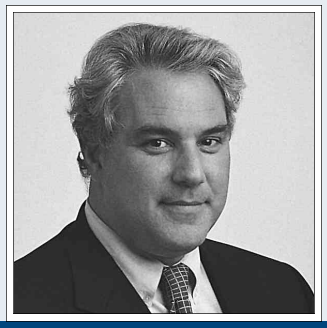


Preoperative magnetic resonance images of a tuberculum sellae meningioma. Tuberculum sellae meningiomas account for 3% to 10% of all intracranial meningiomas. Patients usually present with slowly progressing visual deterioration. The UCSF Department of Neurological Surgery is accelerating its clinical and basic science research into the biology and treatment of meningiomas.



LOOKING TO THE FUTURE

Entering my seventh year as Chairman of Neurological Surgery at UCSF, I look back with pride at the growth of our Residency Training Program, which was recently re-accredited by the Accreditation Council of Graduate Medical Education (ACGME) for five more years without a single citation. This is an achievement to be proud of, and I am very grateful to the department residents, faculty, and staff who worked together to make our re-accreditation process so successful. In addition to re-accreditation, we were approved to extend our residency program to accept three new residents each year, placing us in the 3% of neurosurgery residency programs nationally that have this privilege. We also gained approval for offering fellowship training in spine surgery, functional neurosurgery, and stereotactic radiosurgery. Our Department's Residency Training Program is one of the top training programs in the country, and I have all of our dedicated faculty and staff to thank for this.

One of the hallmarks of a great medical education and research institution is participation of the institution's eminent, talented faculty in multiple aspects of its programs and curriculum. In that tradition, the Vice Chairs of Neurological Surgery have responsibility for major aspects of the Department's functions. Currently, **Russell Pieper PhD** holds the position of Research Vice Chair and **Susan Chang MD** that of Clinical Vice Chair. I am delighted to let you know that, as of this fall, Vice Chairs are taking charge of two other vital aspects of the Department's programs. As the Director of Patient Care Services in Neurological Surgery, **Michael McDermott MD** will manage the clinic and its programs and the inpatient and outpatient services, including the operating room and its schedules. As Director of the Residency Training Program, **Nicholas Barbaro MD** will supervise all aspects of the residents' tenure at UCSF, as well as the program for meeting the Department's training and competency objectives and the compliance objectives regarding the recently implemented 80-hour work week for residents. Both Barbaro and McDermott bring a great deal of experience to these positions, and while I will continue to work with them in these areas while heading up increasingly demanding academic administrative aspects of the Department, I am confident the Department will be well served under their leadership as they take their respective programs to the next level and beyond.

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

UCSF DEPARTMENT OF NEUROLOGICAL SURGERY TARGETS MENINGIOMAS

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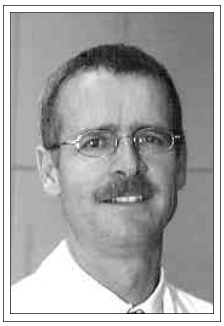
In addition to strong clinical expertise in meningioma treatment, the Department is accelerating its basic science research into the biology of meningiomas. Anita Lal PhD, the new director of the Meningioma Research Laboratory, came to UCSF in February 2003 from Duke University. Her primary focus is on serial array gene expression (SAGE) for the identification of cell-surface receptor targets for potential therapeutic approaches. Lal recently received funding from the Academic Senate for new projects in the laboratory. She is working with McDermott and assisted by a staff research associate *(see p. 3)*.

The Neurosurgery Tissue Bank currently has over 600 meningioma tissue samples – one of the largest collections in the United States. Many basic scientists are using the tissue for studies designed to gain greater insight into the biology of meningiomas. Burt Feuerstein MD, PhD recently published work on comparative genetic hybridization in meningiomas. Tarik Tihan MD, PhD from Neuropathology has developed a tissue array slide with 50 different tumors, and is collaborating with the Mayo Clinic on meningioma pathology and molecular biology research. Joseph Costello PhD and Peter Jun, a Howard Hughes Fellow in his laboratory, are looking at the methylation status of benign and malignant meningiomas. Margaret Wrensch PhD from Epidemiology and Biostatistics is applying for a research grant to look at the relationship between meningiomas and breast cancer. Soonme Cha MD, Tracy McKnight PhD, and Sarah Nelson PhD have been funded to study 30 patients to correlate blood volume measurements in meningiomas with their molecular biology and cell-surface receptors using in vivo and ex vivo spectroscopy.

McDermott recently received a $10 thousand award from the National Brain Tumor Foundation for a study of the biology of meningiomas, and $30 thousand from the North American Brain Tumor Consortium to study magnetic resonance spectroscopy for blood volume and molecular markers. In the near future, the Department plans to apply for a grant for meningioma research from the National Institutes of Health to accelerate and add to the many collaborative projects already underway.

MOLECULAR INSIGHTS INTO MENINGIOMA PATHOGENESIS



Michael McDermott MD holds the Robert and Ruth Halpern Chair in Meningioma Research and is an Associate Professor in the Department of Neurological Surgery at UCSF. McDermott's clinical specialty interests include stereotactic neurosurgery and Gamma Knife® (Elekta AB, Stockholm, Sweden) radiosurgery, in particular for meningiomas and tumors of the central nervous system, and skull-base surgery. He is co-director of both the UCSF Gamma Knife® Radiosurgery program and the Department's Skull-Base Surgery program. His involvement in clinical research includes reviews of surgical outcomes for selected skull-base meningiomas and the results of radiosurgery for meningiomas. He recently received funding to begin a new project comparing the in vitro and in vivo spectroscopy and biochemical correlates of meningiomas.

In addition to his clinical research, McDermott is clinical co-investigator of the Meningioma Research Laboratory, headed by Anita Lal PhD. Lal received her PhD in Biochemistry and Molecular Biology from the University of Georgia and worked as a postdoctoral research associate at the Duke University Medical Center before coming to UCSF in February of 2003 as an Assistant Research Molecular Biologist with the Department of Neurological Surgery.

The primary objective of the Meningioma Research Laboratory is to understand the genetic changes underlying meningioma tumorigenesis with the goal of improved therapy. Of particular interest are the genes and genetic pathways that are altered and contribute to the malignant progression of meningiomas and meningioma recurrence.

Current treatment options for meningiomas are restricted to surgical resection and radiation therapy. They are often inadequate because some meningiomas are not amenable to surgery and others recur even after surgery and radiation treatment. Also, existing criteria for the classification and grading of meningiomas do not adequately predict rates of tumor growth or the likelihood of tumor recurrence. There is a need for the development of novel therapies based on the unique biologic properties of meningiomas and for the development of a molecular classification system that is of better prognostic value, so that appropriate treatment strategies can be directed toward patients according to their need, and so that patients with slower-growing tumors that are unlikely to recur are spared unnecessary treatment.

The laboratory is taking a dual approach to molecularly characterize meningiomas. Firstly, the lab is using serial analysis of gene expression (SAGE) to define the transcriptome of meningiomas. The SAGE technology is attractive because of its ability to evaluate the expression pattern of thousands of genes in a quantitative manner without any prior sequence information. Preliminary data permitted identification of a large number of genes and some genetic pathways that are altered in higher-grade meningiomas, including several cell-cycle and apoptosis regulators. Of particular interest are implications that aberrations of the Notch signaling pathway contribute to the malignant progression of meningiomas. A detailed characterization will enable the laboratory to sort the genes that actually contribute to meningioma pathogenesis from those that simply reflect a cancerous phenotype.

Secondly, in collaboration with the laboratory of Joseph Costello PhD, the Meningioma Research Laboratory is cytogenetically characterizing meningiomas by using array comparative genomic hybridization (CGH). An integration of the SAGE and array CGH profiles will permit correlation of the induction or reduction of expression of specific genes to gains or losses of specific chromosomal regions.

Crucial to understanding the role of individual genes in the pathogenesis of meningiomas is the availability of tumor model systems. There are very few meningioma model systems, and most studies have relied on the use of primary cultures of meningiomas, which have limited utility. The Meningioma Research Laboratory is developing in vitro and in vivo meningioma model systems from bulk meningioma tissue and is developing a genetic model of meningiomas by using primary cultures of arachnoidal cells, the presumed cell of origin for meningiomas.

MENINGIOMA RESEARCH FUND

While we are proud that the Department ranks first in grants awarded to departments of Neurological Surgery by the National Institutes of Health (NIH), the NIH alone cannot fully support our work. Gifts from individuals, corporations, and foundations are vitally important as well. If you are interested in supporting meningioma research, please contact our development officer, David Madson, at 415-514-0590 or dmadson@support.ucsf.edu.

MULTIDISCIPLINARY SPINE CENTER OPENS AT UCSF

The new UCSF Spine Center, which will open in February 2003, is led by neurological and orthopedic surgeons who specialize in the surgical management of spinal disorders. The surgical team has expertise in treatment options that include minimally invasive techniques, motion preservation in the spine, image-guided surgery, and complex reconstruction of the spine. The UCSF Spine Center staff includes, in addition, cancer specialists, neurologists, physiatrists specializing in rehabilitation and non-operative care of spinal disorders, radiologists, rheumatologists and other arthritis specialists, nurses, physical therapists, and complementary medicine specialists.

Minimally invasive endoscopic spinal instrumentation and fusion is one of the procedures available at the new UCSF Spine Center.

The team works together with the patient and with one another to achieve the shared goal of optimizing mobility, reducing pain, and improving each patient's quality of life. The Center's specialists are experienced in diagnosing and treating virtually every kind of adult and pediatric spinal disorder, deformity, and disease, including:

- Curvature of the spine (scoliosis and kyphosis)
- Disc disease, herniated discs, and spinal stenosis
- Spinal deformities
- Tumors of the spine and spinal cord
- Fractures and trauma to the spine
- Osteoarthritis and rheumatoid arthritis affecting the spine.

When surgery is necessary, available techniques include minimally invasive arthroscopic and endoscopic surgery, and leading-edge imaging and navigational devices are used to achieve the highest standards of accuracy. Among the specialty procedures and equipment available at the new center are:

- Discectomy, decompression, disc replacement, and reconstruction of the entire spinal column
- Minimally invasive microendoscopic techniques
- Bio-resorbable spinal fixation implants
- Thorascopic surgery
- Computerized stereotactic image-guided surgery, including the Stealth® Navigation System (Medtronic, Minneapolis, MN)
- Positron emission tomography (PET) scanning for tumors
- The non-invasive CyberKnife® Stereotactic Radiosurgery System (Accuray, Sunnyvale, CA) for treating spinal tumors
- Complex spinal deformity reconstruction
- Kyphoplasty and vertebroplasty for osteoporotic spine fractures
- Spinal fusion.

The UCSF Spine Center also offers referral to a full range of non-surgical treatments, such as physical therapy, acupuncture, bracing, pain management, and stress management. The professionals in these specialties work with surgical patients both before and after surgery to ensure optimal results.

With close collaboration and multidisciplinary consultations among the health care team at the UCSF Spine Center, each patient receives a complete diagnostic evaluation and an individually tailored treatment plan in which all available options are considered.

Toll-free number 866-81-SPINE [866-817-7463]
http://www.ucsfhealth.org/spine

MOLECULAR INSIGHTS INTO MENINGIOMA PATHOGENESIS

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DR. McDERMOTT'S SELECTED PUBLICATIONS

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DR. LAL'S SELECTED PUBLICATIONS

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CURRENT MANAGEMENT OF PEDIATRIC HYDROCEPHALUS AT UCSF

HYDROCEPHALUS

Cerebrospinal fluid (CSF) surrounds and protects the brain and spinal cord from injury. In a healthy child, the large amount of CSF produced by the brain every day (250-400 ml) is balanced by its absorption into the large venous sinuses at the top of the brain. Hydrocephalus occurs when the balance between the production and the absorption of CSF is disrupted. Usually, but not always, this disruption leads to an accumulation of CSF within the brain's ventricles or around the brain in the subarachnoid space.

Left: Magnetic resonance image of a child with massive congenital hydrocephalus. Right: The device used to program or adjust a CODMAN® HAKIM™ programmable shunt (Codman & Shurtleff/Johnson & Johnson, Raynham, MA).

Hydrocephalus may be congenital (affecting one out of every 1000 newborns) or acquired (caused by a tumor, injury, or disease that blocks the normal circulation of CSF). A build-up of fluid may result from any of three causes:

- The flow of CSF through the ventricular system is blocked.
- The CSF produced cannot be reabsorbed back into the bloodstream, usually because of obstruction of the pathways at the very top of the brain.
- An excessive amount of CSF is being produced (as seen with tumors such as choroid plexus papillomas).

COMPLEX HYDROCEPHALUS

Hydrocephalus is a highly heterogeneous disease with a variety of symptoms and different rates of progression. The usual treatment of most types of hydrocephalus is placement of a shunt that redirects the CSF from the brain to another space, usually the abdominal cavity, where it can be absorbed back into the bloodstream. In most cases, a ventriculoperitoneal (VP) shunt is placed to divert the CSF from the ventricles to the peritoneum lining the abdomen. For some complex types of hydrocephalus, however, a standard VP shunt does not adequately treat the symptoms and in some cases may even lead to new complications. Three specific subtypes of hydrocephalus requiring individualized treatment are focal obstructive hydrocephalus, poorly compliant hydrocephalus, and massive hydrocephalus.

NEW TREATMENT STRATEGIES

ENDOSCOPIC COMMUNICATION OF CSF SPACES

The typical example of focal obstructive hydrocephalus is obstruction between the third and fourth ventricles, which is also known as aqueductal stenosis. The primary goal of treatment for this form of hydrocephalus is to avoid having to place a shunt. An endoscopic approach permits selective fenestration of the floor of the third ventricle, permitting CSF to circulate directly past a point of obstruction. Further refinement is possible through the use of image-guidance techniques and endoscopic instruments, which afford greater accuracy and precision in these procedures. Intraventricular cysts are also dealt with most effectively by using endoscopic techniques rather than open surgery.

DEFINITION OF DISTURBANCES IN CSF PHYSIOLOGY

In patients with existing shunts and poorly defined symptoms, often the most difficult problem is measuring the exact intracranial pressure and the contribution of the shunt to the existing symptoms. Slit-ventricle syndrome is an example of a type of hydrocephalus that is associated with high intracranial pressure but reduced brain compliance, which leads to a clinical syndrome characterized by little or no change in the size of the ventricles as measured on imaging studies, even in the presence of complete shunt failure. There are a variety of techniques for defining the exact nature of the disturbance in CSF physiology. The first of these is an accurate measurement of intracranial pressure over time. Usually this requires the placement of a small intracranial monitor that is often used in patients after head trauma. Clearance of CSF can be determined by the use of special tracers that are injected into the CSF pathways and then followed over time. Finally, new magnetic resonance imaging techniques are being developed to measure intracranial pressure noninvasively.

PROGRAMMABLE SHUNTS

In infants who have massive hydrocephalus, the precipitous drainage of CSF can cause additional complications. For this reason, a variety of programmable shunts have been developed to permit adjustment of the opening pressure of the shunt, thereby permitting a controlled drainage of CSF. Programmable shunts are usually adjusted with an external magnet. These shunts have also been useful in patients who have had problems with excessive or insufficient drainage of CSF.

The surgical team for pediatric hydrocephalus at UCSF consists of Nalin Gupta MD, PhD and Victor Perry MD. For more information on the treatment of pediatric hydrocephalus at UCSF, call 415-353-7500.

NEUROSURGERY NOTES

Nicholas Barbaro MD has been appointed Director of the Residency Training Program, and Michael McDermott MD has been appointed Director of the Patient Care Services Program within the department. Both of these new positions will assume the status of Vice Chair of Neurogical Surgery.

Mitchel Berger MD has been awarded the Kathleen M. Plant Distinguished Professorship. In addition, he has been appointed to the Clinical Studies Subcommittee of the National Cancer Institute Review Group. Berger and Neurosurgery Clinic Administrative Director Sarah Geraty have received the UCSF Medical Center Quality Improvement Award for 2003.

Krys Bankiewicz MD, PhD has received a grant from the Accelerate Brain Cancer Cure (ABC^2) Foundation for 1 year starting in June 2003 for his project, Convection-Enhanced Delivery of Immunoliposomes into Brain Tumors Using Real-Time MRI.

The laboratory of Nathalie Compagnone PhD is starting a new collaboration with William H. Frey II PhD, Director of the Alzheimer's Research Center at Regions Hospital, St. Paul, MN to assess the efficacy of intranasal delivery of drugs that do not cross the blood-brain barrier in reducing damage caused by spinal-cord injury in the mouse.

Martin Holland MD has been inducted into the Haile T. Debas Academy of Medical Educators. Founded in 2000, the Academy was named for Dr. Debas in recognition of his commitment to medical education and his leadership in establishing the Academy.

Michael McDermott MD has won a Meningioma Research Grant from the National Brain Tumor Foundation for his project, An Investigation into the Biology of Meningiomas.

Andrew Parsa MD, PhD has received a five-year K08 award from the NIH, which began in September 2003.

Michael Prados MD, Charles B. Wilson MD Professor of Neurological Surgery, has been elected President of the Society for Neuro-Oncology (SNO). Susan Chang MD, Lai Wan Kan Associate Professor of Neurological Surgery, has been elected Vice-President of SNO. Both positions are for a 2-year term beginning in November of 2003.

Philip Starr MD, PhD will serve as Scientific Program Director for the 2004 meeting of the American Society for Stereotactic and Functional Neurosurgery, October 1-3 in Cleveland, Ohio.

Robert Turner PhD has received an industry research grant from Northstar Neuroscience that began in April of 2003.

Charles Wilson MD, DSc, MSHA, Professor Emeritus, has received the Neurosurgical Society of America Medal, which is awarded to a member who has made important and lasting contributions to the field of neurosurgery.

UCSF Staff Achievement and Recognition (STAR) Awards for 2003 were presented to a number of the Neurosurgery Clinic's outstanding staff and nurses: Dannie Austin, Gilbert Baltazar, Anna Bensi, Jessie Castillo, Heidi Clay, Melissa DeGuzman, Melissa Desuasido, Lina Gomez, Lisa Hannegan, Diane Hollander, Jude Sargent, Erica Terry, Bryan Victoria, and Lori Yee.

The UCSF Neurosurgery Service ranks in the top five Neurology and Neurosurgery programs in the United States according to the *US News and World Report's* 2003 Best Hospitals report. UCSF Medical Center once again made the *US News and World Report's* list of the top ten medical centers in the United States.

Cornelia von Koch MD, PhD, was born in Frankfurt, Germany and came to the United States in 1987 to attend the University of Pennsylvania, where she received her BSE in Bioengineering and BA in Biophysics. She then enrolled in the MD-PhD program at Johns Hopkins University School of Medicine, obtaining her PhD in Neuroscience with her thesis on the Molecular Analysis of a Homologue of the Mouse Amyloid Precursor Protein APLP2: Isolation of APLP2 cDNA, Characterization of APLP2 Gene Promoter, and Gene Targeting of APLP2.

She came to UCSF in 1998 and, after completing an internship in general surgery, joined the residency program in the Department of Neurological Surgery in 1999. Her interest in pediatric neurosurgery led her to spend her research year during her Neurological Surgery residency as a postdoctoral fellow in the Fetal Treatment Center at UCSF, working with Diana Farmer MD and Michael Harrison MD. There she studied a sheep model of myelomeningocele and its implications for *in utero* repair. She received an Individual National Research Service Award from the National Institutes of Health for this work.

von Koch is a member of both the Congress of Neurological Surgeons (CNS) and the American Association of Neurological Surgeons (AANS), as well as the AANS/CNS Joint Section on Tumors. She is involved in the UCSF Graduate Medical Education Committee and the Department of Neurological Surgery's Resident Education Committee, and she is currently the Department's Chief Resident. She will be the first participant in the Clinical Instructor year and will focus on tumor and skull-base neurosurgery. After her Clinical Instructor year, she plans to pursue a pediatric neurosurgery fellowship.

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RESIDENTS' ACTIVITIES AND PUBLICATIONS

Alfredo Quiñones-Hinojosa MD received the Ruth L. Kirschstein Individual National Research Service Award from the NIH-NINDS for his project, Neurogenesis in the Human Brain. The period of the award is July 2003 to July 2004. He also took first place in the American College of Surgeons (ACS) Region IX Resident Paper Competition in 2003 for his paper, Report on Childhood Injuries Associated with Automobile Airbag Deployment, presented at the ACS Committee on Trauma meeting in Chicago, March 13, 2003.

Marcus Ware MD, PhD was awarded the Mahaley Clinical Award at the American Association of Neurological Surgeons 2003 Annual Meeting for his paper, Resection and Brachytherapy for Recurrent Atypical and Malignant Meningioma.

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– Selected Recent Publications from the Department of Neurological Surgery –

Alvarez-Dolado M, Pardal R, Garcia-Verdugo JM, **Fike JR,** Lee HO, Pfeffer K, Lois C, Morrison SJ, **Alvarez-Buylla A.** Fusion of bone-marrow-derived cells with Purkinje neurons, cardiomyocytes and hepatocytes. Nature 2003;425:968-73.

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Chute DJ, **Burton EC,** Klement IA, Frazee JG, Vinters HV. Primary intramedullary spinal cord germinoma: case report. J Neurooncol 2003;63:69-73.

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