Byron Pevehouse

THE AMERICAN ACADEMY OF NEUROLOGICAL SURGERY

64th Annual Meeting

October 16-19, 2002

Jointly Sponsored by the
American Association
of Neurological Surgeons

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GENERAL INFORMATION

REGISTRATION DESK LOCATION AND HOURS:

Wednesday, Oct. 16	South Foyer E	2:00 PM – 8:00 PM
Thursday, Oct. 17	East Foyer G	6:30 AM – 3:00 PM
Friday, Oct. 18	East Foyer G	6:30 AM – 3:00 PM
Saturday, Oct.19	South Foyer E	7:00 AM – 1:00 PM

SPEAKER READY ROOM

The Speaker Ready Room is located in the Cypress Room and will be open:

Wednesday, October 16	2:00 PM – 8:00 PM
Thursday, October 17	6:00 AM – 8:00 PM
Friday, October 18	6:00 AM – 8:00 PM
Saturday, October 19	6:00 AM – 1:00 PM

The Phoenician
6000 East Camelback Road
Scottsdale, Arizona 85251
Telephone Number: (480) 941-8200
Facsimile Number: (480) 947-4311

PROGRAM SUMMARY

WEDNESDAY, OCTOBER 16

EVENTS	TIME	LOCATION
Registration	2:00 PM – 8:00 PM	South Foyer E
Speaker Ready Room	2:00 PM – 8:00 PM	Cypress Room
Executive Committee Meeting	2:00 PM – 5:00 PM	Willow Room
OPENING RECEPTION		
Cocktail Dinner (Dressy)	6:00 PM – 10:00 PM	East Fountain & Croquet Lawn

PROGRAM SUMMARY

THURSDAY, OCTOBER 17

EVENTS	TIME	LOCATION
Registration	6:30 AM – 3:00 PM	East Foyer
Speaker Ready Room	6:00 AM – 8:00 PM	Cypress Room
Business Breakfast Meeting **For Academy Members Only**	6:30 AM – 7:30 AM	Ballroom E
Breakfast for Guests and Spouses	6:30 AM – 10:30 AM	Las Brisas Room
Scientific Session	7:30 AM – 12:30 PM	Ball Room F&G
PROGRAM FOR SPOUSES		
Walking Tour of Phoenician Art & Sculpture Collection	9:00 AM – 9:45 AM	Tour Departs from Ballroom Circle Adjacent to Las Brisas Room
Dr. Kathleen Matt Speaker	10:00 AM – 10:45 AM	Las Brisas Room
OTHER ACTIVITIES		
Tennis & Golf		
OFFSITE EVENT		
Taliesin West	2:00 PM – 5:00 PM	*Transportation provided
Shuttles to and from Biltmore Fashion Park	2:00 PM – 5:30 PM	*Transportation provided
(To Biltmore on the hour/Departing Biltmore on ½ Hour)		
DINNER		
Western Barbeque (Casual dress)		Jokake Inn
Reception	6:30 PM – 7:30 PM	(North of the
Dinner	7:30 PM – 10:00 PM	Phoenician Entrance)

*Tours depart from the Ballroom Circle adjacent to Las Brisas Room

PROGRAM SUMMARY

FRIDAY, OCTOBER 18

EVENT	TIME	LOCATION
Registration	6:30 AM – 3:00 PM	East Foyer
Speaker Ready Room	6:00 AM – 8:00 PM	Cypress Room
Business Breakfast Meeting **For Academy Members Only**	6:30 AM – 7:30 AM	Ballroom E
Breakfast for Guests and Spouses	6:30 AM – 10:30 AM	Las Brisas Room
Scientific Session	7:30 AM – 1:00 PM	Ball Room F&G
PROGRAM FOR SPOUSES Book Review	9:30 AM – 11:00 AM	Las Brisas Room
OFFSITE EVENT Fleischer Museum	2:00 PM – 4:30 PM	*Transportation provided
Shuttles to and from Biltmore Fashion Park (To Biltmore on the hour/Departing Biltmore on ½ Hour)	2:00 PM – 5:00 PM	*Transportation provided
OTHER ACTIVITIES Tennis & Golf		
Black Tie Reception **Dinner**	6:30 PM – 7:30 PM 7:30 PM – 10:00 PM	East Foyer & Patio Grand Phoenician Ballroom

*Tours depart from the Ballroom Circle adjacent to Las Brisas Room

PROGRAM SUMMARY

SATURDAY, OCTOBER 19

EVENT	TIME	LOCATION
Registration	7:00 AM – 1:00 PM	South Foyer
Speaker Ready Room	6:00 AM – 1:00 PM	Cypress Room
Breakfast for **All Members, Spouses and Guests**	6:30 AM – 9:30 AM	Las Brisas
Scientific Session	7:30 AM – 1:00 PM	Ballroom EFG
SNS Task Force on Resident Education	12:30 PM – 2:00 PM	Willow Room

SOCIAL ACTIVITIES FOR SPOUSES

The spouses of the American Academy members and guests are welcome to attend all events.

Wednesday, October 16	
6:00 – 10:00 PM	Opening Reception – *East Fountain & Croquet Lawn* Dressy
Thursday, October 17	
6:30 – 10:30 AM	Spouse & Guest Breakfast – *Las Brisas Room* 6:30 – 10:30 AM Buffet
9:00 – 9:45 AM	Walking Tour of Phoenician art & Sculpture Collection *(Tour Departs from Ballroom Circle Adjacent to Las Brisas Room)*
10:00 – 10:45 AM	Dr. Kathleen Matt, Associate Director of Arizona Biomedical Institute and Professor of Neuroendocrinology. *"Stress & Aging: Where did I leave my keys and why can't I touch my toes?"*
2:00 – 5:30 PM	Shopping – *(Transportation departs from Ballroom Circle adjacent to Las Brisas Room)* Departing to Biltmore on the hour and from Biltmore on the ½ hour.
2:00 – 5:00 PM	*Taliesin West Museum – *Bus transportation provided.*
6:30 PM	Dinner – Western Barbeque – *Jokake Inn* Casual Western Wear 6:30 – 7:30 PM Reception 7:30 – 10:00 PM Dinner
Friday, October 18	
6:30 – 10:30 AM	Spouse & Guest Breakfast– *Las Brisas Room* 6:30 – 10:30 AM Buffet
9:30 – 11:00 AM	Book Review – *Ahab's Wife* – Las Brisas Room
2:00 – 5:00 PM	Shopping – *(Transportation departs from Ballroom Circle adjacent to Las Brisas Room)* Departing to Biltmore on the hour and from Biltmore on the ½ hour.
2:00 – 4:30 PM	*Fleischer Museum – *Bus transportation provided.*
6:30 – 10:00 PM	Black Tie Dinner – *Phoenician Grand Ballroom* 6:30 – 7:30 PM Reception 7:30 – 10:00 PM Dinner
Saturday, October 19	
6:30 – 9:30 AM	Members, Spouse & Guest Breakfast – *Las Brisas Room*

Tours will depart from the Ballroom Circle adjacent to the Las Brisas Room.

* Activities require prior registration.

DISCLOSURE INFORMATION

The American Association of Neurological Surgeons and *The American Academy of Neurological Surgery* control the content and production of this CME activity and attempt to assure the presentation of balanced, objective information. In accordance with the Standards for Commercial Support established by the Accreditation Council for Continuing Medical Education, speakers and paper presenters are asked to disclose any relationship they or their co-authors have with commercial companies which may be related to the content of their lecture.

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Faculty Name	Disclosure	Type of Relationship
Issam Awad	NIH (NINDS)	Grants/Research Support
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Lee R. Guterman	Microtherapeutics	Grants/Research Support Consultants
Bermans J. Iskandar	American College of Surgeons	Grants/Research Fellowship
L. Dade Lunsford	Elekta Instruments, Atlanta	Consultants
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	AB Elekta, Stockholm, Sweden	Financial/Material Support
Joseph Madsen	NIH	Grants/Research Support
James Rutka	Canadian Institutes of Health	Grants/Research Support
Theodore Schwartz	NINDS, Dana Foundation	Grants/Research Support
Robert F. Spetzler	Allegians, Zeiss, Medtronic, Synergetics, NMT	Consultants

*Relationship refers to receipt of royalties, consultantship, funding by research grant, receiving honoraria for educational services elsewhere, or any other relationship to a commercial company that provides sufficient reason for disclosure.

Speakers and their paper presenters/authors who have reported they do not have any relationships with commercial companies:

Faculty Name

Daniel Barrow
Peter W. Carmel
Thomas C. Chen
Ralph G. Dacey
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Raymond Sawaya
Christopher B. Shields
Robert Solomon
Gary K. Steinberg
M. Christopher Wallace
Ronald E. Warnick
Martin H. Weiss

Speakers and their paper presenters/authors who have refused to disclose whether they have any relationships with commercial companies:

None

Speakers who have disclosed that their presentations will include discussion of an off-label or investigational drug or device:

None

SCIENTIFIC PROGRAM
AMERICAN ACADEMY
OF NEUROLOGICAL SURGERY
2002 LEARNING OBJECTIVES

Jointly sponsored by The American Association of Neurological Surgeons, October 16-19, 2002.

Upon completion of this program, the participants should be able to: Critique the value of the recommended surgical and non-surgical options presented in the scientific papers.

Evaluate the relevance of research methodologies, and the findings and potential usefulness in practice of the topics presented for cerebrovascular, neoplastic, spinal, and developmental and functional nervous system diseases.

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This activity was planned and implemented in accordance with the essential areas and standards of the Accreditation Council for Continuing Medical Education through Joint Sponsorship of the American Association of Neurological Surgeons and the American Academy of Neurological Surgery. The American Association of Neurological Surgeons is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The American Association of Neurological Surgeons designates this continuing medical education activity for a maximum of 15 hours in category 1 credit towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit he/she actually spent in the educational activity.

SCIENTIFIC PROGRAM
AMERICAN ACADEMY OF NEUROLOGICAL SURGERY

THURSDAY, OCTOBER 17	**Moderator: Mitchel S. Berger**
INVITED LECTURESHIP:	**Restoration of Function in the Central Nervous System, Part I**
7:30 – 8:15 AM	Vascular Mechanisms Underlying Restoration of Function after Spinal Cord Injury. Linda Noble
8:15 – 8:30 AM	Discussion
8:30 – 8:45 AM	A Blinded Randomized Comparison of GPi vs STN Stimulation in Advanced Parkinson's Disease. Kim Burchiel, J. Hammerstad, V. Anderson, J. Favre, P. Hogarth
8:45 – 9:00 AM	Microvascular Decompression for Severe Essential Hypertension: Introduction of a Prospective Controlled Study. Rudolf Fahlbusch, R. Naraghi, H. Frank
9:00 – 9:15 AM	Durability of Carotid Endarterectomy. Fredric B. Meyer, WL Windschitl, RD Ecker
9:15 – 9:30 AM	Meta-Analysis of Carotid Endarterectomy Trials for Symptomatic Stenosis. Marc R. Mayberg
9:30 – 9:45 AM	Spetzler-Martin Grade III Arteriovenous Malformations: Surgical Results and a Modification of the Grading Scale. Michael T. Lawton

THURSDAY, OCTOBER 17 (continued)

9:45 – 10:00 AM	Effects of Increased Use of Endovascular Approaches and Hospital Volume on Treatment Outcome for Cerebral Aneurysms: New York State Experience 1995 – 2000. MF Berman, Robert A. Solomon, SA Mayer, P Yung, ES Connolly
10:00 – 10:15 AM	ApoE ε4 Predicts Cognitive Injury Following Carotid Endarterectomy. E. Sander Connolly, Jr.
10:15 – 10:30 AM	Coffee Break
10:30 – 10:45 AM	Outcomes of Vestibular Schwannoma Surgery at Two Medical Centers: Advantages of Multimodality Intraoperative Facial Nerve Monitoring. Robert L. Martuza, SA Khan, A Khan, SR Ronner
10:45 – 11:00 AM	The Acute Central Cervical Spinal Cord Injury Revisited: Evidence-Based Guidelines for the Management of Acute Cervical Spinal Cord Injuries. Mark N. Hadley
11:00 – 11:15 AM	Epidemiology of Primary Brain Tumors: Current Concepts and Review of the Literature. M. Wrensch, Y. Minn, T. Chew, M. Bondy, Mitchel S. Berger
11:15 – 11:30 AM	Glial Cell-Line Derived Neurotrophic Factor (GDNF) Treatment Increases Remote Neuronal Proliferation After a Focal Stroke. R.J. Dempsey, KK Bowen, KA Sailor, RL Vemuganti
11:30 – 11:45 AM	Injury Induced Alterations in Hippocampal Circuitry. M. Sean Grady, A. Cohen, J. Lifshutz

THURSDAY, OCTOBER 17 (continued)

11:45 AM – 12:00 PM	Increased Beta-Catenin Transcription in PNET Cell Lines. S Chiappa, S McDonough, Y Zheng, Corey Raffel
12:00 – 12:15 PM	Microvascular Decompression: The Cost-Effective Surgery for Trigeminal Neuralgia. Bruce E. Pollock, RD Ecker, DA Gorman
12:15 – 12:30 PM	Genomic Disorder and the Origin of Glioblastomas. Joseph M. Piepmeier

FRIDAY, OCTOBER 18	**Moderator: James T. Rutka**
INVITED LECTURESHIP:	**Restoration of Function in the Central Nervous System, Part II**
7:30 – 8:15 AM	Repairing the Damaged Spinal Cord: From Stem Cells to Activity-Based Recovery Programs. John W. McDonald
8:15 – 8:30 AM	Discussion
8:30 – 8:45 AM	Mortality Following Subarachnoid Hemorrhage Varies with Hospital Case Volume. DWT Cross, DL Tirschwell, MA Clark, D Tuden, Ralph G. Dacey
8:45 – 9:00 AM	Hyperbaric Oxygen is an Effective Treatment for Radiation Necrosis of the Brain. Ronald E. Warnick, LB Gesell, J Racadio, JC Breneman
9:00 – 9:15 AM	Tyrosine Phosphorylation of the NMDA Receptor During Experimental Ischemia. M. Christopher Wallace, HH Cheung, L Teves, JW Gurd
9:15 – 9:30 AM	Multiple Subpial Transections in the Treatment of Pediatric Epilepsy. J Blount, H Otsubo, OC Snead III, James T. Rutka
9:30 – 9:45 AM	Management of Spinal Implant Costs: A Model for Surgeon Participation. Iain H. Kalfas, C Soska, JF Hahn
9:45 – 10:00 AM	Correction of Posttraumatic Hypoxia with Trans Sodium Crocetinate Following Experimental Traumatic Brain Injury. JA Jane Sr, J Gainer, J Wagner, JR Stone, David O. Okonkwo
10:00 – 10:30 AM	Coffee Break

FRIDAY, OCTOBER 18 (continued)

10:30 – 10:45 AM	A Prospective Study of Decision-Making in Spetzler-Martin Grade 4 and 5 Arteriovenous Malformations. PP Han, FA Ponce, Robert F. Spetzler
10:45 – 11:00 AM	Liquid Embolic Agents for the Treatment of Cerebral Aneurysms. Lee R. Guterman, LN Hopkins
11:00 – 11:15 AM	Long Term Results of Surgical Management of Rathke's Cleft Cysts. Martin H. Weiss, D Hinton, D Cummings, P Singer, WT Couldwell
11:15 – 11:30 AM	CT-Demonstrated Infarcts after Surgical and Endovascular Treatment of Aneurysmal Subarachnoid Hemorrhage. Christopher S. Ogilvy, BL Hoh, WT Curry Jr, BS Carter
11:30 – 11:45 AM	**ACADEMY AWARD PAPER** Combined Expression of Sonic Hedgehog and c-MYC Induces Medulloblastoma in Mice. Ganesh Rao
11:45 AM – 12:00 PM	**ACADEMY AWARD HONORABLE MENTION** Autologous Adjuvant Linked Fibroblasts Induce Anti-glioma Immunity: Implications for Development of a Glioma Vaccine. Andrew T. Parsa, JI Miller, A Eggers, AT Ogden III, RC Anderson, JN Bruce
12:00 – 1:00 PM	**PRESIDENTIAL ADDRESS** Naval Aviation and Neurosurgery: 2 Lives. Donald O. Quest

SATURDAY, OCTOBER 19 **Moderator: Jon H. Robertson**

INVITED LECTURESHIP:	**Restoration of Function in the Central Nervous System, Part III**
7:30 – 8:15 AM	Neurosurgery for Restoring and Optimizing Function: The Future Is Not What It Used To Be. Andres Lozano
8:15 – 8:30 AM	Discussion
8:30 – 8:45 AM	A Comparison of Endovascular and Surgical Treatment of Basilar Tip Aneurysms. G Tang, E Ley, H Clott, M Cowley, J Dion, Daniel Barrow
8:45 – 9:00 AM	Use of a Vaccine Strain of Measles Virus Genetically Engineered to Produce CEA as a Novel Therapeutic Agent Against Glioblastoma Multiforme. Loi K. Phuong, C Allen, K-W Peng, C Giannini, C TenEyck, S Russell, E Galanis
9:00 – 9:15 AM	Hemorrhage Complicating Brain AVM Surgery. Michael K. Morgan
9:15 – 9:30 AM	Phase Reset in Human iEEG During Working Memory. Joseph R. Madsen, M Kahana, D Rizzuto
9:30 – 9:45 AM	Unruptured Intracranial Aneurysms: Decision Analysis and Clinical Trials. Robert E. Harbaugh, A Papavasiliou, GD Pope
9:45 – 10:00 AM	Communications Between Malignant Glioma Cells and Vascular Endothelial Cells Via Gap Junctions. Joseph A. DeMattia, W Zhang, WT Couldwell
10:00 – 10:15 AM	Coffee Break

SATURDAY, OCTOBER 19 (continued)

10:15 – 10:30 AM	Radiosurgery Increases the Role of Neurosurgery in the Management of Metastatic Brain Cancer. L. Dade Lunsford, D Kondziolka, JC Flickinger
10:30 – 10:45 AM	Novel Molecular Mechanisms in Cervical Spondylotic Myelopathy: Implications for Innovative Therapeutic Interventions. Michael G. Fehlings
10:45 – 11:00 AM	Frameless Stereotactic Placement of Depth Electrodes for Epilepsy Using the Stealth Station Surgical Navigation System. Theodore H. Schwartz
11:00 – 11:15 AM	Preliminary Results of Convection Enhanced Delivery of TP38 for the Treatment of Infiltrating Gliomas. Allan H. Friedman, DA Reardon, JH Sampson
11:15 – 11:30 AM	Effect of Duraplasty on Collagen Scar Formation and Cystic Cavitation Following Acute Spinal Cord Laceration. Christopher B. Shields, YP Zhang, C Ianotta, Y Han, LBE Shields, DA Burke, X-M Xu
11:30 – 11:45 AM	Necrosis and Glioblastoma: Pathogenesis and Significance. Raymond Sawaya, S Raza, G Fuller, K Hess, W Zhang
11:45 AM – 12:00 PM	MRI Findings in Patients with Failed Operations for Chiari Type I Malformation. Peter W. Carmel, JA Bello
12:00 – 12:15 PM	Differential Gene Expression in Human Cerebral Vascular Malformations. R Shenkar, JP Elliott, K Diener, J Gault, L-J Hu, R Cohrs, L Hunter, Issam A. Awad

SATURDAY, OCTOBER 19 (continued)

12:15 – 12:30 PM	Use of Replication Competent Retroviruses Containing the Suicide Gene Cytosine Deaminase in the Treatment of Malignant Gliomas. Thomas C. Chen, W-J Wang, C-K Tai, N Kasahara
12:30 – 12:45 PM	Post-Ischemic Mild Hypothermia Prolongs the Time Window for Bcl-2 Gene Therapy Protection Against Focal Cerebral Ischemia. Gary K. Steinberg, H Zhao, MA Yenari, RM Sapolsky
12:45 – 1:00 PM	Folic Acid Supplementation Improves CNS Regeneration and Outcome after Spinal Cord Injury in Rats. Bermans J. Iskandar, DK Resnick, N Hariharan, P Gao, A Nelson, C Johnson, CF Cechvala

THURSDAY PROGRAM

THURSDAY, OCTOBER 17 **8:30 –8:45 AM**

A Blinded, Randomized Comparison of GPi vs. STN Stimulation in Advanced Parkinson's Disease

K. Burchiel, J Hammerstad, V Anderson, J Favre, P Hogarth

For practical and theoretical reasons, the subthalamic nucleus (STN) is favored over globus pallidus internal (GPi) as the target for deep brain stimulation (DBS). However, in a blinded, randomized pilot study comparing the two sites we found no difference in clinical efficacy (Burchiel et al. *Neurosurgery* 1999; 45:1375-1384). As a continuation of that study, we now report 12 month follow-up on 18 patients randomized to receive DBS in either the GPi (9 patients) or STN (9 patients). A total of 21 patients were randomized, but 1 death unrelated to the procedure, a severe perioperative stroke, and an unexplained rapid neurologic deterioration prevented acquisition of complete data for 3 patients.

At 12 months, the effect of stimulation alone showed the same improvement in motor UPDRS scores for GPi (44 ± 20%) and STN (44 ± 17%). There was a trend for greater improvement in bradykinesia ($P < 0.15$) and gait ($P < 0.08$) for STN vs. GPi. This was also suggested by the patients' visual analogue scale assessment ($P < 0.10$ for walking, $P < 0.13$ for slowness, $P < 0.07$ for balance). There was no difference between target sites in the overall reduction in dyskinesia ($P < 0.001$ for baseline vs. 12 month on/on) as a result of DBS. After 12 months of DBS, there was a 48% reduction of L-DOPA dose equivalents required for the optimum treatment of STN stimulated patients and no change in dose for the GPi group. The stimulation charge density required for maximum clinical benefit was also lower for DBS of STN than GPi ($P < 0.05$) and increased over the 12 months to a greater degree among GPi patients.

Thus, as others have noted, DBS of STN has some practical advantages over DBS of GPi. STN stimulation requires less power (hence greater battery life) and allows a reduction in medication. However, there was no difference between the targets in clinical efficacy as assessed by the total motor UPDRS, although there was a trend in favor of STN for improvement of bradykinesia and gait. Theoretically, STN stimulation may also provide a neuroprotective benefit, but over the short duration of this study there was no difference between targets in the rate of disease progression as assessed in the off/off state.

Microvascular Decompression for Severe Essential Hypertension: Introduction of a Prospective Controlled Study

Rudolf Fahlbusch, R Naraghi, H Frank

Following Jannetta's first successful experiences on neurovascular decompression in essential hypertension in a retrospective study (1), we initiated in 1995 a prospective protocol together with the department of Nephrology-Medicine of the University of Erlangen-Nuremberg (2,3).

Methods: In accordance to the requirements of the protection of human live and approved by the ethic commission, selection criteria were established, including diagnosis of essential hypertension with a severe course, resistant to medical treatment, detection of abnormal neurovascular contacts at the ventrolateral medulla oblongata by MRT imaging and 3D-visualisation (2,3). As exclusion criteria are renal fixation of hypertension, generalized vascular sclerosis, other vascular malformations in the central nervous system, malignant neoplasm and reduced general medical condition grade 3-4 according to the ASA encountered. Surgery consists of a standard approach to the lower cerebello pontine angle, exploration of the neurovascular relations and microvascular decompression of the ventrolateral medulla and the root entry/exit zone of the cranial nerves IX & X (4). Patient selection for surgery and evaluation of treatment success is carried out independently by the Department of Nephrology–Medicine based on regular follow up examinations every 4-6 months.

Results: In 14 patients we correlate and discuss issues regarding selection, imaging, surgical findings and possible prognostic value of different patterns in the postoperative course of blood pressure (4). Follow up ranges from 4 months up to 7 years with a mean observation period of 4,5 years. Microvascular decompression has been shown to be effective in 12 cases on short term (2) with normalization of blood pressure. On long term we observe an improvement and normalization with a significant reduced medication in 3 out of 8 long term cases with severe hypertension and even almost free of medication in additional 2 cases.

Conclusion: We found support for Jannetta's theory of an association between neurovascular compression and arterial hypertension and advocate to continue collecting more experiences in further carefully conducted prospective controlled multicenter studies.

THURSDAY, OCTOBER 17 **9:00 – 9:15 AM**

Durability of Carotid Endarterectomy

Fredric B. Meyer, WL Windschitl, RD Ecker

One thousand consecutive carotid endarterectomies were followed prospectively with yearly carotid ultrasounds to determine the incidence of restenosis. There were 680 men and 320 women with an average age of 69 ± 6 years. In all cases the arteriotomy was repaired with a patch graft. The 30-day major morbidity and mortality rate was 2.2%. Specifically, there were 4 major strokes, 9 minor strokes with subsequent good to excellent recovery, and 9 deaths. In these 9 deaths, three were cardiac in origin, 4 were secondary to an intracerebral hemorrhage, and 2 were from perioperative strokes in which one occurred during intubation and the other from a documented heparin induced hypercoagulable state. In the follow-up period with a mean of 7 years (range 2-10 years), there were 10 recurrent stenosis of greater than 70%. Compared to the published results regarding carotid angioplasty and stenting, this data demonstrates that carotid endarterectomy is superior to current endovascular techniques with a lower peritreatment complication rate and superior durability.

THURSDAY, OCTOBER 17 **9:15 – 9:30 AM**

Meta-Analysis of Carotid Endarterectomy Trials for Symptomatic Stenosis

Marc R. Mayberg, the Carotid Endarterectomy Trialists Collaborative Group (CETCG)

Three prospective, randomized trials demonstrated that carotid endarterectomy (CEA) provided significant stroke risk reduction for patients with symptomatic carotid stenosis. Because these trials were designed with complementary methodology, a consortium database was established.

All symptomatic patients randomized in the last 20 years from the European Carotid Surgery Trial (ECST); North American Symptomatic Carotid Endarterectomy Trial (NASCET); and Veterans Affairs trial (VA#309) were studied. Data were pooled from the original electronic data files, and certain screening and outcome measures were re-analyzed by uniform criteria to achieve comparability.

Among 6092 patients with 35,000 patient-years of follow-up, surgery increased the 5-year risk of *ipsilateral ischemic stroke* in patients with <30% stenosis (n=1746, absolute risk reduction - ARR = -2.2% p=0.05), had no significant effect in patients with 30-49% stenosis (n=1429, ARR = 3.2%, p=0.6), was of slight benefit in patients with 50-69% stenosis (n=1549, ARR = 4.6%, p=0.04), and was highly beneficial in patients with ≥70% stenosis without near-occlusion (n=1095, ARR = 16.0%, p<0.001). However, there was evidence of less benefit in patients with the most severe disease (near-occlusions). Among 1728 surviving post-operative patients in ECST followed for 3-14 years (median=6.0 years), the 10-year risk of disabling ipsilateral ischemic stroke and any ipsilateral ischemic stroke were 4.4% (95% CI = 3.0-5.8) and 9.7% (95% CI = 7.6-11.7), respectively. Severity of angiographic stenosis, plaque morphology and use of a patch graft during the endarterectomy were unrelated to long-term stroke risk.

Combined analysis of the CEA trials for symptomatic stenosis yielded highly consistent results. Surgery is of some benefit for 50-69% symptomatic stenosis, highly beneficial for ≥70% stenosis, and of uncertain benefit in patients with carotid near-occlusion. The risk of any ipsilateral ischemic stroke following surgery is only 1% per year, and the risk of disabling events is less than 0.5% per year.

Spetzler-Martin Grade III Arteriovenous Malformations: Surgical Results and a Modification of the Grading Scale

Michael T. Lawton

Objectives: To analyze surgical results of the highly variable Spetzler-Martin grade III arteriovenous malformations, to demonstrate that outcomes vary between different types of grade III lesions, and to introduce a simple modification of the grading scale that might improve its utility for these AVMs.

Methods: In a consecutive series of 168 brain AVMs resected in 168 patients over 4.8 years, 76 (45.2%) AVMs were grade III. There were 35 (46.1%) small (S1V1E1), 14 (18.4%) medium-deep (S2V1E0), and 27 (35.5%) medium-eloquent (S2V0E1). No large grade III AVM (S3V0E0) was treated.

Results: Complete AVM resection was accomplished in 74 patients (surgical obliteration rate, 97.4%). Permanent treatment-associated neurological morbidity occurred in 3 patients (3.9%) and three patients died (surgical mortality, 3.9%). Good outcomes (Rankin score ≤ 2) were observed in 57 patients (79.5%). Surgical risks (new deficit or death) by grade III type were: 3.0% for S1V1E1; 7.7% for S2V1E0; 14.8% for S2V0E1.

Conclusions: Grade III AVMs should be viewed as a heterogeneous entity with each type possessing different surgical risks, and the Spetzler-Martin grading scale can be modified accordingly. Grade III– AVMs, or S1V1E1 lesions, have a surgical risk similar to low-grade AVMs and can be treated safely with microsurgical resection. Grade III+ AVMs, or S2V0E1 lesions, have a surgical risk similar to high-grade AVMs and are best managed conservatively. Other grade III AVMs either require judicious patient selection (S2V1E0 lesions) or are exceedingly rare with a surgical risk that is unclear (S3V0E0 lesions).

THURSDAY, OCTOBER 17 **9:45 – 10:00 AM**

Effects of Increased Use of Endovascular Approaches and Hospital Volume on Treatment Outcome for Cerebral Aneurysms: New York State Experience 1995 -2000

MF Berman, Robert A. Solomon, SA Mayer, P Yung, ES Connolly

Introduction: Since 1995, the growth of neuroendovascular surgery for cerebral aneurysms has dramatically changed treatment paradigms. This study investigates the independent contribution of increased use of endovascular techniques on the overall morbidity and mortality of treating cerebral aneurysms.

Methods: The SPARCS database of New York was reviewed for all patient discharges between 1995 and 2000 with diagnosis code for subarachnoid hemorrhage (SAH) or unruptured aneurysm and procedure codes: surgical clipping, endovascular therapy, or craniotomy for wrapping. Adverse outcome was assessed as discharge to any facility other than home. Mortality, length of stay (LOS), and total charges were also evaluated.

Results: Between 1995 and 2000, the percent of patients treated endovascularly increased from 2.9% to 14.8% for SAH; and 12.9% to 24.2% for unruptured aneurysms.
For unruptured aneurysms, multivariate analysis showed that increasing hospital volume of procedures for aneurysms was associated with decreased adverse outcomes, deaths, and LOS. The percent of aneurysms treated with embolization correlated independently with decreased adverse outcomes and LOS, but not with mortality.

For SAH patients, increasing volume decreased adverse outcomes and death but not LOS. Percent embolization was correlated with increased total charges only.

Conclusions: The growth of endovascular therapies has been correlated with decreased adverse outcomes and LOS for unruptured aneurysms, but no change in outcome for ruptured aneurysms. Hospital volume of aneurysms treated continues to be the most significant factor predicting reduced morbidity and mortality. A move towards greater regionalization of aneurysm treatment is suggested by this data.

THURSDAY, OCTOBER 17 **10:00 - 10:15 AM**

ApoE e4 Predicts Cognitive Injury Following Carotid Endarterectomy

E. Sander Connolly, Jr.

Background: Clinical trials have convincingly demonstrated that endarterectomy (CEA) reduces the long term risk of stroke in patients with high grade extra-cranial carotid artery stenosis. Nevertheless, neuropsychometric (NPM) tests show that as many as 25% of CEA patients show significant cognitive deterioration compared to matched surgical controls and that this deterioration is accompanied by elevations in serum markers of cerebral injury such as S100-B. Together these findings have led us to propose CEA as a human model of subclinical stroke which can be used to develop neuroprotective pharmaceutical strategies. In an effort to increase the power of this model we sought to identify genetic risk factors for cognitive deterioration. As apolipoproteinE (ApoE) e4 is a risk factor for cognitive deterioration following cardiopulmonary bypass, potentially due to the failure of e4 to attenuate immune-mediated neuronal injury, we hypothesized that ApoE genotype (ApoE e4) will predict cognitive deterioration one day after CEA owing to its failed role in immunomodulation.

Methods: Forty patients undergoing CEA and 45 age-matched patients having spine surgery were subjected to NPM testing before and 1 day after surgery. Injury in the CEA cohort was defined total deficit score greater than 2 S.D. above the mean for the control cohort. ApoE genotyping was performed by RFLP. Serum concentrations of S100-B were analyzed using commercially available, monoclonal, two-site, sandwich immuno-luminometric assay. Baseline concentrations of S100-B were subtracted out from preclamp, 30 minute, and 24 hour values to compensate for any shift in scale that might have occurred. Total deficit scores for ApoE e4 carriers and non-carriers were compared by Mann-Whitney Test. The frequency of e4 carriers amongst 'injured' patients was assessed by Fisher's Exact Test. Patient demographics were analyzed with Student's T-Test, Mann-Whitney Test, Chi-Square Test, and Fisher's Exact Test where appropriate. ApoE genotype and change from baseline of S100-B were analyzed by Mann-Whitney test.

Results: There were no statistically significant differences between injured and uninjured patients in any demographic variable despite a trend for greater percentage of men having injury. There were 9 (11.25%) carriers of ApoE e4 in the group and no 4/4 homozygotes. Frequencies of E2 (.14), E3 (.75), and E4 (.11) were consistent with those observed in larger studies.

ApoE e4 carriers had significantly higher total test deficit scores by Mann-Whitney test (p=0.04). In the dichotomous injury assessment, 80% of patients carrying ApoE e4 were injured while only 35% of patients carrying other polymorphisms were injured (p=0.1 due to sample size). Preoperative test scores did not significantly differ between ApoE e4 carriers and non-carriers or between injured and uninjured patients for any NPM test. Preoperative and preclamp S100-B data was available for 18 patients. ApoE e4 carriers had significantly elevated S100-B concentrations compared to non-carriers at preclamp (p=0.04). The 30 minute and 24 hour elevations were also greater in e4 carriers but this failed to reach significance (p=NS).

Conclusion: Together these data suggest that ApoE e4 is a risk factor for cognitive decline following CEA. ApoE e4 is also associated with elevations in preclamp serum S100-B, suggesting unmodulated inflammatory response leading to blood brain barrier instability. Elevations in serum S100-B at 30 minutes and 24 hours after cross-clamp were also associated with ApoE e4, though this association failed to reach statistical significance. It is likely that these later elevations are the result of injury mediated by hypoperfusion and thromboembolism as well, thereby diluting the effects of genetic risk. The effect of ApoE e4 on perioperative cognitive decline is not due to poor or borderline preoperative cognitive function. Restricting drug trials to ApoE e4 patients or controlling for this polymorphism may dramatically improve the power of this model to detect pharmacologically induced improvements in outcome.

THURSDAY, OCTOBER 17 **10:30 - 10:45AM**

Outcomes of Vestibular Schwannoma Surgery at Two Medical Centers: Advantages of Multimodality Intraoperative Facial Nerve Monitoring

Robert L. Martuza, SA Khan, A Khan, SR Ronner

We reviewed the medical records, radiographic studies, pathology reports, and audiograms to assess facial nerve outcomes, hearing preservation, involvement of other cranial nerves, postoperative complications and functional outcomes of 200 patients who underwent vestibular schwannoma surgery by the same neurosurgeon (RLM) at two medical centers over 20 years employing two different monitoring technologies and report in detail the results of 164 undergoing surgery by the suboccipital route. Tumors were defined by the largest diameter on MRI or CT as large (> 3 cm), medium (2.1 to 3 cm) and small (≤2 cm). Facial nerve function was defined using the House-Brackmann grading system. Hearing preservation was defined using the new Hanover classification. Intraoperative facial nerve monitoring in both Center 1 and 2 utilized standard EMG assessed from the orbicularis oculi and the orbicularis oris and an intra-operative monopolar hand-held nerve stimulator. At Center 1 two additional facial nerve monitoring techniques were utilized: 1, a closed-circuit camera to view the ipsilateral face; 2, a motion sensor on the face.

Preoperative hearing class was positively correlated with postoperative hearing preservation ($p<0.001$). Overall, in patients with pre-operative hearing operated by the suboccipital approach, some hearing preservation (H1-H4) was achieved in 41% of patients with medium tumors and 80% of patients with small tumors. More important to the patient is preservation of hearing with 40% or greater speech discrimination (H1 to H3). Patients with medium and small sized tumors who presented with preoperative hearing ranging from class H1 to class H3 and were operated upon by the suboccipital approach had 43% and 84% chance respectively that their hearing would be maintained within hearing classes H1 to H3. Comparison of patients with small tumors and preoperative hearing ranging from class H1 to class H3 who were operated upon by the suboccipital approach revealed no difference in hearing preservation between Center 1 (85%) vs. Center 2 (83%).

Tumor size was positively correlated with facial nerve grade immediately postoperatively ($p< 0.04$), at 2 to 3 months postoperatively ($p<0.02$) and at 2 to 3 years postoperatively ($p<0.02$). Overall, good facial nerve outcome (Grade 1 or 2) was achieved at 2 to 3 years for 80% large, 90% medium and 99% small tumors. However, a significantly higher proportion of patients

with large tumors operated on at Center 1 had excellent (Grade 1) facial nerve outcomes immediately postoperatively (50% vs. 31%) ($p \leq 0.03$), 2 to 3 months postoperatively (55% vs. 35%) ($p \leq 0.02$), and 2 to 3 years postoperatively (77% vs. 53%) ($p \leq 0.01$). Also, a higher proportion of patients with medium sized tumors operated on at Center 1 had Grade 1 facial nerve outcomes at 2 to 3 years postoperatively compared to patients with medium sized tumors operated on at Center 2 (93% vs. 73%) ($p \leq 0.03$). For small sized tumors, there was no significant difference in facial nerve outcome at any time point between the two centers.

We suggest that the addition of multimodality monitoring allows facial nerve function to be assessed even during the periods of time that bipolar cautery is used and adds a level of sensitivity to the monitoring that aids in the preservation of excellent facial nerve outcome in medium and large acoustic neuromas.

THURSDAY, OCTOBER 17 **10:45 - 11:00 AM**

The Acute Central Cervical Spinal Cord Injury Revisited: Evidence-Based Guidelines for the Management of Acute Cervical Spinal Cord Injuries

Mark N. Hadley

Central spinal cord injuries are among the most common, well-recognized spinal cord injury patterns identified in neurologically injured patients after acute trauma. Originally described by Schneider et al in 1954, this pattern of neurologically incomplete spinal cord injury is characterized by disproportionately more motor impairment of the upper than of the lower extremities, bladder dysfunction and varying degrees of sensory loss below the level of the lesion. It has been associated with hyperextension injuries of the cervical spine, even without apparent damage to the bony spine, but has also been described in association with vertebral body fractures and fracture-dislocation injuries. The natural history of acute central cervical spinal cord injuries indicates gradual recovery of neurological function for most patients, albeit usually incomplete and related to the severity of the original injury and the age of the patient. Schneider et al stated that "surgery for these patients is contraindicated, and in fact, known to harm rather than improve them."

An extensive medical evidence-based literature review on this subject exposes the reasoning behind Schneider's conclusions and sheds light on the pathophysiology of acute central spinal cord injuries and their ultimate outcome. Indeed, the long-term outcome for these injuries is typically worse than commonly thought. Aggressive medical management and surgery appear to have important roles in the contemporary management of patients with these injuries. Treatment strategies that appear to optimize the potential for recovery following acute cervical spinal cord injuries of all types (including central cord injuries) will be presented.

THURSDAY, OCTOBER 17 **11:00 - 11:15 AM**

Epidemiology of Primary Brain Tumors: Current Concepts and Review of the Literature

M Wrensch, Y Minn, T Chew, M Bondy, Mitchel S. Berger

In this discussion, a review of the current concepts of brain tumor epidemiology will be presented. Molecular tumor markers are being identified that predict survival and treatment response with hope of even greater gains in this area with emerging array technologies. Regarding risk factors, studies of inherited susceptibility and constitutive polymorphisms in genes pertinent to carcinogenesis (e.g., DNA repair and detoxification genes and mutagen sensitivity) have revealed provocative findings. Inverse associations of history of allergies with glioma risk observed in three large studies and reports of inverse associations of glioma with common infections suggest a possible role of immune factors in gliomagenesis or progression. Studies continue to suggest that brain tumors might result from workplace, dietary, and other personal and residential exposures, while studies of cell phone use and power frequency electromagnetic fields have found little to support a causal connection with brain tumors, yet caveats remain. The only proven causes of brain tumors (i.e., rare hereditary syndromes, therapeutic radiation, and immune suppression giving rise to brain lymphomas) account for a small proportion of cases. Progress in understanding primary brain tumors might result from studies of well-defined histologic and molecular tumor types incorporating assessment of potentially relevant information on subject susceptibility and environmental and non-inherited endogenous factors (viruses, radiation, and carcinogenic or protective chemical exposures through diet, workplace, oxidative metabolism, or other sources). Such studies will require cooperation of researchers from many disciplines. As the field of epidemiology and population sciences evolves, it is critical for neurosurgeons to be aware of risk factors associated with brain tumors.

Glial Cell-Line Derived Neurotrophic Factor (GDNF) Treatment Increases Remote Neuronal Proliferation After a Focal Stroke

R.J. Dempsey, KK Bowen, KA Sailor, RL Vemuganti

Focal cerebral ischemia increases cell proliferation in the hippocampal dentate gyrus (DG) of adult rats. Following ischemia, GDNF receptor expression upregulates and exogenous GDNF decreases ischemic neuronal damage. The present study evaluated whether GDNF further increases ischemia-induced cell proliferation in DG. Focal ischemia was induced in adult SHR rats by transient middle cerebral artery occlusion (MCAO). GDNF (200 ng/day) or aCSF was infused for one week into the left lateral ventricle starting immediately after MCAO. Sham-operated rats infused with aCSF or GDNF served as controls. The cell proliferation specific marker bromodeoxyuridine (BrdU) was injected (i.p.) twice a day for 6 days. Rats were sacrificed one day after the last injection and the BrdU immunopositive cells were quantitated in the subgranular and granular cell layers of DG. MCAO significantly increased (by 3 fold, $p<0.05$) the BrdU positive cell number in the ipsilateral DG and GDNF infusion resulted in a further 2 fold increase in the BrdU positive cell number. GDNF had no effect on the BrdU positive cell number in the DG of sham-operated rats. Thus, the present study shows that stroke in adult rats can induce progenitor cell proliferation in hippocampal DG, an area remote from the ischemic insult and the proliferating cells are GDNF responsive in ischemic brain. The effect of GDNF is in contrast to IGF-1, which stimulates DG progenitor cell proliferation in both ischemic non-ischemic rats. Exogenous GDNF can help the natural healing response of adult rat brain following an ischemic insult.

THURSDAY, OCTOBER 17 **11:30 - 11:45 AM**

Injury Induced Alterations in Hippocampal Circuitry

M. Sean Grady, A Cohen, J Lifshutz

Traumatic brain injury (TBI) is a major cause of death in the United States. TBI patients suffer cognitive deficits including impaired learning and memory. The hippocampus, a structure crucial in learning and memory function, is damaged in TBI. The fluid percussion injury technique causes cognitive impairment in animals and has been adapted to mice. We take advantage of inherent differences in mouse strains recognized to have alterations in excitability (C57BL/10) and resistance to excitotoxic hippocampal neuron loss (C57BL/6) to explore hippocampal dysfunction following FPI.

Mice were injured and analyzed 1 week later for spatial memory deficits using a context fear conditioning paradigm. Injured C57BL/6mice showed significantly decreased freezing time suggesting hippocampal injury. This finding may be accounted by changes in hippocampal circuitry and analyses were undertaken in the in vitro slice preparation using field and single cell recording n dentate gyrus and CA1. The dentate proved to be hyperexcitable and CA1 hypoexcitable, evidence for the notion that seizures that follow TBI may have a substrate in dentate gyrus, while the inability to form spatial memories may be a result of decrease output from the CA1 to the limbic system. Immunochemistry showed selective changes in inhibitory neurons that would control extent of activation. Stereologic techniques showed exacerbated loss of CA1 neurons in C57BL/10 animals, compared to C57BL/6, as predicted by the BL/10 strain's inability to handle calcium load.

These results reveal that an episode of moderate to severe FPI influences mouse hippocampal function and circuitry. The impact is manifested in a unique spatial manner, disrupting the delicate balance between inhibition and excitation that is crucial for normal hippocampal function. Furthermore, these regional disequilibria may underlie the cognitive impairments frequently associated with both FPI and TBI.

THURSDAY, OCTOBER 17 **11:45 AM - 12:00 PM**

Increased Beta-Catenin Transcription in PNET Cell Lines

S Chiappa, S McDonough, Y Zheng, Corey Raffel

Oncogenic alterations of beta-catenin, leading to increased beta-catenin/Tcf directed transcription, have been described in a small (7.5%) subset of sporadic medulloblastomas. Nuclear localization of beta-catenin, a marker for such transcription, has been demonstrated in 36.4% of medulloblastoma tumor samples. In this study, we have investigated the activity of the beta-catenin/Tcf transactivator in PNET cell lines. All cell lines examined contain hypophosphorylated beta-catenin in their cytoplasm. As beta-catenin must be hyperphosphorylated to be degraded, this result suggests that undegraded, free beta-catenin may be available for complexing to Tcf in the nucleus of these cell lines. To examine this possibility, we permanently transfected PNET cell lines with two Tcf reporter constructs. The first, TOPFLASH, contains a c-fos promoter in front of a luciferase reporter gene. In front of this promoter are a series of 3 consensus Tcf binding sites. The second, FOPFLASH, is an identical construct except that each of the 3 Tcf binding sites has been altered at a single base. We have examined 6 cell lines for beta-catenin/Tcf transcriptional activity using this method. Two (33%) cell lines (H425 and 458) showed dramatically increased transcription of TOPFLASH compared with FOPFLASH, based on luciferase assays. The activity ratio for these 2 cells lines is similar to that obtained with SW480, a colon carcinoma cell line with unregulated beta-catenin/Tcf-directed transcription. The degradation pathway for beta-catenin involves its being incorporated into a multi-protein complex that includes APC, GSK-3beta, axin 1 and axin 2. To determine whether the increased free beta catenin in the cells lines is related to decreased phophoprylation of beta-catenin by GSK-3beta in this complex, we precipitated the complex with anti-axin 1 antibody. Immunoprecipitation of cell lysates with this antibody, followed by immunoprecipitation of the supernatent with either anti-beta-catenin or anti-GSK-3beta antibodies, revealed that the GSK-3beta in the complex is heavily phosphorylated on serine 9. As serine 9 phosphorylation results in dramatically decreased kinase activity, this result suggests that one mechanism responsible for the increased beta-catenin/Tcf directed transcription in medulloblastomas is decreased phosphorylation of beta-catenin by GSK-3beta, leading to decreased beta-catenin degradation.

Microvascular Decompression: The Cost-Effective Surgery for Trigeminal Neuralgia

Bruce E. Pollock, RD Ecker, DA Gorman

A number of operations are used to manage patients with medically unresponsive trigeminal neuralgia. The purpose of this study was to compare the relative efficacy and cost-effectiveness of microvascular decompression (MVD), glycerol rhizotomy (PRGR), and stereotactic radiosurgery (SR).

Between July 1999 and June 2001, 101 patients with idiopathic trigeminal neuralgia underwent 120 operations (MVD, n=23; PRGR, n=39; SR, n=58). Mean age was 66.7 years; 70 patients (58%) had recurrent pain (mean, 1.7 prior surgeries). Pre-operative characteristics were similar between the groups with respect to pain duration, prior surgeries, and atypical features; the MVD group was younger (54.1 years vs. 69.6 years, $P<0.001$). Outcomes were classified as excellent (no pain, no meds), good (no pain, reduced meds), fair (>50% pain reduction), and poor. Mean follow-up was 18.2 months.

Patients having MVD more commonly achieved and maintained an excellent outcome (83% and 79% at 6 and 24 months, respectively) compared to PRGR (64% and 55%, $P=0.05$) and SR (59% and 50%, $P=0.01$). No difference was detected between PRGR and SR ($P=0.43$). The cost per quality adjusted pain-free year was $3800, $8561, and $9538 for PRGR, MVD, and SR, respectively. The cost-effectiveness of MVD was similar to PRGR ($P=0.17$) and SR ($P=0.57$); PRGR was more cost-effective than SR ($P<0.05$).

Despite costing between 42% and 230% more than the other surgeries, MVD was equally cost-effective due to its greater efficacy and low pain recurrence rate. Based on historical controls, MVD should prove to be the most cost-effective operation when patients are followed for longer intervals.

Genomic Disorder and the Origin of Glioblastomas

Joseph M. Piepmeier

Two of the most important current concepts in neuro-oncology are: 1) primary glioblastomas are associated with specific genetic mutations, and, 2) there appear to be a separate set of genetic mutations that mark the progression from low-grade to high-grade lesion. While these concepts are highly informative, they fail to account for the fact that glioblastomas contain numerous random deletions, amplifications and even loss of entire chromosomes. The current models of evolution of a glioblastoma do not address the temporal and spatial variability in the genomic profile within each tumor. Furthermore, selective growth advantages from loss of a tumor suppressor gene would promote a more uniform phenotype whereas, a single glioblastoma cell can give rise to populations with highly variable phenotypic and genotypic profiles. Finally, the product of one of the canonical tumor suppressor genes associated with gliomas (abnormal p53/mdm2 expression) can be detected in non-neoplastic CNS lesions. It is likely that isolated loss of a suppressor gene is insufficient for tumor formation.

These inconsistencies raise doubt that isolated changes in selected encoding segments of DNA are sufficient to explain the genomic chaos found in malignant gliomas. The above evidence also suggests that rapidly arising tumors like glioblastoma reflect loss of control over the genome. The cause of putative genomic disorder remains to be determined. Macromolecular changes in non-encoding DNA segments (alteration in telomeres) may promote instability by altering chromosome orientation during mitosis. This hypothesis would provide a unifying theory on the origin of glioblastoma and explain the genomic disorder that characterizes these tumors.

NOTES:

FRIDAY PROGRAM

FRIDAY, OCTOBER 18 **8:30 – 8:45 AM**

Mortality Following Subarachnoid Hemorrhage Varies with Hospital Case Volume

DWT Cross, DL Tirschwell, MA Clark, D Tuden, Ralph G. Dacey, Jr.

Background: For certain serious illnesses and surgical procedures, outcome has been associated with hospital case volume. There has been no study to determine whether in-hospital mortality is influenced by hospital case volume in a large population of SAH patients. The objective of this study was to determine whether hospital volume affects mortality rates in subarachnoid hemorrhage patients.

Design, Setting, and Patients: Retrospective all payor administrative database study of 16,399 total *SAH* discharges (9,290 admitted through the emergency room) from acute care hospitals in 19 states representing over 58% of the US population.

Main Outcome Measures: In-hospital mortality rates by total hospital volume quartile.

Results: Patients with SAH who are admitted to low volume hospitals have 1.4 ($P<.0001$) times the odds of dying in the hospital as patients admitted to high volume hospitals after controlling for patient age, gender, Medicaid status, hospital region, database year and co-morbid conditions.

Conclusions: Patients with SAH diagnosis on their discharge records who initially present to hospitals with high SAH volume have significantly lower mortality. Concentrating care for SAH in high volume centers could improve overall survival.

FRIDAY, OCTOBER 18 **8:45 – 9:00 AM**

Hyperbaric Oxygen is an Effective Treatment for Radiation Necrosis of the Brain

Ronald E. Warnick, LB Gesell, J Racadio, JC Breneman

Introduction: Hyperbaric oxygen (HBO) is an emerging treatment for radiation necrosis of the brain by virtue of its ability to reduce tissue edema, stimulate macrophage activity, and induce angiogenesis.

Methods: Twenty-nine patients developed clinical and radiographic evidence of necrosis after radiation therapy for tumor (16 gliomas, 8 metastases, 3 meningiomas, 1 neuroblastoma) or vascular malformation (1 AVM). Radionecrosis was diagnosed by metabolic imaging or biopsy in all tumor patients. Patients received HBO (100% O2 at 2.5 ATA for 90 min.) once every weekday for a total of 20-60 treatments depending on response.

Results: Previous radiation therapy consisted of one or more of the following: stereotactic radiosurgery (17), external beam radiotherapy (21), and I-125 seed implantation (11). All patients had progressive focal neurological deficits (KPS 40-80), increasing steroid requirements (mean dexamethasone 18mg/day), and MRI demonstrating an expanding ring-enhancing mass with extensive surrounding edema. HBO was well-tolerated and there were no cases of barotrauma or treatment-induced seizures. 17/29 patients (59%) experienced neurological improvement and decreased steroid requirement whereas 10/29 (34%) had stabilization of symptoms and steroid dose. Two patients progressed clinically and radiographically during the first month of treatment and were found to have tumor progression. MR scans of responders showed a typical pattern of initial decrease in perilesional edema followed by reduction in the volume of contrast enhancement.

Conclusions: Our experience demonstrates that HBO is a safe and effective treatment for patients with radiation necrosis and may eliminate the need for surgery in the majority of these patients.

FRIDAY, OCTOBER 18 **9:00 - 9:15 AM**

Tyrosine Phosphorylation of the N-Methyl-D-Aspartate (NMDA) Receptor During Experimental Ischemia

M. Christopher Wallace, HH Cheung, L Teves, JW Gurd

The involvement of the NMDA receptor in cerebral ischemia has been established but specific mechanisms of its role have not been determined. Experimental severe transient cerebral ischemia results in increased tyrosine phosphorylation of the NR2 subunits of the *N*-methyl-D-aspartate receptor (NMDAR). The contribution of Protein Kinase C (PKC) to this increase in tyrosine phosphorylation was investigated. Transient (15 minutes) global ischemia was produced in adult rats by four-vessel occlusion. After reperfusion, enhanced tyrosine phosphorylation of the NR2A and NR2B subunits occurred as well as enhanced association of phosphorylated, activated forms of PKC□/β_{II} with the postsynaptic protein PSD-95.

GF109203X (GF) was administered by intravenous injection immediately following the ischemic challenge to assess the role of PKC in tyrosine phosphorylation of the NMDAR. The PKC inhibitor GF inhibited the phosphorylation of NR1 by PKC and selectively reduced the ischemia-induced increases in tyrosine phosphorylation of NR2A and NR2B without affecting the increase in total tyrosine phosphorylation of hippocampal proteins. The inactive homologue of GF, bisindolymaleimide V, had no effect on these parameters.

The results are consistent with a role for PKC in the ischemia-induced increase in tyrosine phosphorylation of NR2A and NR2B.

FRIDAY, OCTOBER 18 **9:15 – 9:30 AM**

Multiple Subpial Transections in the Treatment of Pediatric Epilepsy

J Blount, H Otsubo, OC Snead III, James T. Rutka

Purpose: The technique of multiple subpial transections (MST) affords the epilepsy surgeon the capability to make disconnective lesions in epileptogenic regions of eloquent cortex. While there have been increasing numbers of reports in adults of the efficacy and relative safety of this technique, there are relatively few such reports in children. We present here our experience with 30 children who underwent MSTs during the surgical management of their seizure disorder.

Methods: Thirty consecutive children who underwent MST with or without cortical resection form the basis of this retrospective review. An analysis of neurological adverse effects following MSTs and seizure outcome was performed.

Results: From 1996-2000, MSTs were performed either as stand-alone therapy (4 patients), or in conjunction with planned cortical excisions (26 patients). Twenty-three children underwent invasive monitoring with subdural grid electrodes, and 7 had intra-operative electrocorticography alone. Mean follow up for the group was 3.0 years, and all had at least 24 months follow-up. All 20 who had MSTs in the primary or supplementary motor cortex demonstrated transient hemiparesis (mild 12, moderate 8) that lasted up to 6 weeks; however, no patient in this series demonstrated a permanent motor deficit in long term follow up. For 26 patients undergoing cortical resections followed by MSTs, 12 (46%) were seizure free (Engel Class I) following surgery. Eleven patients (42%) (Engel Class II and III) continued to have seizures but were significantly improved following surgery.

Conclusions: This series demonstrates that MSTs can be performed with acceptable morbidity in children undergoing epilepsy surgery. The precise role of MSTs in controlling seizure frequency and outcome, especially when combined with planned cortical resections, awaits further study.

FRIDAY, OCTOBER 18 **9:30 – 9:45 AM**

Management of Spinal Implant Costs: A Model for Surgeon Participation

Iain H. Kalfas, C Soska, JF Hahn

The surgical management of spinal disorders continues to evolve. Advances in spinal instrumentation technologies have greatly expanded the surgical options available to manage patients with complex spinal problems. These advances have led to a significant increase in the use of spinal implants over the past decade.

A growing problem associated with the use of spinal implants is their steadily increasing costs. Coupled with a declining reimbursement from payors, spinal instrumentation surgery is creating significant budgetary problems at a growing number of hospitals. While professional charges are still able to cover the surgeon's time and expense for these procedures, the technical charges, in many cases, fail to cover the hospital's costs for purchasing the implants in addition to the usual inpatient costs. This is creating an increasing reluctance on the part of hospital administrators to promote and support spinal reconstructive procedures frequently at the expense of patient care.

While this problem can be managed through better contracting with payors and implant vendors, reducing the length of stay and assuring that optimal procedure coding is being done, the greatest impact can be the spinal surgeons' judicious use of the implants. This requires the surgeon to have not only an understanding of the surgical options and indications for reconstructive procedures but also a current knowledge of implant costs and their relative impact on hospital budgets.

We reviewed 1536 spinal procedures performed at the Cleveland Clinic Foundation in 2001 by the departments of Neurosurgery and Orthopedic Surgery. Each surgery was classified into one of three categories by CPT codes. Class I included those cases in which only a decompressive procedure was done. Class II cases were defined as simple reconstructive and consisted primarily of 2-3 level instrumented fusions. Class III cases were defined as complex reconstructive and consisted of > 3 level instrumented fusions.

Using data acquired from the Cleveland Clinic Operating Room Information System (ORIS) as well as a commercial decision support database system ((Transition One), we reviewed the operating room costs (including spinal implants), the perioperative costs and the total patient encounter costs for each case. We compared this data to the reimbursement received to assess the level of profit or loss for each spinal surgery classification. We also stratified the results by surgeon to provide comparative information by which surgeon decision-making regarding the use of spinal implants, the design of an individual construct or the choice of implants could be optimized without compromising patient care. The design and presentation of this model will be reviewed.

Correction of Posttraumatic Hypoxia with Trans Sodium Crocetinate Following Experimental Traumatic Brain Injury

JA Jane Sr., J Gainer, J Wagner, JR Stone, David O. Okonkwo

In traumatic brain injury, the primary injury largely determines a patient's neurological grade upon admission and thereby is the strongest prognostic indicator. However, secondary mechanisms of injury can exacerbate damage and limit restorative processes, and hence, contribute to overall morbidity and mortality. Hypotension and hypoxia leading to brain ischemia following traumatic brain injury is associated with worsened cerebral edema, neurologic damage, and mortality. Trans sodium crocetinate (TSC) is a carotenoid that has been shown to improve oxygen delivery to ischemic tissue and in lower-flow states such as hypotension. We investigated the impact of TSC on brain tissue oxygen delivery after traumatic brain injury (TBI).

To this end, male rats were intubated and ventilated with 21% FiO2. Femoral artery and vein cannulation was achieved and baseline arterial blood gas measures taken. Rats were subjected to impact acceleration TBI following which a small burr hole was drilled into the right parietal bone. A calibrated Licox rat brain PO2 probe was inserted into the cortical parenchyma and PO2 in brain tissue (PbtO2) measured with a Licox brain tissue oxygenation monitoring system. PbtO2 was recorded at 5min intervals over a 2h intravenous infusion of TSC (N=9) or saline (N=10), which was begun at 15 min post injury.

PbtO2 in rat brain following impact acceleration TBI drops from a baseline PO2 of 32mmHg to 25mmHg ($p<0.05$). This drop recovers spontaneously over 60min in the control group administered saline. Recovery to normal PO2 occurs within 15 min of initiation of TSC infusion (30min post injury). Furthermore, TSC increases PbtO2 to 35mmHg and maintains this level of hyperoxia throughout the infusion.

Additional studies will target effect of TSC infusion on histopathologic and functional outcome following traumatic brain injury.

FRIDAY, OCTOBER 18 **10:30 - 10:45 AM**

A Prospective Study of Decision-Making in Spetzler-Martin Grade 4 and 5 Arteriovenous Malformations

PP Han, FA Ponce, Robert F. Spetzler

Between July 1997 and May 2000, we recorded the treatment recommendations of 73 consecutive patients with Grade 4 and 5 arteriovenous malformations (AVMs) who were evaluated by our cerebrovascular team. No treatment was recommended for 75% of the patients, partial treatment was recommended for 10 %, and treatment of associated aneurysms was recommended for another 10%. Complete surgical removal was recommended for only 5% of the patients. The overall retrospective annual hemorrhage rate for Grade 4 and 5 AVMs was 1.5%. Among patients who had received previous partial treatment, the annual risk of hemorrhage was 10.4% compared to an annual risk of 1% in patients who had undergone no previous treatment. We conclude that the low annual risk of hemorrhage associated with Grade 4 and 5 AVMs, as opposed to the higher risk associated with lower grade AVMs, justifies restricting complete treatment for high-grade AVMs to select patients with progressive neurological deficits caused by repeated hemorrhages. This strict selection process is likely reflected in the relatively low morbidity and mortality rate (approximately 20%) associated with the treatment of Grade 4 and 5 AVMs by our group.

FRIDAY, OCTOBER 18 **10:45 - 11:00 AM**

Liquid Embolic Agents for the Treatment of Cerebral Aneurysms

Lee R. Guterman, LN Hopkins

Endovascular therapy for cerebral aneurysms is playing an increasing role since the advent of detachable coil technology in 1990. Over the past decade acceptance of endovascular treatment paradigms have dominated the patient population in some European countries. In North America, the majority of ruptured aneurysms are still treated using open surgical techniques. Endovascular therapies have gained wide acceptance for posterior circulation aneurysms. Recent literature supports the application of endovascular therapy for the treatment of asymptomatic aneurysms, but definitive evidence has not been widely distributed.

Limitations of coil technology for the treatment of cerebral aneurysms centers around aneurysm packing and parent vessel reconstruction. At most, 40% of the aneurysm cavity volume can be replaced by coils. The remainder of the aneurysm cavity volume is occupied by thrombus. This may explain recanalization phenomena in coiled aneurysms. Delivery of liquid embolic agents into ruptured and unruptured cerebral aneurysms is being studied at centers throughout Europe, Asia, and North America. Delivery of polymers such as histoacryl and ethyl vinyl alcohol is presently in clinical trials. Safe delivery of these substances has been technically demanding. The combination of devices such as balloons, stents, neck occlusion devices and standard microcatheters has aided in delivery of liquid embolic materials in the aneurysm cavity without leakage into the parent vessel.

This presentation will focus on our research efforts using liquid embolic agents for the treatment of experimental aneurysms in a canine model of sidewall and bifurcation aneurysms. Results of numerous experiments will be presented, detailing the marriage of aforementioned devices and microcatheter deliver of liquid embolics. Application of this technology in preliminary human aneurysms will be reviewed.

FRIDAY, OCTOBER 18 **11:00 - 11:15 AM**

Long Term Results of Surgical Management of Rathke's Cleft Cysts

Martin H. Weiss, D Hinton, D Cummings, P Singer, WT Couldwell

During 1985-1995, the authors performed trans-sphenoidal surgery on 118 patients with Rathke's Cleft Cysts. Ages ranged from 15-68; 50/118 patients were male. Thirty-eight patients presented with visual loss, 78 had GH deficiency, 62 were hypogonadal, 8 were hypothyroid, 7 were hypocortisolemic and none had preoperative diabetes insipidus.

Trans-sphenoidal surgery was performed primarily on all patients.

Post operatively, 114 of 118 patients had no evidence of residual cyst by MRI at three months. No patient's vision was made worse, 27 of 33 patients with pre-op visual loss had improvement, 6 of 33 had no change in their visual loss. Two of 56 patients sustained hypogonadism whereas 11 of 62 with pre-op hypogonadism improved. No patient was rendered hypothyroid, and none of the 8 patients with pre-op hypothyroidism improved. No patient developed post-op hypocortisolemia; 1 of 7 patients with hypocortisolemia pre-op improved. Twenty-two of the 118 patients develop diabetes insipidus; no patient had worsening in GH function post op, and 14 of 78 with pre-op GH deficiency improved.

After a minimum of 5 year follow up, 19 of the 114 patients with initial complete resolution of the cyst by post-op MR sustained recurrences; 2 of the 4 incomplete resections demonstrated progressive re-growth. One patient in this series had a postoperative CSF leak, and one patient developed meningitis.

FRIDAY, OCTOBER 18 **11:15 - 11:30 AM**

CT-Demonstrated Infarcts after Surgical and Endovascular Treatment of Aneurysmal Subarachnoid Hemorrhage

Christopher S. Ogilvy, BL Hoh, WT Curry Jr., BS Carter

Introduction: Etiologies other than vasospasm for cerebral infarction after subarachnoid hemorrhage (SAH) have not been well-studied. We reviewed delayed CTs of all SAH patients for findings consistent with infarct.

Methods: From 1993-2000, 689 patients were admitted with aneurismal SAH. Delayed CTs of all 689 patients were reviewed. Two reviewers determined the most probably etiologies for infarct. Glasgow Outcome Score was collected from a prospective database.

Results: 514 patients were treated with clipping; 116 with coiling. There were CT findings consistent with infarct in 189 patients (27%): 140 in the surgical group (27%) and 49 in the endovascular group (42%). The etiologies for infarct in the surgical group were vasospasm 79 (15%), perforator occlusion 40 (8%), large vessel occlusion 14 (3%), intracranial pressure 4 (1%), thromboembolism 2 (0.4%), and systemic hypotension 1 (0.2%). Infarcts in the endovascular group were due to vasospasm 20 (17%), thromboembolism 12 (10%), large vessel occlusion/dissection 9 (8%), intracranial pressure 4 (3%), perforator occlusion 3 (3%), and systemic hypotension 1 (1%). Patients with CT-demonstrated infarcts were excellent/good (GOS 5,4), 72 (38%), fair (GOS 3) 38 (20%), poor (GOS 2) 19 (10%), and dead 60 (32%). The majority of infarcts from perforator occlusion were clinically silent with 29 patients (67%) excellent/good outcomes. Vasospasm-induced infarcts, however, were associated with adverse outcomes with 31 patients (31%) fair/poor, and 37 (37%) dead.

Conclusions: Despite advances in the treatment of SAH, there are still significant radiographic infarcts. While a significant number are clinically-silent, vasospasm was associated with adverse outcomes.

FRIDAY, OCTOBER 18 **11:30 – 11:45 AM**

ACADEMY AWARD PAPER

Combined Expression of Sonic Hedgehog and c-MYC Induces Medulloblastoma in Mice

Ganesh Rao Univ. Utah

Medulloblastomas are malignant brain tumors that arise in the cerebellum of young children. The presumed cells-of-origin for medulloblastomas are granule neuron precursors (GNPs) that occupy the external granule layer (EGL) of the developing cerebellum. Over-expression of proteins that normally stimulate proliferation of GNPs may initiate medulloblastoma formation. Two known mitogens for neural progenitor cells are the cellular oncoprotein, c-Myc, and Sonic hedgehog (Shh), the ligand for cell surface receptor, patched (Ptc), and is a crucial determinant of embryonic pattern formation in the central nervous system. We modeled the ability of c-Myc and Shh to induce medulloblastoma in mice using the RCAS-TVA system. This system utilizes an avian retroviral vector, RCAS, to target gene expression to specific cell types in transgenic mice. To express exogenous proteins in neural progenitor cells we used *Ntv-a* mice wherein the *Nestin* gene promoter drives expression of TVA, the cell surface receptor for the virus. We injected RCAS vectors expressing Shh and c-Myc into the cerebella of newborn, *Ntv-a* mice and examined brain sections twelve weeks later. Medulloblastomas developed in 9/39 (23%) mice injected with RCAS-Shh plus RCAS-Myc. Following injection with RCAS-Shh alone, 3/29 (10%) mice developed medulloblastomas and 5/29 showed multi-focal EGL hyperproliferation, possibly a precursor stage of medulloblastoma. All tumors expressed βIII tubulin and NeuN, indicating an origin from neuronal precursors. No tumors developed when these same vectors were injected into the cerebral hemispheres. Tumors and EGL hyperproliferations arose more frequently in $Ptc^{+/+}$ mice (9/16=56%) than in $Ptc^{+/-}$ mice (8/52=15%) (P=0.001), suggesting that the mitogenic effect of Shh requires expression of Ptc.

ACADEMY AWARD HONORABLE MENTION

Autologous Adjuvant Linked Fibroblasts Induce Anti-Glioma Immunity: Implications for Development of a Glioma Vaccine

Andrew T. Parsa, JI Miller, A Eggers, AT Ogden III, RC Anderson, JN Bruce

Objectives: Adjuvant linked vaccines have been shown to induce anti-tumor immunity in patients with a variety of solid tumors. In this study we describe an in vitro model of active immunotherapy using autologous fibroblasts as immunogen. Correlative results from glioma patients immunized with autologous fibroblasts are also described.

Methods: Peripheral blood lymphocytes (PBLs) from normal subjects were immunized in vitro against autologous skin fibroblasts coupled to the adjuvant muramyl dipeptide. The lymphocytes developed cell-mediated cytotoxicity that was measured with a short-term chromium release assay. Results of in vitro experiments were compared to data derived from glioma patients immunized with subcutaneous injection of autologous adjuvant linked fibroblast vaccine. Glioma target cells and fibroblast immunogens were derived from early passage primary tissue culture.

Results: A comparison of autologous versus homologous immunogen indicated that major histocompatibility complex matching was required at the sensitization stage of immunity (17.2 +/- 3.4 % specific lysis versus 0.4 +/- 3.1, $P<0.01$). Pre-treatment of fibroblast immunogen cells with interferon gamma (IFN-γ) was found to significantly increase immunity (42.2 +/- 10.0%, $P<0.01$), as did IFN-γ pre-treatment of tumor target cells (35.8 +/- 9.0%, $P<0.01$). The positive effect of IFN-γ was diminished by treatment of cells with IFN-α . These in vitro results correlated well with in vivo data derived from glioma patients immunized with an autologous adjuvant linked fibroblast vaccine. PBLs from patients developed direct cell-mediated cytotoxicity against autologous tumor cells. Lysis of tumor targets after in vivo immunization increased over a three-week interval (from 1.2 +/- 3.0 % to 21.0 +/- 3.4 %, $P <0.01$) while lysis of a non-MHC matched control cell line remained essentially unchanged.

Conclusions: Specific lysis of glioma targets in vitro was achieved after in vivo sensitization with autologous adjuvant linked fibroblasts. Collectively the data indicate that biochemically modified autologous cells can foster

anti-glioma immunity in humans. The degree of specific immunity seen in our patients compares favorably with other published series using glioma cells as an antigenic source. Accordingly fibroblasts may represent a practical alternative to glioma cells for vaccine construction.

NOTES:

SATURDAY PROGRAM

SATURDAY, OCTOBER 19 **8:30 – 8:45 AM**

A Comparison of Endovascular and Surgical Treatment of Basilar Tip Aneurysms

G Tang, E Ley, H Clott, M Cowley, J Dion, Daniel Barrow

Introduction: Due to difficult surgical access and risk to perforating arteries, basilar apex aneurysms warrant consideration for endovascular management due to the lower reported procedural risk. Past comparisons of surgical to endovascular management have been limited due to selection biases, small series sizes and the use of historical controls. We compare endovascular and surgical treatment of basilar apex aneurysms at a single institution with multivariate analysis.

Methods: Sixty-nine basilar apex aneurysms treated either surgically or endovascularly during a four-year period were reviewed. Data on factors related to risk and outcome were collected and entered into a multivariate logistic regression model.

Results: Thirty-one patients underwent surgery while 38 patients underwent endovascular treatment. In the endovascular group, 61% of aneurysms were ruptured with a mean grade of 2.5. Procedural complications occurred in 8 cases (21%) of which 3 (8%) had a clinical correlate. In angiographic follow-up of 24 cases averaging 16 months, aneurysmal regrowth prompting retreatment occurred in 2 (10%). One patient hemorrhaged following complete coiling of an unruptured aneurysm. In the surgical group, 81% of patients presented with SAH with a mean grade of 2.6. Six operations encountered complications (19%). In multivariate analysis, factors related to clinical complications included SAH ($p<0.0001$), grade ($p=0.008$) and size ($p=0.016$). Endovascular management trended toward fewer clinically evident complications ($p=0.085$). Factors relating to outcome include size ($p=0.021$), grade ($p=0.002$) and SAH ($p=0.004$). Endovascular and surgical management demonstrated no difference in functional outcome.

Conclusions: When compared to surgical treatment, endovascular management of basilar apex aneurysms demonstrated a trend toward lower peri-procedural morbidity and no significant difference in long-term functional outcome. The potential for aneurysmal regrowth following endovascular management requires surveillance angiography.

Use of a Vaccine Strain of Measles Virus Genetically Engineered to Produce CEA as a Novel Therapeutic Agent Against Glioblastoma Multiforme

Loi K. Phuong, C Allen, K-W Peng, C Giannini, C TenEyck, S Russell, E Galanis

Introduction: In this study, we investigate a novel agent, an attenuated vaccine strain (Edmonston-strain) of measles virus genetically engineered to produce carcinoembryonic antigen (MV-CEA), which can serve as a marker of viral expression in vivo, as a novel therapeutic agent against glioblastoma multiforme.

Method and Results: Infection of the U87, U118, and U251 glioma cell lines with MV-CEA caused marked cytopathic effect with syncytial formation and massive cell death. In vivo efficacy was examined in mice employing both subcutaneous and intracranial orthotopic U87 tumor models. Difference in tumor volumes and survival were analyzed using repeated measures analysis of variance and the log rank test, respectively. Four-week-old BALB/c nude mice with established intracranial U87 tumors treated with intratumoral administration of MV-CEA at a total dose of 1.8 x 10^6 pfu had significant tumor regression as assessed by magnetic resonance imaging when compared to mice that received ultraviolet light-inactivated measles virus or no treatment ($p=0.0028$) as well as significantly longer survival ($p=0.02$). Similar results were achieved in mice with subcutaneous tumors treated with intravenous MV-CEA as demonstrated by significant tumor regression ($p<0.001$) and prolongation of survival ($p=0.007$). In addition, CEA titers in the peripheral blood in both the subcutaneous and orthotopic models correlated with viral replication and tumor regression.

Conclusion: MV-CEA has potent antitumor efficacy against a variety of glioma cell lines and against U87 subcutaneous and intracranial orthotopic tumor models. Viral gene expression can be tracked by measuring serum CEA level which can reduce the need for repeat biopsies in vivo.

SATURDAY, OCTOBER 19 **9:00 – 9:15 AM**

Hemorrhage Complicating Brain AVM Surgery

Michael K. Morgan

In a consecutive series of 415 angiographically proven brain AVMs managed between 1989 and 2001 managed by one surgeon, 354 underwent surgical excision. Reasons for non-surgical intervention were management by alternate therapies (4 cases; 2 by embolization alone and 2 by focused irradiation alone), no intervention thought likely to be better than the natural history (29 cases), poor neurological condition (11 cases), and patient refusal (17 cases). Ancillary management used prior to surgical excision include embolization (54 cases) and focused irradiation (5 cases). Ancillary management following surgery to complete ablation include embolization (1 case) and focused irradiation (3 cases).

In the operative AVMs 204 were Spetzler-Martin grade 1 or 2, 97 were grade 3 without lenticulostriate contribution, 13 were grade 3 with lenticulostriate feeders, and 40 were grade 4 or 5. A down-grade in neurological outcome at 12 months occurred in 35 cases (10%). A permanent down-grade in function was due to hemorrhage in 19 cases (5%). The rate of hemorrhage leading to a permanent down-grade in function in the first half of the series was 7.9% compared with 2.8% in the second half. This difference was significant. Identifiable reasons for the reduction in peri-operative hemorrhage were investigated including changing case selection, use of embolization, introduction of peri-operative management protocol and experience of surgeon.

Surgeon's experience and the introduction of a specific peri-operative management protocol can account for the reduction in hemorrhage rate. Embolization rate and case selection were not related to the reduction in hemorrhage rate.

SATURDAY, OCTOBER 19 9:15 – 9:30 AM

Phase Reset in Human iEEG During Working Memory

Joseph R. Madsen, M Kahana, D Rizzuto

Intracranial EEG (iEEG) is a often a useful part of preoperative planning leading to epilepsy focus resection. Techniques to decode and interpret the iEEG benefit surgical planning, while providing unique opportunities to explore mechanisms of human consciousness. Our group has previously reported specific frequencies related to navigational tasks (*Nature* 1999; 399:781-4,), and the gating of such frequencies during recognition of items from lists (*J. Neuroscience* 2001; 21:3175-83). In rodent models, phase, as well as amplitude, of theta-band (4-8 Hz) oscillations are physiological correlates of learning and memory. It is not known whether the phase of human oscillations is related to cognitive operations. We recorded intracranial EEG from 529 electrodes in nine subjects, during performance of a short-term item recognition memory task. Each trial of this task consisted of the presentation of an orienting stimulus followed by a series of four consonants and a memory probe. Across trials, the phase of oscillations in the 6-16 Hz range became aligned following stimulus events. This phase-locking was not associated with increased post-stimulus power, suggesting that stimulus events reset the phase of ongoing oscillations. Different stimulus types selectively modulated this phase reset effect, with topographically distinct cortical sites exhibiting preferential reset to either probe items or to study items. These findings implicate the reset of brain oscillations in working memory function. Such analysis may prove useful in the localization of a wide variety of functional areas in patients for whom resective surgery for epilepsy is planned.

SATURDAY, OCTOBER 19 **9:30 – 9:45 AM**

Unruptured Intracranial Aneurysms: Decision Analysis and Clinical Trials

Robert E. Harbaugh, A Papavasiliou, GD Pope

Objective: We performed a formal decision analysis to interrogate the effectiveness of clipping, coiling and observation for patients with unruptured intracranial aneurysms (UIA).

Methods: A Markov model was constructed with the following baseline assumptions in a 40 year old patient: (1) Annual risk of rupture -1.46%, (2) Morbidity and mortality of clipping -11.1%, (3) Morbidity and mortality of coiling - 5.6%, (4) Efficacy of clipping 95% and (5) Efficacy of coiling 75%. Chances of reaching health outcome states were determined from the literature and utilities were determined using a standard gamble method in a risk averse population of medical personnel. A standard discount rate for later years of life was used and actuarial risks were obtained from 1998 U.S. health statistics. Sensitivity analyses were carried out to determine variables with greatest impact on effectiveness and to investigate how study duration might affect conclusions reached from prospective randomized trials.

Results: Clipping was the preferred treatment in the baseline case.. However, our analysis suggests that a prospective, randomized trial of one year duration would choose observation as the preferred treatment while a five year trial would select coiling. A prospective trial of >10 years would be needed to document the superiority of clipping.

Conclusions: Decision analysis can be used to interrogate various treatment options for patients with UIA. Long-term, prospective studies can determine most effective treatment for but short-term studies are likely to lead to erroneous conclusions.

SATURDAY, OCTOBER 19 9:45 - 10:00 AM

Communication Between Malignant Glioma Cells and Vascular Endothelial Cells via Gap Junctions

Joseph A. DeMattia, W Zhang, WT Couldwell

Object: Extensive invasion and angiogenesis are hallmark features of malignant gliomas. Communication between malignant glioma cells and surrounding astrocytes occurs with evidence of resultant transformation of the astrocytic phenotype. In the present study, the authors examined whether malignant glioma cells and vascular endothelial cells communicate through the formation of gap junctions and whether this communication influences angiogenesis.

Methods: Connexin 43 (Cx43), a gap junction protein expressed in glioma cells, was identified in human umbilical vascular endothelial cells (HUVECs). Immunocytochemical staining for Cx43 demonstrated immunoreactive plaques at areas of cell-to-cell contact among HUVECs as well as between HUVECs and Cx43-expressing glioma cells. Dye transfer with a gap junction permeable dye, dicarboxy-dichlorofluorescein diacetate (CDCF), among these co-cultures indicated these were functional communications. Calcium signaling also occurred from malignant glioma cells to HUVECs. Tube formation by HUVECs co-cultured with Cx43 transfected T98G glioma cells and Cx43-expressing U87-MG glioma cells was increased compared to tube formation by HUVECs alone. Comparison of HUVECs co-cultured with T98G empty vector transfected glioma cells and HUVECs alone did not show statistical significance [tube length, μm/field (mean ± S.D.): HUVECs and T98G-Cx43 transfected cells: 6300 ± 310; HUVECs and U87-MG cells: 8226±2504; HUVECs alone: 4671 +361 $p<0.01$;HUVECs and T98G empty vector transfected cells: 5549 + 736]. Furthermore, the concentration of vascular endothelial growth factor (VEGF), an angiogenic factor important for the induction of angiogenesis and blood vessel formation, was significantly higher in cell culture medium from Cx43-transfected T98G human glioma cells as compared to T98G empty vector transfected control cells. Human malignant glioma U87 cells, which naturally express Cx43, also secreted increased concentrations of VEGF as compared to HUVECs alone.

Conclusions: These results indicate that functional gap junction formation between human malignant glioma cells and vascular endothelial cells occurs. This communication appears to influence tumor angiogenesis.

Radiosurgery Increases the Role of Neurosurgery in the Management of Metastatic Brain Cancer

L. Dade Lunsford, D Kondziolka, JC Flickinger

Background: Brain metastatic disease occurs in approximately 250,000 new patients in the U.S. annually. In the past, the role of the neurosurgeon has largely been limited to an occasional craniotomy. We have analyzed the trends and results in the management of metastatic brain cancer when radiosurgery is added into the paradigm of neurosurgical options.

Methods and Materials: A retrospective review of patients prospectively referred for gamma knife radiosurgery during a 14 year interval was performed. Of a total patient volume of 5,032 patients, 1,088 (5%) had solitary or multiple metastatic brain tumors. Non-small cell lung cancer (NSLC) was the largest group (336 patients). We evaluated clinical imaging results and shifts in the role of radiosurgery during this 14 year interval.

Results: In this series, two factors significantly impacted survival after radiosurgery: primary histology and systemic disease control. For NSLC, overall mean survival was 10.3 months after radiosurgery and 20.3 months after diagnosis of brain metastasis. Tumor control was achieved between 84 and 90% of patients depending upon histological diagnosis. Craniotomy and resection (<5%) was performed for tumors refractory to radiosurgery. Between 1987 and 2001, the annual percentage of patients with metastatic brain cancer selected for radiosurgery increased from <5% to >25%. Radiosurgery alone has increasingly been performed for patients with small to medium size solitary tumors. Additional fractionated external beam whole brain radiation therapy provided a subtle benefit in non-small cell lung cancer, but no apparent benefit for renal cell, melanoma or breast metastatic cancer.

Conclusion: Stereotactic radiosurgery greatly expands the role of neurosurgery in the management of metastatic brain cancer, and can account for as much as 25% of an annual radiosurgical experience at a busy center. Radiosurgery has survival benefits superior to other reported methodologies (fractionated radiation therapy ± craniotomy), can be offered to a much wider selection of patients, and has benefit independent of tumor location. Adjuvant management of metastatic brain cancer with radiosurgery is a significant technology as part of the overall neurosurgical armamentarium.

SATURDAY, OCTOBER 19 **10:30 - 10:45 AM**

Novel Molecular Mechanisms in Cervical Spondylotic Myelopathy: Implications for Innovative Therapeutic Interventions

Michael G. Fehlings

Cervical spondylotic myelopathy is one the commonest causes of spinal cord dysfunction. The pathophysiology involves both static compression from canal stenosis and dynamic compression from repetitive motion. These cause mechanical injury, ischemia and neural cell loss [1]. Our group has recently investigated the molecular mechanisms of cell death and axonal degeneration in this disorder. Evidence will be presented that programmed cell death or apoptosis underlies both neuronal and oligodendroglial degeneration in cervical spondylotic myelopathy. Similar to our work in acute spinal cord injury [2], our data, which is based on a molecular analysis of human postmortem spinal cord tissue, suggest that "death receptors" on the cell surface membrane including FAS and the p75 low affinity neurotrophin receptor become activated by inflammatory cells. This in turn triggers an intracellular cascade which includes the downstream effector Caspase-3 and this leads to apoptosis. To date, our work is the first study to demonstrate that apoptosis of neurons and oligodendrocytes occurs in humans with CSM. Early surgical intervention, neuroprotective approaches, or gene therapy may attenuate this form of genetically programmed cell death.

1. Fehlings MG, Skaf G A review of the pathophysiology of cervical spondylotic myelopathy with insights for potential novel mechanisms drawn from traumatic spinal cord injury. *Spine* 1998 Dec 15;23(24):2730-72.

2. Casha S, Yu WR, Fehlings MG Oligodendroglial apoptosis occurs along degenerating axons and is associated with FAS and p75 expression following spinal cord injury in the rat. Neuroscience2001;103(1):203-18.

Frameless Stereotactic Placement of Depth Electrodes for Epilepsy Using the StealthStation Surgical Navigation System

Theodore H. Schwartz

Introduction: Depth electrodes are useful in the identification of deep epileptogenic foci. CT, MR and angiography-guided frame-based techniques are safe and accurate, but require 4-point rigid skull fixation that can limit cranial access for placement of additional grids and strips. We designed and implemented a custom-built adaptor for use with the StealthStation Frameless Neuronavigation System.

Methods: A slotted, custom-designed adaptor was built (Ad-Tech, Racine WI) to interface with the StealthStation Guide Frame – DT and 960-525 Stealth Fighter. (Medtronic, Louisville, CO). The Mach 4.0 Cranial Navigation Software was used to plan the trajectory and entry site based on a preoperative SPGR MRI. Anatomic accuracy was assessed based on whether the electrode was 1) within, 2) touching or 3) outside of the target tissue. Physiologic accuracy was assessed based on whether adequate recordings were obtained.

Results: Twenty-one depth electrodes were placed into 25 targets in 9 patients. Fourteen electrodes were placed laterally though a craniotomy into either the hippocampus, amygdala or a peri-ventricular heterotopia. Four electrodes were placed through occipital burr holes along the length of the hippocampus into the amygdala. Four electrodes were placed into targets deep in the frontal lobe. Of 25 targets, 25 (100%) had electrode contacts either within or touching the target, 24 of which (98%) provided adequate recordings. There were no complications.

Conclusions: Depth electrodes can be placed safely and accurately using a commercially-available frameless stereotactic navigation system and a custom-made adaptor.

SATURDAY, OCTOBER 19 11:00 - 11:15 AM

Preliminary Results of Convection Enhanced Delivery of TP38 for the Treatment of Infiltrating Gliomas

Allan H. Friedman, DA Reardon, JH Sampson

Convection enhanced delivery while limiting offers the possibility of delivering agents directly to the penumbra of infiltrating glioma cells systemic toxicity. We have initiated a Phase I-II study using convection enhanced delivery to deliver TP38, a chimeric immunotoxin composed of TGf-□ bound to pseudomonas exotoxin. The TP38 is infused through two catheters placed in the white matter surrounding the nucleus of a supratentorial malignant glioma. Radiolabeled albumin was infused along with the TP38 to monitor distribution. Twenty milliliters of fluid were infused through each catheter over 55 hours. Patients are divided into those having undergone resection of the enhancing portion of the tumor and those who have not. The study is designed to evaluate toxicity and efficacy of TP38 and the volume of distribution obtainable with convection enhanced delivery.

Nineteen patients have successfully completed therapy. The total dose of TP38 infused has been escalated from 1-4 mcg without appreciable toxicity. Conservative analysis of preclinical data would indicate that toxicity will not be seen before 10 mcg. One patient with a recurrent glioblastoma has had a nearly complete response to therapy as demonstrated by serial MRI scans over 15 months. Studies tracking the volume of distribution demonstrate a significant amount of TP38 spreading four centimeters from the point of infusion. Patterns of distribution were analyzed.

Convection enhanced delivery is a promising strategy for delivering therapeutic agents to the infiltrating penumbra of a malignant glioma.

SATURDAY, OCTOBER 19 **11:15 - 11:30 AM**

Effect of Duraplasty on Collagen Scar Formation and Cystic Cavitation Following Acute Spinal Cord Laceration

Christopher B. Shields, YP Zhang, C Ianotta, Y Han, LBE Shields, DA Burke, X-M Xu

Laceration and gunshot wounds of the spinal cord lead to extensive scar formation. This injury may result in a CSF leak, extensive transdural scar formation, and further damage to remaining intact spinal cord pathways. We hypothesize that duraplasty following spinal cord laceration may prevent a chronic CSF leak, reduce chronic inflammation, cystic cavitation, fibroglial scar, and axonal loss.

Methods: Following a C5-6 laminectomy and dural incision, a C5-6 dorsal hemisection (1.5mm deep) of the spinal cord was performed using a novel tool to create a sharp laceration (Vibraknife) in 18 Sprague-Dawley rats. The animals were divided into 2 groups of nine. In one group the dura was closed with a $5mm^2$ graft of rat cadaveric dura allograft reinforced by fibrin glue (n=9), and a control group in which the dura was not repaired (n=9). At 1, 5, and 10 weeks following injury and repair the rats underwent imaging studies, histological and stereological assessment, immunofluorescence staining for activated macrophages, reactive astrocytes, extracellular matrix, and axonal survival.

Results: The spinal cord of the duraplasty group displayed reduced hemorrhage and connective tissue scarring at the site of injury. If the dura was not repaired, there was marked transdural thickening and infiltration of acute and chronic inflammatory cells into the spinal cord cavity. In chronic lesions of non-repaired dura there were large and often septated cystic cavities, whereas if the dura was repaired there was marked and significantly attenuated cystic cavity size as well as lesion volume.

Failure to repair dura resulted in the invasion of large, dense collagen scar into the lesion site. Collagen scar demonstrated by immunoreactivity was markedly reduced following duraplasty.

Neurofilament (NF)-IR demonstrated considerable die-back of axons from the injury site and cystic cavities when the dura was not closed, whereas there was secondary sprouting of lesioned axons into the injury site in dural repaired rats.

Neurofilament (NF)-IR indicated that at one week post-injury damaged axons were seen at the rostral and caudal stump. However, at five weeks post-injury there were no axons in the cystic cavities if the dura was not repaired, however secondary sprouting of lesioned axons into the injury site was observed in the dural repaired rats. Immunofluorescence staining revealed intense and widespread laminin-IR indicating within the spinal cord without dural repair. In contrast, laminin-IR was reduced with dural repaired lesions.

Conclusion: Duraplasty may reduce the extent of subdural and subarachnoid fibrosis and decrease the tethering effect at the lesion site following SCI. Duraplasty also decreases the cystic cavitation and infiltration of activated macrophages into and surrounding the lesion site. Attenuation of the fibro-inflammatory response may reduce secondary tissue damage seen if the dura is repaired. Thus attempts to inhibit secondary spinal cord damage and promote a favorable environment for spinal cord repair following SCI should include dural repair.

SATURDAY, OCTOBER 19 **11:30 - 11:45 AM**

Necrosis and Glioblastoma: Pathogenesis and Significance

Raymond Sawaya, S Raza, G Fuller, K Hess, W Zhang

Necrosis is a form of cell death that has been understudied in Neuro-Oncology. Considering the diagnostic and prognostic significance of the presence of necrosis in glioma tissue, a better understanding of the molecular basis for the necrogenesis is desirable, and is likely to result in the identification of novel therapeutic targets.

In two previous clinical studies, we have demonstrated that the degree of necrosis in glioblastomas, as determined on the basis of preoperative MRIs correlated negatively with the survival of the patients, and that the prognostic significance of this biologic variable was shown on multivariate analysis to be independent from the other well-established prognostic variables, such as age and KPS.

In order to identify some of the molecular events associated with the development of necrosis, we have employed a cDNA expression array analysis of 588 human genes in 15 glioblastoma samples, and have correlated the level of gene expression with the degree of necrosis for each tissue sample. A statistically significant correlation was detected for 26 genes, positively in 9 genes, and negatively in 17 genes. The two genes that had the strongest correlation coefficient values were (1) prostaglandin E2 receptor EP4 subtype and, (2) Ephrin type A receptor 1 (correlation coefficient values of 0.78 and 0.77 respectively). Neither molecule was known to be associated with necrosis. All 26 genes relate to specific molecular pathways that can form the basis of a hypothesis explaining the molecular pathogenesis of necrosis. These events include Ras and Akt activation, TNF and NF-Kappa B production with resulting antiapoptotic and procoagulant activities, and hypoxia.

The literature supporting this hypothesis will be presented, and future studies required to confirm it, will be suggested.

SATURDAY, OCTOBER 19 **11:45 AM - 12:00 PM**

MRI Findings in Patients with Failed Operations for Chiari Type 1 Malformation

Peter W. Carmel, JA Bello

Thirty-one patients who underwent re-operation for Chiari I decompression, and in whom MRIs were available, were analyzed. Indications of failure included return of initial symptoms, reappearance of syrinx, new symptoms with "cerebellar slump", new or persistent pain away from the suboccipital region, pseudomeningocele formation, and complications arising from CSF leak.

Return of initial symptoms or return of syrinx were associated with re-development of CSF circulation block at the level of the tonsils, supporting the role of CSF "dissociation" in the genesis of these lesions. Cerebellar slump was seen with inadequate decompression, probably due to the same mechanism. Attempts to deal with CSF leak by lumbar drainage may exacerbate tonsillar prolapse, recreating symptoms. Ventricular drainage or shunting was preferable. Pseudomeningocele often was due to borderline hydrocephalus, unappreciated prior to decompression, or postoperative aseptic meningitis. Persistent pain at the site of a prior syrinx shunt was seen in three patients, and in two was alleviated by removal of the shunt and untethering of the dorsal roots locally.

Many of these problems were apparent on MR scan. CSF flow studies were often pivotal in defining circulation blocks.

SATURDAY, OCTOBER 19 **12:00 - 12:15 PM**

Differential Gene Expression in Human Cerebral Vascular Malformations

R Shenkar, JP Elliott, K Diener, J Gault, L-J Hu, R Cohrs, L Hunter, Issam A. Awad

Objective: To identify genes with differential expression in cerebral cavernous malformations (CCMs), arteriovenous malformations (AVMs), and control superficial temporal arteries (STAs), and to confirm differential expression of genes previously implicated in the pathobiology of these lesions.

Methods: Total ribonucleic acid was isolated from 4 CCM, 4 AVM, and 3 STA surgical specimens, and used to quantify lesion-specific mRNA expression levels on human gene arrays. Scaled ata was analyzed using advanced informatic techniques and two separate methodologies, gene discovery and confirmation analysis.

Results: Gene discovery methods identified 42 genes, which were significantly upregulated and 36 genes, which were significantly down regulated in CCMs compared to AVMs and STAs ($P = 0.006$). These included a robust and previously unreported over-expression of a group of immunoglobulin and histocompatibility antigens implicating a unique immune mechanism in association with CCM, and under-expression of a number of structural proteins consistent with immature vascular phenotype. Similarly, 48 genes were significantly upregulated and 59 genes significantly down regulated in AVMs compared to CCMs and STAs ($P = 0.006$), including several chemokines and interleukin receptors. A second analysis confirmed significant differential expression of angiogenesis factors VEGF and Angiopoetin, receptors Flt1, Flk1, Tie1 and Tie2, structural proteins laminin, smoothelin and fibronectin, endothelial cell adhesion protein CD31 and gap junction protein Connexin 37, and genes associated with familial vascular malformations KRIT1 and Endoglin.

Conclusion: We have identified differential expression of numerous novel genes in CCMs and AVMs, and confirmed differential expression of several genes previously implicated in the pathobiology of these lesions. Future studies will confirm these findings using proteomic techniques, and will investigate the functional significance of novel candidate genes in the pathobiology of these lesions.

SATURDAY, OCTOBER 19 **12:15 - 12:30 PM**

Use of Replication Competent Retroviruses Containing the Suicide Gene Cytosine Deaminase in the Treatment of Malignant Gliomas

Thomas C. Chen, W-J Wang, C-K Tai, N Kasahara

Replication-competent vectors represent an emerging technology that shows considerable promise as a novel treatment option, particularly for locally advanced or recurrent gliomas. We have developed a modified replication competent retrovirus (RCR) vector, which is capable of transducing the human glioma cell lines A-172, U-87, T98G, and U-138 over multiple infections *in-vitro*. Replication incompetent retrovirus (RIR), on the other hand, was only able to transduce glioma cells over one cycle. Intracranial injection of RCR-GFP (green fluorescent protein) into immune competent Sprague Dawley rats did not demonstrate infection in normal brain cells. When RCR-GFP was injected into pre-formed subcutaneous U-87 tumors in athymic nu/nu mice, its transduction efficiency was up to 98% at the end of 6 weeks; whereas, RIR-GFP transduction was only 0.2% at 6 weeks. When RCR-GFP was injected into pre-formed intracranial U-87 tumors, RCR-GFP transduction efficiency at 3 weeks was up to 98%. PCR amplication demonstrated that there was no GFP expression in the peritumoral normal brain, nor in systemic organs. Using RCR, athymic mice with U-87 intracranial tumors were transduced with the suicide gene cytosine deaminase (RCR-CD), activated by the pro-drug 5-fluorocytosine (5-FC), resulting in the intracellular generation of the chemotherapeutic agent 5-fluorouracil (5-FU). Kaplan-Meier survival curves demonstrated significantly greater survival in mice transduced with RCR-CD followed by 5-FC, compared to mice treated with RCR-CD followed by PBS, or mice injected with PBS, followed by 5-FC alone. We conclude that RCR-CD represents a novel gene therapy vector which may be used in the future treatment of malignant gliomas.

Post-Ischemic Mild Hypothermia Prolongs the Time Window for Bcl-2 Gene Therapy Protection Against Focal Cerebral Ischemia

Gary K. Steinberg, H Zhao, MA Yenari, RM Sapolsky

Background and Objective: Viral vectors containing neuroprotective genes can protect against ischemic neuronal death. We previously showed that while Herpes Simplex Viral (HSV) vectors expressing Bcl-2 could improve striatal neuron survival when delivered 1.5 hours post-stroke, they failed to do so when delivered 5 hours after. Here, we determine whether combination therapy with post-ischemic hypothermia might prolong the therapeutic window for gene therapy.

Methods: 43 male rats were subjected to transient middle cerebral artery occlusion for 1h using an occluding intraluminal suture. Hypothermia (33°C) was induced 2h post insult and maintained for 3h. 5h after ischemia onset, bipromoter HSV vectors expressing Bcl-2 plus β-galactosidase (β-gal) as the reporter or β-gal only (control vector) were stereotaxically injected into each striatum. 2d later, brains were harvested and stained with X-gal (a chromogenic substrate of β-gal) and cresyl violet. X-gal positive neurons were counted in each striatum and expressed as the ratio of positive neurons in the ischemic side compared to the nonischemic side.

Results: Striatal neuron survival of Bcl-2 injected animals subjected to hypothermia (n=11) was improved 2-3 fold compared to hypothermic animals injected with control vector (n=11, ANOVA, $p<0.01$) and normothermic Bcl-2 vector injected animals (n=10, $p<0.01$). In contrast, survival among normothermic Bcl-2 injected animals was not different from those of control normothermics (n=11) and control hypothermics (n=11).

Conclusion: Postischemic mild hypothermia can extend the time window for Bcl-2 gene therapy from 1.5 hours to 5 hours. This is the first report demonstrating synergistic effects of gene therapy and hypothermia.

Folic Acid Supplementation Improves CNS Regeneration and Outcome after Spinal Cord Injury in Rats

Bermans J. Iskandar, DK Resnick, N Hariharan, P Gao, A Nelson, C Johnson, CF Cechvala

Introduction: Since folic acid was shown to play a significant role in preventing neural tube defects, we hypothesized a possible role in adult CNS regeneration as well. We have thus studied the effect of folic acid on axonal elongation in vivo in 2 different rat models, and the animals' functional outcome after spinal cord injury.

Methods: In the first CNS regeneration model, the optic nerve was sectioned then grafted with a sciatic nerve segment. The end of the graft was backfilled with a fluorescent tracer 2 months later. The retina was then harvested and studied for the presence of fluorescence, indicating regenerating retinal ganglion cells (RGCs). In the second model, the cervical dorsal columns were injured and a sciatic nerve segment was grafted at the injury site. The dorsal root ganglia were harvested, sectioned, and studied for fluorescence. Folic acid was given intraperitoneally in a dose-escalating pattern. In vitro protocols were used to study axonal elongation in response to injury and folic acid. Finally, a weight-drop model of thoracic spinal cord injury was used to analyze locomotion outcome using a standardized BBB point-score system .

Results: In the optic nerve regeneration model, the mean number of axons elongating into the graft increased from 913+/-SD57 to 1373+/-SD208 per retina after folic acid treatment. In the spinal cord regeneration model, the amount of regeneration in vivo increased from 1.37%+/-0.25% to 16.70%+/-1.21% with maximum dose dependence ($p<0.001$). In the spinal cord injury model, folic acid improved the median BBB score at 6 weeks post injury by 6 points ($p=0.01$).

Conclusions: These results suggest that folic acid and folate metabolism play a significant role in CNS regeneration and recovery. The impact of these findings on the treatment of head and spine trauma and other neurological disorders might be considerable and warrants investigation.

NOTES:

SPECIAL GUESTS

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Linda Noble San Francisco, CA	Academy
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Stephen Ondra, MD Chicago, IL	Hunt Batjer
Nelson Oyesiku Atlanta, GA	Arthur Day
Andrew Parsa (resident)	Academy Award

San Francisco, CA Loi Phuong (resident) Rochester, MN	Honorable Mention David Piepgras
Joseph Piepmeier New Haven, CT	Dennis Spencer
Bruce Pollock Rochester, MN	Peter Jannetta
Ganesh Rao (resident) Salt Lake City, UT	Academy Award Winner
Charles Rich Salt Lake City, UT	J. Charles Rich
Gerald Rodts Atlanta, GA	Daniel Barrow
Raymond Sawaya Houston TX	Lawrence Pitts
Gabriele Schackert Dresden, Germany	Academy
Johannes Schramm Bonn, Germany	Michael Apuzzo
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M. Christopher Wallace Toronto, Ontario	James Rutka
Philip Weinstein San Francisco, CA	Robert Ratcheson
Richard Zimmerman Scottsdale, AZ	Harold Young

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Earle E. Crandall 1964
Stephen Mahaley, Jr. 1965
Chun Ching Kao 1966
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Yoshio Hosobuchi 1968
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Howard J. Senter 1978
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David Dubuisson 1980
Dennis A. Turner 1981
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Kevin J. Kiwak 1984
Terry Lichtor 1985
Michael G. Nosko 1986
Joseph R. Madsen 1987
James T. Rutka 1988
Christopher D. Heffner 1989
Scott I. Gingold 1990
Mary Louise Hlavin 1991
Adam P. Brown 1992
Michael Tymianski 1993
David Garrett, Jr. 1994
L. Brannon Thomas 1995
John S. Yu 1996
Gregory Canute 1997
Nathan R. Selden 1998

MEETINGS OF THE ACADEMY

Hotel Netherland Plaza, Cincinnati, Ohio ..... October 28-29, 1938
Roosevelt Hotel, New Orleans, Louisiana ..... October 27-29, 1939
Tudor Arms Hotel, Cleveland, Ohio ..... October 21-22, 1940
Mark Hopkins Hotel, San Francisco, California ... November 11-15, 1941
Ambassador Hotel, Los Angeles, California..... November 11-15, 1941
The Palmer House, Chicago, Illinois ..... October 16-17, 1942
Hart Hotel, Battle Creek, Michigan..... September 17-18, 1943
Ashford General Hospital, White Sulphur Springs,
West Virginia ..... September 7-9, 1944
The Homestead, Hot Springs, Virginia ..... September 9-11, 1946
Broadmoor Hotel, Colorado Springs,
Colorado ..... October 9-11, 1947
Windsor Hotel, Montreal, Canada ..... September 20-22, 1948
Benson Hotel, Portland, Oregon ..... October 25-27, 1949
Mayo Clinic, Rochester, Minnesota..... September 28-30, 1950
Shamrock Hotel, Houston, Texas ..... October 4-6, 1951
Waldorf-Astoria Hotel, New York City,
New York ..... September 29-October 1, 1952
Biltmore Hotel, Santa Barbara, California ..... October 12-14, 1953
Broadmoor Hotel, Colorado Springs, Colorado ..... October 21-23, 1954
The Homestead, Hot Springs, Virginia ..... October 27-29, 1955
Camelback Inn, Phoenix, Arizona ..... November 8-10, 1956
The Cloister, Sea Island, Georgia ..... November 11-13, 1957
The Royal York Hotel, Toronto, Canada ..... November 6-8, 1958
Del Monte Lodge, Pebble Beach, California..... October 18-21, 1959
Copley Sheraton Plaza, Boston, Massachusetts ..... October 5-8, 1960
Royal Orleans, New Orleans, Louisiana ..... November 7-10, 1962
El Mirador, Palm Springs, California ..... October 23-26, 1963
The Key Biscayne, Miami, Florida..... November 11-14, 1964
Terrace Hilton Hotel, Cincinnato, Ohio ..... October 14-16, 1965
Fairmont Hotel & Towers, San Francisco,
California ..... October 17-19, 1966
The Key Biscayne, Miami, Florida ..... November 8-11, 1967
Broadmoor Hotel, Colorado Springs, Colorado ..... October 6-8, 1968
St. Regis Hotel, New York City ..... September 21, 1969
Camino Real, Mexico City, Mexico..... November 18-21, 1970
Sahara-Tahoe Hotel, Stateline, Nevada ..... September 26-30, 1971
New College, Oxford, England ..... September 4-7, 1972
Huntington-Sheraton Hotel, Pasadena, California November 14-17, 1973
Southampton Princess Hotel, Bermuda..... November 6-9, 1974
The Wigwam (Litchfield Park), Phoenix, Arizona ... November 5-8, 1975
Mills Hyatt House, Charleston, South Carolina .... November 10-13, 1976
Mauna Kea Beach Hotel, Kamuela, Hawaii ..... November 2-5, 1977

Hotel Bayerischer Hof, Munich, Germany ..... October 22-25, 1978
Hyatt Regency, Memphis, Tennessee ..... November 7-10, 1979
Walforf-Astoria Hotel, New York City, New York ..... October 1-4, 1980
Sheraton Plaza, Palm Springs, California ..... November 1-4, 1981
Ritz-Carlton Hotel, Boston, Massachusetts ..... October 10-13, 1982
The Lodge at Pebble Beach, California ..... October 23-26, 1983
The Homestead, Hot Springs, Virginia ..... October 17-20, 1984
The Lincoln Hotel Post Oak, Houston, Texas ..... October 27-30, 1985
The Cloister, Sea Island, Georgia ..... November 5-8, 1986
Hyatt Regency, San Antonio, Texas ..... October 7-10, 1987
Omni Netherland Plaza, Cincinnati, Ohio ..... September 13-17, 1988
Loews Ventana Canyon, Tucson,
Arizona ..... September 27-October 1, 1989
Amelia Island Plantation, Amelia Island, Florida ..... October 2-7, 1990
Salishan Lodge, Gleneden Beach, Oregon ..... September 22-26, 1991
Ritz-Carlton Hotel, Naples, Florida ..... October 21-25, 1992
The Wigwam, Phoenix, Arizona ..... October 27-30, 1993
The Cloister, Sea Island, Georgia ..... November 3-6, 1994
Loews Ventana Canyon Resort, Tucson, Arizona ..... November 1-5, 1995
The Greenbrier, White Sulphur Springs,
West Virginia ..... September 18-22, 1996
Rimrock Resort, Banff, Alberta, Canada ..... September 10-14, 1997
Four Seasons Biltmore, Santa Barbara, California .... November 4-7, 1998
Ritz-Carlton, Amelia Island, Florida ..... November 10-13, 1999
The Broadmoor, Colorado Springs, Colorado ..... October 11-14, 2000
The Breakers, Palm Beach, Florida ..... November 14-17, 2001
The Phoenician, Scottsdale, Arizona ..... October 16-19, 2002

PAST PRESIDENTS

Dean H. Echols..... 1938-39
Spence Braden..... 1940
Joseph P. Evans..... 1941
Francis Murphey 1942
Frank H. Mayfield..... 1943
A. Earl Walker 1944
Barnes Woodhall..... 1946
William S. Keith..... 1947
Howard A. Brown 1948
John Raaf..... 1949
E. Harry Botterell..... 1950
Wallace B. Hamby 1951
Henry G. Schwartz..... 1952
J. Lawrence Pool..... 1953
Rupert B. Raney..... 1954
David L. Reeves..... 1955
Stuart N. Rowe..... 1956
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George S. Baker..... 1960
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Samuel R. Snodgrass 1963
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Benjamin B. Whitcomb..... 1974
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Robert B. King 1979
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Henry Garretson..... 1992
George Tindall 1993
William A. Buchheit 1994
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Edward Connolly 1998
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Roberto C. Heros..... 2001

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Francis Murphey 1941
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Howard M Eisenberg 2000
Richard B Morawetz 2001

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Francis Murphey 1938-40
A. Earl Walker 1941-43
Theodore C. Erickson..... 1944-47
Wallace B. Hamby 1948-50
Theodore B. Rasmussen.... 1951-53
Eben Alexander..... 1954-57
Robert L. McLaurin..... 1958-62
Edward W. Davis 1963-65
Robert G. Fisher 1966-68
Byron C. Pevehouse 1969-72

PAST SECRETARIES

Byron C. Pevehouse 1973
Russel H. Patterson, Jr. 1974-76
Phanor L. Perot, Jr..... 1977-80
John T. Garner..... 1981-83
James T. Robertson..... 1984-86
Nicholas T. Zervas..... 1987-89
William A. Buchheit..... 1990-92
Julian T. Hoff 1992-95
Roberto C. Heros..... 1995-98
David G. Piepgras..... 1999-01

PAST TREASURERS

Russel H. Patterson, Jr. 1973
Phanor L. Perot, Jr 1974-76
John T. Garner 1977-80
James T. Robertson 1981-83
Nicholas T. Zervas 1984-86
William A. Buchheit 1987-89
Julian T. Hoff 1990-92
Roberto C. Heros..... 1992-95
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L. Nelson Hopkins..... 1999-01

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E. HARRY BOTTERELL Kingston, Ontario, CANADA (Senior)	1938	1997
ROBERT S. BOURKE Rockville, Maryland (Senior)	1983	1996
SPENCER BRADEN Cleveland, Ohio (Active)	Founder	1969
F. KEITH BRADFORD Houston, Texas (Active)	1938	1971
JEAN BRIHAYE Bruxelles, BELGIUM (Senior Corresponding)	1975	1999

KARL-AUGUST BUSHE 1972 1999
Wurzburg, GERMANY
(Senior Corresponding)

HOWARD BROWN 1939 1990
San Francisco, California
(Senior)

JUAN CARDENAS 1966 1996
Mexico City, MEXICO
(Senior Corresponding)

SHELLEY CHOU 1974 2001
Rio Verde, Arizona
(Senior)

GALE CLARK 1970 1996
Oakland, California
(Senior)

DONALD COBURN 1938 1988
Wilmington, Delaware
(Senior)

WINCHELL McK. CRAIG 1942 1960
Rochester, Minnesota
(Honorary)

EDWARD DAVIS 1949 1988
Portland, Oregon
(Senior)

PEARDON DONAGHY 1970 1991
Burlington, Vermont
(Senior)

CHARLES DRAKE 1958 1998
London, Ontario, CANADA
(Senior)

FRANCIS ECHLIN 1944 1988
New Poaltz, New York
(Senior)

DEAN ECHOLS ..... Founder 1991
New Orleans, Louisiana
(Senior)

GEORGE EHNI 1964 1986
Houston, Texas
(Senior)

ARTHUR ELVIDGE 1939 1985
Montreal, Quebec, CANADA
(Senior)

THEODORE ERICKSON 1940 1986
Madison, Wisconsin
(Senior)

JOSEPH EVANS ..... Founder 1985
Kensington, Maryland
(Senior)

JOHN FRENCH 1951 1989
Los Angeles, California
(Senior)

JAMES GALBRAITH 1947 1997
Birmingham, Alabama
(Senior)

EVERETT GRANTHAM 1942 1997
Louisville, Kentucky
(Senior)

JOHN GREEN 1953 1990
Phoenix, Arizona
(Senior)

JAMES GREENWOOD, JR. 1952 1992
Houston, Texas
(Senior)

WESLEY GUSTAFSON 1942 1975
Jensen Beach, Florida
(Senior)

WALLACE HAMBY 1941 1999
Pompano Beach, Florida
(Senior)

HANNIBAL HAMLIN 1949 1982
Providence, Rhode Island
(Senior)

JOHN HANBERY 1959 1996
Palo Alto, California
(Senior)

E. BRUCE HENDRICK 1968 2001
Toronto, Ontario, CANADA
(Senior)

JESS HERRMANN 1938 1994
Oklahoma City, Oklahoma
(Senior)

HENRY HEYL 1951 1975
Hanover, New Hampshire
(Senior)

WILLIAM HUNT 1970 1999
Columbus; Ohio
(Senior)

OLAN HYNDMAN 1942 1966
Iowa City, Iowa
(Senior)

KENNETH JAMIESON 1970 1976
Brisbane, AUSTRALIA
(Corresponding)

SIR GEOFFREY JEFFERSON 1951 1961
Manchester, ENGLAND
(Honorary)

HANS-PETER JENSEN 1980 2000
Kiel, GERMANY
(Senior Corresponding)

RICHARD JOHNSON 1974 1997
Cheadle Hulme, ENGLAND
(Senior Corresponding)

WILLIAM KEITH ..... Founder 1987
Toronto, Ontario, CANADA
(Senior)

RICHARD KRAMER 1978 2001
Durham, North Carolina
(Inactive)

HUGO KRAYENBUHL 1974 1985
Zurich, SWITZERLAND
(Honorary)

KRISTIAN KRISTIANSEN 1967 1993
Oslo, Norway
(Senior Corresponding)

THEODORE KURZE 1967 2002
Newport Beach, California
(Senior)

WALPOLE LEWIN 1973 1980
Cambridge, ENGLAND
(Corresponding)

VALENTINE LOGUE 1974 2000
London, ENGLAND
(Honorary)

HERBERT LOURIE 1965 1987
Syracuse, New York
(Senior)

WILLEM LUYENDIJK 1973 1995
Oegstgeest, NETHERLANDS
(Senior Corresponding)

ERNEST MACK 1956 2000
Reno, Nevada
(Senior)

M. STEPHEN MAHALEY 1972 1992
Birmingham, Alabama
(Active)

GEORGE MALTBY 1942 1988
Scarsborough, Maine
(Senior)

FRANK MARGUTH 1978 1991
Munich, GERMANY
(Senior Corresponding)

DONALD MATSON 1950 1969
Boston, Massachusetts
(Active)

FRANK MAYFIELD ..... Founder 1991
Cincinnati, Ohio
(Senior)

AUGUSTUS McCRAVEY 1944 1990
Chattanooga, Tennessee
(Senior)

KENNETH McKENZIE 1960 1964
Toronto, Ontario, CANADA
(Honorary)

WILLIAM MEACHAM 1952 1999
Nashville, Tennessee
(Senior)

JAMES MEREDITH 1946 1962
Richmond, Virginia
(Active)

J. DOUGLAS MILLER 1988 1995
Edinburgh, SCOTLAND
(Corresponding)

W. JASON MIXTER 1951 1968
Woods Hole, Massachusetts
(Honorary)

EDMUND MORRISSEY 1941 1986
San Francisco, California
(Senior)

FRANCIS MURPHEY ..... Founder 1994
Naples, Florida
(Senior)

GOSTA NORLEN 1973 1985
Goteborg, SWEDEN
(Honorary)

FRANK NULSEN 1956 1994
Naples, Florida
(Senior)

SIXTO OBRADOR 1973 1978
Madrid, SPAIN
(Honorary)

GUY ODOM 1946 2001
Durham, North Carolina
(Senior)

PIETRO PAOLETTI 1989 1991
Milan, ITALY
(Corresponding)

HANS-WERNER PIA 1978 1986
Giessen, WEST GERMANY
(Corresponding)

WILDER PENFIELD 1960 1976
Montreal, Quebec, CANADA
(Honorary)

HELMUT PENZHOLZ 1978 1985
Heidelberg, WEST GERMANY
(Corresponding)

BERNARD PERTUISET 1986 2000
Paris, FRANCE
(Honorary)

ROBERT PUDENZ 1943 1998
South Pasadena, California
(Senior)

JOHN E. RAAF 1938 2000
Portland, Oregon
(Senior)

AIDAN RANEY 1946 2002
Los Angeles, California
(Senior)

JOSEPH RANSOHOFF 1965 2001
Tampa, Florida
(Senior)

THEODORE RASMUSSEN 1947 2002
Montreal, Quebec, CANADA
(Senior)

BRONSON RAY 1992 1993
New York, New York
(Honorary)

DAVID REEVES 1939 1970
Santa Barbara, California
(Active)

DAVID REYNOLDS 1964 1978
Tampa, Florida
(Active)

R. C. L. ROBERTSON 1946 1985
Houston, Texas
(Senior)

STEWART ROWE 1938 1984
Pittsburgh, Pennsylvania
(Senior)

RICHARD SCHNEIDER 1970 1986
Ann Arbor, Michigan
(Senior)

HENRY SCHWARTZ 1942 1998
St. Louis, Missouri
(Senior)

WILLIAM SCOVILLE 1944 1984
Hartford, Connecticut
(Senior)

R. EUSTACE SEMMES 1955 1982
Memphis, Tennessee
(Honorary)

SAMUEL SNODGRASS 1939 1975
Galveston, Texas
(Senior)

GLEN SPURLING 1942 1968
La Jolla, California
(Honorary)

C. WILLIAM STEWART 1948 1948
Montreal, Quebec, CANADA
(Corresponding)

THORALF SUNDT, JR. 1971 1992
Rochester, Minnesota
(Active)

KENICHIRO SUGITA 1988 1994
Nagoya, Japan
(Senior Corresponding)

HENDRIK SVIEN 1957 1972
Rochester, Minnesota
(Active)

HOMER SWANSON 1949 1987
Atlanta, Georgia
(Senior)

WILLIAM SWEET 1950 2001
Brookline, Massachusetts
(Senior)

ALFRED UIHLEIN 1950 1990
Rochester, Minnesota
(Senior)

A. EARL WALKER 1938 1995
Albuquerque, New Mexico
(Senior)

ARTHUR WARD, JR. 1953 1997
Seattle, Washington
(Senior)

THOMAS WEAVER, JR. 1943 1985
Dayton, Ohio
(Senior)

W. KEASLEY WELCH 1957 1996
Waban, Massachusetts
(Senior)

BENJAMIN WHITCOMB 1947 1998
Surrey, Maine
(Senior)

BARNES WOODHALL 1941 1985
Durham, North Carolina
(Senior)

FRANK WRENN 1973 1990
Greenville, South Carolina
(Senior)

FUTURE MEETING

2003 – October 29–November 1
Colonial Williamsburg–Williamsburg, VA

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