Abstracts: Poster Session

POSTER PRESENTATION:
PEDIATRIC NEUROLOGY

P1. Childhood Guillain-Barré Syndrome in Paraguay: 1989–1991
David E. Hart, Laura A. Rojas, Joana Rosario, Humberto Recalde, and Gustavo
To identify recent pediatric cases of Guillain-Barre syndrome in Paraguay, we screened all cases of childhood acute flaccid paralysis reported to the Paraguayan Ministry of Health during 1989 to 1991. All cases were reviewed independently by 2 neurologists using National Institute of Neurological Disorders and Stroke diagnostic criteria. Of 59 patients, 46 (29 males, 17 females) were considered to have GBS. The average age was 4.0 years (range, 11 mo–14 yr). Ninety-three percent had nerve conduction studies and 46% had lumbar puncture. Seventy percent of cases had onset in January through April, corresponding to Paraguayan summer and early fall. The average annual incidence for the years 1990 to 1991 was 1.1/100,000 population. Of note were the low rates of hospitalization (54%), respiratory compromise (6.5%), and death (4.3%). Twenty-eight percent of patients had definite or possible exposure to organophosphate insecticides (peak use in December–March). We examined the association of such factors as prior immunization, preceding illness, possible toxin exposure, and age and sex, with length and severity of clinical course, likelihood of hospitalization and intubation, and prognosis. The relatively low rates of hospitalization and intubation observed may reflect differences in incidence and severity of childhood GBS, or differences in access to, and patterns of, health-care delivery in developing countries.

P2. Evaluation of Acute Cerebellar Ataxia of Childhood for Antibody Against Cerebellar Neurons
J. Adair, K. Jaekle, F. Filioux, G. Fouad, J. Thompson, V. Tait, and J. Greenlee, Salt Lake City, UT
An immune etiology has been postulated for acute cerebellar ataxia of childhood (ACAC) since it frequently follows viral infections. We analyzed serum and cerebrospinal fluid (CSF) from 6 ACAC patients for antibody cross-reacting with cerebellar neurons. Serum and CSF were obtained within 7 days of onset of cerebellar ataxia from subjects aged 3.5 to 11 years. Varicella infection preceded 4 cases. Results of enhanced cranial CT scans were normal; CSF demonstrated 2–122 cells/mm³ with sterile cultures. Serial dilutions from 1:20 of serum and undiluted CSF were screened for antineuronal antibody by indirect immunofluorescence (IIF) using frozen, unfixed normal human cerebellum. Serum (1:400) was examined further for antineuronal antibody by Western immunoblotting using purified cerebellar neuronal extracts as antigen. Serum from age-matched, neurologically normal pediatric inpatients served as the control group for IIF and immunoblot experiments. In ACAC patients, no antineuronal immunoreactivity was observed by IIF. Immunoblots demonstrated no consistent pattern of immunoreactivity when comparing ACAC to controls, though 1 patient exhibited distinct bands at 200 kd (neurofilament protein) and 54 kd. Although antecedent infection suggests an immune etiology for ACAC, our preliminary results do not support a humoral mechanism for this disorder.

P3. Initial Experience with Magnetic Resonance Angiography in Pediatric Cerebrovascular Disease
Ingrid Taff, Joseph Zito, Robert Gould, and Steven Pavlakis, Great Neck and Manhasset, NY
In a 20-month period we studied 69 patients between the ages of 7 weeks and 21 years with magnetic resonance angiography (MRA). Studies were performed on a 1.5T magnet (Siemens Magnetom SP) with a circular polarized head coil. A three-dimensional time-of-flight technique was utilized. Occasionally, images were obtained after gadopentetate di-meglumine infusion. Two-dimensional projection images were calculated using a maximum intensity projection algorithm and recorded on laser film. Sixty-seven patients also had routine MRA. A sampling of vascular lesions was demonstrated. Nineteen patients had clinical and MRI evidence of stroke. MRA revealed intracranial vascular occlusion in 2 patients, diminished focal cerebral flow in the affected area in 4, and generalized ipsilateral underdeveloped cerebral circulation in 4. A Moy-Moya vascular pattern was found in 4 and sickle-cell vasculopathy was found in 1 patient. Seven MRAs were normal. Seventeen vascular hamartomas were demonstrated including 2 vein of Galen malformations, 7 arteriovascular malformations, and 8 venous angiomas. Three aneurysms were found. Thirty-one MRAs were normal. We find MRA to be a valuable adjunct to routine MR imaging in the evaluation of pediatric patients with potential cerebrovascular disease. It demonstrates a spectrum of pathology, is noninvasive, and allows for serial follow-up examinations.

P4. Thalamic Change in Acute Encephalopathy of Early Childhood
Huei-Shyong Wang, Song-Chi Huang, Li-Tong Huang, and Po-Cheng Hung, Taipei, Taiwan
Involvement of the bilateral thalami in asphyxiated neonates or young infants has been reported before. Their pathological changes include hemorrhage, calcification, or status marmoratus. However, in an older infant or even preschool child, symmetrical and bilateral thalamic change rarely is reported to our best knowledge. Seven Chinese children (age range, 5–46 mo) acutely developed seizure and consciousness change after minor prodrums such as vomiting, diarrhea, and/or low-grade fever. Their thalamic areas were demonstrated to be hyperechogenic on ultrasonogram and hypodense on computed tomographic brain image bilaterally and symmetrically; 4 had magnetic resonance imaging showing low signal on T1- and high signal on T2-weighting over the same areas. Four patients also had abnormal periventricular findings. One of them died after this kind of episode. Five patients survived with neurological sequelae. Recovery occurred completely in the remaining 1 patient. We suggest that thalamic vulnerability may result in a specific pattern of brain damage, not only in postasphyxial neonates but also in older infants and even preschool children with acute encephalopathy.
POSTER PRESENTATION: TRAUMA

P5. Differentiation of Reactive Astrocytes
Dennis M. D. Lands, Cleveland, OH

Astrocytes responding to injury in the mammalian central nervous system alter the expression of preexisting cellular components and acquire new characteristics. For example, the monoclonal antibody 8C10, one of a panel of antibodies we generated by immunization with membranes isolated from cultured astrocytes, binds to an epitope expressed on the surface of normal astrocytes. When rat frontal cortex is injured by implantation of a millipore filter, astrocytic processes in the vicinity of the filter increase their expression of the 8C10 epitope. To identify properties of reactive astrocytes that are not expressed by normal astrocytes, we have placed similar filters in rat brain, and then removed them 10 days later and used them as an immunogen in the generation of monoclonal antibodies. This technique has generated several antibodies, such as 13A11, which do not stain normal brain, but do stain reactive astrocytes in traumatized cortex. Monoclonal antibodies that bind to reactive astrocytes may serve as labels to identify the reactive cells, as probes to characterize the properties of the reactive cells, and as tools with which to modulate the reactive process itself.

P6. EEG Predicts Neurological Recovery of Dogs Undergoing Profound Hypothermic Circulatory Arrest
Santiago Arroyo, Ronald P. Lesser, J. Mark Redmon, A. Mark Gillinov, Darryl Jackson, and William A. Baumgartner, Baltimore, MD

Deep hypothermia (DH) (18–20°C) during prolonged circulatory arrest and cardiac bypass is used to repair complex intracardiac lesions and vascular neurosurgical lesions. DH diminishes the risk of ischemic damage and multigorgan failure after circulatory arrest. Profound hypothermia (PH) to 6 to 7°C recently has been reported to improve neurological outcome in dogs after 2 hours of circulatory arrest. There are relatively limited data, however, regarding how best to monitor patients undergoing these procedures and how best to predict eventual clinical outcome. As part of a controlled study of cardiopulmonary bypass and 2 hours of cardiac arrest, we compared EEG recovery to neurological outcome in 2 groups of dogs: 4 under DH and 4 under PH. Overall results were: all of the dogs under PH had a good outcome (mean neurological score [MNS] 6.25/500), compared with DH (MNS 314.95/500) (p < 0.01). EEG activity 2 hours after reperfusion was able to predict the neurological outcome. EEG variables associated with good outcome were main frequency and degree of rhythmicity of the activity. We conclude that PH exerts a protective effect after 2 hours of circulatory arrest and that EEG is a useful tool for predicting neurological outcome.

P7. Studies on Transplantation of Embryonic Rat Spinal Cord to Adult Rat Spinal Cord
Yasuo Iwatsuki, Masato Kinoshita, Ken Ikeda, Toshiya Shijima, Nozomi Tagaya, and Tomoko Kobayashi, Tokyo, Japan

Spinal cord tissue was obtained from 13- and 14-day-old embryonic rats and grafted to the hemisectioned spinal cord of adult rats. Twelve weeks after grafting, clinical and histological studies were performed. We developed a protocol for evaluating functional deficits that follow spinal cord injury in the rat. The survival, growth, differentiation, and parenchymal integration of the graft were documented histologically on semi-thin section. Animals that received the transplants demonstrated qualitative and quantitative improvements in several parameters of locomotion. Donor tissue integrated most often with the host spinal cord at interfaces with host gray matter; however, some implants also exhibited sites of fusion with damaged host white matter. We suggest embryonic rat spinal cord transplantation may be a useful treatment of spinal cord injury and a possible therapeutic strategy in human spinal cord injury and amyotrophic lateral sclerosis.

Monday, October 19

POSTER PRESENTATION: BEHAVIORAL NEUROLOGY

P8. Visual Opportunity and Lateralized Attention in Hemineglect
Ruthmary K. Deul, St Louis, MO

The basic neuropathophysiology of hemineglect after unilateral cerebral lesions is still not clear. One theory holds that degraded perceptual processing occurs in the damaged hemisphere due to intrahemispheric deficits. Another holds interhemispheric interaction at fault, with the intact hemisphere actively inhibiting spatial cognitive processes in the damaged one. We tested 11 adult Macaca fascicularis with acute neglect on a task in which the whole visual surround was restricted to 15 degrees from central fixation, and a second in which an opaque lens occluded the eye either ipsilateral (ipsi) or contralateral (contra) to the lesion. Using paired t tests, in the first task there were no differences in reaction time to the ipsi and contralesional hemifields. In the second, there was no change in extent of the ipsilesional field (obtained with the contralesional eye occluded), as compared to its extent without occlusion. The contralesional field, however, improved significantly (p < 0.03) with the ipsilesional eye occluded. Since reducing sensory input to both hemispheres leads to no worsening of hemineglect, but reducing sensory input to the intact hemisphere alone leads to improvement of hemineglect, we conclude that adverse interhemispheric interactions play a major role in the pathophysiology of hemineglect.

P9. A Rapid, Sensitive Combined Cognitive and Mood Screen for Relapsing and Progressive Multiple Sclerosis
Glenn A. Mackin, Philadelphia, PA

We assessed the sensitivity and applicability of a new, combined cognitive and mood screening battery for multiple sclerosis (MS). Sixty consecutive, untreated clinically active MS patients, 30 each relapsing-remitting and chronic progressive, underwent the battery and had MRI upon entering 2 concurrent treatment trials. The battery combines the Faust-Fogel Brief Cognitive Screen and Visual Analogue Dysphoria Scale, both previously validated in other neurological diseases. Cognitive domains tested were immediate and delayed sentence and word-pair recall, verbal fluency, and conflicting response suppression. Patients marked "usual mood" along a "happy-sad" cartoon continuum. Relapsing patients were
This combined cognitive and mood screening battery is sensitive and administered within 10 minutes without special equipment.

Despite similar "sadness" rates (20% vs 23%), subjective dysphoria in both groups correlated with denser periventricular lesion burdens. The battery was well tolerated and easily administered within 10 minutes without special equipment. This combined cognitive and mood screening battery is sensitive and convenient for clinically active MS. Alternate forms of the battery are needed for repeatability.

P10. Informant-based Information Correlates with Objective Measures of Memory and Cognition in Alzheimer's Disease

E. Kass, M. B. Patterson, R. L. Ownby, J. Stucky, and P. J. Whitehouse, Cleveland, OH

Questionnaires may be reliable and valid supplements to laboratory tests for brain-damaged patients, as they can be applied to situations for which laboratory testing is not possible. We investigated the usefulness of informant-based data in Alzheimer's disease (AD) by comparing caregivers' subjective evaluations of 83 probable AD patients' performance on an abbreviated version of the Memory Self-Report Questionnaire to objective evaluations derived from an extensive battery of neuropsychological tests and to clinicians' evaluations. Similar information was obtained from 39 healthy age-matched controls. Caregivers' subjective appraisals of patients' memory correlated significantly with objective measures of secondary memory, with all cognitive variables, measures of Activities of Daily Living, and clinicians' evaluations of dementia staging. Scores were independent of clinical indicators of depression. The abbreviated Memory Questionnaire showed good reliability, internal consistency, and external validity. Its positive predictive value is 63.5% and its negative predictive value is close to 100%. Results suggest that (1) informant-based questionnaires may be useful for obtaining valid information on cognitive ability outside of laboratory settings; (2) the scale reflected more than just memory functions; and (3) the scale may be promising for screening cognitive difficulties in epidemiological or clinical settings.

P11. Neglect of Upper Vertical and Far Radial Space

Steven Z. Rapcsak, Mark Mennemeier, and Alan B. Rubens, Tucson, AZ

Although neglect along the horizontal dimensions of extrapersonal space is well recognized, there are only a limited number of observations documenting neglect along the vertical and radial spatial dimensions. We report an investigation of neglect along the 3 principal dimensions of extrapersonal space in a patient with bilateral mesial temporo-occipital infarctions. Neglect was assessed by asking the patient and controls to bisect lines of 4 lengths oriented in 3 directions with respect to the body: horizontal, vertical, and radial. Our patient showed significant neglect of upper vertical and far radial space, as well as neglect of left hemispace. His line bisection errors were consistently in a direction opposite the slight directional biases shown by controls for all 3 line orientations (p < .05). The magnitude of the patient's bisection errors increased by moving the lines toward the neglected sectors of 3-dimensional space. Neglect of upper vertical and far radial space was also evident on line cancellation tasks. Our results suggest that following focal brain injury, neglect may be observed along all 3 dimensions of extrapersonal space. These findings provide further empirical support for functional specialization within inferior and mesial temporo-occipital regions for attending to upper vertical and far visual space (Previc, 1990).

P12. Posterior Cortical Atrophy: Degenerative Disease with Primary Visuospatial and Visuosemantic Deficits

A. Kertesz, M. Polk, and A. Kirk, London, Ontario, and Saskatoon, Saskatchewan, Canada

Posterior cortical atrophy is a recent, and Heidenhain's disease is an old, label for a miscellaneous group of patients with imaging or pathological and clinical evidence of visuo-cognitive deficits and cortical atrophy localized to the posterior cortex. The extent of this cortical localization and the nature of the pathological findings are not fully agreed upon, but spongiform degeneration and Alzheimer pathology have been described. Detailed examination of patients who are representative of the problem and who have uniquely specific deficits is presented. One patient had visual associative agnosia, prosopagnosia, and transcortical sensory aphasia. Lexico-semantic experiments of categorization, word retrieval, and comprehension of auditory and visual stimuli showed a specific impairment of visuo-semantic semantics. A striking preservation of phonological, orthographic and visual structural input, and intercategory dissociations was demonstrated. Consistency of errors argued for specific loss of semantic knowledge. Another patient with apraxia, primary visuospatial deficit, agraphia, and amnesia at the beginning had predominantly right-sided posterior cortical atrophy, demonstrating further fractionation of the entity and the striking specificity of visuospatial function. The behavioral specification of degenerative disease is clinically and theoretically important.

P13. Circulating Intercellular Adhesion Molecule-1 Levels and Neutrophil Adhesion in Stroke

Wayne M. Clark, Bruce M. Coull, Dennis P. Briley, and Robert Rothlein, Portland, OR, and Ridgefield, CT

Activated leukocytes appear to be directly involved in potentiating central nervous system ischemic injury. After initial endothelial adherence mediated by intercellular adhesion molecule (ICAM-1) and its ligand, leukocyte adhesion molecule (CD-18), neutrophils can produce capillary plugging with subsequent parenchymal infiltration and resulting cytotoxic neuronal injury. Recently a circulating form of ICAM-1 has been discovered (clCAM-1). To examine whether changes in leukocyte adhesion properties are of clinical significance, we measured clCAM levels and neutrophil adhesion in acute stroke (within 72 hr) or in patients at high risk of stroke (2 or more risk factors) compared to matched controls. Levels of circulating ICAM were determined by sandwich enzyme-linked immunosorbent assay (ELISA). Se rum levels of clCAM were significantly lower (p < .05) in the stroke group (186.2 ± 15.6 ng/ml) compared to controls (257.7 ± 24.8) and risks (257.7 ± 16.5). Neutrophil adherence to laminin was determined using a myeloperoxidase assay. Neutrophil adhesion was significantly higher (p < .05)
in the stroke group (23.6 ± 4.3%; n = 14) compared to controls (9.7 ± 2.3%; n = 12) with the risk group being intermediate (12.7 ± 2.5%; n = 13). Overall, there was a poor correlation between cCAM levels and neutrophil adhesion (r² = 0.06). These data support the involvement of leukocytes in ischemia and indicate that changes in leukocyte-adhesion dynamics are occurring in acute stroke.

P14. Value of Single Photon Emission Computed Tomography in Acute Stroke
A. V. Alexandrov, A. Pirisi, S. E. Black, L. Ehrlich, and J. W. Norris, Toronto, Ontario, Canada

Although single photon emission computed tomography (SPECT) scanning is widely used as a measure of cerebral perfusion, its clinical value in stroke patients remains uncertain. We evaluated 191 of 290 consecutive stroke patients with CT and SPECT scanning. In 180 of these, SPECT was performed twice in the acute period. On clinical/CT grounds, 77/191 (40%) were embolic, 82/191 (43%) were "cryptogenic," 15/191 (8%) were lacunar, and 17/191 (9%) were cerebral hemorrhage. Cerebral lesions were measured volumetrically on CT by a special computer program (Sigma Scan). High flow (HF) on SPECT was significantly more prevalent in the embolic group (38 HF:81 non-HF in the embolic group, vs 22 HF:121 non-HF in the nonembolic group; p = 0.001), indicating "luxury perfusion" in the acute stage. Normal flow (NF) was predominant in lacunes (12 NF:15 non-NF, vs 13 NF:222 non-NF; p < 0.00001). In small lesions (<10 cm³) normal flow was seen in lacunes, and low flow in embolic lesions, while "cryptogenic" small lesions showed a tendency to normal flow. SPECT is an adjunct to clinical examination in deciding on etiology in patients with stroke, but interpretation depends also on the size of the lesion.

P15. Spontaneous Echo Contrast, Ischemic Stroke, and Risk of Recurrent Stroke
Dennis P. Briley, George Giraud, Gene Spear, Bruce M. Coall, James Edwards, and Wayne M. Clark, Portland, VA, and Portland, OR

Spontaneous echo contrast (SEC), a smokelike appearance of blood in the heart, detected by transesophageal echocardiography (TEE), has retrospectively been associated with cardioembolic stroke. We prospectively performed TEE, neurological examination, hematocrit, and fibrinogen determinations on 31 stroke/transient ischemic attack (TIA) and 6 risk subjects to further investigate SEC and brain ischemia. Strokes were classified by standard criteria, and TEEs were interpreted by a blinded observer. SEC was present in 54% (8/15) of patients with cardioembolic, and 17% (3/18) with noncardioembolic stroke or TIA (p = 0.05). Patients with atrial fibrillation more often had SEC (64% [7/11] vs 17% [3/18], p < 0.02). Fibrinogen levels were higher in patients with SEC (mean 407 ± 110 vs 376 ± 82 mg/dl, p < 0.001, Wilcoxon rank), but hematocrits were similar (mean 43 ± 4 and 43 ± 6%, respectively). During 6 months' follow-up, 55% (6/11) of patients with SEC and 14% (3/21) without SEC had recurrent vascular events (p = 0.035). These results support the association between SEC and cardioembolic stroke and possibly stroke of other causes. SEC also may mark an increased risk of recurrent cerebrovascular events. The elevation of fibrinogen observed suggests SEC represents intracardiac erythrocyte microaggregates. Further study of SEC may lead to new stroke prevention strategies and improve stroke-risk stratification.

P16. Overstimulation of Capillary N-Methyl-D-Aspartate Receptors Triggers Blood-Brain Barrier Breakdown by Osmotic and Cryogenic Injury
Harold Koenig, Alfred D. Goldstone, Ching Y. Lu, and Jerome J. Trout, Chicago, IL

We previously found that reversible opening of the blood-brain barrier (BBB) by the intracarotid infusion of hyperosmolar (1.5 M) mannitol (HM), and persistent breakdown of the BBB after focal cryogenic injury (CI) involves a rapid increase in brain capillary polyamines and the activity of their regulating enzyme ornithine decarboxylase (ODC) (Koenig et al, Brain Res 1989a;483:110-116; J Neurochem 1989;52:101-109). BBB breakdown (BBBDD) by CI, and probably by HM, is mediated by activated transcytosis across brain capillaries (BC) (Trout et al, Lab Invest 1986;55:622-631). We tested the hypothesis that N-methyl-D-aspartate (NMDA) receptors (R) are involved in mediating activation of ODC and BBBDD in these models. The potent, noncompetitive NMDA-R antagonist MK-801 (1-10 mg/kg) prevented the HM- and CI-induced stimulation of ODC activity and BBBDD, monitored by leakage of fluorescein, α-[14C]diaminobutyrate, and horseradish peroxidase (HRP).

NMDA-R coupled to ODC are present on rat BC and appear to regulate HRP endocytosis and transport of Ca²⁺ and glucose (Koenig et al, Soc Neurosci Abstr 1991;17:7). These results support the conclusion that HM, CI, and neuropathological conditions associated with abnormally elevated extracellular glutamate would result in overstimulation of NMDA-R, thereby triggering activation of the ODC/polyamine cascade and BBBDD. (Supported by the VA Research Service and NIH grants NS 18047 and HL 26835.)

P17. Recovery of Poststroke Aphasia Is Related to Glucose Metabolism at Rest and During Activation
W. D. Heiss, J. Kasier, H. Karbe, and G. Fink, Klin, Germany

 Permanent neurological deficits after ischemic stroke are mainly determined by the location and size of the infarct. Clinical recovery also depends on the functional state of adjacent brain tissue, where both neuronal loss and deactivation without gross morphological damage may affect flow and metabolism to a varying degree (G. Mies et al, Stroke 1983;14:22-27), and where the ability to respond to stimulation by appropriate neuronal recruitment may be impaired. Therefore, degree of resting hypometabolism and of responsiveness to functional activation may provide a measure of prognosis. In 26 patients (age 60.7 ± 10.9 yr) with aphasia consequent to ischemic stroke of the dominant hemisphere, regional cerebral metabolic rate of glucose (rCMRGl) was measured at rest and in 17 of them also during spontaneous speech, using positron emission tomography (PET) of 2-(F18)fluoro-2-deoxy-D-glucose (FDG). The PET study and a standardized neuropsychological test battery to assess the main aspects of language were performed around the fourteenth day after the stroke, and the language functions were assessed again 3 to 5 months later. Performances in various dimensions of language 2 weeks and 3 to 5 months after stroke were related to rCMRGl in topographically meaningful areas at rest and during activation using Wilcoxon-rank
was assessed by the Token test, which showed a bimodal sum test and multiple regression analysis. Severity of aphasia Token test at first and second examination, with the highest and during activation were significantly correlated to scores in KMRGI, but with lower coefficients that slightly increased for the recovery state. Language performance at different stages in the course after ischemic stroke was significantly related ($r = 0.84$ for Token test, $r = 0.93$ for verbal fluency). However, there exists a high variability in recovery that may be explained by stepwise regression of metabolic values. Significant effects were observed only for CMRGl of the left hemisphere outside the infarct (partial $R^2 = 0.21$) at rest and for CMRGl within the infarct (0.27), the contralateral mirror region (0.16), and Broca’s region (0.17) during activation, with a sum of all partial weight factors of 0.46 at rest and 0.72 during activation. Our results furnish 2 indicators for recovery of aphasia: the resting metabolism of the left hemisphere outside the infarct, and the activated metabolism in residual tissue within the infarct and in language-related areas. Although the hemispheric metabolism at rest might be related to neuronal loss and thereby to the brain’s reserve capacity, the extent of metabolic activation indicates neuronal recruitment and the capability of neuronal networks for functional recovery.

P18. Ischemic Cerebral Infarction after rt-PA and Heparin Therapy for Acute Myocardial Infarction: The TIMI-II Pilot and Randomized Trial Combined Experience

M. A. Sloan, T. R. Price, M. L. Terrin, and S. Forman for the TIMI Investigators, Baltimore, MD

Of 3,924 myocardial infarction (MI) patients treated with rt-PA and heparin, 29 (0.7%) developed ischemic cerebral infarcts (CI). All CI patients had detailed neurological evaluations and 27 (93%) had CT scans. Age range was 40 to 74 years (mean 60 yr), 25 were male, and 22 were Caucasian. Electrocardiographic location of MI was anterior in 22 (76%) and nonanterior in 7 (24%). Six CIs occurred within 6 hours; 1 between 6 and 12 hours; 2 between 12 and 24 hours; 4 between 24 and 48 hours; 13 during the second week; and 3 others distributed over the 4 weeks after study entry. Six of 29 CIs did not involve cerebral cortex; 9 (31%) had multiple CIs. Of 24 CIs thought to be embolic in origin, 17 had at least 1 cardiac abnormality (mural clot, wall motion abnormality, aneurysm, or transient atrial fibrillation) known to be associated more specifically with embolism than just the diagnosis of myocardial infarction. Eight of 27 (30%) with CT scans had hemorrhagic conversion of varying degrees. The time of occurrence and sites of CI after rt-PA and heparin therapy for acute MI are similar to those reported in the prethrombolytic area.

P19. The Ultrastructure of Photochemically Induced Thrombi and Emboli

Nancy Parrell and Jeanne M. Riddle, Detroit, MI

Photochemical irradiation of the carotid artery of rats has been used to induce endothelial damage, producing a nonocclusive thrombus (that apparently embolizes spontaneously) and multiple cerebral infarcts. Evidence for embolism generally has a presumptive component. To document further that cerebral infarcts in this model are indeed due to embolism, we studied the ultrastructure of the carotid thrombi and the presumed cerebral emboli using scanning and transmission electron microscopy (SEM, TEM). The right carotid artery of 9 Wistar rats was irradiated with a laser (632 nm, 200 mW/cm², 15 min) following the injection of the photosensitizing dye Photofrin II, 12.5 mg/kg. Rats were sacrificed from 1 to 24 hours later. Endothelial damage with formation of a fragmenting thrombus, composed mainly of platelets and erythrocytes (with no fibrin in most areas), was present in the carotid arteries of all rats by SEM. SEM was done on 36 cerebral vessels, 31 containing peripheral blood elements, with single (1) and aggregated (6) platelets (causing occlusion in 3), single (10) and aggregated (10) erythrocytes (without occlusion), and single (1) and aggregated (3) leukocytes (without occlusion). TEM demonstrated that the platelet aggregates did not adhere to the cerebral endothelium. The endotherial surface of all cerebral vessels was normal, which provided additional evidence that the mechanism of cerebral infarction in this model is embolism.

P20. CGS-19755 is Neuroprotective in Cell Culture Model of Repetitive Ischemia: This Effect is Significantly Enhanced When Combined with Mild Hypothermia

Ashfaq Shuaib and Elisabeth Sebocka, Saskatoon, Saskatchewan, Canada

There is considerable evidence that glutamate release resulting in activation of postsynaptic receptors (especially N-methyl-d-aspartate) is a major mechanism of ischemic neuronal injury. In vivo experiments have shown that a more severe release of glutamate may be responsible for the excessive damage seen with repeated ischemic insults. We have shown that in cell cultures the effect of brief repeated insults is more severe than a single insult of similar duration. In the present study, we tested the protective effects of CGS-19755 in a cell culture model of single ischemic and multiple-insult paradigm. In the multiple-insult paradigm, in some cultures CGS-19755 was combined with mild hypothermia to see if this would offer additional protection. CGS-19755 offered a dose-dependent protection in cell cultures exposed to a single ischemic insult. CGS-19755 was protective to cultures exposed to repeated ischemic insults. The protective effects were enhanced significantly when they were combined with hypothermia, resulting in almost complete protection of the cultures. The combination of therapies appears to be a valuable strategy in neuronal protection during cerebral ischemia.

P21. Cerebral Hyperemia in MELAS?

Toby I. Greppin, I. Prokopenik, T. K. Tatemiichi, Z. Sharif, and M. Hirano, New York, NY

Although a rare syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke (MELAS) may offer a unique insight into stroke mechanisms. We report novel observations in a patient with MELAS studied with serial and quantitative cerebral perfusion after stroke using $^{99m}$Tc-Ceretec SPECT and $^{133}$Xe rCBF. A 24-year-old man with MELAS presented with left-sided headache, generalized seizures, fluent aphasia, and right hemianopia. Serial CT and MRI showed infarction of the posterior left hemisphere in a multi-territorial distribution. SPECT performed 15 days after stroke showed 20 to 30% greater flow in the infarct than in...
normal brain, which reversed 109 days after stroke. Quantitative rCBF (M2 ISI, reflecting mostly gray matter), when corrected for severe hypopacia, was 86 ml/100 gm/min in the infarct region but 96 ml/100 gm/min in noninfarcted areas at 26 days. The corresponding values at 109 days after stroke were 74 ml/100 gm/min and 88 ml/100 gm/min. Thus, perfusion within the infarct region decreased slightly on later examination but remained mildly hyperemic. Perfusion of noninfarcted areas was consistently hyperemic. This study suggests that a generalized cerebral hyperemia occurs in MELAS, perhaps reflecting compensation for limited substrate utilization or lactic acidosis. This study also suggests that nonquantitative functional imaging may be misleading in MELAS, and that even within the infarcted region there may be stable, perhaps chronic, hyperemia.

P21. Central Venous Pressure Does Not Reflect Changes in Circulating Blood Volume Following Aneurysmal Subarachnoid Hemorrhage
Stephan A. Mayer, Matthew E. Fink, Laura Lennihan, Louis M. Klebanoff, Alex Beckford, Isak Probeninth, William Yang, and Robert A. Solomon, New York, NY
Reduction of blood volume (BV) has been implicated as a risk factor for delayed cerebral ischemia (DCI) due to vasospasm after aneurysmal subarachnoid hemorrhage (SAH). Volume expansion guided by target filling pressures has gained popularity as a means of preventing or reversing DCI; however, the adequacy of central venous pressure (CVP) as a reflection of BV in this setting remains unclear. We measured BV and CVP concurrently in 10 patients (5 males, 5 females; mean age 57 yr) 1 day after craniotomy (mean 3.5 days after SAH) and an average of 5.5 days later. The mean BV (ml/kg) measured using chromium51-labeled red blood cells (RBCs) fell from 69.7 to 55.3 (normal range 55–80), a reduction of 21% (p = .05, paired Student's t test). Despite this, mean CVP (mm Hg) remained unchanged (7.1 vs 7.9). Similar reductions of plasma volume (21%) and RBC volume (24%) accounted for no change in mean hematocrit (33.2 vs 33.5). BV fell 25.7% among grade III/IV patients (n = 5) compared to 14.7% among grade I/II patients (n = 5). A moderate correlation between BV and CVP (r = .48, p = .16) was found only with the first set of measurements. Time-related alterations in venous capacitance, myocardial contractility, or systemic vascular resistance may explain our findings.
P26. Cranial-Specific Hemostasis Findings in Acute Ischemic Stroke
Sebastian E. Ameriso, Vicky L. Y. Wong, Andreas Graber, Hidemi Iishi, and Mark Fisher, Los Angeles and La Jolla, CA, and Kanagawa, Japan

Hemostasis abnormalities are associated with ischemic stroke. These changes typically are demonstrated in antecubital venous blood samples and may not necessarily represent changes within the vasculature of the brain. The purpose of this study was to identify potential differences in hemostatic changes within the vasculature of the brain. The purpose of this study was to identify potential differences in hemostatic changes within the vasculature of the brain. Eight patients were studied within 7 days of acute brain infarction. Some patients were studied on 2 separate days. Blood was drawn from the external jugular vein and immediately thereafter from an antecubital vein without the use of tourniquet. We measured hemocrit, leukocyte count, platelet count, fibrin D-dimer (cross-linked fibrin fragment), plasminogen activator inhibitor-1 (PAI-1, an important antifibrinolytic protein), and anti-coagulant proteins thrombomodulin and activated protein C. A jugular-to-antecubital ratio was calculated for each paired blood sampling. Thirteen paired samples were obtained from the eight patients. External jugular-to-antecubital ratios (mean ± SD) were: hemocrit, 1.02 ± 0.02; leukocyte count, 1.02 ± 0.04; platelet count, 0.96 ± 0.13; fibrin D-dimer, 1.36 ± 0.98; PAI-1, 3.35 ± 3.83; thrombomodulin, 0.94 ± 0.29; and activated protein C, 0.89 ± 0.22. Jugular-to-antecubital ratio for PAI-1 was significantly different from 1 (< p < 0.05), with higher concentrations in jugular samples. In conclusion, levels of hemostatic proteins measured from cranial venous blood may differ from antecubital samples in patients with acute ischemic stroke.

P27. Hypothermia Protects Neural Cells from the Effects of Repetitive Ischemia
Ashfaq Shuaib and Elisabeth Secbocka, Saskatoon, Saskatchewan, Canada

In animal models of transient cerebral ischemia, the effects of repetitive insults are more severe than a single ischemic episode of similar duration. We used the cell culture model of ischemia to determine if the effects of repetitive ischemia are similarly more severe in this model of ischemia. For cell culture, we used fetal mice cortical astrocytic and postnatal cerebral (glutamatergic) granular neurons and cerebral gamma-aminobutyric acid (GABA)ergic cells. Lactic dehydrogenase (LDH) (activity per gram protein) release in the medium was used as a measure of cellular damage. Compared to a single insult, there was a large increase in LDH release during repetitive ischemia in astrocytes (233 vs 75, p < 0.02) and granular cells (129 vs 41, p < 0.001) (highly significant) and a modest (but significant) increase in the cortical neurons (11.6 vs 7.5 p = 0.05). The demonstration that repetitive ischemia produces more severe damage in cell culture would suggest that the mechanisms are not predominantly vascular. Cell culture could prove useful to study the mechanisms of neuronal damage with repetitive ischemia.

P28. Serial Assessment of Acute Stroke Using the NIH Stroke Scale
Robert J. Wityk, Michael S. Pesin, Richard F. Kaplan, and Louis R. Caplan, Boston, MA

We studied the spontaneous recovery of neurological function after acute ischemic stroke using a standardized stroke scale (NIH Stroke Scale) to assess the extent of improvement, differences in stroke types, and early predictors of later outcome. We performed serial neurological assessments on admission; 24, 48, and 72 hours after admission; and 7 to 10 days and >30 days after admission. Twenty-six patients had presumed embolic occlusion of the middle cerebral artery (MCA) and 14 had a clinical diagnosis of lacune. Admission score was better in the lacune group compared to the MCA group. The mean scores for all patients improved by the 7- to 10-day and the >30-day examination, but the degree of improvement was greater in the MCA group than in the lacune group at >30 days (p < 0.004). The degree of change at 7 to 10 days correlated with the change in score at 24 hours (r = 0.45, p < 0.05) and 48 hours (r = 0.86, p < 0.05). Most patients improve after acute ischemic stroke, but to variable degrees and at different rates.

P29. Cognitive Dysfunction Following Lacunar Infarction
David W. Demond, Thomas K. Tatamichi, Miguel Figueroa, DeWitt T. Cruss, and Yaakov Stern, New York, NY

To investigate the effects of lacunar infarction (LI) on cognitive function, we examined 59 LI patients 3 months after stroke (age = 71.6 ± 9.0 yr; education = 9.2 ± 4.9 yr) and 241 stroke-free nondemented control subjects (age = 70.6 ± 6.5 yr; education = 12.4 ± 4.5 yr) with a battery of neuropsychological tests. LI was defined as a presenting infarct of ≤2 cc and a mean volume of any additional subcortical infarctions of ≤2 cc on CT scan. Using multiple regression analyses, with significance set at p < 0.01 to minimize the risk of Type I error, we considered the role of LI as a correlate of performance in multiple cognitive domains. Controlling for the effects of demographic factors, vascular risk factors, alcohol use, and depression within the multivariate models, LI was a significant independent correlate of deficits in memory (β = -0.40, p = .0002), verbal (β = -0.28, p = .0025), visuospatial (β = -0.51, p < .0001), abstract reasoning (β = -0.31, p = .0029), and attentional skills (β = -0.50, p < .0001). We further investigated the effects of infarct number, volume, and location, as well as atrophy, on global cognitive function within the LI group. The only significant independent correlate of global cognitive performance was a preponderance of left-hemisphere infarctions (β = -0.07, p = .0545). These results suggest that LI may produce dysfunction in multiple cognitive domains, particularly when the left hemisphere is differentially involved.

P30. Increased Intracranial Atherosclerotic Stroke in Hispanics and Blacks from Northern Manhattan
Ralph L. Sacco, Christina Zamanillo, T. Shi, and J. P. Mohr, New York, NY

Intracranial atherosclerosis has been found to be more frequent in blacks compared to whites, whereas Hispanics have rarely been characterized. Among 210 consecutive patients from northern Manhattan over age 39 hospitalized at the Presbyterian Hospital from 1990 to 1991, cerebral infarction occurred in 32 whites, 84 blacks, and 94 Hispanics. All patients had at least one CT scan, 96% had duplex Doppler, 94% transcranial Doppler, and 12% angiography. Strokes were classified as atherosclerotic (ATH), cardioembolism, lacunar, and as infarcts of undetermined cause. ATH was further subdivided into extracranial (EATH) or intracranial
J. W. A. Evans, and Ethnic differences in stroke risk factors may help explain the higher rate of ischaemic stroke than blacks and Hispanics (white different in whites compared to blacks and Hispanics. Whites had more EATH stroke than blacks and Hispanics (white 17%, black 7%, Hispanic 10%), while IATH was similar in blacks and Hispanics and greater than in whites (white 3%, black 8%, Hispanic 10%). Nonwhites have more IATH stroke than whites. The similarity in the distribution of atherosclerosis between blacks and Hispanics argues for shared environmental risk factors, rather than genetic differences. Ethnic differences in stroke risk factors may help explain differences in infarct subtype.

POSTER PRESENTATION: DEMENTIA AND AGING

P31. Increased Anterior Cingulate Activation during Cognitive Processing in Alzheimer's Disease Patients
H. Cherkiou, E. Hamel, D. Bub, G. Waters, E. Meyer, A. Brent, and V. Whitehead, Montreal, Quebec, Canada

We studied 10 mild to moderate Alzheimer's disease (AD) patients with a series of 15O water bolus positron emission tomographic (PET) activation studies, and compared them to similar studies in 10 age-matched normal controls. For each group, PET images were mapped onto the subjects' MRI scan, and results of a particular activation condition were averaged across the group. Naming a series of pictures (line drawings of animals) minus counting abstract designs as a baseline produced strong activation of the anterior cingulate gyrus only in the AD group. Silent reading of words minus viewing a baseline series of "Xs" similarly showed strong activation of the anterior cingulate gyrus in the AD subjects but not the normals. Naming 1 block (activation condition) of 80% unnamed pictures, minus a second block (baseline) of easily named pictures, demonstrated much greater cingulate activation in the AD patients, for naming of the more difficult pictures. We conclude that this cingulate activation may reflect the greater involvement of an attentional network (of which the anterior cingulate is a part) in tasks requiring a higher degree of "mental work" on the part of AD patients.

P32. Erythrocyte Membrane Changes Correlate with Dementia in Alzheimer's Disease
J. W. Petegrew, K. Panchalingam, W. E. Klunk, and R. J. McClure, Pittsburgh, PA

Alzheimer's disease (AD) predominantly affects the brain, resulting in the loss of multiple cognitive abilities. Some studies suggest the membranes of peripheral cells are involved in the disease. To investigate erythrocyte membrane molecular dynamics in AD patients and age-matched controls, we investigated erythrocyte membrane molecular motion at the surface (fluorescence), aqueous-hydrocarbon interface (DPPE-ANS), and hydrocarbon core (12(9);AS: PPC-DPH) by steady-state fluorescence anisotropy measurements of 16 probable AD patients (5 males; 11 females) and 20 (11 males; 9 females) age-matched controls. Cognitive function was assessed by the Mini-Mental, Mattis, and Blessed scales. We found that intergroup comparisons revealed decreased motion at the surface (p = 0.001) and aqueous-hydrocarbon interface (p = 0.03) and increased motion in the hydrocarbon core (p = 0.01) of the moderately to severely impaired AD patients compared to the controls. In the AD patients, there were significant correlations between decreasing membrane surface motion and worsening Blessed scores (males p = 0.05; r = 0.7; females p = 0.04; r = 0.5). These findings suggest that molecules are being produced in the brain of AD patients that gain access to the circulation. These molecules insert into the erythrocyte membrane and secondarily alter erythrocyte membrane molecular motion. The production of these molecules correlates with the dementia and could contribute to the molecular pathophysiology of the disease.

P33. Simultaneous Versus Sequential Alzheimer's Disease Onset in Parkinsonism
Alex Rajput, B. Rozdilsky, and A. H. Rajput, Saskatoon, Saskatchewan, Canada

Parkinson's disease (PD) and Alzheimer's disease (AD) are 2 common disorders of old age and may therefore coexist. The prognosis in demented PD patients is poor and early recognition of such cases is therefore desirable. The objective of this study was to identify characteristics that distinguish PD + AD from PD patients during early stage. All patients were clinically evaluated over a 22-year period (1968-1990). Clinical diagnosis of dementia was made only when unequivocal clinical evidence of progressive decline in memory and cognitive function was documented, and pathological diagnosis of AD and PD was made using standard criteria. Twenty-six patients who had only PD or PD + AD were identified; 20 had no dementia and at autopsy had PD. Six patients had clinical evidence of parkinsonism and dementia and at autopsy had 2 distinct pathological findings—PD and AD. These 6 cases could be classified as having simultaneous or sequential evolution of PD + AD. Those with sequential onset had PD before age 65 years but were inexplicably functionally disabled early on, whereas those with simultaneous onset manifested PD after age 65 years. PD + AD patients had rapid disease progression, shorter survival, poorer drug response, and more side effects of levodopa than PD patients.

P34. White Matter Lesions on Magnetic Resonance Imaging and Vascular Risk Factors:
The Rotterdam Elderly Study
M. M. B. Breieter, J. C. van Swieten, M. L. Bot, J. H. W. van den Hout, F. van Harckamp, H. L. J. Tanghe, J. J. Claas, D. E. Grobbe, J. van Gijn, and A. Hofman, Rotterdam and Utrecht, The Netherlands

To study the prevalence of white matter lesions in the general elderly population, and to investigate whether white matter lesions were relatively frequent in subjects with classic vascular risk factors and with hemostatic risk factors, magnetic resonance scans were obtained of 111 participants, aged 65 to 85 years, of the Rotterdam Elderly Study. The subjects for the imaging study were a random sample from the general population, stratified by age and gender. T2-weighted images were obtained in the axial plane. White matter lesions were considered present when moderate or severe periventricular hyperintensities or when more than 5 small focal lesions or focal confluent lesions were found. Overall, 27% of subjects had white matter lesions. The prevalence and severity of le-
sions increased with age. History of stroke or myocardial infarction, presence of peripheral arterial disease, factor VIIc activity, and fibrinogen level were each significantly and independently associated with the presence of white matter lesions. Significant relations with actual systolic as well as diastolic blood pressure, with a history of hypertension, and with plasma cholesterol were observed only for subjects between 65 and 74 years. This study suggests that white matter lesions in the elderly may be related not only to the classic cardiovascular risk factors, but also to hemostatic factors.

P35. Predicting Aberrant Behaviors in Dementia Joan M. Swearer, Paula Nelligan, Hanns Mueller, Beatrice Woodward, and David Drachman, Worcester, MA

Although behavioral disturbances occur frequently in Alzheimer’s disease and other dementing disorders, little is known about the factors that predict their development or predispose to their occurrence. In the present study we examined 2 sets of possible predictive/predisposing factors retrospectively in 18 patients with dementia in 35 mildly to severely demented, community-dwelling patients. The factors examined included: individual distinguishing features (age, gender, age of onset, premorbid personality traits, prior psychiatric history) and dementia severity (dependence in Activities of Daily Living [ADLs] and self-care, duration of dementia, global disease severity). Spearman correlations and t tests were used to assess the relative influence of these factors on the occurrence of 3 types of aberrant behaviors: aggressive behaviors, disordered ideation, and motor abnormalities. Forty percent of the patients exhibited aggressive behaviors, 77% exhibited disordered ideation, and 63% had motor abnormalities. Neither a prior history of psychiatric disorders nor premorbid personality traits were associated with the occurrence of the target behaviors. Dependence in ADLs and self-care and greater global severity were associated (p < .01) with the frequency and severity of aggressive behaviors, disordered ideation, and motor abnormalities. These results suggest that severity of dementia is a consistent and reliable factor in the development of aberrant behaviors, whereas preexisting personality traits are not.

P36. Results of an 8-Month Trial of 1-Deprenyl in Dementia of the Alzheimer Type W. J. Burke, A. Ranno, W. H. Roccaforte, S. P. Wengel, B. L. Bayer, and N. K. Willeckson, Omaha, NE

1-deprenyl is an irreversible inhibitor of MAO-B that has been reported to cause modest improvements in short-term memory and behavioral symptoms in persons with dementia of the Alzheimer type (DAT). Thirty-eight subjects meeting research criteria for mild DAT were enrolled in a placebo-controlled, double-blind trial of 1-deprenyl at a dose of 5 mg twice a day. Subjects underwent extensive clinical and neuropsychological assessments at entry, and at 2 and 8 months. After 8 months, subjects taking both 1-deprenyl and placebo showed a significant decline in their scores on the Mini-Mental State Examination, the Clinical Dementia Rating (CDR) scale, and the Sum-of-Boxes score derived from the CDR. When the change in scores on these clinical measures was examined across the 2 groups, there was no significant difference. There were no significant differences within or between groups on several behavioral measures including the Brief Psychiatric Rating Scale and the Cornell Rating Scale for Depression in Dementia. Neuropsychological testing demonstrated no significant differences between groups based on mean score change. 1-deprenyl did not affect cognitive or behavioral symptoms of DAT in this 8-month study.

P37. Risk Factors for Dementia in Parkinson’s Disease K. M. Mer, M-X. Tang, R. Ottman, L. Cote, Y. Stern, and R. Mayeux, New York, NY

The etiology of dementia in Parkinson’s disease (PD) is probably multifactorial but there may be a shared susceptibility for PD and Alzheimer’s disease (AD). Reliable risk factor interviews were conducted with informants of 151 non-demented PD patients (PD-D) and 65 demented PD patients (PD+D) enrolled in a longitudinal community study of PD. PD+D were older (78.9 yr) than PD-D (71.4 yr) and had later age at onset of motor signs (71.1 yr) than PD-D (64.8 yr) (p < .001). The frequency of smoking, alcohol use, head injury, and family history (FH) of PD did not differ but FH of AD was significantly more frequent in the PD+D group (OR 2.25, CI 1.01–5.01). Using stepwise logistic regression, only age of onset of motor signs ≥65 (OR 2.86), education ≥8 years (OR 2.53), and the interaction of age of onset of motor signs and FH of AD (OR 3.49) were independent predictors of dementia in PD. To address variable years at risk of dementia, life table analysis revealed the cumulative risk of AD to age 90 in first-degree relatives of PD+D was .312, and .119 in PD-D relatives (p < .05). Cox proportional hazards analysis controlling for the differences in ages of the relatives of both groups yielded a rate ratio of 2.06 (CI 1.2–3.7) for the development of AD among PD+D compared to PD-D relatives. We conclude that a genetic susceptibility to AD may raise the risk for dementia in patients with PD.

P38. Can Vascular Dementia Be Clinically Differentiated from Alzheimer’s Disease? John C. Morris, Elizabeth Grant, Rita Canfield, Eugene Rubin, and Daniel McKeel, Jr, St Louis, MO

Vascular dementia (VD) is believed to account for 20 to 30% of all US cases of dementia; however, pathologically confirmed cases are quite rare. This discrepancy suggests that current diagnostic criteria lead to the clinical overdiagnosis of VD. Twenty VD subjects (mean age 78.5 yr; 9 men, 11 women) were diagnosed solely on the basis of the presence of dementia, a history of stroke(s), and a documented relationship of stroke to onset and/or course of dementia; isch-lamic scores (IS) and neuroradiographic findings were not used for diagnosis. Compared with 89 subjects (mean age 75.2 yr; 34 men, 55 women) with dementia of the Alzheimer type (DAT), there were no significant group differences for comparable Clinical Dementia Rating stages of dementia for measures of language, Activities of Daily Living, or general cognition. The VD group scored significantly higher than the DAT group on the modified IS (F[91,64] = 138.2, p < .0001). All 27 autopsied DAT subjects had verified Alzheimer’s disease (AD); 8 also had cerebral infarctions. The 3 autopsied VD subjects had 168, 160, and 55 cc of brain tissue affected by stroke; 1 (168 cc) also satisfied histological criteria for AD. We conclude that (1) the clinical features of VD and AD overlap considerably; (2) diagnostic criteria based on the temporal association of stroke with dementia may have predictive value for VD; and (3) the frequency of coexistence of AD and strokes indicates that refinement of criteria is needed to distinguish "mixed" and "pure" VD. Clinicopathological correlation remains essential for any study of putative VD.
P39. Handicapped and Longevity in Autopsy-Confirmed Alzheimer's Disease

Victor W. Henderson, J. Galen Backwalter, and Gaittiri Mytvananam, Los Angeles, CA

Left-handedness has been proposed as a marker for decreased survival in the general population, but possible effects of handedness on longevity in Alzheimer's disease (AD) have not been examined. We hypothesized that left-handed AD patients would evince more rapid deterioration and therefore die at an earlier age than right-handed patients. Subjects were 105 demented patients consecutively confirmed at autopsy to meet NINCDS-ADRDA criteria for "definite" AD. Handedness was determined from structured interviews with primary caregivers and validated for most subjects with the Edinburgh Inventory of Handedness. Age at onset of dementia symptoms retrospectively determined by caregivers was used to calculate the duration of illness at the time of death. Because of reported gender differences with regard to longevity, we first partialled out effects of gender before using hierarchical regression procedures to test the hypothesis. Four of 34 patients with very mild AD (i.e., with a Mini-Mental State score of 24 or greater) and 34 age- and sex-matched controls. We assessed performance on 2 memory measures: the Rey Auditory Verbal Learning Test and the Buschke Free and Cued Selective Reminding Test (FCSRT). The 3 parameters evaluated included a measure of acquisition, total learning over trials (TL), and delayed recall (DR). On the FCSRT, an index of facilitation of performance with semantic cues (SC) was assessed. Results indicated that all 3 indices, TL, DR, and SC, were capable of separating the mild AD group from the controls (p < 0.001). Using a linear discriminant analysis with stepwise variable entry, the measure that assessed the patient's ability to use semantic cues (SC) was the most sensitive parameter for separating the 2 groups (F = 15.38, p < 0.0002), and the acquisition parameter (TL) was also useful at adding some additional predictive power (F = 8.48, p < 0.005). The delayed recall measure, however, did not add anything to the previous 2 measures. It appears that very early AD can be detected using appropriately structured memory tasks, and these procedures can be helpful in identifying at-risk individuals.

P40. Brain Optical Spectroscopy in Alzheimer's Disease

Christopher M. Clark, Britton Chance, Steven Carter, N. G. Wang, and H. Haidz, Philadelphia, PA

Alterations in the optical properties of brain can be used to detect pathological changes in patients with Alzheimer's disease (AD). Using time-resolved spectroscopy (TRS) and phase-modulation spectroscopy (PMS), we measured the absorption (Ua) coefficient, scattering (Us) coefficient, and mean photon pathlength (PL) of red light directed through the base of the frontal lobes of 28 patients with AD and 11 age-matched control subjects. The measured values and the asymmetry index (AI) (an indication of the symmetry of the measurements between the left and right side of the brain) were correlated with the severity of disease as determined by Mini-Mental State score. There were significant differences between the AD and control group for Ua, Us, PL, and the standard deviation of AI. There was no correlation between the MMS score and Ua, Us, or PL. However, the highest asymmetry index values were seen in moderately impaired patients (MMS 10-20), which suggests that the asymmetrical nature of the pathological process detected by optical spectroscopy is most marked during this stage of the illness. This noninvasive technique may provide a convenient method to detect and monitor the pathological changes that occur in the brain of patients with AD.

P41. Memory Impairment in Very Mild Alzheimer's Disease

R. C. Peterson, E. Tangalos, G. Smith, R. J. Ivnik, and E. Kokmen, Rochester, MN

A memory impairment is often the earliest indication of Alzheimer's disease (AD). We investigated 3 components of learning and recall to determine which aspect of memory function is impaired the earliest in incipient AD. Using the Mayo Clinic Alzheimer's Disease Patient Registry, which is a longitudinal prospective project on AD and normal aging, we identified 34 patients with very mild AD (i.e., with a Mini-Mental State score of 24 or greater) and 34 age- and sex-matched controls. We assessed performance on 2 memory measures: the Rey Auditory Verbal Learning Test and the Buschke Free and Cued Selective Reminding Test (FCSRT). The 3 parameters evaluated included a measure of acquisition, total learning over trials (TL), and delayed recall (DR). On the FCSRT, an index of facilitation of performance with semantic cues (SC) was assessed. Results indicated that all 3 indices, TL, DR, and SC, were capable of separating the mild AD group from the controls (p < 0.001). Using a linear discriminant analysis with stepwise variable entry, the measure that assessed the patient's ability to use semantic cues (SC) was the most sensitive parameter for separating the 2 groups (F = 15.38, p < 0.0002), and the acquisition parameter (TL) was also useful at adding some additional predictive power (F = 8.48, p < 0.005). The delayed recall measure, however, did not add anything to the previous 2 measures. It appears that very early AD can be detected using appropriately structured memory tasks, and these procedures can be helpful in identifying at-risk individuals.

P42. A Reliable Standardized Technique for Dating the Onset of Alzheimer's Disease

M. Sano, D. Devanand, M. Richard, L. Miller, K. Marder, K. Bell, G. Dooneief, F. Bylina, G. Lafehle, and Y. Stern, New York, NY, Baltimore, MD, and Boston, MA

Alzheimer's disease (AD) has an insidious onset that is difficult to date reliably. We developed a standardized interview to provide objective criteria for dating the onset of 7 different symptoms (memory complaint, performance problems, language deficits, disorientation, depression, behavior problems, and psychosis), yielding an estimated disease onset date. Interrater reliability (ICC = 0.99, p < .001) and interinformant reliability (ICC = 0.85, p < .001) for the onset of first symptom was high. Interrater agreement for the order in which symptoms appeared was high (ICC = 0.72-0.98) as was interinformant reliability for all symptoms except memory complaint. The interview was administered to 216 patients with AD. Mean estimate duration of illness was 4.26 years ± 3.47 years and correlated significantly with problems in instrumental Activities of Daily Living. Sixty-six percent had memory complaint and 45% had performance problems as their initial symptom. This technique provides a reliable characterization of disease onset. Longitudinal studies will determine if particular onset symptoms differentially predict disease progression.

P43. White Matter Disease in Alzheimer's Disease: MRI and Pathological Study

S. Pascol, B. Bowen, W. W. Barker, J. Bruce, J. Sheldon, and R. Duara, Miami and Miami Beach, FL

The purpose of this study was to determine whether there is an excess of white matter disease (WMD) in Alzheimer's disease (AD). Brun and Englund (1986) reported an excess of WMD in brains of patients with AD vs age-matched controls. There have been reports both confirming (Bowen et al., 1990; Fazekas et al., 1990) and refuting (Levy, 1990) these findings using CT and MRI in patients with clinically diagnosed AD. Postmortem T2-weighted MRI scans and
neuropathology were graded on 9 brains of pathologically confirmed AD subjects and 6 brains of age-matched neuropathologically normal controls. White matter lesions were scored on a 0 to 3 scale (none, mild, moderate, severe) separately for periventricular (PVL) and deep white matter (DWM) areas in MRI scans and luxol fast blue (LFB)--stained brain sections. Correlations between MRI and neuropathology were good ($r = 0.61$ for PVL, $r = 0.66$ for DWM). PVL scores were higher in AD than in normal subjects on MRI (AD: 2.2 ± 0.9 vs controls: 0.2 ± 0.3; $p < .005$). On pathology the difference in scores did not reach significance (AD: 1.3 ± 0.7 vs controls: 0.5 ± 0.4; $p = 0.2$). Similarly, DWM scores were higher in AD subjects than on normals on MRI, but not neuropathology. In conclusion, AD brains have a significant excess of WMD on MRI compared to controls. Although the PVL and DWM scores for pathological sections are not different in the 2 groups, MRI is much more sensitive than LFB-stained sections for WMD.

P44. Clinical-Pathological Heterogeneity in Progressive Supranuclear Palsy
David A. Olson, Marla Gearing, Ray L. Watts, and Suzanne S. Mirra, Atlanta, GA

Thirteen autopsy cases of progressive supranuclear palsy (PSP) were investigated for clinical-neuropathological correlations and heterogeneity. We reviewed clinical records of 11 men and 2 women aged 61 to 89 years (mean age 72 yr) with disease duration ranging from 4 to 12 years. Most patients had classic features of PSP including ophthalmoplegia, postural instability, and extrapyramidal signs. Dementia was eventually observed in 9 of the 13 patients (69%). Six of 9 patients (67%) on whom adequate initial documentation was available presented with memory loss or behavior change. Five of the 13 patients (39%), including 4 with an initial presentation of memory loss, were diagnosed clinically as having Alzheimer's disease (AD) rather than PSP; neuropathological diagnoses in these cases varied: 1 had combined AD-PSP; 1 had AD-PSP combined with Parkinson's disease (PD) changes; 1 had PSP-PD; and 2 had "pure" PSP. The 2 patients with concomitant PD changes showed Lewy bodies in the substantia nigra, locus coeruleus, nucleus basalis, and neocortex. The remaining 8 patients were clinically diagnosed as having PSP; neuropathological diagnoses in these cases included 4 with "pure" PSP and 4 with PSP that also met neuropathological criteria for AD (PSP-AD). These findings emphasize the clinical and neuropathological heterogeneity in PSP.

P45. Mitochondrial Cytopathy with Dementia, Myoclonus, and Lactic Acidosis in an Older Adult: Unusual or Unrecognized?
Peter A. Engel, Margaret Gruenert, Marvin Natowicz, and Sara Shanske, Hartford and Farmington, CT, Waltham, MA, and New York, NY

Mitochondrial disorders are rarely recognized as the cause of dementia in later life and dementia is usually not the initial manifestation of recognized mitochondrial syndromes. This unusual, nonfamilial case suggests the need for better characterization of late-life mitochondrial encephalomyopathies. A 54-year-old woman became severely demented, paucilalic, and aphasic over 6 years. Myoclonus developed in the third year at age 56, upper limb apraxia in the fourth, gait apraxia, rigidity, optic ataxia, and ptosis in the fifth. Primitive reflexes were prominent. Lactic acidosis (4.1 mEq/L) and high urinary levels of lactate and Krebs cycle intermediates were detected. Muscle biopsy specimens revealed myopathic changes with type 11 fiber atrophy and increased numbers of very small mitochondria, while activities of mitochondrial enzymes, cytochrome oxidase, and NADH dehydrogenase were significantly depressed ($p < 0.05$) at 33 and 44% normal (courtesy S. DiMauro, MD). Southern blot identified no deletions in mitochondrial DNA and the tRNA gene point mutation of myoclonic epilepsy with ragged red fibers was absent. Although not establishing its genetic basis, these data indicate a primary mitochondrial defect. Mitochondrial disorders should be suspected in older adults presenting with atypical dementias.

P46. Performance of the Normal Elderly on the CERAD Battery
Kathleen A. Welsh, Nelson Butters, Durwayne Beekly, Gerda Fillenbaum, Richard Mols, and Albert Heyman, Durham, NC, San Diego, CA, Seattle, WA, and New York, NY

The neuropsychological battery developed for the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) is currently used in many research studies to index the cognitive impairments of Alzheimer's disease. In spite of its widespread use, normative information on the battery, important for interpretation of performance, has not been available. We report norms for the CERAD battery based on a large sample of elderly control subjects ($n = 398$; white men and women; ages 50–89 yr) enrolled in the national study of CERAD. Performance on the neuropsychological measures was examined separately for subjects with high ($\geq 12$ yr) and low ($< 12$ yr) education. Distribution of scores and basic descriptive information (means and SD) for each measure were determined. Significant age and sex effects were observed on most cognitive measures in the highly educated group. In contrast, no significant age effects were observed in the low education group. Effect of sex was not explored in this group due to the limited sample size ($n = 48$). Further exploration of CERAD performance in normal controls from underrepresented groups including minorities, residents of rural communities, and individuals with low education is in progress.

P47. Increased Cytoskeletal Proteins in Brain Axons of Aged Rats
Danny F. Watson, Detroit, MI

Intraneuronal inclusions of cytoskeletal proteins appear in several neurological diseases; for example, the neurofibrillary tangles of Alzheimer's disease contain a cytoskeletal protein, tau. Because the previously described slowing of axonal transport in aged animals might lead to accumulation of cytoskeletal proteins in nerve-cell bodies and axons, we assessed the abundance of 2 major cytoskeletal proteins in brain tracts of rats at age 4 months or 25 months. Immunohasay was performed with monoclonal antibodies to alpha and beta tubulin and to NF-L (the core neurofilament protein) by published methods. Samples were dissected in a standardized fashion and 2-mm pieces of the following tracts were assayed: optic nerve, corticospinal tract (medulla), superior cerebellar peduncule, L3 dorsal root, and L3 ventral root. Between 4 months and 25 months, the NF-L content approximately doubled in each brain site. Tubulin substantially increased at
all sites except the fimbria-fornix. In contrast, tubulin did not change in the spinal roots. NF-L increased slightly in the ventral but not the dorsal root. This tendency of senescent brain neurons to accumulate cytoskeletal proteins in their axoplasm may predispose them to formation of intraneuronal inclusions in various degenerative diseases.

POSTER PRESENTATION:
EPILEPSY

P48. MRI-Detected Hippocampal Formation Atrophy in Temporal Lobe Lesional Epilepsy: Identification of Dual Pathology
Gregory D. Cassis, Clifford R. Jack, Jr, Joseph E. Parisi, Frank W. Shabrough, Curtis P. Schreiber, and Patrick J. Kelly, Rochester, MN

We performed a prospective study of preoperative magnetic resonance imaging (MRI) in 13 consecutive patients with intractable partial epilepsy who underwent a stereotactic resection of an extrahippocampal temporal lobe foreign-tissue lesion, "lesionectomy," between June 1986 and January 1991. Interpretation of the MRI studies was performed by an investigator blinded to the presurgical evaluation, surgical outcome, and pathology. Hippocampal formation (HF) atrophy was assessed using MRI-based volumetry (n = 10) and visual grading of the HF (n = 13). MRI-detected HF atrophy has been shown to be a reliable marker of moderate to severe mesial temporal lobe sclerosis (MTS) (Cascio GD, et al, Ann Neurol 1991;30:31–36). HF atrophy was identified in 3 of the 13 patients ipsilateral to the temporal lobe lesion. All patients with HF atrophy had an unfavorable outcome. Six of the 10 patients without HF atrophy were rendered seizure-free after lesionectomy. Pathological examination of the hippocampus in 1 patient with HF atrophy who subsequently underwent a temporal lobectomy revealed MTS. The surgically excised hippocampus was unremarkable in 1 patient without HF atrophy who later received a temporal lobectomy for recurrent seizures. Results of this study have modified the surgical approach taken at this institution in patients with MRI-defined dual pathology.

P49. Decreased In Vivo Glucose Metabolism and Central Benzodiazepine Binding in Mesial Temporal Lobe Epilepsy
T. R. Henry, K. A. Frey, J. C. Sackellares, S. Gilman, R. A. Kapppe, J. A. Brunberg, D. A. Rau, S. Berent, A. B. Young, and D. E. Kuhl, Ann Arbor, MI, and Boston, MA

We studied interictal cerebral metabolism and central benzodiazepine receptor (BZR) binding in 10 patients with unilateral mesial temporal lobe epilepsy (TLE) and 10 age-matched normal volunteers by positron emission tomography. Dynamic scanning with 22.5 mCi of [C-11]fluorodexyglucose imaged metabolism. Quantitated metabolism and BZR binding were measured in anterior and posterior mesial temporal, lateral temporal, frontal, parietal, occipital, cingulate, basal ganglial, and thalamic areas (bilateral), using anatomically configured regions of interest. Regional decreases greater than 3 standard deviations from the normal mean were considered significant in TLE patients. Each TLE patient had anterior mesial temporal (and 1 had additional posterior mesial temporal) BZR decrease on the epileptogenic side, without other cortical BZR decrease. Eight TLE patients had ipsilateral mesial temporal, lateral temporal, and thalamic (and 4 also had other extratemporal) hypometabolism; 1 had ipsilateral anterior mesial temporal hypometabolism only; 1 had normal metabolism. Decreased central BZR density appears to be restricted to the epileptogenic zone, while interictal metabolic dysfunction is usually more extensive, in mesial TLE.

P50. Electrical Stimulation of the Vagus Nerve for the Treatment of Epilepsy: Support from Experimental Models
R. S. McLachlan, London, Ontario, Canada

Chronic intermittent stimulation of the vagus nerve is a new treatment for intractable seizures in temporal lobe epilepsy. Few observations have been made of the effect of this technique in experimental models of epilepsy. Focal epileptiform activity was established in the somatosensory cortex of 13 urethane-anesthetized rats by direct application of potassium penicillín G (100,000 IU/ml) to the left hemisphere. Electroencephalographic (EEG) and respiration were recorded. Intermittent electrical stimulation of the exposed left vagus nerve in the neck was done using a bipolar electrode (0.1–1.2 mA, 10–50 Hz, 0.5 m/sec, 1–20 sec). Interictal spike frequency decreased from 42 ±11 to 28 ±11 spikes/minute (p < .001) during stimulation and remained low for up to 90 seconds afterward. Heating the animals’ tails produced a similar change from 41 ±12 to 25 ±11 spikes/minute. Intraperitoneal pentylentetrazol was given to 4 rats to induce generalized seizures. Vagus stimulation within 3 sec of ictal onset decreased mean seizure duration from 30.2 ±15.7 to 5.0 ±1.8 seconds (p < .01) in 3 of 4 animals. The stimulus threshold for decrease in respiration or heart rate was less than that for spikes and seizures. These findings suggest that vagal stimulation is a potent but nonspecific method to inhibit cortical epileptiform activity probably through an indirect effect mediated by the reticular-activating system.

P51. Platelet-derived Growth Factor–Responsive 0-2A Progenitor Cells in Astrocyte-rich Cultures Derived from Epilepsy Brain
M. L. Estes, B. Jacobs, C. H. Block, I. A. Awad, H. H. Morris III, and B. P. Barna, Cleveland, OH

Evidence from experimental animals indicates that endogenously produced platelet-derived growth factor (PDGF) is an important regulator of glial proliferation and differentiation. Because of the striking degree of glial proliferation in chronic epilepsy, we sought to determine whether cultured glia from human epilepsy tissue would be responsive to PDGF. The effects of PDGF on DNA synthesis, proliferation, and relative distribution of A2B5+ glia were studied in a cell culture derived from temporal lobe white matter of adult epilepsy lobectomy tissue. By immunocytochemistry, glial fibrillary acidic protein (GFAP) was detectable in 90% of cells in untreated or 4-day PDGF-treated (10 ng/ml) cultures, which confirmed their astrocytic nature. In contrast, A2B5+ cells increased from 10 to 30% in untreated cultures to 75% after PDGF treatment. The results suggested that type 2 astrocytes (A2B5+GFAP+) had been elicited. DNA synthesis of cells resembling oligodendrocyte-type 2 astrocyte (0–2A) progenitors occurred within 24 hours after...
P52. Results of Surgical Treatment in Patients with Bitemporal Independent Foci: The Usefulness of Intracranial Interictal Markers
J. Reiher, L. F. Quesney, N. So, Sherbrooke and Montreal, Quebec, Canada, and Cleveland, OH

A favorable outcome after surgical therapy for epilepsy is observed in patients with bitemporal extracranial epileptiform abnormalities when intracranially recorded seizures originate exclusively or predominantly from the resected temporal lobe (47% of patients; So et al, 1989). We studied 48 patients investigated with chronically implanted depth electrodes simultaneously recording from mesial and neocortical temporal lobe structures bilaterally, in an attempt to assess whether intracranial interictal findings, either alone or in combination with ictal data, would discriminate candidates who are likely to benefit from operation. The presence of highly repetitive interictal amygdalo-hippocampal spikes and the absence of extra-amygdalo-hippocampal spiking correlate with a favorable surgical outcome, as seen in 12 of 15 patients (80%) with exclusively or predominantly unilateral seizures and in 12 of 16 patients (75%) regardless of seizures’ laterality. The statistical difference between favorable outcomes measured as a function of ictal markers (47.7%) or interictal spiking (75%), or combined ictal and interictal markers (80%), is significant (p = 0.01 and 0.004, respectively). Higher rates of favorable surgical outcome are observed when ictal data, alone or combined with interictal data, are considered.

P53. The Usefulness of the Electroencephalogram in the Management of the Institutionalized Epileptic
Steven A. Phillips, Judith E. Hogg, Sylvia Gomez, Alfred L. Scherer, and Joseph B. Green, Lubbock, TX

We reviewed 271 electroencephalograms (EEGs) of 215 institutionalized epileptic clients at the Lubbock State School between November 1990 and February 1992. There were 129 males and 86 females aged 9 to 54 years, with an average age of 30. An EEG had not been obtained in the preceding 5 years in 85% of clients. An interpretable EEG was obtained in 76% of clients on the first attempt, 48% on the second attempt, and 35% on 3 or more attempts. Chloral hydrate was used for sedation in 78%. Abnormalities were noted in 81% of interpretable EEGs, including epileptiform activity in 75% (focal 49%, multifocal 9%, generalized 42%) and generalized slowing in 25%. The probability of the EEG altering the care of the client was categorized as probable (72%), possible (12%), or unlikely (16%). Factors used to determine the significance of the EEG included reclassification of epilepsy that resulted in simplifying antiepileptic drugs, differentiating epileptic from nonepileptic events, and supporting the discontinuation of medications in clients who had no seizures for several years. We conclude that for the majority of institutionalized clients, an interpretable EEG can be obtained and may assist in the care of their epilepsy.

P54. Detection of Subclinical Seizures in Adults
Elson L. So, Kevin H. Ruggles, Peter A. Ahmann, and Sue Trudau, Rochester, MN, and Marshfield, WI

Subclinical seizures are electrographic seizures that occur without overt clinical manifestations. Their incidence and clinical significance currently may be underestimated. Over a 4-year period, we used cassette EEG monitoring to identify prospectively adult patients with subclinical seizures. Patients were considered for the study: (1) when sensorium failed to recover after a single seizure or multiple epileptic seizures; (2) when unexplained sensorium abnormality developed acutely in patients with known epilepsy; or (3) when unexpected sensorium abnormality developed in the presence of potentially epileptogenic central nervous system lesions. The following information also was collected: demographic data, Glasgow Coma Scale rating, neurological examination, CT/MRI findings, and mortality up to 30 days after hospital discharge. We detected subclinical seizures in 9 of the 16 patients studied. Six of the 9 patients were in subclinical status epilepticus. In those who presented with clinical status epilepticus, 85% had subclinical seizures even after their status epilepticus was controlled clinically. Subclinical seizures also occurred in 33% of the patients who had no preceding clinical status epilepticus. Mortality was 66% in those with and 14% in those without subclinical seizures. However, mortality also could be associated with underlying CT/MRI pathology.

P55. Vagal and Esophageal-Evoked Potentials in Normal, Epileptic, and Diabetic Patients
G. Tougas, D. Fitzpatrick, R. Hunt, B. Clarke, and A. R. M. Upson, Hamilton, Ontario, Canada

We have recorded vagal and esophageal-evoked potentials after electrical (E) and balloon (B) stimulation in 10 epileptic patients who had vagal stimulators for the control of intractable epilepsy and the results were compared with esophageal-evoked potentials in 10 healthy controls and 3 diabetic patients. The vagal and esophageal-evoked potentials showed similar configurations with 3 major positive and negative potentials.

The amplitudes of the responses habituated rapidly over 30 trials at 2 per second up to 1 per 6 seconds. Latencies were shorter from the upper esophagus (20 cm above lower esophageal sphincter LES) cf. lower esophagus (5 cm above LES) yielding conduction velocities of 5 to 7 meters per second but conduction was significantly slower in the diabetics. The vagal-evoked potentials have validated the use of esophageal-evoked potentials as a practical method of assessment of the integrity and speed of conduction in vagal afferent pathways in man.

P56. Toluene Abuse and Seizure Disorders
Ronald E. Kramer and Neil L. Rosenberg, Englewood, CO

Seizure disorders were analyzed in patients in whom toluene was the sole or major drug of abuse. Toluene abuse is increasing; therefore, physicians should gain experience with its neuropathological and clinical sequelae. A retrospective chart
review found 15 patients meeting criteria. The average patient age was 28 years; abuse onset averaged 16.7 years; abuse averaged 10.7 years; and 11 patients were male. Ten were daily, 3 were weekly, and 2 were intermittent users. Seizures occurred in 2. One suffered a single generalized tonic-clonic seizure without recurrence and without treatment. His MRI was the only one showing a focal cerebral contusion. Another suffered from seizures prior to toluene use. Toluene did not exacerbate his seizure frequency or intensity. Of the remaining 13 patients, 8 had abnormal examinations; 5 had abnormal MRI results; and 6 had other additional seizure risk factors. In conclusion, (1) physicians should seek other etiologies in toluene abusers if they present for evaluation of seizure disorders, and (2) withdrawal, acute symptomatic and recurrent seizure disorders, which are seen with other abused substances, are not seen with toluene. The absence of seizures in toluene abuse is most probably because the neuroanatomical structures pathologically affected are not those believed to be involved in seizure initiation or epileptogenesis.

POSTER PRESENTATION: HEADACHE AND PAIN

P57. Continuous Intravenous Levodopa Shifts Dose Response for Production of Dyskinesias But Not for Relief of Parkinsonism in Patients with Advanced Parkinson’s Disease
Lori A. Schub and James P. Bennett, Jr, Charlottesville, VA

We characterized the clinical dose-response curves for relief of parkinsonism and production of dyskinesias as a function of plasma levodopa and 3-0-methyldopa levels in 6 patients with Parkinson’s disease (PD) and fluctuating responses to oral levodopa/carbidopa. Dose response tograded intravenous levodopa was measured after overnight drug withdrawal on 2 occasions, first after chronic, intermittent oral levodopa/carbidopa and second after 3 to 5 days of continuous intravenous levodopa. Continuous intravenous levodopa shifted the dyskinesia dose-response curve to the right, and reduced maximum dyskinesia activity, but did not significantly alter dose response for relief of parkinsonism. Improvement in dyskinesia was apparent by the second day of continuous levodopa, during which ratios of plasma dopa/3-0-methyl-dopa remained constant. Our results support the hypothesis that relief of parkinsonism and production of dyskinesias occur by separate mechanisms. Continuous dopamine-mimetic therapy should be sought as a therapeutic goal for advanced PD.

P58. Autosomal-Recessive Dopa-Responsive Dystonia in an Arabic Family
N. Biary, S. M. Al Deb, H. Maddab, and W. Khoja, Riyadh, Saudi Arabia

Dopa-responsive dystonia (DRD) is a distinct subset of idiopathic dystonia with diurnal fluctuation and a dramatically beneficial response to l-dopa. It has hitherto been considered an autosomal-dominant disease with reduced penetration (McKusick No. 12823). We studied an Arabic family of 67 members with DRD spanning 6 generations. We examined 43 members and 6 of their spouses. l-dopa was withheld for 24 hours from patients in treatment. Five family members had generalized dystonia with diurnal fluctuation (1 male, 4 females). Dystonia started between the age of 2 and 7 years with gait difficulty and involvement of the legs. MRI, EEG, evoked potentials, and screening for Wilson’s disease were negative. An excellent response to l-dopa was noted in all 5 patients with continued long-term clinical stability for as long as 17 years. The 5 patients were the products of 2 consanguineous marriages, and their 7 siblings were normal. The patients were descendants of the same great-great-grandparents. This pedigree suggests an autosomal-recessive type of inheritance. We believe this is the first report of DRD with an autosomal-recessive type of inheritance.

P59. Idiopathic Progressive Pure Freezing Gait
A. Abrish, M. Gornish, H. Goldberg, I. Ziv, R. Djaldetti, Y. Zoldan, H. Sroka, and E. Melamed, Petah Tiqva, Israel

Freezing gait is an incapacitating symptom that occurs often in advanced Parkinson’s disease and also in other neurological disorders, e.g., multifarctate state, multisystem atrophies, and normotensive hydrocephalus. We evaluated, videotaped, and rated 18 patients (15 men, age 74 ± 6, 60–82 yr) who developed pure progressive freezing gait during 2.5 ± 1.9, 0.5–6 years. Severity was mild in 4 with sudden motor blocks mainly when confronted with obstacles; moderate in 9 with gait arrests upon any attempt to initiate walking and changing direction, requiring a walking stick or partial external assistance; and severe in 5 with total inability to start walking, requiring a walker, massive assistance, or a wheelchair. In all, freezing was associated with postural instability. They could mimic normal gait when seated or lying prone and could overcome arrests by the “walking over lines" maneuver. Neurological examination was otherwise normal with no signs of dementia, parkinsonism, or pseudobulbar palsy. Ischemic risk factors including ischemic heart disease, hypertension, and diabetes occurred in 7 and previous strokes in 6. Brain CT and MRI were normal or showed mild cortical atrophy in 12 and putative lacunae in only 6 patients. None responded to levodopa or dopamine agonists. Progressive pure freezing gait should be recognized as a separate nonparkinsonian neurological entity. It may be due to degenerative or ischemic non-nigral brainstem lesions.

P60. The Causalgic Syndrome and Dystonia: Clinical Evidence of a Central Origin
K. Bhatia, M. H. Bhatt, and C. D. Marsden, London, UK

We describe 19 patients with causalgia and dystonia, triggered by peripheral injuries in 15 patients and occurring spontaneously in 4 patients. The injury was often trivial. The mean age at presentation was 28.6 years. The legs were affected in 12 patients, and the arm was affected in the remaining 7 patients. All had burning pain, allodynia, and hyperpathia, along with vasomotor, sudomotor, and trophic changes. All developed typical dystonic muscle spasms in the affected part. The spasms typically were sustained, producing a fixed dystonic posture, in contrast to the mobile spasms characteristic of idiopathic torsion dystonia. Dystonia always followed the causalgia and was painful. There was spread of the causalgia and of the dystonia from its initial site both in the affected limb and to other extremities, the latter in a hemiplegic, transverse, and triplegic distribution. All forms of conventional treatment failed to relieve either the pain or the dystonia. We suggest that functional changes in the corticobasal ganglia-thalamic system are responsible for this painful dystonic syndrome.
The efficacy and mechanisms of levodopa (LD) drug holiday for Parkinson’s disease (PD) remain controversial. We performed a double-blind, randomized study with 11 advanced PD patients (5 men, 6 women; aged 52-79 yr) with entry criteria of inadequate response to LD plus dose-limiting LD-induced side effects (dyskinesias, hallucinations, and confusion). Subjects were assigned to: (1) 100% placebo for LD (complete drug holiday) or (2) 50% LD and 50% placebo for LD (50% drug reduction) for 6 days. After subsequent open-label LD dose optimization, subjects were followed to end point (defined as the time when entry criteria were again satisfied or a maximum of 1 year). Median survival time to end point was not significantly different for the complete drug holiday (182 days) and 50% drug reduction (100 days) groups (p = 0.85). Aspiration pneumonia occurred in 2 complete drug holiday patients and no significant morbidity occurred with drug reduction. After a 100-mg dose of LD, clinical and pharmacological responses were no different before and after drug holiday (p = 0.75) or reduction (p = 0.84). Subject to the limitations of our small sample size, we conclude that complete drug holiday is associated with greater morbidity and confers no major advantage over 50% drug reduction. We found no evidence of significant alterations of pharmacokinetic or pharmacodynamic properties of LD after drug holiday or reduction. (Supported by United Parkinson Foundation, CRC #RR-00044.)

The diagnosis of Huntington’s disease (HD) is usually based on the characteristic neurological features and a positive family history. The demonstration of caudate hypometabolism with positron emission tomography (PET) has been reported in symptomatic HD patients and may provide a useful adjunctive test in the diagnosis. We have reviewed 63 PET scans performed in 52 patients, aged 18 to 76 years, all of whom had a clinical diagnosis of HD, were symptomatic for 1 to 14 years, and had a positive family history. Significant caudate hypometabolism was judged present if either caudate/thalamus or caudate/global ratios were more than 2 SD below the mean of age-matched controls (n = 26). By these criteria, 50/52 patients had abnormal findings on their initial PET scan. Follow-up scans in 10 patients within 5 years of the initial investigation confirmed the abnormality. These results suggest that the demonstration of caudate hypometabolism as judged by these criteria has a high sensitivity in the diagnosis of HD in symptomatic patients.

The purpose of this study was to compare [3H]-dopamine uptake by platelet storage granules (PSG) in Parkinson’s disease (PD) and healthy controls (HC) and the effect of reserpine (RES) and haloperidol (HAL) on dopamine (DA) uptake by PSG in vitro. Platelets (PL) were proposed as a model for normal PSG and were analyzed in vitro. The purpose of this study was to compare [3H]-dopamine uptake by platelet storage granules (PSG) in Parkinson’s disease (PD) and healthy controls (HC) and the effect of reserpine (RES) and haloperidol (HAL) on dopamine (DA) uptake by PSG in vitro. Platelets (PL) were proposed as a model for normal PSG and were analyzed in vitro. The purpose of this study was to compare [3H]-dopamine uptake by platelet storage granules (PSG) in Parkinson’s disease (PD) and healthy controls (HC) and the effect of reserpine (RES) and haloperidol (HAL) on dopamine (DA) uptake by PSG in vitro. Platelets (PL) were proposed as a model for normal PSG and were analyzed in vitro. The purpose of this study was to compare [3H]-dopamine uptake by platelet storage granules (PSG) in Parkinson’s disease (PD) and healthy controls (HC) and the effect of reserpine (RES) and haloperidol (HAL) on dopamine (DA) uptake by PSG in vitro. Platelets (PL) were proposed as a model for normal PSG and were analyzed in vitro. The purpose of this study was to compare [3H]-dopamine uptake by platelet storage granules (PSG) in Parkinson’s disease (PD) and healthy controls (HC) and the effect of reserpine (RES) and haloperidol (HAL) on dopamine (DA) uptake by PSG in vitro. Platelets (PL) were proposed as a model for normal PSG and were analyzed in vitro. The purpose of this study was to compare [3H]-dopamine uptake by platelet storage granules (PSG) in Parkinson’s disease (PD) and healthy controls (HC) and the effect of reserpine (RES) and haloperidol (HAL) on dopamine (DA) uptake by PSG in vitro. Platelets (PL) were proposed as a model for normal PSG and were analyzed in vitro.
Vmax (fmol/mg protein) was significantly lower in PD (mean ± SD) (218.9 ± 82) than HC (308.3 ± 71.5) (p < 0.005 Student's t test). The Michaelis constant (Km, μM) also differed significantly (PD 4.63 ± 1.8, HC 2.22 ± 0.8). RES inhibited DA uptake (55% at 10⁻³, 45% at 10⁻⁴). HAL did not affect uptake. DA uptake by P5G is diminished in PD, perhaps reflecting an alteration in the capacity of vesicles to accumulate catecholamines. Long-term levodopa treatment could play a role (LD overloading).

P66. Driving Performance in Parkinson's Disease
Richard M. Dubinsky, Bradley J. Schnirer, and Anthony C. Stein, Kansas City, KS, and Hawthorne, CA

To determine how driving performance is altered in Parkinson's disease (PD), we studied 16 subjects with PD and 16 control subjects with an interactive computer-based driving simulator (STI, Hawthorne, CA) mounted in a 1981 Dodge Aries Coupe. All subjects completed a 45-minute training session prior to taking the 15-mile drive. Subjects were required to maintain lane position, drive at highway speeds, pass other vehicles, negotiate curves, and respond to divided attention (DA) tasks (an important component of the driving task that is analogous both to using the rearview mirrors and route-finding tasks) using the horn and turn indicators. Statistical analysis was by analysis of variance for repeated measures (p < .05). The PD subjects drove slower, had more off-the-road accidents, had poorer lane position control, made more mistakes on the DA task, and reacted slower on the DA task than the controls. There was no difference in the number of head-on collisions or incidents of excessive speed. The poor lane control combined with the slower speed and increased number of mistakes on the DA tasks indicate that the PD subjects are at significant risk for rear-end collisions and for accidents when they are distracted by a DA task.

P67. Initial Resistance to BOTOX Treatment in Cervical Dystonia
Drake D. Duane, Scottsdale, AZ

Perhaps 10% of patients with cervical dystonia (CD) do not improve after botulinum toxin A treatment (BOTOX Tx) (Jankovic and Bein, NEJM, 1991). Such resistance within 2 exposures is not likely due to toxin antibody formation. Of 61 CD patients evaluated per protocol receiving 2 or more BOTOX Tx under multichannel EMG monitoring, 7 (11.5%) showed no benefit after the first and second Tx, despite mild neck weakness on static muscle testing and, in some instances, EMG signs of denervation. The 54 responders (16 men, 38 women) had younger age onset CD (mean 45 yr vs 60 yr), but similar duration (mean 10 yr vs 9 yr) compared to the 1 male and 6 female nonresponders (in contrast to Jankovic and Schwartz, Arch Neurol, 1991). Both groups had similar degrees of severity and Tx dose (mean 200 IU, range 112.5–300). Although disparate group size prohibits statistical analysis, some interesting comparisons include: nonresponders were more apt to have extracranial dystonic sites (72% vs 33%), antecollis (29% vs 4%), dark eyes (57% vs 19%), women with elevated antinuclear antibody titer (67% vs 24%), history of intracranial operation (29% vs 0%), significant for age focal MRI abnormality (5 of 6 vs 3 of 19). History of cervical operation (6 patients) did not limit responsiveness. Rates of prior remission, perinatal stress, antecedent trauma, left-handedness, and family history of movement disorder were similar for both groups. Antecollis presents problems for optimizing Tx to affected muscles, but central mechanisms may play a role in why some patients with focal dystonia do not improve with BOTOX Tx from the outset.

P68. Symptomatic Effects of Deprenyl on Patients with Parkinson's Disease
Enrico Fazzini, New York, NY

Does deprenyl have a symptomatic effect on patients with untreated and l-dopa-treated Parkinson's disease (PD)? Once deprenyl is started, how long is it before another medication is needed to control symptoms of continued disease progression? There has been controversy over whether deprenyl has effects on delaying disease progression (NEJM 1989;321:1364) and/or in alleviating the symptoms of PD. One hundred seventy-five patients already taking l-dopa (Group 1) and 33 patients who had never taken l-dopa (Group 2) were treated with deprenyl 10 mg/day. Unified PD Rating Scale (UPDRS) scores were measured before and after deprenyl. Patients were followed until PD symptoms progressed to the point of requiring additional medication. One hundred eighteen of 175 (67%) patients in Group 1 (reduced UPDRS mean Activities of Daily Living [ADL] 11 to 9, motor [MTR] 30 to 22) and 29/33 (88%) patients in Group 2 (reduced UPDRS mean ADL 11 to 6, MTR 26 to 20) reported symptomatic benefit. An average of 12 months' duration was found in both groups before further medication adjustments were needed. Deprenyl provides symptomatic benefit for an average of 12 months in the majority of patients with PD regardless of whether or not they are being treated with l-dopa.

P69. A Significant Elevation of Plasma Amino Acids in Parkinsonian Patients
Yasuo Iwasaki, Masao Kinoshita, Toshiya Shojima, and Ken Ikeda, Tokyo, Japan, and Cleveland, OH

We measured fasting plasma amino acids in 30 Parkinson's disease patients and 30 controls matched for age and sex. All patients were receiving l-dopa and they were free of any medications other than l-dopa. Normal controls were free of any medication. There were no differences in diets between patients and controls. Fasting blood specimens were collected in heparinized tubes and immediately were centrifuged at 20,000 g for 10 minutes. Analysis of plasma amino acids was performed by automated ion-exchange chromatography with lithium-based buffer and an amino-acid analyzer. Parkinsonian patients had significant elevations of aspartate, glutamate, and glycine. The other amino acids were not significantly different from those in controls. No correlation between severity or activity and degree of abnormality in plasma level of amino acids in patients was established. We conclude that excitatory amino-acid metabolism is altered in patients with Parkinson's disease.

P70. Obsessive-Compulsive Symptoms in Parkinson's Disease
Bonnie E. Levin, Rachel Tomer, and William Weiner, Miami, FL

There is evidence linking obsessive-compulsive symptoms (OCS) to basal ganglia dysfunction. We investigated the presence and severity of OCS in a sample of 44 patients with an unequivocal diagnosis of idiopathic Parkinson's disease (PD) using the Leyton Obsessional Inventory. OCS was found in the majority of the patients, with 24 (55%) scoring above

Program and Abstracts, American Neurological Association 249
the normative cutoff for the symptom score and 32 (73%) scoring above the normative cutoff for the trait score. When severity of OC symptoms was correlated with a battery of neuropsychological measures, significant relationships were observed between OCS and a preponderance of tests associated with right-hemisphere functions. These findings were observed especially on those tests with a strong frontal lobe component (block design: $r = -0.50$, embedded figures: $r = -0.534$; set shifting: $r = -0.42$; and perseverative responses: $r = 0.58$; $p < .005$ for all measures). In all cases, the more severe OC symptoms, the poorer the performance. A similar trend was observed between the Reyton trait scores and the cognitive measures. These findings suggest that OCS is present in a subgroup of PD patients, which may reflect greater compromise of right-hemisphere basal ganglia—frontal lobe pathways.

P71. Interrater Reliability and Factor Structure of the Unified Parkinson’s Disease Rating Scale Motor Examination

M. Richards, K. Marder, L. Cote, Y. Stern, and R. Mayeux, New York, NY

Patients with Parkinson’s disease (PD) were double-rated using the Unified Parkinson’s Disease Rating Scale (UPDRS). Intraclass correlations (ICCs) were calculated for the total motor score and for each individual sign. Results indicated excellent agreement (ICC > .7) for the total motor score, resting tremor, gait, arising from a chair, and speeded, repetitive movements; good agreement (ICC > .5) for rigidity, action tremor, posture, postural stability, and bradykinesia; and poor agreement (ICC < .2) for speech and facial mobility. A factor analysis was then performed on UPDRS motor scores for 146 PD patients from a community-dwelling cohort. Three factors were extracted by principal components analysis with subsequent varimax rotation, accounting for 63.5% of the total variance: Factor 1—balance and stability (posture, postural stability, gait, arising from a chair, and bradykinesia); Factor 2—rigidity and motor speed (rigidity, speech, facial mobility, rapid alternating movements, leg agility, hand movements, and finger tapping); Factor 3—tremor (resting and action). These results indicate that the UPDRS motor examination is reliable between raters and measures the cardinal signs of PD.

P72. Botulinum A Toxin Injections for the Treatment of Hand Tremors

Richard Trnuch and Seth L. Pullman, Bingham Farms, MI, and New York, NY

An open pilot study was performed to evaluate the efficacy of botulinum A toxin (BOTOX) injections for disabling hand tremors. A previous report on the use of BOTOX for hand tremors suggested that it was helpful, but relied on subjective clinical rating scales. The extent of normal clinical fluctuations or a placebo response could not be determined. To investigate these issues more objectively, 7 patients with Parkinson’s disease and 1 with essential tremor with refractory hand tremors underwent electromyographically guided intramuscular injections of BOTOX into wrist flexors and extensors. Patients without great medication-related tremor fluctuations were selected. Results before and after BOTOX were determined by comparing (1) patient perceptions of functional improvement, (2) clinical assessments using the Unified PD Rating Scale for tremor and the Webster Rating Scales, and (3) physiological measurements using accelerometric analysis of tremor frequency, amplitude, and waveform characteristics. All patients reported some improvement, ranging from mild to marked with a mean of 2.0 on a 0 to 4 (4 = marked) global rating scale. However, only 3/8 patients showed a significant improvement in the clinical rating scales, confirmed by >50% reduction in tremor amplitudes. These findings show that most patients reported improvement not confirmed by the clinical or physiological measures. Efficacy of BOTOX injections for tremors is implied, but controlled trials are needed before this procedure can be generally recommended.

P73. Risk Factors for Nursing Home Placement in Parkinson’s Disease

Christopher G. Goetz and Glenn T. Stobins, Chicago, IL

We tested whether hallucinations, motor disability, and cognitive decline were risk factors for nursing home placement in advanced Parkinson’s disease (PD) and whether these effects were independent or synergistic. Between 1987 and 1991, we identified 11 patients admitted to long-term nursing homes. Using case control methodology, we matched each for age, PD duration, and sex with 2 control PD patients remaining at home. Parkinsonism was assessed by the motor and Activities of Daily Living subscales of the Unified PD Rating Scale (UPDRS); hallucinations and dementia were determined by scores ≥2 on the thought disorder and intellectual impairment items of the UPDRS. Tests of synergy were based on a Mantel-Henzel model. Hallucinations were a significant risk factor with odds ratio = 18.0, $x^2 = 17.0$, $p < .001$. Motor impairment alone and cognitive impairment alone were not significant risk factors for nursing home placement ($x^2$ for motor severity = .00084, $p > .05$, and $x^2$ for cognitive impairment = .0023, $p > .05$). Furthermore, combined odds ratios for hallucinations/motor severity and hallucinations/cognitive impairment showed no synergy of effect ($x^2 < 1.0$ for both, $p > .05$). Of the 3 variables studied, hallucinatory behavior is the most prominent and independent risk factor for nursing home placement in these patients; the data suggest that aggressive control of hallucinations may be warranted to prevent nursing home admission.

P74. Genetic Heterogeneity in Patients with the Temperature-Sensitive Paramyotonia Congenita Phenotype

Louis J. Piatetz, Philip McManus, Hubert Kubieschnik, Alfred George, Robert Barchi, Laurence Cowu, and Mark Lepirt, Salt Lake City, UT, Rochester, MN, Warsaw, Poland, and Philadelphia, PA

The periodic paralyses are a group of autosomal-dominant muscle diseases sharing a common feature of episodic paralysis. In one form, paramyotonia congenita (PC), the paralysis is temperature-sensitive, usually occurring with muscle cooling. Electrophysiological studies of muscle from patients with PC have revealed temperature-dependent alterations in sodium channel (NaCh) function. This observation led to the identification of 2 distinct mutations in an S4 segment of a skeletal muscle NaCh in 3 unrelated PC families. We describe the use of the single-strand conformation polymorphism (SSCP) technique to define a third allele specific to PC patients in
an additional family. This aberrant pattern, though distinct from the first 2, occurs in the same exon of this NaCh gene. Sequencing is currently underway to define the molecular alteration causing this aberrant pattern. Two additional families with the PC phenotype have been sampled and do not demonstrate these 3 SSCP variants. We are currently searching for new mutations in these 2 families to define further the molecular heterogeneity of this temperature-sensitive PC phenotype.

P75. Withdrawn

P76. Dramatic Creatine Kinase Lowering Effect of Dantrolene in Myopathies
Parag Mehta and Roger W. Kula, Brooklyn, NY

Abnormal accumulation of calcium (Ca) in myofibers is thought to play a role in pathogenic myonecrosis. Attempts at reducing intracellular Ca content with Ca channel blockers in Duchenne muscular dystrophy (DMD) have been clinically unsuccessful. Dantrolene, however, which acts at the sarcoplasmic reticulum to inhibit Ca release from intracellular stores, has produced dramatic reductions in serum creatine kinase (CK) in dystrophic mice and more recently in DMD. We investigated the effect of low-dose dantrolene in a group of 20 patients with limb girdle dystrophy (LGD), DMD, and other myopathic disorders. All subjects received dantrolene in incrementing doses from 25 to 100 mg daily over a 6- to 12-week period. Mean baseline CK was compared to CK with dantrolene treatment. Dramatic reductions in serum CK levels averaging 50% were seen at 50- to 100-mg doses in LGD patients (8). DMD patients (3) and patients with other myopathies (9) showed a similar but less dramatic reduction in CK. Three of the weakest patients complained of increased muscle strength and function. Dantrolene in dosages well below conventional antispastic doses has a dramatic effect on serum CK and possibly myofiber necrosis in LGD, other dystrophies, and other muscle disorders.

P77. Antigen-specific Therapy in Myasthenia Gravis: An Experimental Approach Studied In Vitro
M. Nicolle, B. Naq, S. Sharma, N. Willox, A. Vincent, and J. Newson-Davis, Oxford, UK, and Redwood City, CA

Myasthenia gravis (MG) is mediated by anti-acetylcholine receptor (AChR) antibodies, believed to be T-cell dependent, and antigen-specific therapy would be preferable to current nonspecific immunosuppression. Exposing mouse T-cell clones to MHC Class II molecules complexed with relevant antigen on planar membranes induced proliferative unresponsiveness (Quill and Schwartz, 1987), and soluble MHC Class II molecules complexed with myelin basic protein (MBP) peptide resulted in unresponsiveness of specific T-lymphocyte clones in vitro (Sharma et al, 1991). We have used our well-defined DR4-restricted T-cell clone (Ong et al, 1991) isolated from an MG patient and specific for p138-167 of the AChR alpha subunit. Overnight incubation of these T cells with a soluble p138-167:DR4 complex substantially inhibited the subsequent response to challenge with soluble antigen and presenting cells. In contrast, antigen response after preincubation with DR4 complexed to an irrelevant peptide (MBP 1-14), soluble DR4 alone, or p138-167 alone (at equimolar concentrations) did not differ appreciably from that in untreated cells. The p138-167:DR4 complex had no effect on other non-AChR-specific cell lines/clones. These results suggest that the use of soluble MHC-peptide complexes may be an approach to selective immunotherapy in MG patients.

P78. High-Dose Intravenous Immunoglobulin in the Treatment of Inclusion Body Myositis
Shawke A. Soutoian and Marrinos C. Dalakas, Bethesda, MD

Inclusion body myositis (IBM) is a severe disabling inflammatory myopathy with characteristic clinical and histological features. It is commonly suspected when a patient with presumed polymyositis does not respond to available immunotherapies. The need for an effective treatment in patients with IBM prompted the present pilot study using high-dose intravenous immunoglobulin (HD-IVIg), an apparently effective immunomodulating agent in several autoimmune neuromuscular disorders. We treated 4 patients with muscle biopsy-proven IBM with up to 2 monthly infusions of 2 gm/kg IVIg. After the first infusion, 3 of the 4 patients showed definite functional improvement consisting of independent ambulation, fewer falls, and increased ability to lift weights. The muscle strength of the proximal and less atrophic muscle groups improved by one grade MRC scale (from 4 to 5), whereas the distal and atrophic muscles remained unchanged. The improvement, sustained up to 7 months, was greater in patients with the most severe endomysial inflammation. We conclude that HD-IVIg may be the first promising agent that can improve the strength of certain muscle groups in patients with IBM. Because IVIg is prohibitively expensive, the present encouraging results warrant a large-scale controlled therapeutic study.

P79. Antibodies to MAG and SGPG in Neuropathy
Leonard H. van den Berg, L. J. Kinsella, M. Corbo, D. Younger, S. A. Sadiq, E. Nebili-Ornazio, A. P. Hays, and N. Latov, New York, NY, and Milan, Italy

Anti–myelin-associated glycoprotein (MAG) antibodies from patients with neuropathy cross-react with the glycolipid 3-sulfated glucuronyl paragloboside (SGPG). Among 24 patients tested by enzyme-linked immunosorbent assay and Western blot, 15 had highly elevated antibody titers (>6,400) to both MAG and SGPG, 2 had highly elevated titers to MAG alone, and 7 had highly elevated titers to only SGPG. Immunostaining of normal nerve myelin by the antibodies correlated better with anti-MAG than anti-SGPG activity. Twenty-one of the patients, including patients in all 3 groups, had predominantly sensory or sensorimotor neuropathy, and biopsy specimens revealed deposits of IgM and complement on affected myelin sheaths. Three patients presented with motor syndromes, all with antibodies specific for SGPG; 1 had a predominantly motor demyelinating neuropathy, 1 had upper and lower motor neuron signs and peripheral neuropathy, and 1 had amyotrophic lateral sclerosis confirmed post mortem. All 3 had deposits of complement on peripheral nerve myelin sheaths. These studies suggest the following: (1) that anti-MAG or SGPG antibodies may differ in their fine specificities and biological activities, (2) that anti-SGPG antibodies also may occur in motor neuron diseases, complicating the clinical presentation, and (3) that both MAG and SGPG should be used as antigens in testing for autoimmune activity in peripheral neuropathy.

Program and Abstracts, American Neurological Association 251
P80. Changing Prevalence of Amyotrophic Lateral Sclerosis and Parkinsonism-Dementia Complex on Guam and the Northern Mariana Islands

David B. Williams, John Steele, Ulla-Katrina Craig, Sandra Bryant, Peter O'Brien, and Leonard Kurland, Newcastle, New South Wales, Australia, Mangilao, Guam, and Rochester, MN.

Continuing surveillance of neurodegenerative diseases in the Mariana islands reveals changes in frequency and clinical characteristics since the 1950s that resemble those in other known Western Pacific foci (Kii Peninsula, Japan, and Irian Jaya, New Guinea). Recent surveys of patients 50 years and older were conducted on Rota, Tinian, and Yigo, Guam. Possible cases of dementia, parkinsonism, and amyotrophic lateral sclerosis (ALS) were identified by local trained personnel using a questionnaire, World Health Organization neuropsychological test, and cognitive screening. Those who failed the screening were examined by a neurologist. In the small populations of Rota and Tinian, there were no definite cases of ALS compared to 1 to 3 cases present in previous surveys. The high prevalence of parkinsonism-dementia complex (PDC) was unchanged and dementia was increased compared to earlier surveys. In Yigo, ALS and PDC continue to be prevalent; however, the ALS patients are predominantly long-term survivors (>10-year disease duration). In areas of previous high prevalence of ALS/PDC, dementia (as PDC) was associated with extrapyramidal signs, whereas in areas of previously low prevalence of ALS/PDC, dementia alone, possibly of Alzheimer type, predominated. These observations help to confirm previous reports of changing clinical patterns, but suggest that the geographic distribution of the (presumed) environmental etiologic agent for ALS/PDC remains stable after almost 40 years.

P81. Cardiac Conduction Disturbances in Myotonic Dystrophy

P. V. Frangillo, D. Frangillo, M. Michisanti, G. Antonini, R. Vichi, and D. Cannata, Rome, Italy.

Dernagements of the cardiac conducting system are the most common features of heart involvement in myotonic dystrophy (MD). In view of this 65 patients with various grades of MD (43 males and 22 females, mean age 37 yr) underwent 12-lead ECG and Holter monitoring. In 31 patients (48%), almost all with a severe grade of MD, 1 or more conduction defects were found: first-degree atrioventricular block (1-AVB) in 21 cases, second-degree AVB in 1 case, right bundle branch block in 3 cases, left anterior hemiblock in 2 cases, left bundle branch block in 2 cases, and trifascicular block in 1 case (pacemaker implanted). An 18-year-old boy had a chronic atrial fibrillation with slow ventricular rate; he died suddenly while awaiting electrophysiologic study. Thirty-seven patients were followed over a mean period of 40 months (range 11–75 mo). A 54-year-old woman experienced a myocardial infarction and was excluded from subsequent considerations. Conduction defects de novo appeared in 6 patients: I-AVB in 5 and I-AVB plus II-AVB (Mobitz 1 and II type) in 1. Nine patients, all with I-AVB at initial evaluation, showed deterioration of their defects' conduction: a bifascicular block was observed in 6 cases and a trifascicular block in 3 cases (pacemaker implanted). Conduction defects may run a malignant course in MD, mainly in patients with more severe grades of the neuromuscular disease; thus, a close cardiological evaluation is mandatory for a proper therapeutic approach in single cases.

P82. Intravenous Immunoglobulin Treatment in Amyotrophic Lateral Sclerosis

Hiroshi Mitsumoto, Sarath Kumar, Kerry H. Levin, Robert W. Shields, Jr, Michele Secic, Asa J. Wilbourn, and Rayendra G. Desai, Cleveland, OH, and Santa Ana, CA.

Twenty patients with amyotrophic lateral sclerosis (ALS) entered a pretreatment study with monthly quantitative isometric muscle strength tests (4 muscles in each extremity) and quantitative Tufts scales including vital capacity, bulbar dysphagia, and gait. In 21 cases, second-degree AVB in 1 case, right atrioventricular block in 2 cases, left bundle branch block in 3 cases (pacemaker implanted). Conduction defects de novo appeared in 6 patients: I-AVB in 5 and I-AVB plus II-AVB (Mobitz 1 and II type) in 1. Nine patients, all with I-AVB at initial evaluation, showed deterioration of their defects' conduction: a bifascicular block was observed in 6 cases and a trifascicular block in 3 cases (pacemaker implanted). Conduction defects may run a malignant course in MD, mainly in patients with more severe grades of the neuromuscular disease; thus, a close cardiological evaluation is mandatory for a proper therapeutic approach in single cases. Our results warrant a double-blind, controlled study with IVIg for the treatment of ALS.

P83. Leber's Hereditary Optic Neuropathy Associated with Peripheral Neuropathy and Corticospinal Tract Signs: A Kindred with Unusual Neurological Manifestations

Anhal Prentice and W. King Engel, Los Angeles, CA.

Leber's hereditary optic neuropathy (LHON) is a mitochondrial disorder with predominantly optic nerve abnormality. It can be associated with dystonia, ataxia, encephalopathy, cardiac abnormalities, and other less well-characterized neurological syndromes. We describe 2 members of a family with LHON with a slowly progressive motor polyneuropathy. A 22-year-old man and his 11-year-old sister have had mild motor impairment since early childhood. A gait disorder and distal muscle weakness became evident at puberty. The girl, but not the man, also has blindness, distal numbness, type 1 diabetes mellitus, and short stature. Physical examination showed in both: bilateral foot drop, limb hyperreflexia but absent ankle reflexes, distal sensory loss, and a slight brownish scaly skin discoloration over the forearms. Only the girl had clonus and optic nerve atrophy. The man had peripapillary telangiectasias. The jaw jerk was normal in both. Motor nerve conductions in both showed absent tibial and peroneal responses, whereas other motor and sensory nerve conductions were normal. EMG revealed denervation, more so distally. Muscle biopsy findings showed recent denervation and previous denervation followed by reinervation. No ragged-red fibers were observed with the modified trichrome and SDH stains. Brain MRI was normal in both. Cerebrospinal fluid in the girl was normal. Blood samples from both patients and maternal related family members revealed a mitochondrial DNA point mutation at position 11778 (D. C. Wallace).

In this family, only 1 male had LHON; 3 females had LHON and 2 others, including the patients' mother, were asymptomatic carriers. This association of chronic motor neuropathy and hyperreflexia with LHON appears to be a distinct syndrome. The pathogenic mechanism by which the mitochondrial DNA defect causes the neuropathy (and other neurological defects) requires analysis.
P84. Saccades Are Not Slowed in Advanced Duchenne/Becker Muscular Dystrophy
Henry J. Kaminski, Mazen Al-Hakim, R. John Leigh, Bashar Katriji, and Robert L. Ruff; Cleveland, OH

Fast-twitch extremity muscle fibers are preferentially affected in Duchenne/Becker muscular dystrophy (DBMD). Since saccades are thought to be mediated by fast-twitch fibers, saccadic velocities would be expected to be decreased among these patients. To investigate involvement of extraocular muscle (EOM) by DBMD, we studied with infrared oculography 3 patients who were wheelchair-bound and able to perform only minimal Activities of Daily Living. Saccades were slightly slowed but were within 95% confidence limits of normal. All 3 patients showed square wave jerk movements (SWJ). In 2 patients, the frequency of the SWJ exceeded that of normal subjects, which suggested central nervous system dysfunction. Clinical neuroophthalmological examination of 7 other DBMD patients was normal. This investigation is the first study of ocular motility in DBMD and demonstrates that EOM function is relatively preserved even in far advanced patients. EOM is composed of a heterogenous mix of fiber types that differ in anatomic and physiological characteristics from extrinsic muscle. Study of EOM in DBMD may prove to be useful in understanding why some muscles are resistant to DBMD and in characterizing properties that limit muscle degeneration. (Supported by NIH grants EY09186, EY06717, the Department of Veterans Affairs, and the Evenor Armington Fund.)

P85. Forearm 3-Methylhistidine Release in Myotonic Dystrophy
Ziad Rafii, William J. Kingston, Brian McGrath, and Richard T. Mussey III, Rochester, NY

Since patients with myotonic dystrophy (MTD) exhibit a marked resistance to insulin effect on glucose uptake and an impaired handling of the insulin-sensitive amino acids, it is possible that muscle wasting in MTD may reflect a derangement of insulin action on muscle protein metabolism. Increased muscle protein breakdown in MTD would be expected if the normal inhibitory effect of insulin on protein catabolism is impaired. The forearm perfusion technique combined with measurements of 3-methylhistidine (3-MH) arteriovenous (A-V) differences by high-performance liquid chromatography provides a unique method to investigate skeletal muscle myofibrillar protein degradation in vivo. We studied 3-MH (A-V) and efflux from the forearm muscles in 8 men moderately affected with MTD and 10 normal men. Efflux values (Q) were calculated as the product of 3-MH (A-V) times forearm plasma flow measured by the indicator dilution technique. Forearm 3-MH release (estimated as [A-V] or Q) of MTD patients did not differ significantly from normal controls. We conclude that myofibrillar degradation is not increased in MTD even when measured in a muscle compartment selectively affected by wasting. The possibility of an impaired anabolic action of insulin in MTD has yet to be determined.

P86. Ragged Red Fibers and Aging
S. J. Oh, T. D. Thomas, and H. R. Kurosula, Birmingham, AL

To study the relationship between the ragged red fibers (RRF) and age, we have reviewed 500 muscle biopsy specimens prospectively. Patients with well-established mitochondrial myopathy syndrome and with myopathies known to produce secondary RRF were excluded. The number of ragged red fibers (RRF) was counted under 40 X (LPF) magnification. RRF were identified by the modified trichrome and SDH stain. For the final analysis, the SDH staining was used. The frequency of RRF was analyzed in relation to patients’ ages. The frequency of cases with more than 1 RRF increased with aging; 8% in the first decade, 16% in the fourth decade, and 53% in the eighth decade. The frequency of cases with more than 10 RRF also increased with aging; 0% in the first three decades, 4% in the fourth decade, and 19% in the eighth decade. Of 25 patients with well-established mitochondrial myopathy syndrome, 24 had more than 10 RRF under LPF. The number of RRF in muscle increases with aging, indicating that mitochondrial activity in muscle is affected by aging. This finding may complicate the diagnostic criteria of mitochondrial myopathy in older individuals. Ten RRF under LPF seems to be a reasonable cutoff point for the diagnosis of mitochondrial myopathy.

P87. Schwartz-Jampel Syndrome—Evidence of Central Nervous System Dysfunction
B. Singh, N. Biary, A. A. Jamil, S. M. Al Deeb, and A. M. Al Souailem, Riyadh, Saudi Arabia

Schwartz-Jampel, a rare autosomal-recessive syndrome characterized by short stature, myotonia, skeletal abnormalities, and peculiar facies, was reported by Aberfeld in 1965. The same sibship was earlier reported by Schwartz and Jampel in 1962 with emphasis on blepharophimosis. As of this writing about 30 cases have been reported in the literature. Most of the features of this syndrome are believed to be secondary to primary muscle disease. Several peripheral electrophysiological studies showing features of myotonia have been reported. We describe 4 patients with Schwartz-Jampel syndrome showing evidence of central conduction disturbance documented by somatosensory-evoked potentials (SEPs). Median nerve SEPs showed normal latencies to Erb’s point and N-13 in all. Interpeak latencies between N13 and N19 were prolonged in 3 with complete block in 1. EMG showed typical myotonic discharges in all. Motor nerve conduction velocities, visual and brainstem auditory-evoked potentials, CT, and MRI were normal in all. SEPs in the parents were normal. We believe this is the first report documenting evidence of central nervous system (CNS) involvement in Schwartz-Jampel syndrome. Schwartz-Jampel syndrome and myotonic dystrophy may have similar CNS lesions as SEP abnormalities also have been shown in myotonic dystrophy.

P88. Pathological Changes in Rat Muscle Induced By 1,1′-Ethylenebis[Tryptophan], an l-Tryptophan Contaminant Implicated in the Eosinophilia-Myalgia Syndrome
A. M. Emiliie-Smith, A. N. Mayeno, S. Nakano, G. J. Gleich, and A. G. Engel, Rochester, MN

Epidemiological studies have associated consumption of certain batches of l-tryptophan (LT) with development of the eosinophilia-myalgia syndrome (EMS). 1,1′-Ethylenebis[tryptophan] (EBT or peak E), a derivative of LT, is a trace contaminant associated with implicated batches of LT. Three female Lewis rats received EBT, 4 mg per 100 gm daily, by intraperitoneal injection. Four control rats received unimplicated LT. No peripheral eosinophilia, rash, or weakness were observed in either group. One rat from each group died during the experiment (control—bowel infarct; EBT—death under anesthetic). After 132 days, forelimb and hindlimb muscles of the remaining animals were frozen and fixed for light microscopy.
ultrastructural and histological studies. Two EBT rats had a myopathy involving soleus with a perimysial infiltrate containing lymphocytes, macrophages and sparse eosinophils, and necrotic fibers; the other showed few necrotic fibers in gastrocnemius. Occasional eosinophils were seen in fascia in that EBT is the causative agent of the disease. 

P89. Motor Neuron Disease After Silicone Breast Implants and Silicone Injections into the Face
Britta Ostermeyer-Shoaib, Bernard M. Patten, and Tetsuo Ashizawa, Houston, TX

Five women (Patients 1–5) developed motor neuron disease (MND) 10 years (range 2–23 yr) after receiving silicone gel–filled breast implants. At explant in 4 patients, 2 had both and 2 had the left implant ruptured with silicone spilled into tissue. One woman (Patient 6) developed amyotrophic lateral sclerosis (ALS) 5 years after numerous injections of free silicone into her face. Biceps muscle biopsy specimens in all 6 showed neurogenic atrophy. Patient 1 developed ALS with bulbar involvement and died 7 years later of respiratory failure. She had anti-GM1 antibodies and autopsy findings confirmed the diagnosis of typical ALS. Patient 2 developed ALS, but also fatigue, myalgia, arthralgia, and skin rash. She had anti-GM1 antibodies, antisilicone antibodies, positive antinuclear antibodies (ANA), and decreased serum IgG, IgA, and C3, but increased IgM and creatine phosphokinase (CPK) and chronic inflammation was revealed in muscle biopsy specimens. Patient 3 developed ALS, but also had hair loss, skin rash, fatigue, headache, Sjögren’s syndrome, and positive ANA. Patient 4 developed ALS, but also had myalgia and arthralgia. Patient 5 developed lower MND, but also fevers, arthralgia, and joint stiffness. She had anti-GM1 antibodies, antithetical antibodies, positive antinuclear antibodies, and decreased serum IgG and IgA with chronic inflammation shown in nerve biopsy findings. Patient 6 developed a steroid-responsive and steroid-dependent ALS with bulbar involvement. She had a monoclonal gammopathy in the cerebrospinal fluid and increased CPK. We suggest that silicone acts as an adjuvant that damages motor neurons via an indirect autoimmune mechanism.

P90. Silicone Adjuvant Breast Disease: More Neurological Cases
Britta Ostermeyer-Shoaib and Bernard M. Patten, Houston, TX

Forty-five women developed mixed sensory-motor neuropathy (35), motor neuron disease (5), multiple sclerosis (2), multiple sclerosis-like syndrome (2), or myasthenia gravis (1) 7 years (range 1 mo–23 yr) after receiving silicone-gel breast implants (38), saline-filled silicone-covered breast implants (6), or direct injections of silicone into the breast (1). Most patients had, in addition, severe fatigability, myalgia, arthralgia, morning stiffness, skin rash, lymphadenopathy, Sjögren’s syndrome, and short-term memory problems. Laboratory results revealed in most of the women decreased or increased serum immunoglobulins, autoantibodies, a serum monoclonal gammopathy, or oligoclonal bands in cerebrospinal fluid. At explantation in 34, 14 had both and 7 had 1 implant ruptured. Biopsy of the fibrous implant capsule in most patients showed foreign-body giant cells containing refractile material consistent with silicone whether or not the elastomer shell was ruptured, indicating silicone bleed. The major finding on sural nerve biopsy was loss of myelinated fibers, on biceps muscle biopsy was neurogenic arrophy, and on pectoralis muscle biopsy was myositis with vasculitis and free silicone in some. We suggest that silicone may provoke damage to nerve and muscle, probably indirectly promoting autoimmunity.

P91. Urinary Incontinence in Myasthenia Gravis: A Single-Fiber Electromyographic Study
James F. Howard, Jr, M. Kathleen Donovan, and M. Susan Tucker, Chapel Hill, NC

Urinary symptoms of urgency and incontinence have been reported only rarely in patients with myasthenia gravis (MG) and then most often in association with myasthenic crisis. We report the case of a 31-year-old woman who in December 1987 had the onset of chest pain and was found to have a lymphocytic thymoma. In June 1989 she developed urinary incontinence, was found to have an open bladder neck, and underwent a suspension procedure for stress incontinence in January 1990. Eight months later she developed exertional fatigue and a diagnosis of MG was made. In July 1991 there was a recurrence of urinary incontinence. These symptoms clustered toward the end of the day and at trough Mestinon dose. Neuro-urophysiological studies demonstrated her previous open bladder neck, the inability to sustain a pelvic floor contraction, and increased bladder wall contraction. Single-fiber electromyography (SFEMG) recordings from the anal sphincter demonstrated a mean consecutive difference (MCD) of 88 μsec, and 11% of fiber pairs had impulse blocking while recordings in the extensor digitorum communis muscle were normal. Following a course of plasma exchange, there was significant clinical improvement with a reduction in the frequency of urinary incontinence, and improvement in anal sphincter SFEMG studies (MCD, 60 μsec with no blocking). This case demonstrates that in those myasthenic patients with predisposing bladder outlet dysfunction, urinary incontinence may be a manifestation of worsening MG.

P92. T-Cell–mediated Demyelination in Guillain-Barré Syndrome
Diana M. Escobar, Mohamed Eldady, and Jaime Rich, Boston, MA

Debate still exists as to the role of antibody versus cell-mediated factors in the pathogenesis of Guillain-Barré syndrome (GBS). We describe a patient with increased proportion of circulating T cells and a T-cell lymphoma who developed GBS and responded to intravenous immunoglobulin (IVIg). A 57-year-old man with T-cell lymphoma developed GBS by clinical, nerve conduction, and cerebrospinal fluid criteria. He had an elevated proportion of T cells and markedly reduced B cells with a normal CD4/CD8 ratio. He responded rapidly to IVIg, with return of nearly normal motor function in 1 week. Three weeks later, he relapsed and his vital capacity dropped. IVIg was again administered and within 24 hours he nearly recovered. A third relapse, 21 days later, again responded to IVIg. He has remained asymptomatic with IVIg maintenance. The role of T-cell lymphocytes in initiating experimental autoimmune neuritis has been shown by adoptive transfer experiments. This patient with T-cell neoplasia may represent an analogous model in hu-
P93. Sympathetic Skin Response: Age Effect
V. F. Drory and A. D. Korczyn, Tel Aviv, Israel

It is frequently stated that the sympathetic skin response (SSR) can be elicited in all normal subjects, but the age of the investigated population usually is not considered to be a significant factor. We have examined the SSR in the upper and lower limbs of 100 normal subjects, aged 20 to 88 years (55 of them males). The SSR was elicitable in the lower limbs in all subjects under the age of 60 years and in the upper limbs in all subjects younger than 70 years. In contrast, it could be elicited in the lower limbs in only 34% and in the upper limbs in 65% of octogenarians. The amplitude of the response, though highly variable, showed a remarkable decline with age, both in the upper (p < 0.0001, r = 0.53) and in the lower (p < 0.0001, r = 0.65) limbs. These results indicate that age affects both the elicitability and the amplitude of the SSR. This has to be taken into consideration when evaluating the autonomic function in the elderly.

P94. Immunosuppression in Atypical Motor Neuron Disease
D. A. Krendel, D. A. Castigan, L. C. Hopkins, and M. A. Polsak, Atlanta, GA

We reviewed records of patients appearing to have motor neuron disease (MND) to whom we recommended immunosuppression over 4 years (17 of 210 MND patients). Atypical findings engendered hope that they might have treatable neuropathy. Electrophysiological studies were largely consistent with MND, but also showed conduction block or other evidence of mildly peripheral nerve disease in 12. Sensory symptoms were present in 7; 1 or more reduced or absent deep tendon reflexes in 6; elevated cerebrospinal fluid protein in 8; and nonspecific abnormalities on sural nerve biopsies in 6 of 7. Anti-GM1 levels were measured in 6 (including 1 who improved), but none was significantly elevated. Immunosuppression included cyclophosphamide (12 patients); prednisone (10); plasma exchange (4); intravenous gamma globulin (1); cyclosporine (1); and total lymphoid irradiation (1). Seven treated patients died, 6 worsened, 1 remained stable for 2 years, and 1 improved. Two patients declined treatment. One died and the other did not worsen in 3 years. We conclude that immunosuppression by our methods is, at best, rarely effective in atypical MND.

P95. Serum Anti-GQ1b Antibody Is Associated with Impaired Eye Movement in Miller Fisher Syndrome
Atsuro Chiba, Susumu Kusunoki, and Ichiro Kanazawa, Tsukuba, Japan

We studied serum antiglycolipid antibodies by enzyme-linked immunosorbent assay in 11 patients with typical Miller Fisher syndrome (MFS), 6 patients with atypical MFS who were lacking in some of the 3 cardinal signs, 4 patients with Guillain-Barré syndrome (GBS) with ophthalmoplegia, 20 patients with GBS without ophthalmoplegia, 20 patients with multiple sclerosis (MS), and 17 patients with other immunological disorders (OID) including systemic lupus erythematosus, polymyositis, and mixed connective tissue disorder. All patients with typical MFS had increased activity of IgG antibody against ganglioside GQ1b in the early phase, and it reduced with time. Such anti-GQ1b IgG activity also was detected in 3 of the 6 patients with atypical MFS and in 3 of the 4 patients with GBS with ophthalmoplegia. In atypical MFS, the only patient without increased anti-GQ1b IgG activity demonstrated normal eye movement with ptosis, whereas eye movement was impaired in the other 5 patients. No patients with GBS without ophthalmoplegia, MS, or OID had increased anti-GQ1b IgG activity. These findings suggest the close association between increased anti-GQ1b IgG activity and impaired eye movement in MFS and GBS. Serum anti-GQ1b IgG activity possibly plays a role in impaired eye movement in MFS.

P96. Effects of Recombinant Interferon β on T-Cell Activation in Multiple Sclerosis Patients
R. A. Rudick, C. S. Carpenter, V. K. Tsuhy, D. L. Cookfair, and R. M. Remisoff, Buffalo, NY, and Cleveland, OH

Our goal is to develop an assay that can be used to monitor a relevant immune effect of interferon β (IFNB) in multiple sclerosis (MS) patients during the course of IFNB immunotherapy, since recombinant IFNB is being tested in multicenter clinical trials. This report extends our prior studies of the inhibitory effect of IFNB on T-cell activation. Peripheral blood mononuclear cells (PBLS) from 11 healthy donors and 10 clinically stable MS patients were studied. PBLS were stimulated with ConA, mAb to CD3, or with the phorbol ester PMA in the presence of the calcium ionophore ionomycin. Parallel cultures were studied in the presence of IFNB, 100 U/ml. T-cell activation was monitored by determining the percent cells positive for IL-2 receptor (IL-2r) using FACs analysis, or with a sensitive enzyme-linked immunosorbent assay for IFNY. IFNB markedly inhibited IL-2r expression induced by ConA, by mAb to CD3, or by PMA and ionomycin, which activate T cells via different pathways. The results suggest that IFNB inhibits T-cell activation by actions independent of membrane receptors. We observed significant inhibition of ConA-induced T-cell IL-2r expression in both MS patients (20.6% inhibition, p < 0.05) and controls (26.8% inhibition, p < 0.05). There was no significant difference in percent inhibition between MS and controls, but there was more variance among the MS patients. Variability of biological effects of IFNB on T cells may relate to differential therapeutic responses to exogenously administered IFNB in MS patients. Preliminary experiments suggested that IFNB inhibited IFN gamma secretion by PBLs stimulated with ConA. IFNB inhibits a number of events associated with T-cell activation, in both normal and MS T cells. Response to IFNB appears more variable in the MS cases. Immunological monitoring of T-cell activation in patients receiving IFNB may assist in understanding the observed therapeutic responses and planning clinical protocols.
substance assay for production of malondialdehyde (nmol/ml). Myelin oxidation by monocytes was 1.80 ± 0.10 (mean ± standard error of mean) without U74500A and was reduced to 0.76 ± 0.15 by 100 μM U74500A (p < 0.005). PMN-mediated myelin oxidation was 1.89 ± 0.44 without drug and 0.64 ± 0.10 with drug (p < 0.02). These results demonstrate that U74500A markedly inhibits monocyte- and PMN-mediated myelin oxidation and suggest that the 21-aminosteroids may help disorders associated with inflammatory cell-induced myelin injury.

P98. Immune-Accessory Properties of Human Adult-derived Microglia Cells
Kenneth Williams, JoAnne McLaurin, V. Wei Yong, and Jack P. Antel, Montreal, Quebec, Canada

Microglia cells participate in the pathological reactions of the CNS to multiple insults including trauma, inflammation, and neuronal degeneration. Functional roles for these cells could include mediating tissue injury, promoting repair, or modulating immune responses. With regard to the latter, we have observed that the majority of human-derived microglia express major histocompatibility complex (MHC) Class II molecules under basal culture conditions, in contrast to astrocytes derived from the same surgical biopsy specimens. All morphological subtypes of the microglia (ameboid, bipolar, and ramified) expressed MHC Class II molecules, indicating a discordance between morphology and MHC antigen expression as markers of microglia activation. The microglia actively ingest myelin constituents, as assessed using fluorescein-labeled myelin basic protein and laser confocal microscopy. Autologous T cells (E+∗) freshly isolated from the systemic blood and cocultured with Candida antigen underwent active proliferation in the presence of 1 to 10% microglia, indicating the functional capacity of the microglia to serve as antigen-presenting cells. γ-Interferon augmented both MHC Class II expression and functional antigen-presenting capacity. These results indicate the potential of the adult human microglia to promote immune reactivity within the CNS.

P99. Selected Synthetic Peptides of Myelin Basic Protein (MBP) Neutralize Anti-MBP Purified from Multiple Sclerosis Cerebrospinal Fluid
K. G. Warren and I. Catts, Edmonton, Alberta, Canada

Active phases of multiple sclerosis (MS) are associated with increased titers of intrathecal produced antemyelin basic protein (anti-MBP). Anti-MBP can be purified by antigen-specific affinity chromatography from CSF IgG of patients with acute relapses of MS. Eighteen synthetic peptides of human myelin basic protein (h-MBP) containing between 8 and 25 amino-acid residues and covering the entire length of the molecule were synthesized by the Fmoc method. Purified anti-MBP was reacted with increasing amounts of h-MBP as well as each of the 18 peptides in an initial liquid phase assay, and subsequently titers of F-anti-MBP in all resulting mixtures were measured by a solid-phase radioimmunoassay. Purified anti-MBP was neutralized by h-MBP and 6 of the 18 synthetic peptides containing overall residues corresponding to 61 to 106 of h-MBP. The remaining 12 synthetic peptides covering both the amino and carboxyl terminals of h-MBP did not significantly react with purified anti-MBP from these patients. In conclusion, anti-MBP purified from CSF of MS patients has affinity for epitopes located between residues 61 and 106 of h-MBP.

P100. A Comparison Between 4-Aminopyridine and 3,4-Diaminopyridine in the Treatment of Multiple Sclerosis
Frits W. Bertelmann, Chris H. Palmer, Harriet A. M. van Diemen, Ron de Waal, and Johan C. Kostier, Amsterdam, The Netherlands

In a double-blind study involving 70 patients, we recently demonstrated that 4-aminopyridine (4-AP) is superior to placebo in the treatment of multiple sclerosis (MS) (Ann Neurol, in press). The related agent, 3,4-diaminopyridine (DAP) is also appears to be effective. To enable a preliminary comparison, 14 patients, who in our previous study had not benefitted from 4-AP, were now treated (4 wk) with DAP (up to 1.0 mg/kg/day) for 4 weeks in an open-label fashion. Instruments for assessment and registration of side effects were the same as in the previous trial. The optimal dose of DAP was 56.4 mg/day compared to 30.7 mg/day for 4-AP. Significant changes in the EDSS (1.0 point or more) were not found, whereas significant improvements in neurophysiological parameters were found (no difference between 4-AP and DAP, all p > 0.05). Subjective side effects during 4-AP (8 patients) mainly suggested CNS-function disturbance (dizziness and gait disturbance) and during DAP (10 patients) mainly suggested peripheral nervous system-function disturbance (paresthesias). Systemic tolerability clearly was diminished for DAP compared to 4-AP, with 2 patients withdrawing because of severe gastric complaints and 1 developing liver function abnormalities. These data suggest that 4-AP is more valuable than DAP in the treatment of MS.

P101. Pilot Study of Three-Year Intermittent Pulse Cyclophosphamide/Methylprednisolone Therapy in Multiple Sclerosis
Marika J. Holol, Glenn A. Mackin, David M. Dawson, David A. Hafler, Sarija J. Khouery, Lynn Stazzone, and Howard L. Weiner, Boston, MA

Multiple sclerosis (MS) is a presumed autoimmune disease in which various forms of immunotherapy have been attempted. MRI studies show the disease to be more chronically active than is clinically evident, thus a single treatment is unlikely to provide lasting benefit. Recently, the Northeast Cooperative Treatment Group found that pulse cyclophosphamide (700 mg/m² every other month for 2 years) slows progressive MS. We initiated a pilot study to determine the effect of a more intensive and prolonged pulse therapy regimen in both progressive and earlier stages of the disease. Pulse therapy was given after induction with either IV cyclophosphamide or corticosteroids (600 mg/m² × 5 over 8 days) or IV methylprednisolone (1 gm × 7 over 7 days). Patients received a single IV dose of cyclophosphamide (800–1,400 mg/m²)
mg/m²) adjusted to produce leukopenia plus 1 gram of IV methylprednisolone monthly for a year, every 6 weeks for the next year, and every 2 months in the third year. Another group received pulse methylprednisolone without cyclophosphamide. As of this writing, 128 patients have been treated, of which 24 have completed 3 years. Interim analysis shows toxicity, however, was higher in the pulse cyclophosphamide group. Current regimens involve methylprednisolone induction alone followed by pulse cyclophosphamide/methylprednisolone, analogous to lupus nephritis pulse therapy. This regimen can be given solely on an outpatient basis, does not cause alopecia, and is more amenable for use in earlier stages of the disease.

P102. Incidence of Malignancy Following Cyclophosphamide or Azathioprine Treatment of Multiple Sclerosis

D. E. Goodkin, M. M. Daughtry, and S. V. Vanderlaid-Medendorp, Cleveland, OH

To determine the incidence of pathologically confirmed malignancy in multiple sclerosis (MS) patients in funded clinical trials of cyclophosphamide (CTX) and of azathioprine (AZA), data were collected longitudinally using telephone interviews, written questionnaires, physical examinations, and medical records for CTX and AZA patients from a community in-hospital and out-patient MS clinic in Fargo, ND. In the CTX study (Goodkin et al, Arch Neurol 1987;44:823–827), 51 clinically definite (CD), chronic progressive MS patients were enrolled. Twenty-four were controls and 27 received a mean induction dose of 6.08 grams. Fourteen of the induced patients then received boosters every other month for 24 months resulting in a mean total dose of 15.92 grams. No malignancies were detected. In the AZA study from days 3 to 7 after cell transfer and had disappeared on day 10. At day 2 they entered the spinal cords predominantly through subpial vessels. IFN-γ-positive cells could be identified as W3/13+ leukocytes as well as ED1-positive macrophages. As in naïve rats, astrocytes in AT-EAE were labeled only with mab DB-1, but not DB-12. We never observed labeling of motor neurons with these mab. The transient presence of IFN-γ in the rat spinal cord at the onset of AT-EAE suggests a pathogenic role of this cytokine in acute immune-mediated demyelination of the CNS probably as a local stimulus for expression of MHC class II antigens and adhesion molecules, as well as for the release of TNF-α and toxic oxygen radicals from macrophages and microglia.

P103. Endothelial Cell Activation in Experimental Allergic Encephalomyelitis

Paula Dore-Duffy, Raith Washington, and Robert H. sweatbog, Detroit, MI

Postcapillary endothelium at sites of inflammation undergoes many changes referred to as activation. Activated endothelial cells (EC) exhibit increased surface expression of immunorelevant proteins (ICAM-1; NCAM, ELAM, and MHC class I and class II antigens [Ags]). The sequence of events that characterizes EC activation may be important in susceptibility, induction, and perpetuation of experimental allergic encephalomyelitis (EAE). In this study we examine expression of EC activation antigens in central nervous system (CNS) microvessels in response to interferon gamma (IFN-γ). CNS microvessels from SJL and B10.S mice were incubated for 18 hours in IFN-γ (500 U/ml), fixed, permeabilized, and then stained with an antibody that recognizes class I, class II MHC antigens, ICAM-1, and factor VIII. Relative fluorescence intensity was determined using a laser cytometer. Results indicate that microvessels from all strains tested expressed no detectable ICAM-1 and class II Ags. Little class I antigen and transferrin receptors were expressed. Upon stimulation with IFN-γ, SJL microvessels exhibited increased surface expression of all EC activation Ags. B10.S microvessels exhibited ICAM-1 and class I MHC but MHC class II Ags were not upregulated. Results indicate that there are strain differences in the EC response to IFN-γ. Resistance of B10.S mouse EC to activation by IFN may be a factor in decreased susceptibility or induction of EAE, or both.

P104. Interferon-Gamma in Myelin Basic Protein–T-Cell Line–Mediated Experimental Allergic Encephalomyelitis: An Immunocytochemical Study

G. Stoll, S. Kapke, S. Jung, B. Schmidt, and H.-P. Hartung, Düsseldorf, Würzburg, Germany

To investigate a possible pathogenic role of interferon-gamma (IFN-γ) in experimental allergic encephalomyelitis (EAE), an immunocytochemical study was undertaken to localize this cytokine in the spinal cord of Lewis rats in which EAE was produced by adoptive transfer of myelin basic protein–specific T cells. One μm-thick cryosections of spinal cord were labeled with monoclonal antibodies (mab) DB-1 and DB-12 recognizing different epitopes of rat IFN-γ. In the spinal cord of naïve rats, mab DB-1, but not DB-12, stained processes of astrocytes. Suggesting that astrocytes contain a protein with an epitope cross-reacting with IFN-γ. In rats with AT-EAE, numerous IFN-γ-positive cells stained with both mab DB-1– and DB-12–positive cells were present from days 3 to 7 after cell transfer and had disappeared on day 10. At day 2 they entered the spinal cords predominantly through subpial vessels. IFN-γ–positive cells could be identified as W3/13+ leukocytes as well as ED1-positive macrophages. As in naïve rats, astrocytes in AT-EAE were labeled only with mab DB-1, but not DB-12. We never observed labeling of motor neurons with these mab. The transient presence of IFN-γ in the rat spinal cord at the onset of AT-EAE suggests a pathogenic role of this cytokine in acute immune-mediated demyelination of the CNS probably as a local stimulus for expression of MHC class II antigens and adhesion molecules, as well as for the release of TNF-α and toxic oxygen radicals from macrophages and microglia.

P105. Myelin Basic Protein and a Mycobacterial Stress Protein

Gay Birnbaum, Patrick M. Schliefert, and H. Brent Clark, Minneapolis, MN

Immune responses to stress or heat shock proteins are implicated in the pathogenesis of several autoimmune diseases, including multiple sclerosis (MS). We examined the hypothesis that antigens in myelin cross-react with stress protein antigens. Two techniques were used; immunocytochemistry and Western blotting. Frozen histological sections were prepared from normal human central and peripheral nervous system tissues. Sections were incubated with 4 murine monoclonal antibodies to different mycobacterial stress proteins. Antibody binding was determined using avidin-biotin complexed antimurine antibody linked to alkaline phosphatase.
A monoclonal antibody to the stress protein SP65 from M. leprae strongly stained both central and peripheral nervous system myelin. No myelin staining was noted with antibodies to SP70 or SP17. Proteins from purified central and peripheral nervous system myelin were separated by SDS-PAGE. Western blots were prepared using a monoclonal antibody to SP65 and a polyclonal rabbit antibody to myelin basic protein (MBP) as primary antibodies. Antibody binding was determined using antimurine or antirabbit IgG antibody coupled to alkaline phosphatase. Strong staining of central but not peripheral MBP by the anti-SP65 antibody was observed. The rabbit anti-MBP antibody stained both central and peripheral nervous system MBP. The presence of antigenic epitopes shared by a stress protein and the potential autoantigen, MBP, supports the hypothesis that immune responses to stress proteins may be involved in the pathogenesis of presumed autoimmune diseases such as MS. (Supported by a grant from the National Multiple Sclerosis Society.)

P106. Significance of Reactive Lyme Serology in Multiple Sclerosis
P. K. Cosyle, Lauren B. Krupp, and Carol Doscher, Stony Brook, NY

Seven percent of patients (19/283) evaluated in a multiple sclerosis (MS) comprehensive care center had an incidental neurological syndrome that suggested MS. Seventeen had definite MS; 2 presented with an initial neurological syndrome that was not peripheral MBP by the anti-SP65 antibody was observed. The rabbit anti-MBP antibody stained both central and peripheral nervous system MBP. The presence of antigenic epitopes shared by a stress protein and the potential autoantigen, MBP, supports the hypothesis that immune responses to stress proteins may be involved in the pathogenesis of presumed autoimmune diseases such as MS. (Supported by a grant from the National Multiple Sclerosis Society.)

P107. Sample Size Estimates for Therapeutic Trials for Multiple Sclerosis
Laurence W. Myers, George W. Ellison, and Barbara D. Leake, Los Angeles, CA

For therapeutic trials for multiple sclerosis, investigators often enroll patients with a Disability Status Scale (DSS) score between 3 and 6. Survival analysis may be used to evaluate the results, with time to sustained worsening of one step of the DSS as the milestone. To estimate sample sizes for this design, we did a survival analysis on data collected over 20 years in the UCLA Multiple Sclerosis Research and Treatment Program. Patients (n = 262) had an initial DSS between 3 and 6 and 3 or more visits to the clinic over 1 or more years. Actuarial analysis revealed that, after 1-year follow-up, 62 patients (24%) had worsened and 11 patients (4%) were lost to follow-up. By 2 years, 91 (35%) worsened and 28 (11%) were lost to follow-up. By 3 years, 118 (45%) worsened and 46 (18%) were lost. Based upon these data, Kaplan-Meier estimates for worsening by 1 year equaled 24%; for 2 years, 36%; and for 3 years, 50%. With these estimates, we would require a sample size of 82 patients per group to detect a 50% reduction in the rate of worsening in 2 years and 65 per group at 3 years (with a power of 80% and p = 0.05). Such sample sizes usually mandate multicenter therapeutic trials. (Partially supported by USPHS grant NS 08711, the Conrad N. Hilton Foundation, and various donors.)

P108. A Clinical-Pathological Study of Devic's Neuromyelitis Optica
Raul N. Mandler, Larry Davis, Douglas Jeffery, and Mario Karnfield, Albuquerque, NM

We present the clinical imaging, laboratory, and pathological features of 7 patients with Devic's neuromyelitis optica. All patients had clinical involvement of spinal cord and optic nerves, without involvement of other CNS areas, even after many years of disease. MRI demonstrated spinal cord abnormalities in the absence of MS and normal IgG daily synthesis. CSF abnormalities included abnormal blood-brain barrier permeability to albumin with normal CNS IgG daily synthesis and absence of oligoclonal bands. Complete aquaporin 4 antibodies revealed optic nerve demyelination, severe necrosis of both spinal cord gray and white matter, and marked enlargement of small and medium-size spinal cord blood vessels, without inflammatory infiltrates. No white matter abnormalities were found elsewhere in the CNS. The necrotizing spinal cord lesions involve both gray and white matter with thickened vessel walls, the absence of inflammatory infiltrates, and the normal CSF IgG profile place Devic's neuromyelitis optica among a distinct nosological category of necrotizing myelopathies, different from multiple sclerosis.

P109. Disability Status Scale Influence on Rate of Worsening of Multiple Sclerosis Patients
George W. Ellison, Laurence W. Myers, and Barbara D. Leake, Los Angeles, CA

When designing and analyzing therapeutic trials for multiple sclerosis (MS), investigators commonly compare the proportion of patients in the experimental and control groups who worsen one or more steps on the Disability Status Scale (DSS) or Expanded DSS during the study (typically 2 years' duration). However, the intervals between the scores in the DSS may not be equal. It may be easier to change by one or more steps in the lower end of the scale (e.g., DSS = 1–3) than in the midportion of the scale (e.g., DSS = 4–6). To evaluate this possibility, we compared the proportion of patients who worsened by one or more steps in the 2 years after entering our program with DSS = 3 or with DSS = 6. Fifty-one percent (29/57) of the patients entering at DSS 3 had persistent worsening (lasting more than 3 months) by one or more steps on the DSS within 2 years. Thirty percent (32/105) entering at DSS 6 had persistent worsening. These
Monday, October 19

proportions are significantly different statistically \( (p < .025, \text{ Chi squared} = 5.71) \) and support the contention that change is more likely to occur at the lower scores. Our results indicate that the study groups should be stratified and balanced by DSS score in therapeutic trials for MS. (Partially supported by USPHS grant NS 08771, the Conrad N. Hilton Foundation, and various donors.)

P110. Cerebrospinal Fluid Immunoreactivity to Heat Shock Protein is Elevated in Multiple Sclerosis
M. S. Freedman, S. Prabhakar, R. S. Gupta, E. Kurien, and J. P. Antel, Montréal, Québec, and Hamilton, Ontario, Canada, and Vellore, India

Heat shock proteins (HSP) are expressed in oligodendrocytes bordering multiple sclerosis (MS) lesions containing T-cell infiltrates; this raises the possibility that damage to the oligodendrocyte-myelin unit might reflect HSP-immune interactions. Using recombinant human HSP60 and a monoclonal antibody (Ab) to HSP60, we developed an enzyme-linked immunosorbent assay to quantify specific HSP60 Ab titers in patients with MS (18), acute disseminated encephalomyelitis (ADEM) (8), demyelinating polyneuropathy (DPN) (12), and other neurological diseases (OND) (59), and correlated Ab titers with the presence or absence of oligodendrocyal bands (OCB). We found overall that patients with OCB+ CSF \((n = 30)\) had significantly \((p = .005; \text{ Mann-Whitney})\) higher HSP60 Ab titers compared with those with OCB− CSF \((n = 67)\). If the patients with MS were excluded, HSP60 titers in OCB+ CSF \((n = 15)\) did not differ significantly from the OCB− group \((n = 64)\). Comparing HSP60 titers among patient groups, we found significantly higher levels in MS patients compared to the OND \((p = .0005, \text{ analysis of variance})\), whereas only borderline significant differences were observed between MS and the ADEM \((p = .0487)\) or DPN \((p = .0597)\) patient groups, neither of whose levels were significantly different from OND. No significant correlation was observed between HSP60 titer and IgG content in the CSF. The elevated HSP60 Ab titers in patients with MS suggest an in vivo interaction between HSP60 and the immune system.

P111. Use of Survival Analysis to Describe the Course of Multiple Sclerosis
Lawrence W. Myers, Barbara D. Leake, and George W. Ellison, Los Angeles, CA

Natural history data may be useful for designing therapeutic trials for multiple sclerosis (MS). Since 1971, we have collected such data in a standard format on patients in the UCLA Multiple Sclerosis Research and Treatment Program. To describe the course in our group, we have performed survival analysis (Kaplan-Meier) of patients with 3 or more assessments who entered the clinic with Disability Status Scale (DSS) scores of 1 to 7 \((n = 395)\). An increase of one or more steps in the DSS score persisting for more than 3 months defines worsening. Median times to worsening for a DSS at entry of 1 to 5 were approximately 2 years \((\text{range} 1.7–2.2)\); but were 4.6 years for DSS 6 and 3.6 years for DSS 7. For those starting at DSS 6 \((n = 129)\), only 15% worsened by 1 year, 26% by 2 years, and 39% by 3 years. The percent worsening when starting at DSS 3 \((n = 61)\) were 41%, 48%, and 54%, respectively. These variable rates of worsening \((\text{i.e., time spent at each starting level})\) influence therapeutic trial design. Including patients with DSS 6 or 7 will increase the sample size and study duration. For testing non-toxic agents, we recommend enrolling patients with DSS 1 to 5. For more toxic treatments, we suggest DSS 3 to 5. (Partially supported by USPHS grant NS 08771, the Conrad N. Hilton Foundation, and various donors.)

P112. Cholinergic Antagonists and β-Adrenergic Agonists Inhibit Experimental Allergic Encephalomyelitis in an Additive Manner
Mark A. Jenzen, Avetaron Noronha, and Barry G. W. Arnason, Chicago, IL

Lymphoid organs receive a sympathetic (SNS) and possibly a parasympathetic innervation. Lymphocytes express β-adrenergic and cholinergic receptors and thus are sensitive to regulation by these neurotransmitters. The severity of experimental allergic encephalomyelitis (EAE) is increased in SNS-ablated animals. Local parasympathectomy decreases plaque-forming responses in submamdbular nodes. β-adrenergic agonists are upregulated on CD8 T cells in progressive multiple sclerosis, as are M3-muscarinic acetylcholine receptors on CD4 T cells. We examined the effect of isoprotenerol, a β-adrenergic agonist, and scopolamine, a cholinergic antagonist, on the course of EAE in Lewis rats. EAE was induced by injection of 0.1 ml of incomplete Freund's adjuvant containing guinea pig spinal cord (25% w/v) and M. tuberculosis (3 mg/ml) in one hind footpad. Scopolamine (0.6 mg/kg, twice daily) and/or isoproterenol (0.15 mg/kg, twice daily) or saline were injected subcutaneously starting on the day of immunization. Scopolamine or isoproterenol alone reduced severity \((p < 0.05, t \text{ test})\) and duration \((p < 0.05, t \text{ test})\) of disease compared to controls. The combination of scopolamine and isoproterenol further reduced disease severity compared to either agent alone \((p < 0.05, \chi^2 \text{ test})\), suggesting an additive protective effect of cholinergic antagonists and β-adrenergic agonists in EAE.

P113. Fifty Percent of Postmortem Multiple Sclerosis Plaques Show No Demyelinating Activity or Antigen-Presenting Cells
A. Conrad, V. Sanders, P. Schmidt, and W. W. Tourtellotte, Los Angeles, CA

Tissue is cryopreserved by the method of Tourtellotte; this procedure minimizes or eliminates ice artifacts and preserves surface protein markers. The dissected plaques are lightly fixed in 5% paraformaldehyde and then suspended in 30% sucrose. Blocks are mounted in OCT, cryosectioned at 20 μM, and picked up on gelatinized slides. The activity of plaques is determined by the presence or absence of myelin debris (antimyelin basic protein stain or Luxol fast blue) or presence or absence of neutral lipids indicating myelin digestion as seen by oil red O (ORO) staining and the presence or absence of a Class II major histocompatibility complex antigen \((\text{evidence for an antigen-presenting cell})\) on macrophages or microglia as seen by immunocytochemically staining for HLA-DR (HB104 ATCC). The following is our classification of the activity of multiple sclerosis (MS) plaques. Type I, the most active, is defined as an area of hypercellularity, positive for HLA-DR with no ORO staining or staining for myelin debris. Type II, or active, is defined as an area of HLA-DR− positive cells that stain mildly with ORO at the plaque edge but positive for myelin debris; evidence for demyelinating activity <72 hours \((\text{Prineas; Raine})\). There is an inner area of plump cells that are positive for HLA-DR and ORO. Type III, or modestly active, is defined as a "shell" of plump HLA-DR− positive cells at the edge loaded with...
Susumu Kusunoki, Atsuro Chiba, Tadashi Tai, and Ichiro Kanazawa, Tokyo, Japan

GGR12 also recognized some myelin, including paranodal P114. Localization revealed similar differences in T lymphocytes, with higher levels. Differences in serotonin binding to mononuclear cells have been noted in migraine patients. A decreased sensitivity of the lymphocyte beta-adrenergic receptor in migraine patients was suggested by one study. After lymphocyte incubation with IL-2, the natural cytotoxic response is augmented with IL-2 receptor defect was independent of whether the clusters were present. There is a loss of high-affinity binding sites for serotonin on lymphocytes in both episodic tension and chronic tension headaches.

POSTER PRESENTATION:
NEUROOPHTHALMOLOGY

P116. Cortical Control of Reflexive and Memory-Guided Saccades: Study of Activation in Cerebral Blood Flow with Positron Emission Tomography*
Robert C. Knowlton, Roger P. Woods, Mark J. Morrow, and John C. Mazzotta, Los Angeles, CA

We used positron emission tomography (PET) to measure local cerebral blood flow in 6 volunteer subjects while they performed tasks of memory-guided saccades and a visual fixation control. Tasks were performed continuously for 70 seconds during emission scans, after bolus injection of H115O. Eye movements were verified with electrooculography. Areas of significant increase in regional blood flow between tasks were matched to three-dimensional reconstructions of brain magnetic resonance images of each subject. Compared to the visual fixation control, saccade tasks evoked bilateral activation in the posterior superior parietal lobule with extension into the inferior parietal lobe. Activation was also seen bilaterally in an area of frontal cortex immediately rostral to the precentral gyrus extending from the superior frontal gyrus to the inferior frontal sulcus. The increased blood flow in the posterior parietal cortex most likely corresponded to enhancement of visual attention required during saccades, while that in the frontal lobe, which included the frontal eye fields, indicated activation for saccade motor output.

P117. Magnetic Resonance Imaging in Third Nerve Palsy
Pamela Blake, Alexander S. Mark, Martin Kelsoy, and Jorg Kattah, Washington, DC

Fifty patients with third cranial nerve (CN) palsy underwent precontrast and postcontrast MRI to assess the utility of this study in this clinical context. MRI demonstrated an appropriate lesion in 32 cases. Six patients had brainstem lesions (2 infarcts, 1 mass lesion, 1 cryptic vascular malformation, 1 hemorrhagic shearing injury, 1 with Compound Q toxicity). Lesions of the cisternal segment of the nerve were present in 12 patients (4 aneurysms, 4 lymphomas, 1 ophthalmoplegic migraine, 1 viral meningitis, 1 coccidioidomycosis, 1 nerve avulsion), with enhancement of this segment in 7 patients. Fourteen patients had cavernous sinus lesions (2 lymphomas, 2 nasopharyngeal carcinoma, 4 Tolosa-Hunt syndrome, 2 cavernous carotid aneurysms, 3 pituitary apoplexy, 1 aspergillosis). Eighteen patients, all with history of diabetes or vascular disease, had normal MRI results, suggesting microvascular infarction of CN III. In patients with CN III palsy, MRI can detect the presence of brainstem or cavernous sinus lesions often can suggest their cause. MRI with contrast enhancement can demonstrate involvement of the cisternal segment of CN III in patients with inflammatory or infiltrative processes that previously could not be radiographically demonstrated. Our study suggests microvascular infarction does not cause nerve enhancement on contrast-enhanced MRI.
We describe 2 patients with acute hyperglycemic, hyperosmolar, nonketotic stupor who had ocular fluctar or opso-邨us clinically. These are the fourth and fifth adult patients reported with the acute onset of stupor and opso-邨us clinically. These are the fourth and fifth patients reported with the acute onset of stupor and opso-邨us; all patients had nonketotic hyperglycemia and hyperosmolality (rapid eye movement sleep also causes stupor and saccadic eye movements). Three of the 5 patients had myoclonic jerks in addition to opso-邨us. In the 5, opso-邨us began when glucose and osmolality acutely increased, and completely resolved when glucose and osmolality became normal, showing that opso-邨us is a specific and reversible effect of the metabolic disorder and implying that either acute hyperglycemia or hyperosmolality directly causes opso-邨us. Since acute hyperosmolality caused by NaCl or sucrose can cause a similar syndrome in experimental animals (Trans Am Neurol Assoc 1962:87:33–36) and infants, hyperosmolality is probably more important. Opso-邨us is thought to be due to abnormal activity of saccadic "burst" cells in the pons. Acute hyperosmolality may cause spontaneous saccades by disinhibiting burst cells from normal "pause" cell inhibition or by directly activating burst cells. The combination of acute deterioration in mental status and either ocular fluctar or opso-邨us should suggest acute hyperosmolality, in particular, nonketotic hyperglycemia.

POSTER PRESENTATION: NEUROREHABILITATION

P119. Neural Cell Adhesion Molecules: Role in Central Nervous System Adult Lesion-Induced Axonal Sprouting and Synaptogenesis

S. T. DeKosky, P. D. Miller, S. Styren, and C. F. Lugenaur, Pittsburgh, PA

Neural cell adhesion molecule (N-CAM) and the related cell adhesion molecule L1 play significant roles in axon outgrowth and mediation of cell-cell contact in development, and after peripheral nervous system injury. To understand the role of these molecules after injury in the adult CNS, we studied alterations in N-CAM and L1 in the rat brain's response to entorhinal cortex (ERC) lesion. Post lesion, reactive synaptogenesis and axonal sprouting follow a well-defined temporal course in restoring the synaptic density of the deafferented outer two-thirds of the hippocampal dentate gyrus molecular layer (ML) to near prelesion levels. We found striking regional and lamina-specific staining of N-CAM and L1 in the normal hippocampus and marked alterations in these molecules after injury. Embryonic N-CAM, present in high amounts during development but expressed at very low levels in the adult hippocampus, was massively re-expressed in the denervated zone; the embryonic form was still heavily expressed 60 days later, when synapse number returned to >80% of prelesion levels. L1 staining, normally evenly distributed through the ML of the dentate, was completely lost in the outer ML, which is denervated by the ERC lesion. This staining had not returned by 60 days after lesion. Neural cell adhesion molecules play a role in specificity of neural connectivity both in development and after injury. In reactive synaptogenesis and axonal sprouting after injury, both ontogenetic (the reexpression of embryonic epitopes) as well as uniquely adult sequences of repair are utilized.

P120. Reorganization of Human Motor Pathways Following Hemispherectomy

A. Paracuellos, H. T. Chung, L. G. Cohen, J. P. Brazil-Neto, E. M. Wissmann, J. Vali-Soldi, P. Vuhr, and M. Hallett, Bethesda, MD, and Los Angeles, CA

We studied 7 subjects, aged 18 months to 32 years, who underwent hemispherectomy 6 months to 25 years earlier for intractable epilepsy. All had a spastic hemiparesis contralateral to the resected hemisphere, which was present presurgically. We used focal transcranial magnetic stimulation to map the areas of the preserved hemisphere targeting the abductor pollicis brevis (APB), the biceps, and the deltoid ipsilaterally and contralaterally. In 2 subjects who had hemispherectomy after age 10, the same area targeted ipsilateral and contralateral muscles. In the remaining 5 subjects, who were more functional, 2 areas targeted ipsilateral muscles. One area coincided with the contralateral representation, but stimulation induced motor-evoked potentials (MEPs) of lower amplitude and longer latency in the ipsilateral muscles. The other area, 2 to 4 cm anterolaterally, targeted exclusively ipsilateral muscles and stimulation induced MEPs of normal amplitude and latency. This separate ipsilateral representation was more distinct in subjects studied a long time after the hemispherectomy and in those who were younger at the time of the operation. These results show evidence of motor reorganization after hemispherectomy. Better motor function is associated with topographically differentiated ipsilateral and contralateral representations, which may depend on age at the time of hemispherectomy and the time since then.

P121. A Crossover Study of Physical Rehabilitation in Parkinson's Disease

Cynthia L. Comella, Glenn T. Steele, Nancy Brown-Toni, and Christopher G. Goetz, Chicago, IL

In a single-blind, crossover study, we evaluated the effect of an intensive outpatient physical rehabilitation program (REHAB) on the severity of Parkinson's disease (PD). The REHAB program consisted of 3 2-hour sessions per week for 4 weeks. Sixteen patients completed 2 phases, a REHAB phase and a CONTROL phase, separated by 6 months. The order of participation in each phase was randomized. All patients were evaluated using the Unified PD Rating Scale with subscales for mentation (MENT), Activities of Daily Living (ADL), and motor function (MOT) by an investigator blinded to the hemispherectomy and in those who were younger at the time of the operation. These results show evidence of motor reorganization after hemispherectomy. Better motor function is associated with topographically differentiated ipsilateral and contralateral representations, which may depend on age at the time of hemispherectomy and the time since then.

P122. Occupational Spinal Cord Injury

Neil L. Rosenberg, Kenneth A. Garabari, and Gale G. Whiteneck, Englewood, CO

Most spinal cord injuries (SCIs) are the result of motor vehicle accidents (MVAs) and no published reports have specifically addressed spinal cord injuries that occur in the workplace. The objectives of this cohort survey study were to...
were analyzed in detail. There were a total of 566 course of employment. The most common causes of occupa-
tional SCI were the result of falls at 37 (50.9%) compared to object in 14 (18.9%), gunshot wound in 3 (1.8%), and in 1 (1.4%) of each of the following: skiing, stabbing, being struck in the head, and unknown. Construction occupations were overrepresented in occupational SCI with 41.9% of cases compared to only 6.3% for the nonoccu-
Table 1:

| Causes          | Percentage |
|-----------------|------------|
| Falls           | 37 (50.9%) |
| Object          | 14 (18.9%) |
| Gunshot wound   | 3 (1.8%)   |
| Skiing          | 1 (1.4%)   |
| Stabbing        | 1 (1.4%)   |
| Being struck    | 1 (1.4%)   |
| Head            | 1 (1.4%)   |
| Unknown         | 1 (1.4%)   |

P123. Serial Quantitative Determinations of Leg Strength in Multiple Sclerosis Patients: Reproducibility and Applications in Clinical Trials

Christopher Bever, Paul Anderson, Hilllel Panitch, and Kenneth Johnson, Baltimore, MD

Sensitive and quantitative measurements of leg weakness, one of the most common deficits in multiple sclerosis (MS) patients, can be made using specialized extremity testing equipment. To determine whether such determinations could be used in clinical trials, 6 MS patients with leg weakness that had been stable for at least 2 months were evaluated every 60 days over a 4-month period. Each testing session was carried out at the same time of day and medication dos-

POSTER PRESENTATION:
NEUROVIROLOGY

P124. Different Effects of Persistent Enterovirus Infection in Polymyositis and Postviral Fatigue Syndrome

Wilhelmina M. H. Behan, Kaithleen S. Simpson, H. M. Cavanagh, J. W. Gow, J. S. Gillespie, and Peter O. Behan, Glasgow, Scotland

Polymyositis (PM) is an inflammatory myopathy of unknown cause, but the accumulating data strongly suggest an autoim-
mune pathogenesis. The histological picture is of muscle fiber necrosis and inflammation, whereas in postviral fatigue syn-
drome (PFS), a disorder characterized by severe fatigue with myalgia and psychiatric symptoms, the histological picture of muscle is essentially normal. Enteroviruses have been impli-
cated on epidemiological and serological studies in both. We have used the polymerase chain reaction (PCR) and an enteroviral-specific probe and found persistent enteroviral genomic material in both PM and PFS muscle biopsy speci-
men. Furthermore, we used a radiolabeled full-length cDNA probe derived from coxsackie B1 in an in situ tech-
nique to look for viral DNA in PCR-positive cases. Cox-
sackie genome was clearly identifiable in the muscle biopsy specimens of patients with PM but negative in PCR enterovir-
ous cases of PFS. The virus excites an inflammatory reaction only in PM. A murine animal model for PFS devel-
oped in our laboratory showed positive muscle PCR using enterovirus probes and a conspicuous increase in interleukin 6 within the brain. These results provide major clues in the search for the etiology of these two puzzling disorders.

P125. Spastic Paraparesis Associated with Human T-Lymphotropic Virus Type I Infection: A Clinical, Serological, and Polymerase Chain Reaction Study in Mashadi Jews*

A. Achiron, O. Hamiel, R. Djaldetti, L. Doll, A. Chen, I. Zin, G. Frankel, B. Shout, and E. Melamed, Petah-Tiqva and Rehovot, Israel

Human T-lymphotropic virus type I (HTLV-I) is a cause of adult T-cell leukemia and tropical spastic paraparesis. In a specific population of Iranian Jews originating from the city of Mashad, there is a high incidence of HTLV-I infection (11.5%) and associated T-cell leukemia. We evaluated the incidence of possible correlation between HTLV-I infection and spastic paraparesis in Israeli Mashadi-born Jews. We have examined 41 Mashadi-born immigrants in a Mashad Community Center (16 men, 25 women, mean age 65 ± 13.7 yr) and 40 non-Mashadi Iranian-born Jews. Blood samples were tested for HTLV-I antibodies by particle agglutination test. The polymerase chain reaction (PCR) was used to amplify HTLV-I sequences of DNA from peripheral blood mononu-
clear cells. Twelve Mashadi-born immigrants (29%) were seropositive for HTLV-I. In 10 of those serologically positive for HTLV-I (85%), neurological examination revealed spas-
tic paraparesis of varying severity. None of the non-Mashadi Iranian Jews were seropositive for HTLV-I or had clinical signs of spastic paraparesis. These results support other stud-
ies of HTLV-I-associated myelopathy. The high incidence of HTLV-I-associated spastic paraparesis in the Mashadi community might be related to their unique history of a high rate of intermarriage among members of this ethnically segregated group. Further epidemiological studies are under-
way to evaluate the incidence of HTLV-I in Mashadi families as well as in Mashadi-originating Jews born in Israel, to iden-
ify whether infection might be genetically transmitted.

P126. Neurological Abnormality in Human T-Cell Lymphotropic Virus Type I–Associated Acute T-Cell Leukemia/Lymphoma

William J. Harrington, Jr, William A. Shermata, Susan Snodgrass, and Mark Raven, Miami, FL

Human T-cell lymphotropic virus type I (HTLV-I)–associated acute T-cell leukemia/lymphoma (ATL) is thought to produce important CNS disease infrequently. We wish to
correct this impression by presenting neurological findings in 15 patients seen between 1989 and the present. All had positive Western blots to HTLV with polymerase chain reaction confirmation of HTLV-I infection. Only 2 had a concomitant human immunodeficiency virus infection. All were black, aged 31 to 86 years, 7 were men and 8 women. All but 3 were African Americans came from the Caribbean nations of Haiti (5), Dominican Republic (1), Jamaica (6), and Trinidad (1). Sexual transmission was the risk factor for HTLV-I for all except for 1 intravenous drug user. All patients were systemically ill. Three had preceding neurological abnormality (1, 8 months, and 14 yr) and 8 had major neurological disease concomitantly. Two of these had tumor masses demonstrated in brain and 1 in the spinal canal. One had a minor facial sensory abnormality; only 3 had no deficits. We conclude that CNS disease is commonly associated with ATL, and that in the US ATL occurs principally in Caribbean natives.

P127. Susceptibility and Cytopathicity of Human Immunodeficiency Virus Infection in Human Microglia and Astrocytes
A. Nath, V. Hartloper, and M. Farer, Winnipeg, Manitoba, Canada

Microglia and astrocyte cultures were established from human fetal brain. Microglia were infected with human immunodeficiency virus (HIV) strains, H11, H51, HIV 32, resulting in a rising titer of p24 antigen in the supernatants. Multinucleated giant-cell formation, vacuolar changes, and rising levels of lactate dehydrogenase in the supernatants were seen, indicating a cytopathic infection of microglia. Astrocytes were infected with free virus or cocultivated with an HIV-infected lymphocyte cell line (HuT-78). After a productive phase (rising titers of p24 antigen and detection of HIV antigens by immunocytochemistry), the cells went into a latent phase where HIV could be detected only by DNA polymerase chain reaction. A 10-fold increase in astrocytes staining for HIV antigens was seen after cocultivation with HuT-78 cells. Lymphocytes adhered to astrocytes by 3 hours of cocultivation. No adhesion was seen to microglia. Fusion of plasma membranes was seen on electron microscopy. Infected astrocytes did not show cytopathic or morphological changes. Cell-to-cell contact may be important in viral transmission to astrocytes.

P128. The Role of Theiler's Virus 5' Untranslated Region
Hsiao-Huei Chen, Steven B. Stein, Wing Kong, and Raymond P. Ross, Chicago, IL

One of our goals is to delineate molecular determinants for disease phenotypes produced by Theiler's virus (TV), a mouse picornavirus. The identification of these genes and gene products may clarify viral pathogenesis and also lead to the identification of genes that are important in normal CNS function and nonviral CNS disease. Members of the GDVII subgroup of TV cause an acute, fatal neuronal infection, whereas members of the TO subgroup are less neurovirulent and produce a demyelinating persistent infection. Our studies of infectious TV cDNA clones have demonstrated that the GDVII 1B(VP2)-2C segment is critical for neurovirulence. Several other areas of the genome, including the 5' untranslated region (5'UTR), also affect TMEV-induced disease. The 5'UTR of poliovirus, another picornavirus, has a critical role in paralysis; this effect on neurovirulence is believed to result from an altered translational efficiency related to binding of neural cell proteins. TV 5'UTR has an unusual predicted secondary structure, even for picornviruses. Our studies demonstrate that the TV 5'UTR affects translational efficiency and has a distinctive protein-binding pattern. Investigations of the TV 5'UTR may clarify features of translational regulation of CNS genes in general.

P129. Coronavirus Infect Primate Brain from Peripheral Routes
Gary F. Cabrera, Ronald S. Murray, Galen Cat, Kristen Hoel, and Kenneth Suikle, Englewood, CO, and Covington, LA

Recently, we described finding coronavirus (CV) RNA and antigen in active demyelinating plaques of multiple sclerosis (MS) brain tissue (Murray et al, Ann Neurol, in press). Molecular analysis showed the CV RNA to be more closely related to murine CVs than to human CVs. We then demonstrated that, following intracerebral inoculation, the murine CV JHM and the putative MS isolate CV-SD could infect and cause demyelination in primate brain (Murray et al, Virology, in press). We now have data showing that murine CV can infect primate brain following intranasal or intravenous routes of inoculation. Standard virology, histopathology, and the molecular analysis of viral cytopathism will be presented. We conclude that CVs related to murine CVs can infect primate CNS from peripheral routes and warrant consideration as potential human pathogens.

P130. Tropical Spastic Paraparesis/HTLV-I–Associated Myelopathy in Americans: Risk Associated with Transfusion
W. A. Shermata, W. J. Harrington, Jr, S. Snodgrass, J. R. Berger, and M. Raven, Miami, FL

Tropical spastic paraparesis/HTLV-I–associated myelopathy (TSP/HAM) is diagnosed in Americans living in Florida with increasing frequency. Approximately one-third of our TSP/HAM patients are born and reside in the US. We report 20 (9 male and 11 female) human T-lymphotropic virus type I and II–seropositive patients without human immunodeficiency virus or other infections. Fourteen of 14 were polymerase chain reaction–positive using probes for at least 2 probes (gag, pol, or env). Eleven were white and 9 were black. A history of transfusion was obtained in 8, and sexual risk of transmission was present in 8 but not in 4 others. Fulminant disease occurred in 4 transfused men 3 months to 4 years later but such disease was only seen in 1 woman (in 1 month). In contrast, 2 of 3 women with multiple sexual partners had rapid progressive disease. The male-to-female ratio was 4:4 for transfusion association and 5:3 for those at sexual risk but 0:4 for unknown risk. Transfusion is an important risk for TSP/HAM and the diagnosis must be considered in all gay men, regardless of the "diagnosis." Transfusion association should decrease with regular testing of blood donors, but this will not affect the risk of sexual transmission.

P131. Human T-Cell Lymphotropic Virus Type I Infection in Severe Combined Immunodeficient Mice
E. F. Salazar-Gruzo, G. Martino, S. Kim, R. Furlan, H. Kim, M. H. Kotelik, L. M. E. Grimaldi, and R. P. Ross, Chicago, IL, and Milan, Italy

Human T-cell lymphotropic virus type I (HTLV-I) is the etiologic agent of adult T-cell leukemia (ATL) and tropical
produce HTLV-I disease. Two weeks after transplantation of Theiler's virus produces an encephalomyelitis in susceptible PBM from 2 TSPlHAM patients, we detected anti-HTLV-I and no suitable animal models of HTLV-I infection that can ganglia, and nucleus raphe dorsalis often were involved. In plantation, we detected anti-HTLV-I IgG to p19, p24, gp46, spastic paraparesisHTLV-I-associated myelopathy (TSP/HAM). It is unclear why HTLV-I infection causes ATL in some individuals and TSP/HAM in others. Differences in the genome of viral isolates or immunological and host factors have been hypothesized to play a role in disease expression. At present there are no animal models of TSP/HAM and no suitable animal models of HTLV-I infection that can address these issues. We transplanted severe combined immunodeficient (SCID) mice with peripheral blood mononuclear cells (PBM) from TSP/HAM patients in an attempt to produce HTLV-I disease. Two weeks after transplantation of PBM from 2 TSP/HAM patients, we detected anti-HTLV-I IgG in serum samples of 7 of 8 SCID mice by enzyme immunoassay using sonicated whole virus. Five weeks after transplantation, we detected anti-HTLV-I IgG to p19, p24, gp46, or gp61/68 in serum samples of 5 of 7 SCID mice by immuno blot of disrupted virus. These findings suggest that SCID mice may be valuable in the study of molecular and pathological determinants of HTLV-I-induced disease.

P132. Theiler’s Virus Infection in Nude Mice: The Significance of Viral Dissemination Through the Olfactory Pathway and the Limbic System

Yoshitsuki Wada and Robert S. Fujinami, Salt Lake City, UT

Theiler’s virus produces an encephalomyelitis in susceptible mice. During the course of the disease, specific regions in the CNS become infected. Compared to the immunocompetent mouse, the nude mouse provides a useful model where viral dissemination can be studied in the absence of functional T lymphocytes and antibodies. We investigated the distribution and spread of the DA strain of Theiler’s virus in the CNS of nude mice. By immunohistochemistry, the hippocampus, amygdaloid nuclei, entorhinal cortex, cingulate cortex, thalamus (anteroventral nuclei), midbrain, and spinal cord all contained viral antigens by 2 weeks after infection. In addition, the olfactory nuclei, mamillary body, hypothalamus, basal ganglia, and nucleus raphe dorsalis often were involved. In the brain, the limbic system was the site commonly infected by Theiler’s virus. The time course of virus dissemination varied depending on the site of initial virus infection, though the final distribution of virus was the same. Olfactory bulb injection, which is a direct inoculation into the olfactory pathway, resulted in more rapid spread than did cortex injection. We demonstrated the constant presence of viral antigen in the limbic system and a different kinetics of viral dissemination between the two different routes of intracerebral inoculations. These results suggest that limbic structures and their connections are important to the dissemination of Theiler’s virus.

P133. Human T-Lymphotropic Virus Type I–Associated Myelopathy in a Northwest Native Indian

D. Foti, D. Werker, G. Dekaban, G. P. A. Rice, and J. Oger, Vancouver, BC, and London, Ontario, Canada

A 59-year-old Indian of the Oweekeno tribe was admitted on Monday, October 19/Tuesday, October 20 of blood lymphocytes. HTLV-I–associated myelopathy, or tropical spastic paraparesis, is endemic in southern Japan, the Caribbean basin, and several tropical islands but has not been reported in natives of northwest Canada. This patient’s only risk factors for HTLV-I infection were 3 blood transfusions 30 years previously. Ongoing familial and epidemiological studies as well as virus sequencing should indicate if this case represents an indigenous or an imported infection.

P134. Cervical Myelitis and Paroxysmal Dystonia Caused by Herpes Simplex Virus Type 1

Larry Blankenship and Herbert B. Newton, Columbus, OH

Myeloradiculitis occasionally occurs secondary to herpes simplex virus type 2 (HSV2) infection, but rarely has been reported after herpes simplex virus type 1 (HSV1) infection without encephalitis. We describe a 30-year-old man who developed cervical myelopathy and radiculitis, never developed symptoms of encephalitis, and had positive HSV1 spinal fluid cultures. He initially developed extremity weakness, sensory symptoms, and neck pain. Evaluation was negative except for MRI results, which showed a high-signal lesion centrally within the cervical cord. The weakness, sensory loss, and radicular pain progressed over several months. Subsequent MRI showed extension of the high-signal abnormality and mild enlargement of the cervical cord. Symptoms stabilized briefly with dexamethasone but soon worsened, and were accompanied by paroxysmal kinesigenic dystonic episodes of his arms and right leg. Repeat evaluation was unremarkable except for the spinal fluid, which grew out HSV1. The patient was treated with dilantin and a 1-month course of intravenous acyclovir, with slow improvement of neurological status and resolution of the dystonic episodes. This case illustrates that HSV1 can cause a myelopathy with a subacute and protracted course, requiring serial spinal fluid cultures for diagnosis. Extended treatment with acyclovir (>4 weeks) is necessary.

POSTER PRESENTATION:
CEREBROVASCULAR DISEASE

P135. Memantine, a Clinically Tolerated Amantadine Derivative, Blocks N-Methyl-d-aspartate–Activated Channels and Decreases Infarct Size in Rodents

Stuart A. Lipton, Hai-Steng Vincent Chen, James W. Pellegrini, Sanjay K. Aggarwal, Sizbeng Z. Lei, Steven Warabi, and Frances E. Jensen, Boston, MA

Excessive activation of N-methyl-d-aspartate (NMDA) receptors is believed to mediate neurotoxicity associated with hypoxic-ischemic brain injury, trauma, epilepsy, and several neurodegenerative diseases. In this study, memantine, an ad amantane derivative similar to the antiviral drug amantadine, is shown to prevent NMDA receptor–mediated neurotoxicity. Whole-cell and single-channel recordings demonstrate that the mechanism of action of memantine is open-channel block, similar to MK-801; however, unlike MK-801, memantine is well tolerated clinically. Compared to MK-801, mem antine’s safety may be related to its faster kinetics of action.
with rapid blocking and unblocking rates at micromolar concentrations. At these levels, memantine is an uncompetitive antagonist and should allow near-normal physiological NMDA activity throughout the brain even in the face of pathologically high focal concentrations of glutamate. Memantine is increasingly effective against escalating levels of glutamate, such as those observed during stroke. Micromolar concentrations of memantine, known to be tolerated by patients receiving the drug for Parkinson's disease, prevent NMDA receptor-mediated neurotoxicity in rodent cortical or retinal cultures and in a neonatal rat stroke model (bilateral carotid occlusion plus hypoxia); at these concentrations memantine has no apparent neurobehavioral side effects.

P136. Noninvasive Tests in Vertebrobasilar Occlusive Disease
Axel Rosengart, L. Dana DeWitt, Louis R. Caplan, Michael S. Pessin, and Samuel Wolpert, Boston, MA

To determine the value of transcranial Doppler (TCD) and MR angiography (MRA) in evaluation of patients with intracranial verteobasilar occlusive disease (VBOD), we studied blindly 60 patients with TCD and MRA, of whom one-third also had conventional angiography. In 170/180 (94%) vessels (intracranial vertebral [VA] and basilar artery [BA]) TCD and MRA findings were identical in terms of normal, stenotic, or occluded artery. In 5 vessels, TCD showed high-grade stenosis, whereas MRA showed occlusion. In 5 arteries, TCD and MRA did not agree. In patients who also had additional conventional angiography, TCD did not agree in 2/60 vessels and MRA did not agree in 4/60. TCD and MRA showed 95% agreement with angiographic pathology for the right VA, and 99% for the left VA and BA. These values were not statistically different. There was 95% agreement between TCD and MRA with conventional angiography in each group. No case was misdiagnosed when TCD and MRA were both used. Agreement between TCD and MRA is excellent and when both are used, the likelihood of missing severe intracranial VBOD is very low.

P137. Crossed Cerebellar Diaschisis in Acute Stroke: HMPAO SPECT, CT, and Clinical Correlations
S. E. Black, L. Ebright, C. Caldwell, S. Stapleton, L. Lee, C. Leonard, and M. J. Yaffe, Toronto, Ontario, Canada

Cerebellar hypoperfusion contralateral to hemispheric stroke is frequently seen on blood-flow imaging. It is attributed to functional disconnection of corticopontine-cerebellar fibers, but its clinical implications remain unclear. In an ongoing longitudinal study of consecutive stroke admissions, 100 patients have undergone standardized clinical and functional assessments and hexamethylpropyleneamine oxide–single photon emission computed tomography (HMPAO SPECT) scanning within 1 week of onset, and this is being repeated at 1 year. Visual analysis of the acute SPECT scans of 44 patients with CT-confirmed, single lesions revealed crossed cerebellar diaschisis (CCD) in 61%, equally with right and left lesions. Intra- and interrater reliability was 90% when scans were reoriented parallel to the orbitomeatal line and corrected for nonlinear HMPAO uptake. Mean clinical scores and subscors for language, sensory, and motor function were significantly higher in the CCD group. CCD was present in 90% of patients with significant hemiparesis, compared to 30% of patients with no motor weakness. When lesion location in 12 cortical and subcortical regions was examined on CT, only the inferior frontal region emerged as significantly associated with CCD. Crossed cerebellar diaschisis is common in acute hemispheric stroke, especially with inferior frontal damage, and accompanies more severe neurological impairments, particularly hemiparesis. Semiquantitative analysis currently underway will allow detection of changes over 1 year in correlation with clinical recovery and will further elucidate the long-term clinical significance of CCD.

P138. Differences in Risk Factors for Symptomatic Carotid Artery Disease Among Elderly and Middle-aged Patients
Jonathan Y. Streifler, Vladimir C. Hachinski, Michael Eliasziw, and Henry J. M. Barnett, for the NASCET Group, London, Ontario, Canada

We have previously shown that stroke risk factors in the elderly differ from those in middle-aged people. Similar information for patients with extracranial carotid artery disease (ECAD) is lacking. The prevalence of risk factors in 732 elderly patients (65–80 yr, mean 70.4 yr) was compared to 628 middle-aged patients (< 65 yr, mean 57.4 yr). All were recruited by the NASCET Study, had symptomatic ECAD, and no clear cardiac source of embolism. More prevalent in the elderly were symptomatic coronary artery disease (SCAD) (37% vs 52%), history of remote episodic atrial fibrillation (AF) (2.5% vs 6%), and higher mean systolic blood pressure (148 vs 143 mm Hg) (p = 0.023, p = 0.008, p = 0.0001, respectively). In contrast, history of recent smoking (74% vs 42%) and hyperlipidemia (35% vs 27%) was more frequent in the middle-aged group (p < 0.0001, p = 0.001). History of hypertension, previous strokes, diabetes mellitus, and antithrombotic treatment was similar, as were sex ratio, qualifying event type (transient ischemic attack or nondisabling stroke), and angiographic features; stenosis severity in either side and presence of ulceration were all similar. In elderly patients, ECAD is associated with symptomatic cardiac disease (SCAD or AF), whereas in middle-aged patients it is associated with presence of generalized atherosclerosis (smoking and hyperlipidemia).

P139. Application of the Framingham Stroke Risk Profile to Stroke Recurrence: The Oregon Stroke Center Database
Bruce M. Coull, Pat L. de Gamzo, Nancy B. Beam, Dennis P. Brierley, and Wayne M. Clark, Portland, OR

Based on the Framingham population, the Framingham Stroke Risk Profile (FSRP) provided an accurate probability estimate of both initial and recurrent stroke, but has not been tested for prediction of stroke recurrence in other populations. The FSRP incorporates gender, age, systolic blood pressure, diabetes, atrial fibrillation, left ventricular hypertrophy by electrocardiogram, prior heart disease, and cigarette and antihypertensive use. We utilized the FSRP to determine (1) if the FSRP was predictive of recurrent vascular events in 109 stroke subjects (91 men, 18 women) and (2) whether the addition of a scaled fibrinogen level (SFL) enhanced the utility of the FSRP. During an average of 18 months follow-up, there were 18 recurrent strokes, 1 myocardial infarction, and 12 vascular deaths for a recurrent stroke rate of 11% per year. The FSRP score was higher in subjects with recurrent events (16.9 ± 6.8 vs 13.6 ± 6.0, p = 0.015). Based on FSRP quartiles, 44% (10/23) of subjects in the
P140. Stroke in Young Adults
Larry B. Goldstein and April Perry, Durham, NC

We identified all stroke patients admitted to Duke Hospital over 3 years (n = 637). Younger patients (age 18–40 yr, n = 36, 5.7%) less frequently had diabetes (6 vs 27%; χ² = 7.2, p = 0.007) and hypertension (19 vs 66%; χ² = 30.2, p = 0.0001) and more frequently were non-Caucasians (64 vs 39%; χ² = 7.0, p = 0.008) than older patients (age ≥40 yr). Younger and older patients differed in gender distribution (p = 0.1), smoking (p = 0.2), and obesity (p = 1.0).

Younger and older patients differed in stroke subtype (ρ = 0.01). Younger patients more frequently had “other” identified causes of stroke (14 vs 1%; χ² = 26.1, p = 0.001) and less frequently had uncertain causes of stroke (6 vs 22%; χ² = 4.7, p = 0.03), possibly due to more extensive evaluations.

The frequencies of intracerebral hemorrhage (14 vs 14%), subarachnoid hemorrhage (11 vs 5%), cardiogenic embolism (36 vs 22%), large-vessel thrombosis (11 vs 10%), lacunes (3 vs 11%), and transient ischemic attacks (6 vs 14%) were similar (p > 0.05 for each comparison). Strokes in younger individuals were associated with a variety of unusual causes including single cases of air embolism, cocaine use, Takayasu’s arthritis, homocystinuria, fibromuscular dysplasia, and oral contraceptive use in conjunction with cigarette smoking. Young adults with stroke represent a heterogeneous group of patients. Stroke etiology usually can be established with an extensive evaluation.

P141. CT Correlates of Dementia in Lacunar Infarction
M. Figueredo, T. K. Tatemiobi, D. W. Desmond, and D. T. Cross, New York, NY

To identify the anatomic factors correlating with dementia in patients with lacunar infarctions, we examined digitized CT data on 58 elderly patients (mean age = 71.6 yr; education = 9 yr) who presented with acute lacunar infarction. Demen- tia was diagnosed in 13 patients (22.4%) based on neuropsychological tests given 3 months after stroke onset. The following CT variables were assessed: infarct location and number, total infarct volume, brain parenchymal and CSF areas at 3 levels, and width of the frontal horn, third ventricle (TVW), and lateral ventricle plus their ratio to the intracranial width. Atrophy and leukoaraiosis were rated semiquantitatively using a standard scoring method. In the group overall, mean infarct volume was 0.64 cc and mean infarct number = 7 yr) who presented with acute lacunar infarction. Demen- tia status limited to the hand and mouth. This syndrome has

P142. Presynaptic Calcium Accumulation Is Blocked by an In Vitro Model of Brain Ischemia by R56865
Stanley L. Cohan and Mei Chen, Washington, DC

Brain ischemia results in potassium (K⁺)-induced voltage-regulated presynaptic calcium (Ca⁺²) accumulation, which may contribute directly to neuronal injury presynaptically, and also promote excessive release of excitatory neurotransmitters leading to cell damage postsynaptically. K⁺-induced depolarization of brain synaptosomes may be used as an in vitro model to study the therapeutic potential of pharma- colloidal agents to alter ischemia-induced presynaptic Ca⁺² accumulation. We preincubated gerbil cerebral cortical synaptosomes in R56865 (Janssen Pharmaceutical) at concentrations of 10⁻³ to 10⁻⁶ M, subsequently depolarized the synaptosomes with K⁺, at concentrations of 5 to 60 mM, and measured intrasynaptosomal Ca⁺² ([Ca⁺²⁺]) with the fluorescent indicator FURA 2. R56865 had no effect on [Ca⁺²⁺] when utilizing Ca⁺²⁻free incubation media, it was demonstrated that R56865 prevents depolarization-induced [Ca⁺²⁺] increase by blocking voltage-regulated influx. Because R56865 appears to block voltage-regulated presynaptic Ca⁺² accumulation, it should be further evaluated as a potential therapeutic agent after cerebral ischemia.

P143. Cerebrovascular and Immunological Studies in Sneddon’s Syndrome
O. W. Farronay, L. A. Kalashnikova, N. V. Verschaggin, S. M. Leznikova, I. G. Liudkouskaya, V. V. Borisenko, V. B. Usman, and V. A. Morganov, Moscow, Russia

Sneddon’s syndrome (SS) is a focal and diffus e arthropathy affecting mainly the vascular wall of the skin and cerebral arteries. Etiology is not determined. We studied 39 patients with SS (27 females, 12 males), aged 15 to 56 years. Clinical, radiological, and immunological studies were done. All patients developed cerebrovascular disorders: ischemic stroke in 82%, transient ischemic attack (TIA) in 64%, and ischemic stroke and TIA in 46%. Cerebral scan showed small and medium (less than 3 cm) ischemic lesions in 97%. These lesions were superficial in the cerebral cortex (57%); deeper in the centrum semiovales, internal capsule, and basal ganglia (18%); and both superficial and deeper (25%). Ultrasonic and angiogram studies revealed obstruction of intracranial arteries in 30%, and of extracranial arteries in 3%. Partial or complete improvement of cerebrovascular symptoms was observed in 81%. Immunological studies showed increased content of B-cell lymphocytes (p < 0.05), increased levels of IgM (p < 0.0001), and circulating immune complexes (p < 0.001). Anticardiolipin antibodies were increased (58%) and lupus anticoagulant detected (51%). Cerebrovascular disorders in SS that lead to small ischemic cortical lesions have a good prognosis. Pathogenesis of this syndrome may be related to antiphospholipid antibodies.

P144. Inverse Cheiro-Oral Syndrome
Samuel Koser and Steven A. Sparr, Bronx, NY

The cheiro-oral syndrome is characterized by pure sensory deficit limited to the hand and mouth. This syndrome has...
been described in diverse lesions of the parietal operculum and brainstem, but occurs most commonly due to lesions of the contralateral thalamus, and suggests a humuncular representation of sensation in the ventral posterior lateral (VPL) and ventral posterior medial (VPM) nuclei. We describe a 54-year-old hypertensive woman who presented with sudden onset of numbness of the left side of her body. Examination revealed a left hemisensory deficit to all modalities that spared the hand and peri-oral regions. CAT scan and MRI demonstrated an acute infarction of the posterolateral right thalamus, with a rim of preservation adjacent to the internal capsule. Pure hemisensory loss with sparing of the hand and mouth ("inverse cheiro-oral syndrome") has not been reported previously, and complements previously published studies of the cheiro-oral syndrome in demonstrating somatosensory representation in the thalamus.

P145. Depression and Intellectual Impairment After Stroke: Causally Linked? Thomas K. Tatemichi, Beth Rosenstein, Robert H. Remien, Janet B. W. Williams, David W. Desmond, Mary Sano, Yaakov Stern, and Richard Mayeux, New York, NY

To examine the relationship between depression and dementia after stroke, we administered the 17-item Hamilton Depression Rating Scale (HDRS) and neuropsychological tests to 237 elderly patients 3 months after ischemic stroke. Using DSM-III-R criteria, we found dementia in 57 (24.1%). HDRS score was 5.0 ± 4.6 overall, and higher in demented compared to nondemented patients (6.2 ± 3.0 vs 4.6 ± 4.5, p = 0.025). The frequency of depression (total HDRS score >11) was also higher with dementia (17.5% vs 7.8%, p = 0.03). However, demented patients did not differ from nondemented patients on ratings of depressed mood. Instead, HDRS items for psychomotor retardation, reduced work activities, and impaired insight best distinguished the 2 groups. In multiple regression analysis, stroke severity (β = 0.23, p = 0.0003) was the most important correlate of HDRS score; dementia status was not correlated independently. Mean scores on Mini-Mental State Examination and neuropsychological tests assessing memory, orientation, verbal, spatial, attentional, and abstract reasoning skills did not differ by depression status. Although weakly related to intellectual impairment, HDRS score in our stroke sample was most importantly associated with stroke severity. Higher scores on HDRS in demented stroke patients may be explained by physical and cognitive symptoms that are expected with dementia. These findings do not support a causal link between depression and dementia, and argue against the importance of "depressive pseudodementia" as an explanation for intellectual decline after stroke.

P146. Evaluation of Regional Cerebral Water Content and Effective pH in Binswanger-type Encephalopathy Using Positron Emission Tomography

K. Ishii, M. Sendi, M. Ohya, K. Oda, H. Toyama, T. Sasaki, S. Ishii, and H. Yamanouchi, Tokyo, Japan

To investigate the pathophysiological mechanism of the white matter lesions in progressive subcortical vascular encephalopathy (PSVE) of Binswanger type, we measured regional cerebral water partition coefficient (pc) (reflecting water content) and effective pH (pHe) (weighted average of intra- and extracellular pH) with dynamic positron emission tomographic technique using O-15 CO2, O2, and C-11 CO2. Simultaneously, regional cerebral blood flow (rCBF) and regional cerebral metabolic rate of oxygen (rCMRO2) were evaluated. Eight subjects (3 normal, 3 PSVE, 2 multiple infarction) were examined. In the white matter lesions in PSVE, corresponding to high-intensity areas in T2-weighted images of MR, the pc increased and pHe was unchanged or decreased, whereas both rCBF and rCMRO2 declined. The ratio of white matter pc to gray matter pc was 0.92 in PSVE and 0.87 in normals. In the frontal gray matter, the pc decreased in PSVE, whereas rCBF and rCMRO2 also decreased. These results suggest that tissue water content increases in the white matter lesions in PSVE reflecting the edematous status of the damaged regions. Elevated pHe with high pc may reflect the increase of extracellular water of the tissue. Measurement of pc and pHe provides useful information about the pathogenesis of PSVE.

P147. A Hospital-Based Study of Stroke Risk Factors in Korea Chin-Sang Chung, Taejon, Korea

Stroke has been the second most common cause of death in Korea but its risk factors (RFs) have not been studied intensively, so the RFs or causes were investigated prospectively in 1,507 consecutive stroke patients who were admitted to the Chungnam National University Hospital, Taejon, Korea, between 1989 and 1991. They included 775 cases of cerebral ischemia (CI) (51.4%), 467 cases of intracerebral hemorrhage (ICH) (31.0%), and 265 cases of subarachnoid hemorrhage (SAH) (17.6%). Control data were obtained from 209 healthy spouses of the patients. Multivariate analyses showed that hypertension (HT) was the strongest RF for all stroke types and was followed by old age, diabetes mellitus (DM), smoking, high-density lipoprotein cholesterol, and fibrinogen. The RFs for atherothrombotic CI included old age, HT, DM, smoking, fibrinogen, and cholesterol. For lacunar infarcts, HT, DM, old age, fibrinogen, alcohol abuse, smoking, and female sex were the significant RFs. HT was the cause of ICH in 347 (74.3%) and alcohol abuse (44, 9.4%) and vascular anomalies (32, 6.9%) followed. Most alcohol-associated ICHs occurred characteristically in the posterior fossa. Frequencies of hospital admission of ICH patients correlated positively with diurnal variation of temperature (r = 0.5229, p < 0.001). Aneurysmal rupture was the cause of SAH in 222 patients (83.8%). Three major sizes of 247 aneurysms identified on cerebral angiograms were the anterior communicating artery (83, 33.6%), the middle cerebral artery (70, 28.3%), and the posterior communicating artery (56, 22.6%). Thirty-nine patients (14.7%) had no identifiable cause of SAH.

P148. Linear Subinsular MR Hyperintensities Patrick Pullicino, Lucy Miller, Frederick Munschauer, and Peter Ostrow, Buffalo, NY

Curvilinear subinsular lesions have been noted on CT but the underlying pathology is unknown. We reviewed the cranial MR scans (1.5 tesla GE machine) of 49 serial patients over the age of 60 who had no cause for MR hyperintensities (HI) other than age or vascular risk factors. Seven (14%) had linear subinsular HI (SIHI). Four of 7 (57%) patients with SIHI and 4 of 42 (12%) without SIHI had marked periventricular HI compatible with subcortical arteriosclerotic encephalopathy (PAVH) (p < 0.05). Patients with SIHI were older (73.5 yr) than patients without SIHI (69.1 yr) (p < 0.05). Four of 7 (57%) patients with SIHI had hypertension.
James L. Frey, Phoenix, AZ

The brain arteries were injected postmortem with a lead/gelatin suspension, and MR of the whole brain and x-ray films of the brain slices were taken. Bilateral SIHI were seen on MR and corresponded with linear cavitary infarction on MR and corresponded with linear cavitary infarction. We conclude that SIHI are associated with older age and PVHI, and can be due to infarction in a deep watershed territory and can be associated with clinical deficits.

P149. Lacunar Infarction Responds to Hemodilution—Treatment Results in 12 Consecutive Cases

James L. Frey, Phoenix, AZ

Because precipitous neurological deterioration occurred during blood pressure reduction in a seminal case of lacunar infarction, 11 subsequent patients with partial or evolving lacunar deficits were treated with hemodilution and blood pressure non-intervention to test the hypothesis that lacunar strokes represent perfusion failure. Isohemodilute hemodilution was performed using hetastarch with target hematocrit of 30 to 33. Results of pretreatment CT brain scans, carotid ultrasound, and echocardiograms were normal. Nine patients recovered normal neurological function, and 2 regained complete functional independence in close temporal correlation with hemodilution. MRI brain scans demonstrated appropriate single white matter lesions in 9 cases. No specific risk factor combination could be identified. No patient had recurrent stroke in follow-up from 12 to 30 months. Response to hemodilution suggests a hemodynamic pathophysiology. Successful treatment requires (1) blood pressure non-intervention and (2) hemodilution prior to severe clinical deterioration.

P150. Noninvasive Hemodynamic Classification of Carotid-Cavernous Sinus Fistulas by Duplex Sonography

H. J. Lin, P. K. Yip, H. M. Liu, B. S. Huang, and R. C. Chen, Taipei, Taiwan

The hemodynamic classification for the carotid-cavernous sinus fistula (CCF) is important for the implication of prognosis and therapy, but satisfactory objective criteria for such differentiation is still lacking. Retrospectively, we studied the application of extracranial duplex sonography in 9 cases of CCF with emphasis on the hemodynamic parameters of resistivity index and flow volume. A correlation was made with the angiographic findings in an attempt to evolve an objective hemodynamic classification by this noninvasive method. The 9 cases comprised all of the 4 types of fistula described by Barrow et al: 4 direct shunts arising from the main trunk of the internal carotid artery (ICA) (Type A) and 6 dural shunts fed by the dural branches of the ICA and/or external carotid artery (ECA) (Type B, C, and D). We conclude with a proposed duplex sonographic criteria for the hemodynamic classification: (1) low-resistivity index with/without increased flow volume in the ICA: direct ICA-cavernous sinus fistulas (Type A); (2) normal resistivity index and flow volume in the ICA and ECA: dural branch of ICA-cavernous sinus fistulas (Type B); and (3) low resistivity index with/without increased flow volume in the ECA: dural branch of ECA-cavernous sinus fistulas (Type C) or dural branches of ICA and ECA-cavernous sinus fistulas (Type D).

POSTER PRESENTATION:
Dementia and Aging

P151. Brain Metabolic Alterations Associated with Clinical Onset and Course of Alzheimer's Disease

W. E. Klank, K. Panchalingam, R. J. McClure, and J. W. Pettigrew, Pittsburgh, PA

Alterations in membrane metabolism and structure could be the primary etiological event in Alzheimer's disease (AD) that results in the clinical and neuropathological findings. To investigate in vivo brain membrane phospholipid and high-energy phosphate metabolism in probable AD patients and control subjects, the building blocks (PME) and breakdown products (PDE) of membranes and the high-energy phosphates PCr and ATP were measured noninvasively by in vivo brain 31P MRS in 11 probable AD patients (5 males; 6 females) and 18 controls (9 males; 9 females). All subjects were assessed by Mini-Mental, Mattis, and Blessed scales. We found that, at clinical onset, AD females had elevated PME (p = 0.004), decreased PCr (p = 0.001), and decreased ATP (p = 0.03). Similar changes were not seen in AD males at clinical onset, but the severely demented AD males had increased ATP (p = 0.05). Correlation analysis for the AD patients revealed that increasing dementia was associated with decreasing PME (p = 0.05; r = 0.4), increasing PDE (p = 0.08; r = 0.4), increasing PCr (p = 0.05; r = 0.4), and increasing ATP (p = 0.02; r = 0.5). Similar metabolic-cognitive correlations were not seen in the controls. These results demonstrate alterations in membrane and energy metabolism at the earliest clinical stages of AD. Increasing dementia correlates with markers of membrane degeneration and decreased utilization of high-energy phosphates. Both of these findings suggest the dementia in AD is secondary to membrane changes resulting in synapse loss.

P152. Morphometric Analysis of the Hippocampus in Alzheimer's Disease: Postmortem MRI and Histological Correlates

Fen-Lei Chang, J. E. Purtis, C. R. Jack, Jr, and R. C. Petersen, Rochester, MN

Hippocampal atrophy, defined by MRI-derived volumetric measurement, has been useful in differentiating Alzheimer's disease (AD) patients from normals. Since several studies have demonstrated anatomical and functional gradients along the rostral-caudal (r-c) axis of the hippocampus, it is tempting to speculate on the existence of a differential distribution of morphometric changes along this axis. The hippocampi from 19 patients with clinically and pathologically confirmed AD were studied by postmortem MRI and by reconstruction of serial histological sections. There was good correspondence between these two methods. The r-c length of the hippocampus in AD was preserved compared to normal. This length was longer on the left, both in normals and AD. The AD-associated atrophy was due primarily to the reduction of the coronal cross-sectional area of the hippocampus. With increasing hippocampal atrophy, volume reduction was more prominent in the rostral area (pes hippocampus). This non-uniform reduction in volume may be associated with different connectivity patterns between rostral and caudal hippocampus.
**P153. Neuropathological Verification of Probable and Possible Alzheimer's Disease**

R. Dauro, S. Pascal, W. W. Barker, J. Bruce, and M. Noremburg, Miami and Miami Beach, FL

The purpose of this study was to determine the neuropathological validity of NINCDS-ADRDA criteria (NAC) for probable and possible AD. McKhann et al (1985) provided clinical criteria for the categories probable AD and possible AD. The validity of these categories has not yet been reported. A retrospective, blinded evaluation of the complete neurological history, examination, neuroimaging, laboratory, and psychometric data was done for 68 subjects from the State of Florida Brain Bank. Pathological classification, which was blind to clinical diagnoses, was in 3 categories: pure AD, AD+, and other dementias. Ninety-three percent of probable AD (n = 42), whereas only 75% of possible AD (n = 26) patients, had AD or AD+ (p = 0.1). Pure AD was found in 62% of probable AD and 38% of possible AD patients (p = 0.1). Pathological evidence of coexisting Parkinson's disease was present in 14% of all AD brains. These results suggest differential predictive power of NAC for probable and possible AD, as suggested by the labels. NAC are, therefore, useful for research and clinical purposes.

**P154. White Matter Low Attenuation on CT Scan Is Associated with Rapid Rate of Decline on Mental Status Testing**

H. Crystal, M. Sluzewski, R. Lipton, M. Katz, L. Wolfson, C. Derby, R. Golden, G. Lantos, and J. Maidou, Bronx, NY

Our prior study of falls in the elderly had shown significantly more white matter low attenuation (WMLA) on CT scan among fallers than nonfallers, but no association between WMLA and cognitive impairment among nondemented subjects. As these subjects were followed over time, it appeared that fallers were becoming demented at a more rapid rate than nonfallers. As a result, we analyzed the relationship between WMLA and rate of change on the Blessed Test of Information, Memory, and Concentration (BIMC) in a combined cohort of 144 subjects from the falls study and from a longitudinal study of dementia and normal aging. We selected 61 of the 144 subjects whose initial BIMC score was less than 25 (i.e., not already severely impaired) and who had at least 4 yearly BIMC evaluations. CT scans were scored on an 8-point ordinal scale for hemispheric WMLA. Linear regression was used to summarize the rate of change for each subject's test scores. The rate of change on BIMC was 2.3 points per year with standard error (SE) of 0.2 among subjects who eventually became demented; nondemented subjects declined at 0.4 points per year with SE of 0.2. Multiple regression analysis was performed with initial BIMC score and WMLA as the independent variables and rate of change of BIMC as the dependent variable. WMLA accounted for 16% of the variance (partial r = 0.396, t = 3.26, p < .05). These data suggest that elderly subjects with WMLA may be at increased risk for rapid cognitive decline.

**P155. The Effect of Alzheimer's Disease on the Activities of Adenylate Cyclase and Glutamyl Transpeptidase**

Brian M. Ross, Mark McLaughlin, Graeme Milligan, John T. Knwler, and James Muddoch, Glasgow, UK

Numerous investigations of Alzheimer-diseased (AD) brains have demonstrated alterations in a variety of neurotransmitters and their receptors. However, there have been relatively few studies of other signal transduction system components, such as G proteins and adenylate cyclase. The activities of adenylate cyclase, and of the G protein–associated enzyme activity, low-Km glutamyl transpeptidase (GTase), were assayed in membranes prepared from the postmortem brains of 8 Alzheimer-diseased and 8 age-matched control subjects. Both basal and fluorocitrate-stimulated adenylate cyclase activities were significantly reduced in AD frontal cortex compared to control subjects (p < 0.01; two-tailed Student's t test). In addition, a significant, though smaller, reduction in basal GTase activity also was detected in AD frontal cortex (p < 0.05). In contrast, no significant change in the activity of either enzyme was detected in the hippocampus. The stimulation of GTase activity by muscarinic and GABAA receptor agonists was not altered significantly by the presence of Alzheimer's disease. However, the degree of stimulation was much lower in human tissue compared to that observed using fresh rat brain, suggesting that the ability of receptors to activate G proteins declines post mortem. These results suggest that Alzheimer's disease causes alterations in some key components involved in signal transduction.

**P156. Cerebral Amyloid Angiopathy, Cerebral Hemorrhage, and Alzheimer's Disease**

Michael Chen, David Nocchin, Donald Born, Takeshi Imaio, and S. M. Sani, Seattle, WA

The association of lobar hemorrhage (LH) with cerebral amyloid angiopathy (CAA) and that of CAA with Alzheimer's disease (AD) are well known. To determine how frequently LH and CAA occur in AD, we reviewed 13 patients with cerebral or cerebellar hemorrhage and CAA. Five patients were treated surgically, none was demented, 2 died, and 1 came to autopsy. Eight patients died of LH and came to autopsy. Of the 9 autopsied patients, 3 had AD, both clinically and neuropathologically. They comprised 1.2% of 258 cases of autopsy-confirmed AD in our laboratory. None of the other patients were known to be demented. Five had senile plaques, with or without neurofibrillary tangles, in the hippocampus, and occasional senile plaques in the cortex, but none met the Consortium for Establishing a Registry for Alzheimer's Disease neuropathological criteria for AD. AD patients were 70, 85, and 85 years old and the ages of the 10 nondemented patients ranged from 63 to 87 (mean = 73.1 yr). Seven were younger than 75 years of age. Despite the frequent occurrence of CAA in AD, we found that LH was uncommon. In addition, most of our patients with LH and CAA were not demented and tended to be younger than AD patients with LH.

**P157. Magnetic Resonance Volumetry of the Hippocampus and Memory Function in Normal Aging**

R. C. Petersen, C. R. Jack, Jr, and G. Smith, Rochester, MN

Magnetic resonance–based volumetric measurements of the hippocampal formation (HF) have been shown to be useful in differentiating Alzheimer's disease from normal aging. We evaluated the relationship between volumetric measurements of the HF and several indices of memory in normal aging. Volumetric measurements of the HF were taken of 34 normal controls from the Mayo Clinic Alzheimer's Disease Patient Registry who had undergone medical, neurological, laboratory, and neuropsychological evaluations. The volumetric measurements were performed by neuroradiologist (C.R.J.) who was blinded to the patient's clinical state, age, and sex. The correlation between HF volume and age was the most significant (p < 0.02), while the next most significant relationship existed between an index of learning or acquisition
These findings relate to memory and structural brain changes and measures from the Wechsler Adult Intelligence Scale-HF is involved primarily in acquisition or learning processes. Ross Callaway, Linda Duke, A. Bartolucci, Lindy, and ADiDEP than AD or NOR. Overall cholinergic measures were significantly lower in AD and AD/DEP than DEP or NOR, whereas HAM and BPRS scores were significantly greater in DEP and AD/DEP than AD or NOR. Overall cholinergic measures were similar among all groups. MDS and MMS were significantly lower in AD and AD/DEP than DEP or NOR, whereas HAM and BPRS scores were significantly greater in DEP and AD/DEP than AD or NOR. Overall cholinergic measures were similar among the groups at baseline and 1 year later. Because of the large number of comparisons, significance was set at p < .05 for the correlation analysis. Utilizing this cutoff, the attention subscale (MDS) and R subcale (BPRS) were found to correlate to RBC choline in AD/DEP, whereas plasma choline correlated to subscale P (BPRS) and RBC acetylcholinesterase to HAM in AD. No correlations were found in DEP or NOR. Our results suggest little relationship between systemic cholinergic processes and cognitive or psychiatric dysfunction, or both, in AD.

P159. Relationship Between Occupational Demands and Parietotemporal Perfusion in Alzheimer’s Disease
Y. Stern, L. Strick, G. Alexander, I. Prohovnik, and R. Mayeux, New York, NY

There is an inverse relationship between parietotemporal cerebral blood flow and years of education in Alzheimer’s disease (AD) patients matched for clinical severity, which suggests delayed clinical manifestation of AD in patients with higher education (Stern et al, Soc Neurosci Abstr 1991). We classified the lifetime primary occupations of 51 AD patients using the Dictionary of Occupational Titles of the US Department of Labor and derived 6 factor scores describing intellectual, interpersonal, and physical job demands. After controlling for age, education, age at onset, illness duration, and dementia severity (mental status and Activities of Daily Living), relative perfusion in the parietotemporal region (assessed using 133-xenon inhalation) showed significant correlations with job complexity (P1: r = −.36, p < .008) and interpersonal (P2): r = −.44, p < .001) factor scores. In a stepwise multiple regression, job complexity and interpersonal skills increased explained parietotemporal flow variance by 7.5% (F = 4.7, p < .05) over that explained by demographic and severity indices; physical demands then accounted for another 11.5% of the variance (F = 8.4, p < .01). We conclude that occupational demands, similar to but independent of education, may provide a reserve that delays the clinical expression of AD.

P160. Head Injury As a Cause of Alzheimer’s Disease
Richard Mayeux and Ming-Xin Tang, New York, NY

Risk factors for Alzheimer’s disease (AD) were collected from 223 patients with AD and 278 healthy elderly controls in an urban community population consisting of 3 ethnic groups: black, Hispanic, and white. Advanced age (>80 yr) (OR = 10.9; 95% CI 6.2–19.1) and head injury with loss of consciousness (OR = 2.90; 1.2–7.3) were associated with AD, controlling for all known putative risk factors. Factors such as low education (<8 yr) (OR = 1.5; 0.8–2.6) and family history of AD (OR = 1.7; 0.9–3.0) were not found to be significantly related to AD. Head injury occurred in 15.9% of the patients and 6.7% of controls. Most (90%) head injuries in the patients with AD occurred after age 50, prior to disease onset. In controls with head injury, 55% had experienced a head injury before age 50. The duration of unconsciousness was consistently longer in patients with AD than in the controls. The overall effect in each ethnic group was similar (OR, 2.5; 1.3–4.8). These results confirm and strengthen the previously described putative relationship between head injury and AD. We also conclude that both the severity and the timing of the head injury as well as the frequency of head injury in the population at risk may be important factors in understanding the causal relationship between head injury and AD.

P161. Ethnic and Language Factors in the Diagnosis of Dementia
D. Loevenstein, W. W. Barker, S. Pasical, M. Zatinsky, A. Torres, and R. Dhara, Miami Beach, FL

The purpose of this study was to determine how native language affects the cutoff scores in screening tests for dementia. There is a paucity of data on this issue at present. Screening tests used in the study were: Folstein Mini-Mental State (MMS); Clockdrawing (CLOCK); preparing a letter for mailing (MAIL); 4-item grocery list (LIST); and Hamilton Depression Scale (HAM). The subjects included 175 (94 demented) native English speakers (ENG) and 72 (22 demented) native Spanish speakers (SPA) with memory complaints. Diagnosis of dementia was determined by neuropsychological, neuropsychological, and psychiatric evaluation. Age and gender were unrelated to MMS. In SPA only, education was positively related to MMS. HAM scores were higher in demented (p = .001) and nondemented (p = .05) SPA than ENG. Areas under the receiver operating characteristic curves (graph of true-positives vs false-positives) for MMS were 0.89 (ENG), 0.74 (SPA); MMS + MAIL: 0.93 (ENG) and 0.77 (SPA); CD and LIST did not add discriminative power to MMS for ENG but did so for LIST in SPA. MMS discriminates between demented and nondemented far better in English than in Spanish speakers. Only MAIL adds discriminative power to MMS.

P162. Clinical Misdiagnosis of Alzheimer’s Disease—A Review of CERAD Autopsy Findings
A. Heyman, G. Fillenbaum, S. Mirra, and participating CERAD neuropathologists, Durham, NC, and Atlanta, GA

The clinical diagnosis of Alzheimer’s disease (AD) has become more accurate in recent years due to the application of...
specific clinical criteria, wider use of neuroimaging procedures, and greater expertise among physicians. We report the frequency of clinical misdiagnosis of AD among 52 patients who at autopsy were found to meet the rigorous clinical diagnostic criteria imposed by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) study. These patients included 31 men and 21 women (mean ages 78 and 76 yr, respectively) who were among the group of 95 patients who died in 13 CERAD medical centers in the US between 1987 and 1991. The clinical diagnosis of AD was neuropathologically confirmed in 47 (88.5%) of the 52 cases. Of these 47 cases, varying degrees of concomitant cerebrovascular disease were present in 26% and coexisting Parkinson’s disease changes were found in 19%. In 4 of the 5 patients without neuropathological evidence of AD, the diagnoses were: lobar atrophy, diffuse Lewy body disease, nonspecific neurodegenerative changes, and mesocorticolimbic dementia, respectively. The fifth patient showed no morphological abnormalities. On the basis of these results, it would appear that application of strict diagnostic criteria, as well as the use of brain scans and detailed clinical and neuropsychological tests by experienced clinicians, cannot yet distinguish some types of primary degenerative dementias from Alzheimer’s disease.

P163. Assessing Dependence, a Unique Feature of Functional Decline in Alzheimer’s Disease

Y. Stern, M. Sano, L. Miller, M. Richards, K. Marder, K. Bell, F. Byloma, and G. Laffleche, New York, NY, Baltimore, MD, and Boston, MA

We designed a scale that measures an underexplored facet of functional decline in Alzheimer’s disease (AD): the patient’s dependence on others for supervising or performing activities. Two hundred twenty-three informants for patients with mild AD (clinical dementia rating [CDR] = 1 for 200; CDR = 2 for 23) were interviewed and dependence was staged from 0 to 5. Interrater reliability was assessed by separate interviews of 20 informants; agreement was 100% for dependence stage. Dependence stage differed significantly at the 2 CDR levels (Chi square = 41.0, p < .01) and correlated significantly with modified Mini-Mental State (mMMS) (r = -.30, p < .001) and Blessed Dementia Rating Scale-Part 2 (BDRS) (r = .41, p < .001). Seventy-eight percent of patients in a health-related facility were at stage 3 or higher vs 25% of patients living at home. In a multiple regression model, both the BDRS and dependence scale accounted for unique portions of the variance in mMMS, suggesting that they assess unique aspects of functional ability. Dependence increased significantly in 118 patients retested at 1 year. We conclude that the dependence scale is reliable and relates to both disease severity and progression. Formal assessment of dependence should prove useful for studies of the natural history of AD as well as for clinical trials.

P164. Dementia with Pathological Findings of Cortical-Basal Ganglionic Degeneration

A. Lerner, R. Friisland, D. Riley, P. Whitehouse, D. Lanska, N. Vick, E. Cochrane, N. Tessler, M. Cohen, and P. Gambetti, Cleveland, OH, Lexington, KY, and Chicago, IL

Cortical-basal ganglionic degeneration (CBGD) is a disorder characterized by an asymmetrical akinetic-rigid syndrome and cortical signs such as apraxia, alien limb phenomena, and cortical sensory loss. Dementia has been present in many cases, but always as a late manifestation. We report 2 cases pathologically consistent with CBGD, presenting as primary degenerative dementia, fulfilling NINCDS-ADRDA criteria for probable Alzheimer’s disease (AD). The first patient presented with changes in memory and personality, language dysfunction, decreased verbal output, and shuffling gait. Follow-up examinations over 3 years showed progressive dementia, wide-based gait, and frequent falls. The second patient presented with complaints of memory loss. Neuropsychological examinations showed progressive deficits in memory, attention, calculations, and visuospatial functioning. No movement disorder developed over 6 years of follow-up. At autopsy, both patients had typical changes of CBGD and lacked pathological features of AD. Definitive diagnosis of CBGD rests on both clinical and pathological criteria. CBGD should be considered in the differential diagnosis of patients with dementia resembling that found in AD, especially if extrapyramidal signs are present.

P165. Screening Tests for Praxis in Neurology Outpatients

Emre Kokmen and Fatma Sibel Ozcakmak, Rochester, MN, and Istanbul, Turkey

A quick, easily administered and scored test for praxis is desirable in evaluation of neurological patients. During 2 months in 1991, each patient seen in the outpatient setting by the principal investigator (E. K.) received 1 of 2 praxis screening batteries. Thirty-six patients were tested with a short battery. Eleven had normal cognition based on neurological history, examination, and a short test of mental status. Twenty-five had cognitive decline (CD). Handedness, male/female ratio, education, and mean age were similar in both groups. Mean time of completion of the test was 102 ± 10 seconds in normals and 136 ± 41 seconds in patients with CD. Total scores (maximum score 50) were 47.6 ± 1.8 in the normals and 41.2 ± 9 in the cognitively declined patients. Twenty-five other patients, 12 with CD and 13 with normal cognition, were tested with a longer battery containing oral/facial, upper and lower limb, axial, sequential, and imitation subtests (maximum score 110). Normals completed the battery in 297 ± 56, and cognitively declined patients completed the battery in 359 ± 53 seconds. Of the various subtests, tests of sequential praxis were performed most poorly by patients with CD: 8.3 ± 1.8 in normals vs 4.9 ± 3.0 in patients with CD. Oral/facial praxis was least affected by CD: 16.7 ± 4.3 in cognitively declined patients vs 19 ± 1.2 in normals. Cognitive decline affects praxis, but its effect on subtests is variable.

POSTER PRESENTATION: DEGENERATIVE DISEASE

P166. Neuropeptide Abnormalities in Cerebral Cortex of Olivopontocerebellar Atrophy Postmortem Brain

Michael F. Mazurek and Stephen J. Kish, Hamilton and Toronto, Ontario, Canada

Olivopontocerebellar atrophy (OPCA) is generally understood to be a nondementing neurodegenerative disorder affecting the cerebellum, lower brainstem, and spinal cord. One of us (S. K.) recently reported that postmortem cerebral cortex from patients with dominantly inherited OPCA shows a widespread reduction of cholinergic markers similar to that observed in Alzheimer’s disease (AD). We were interested to determine the status of other neurotransmitter systems in OPCA postmortem cerebral cortex. Samples of frontal,
parietal, temporal, and occipital cortex were dissected from 10 confirmed cases of OPCA and 11 age-matched controls. After processing, neuropeptide levels were measured by radioimmunassay. Concentrations of somatostatin were significantly reduced by 42 to 58% in 3 of the 4 cortical areas of OPCA brain that were examined. The area that was spared was the inferior temporal gyrus, a region in which somatostatin levels are markedly reduced in AD. Levels of neuropeptide Y were normal in all 4 areas, while concentrations of cholecystokinin, vasoactive intestinal polypeptide, and substance P were significantly increased in 2 of the 4 areas. These data show widespread neuropeptide changes in the cerebral cortex of OPCA postmortem brain. In contrast to cholinergic markers, the pattern of neuropeptide changes is different from what is observed in AD.

P167. Corticomotoneurons Are Hyperexcitable Early in Amyotrophic Lateral Sclerosis: A Magnetic Stimulation Study
Andrew Eisen, Bhanu Pant, and Heather Stewart, Vancouver, BC, Canada

It has been postulated that demise of the corticomotoneuron is the initial event in amyotrophic lateral sclerosis (ALS) and that the anterior horn cell dies as the result of antegrade glutamatergic excitotoxicity (Muscle Nerve 1992;15:219). Excitability of the corticomotoneuronal system can be tested by measuring threshold-to-cortical magnetic stimulation and the motor-evoked potential (MEP)/compound muscle action potential (CMAP) ratio, which estimates the number of corticomotoneurons stimulated. Cortical threshold and MEP/CMAP ratio were measured in 39 patients early in the course of ALS. The mean time interval from onset of first symptoms was 8.5 months. Mean threshold and MEP/CMAP ratio were 64.2 ± 16.6% and 22.0 ± 21.2%, respectively. In 12 (30.8%) patients, threshold was paradoxically low (<55%), mean 49.1 ± 4.3% and in 7 (17.9%) patients there was no response. There was a significant ($r^2 = 0.698$) inverse power relationship between cortical threshold and MEP/CMAP ratio. Six months later, 7/24 (29.2%) patients still had low thresholds but the mean MEP/CMAP ratio had dropped to 24.9 ± 24.5% and in 33.3% there was no response. We conclude that early in ALS the corticomotoneuronal pathways are abnormally excitable. This may explain early cramping and fasciculation, which characteristically diminishes as ALS progresses.

P168. Elastin Cross-Linking in the Skin from Patients with Amyotrophic Lateral Sclerosis
Seiitsu Ono and Mitsuo Yamauchi, Ichihara, Japan, and Chapel Hill, NC

One of the distinct clinical features in patients with amyotrophic lateral sclerosis (ALS) is loss of elasticity of skin. However, little is known concerning the biochemical nature of skin elastin in ALS. In our study, 2 cross-links unique to elastin, desmosine and isodesmosine, were measured and compared in skin tissue (left upper arm) from 10 patients with ALS and from 7 age-matched controls. The contents of desmosine and isodesmosine were decreased significantly ($p < 0.01$ and $p < 0.01$, respectively) in patients with ALS (mean ± SD, 0.94 ± 0.33 and 0.74 ± 0.30 nmol/mg dry weight; range 0.36–1.51 and 0.29–1.33 nmol/mg dry weight, respectively) as compared with those of controls (mean ± SD, 1.43 ± 0.30 and 1.19 ± 0.21; range 1.11–2.03 and 0.92–1.52, respectively), and were negatively and significantly associated with duration of illness in patients with ALS ($r = -0.77$, $p < 0.01$, and $r = -0.65$, $p < 0.05$, respectively). The ratio of desmosine and isodesmosine was constant (1:3) in all samples analyzed. The decline in skin desmosine and isodesmosine is more rapid in ALS than in normal aging. Thus, cross-linking of skin elastin is affected in ALS. (Supported in part by NIH Grants DE 18522, DE 11235, DE 08611, AR 19569, AR 30587, and NASA grant NAG-2-181.)

P169. Natural History of Amyotrophic Lateral Sclerosis: Effect of Data Transformation (Z Score, Simple Average, Percentile) on Sample Size Requirements for Placebo-Controlled Therapeutic Trials
B. R. Brooks, R. Rao, F. Samaha, B. Jubelt, and T. Siddiquie, Madison, WI, Chicago, IL, and Cincinnati, OH

Biological variability, defined by the standard deviation of a clinical measurement in a population of patients, is a crucial determinant of the sample size required to perform a placebo-controlled therapeutic trial with appropriate power. Several attempts to minimize this variability in prospective natural history studies have been made. In a prospective natural history study in 86 amyotrophic lateral sclerosis (ALS) patients. Isometric muscle strength in 8 arm muscles and 10 leg muscles was measured serially over 1 year. Data transformations tested were (1) Mega Limb Z score based on mean of standard (Tufts ALS Clinical Center), ALS patients uncorrected for gender and age (MZALS); (2) Mega Limb Z score based on mean of control population controlled for gender and age (MZCOPH); (3) Simple Limb Average of raw isometric muscle strength in kg (SAkg); and (4) Simple Limb Average of percentile strength controlled for gender and age (SA%gam). Rates were calculated at 0- to 6- and 7- to 12-month intervals. ALS deterioration in arms or legs correlated excellently within each interval across transformation and across structure ($r = 0.62026$–$0.9805$; $p \leq 0.001$). Across time there was no significant difference in arms or legs within each transformation ($r = 0.089–0.613$). However, correlation of rates of deterioration in individuals across time was poor ($r = 0.0003–0.0566$; $p = 0.098–0.905$), suggesting that there may be difficulty with predicting simply the course of ALS deterioration in individuals using the current statistical models. Although the course in individuals is dramatically presented by SA%gam, its usefulness in controlled trials may be limited by the large population standard deviation of ALS patients compared with the 3 other data transformations (MZALS, MZCOPH, SAkg). Sample size determinations for clinical therapeutic trials of varying power will be presented. (Supported in part by MDA ALS Midwest Research and Treatment Program.)

P170. National UK Motor Neuron Disease Twin Study Using the Death Discordant Approach
C. H. Hawkes and A. J. Graham, Ipswich, Suffolk, England

Collection of large numbers of twin pairs in disease of low prevalence is difficult. To circumvent this, we devised a new approach termed the “death discordant twin pair” method. Eleven thousand deaths from motor neuron disease (MND) were extracted from the Office of Population Censuses and Surveys during 1979 to 1989. Birth indexes from 1900 onward were searched for possible twins. For each twin so identified (151 pairs), the National Health Service Central Registry located the relevant family practitioner committee and thence the co-twin’s general practitioner. The search produced: (1) 53 living co-twins; (2) 5 embarked; (3) 60 dying as adults or infants; (4) 3 not MND; and (5) 10 untraceable.
Valid data have been obtained on 70 twin pairs that include 17 pairs where both twins were deceased. Using validated zygosity–related questions with co-twins or relatives, or both, we have identified (1) 48 dizygous pairs, all discordant for MND; and (2) 22 monzygous pairs of whom 2 were concordant but 1 of these gave a family history of MND. The index of heritability ($h^2$) for this sample is approximately 0.7. The new method has proven successful although time-consuming. The heritability index infers a major genetic contribution but it is probably an overestimate because of the low prevalence rate of MND and the absence of concordant dizygotic twins. It does infer that genetic influences are important in sporadic MND.

P171. Relative Importance of Clinical and Electrodiagnostic Data in the Diagnosis of Amyotrophic Lateral Sclerosis: A Clinicopathological Study of "El Escorial" Working Group Criteria in 36 Autopsied Patients

J. Gaffney, R. L. Sufti, B. R. Beinlich, P. L. Eichman, H. Hartmann, J. Miles, G. ZuRehrn, and B. R. Brooks, Madison, WI

Validity of the accuracy, sensitivity, and specificity of the World Federation of Neurology (WFN) Subcommittee on Motor Neuron Disease Working Group criteria for the clinical diagnosis of amyotrophic lateral sclerosis (ALS) has been tested against neuropathological criteria in 36 autopsied patients (Neurology, in press). Integration of clinical and electrodiagnostic data to meet WFN criteria for possible, probable, and definite ALS was studied in this same group. Patients received 1.7 ± 1.1 (mean ± standard deviation) electromyograms (EMGs) per patient and included 1.7 ± 0.9 EMG levels (bulbar, cervical, thoracic, lumbar) per patient.Proportionately fewer EMGs were performed as the level of diagnostic certainty at presentation increased: suspected (34.3%), possible (31.4%), probable (25.7%), definite (8.6%). In only 4.8% of all patients studied did the first EMG alone change the level of diagnostic certainty of the diagnosis of ALS. Only 16.7% of patients presenting with suspected ALS alone or with possible or probable ALS were associated with a change in level of diagnostic certainty following 1 or more EMGs. However, although increasing the number of EMGs performed per patient may be associated with an increasing chance of increasing the level of diagnostic certainty (≤2 EMGs/patient = 33.3%; ≥3 EMGs/patient = 60.0%), selection of the level of EMG analysis was more crucial. The "El Escorial" criteria emphasize the importance of EMG evidence of lower motor neuron involvement in a limb with clinical upper motor neuron signs. Our analysis of EMG studies in autopsy-confirmed ALS patients suggests that complete evaluation of bulbar and thoracic levels for lower motor neuron changes and complete evaluation of motor unit recruitment patterns are important for the integration of EMG data with clinical data in the application of the "El Escorial" criteria for the diagnosis of possible, probable, and definite ALS.

P172. Patterns of Amyotrophic Lateral Sclerosis/Parkinsonism-Dementia Complex in Selected Sibships on Guam

Annette Grefe, John Steele, Linda Flores, and Stephen Waring, Birmingham, AL, and Umatat and Mangilao, Guam

Reports in the 1950s indicated that 40% of Guamanian Chamorro patients with amyotrophic lateral sclerosis (ALS) gave a positive family history. Subsequent investigators have inferred that purely genetic factors are not responsible for Guamanian ALS or its clinical variant, parkinsonism-dementia complex (PDC). We report the first 4 Chamorro sibships selected in an ongoing study of 171 familial aggregations. The basis for the initial selection was that the youngest patient in the sibship had ALS. Age of onset was 30 to 46 years (mean 35 yr). Fourteen of 23 persons in these sibships were affected. Others in the sibship developed PDC, progressive supranuclear palsy, or pure dementia later in life (mean 61 yr, range 50–74 yr). These cases developed 14 to 47 years (mean 25 yr) after onset of disease in the first sibling. The age at onset of the first case and the intervals between earliest and latest cases in such sibships may help to determine minimal and maximal latency (i.e., interval between exposure to an exogenous agent and onset of symptoms). Our observations suggest that exposure may have occurred early (before age 30) with varying and often long latency (up to 47 yr). We also find that variability of clinical expression may be correlated with the age at onset. Concentrating on the study of familial cases on Guam may enhance the identification of the etiologic agent(s) of this prevalent and tragic disorder.

P173. Spinocerebellar Ataxia in South Africa

A. Bryer, R. W. Martell, and P. Brightly, Cape Town, South Africa

The spinocerebellar ataxias are an uncommon group of genetic disorders that have been well characterized in North America and Europe. Information concerning these conditions in Africa and other parts is scant. To address this problem, a large-scale survey has been undertaken in the Cape Province of South Africa. In this investigation, more than 500 persons in 18 affected families have been appraised and investigated and phenotypic features have been analyzed in detail. Linkage studies have been undertaken in 4 families with similar phenotypes in which the condition was transmitted as an autosomal-dominant trait. Human lymphocyte antigen (HLA) typing was carried out on 79 members of the 4 families and linkage analysis was undertaken using the LIPED program to analyze the data with a correction factor for age of onset. Maximum LOD scores were: Family A: 4.13 ($\theta = 0.005$); Family B: 0.6 ($\theta = 0.001$); Family C: 0.50 ($\theta = 0.30$); Family D: 0.0 ($\theta = 0.50$). These results indicate linkage to HLA in 1 out of 4 families. These findings provide support for the concept of genetic heterogeneity in these phenotypically homogeneous families. PCR typing with the reportedly more closely linked D6S89 locus is now being undertaken in these South African families.

P174. Two Adult Cases of L-2-Hydroxyglutaric Acidemia

H.-P. Hartung, G. F. Hoffmann, and G. Becker, Würzburg, Heidelberg, Germany

Recently, L-2-hydroxyglutaric acidemia has been described as a novel metabolic disorder in 6 children. We report the occurrence of this disease in adults. One of 2 brothers developed at the age of 10 an abnormal gait and dysarthria; in the other 1, clumsiness and walking delay were noted at age 3. Symptoms progressed and at the time of admission, when the patients were 33 and 39 years, neurological examination revealed a spastic ataxic gait, limb ataxia, dysmetria, dystar- thria, dystonic posturing, and mental retardation. CT and MR imaging revealed subcortical white matter changes with loss of arcuate fibers, folial atrophy, and leakage in the cerebellar vermis, as well as atrophic changes in the cerebellar hemi-
spheres. On biochemical screening, highly elevated concentrations of L-2-hydroxyglutaric acid were found in CSF, plasma, and urine. The pathological accumulation of L-2-hydroxyglutaric acid in these 2 adults, along with the clinical picture characterized by cerebellar, extrapyramidal, and pyramidal symptoms and oligophrenia, and the neuroradiological findings of severe loss of myelinated arcuate fibers in subcortical white matter, conform with what previously has been described in the few neuropediatric cases. The biochemical abnormality underlying accumulation of this organic acid remains elusive.

P175. Positron Emission Tomographic Findings of Slowly Progressive Aphasia: Comparison of Resting Study and Activation Study
K. Ishii, M. Senda, M. Bando, M. Ohyama, K. Oda, H. Toyama, K. Ishiwata, T. Sasaki, S. Ishii, and H. Yamanouchi, Tokyo, Japan

This study was undertaken to differentiate primarily affected areas from functionally suppressed areas due to remote effect in aphasic patients with focal brain degeneration, using an activation method with O-15 water, in comparison with [18F]2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomographic examination at rest. The subjects were 2 patients with slowly progressive aphasia showing contrasted clinical symptoms (nonfluent type vs fluent type). Regional cerebral metabolic rate of glucose (CMRGluc) was measured with intravenous injection of 130MBq of F-18 FDG at rest. Regional cerebral blood flow (CBF) was measured with intravenous bolus injection of 1.5GBq of O-15 water in 3 different conditions: at rest, under repetition tasks, and under naming tasks. Changes of CBF were evaluated between a resting condition and task-performing conditions. Regional CMRGluc was decreased focally in both Broca’s and Wernecke’s areas similarly in these cases in spite of the difference in clinical symptoms, whereas the patterns of regional CBF changes were different. The fluent patient showed prominent activation in the bilateral frontal areas on repetition tasks. The nonfluent patient showed, whereas the fluent patient did not show, focal activation in the left occipitoparietal area on a naming task. Evaluation with an activation method can provide detailed information about the pathophysiological process and the location of primary lesion.

P176. Autoradiographic Distribution of Complex I in Brain
J. T. Greenamyre, D. S. Higgins, and R. V. Eller, Rochester, NY

Defective complex I activity has been linked to Huntington’s disease (HD) and Parkinson’s disease (PD). Intrastriatal injection of inhibitors of complex I reproduces the pathological features of HD, and the neurotoxin MPP+ kills dopaminergic neurons by inhibiting complex I. Defects in complex I have been reported in HD and PD, but the distribution of this enzyme in the brain is unknown. To map complex I in brain quantitatively, we developed an assay using [3H]labeled rotenone to label the enzyme in tissue sections. This high-affinity binding is saturable and is displaceable by rotenone and MPP+. Using 100 μM rotenone to define nonspecific binding, more than 95% of binding is specific. Highest levels of binding are found in kidney, followed by myocardium. Moderate levels of complex I are seen in striated muscle and some brain regions. Within the brain, binding varies more than 20-fold and is heaviest in the cerebellar molecular layer and dentate gyrus. Lower levels of binding are found in cortex and striatum and very low levels are located in substantia nigra. This assay may help to clarify the role of complex I in neurodegenerative disorders. (Supported by the United Parkinson Foundation, the American Academy of Neurology, and USPHS Grants NS01487 and S7RR05403-29.)

P177. Have Adrenal-to-Brain Transplants Altered Progression of Parkinson’s Disease? A 4-Year Follow-Up
Shirley G. Diamond, Charles H. Markham, Robert W. Rand, and Donald P. Becker, Los Angeles, CA

In 1988, 4 patients with medically intractable Parkinson’s disease underwent autologous adrenal medullary-to-caudate transplants at the University of California–Los Angeles (UCLA). These persons had been followed for several years before operation at 3- or 4-month intervals. At each visit, their disability had been rated on the quantified UCLA scale and the Hoehn and Yahr stage of disease. These provided a longitudinal assessment of the progression of disease in each patient, which could be compared to the rate of progression in the cohort of cases followed at UCLA for 15 years. In addition, the Unified Parkinson’s Disease Rating Scale provided supplementary data for the immediate preoperative and subsequent postoperative evaluations. The hours “off” also were recorded for the preoperative and postoperative periods. After operation, the same evaluations were performed by the neurologist who previously had cared for the patients. The longitudinal postoperative data revealed that at 1 to 4 months after operation, all 4 patients improved. After 4 years, 3 continue to be less disabled than their preoperative baselines. The progression of their disease, while still evident, is nonetheless proceeding at a slower rate than before transplant. The fourth patient had brief improvement shortly after operation, but then rapidly worsened to his previous level. His disease has continued to progress at a rapid pace, unchanged from progression before operation.

P178. Positron Emission Tomography Scanning in Individuals at Risk for Huntington’s Disease
H. P. H. Kremer, W. Shtybel, B. Snow, C. Clark, J. Theilmann, M. R. Hayden, and W. R. W. Martin, Vancouver, BC, and Edmonton, Alberta, Canada

In Huntington’s disease (HD), caudate hypometabolism as demonstrated by positron emission tomography (PET) is a well-established feature in symptomatic patients. In individuals at risk, however, conflicting findings are reported. Since 1984 we have performed 61 PET scans in 44 asymptomatic persons at risk for HD (age 27–76 yr). Linkage analysis with 9 independent DNA probes or subsequent evolution to clinical HD (in 3 patients) allowed a risk estimate for 35 subjects. Twenty were considered to be at increased risk (>95%), 14 at decreased risk (<15%), and in 1 individual no modification could be given. Nine subjects were not tested. A PET scan was considered abnormal if either the caudate/thalamus ratio or the caudate/whole-brain ratio of rCMRGluc was more than...
2 SD below the mean of age-matched controls (n = 26). By these criteria, 8 scans in 6 individuals were abnormal. None had received a decreased risk. Comparison of the ratios of increased risk, decreased risk, unmodified risk, and control subjects failed to show statistically significant differences (analysis of variance). Follow-up of 3 persons with an abnormal scan showed conversion to symptomatic status within 5 years after the initial abnormal scan. This result suggests that an abnormal PET scan in a person at risk for HD heralds the onset of choreic movements.

P179. Striatal Dopamine in Dominantly Inherited Olivopontocerebellar Atrophy
S. Kish, Y. Robitaille, M. El-Assaw, B. Clark, L. Schut, M. Ball, L. Young, R. Currier, and K. Shannak, Toronto, Ontario, and Montreal, Quebec, Canada; Pittsburgh, PA, Minneapolis, MN, Portland, OR, and Jackson, MS

We measured the levels of dopamine in striatum of 14 patients with end-stage dominantly inherited olivopontocerebellar atrophy (OPCA). On average, dopamine levels were reduced in putamen (−53%), as compared with controls, caudate (−55%), and nucleus accumbens (−31%). However, individual patient values showed a wide variation (normal to −99%), indicating that striatal dopamine loss is a common, but not constant feature of OPCA. Seven patients had marked putamen dopamine loss (−62 to −81%) but without corresponding severe substantia nigra cell damage; this suggests a “dying-back” phenomenon in which nerve terminal loss precedes cell-body degeneration. In this regard, OPCA may offer the possibility of examining nigrostriatal dopamine neuronal degeneration at an early stage. Although 2 patients were found to have severe nigral cell loss with near total (−93 to −99%) striatal dopamine loss, none had received a clinical diagnosis of parkinsonism or antiparkinsonian medication. Clinicians involved in the care of OPCA patients should consider the possibility that a minority of their patients, although having a primary diagnosis of ataxia, may well have unrecognized and clinically significant parkinsonism. (Supported by US NINDS NS26034.)

P180. Serotonin Turnover Is Reduced with Levodopa
Jonathan H. Pincus and Patricia J. Karstaedt, Washington, DC

Depression in Parkinson’s disease (PD) has been correlated with low cerebrospinal fluid (CSF) levels of 5-hydroxydoleacetic acid (5-HIAA). l-dopa may precipitate or exacerbate depression in 30% of PD patients. To determine if l-dopa affects 5-hydroxytryptamine (5HT) metabolism, 8 patients were studied. Four had PD. Of these, 2 were taking l-dopa and both were depressed. The diagnoses in the remaining 4 were progressive supranuclear palsy (PSP), striatonigral degeneration (SND), normal pressure hydrocephalus, and pseudosseudes with depression. Neuropsychological examinations and LPs of all 8 patients were done. Three patients were started on l-dopa (the 2 previously untreated PD patients and the PSP patient) and retested 3 days later. One PD patient started on l-dopa became depressed. Mood in the others was unchanged. CSF was analyzed for 5HT and 5-HIAA. 5HT could not be detected in the CSF of patients who were not taking l-dopa, but was easily detectable in all of the patients who were taking l-dopa. 5-HIAA levels were low in the untreated PD patients, and also in the patients with PSP, SND, and pseudosseudes with depression. 5-HIAA levels were even lower in the l-dopa-treated patients. The ratio of 5-HIAA:5HT (an index of 5HT turnover) was lowest in the l-dopa-treated PD patients who were depressed. Low CSF 5-HIAA in untreated PD may reflect depletion of brain 5HT. l-dopa may induce depression by inhibiting 5HT turnover in 5HT-depleted brain.

P181. Ventroposterolateral Medial Pallidotomy in the Treatment of Parkinson’s Disease
E. Fazzini, M. Dogali, A. Beric, D. Eidelberg, J. Gianutsos, T. Kay, B. Newman, S. Loisius, D. Samelson, and L. Laritinen, New York, NY, and Stockholm, Sweden

In patients with Parkinson’s disease (PD), as a consequence of low dopamine there exists an increase in inhibitory output from the globus pallidus. Ten patients (5 men and 5 women) with PD received unilateral (6 right, 4 left) ventroposterolateral medial globus pallidotomy (VPLMP). The average patient age was 61 years (range 55–73 yr), and the average duration of disease was 14 years (range 6–24 yr). Patients fluctuated between “on” and “off” states and “on” was defined by Hoehn and Yahr stage “on” was II in 7, III in 3, and “off” was III in 5, IV in 2, and V in 3 patients. Unified PD Rating Scale (UPDRS) score averages 12 hours off medicines (12HOM) were Activities of Daily Living (ADL): 20 and Motor (MTR): 40 preoperatively (preop). CAPIT score averages preop 12HOM were pronation-supination (PS): 31 seconds (s), finger tap (FT): 31s, board (B): 39s for the most affected contralateral side, and gait: 57s (2 patients could not walk). Re-examination was done 2 to 5 days after pallidotomy. UPDRS scores 12HOM decreased an average of 60%. Three patients had major bilateral improvement in bradykinesia. Rest tremor, prominent in 3 patients, also was diminished. CAPIT scores 12HOM decreased to PS: 19s, FT: 20s, B: 22s; the average gait of the 8 patients who could walk preop improved to 36s. There were no side effects. VPLMP leads to an immediate overall significant improvement in patients with PD.

P182. Three Families with Dominantly Inherited Parkinsonism
Z. K. Wizolek, M. Cordes, C. Lee, I. Cordes, M. D. Muenter, R. F. Pfeiffer, and D. B. Calne, Omaha, NE, Vancouver, BC, Canada, and Scottsdale, AZ

There is a growing interest in the genetic aspects of Parkinson’s disease and other basal ganglia disorders. We have studied 3 families whose ancestors immigrated to North America from contiguous regions of northern Germany and southern Denmark. The pedigrees contain 77, 206, and 376 individuals spanning 6, 7, and 8 generations with 7, 6, and 9 affected members, respectively. Autosomal-dominant inheritance is clearly present in 2 families and probable in the third. Typical levodopa-responsive parkinsonism with bradykinesia, rigidity, resting tremor, and impaired postural reflexes uniformly develops in affected individuals from all 3 families. No downstate impairment, pyramidal signs, sensory disturbances, cerebellar dysfunction, or orthostatic blood pressure changes have been observed. Dementia, however, has developed in a few elderly individuals, especially in 1 family. Laboratory studies are normal. MRI shows moderately enlarged ventricles and cortical atrophy, 6-FlD positron emission tomography demonstrated reduced striatal uptake in 1 examined patient and normal uptake in 1 individual at risk. Autopsy of only 1 subject has been performed (1975). Brain weight was 1,380 grams and there were no obvious gross abnormali-
ties, but microscopic examination was limited. Further research on these 3 families is planned.

P183. Inherited Mirror Movements: An Electrophysiological Study
S. Mauri, M. Cincotta, A. Ragazzoni, G. DeCisciolo, and F. Barontini, Florence, Italy

Many neurophysiological examinations were conducted of a 32-year-old woman with familial mirror movements. No other neurological abnormalities were detected. Examination included voluntary electromyographic (EMG) activity from various muscles, F-wave as well as short- and long-latency reflex responses of the thenar muscles from electrical stimulation of the median nerve, mapping of motor-evoked potentials (MEPs) to transcranial magnetic stimulation, movement-related cortical potentials (MRCPs), and somatosensory-evoked potentials (SEPs). EMG documented mirror imitation of the median nerve, mapping of motor-evoked potentials from median nerve stimulation were reflex responses of the thenar muscles from electrical stimulation. Long-latency responses from median nerve stimulation were recorded on contralateral as well as ipsilateral thenar muscles. Short-latency reflexes and F wave were strictly ipsilateral. Unilateral scalp magnetic stimulation evoked bilateral responses at similar latencies in the thenar muscles; midline scalp stimulation activated no responses. Scalp distribution of responses was identical in active and mirror muscle. Onset latency of EMG activity in response to an auditory stimulus was identical in active and mirror muscle. Our findings suggest that congenital inherited mirror movements in otherwise normal subjects can be generated by corticospinal fibers projecting to ipsilateral motoneurons of the spinal cord.

P184. Effects of Apomorphine on Swallowing and Defecation in Parkinson’s Disease
R. F. Pfeiffer, L. L. Edwards, R. K. Harned, E. M. M. Quigley, and R. Hofman, Omaha, NE

We have previously identified dysphagia and constipation (both slow transit and defecatory dysfunction types) as common gastrointestinal (GI) problems in Parkinson’s disease (PD). Since apomorphine has been shown to be capable of terminating off-periods when injected subcutaneously, we have evaluated the effects of apomorphine injection on objective parameters of dysphagia and bowel dysfunction in PD patients. Nine subjects underwent the following battery of studies to characterize their PD features, swallowing, and bowel function: GI assessment survey, Unified PD Rating Scale, videoradiography, and anorectal manometry. Specific abnormalities on the studies were noted and the most abnormal study was repeated after subcutaneous administration of 6 mg apomorphine. All individuals were pretreated with domperidone 20 mg four times daily for 3 days prior to injection. Improvement in both esophageal motility and deglutition was noted in 1 individual in whom videoradiography was repeated. For the other 8 papers, defecography or anorectal manometry was performed. Significant improvement in specific parameters was demonstrated after apomorphine administration, but 2 individuals experienced syncpe during radiographic procedures. We conclude that subcutaneous apomorphine administration holds promise as a potential therapeutic approach to dysphagia and, especially, bowel dysfunction in PD, but that further investigation and refinement are necessary.

P185. Blinded Evaluation Confirms Long-Term Asymmetrical Effect of Unilateral Thalamotomy or Subthalamotomy on Tremor in Parkinson’s Disease
Nico Dauden, Christopher G. Gootz, Glenn T. Stibbins, Harold L. Klawans, K. Nittner, A. Kouloukis, F. Sander, and V. Stram, Cologne, Germany, and Chicago, IL

In the past, stereotactic operation was a regular treatment for unilateral tremor in Parkinson’s disease (PD). However, follow-up studies were usually short term and always unblinded. We examined 17 PD patients in long-term follow-up (mean 10.9 yr after operation) who underwent unilateral thalamotomy for parkinsonian tremor. We used videotapes and the Unified Parkinson’s Disease Rating Scale to blindly compare tremor ipsilateral and contralateral to the side of operation. Since the patients were specifically selected for stereotactic operation because of asymmetric tremor, we reasoned that a sign of long-term efficacy would be current postoperative reversal of tremor side predominance. Upper extremity tremor was significantly better contralateral to the side of operation compared to the ipsilateral side (Z = 3.29, p < 0.025). For the lower extremities the difference was not statistically significant. In chronic follow-up, stereotactic operation improved the absolute magnitude of arm tremor or ameliorated its rate of progression. Since symmetric bradykinesia and dyskinesia were not prerequisites for the choice of surgical side, we cannot make any conclusion about long-term impact of operation on these features.

P186. Cognitive Function in Normal Individuals with Subtle Extrapyramidal Signs Reminisce that of Patients with Parkinson’s Disease
M. Richards, K. Marder, L. Cote, Y. Stern, and R. Mayeux, New York, NY

To investigate the relationship between extrapyramidal signs (EPS) and cognition, EPS severity and neuropsychological function were assessed in 307 normal elderly individuals and 130 nondemented patients with idiopathic Parkinson’s disease (PD) from a community-dwelling cohort in New York City. Multivariate analysis of variance (MANOVA) indicated poorer neurocognitive performance (p < .001) in PD patients on verbal memory, orientation, verbal fluency, visuomotor construction, and psychomotor speed, but not naming, abstract reasoning, or matching. Controlling for EPS severity abolished these differences. One hundred fourteen (37%) of the normal individuals had subtle EPS (mostly postural abnormality, bradykinesia, or rigidity) but no identifiable neurological disorder. MANOVA indicated poorer neuropsychological test performance (p = .001) in these individuals than in normals without EPS on verbal memory, orientation, abstract reasoning, naming, verbal fluency, matching, and psychomotor speed but not visuomotor construction. We conclude that: (1) cognitive impairment in PD is specifically associated with EPS, and (2) a similar association occurs in individuals with subtle EPS but no neurological disorder. Whether this represents a preclinical stage of PD or AD is yet to be determined.

P187. Incidence and Prevalence of Huntington’s Disease in Olmsted County, Minnesota
Enure Kokmen, Fatma Sibel Ozekmekci, C. Mary Beard, and Peter C. O’Brien, Rochester, MN, and Istanbul, Turkey

There have been many studies of prevalence of Huntington’s disease (HD) in diverse populations around the world. To
study the incidence, we took advantage of the availability of detailed health care records for the population of Olmsted County, MN, from Mayo Clinic, its affiliated hospitals, Olmsted Medical Group, county hospital, state hospital, records of solo practitioners, nursing homes, death certificates, and autopsy records. We reviewed all records with a diagnosis of HD, Huntington's chorea, choreas major, and chorea otherwise unidentified, and sought evidence for progressive chorea, progressive cognitive and/or behavioral dysfunction, and family history compatible with autosomal-dominant inheritance with onset of symptoms in the period between January 1, 1950, and December 31, 1989, while the patient lived in the geographic boundaries of Olmsted County. We found 3 males and 6 females who met these criteria. Average annual incidence rate (age/sex adjusted to 1960 US white population) for HD for this 40-year period was 0.3 cases/year/100,000 population. We also estimated prevalence by taking account of in-migration, out-migration, and deaths. The age/sex adjusted (1960) prevalence for 1-1-60 was 7.5/100,000 and for 1-1-90 it was 2.4/100,000. The small number of cases caused the instability of the prevalence rates, but our rates are similar to rates reported in other populations.

P188. Psychogenic Movement Disorders: Diagnosis by Induction
Alton E. Bryant, III, L. Breeden Holli, John A. Hamjian, John D. Wooten, III, and Francis O. Walker, Winston-Salem, NC
We described 4 patients with unusual episodic movement disorders and normal diagnostic work-ups: a 34-year-old woman who had recurrent episodes of tonic jaw deviation and forced right-eye closure; a 30-year-old woman who developed unexplained pain and subsequent spells of tonic inversion of the left leg; a 61-year-old man who presented with a bizarre episodic right-arm tremor; and a 15-year-old woman who experienced intermittent abdominal undulations. Examination of the affected body part provoked or enhanced symptoms in all patients. Using suggestion and placebo activation in the form of a medicated patch, intravenous saline, or cervical massage, we first induced and then aborted typical episodes of their abnormal movements. Postinduction discussions of the procedure led to a marked reduction in the frequency of attacks in 2 patients. Activation procedures are useful in diagnosing psychogenic disorders because they demonstrate that situational, not medical, factors govern the expression of the abnormal behavior. We speculate that patients who are refractory to simple suggestion may respond to induction because it offers the potential of validating their symptoms. As in the case of psychogenic respiratory distress or pseudoseizures, positive induction can assist in counseling and symptom control.

P189. Clozapine for Movement Disorder Patients: A Retrospective Analysis of 38 Patients
Joseph H. Friedman, Margaret C. Lannon, and Charles Caley, Providence, RI
Since 1985 we have used clozapine in 39 patients with various movement disorders on 41 occasions. Thirty-three had Parkinson's disease (PD), 3 had tardive dystonia (Dys), 2 had Alzheimer's disease with parkinsonism (ADP), 1 had essential tremor (ET), 1 had cerebellar tremor in multiple sclerosis (MS), and 1 had tardive dyskinesia (TD). Clozapine was used either to treat psychosis (20 PD, 2 ADP, 3 Dys, 1 TD) or tremor (15 PD, 1 ET, 1 MS). Two PD patients were counted twice, 1 who was treated for psychosis and then tremor and 1 who was treated on 2 separate occasions for psychosis with different responses. All 3 Dys patients improved, 2 with complete resolution of their dystonia on changing antipsychotic drugs. The patients with ET (75 mg) and MS (25 mg) improved mildly but sedation and clumsiness caused drug discontinuation in the MS patient. One ADP patient (112.5 mg) responded well and the other became sedated and confused (25 mg). The PD responses for psychosis at a dose range of 6.25 to 400 mg daily were good (5), very good (2), and excellent (8), whereas 4 were intolerant. PD tremor responses were good (5), very good (4), excellent (2), and poor (3) at doses of 12.5 to 100 mg daily. One patient died of unrelated causes shortly after initiation of the drug. Adverse effects included sedation, weight gain, hypersalivation, fainting, clumsiness, transient granulocytopenia, and "spasms" necessitating discontinuation in 9 patients (7 PD, 1 TD, and 1 MS).

P190. A Comparison of Impaired Attention in Adult Tourette's Syndrome and Attention-Deficit Disorder Patients
S. M. Silverstein, P. G. Como, D. Palumbo, L. West, and R. Karlan, Rochester, NY
Impaired attention is a common comorbid behavioral feature of Tourette's syndrome (TS) and a key clinical feature of attention-deficit hyperactivity disorder (ADHD). However, the pattern of attentional impairments reported in ADHD has not been observed in TS. We therefore compared 17 TS patients (9 male, 8 female; mean age 32 ± 11 yr), 17 ADHD patients (8 male, 9 female; 36 ± 12 yr), and 17 normal controls (8 male, 9 female; 31 ± 9 yr) on specific neuropsychological (NP) and computer-administered tasks of attentional ability. ADHD, but not TS, subjects performed significantly worse than controls on the NP tasks (digit symbol, perceptual speed) and had a trend toward poorer performance on a computerized measure of attention. However, both the ADHD and TS groups had significantly greater test performance variability on some, but not all, tasks and had more subjects with deviant scores. Among TS patients, higher scores on an obsessive-compulsive disorder (OCD) inventory and a greater number of ADHD symptoms correlated significantly with poorer performance on the attentional tasks. Moreover, TS patients with observed tics during testing had greater attentional impairment than those without tics. These results suggest that: (1) many adult TS patients do not have impaired attention; (2) attentional impairment in TS differs from that observed in ADHD; and (3) attentional impairment in TS is associated with the full neurobehavioral spectrum of TS (i.e., tics, OCD, and ADHD).

P191. Pseudochoreoathetosis: Case Reports and a Hypothesis
Frank R. Sharp, Cathleen Miller, Thomas Rando, and Steven Grenberg, San Francisco and Palo Alto, CA
Six patients are described with choreoathetoid movements and marked proprioceptive sensory loss. One patient had a traumatic injury to the right parietal cortex that produced severe proprioceptive sensory loss and choreoathetosis in the left arm. Another patient had a left thalamic infarction that resulted in profound proprioceptive sensory loss and chorea on the right side of the body. Two patients had cervical spinal cord disease, proprioceptive sensory loss, and diffuse choreoathetosis. Another patient had dorsal root ganglionitis associ-
ated with small-cell lung carcinoma that produced diffuse loss of all sensory modalities and chorea. The last patient had an ulnar sensory neuropathy and choreic movements of the fifth finger. Lesions anywhere along the pathway that transmits limb proprioception may cause pseudochoreoathetosis. Furthermore, choreoathetosis without sensory loss caused by focal lesions of striatum may occur because of disruption of cortical proprioceptive inputs to striatum—perhaps explaining why most focal lesions of striatum do not produce chorea.

POSTER PRESENTATION: NEUROMUSCULAR DISEASE

P192. Immunoreactive β-Amyloid Precursor Protein, β-Amyloid Protein, and Ubiquitin in Vacuolated Muscle Fibers of Sporadic and Hereditary Inclusion-Body Myositis

Valeria Aikanas, W. King Engel, and Renate B. Alvarez, Los Angeles, CA

Sporadic inclusion-body myositis (S-IBM) and autosomal-recessive hereditary inclusion-body myositis (H-IBM) are of unknown cause and pathogenesis. In both there are muscle fibers with rimmed vacuoles containing 15- to 21-nm cytoplasmic tubulofilaments (CTFs) and denervation atrophy; in S-IBM, but not H-IBM, there is a varying degree of inflammation. Vacuolated fibers contain ubiquitinated inclusions (Aikanas 1991) and Congo-red positivity indicating amyloid (Mendell 1991). Because immunoreactive β-amyloid precursor protein (APP) and β-amyloid protein (β-AP) are constituents of ubiquitinated senile plaques in Alzheimer’s disease (AD) brain, we studied immunolocalization of APP and β-AP fibers in IBM muscle using antibodies against: (1) non-β-AP fragments of APP, viz. (a) C-terminus (residue 676-695 courtesy D. Selkoe) and (b) N-terminus (residue 43-62 courtesy B. Frangione and D. Levartovsky); (2) β-AP (sequence 8-17, courtesy G. Glenner, and sequence 1-40 courtesy D. Selkoe); (3) Ub (Chemicon). In 13 of 13 IBM patients, including one H-IBM, 100% of the vacuolated muscle fibers contained large or several small APP and β-AP immunoreactive (IR) inclusions, which by double-labeling fluorescence were closely colocalized with each other and with Ub-IR. None of 18 control muscle biopsy specimens (including 7 polymyositis) contained APP-IR, β-AP-IR, or Ub-IR inclusions characteristic of IBM. Control experiments utilizing omitted, replaced, or absorbed primary antisera were negative. β-AP, a product of proteolytic cleavage of APP, is receivng attention regarding the pathogenesis of AD. Our study provides (1) the first demonstration of APP and β-AP accumulations in abnormal human muscle, and (2) raises the possibility that in IBM muscle and AD brain they may form from similar cellular events.

P193. Chronic Glutamate Transport Defect: A Model of Motor Neuron Degeneration

Jeffrey D. Rothstein, Lin Jin, and Ralph Kuncl, Baltimore, MD

The pathogenesis of motor neuron death in amyotrophic lateral sclerosis (ALS) is unknown. Accumulating evidence suggests that the disease is characterized neurochemically by a derangement in the control of neurotransmitter glutamate metabolism. CSF levels of glutamate and aspartate are elevated and their high-affinity transporter is defective in brain and spinal cord. Inefficient glutamate transport, and subsequent chronic increase in extracellular glutamate, could be responsible for selective motor neuron death. To test the hypothesis that chronic defects in glutamate uptake can produce motor neuron toxicity, we developed a tissue culture model employing organotypic rat spinal cord maintained under conditions of chronic glutamate uptake inhibition. Slices (300 µM) of lumbar spinal cord from 8- to 14-day-old rat pups were cultured on multicelle membranes. Chronic uptake inhibition was produced by culturing tissue in the presence of threohydroxysapparate (THA) or pyrrolidine-dicarboxylic acid, both known to be specific inhibitors of glutamate transport. THA produced chronic elevation of glutamate in the medium and produced motor neuron toxicity after 25 to 30 days in culture using 100 µM THA, and after 18 days using 300 µM THA, as determined by assay of tissue choline acetyltransferase (ChAT) activity and by histological analysis of 1-micron plastic sections. Motor neuron toxicity was completely blocked by the non-N-methyl-D-aspartate (NMDA) antagonists CNQX or NBQX, but not by the NMDA antagonist MK-801. This model demonstrates that the chronic loss of glutamate transport in ALS can produce motor neuron degeneration and that motor neurons appear to be susceptible to non-NMDA-mediated glutamate toxicity.

P194. Nerve Conduction Studies in Young Guillain-Barré Syndrome Patients: Comparison to Patients with Chinese Paralytic Syndrome

D. R. Cornblath, G. M. McKhann, T. W. Ho, C. Y. Li, H. S. Wu, Q. F. Ye, W. C. Zhang, Z. F. Jiang, J. W. Griffin, and A. K. Ashbury, Baltimore, MD, Boston, MA, China, and Philadelphia, PA

Last year, we described a distinct acute paralytic syndrome in children and young adults from northern China and differentiated it from Guillain-Barré syndrome (GBS) by epidemiological, clinical, and nerve conduction (NC) features. To distinguish Chinese paralytic syndrome (CPS) from GBS more clearly, we measured NC in 21 CPS patients (mean 8 yr, range 1.5-35 yr) and in 21 GBS patients from Johns Hopkins (mean 14 yr, range 5-24 yr). Sensory NC was normal in all (n = 62) but 1 nerve of CPS patients, whereas sensory NC was frequently abnormal in GBS patients: median nerve, 65%; ulnar nerve, 87%; and sural nerve, 21%. Motor NC also differed between the groups. In all nerves, distal latency (DL) was significantly longer in GBS than in CPS. For example, in the median nerve, mean DL was 8.6 ms (SE 1) in GBS and 2.8 ms (0.2) in CPS (p < 0.005). Motor conduction velocity was significantly reduced in GBS median and ulnar nerves compared with CPS nerves. F-wave latency was significantly longer in GBS median nerves than in CPS nerves. These data support the distinction both clinically and electrodagnostically between CPS and North American GBS. The use of NC may be especially important in field epidemiological studies in separating the 2 disorders.

P195. Familial Amyloidotic Polynuropathy Type IV: Clinical Manifestations and Gene Analysis of the First Japanese Kindred

Yoshihide Sunada, Teruo Shimizu, Ichiro Kanazawa, and Toru Mannen, Tokyo, Japan

Familial amyloidotic polyneuropathy type IV (FAP IV) has been clustered in the Finnish population and only a few cases have been reported from the Netherlands. Denmark, and
United States. We describe the first Japanese family with FAP IV. The family originates from Nagano prefecture, a mountainous district in middle part of Japan, and has no relationship to the Finnish population. This family has 42 members in 3 generations, and 14 individuals are affected. Polarizing microscopy and immunohistochemistry show abundant amyloid deposits reactive to an anti-gelsolin monoclonal antibody. Direct sequence analysis of a DNA fragment spanning codon 187 of the plasma gelsolin cDNA from the propositus, and restriction analysis using a modified PCR from other family members demonstrate a single base substitution, G to A at the first base of codon 187, which is identical to the mutation of Finnish FAP IV. This suggests that the mutation causes the FAP IV phenotype regardless of ethnic background.

P196. Focal Skeletal Muscle Injury Induces a Selective and Specific Pattern of Immediate Early Gene Expression
Sawsan Abu Shakra, Andrew J. Cole, and Daniel B. Drachman, Baltimore, MD

Focal puncture injury has been used as a model to study degenerative and regenerative responses of skeletal muscle. Previous studies have demonstrated the ultrastructural and metabolic effects of muscle injury. However, the early genomic response to focal injury is presently unknown. We asked whether the immediate early genes (IEGs) or early response genes—zif268, c-jun, nur77, and junB—are responsive to muscle injury. These IEGs encode transcription factors and are expressed rapidly after cell-surface stimulation. We have previously shown that surgical denervation and neural stimulation of muscle induced differential patterns of IEG expression. In this study, we produced injury of mouse gastrocnemius muscle by injection of 20 μl of normal saline. We used the contralateral (uninjected) muscle as a control and examined the mRNA levels of each of these 4 IEGs. We found that zif268 and junB were increased at 1 and 4 hours and returned to basal levels by 24 hours. In contrast, mRNA levels of nur77 and c-jun remained unchanged. This pattern of IEG expression is distinct from that seen after muscle stimulation or denervation. The selectivity of this pattern suggests that IEG expression may play a role in the response of muscle to injury.

P197. Molecular Studies of Motor Neurons (MN) Using Clonal Hybrid Cells Derived from Mouse Spinal Cord MN
Edgar F. Salazar-Greues, Howard Kim, and Sandra Kim, Chicago, IL

Amyotrophic lateral sclerosis (ALS) is a degenerative disease that leads to the restricted loss of motor neurons (MN). The reason for the selective death of MN remains unknown. We hypothesize that MN-enriched or MN-specific genes are important for normal MN function and that their disturbance may play a role in the pathogenesis of ALS. We have produced clonal hybrid cells derived from embryonic and neonatal spinal cord MN for the study of MN gene properties. Some of these hybrid MN clones express traits typical of MN, such as high levels of choline acetyltransferase enzyme activity and message, glycine receptor message, and neurofilament and neural cell adhesion molecule proteins. We are using molecular techniques to identify novel MN-enriched or MN-specific genes in these cells. With this strategy, we have identified several cDNA clones preferentially expressed in MN hybrid cells but not in the parental neuroblastoma cells by differential hybridization of an embryonic MN hybrid cDNA phage library. We are extending these observations by performing subtraction hybridization experiments.

P198. Intravenous Immunoglobulin: Excellent Benefit in Otherwise Refractory Progressive Muscular Atrophy with IgM Monoclonal Gammopathy
W. King Engel and Carol J. Hanna, Los Angeles, CA

There is a syndrome of slowly progressive, mid-adult–onset fasciculating progressive muscular atrophy (PMA) affecting upper more than lower limbs, without bulbar or corticospinal signs, more often in males, associated with IgM monoclonal gammopathy, and no nerve conduction block. Two such men, ages (A) 59 years and (B) 64 years, duration 11 and 3 and one-half years, CSF protein 28 and 60, had failed to achieve sustained improvement with: prednisone, cyclophosphamide, total-body irradiation, and multiple lymphoplasmaphereses in A; and interferon alpha 2A in B. Intravenous immunoglobulin (IVIg), 0.4 gm/kg/day, has provided dramatic benefit, sustained and increasing for >5 and >4 months to date. (There is a continuing base of depo-testosterone, 200 mg weekly, which initially alone provided very minimal improvement.) Strength increase was evident at 1 and 3 days after the first course of 5 daily IVIg infusions. It further increased for 2 to 2 and one-half weeks after treatment, and then began to diminish. Repeat 5-day treatment 3 weeks after the first course resulted in summated improvement, now sustained and enhanced by an average of 1 treatment per week. Quantitated strength testing by a blinded observer has shown a 2-fold to >100-fold gradually increasing muscle function in all limbs. Patient A regained the ability to feed himself, get out of a chair, walk unaided, and go up steps; quantitated hip flexors increased 2- and 20-fold. Patient B regained the ability to feed himself, take care of personal toilet needs, walk securely, and drive 500 miles; quantitated hip flexors increased 5-fold, and biceps flexions increased from 0 with no weight to >130 reps while holding 10-pound weights.

P199. Oculopharyngeal Muscular Dystrophy Among Bukhara Jews: A New Cluster with Typical Intranuclear Inclusions
S. C. Blumen, M. Sadeh, P. Nistiass, A. D. Korczyn, Y. Wirguin, and F. M. S. Tome, Kefar Sava, Tel Aviv, and Jerusalem, Israel, and Paris, France

Oculopharyngeal muscular dystrophy (OPMD) is a rare, late-onset myopathy with autosomal-dominant inheritance. Its ultrastructural hallmark is the finding in muscle fibers of intranuclear tubular filaments of 8.5-nm outer diameter. Most OPMD cases were described among French Canadians; in France, the homeland of their ancestors, the prevalence is 1/200,000 (Brunet et al, 1990). In Israel's central area live approximately 40,000 Jews who have immigrated from the Bukhara and Samarkand regions in Uzbekistan. They represent a homogeneous ethnic group with its own language and community life. Among them we have identified OPMD in 15 families (55 affected individuals). The inheritance, clinical, electrophysiological, and histological features of these pa-
Patients are similar to those described in other parts of the world, with typical intranuclear inclusions seen on electron microscopy. The minimal estimated prevalence of OPMD in this population is approximately 1:750. This cluster of OPMD among Bukhara Jews is the second largest in the world. Because many Bukharan families are large, they may be suitable for linkage genetic studies.

P200. Human Lymphocyte Antigen Expression in Human Muscle during Ontogenesis

E. Scarpini, G. Conti, P. L. Baron, and G. Scarlato, Milan, Italy

Myoblast transfer has been proposed recently as a possible therapy for Duchenne muscular dystrophy patients. Because immune rejection can represent a major problem in myoblast implantation, immunological characteristics of human muscle should be investigated. Previous studies showed that human muscle cells cultured in vitro can constitutively express human lymphocyte antigen (HLA) class I, but not HLA class II. Furthermore, human γ-interferon induces the surface expression of HLA class II on mononuclear myoblasts, but not on multinucleated myotubes. However, whether the cells produce and present the antigen by themselves or take this material from the environment, where it could be released by infiltrative cells, is not yet clear. In this study, we analyzed HLA molecules at the protein level by immunocytochemistry with monoclonal antibodies against different HLA-DR epitopes and HLA-ABC molecules on frozen serial sections of human muscle during development and at the adult stage. Human muscle infiltration by macrophages and monocytes-macrophages also were studied with M718- and LeuM3-specific monoclonal antibodies at the same stages of development. Our results show that during muscle development and maturation, HLA-DR and HLA-ABC antibodies do not label muscle fibers but some M718- and LeuM3-positive cells within the muscle. These data can be useful to understand the role of infiltrating monocytes-macrophages in the muscle immune response.

P201. Long-Term High-Dose Dextromethorphan in Amyotrophic Lateral Sclerosis

D. Hollander, J. Pradas, R. Kaplan, H. McLeod, W. Evans, and T. Munisat, Boston, MA, Barcelona, Spain, and Memphis, TN

Mounting evidence suggests that excitotoxicity, mediated via the glutamate receptor, is involved in the pathogenesis of amyotrophic lateral sclerosis (ALS), as well as in other neurological diseases. We therefore initiated an open label, phase, I trial of high-dose dextromethorphan (DM), a noncompetitive, selective N-methyl-D-aspartate antagonist, in ALS. Patients began with 2 mg/kg/day, divided into 4 doses, and incrementally escalated their medication to 10 mg/kg/day or their maximum tolerable dose. Thirteen patients, all extensive metabolizers of DM, were enrolled. Total daily doses ranged from 4.75 to 10 mg/kg. Major side effects were light-headedness (8), slurred speech (7), and fatigue (6). No biochemical, hematological, or neuropsychiatric abnormalities occurred after up to 6 months of maximal therapy, except for depression in 1 patient. Plasma kinetics of dextrophorphan (DT) (the major metabolite of DM) were studied after an acute oral dose of 2.5 mg/kg DM. Median elimination half-life was 2.5 hours. Plasma DT concentration peaked at a median of 2 hours, with a median Cmax of 14.4 μM. Median cerebrospinal fluid/plasma DT ratio was 9.7%. This study demonstrates the feasibility of long-term, high-dose DM therapy. We are now conducting a phase II study of high-dose DM in ALS, designed to assess its efficacy.

P202. Acquired Pure Sensory Demyelinating Polyneuropathy: A Chronic Inflammatory Demyelinating Polyradiculoneuropathy Variant?

D. Cros, K. H. Chiappa, S. Patel, and S. Gominak, Boston, MA, and Sunnyvale, CA

We describe 4 patients (3 men, 1 woman) with a pure, adult-onset sensory neuropathy. The course was chronic in all cases. Three patients had a relapsing-remitting course over 2 to 22 years with several attacks every year; the onset was gradual and followed by a plateau in the fourth patient. All patients had positive and negative sensory symptoms, and 2 had positive motor symptoms (fasciculations). In all patients, muscle power was normal at the time of peak deficit. All were areflexic and had large fiber sensory deficits, and 3 patients had sensory ataxia. Three patients had elevated CSF protein, whereas the CSF was normal in 1 patient. MRI demonstrated marked thickening of the lumbosacral spinal roots in 1 patient. Motor conduction studies were normal in all patients, but mild F-response abnormalities were noted in 2. Neuropathological investigations of the sensory pathways were abnormal in all. Three patients had several studies over a 2-year period. Sensory nerve action potentials were unobtainable in 2 patients, and normal in the others. Median and tibial somatosensory-evoked potentials showed conduction slowing consistent with demyelinating lesions affecting the peripheral sensory pathways, either globally or focally in the proximal segments. Two patients appeared to respond to plasma exchange or intravenous immunoglobulin therapy, or both.

P203. Developmental and Topographic Expression of Gial Fibrillary Acidic Protein Cells in Experimental Motoneuron Disease

Raul N. Mandler, Pam C. Allgood, and James A. Wallace, Albuquerque, NM

Neuronal degeneration in human and animal motoneuron disease has been emphasized, but gial phenotype alterations have not been studied as extensively. We carried out a developmental and topographic study of astrocyte expression in the Wobbler mouse model of motoneuron disease. Wobbler mice and normal littermates were studied at 3, 4, 5, and 6 weeks of postnatal development. Anesthetized animals were perfused intracardially with paraformaldehyde. Spinal cords were dissected and landmarks were identified carefully for systematic study. Sections were stained with monoclonal antibodies against gial fibrillary acidic protein (GFAP) neurofilament and neuron-specific enolase. Cell quantitation was done with video-enhancing microscopy. In symptomatic animals, marked increases in GFAP staining were found in rostral and caudal spinal cord areas. Quantiative studies revealed a 15- to 20-fold increase in GFAP+ cells in the Wobbler. We conclude that GFAP+ cells are markedly increased in the Wobbler mouse at cervical, thoracic, and lumbar areas. This cell may also be relevant in motoneuron disease pathogenesis. (Supported by NIH grant NS 27698 to R.N.M.)
P204. Polio Virus RNA Is Not Found in Central Nervous System Tissue of Patients with Old Poliomyelitis

Henry J. Kaminski, Edward Hogan, Robert A. Fenstermaker, Eric Martin, and Robert L. Rajff, Cleveland, OH

Indirect evidence suggests that polio virus may persist in the human CNS years after initial infection and may be a cause for the post-polio syndrome. To evaluate whether the polio virus genome can be detected in the CNS of patients with previous polio infection, we identified 11 patients who had died with autopsy findings and clinical history consistent with poliomyelitis. RNA was extracted from paraffin-embedded sections of brain or spinal cord and subjected to reverse transcription followed by DNA amplification by polymerase chain reaction (RT-PCR) using primers specific for heat shock protein 70 (hsp70) and a conserved region of the polio viruses. Hsp70 mRNA could be detected in all specimens, indicating that amplifiable RNA had been isolated. In no specimens could polio virus RNA be detected. This study suggests that polio virus does not persist in the human CNS in quantities detectable by the sensitive PCR method. (Supported by a grant from the Ohio Regents Fund, Merit Review Committee, and a Career Development Award [HJK] from the Department of Veterans Affairs.)

P205. Selective Calf Weakness as a Distinguishing Feature of Distal Spinal Muscular Atrophy

Kevin B. Boylan and David R. Cornblath, Jacksonville, FL, and Baltimore, MD

Weakness in Type I and Type II Charcot-Marie-Tooth (CMT) neuropathy is prominent in ankle dorsiflexion and eversion (anterior compartment muscles), a distribution of weakness also reported in distal spinal muscular atrophy (SMA). Borque and Dyck (Arch Neurol 1990;47:79), however, noted distal SMA with weakness of ankle plantar flexion (posterior compartment muscles) exceeding anterior compartment weakness, and selective calf weakness was not seen in their patients with CMT Type I. We reviewed records of 66 unrelated patients (44 male, 22 female; ages 10–86 yr) with CMT Type II, seen at Mayo Clinic Rochester between 1981 and 1991, for the frequency of selective calf weakness in CMT Type II, the form of CMT most similar clinically to distal SMA. Anterior compartment weakness exceeded calf weakness in 49 patients (74%); anterior and posterior involvement was equal in 16 (24%). Calf weakness exceeded anterior compartment weakness in 1 patient (2%). Selective calf weakness in distal SMA thus helps distinguish this disorder from CMT Type II, and similarly from distal SMA with weakness resembling CMT, in that we are unaware of the 2 distributions in distal SMA occurring in the same family. Given the possibility of genetic heterogeneity, linkage studies of distal SMA probably should include patient selection criteria such that the distribution of leg muscle weakness is homogeneous.

P206. Conjugal Amyotrophic Lateral Sclerosis: Clue to Etiology?

David R. Cornblath, Kevin Boylan, Leslie Morrison, and Maxine Montgomery, Baltimore, MD, Jacksonville, FL, and Lancaster, PA

Amyotrophic lateral sclerosis (ALS) is a sporadic neurodegenerative disorder of unknown cause. Unusual cases may provide etiologic clues. We report a married couple, both of whom developed ALS in 1 year. The couple grew up in southeastern Pennsylvania and attended the same schools. They married after high school and have 2 healthy children. In September 1990, a 38-year-old woman noted right-hand weakness and associated fasciculations that progressed to the entire right upper extremity. By January 1991, the lower extremities were asymmetrically weak and fasciculating. She then developed left-arm weakness, dysarthria, dysphagia, and emotional incontinence. She had hyperreflexia and bilateral extensor plantar responses. Then, in May 1991, her husband, aged 38, noted difficulty whistling, which progressed to frank dysarthria. Later, he developed dysphagia, emotional incontinence, and weakness, wasting, and fasciculations in the upper extremities. Hyperactive gag, jaw, and limb reflexes were present. In both, electrodiagnostic testing revealed widespread evidence of lower motor neuron degeneration. Numerous laboratory tests were normal. Although these cases may represent a chance association, the development of ALS in a young husband and wife suggests a possible environmental cause. The authors welcome suggestions about these cases from the neurological community.

P207. The Relative Contributions of Conduction Block and Phase Cancellation to Reductions in M-Potential Size in Demyelinating Neuropathies

W. F. Brown and B. V. Watson, London, Ontario, Canada

Conduction block in demyelinating neuropathies usually is assessed from differences in the sizes of surface-recorded maximum M-potentials evoked by supramaximal stimulation at successively more proximal sites along the course of motor nerves. As the maximum M-potential is comprised of many bitrophic surface-recorded motor unit action potentials (MUAPs), differences in the relative latencies between MUAPs may lead to phase cancellations, reducing the M-potential size and rendering any quantitative assessment of the extent of conduction block relative to phase cancellation difficult. Cooling a muscle (not the nerve), however, by as much as 15°C increases the negative peak durations of MUAPs by as much as 2 to 3 times and moves the point at which maximum phase cancellation might occur to some theoretical point well proximal to the spinal roots. In 5 cases of Guillain-Barré syndrome (GBS) studied to date, cooling produced little change in percent reductions in M-potential negative peak areas between successively more proximal sites of stimulation. This finding suggests that "true" conduction block rather than interpotential phase cancellation best explains reductions in M-potential size at successively more proximal sites of stimulation in GBS.

P208. Sensory and Autonomic Polyneuropathy Associated with Trimethoprim-Sulfamethoxazole

William Craven and Peter D. Donofrio, Winston-Salem, NC

Rare cases of primarily motor polyneuropathy have been associated with the use of sulfonamides. The incidence of polyneuropathy has diminished substantially with the abandonment of earlier methylated compounds. We describe 2 patients who developed allergic phenomena, including a skin rash and debilitating, painful sensory and autonomic polyneuropathy within days of receiving trimethoprim-sulfamethoxazole. In 1 patient, examination revealed resting tachycardia, marked blood pressure orthostasis and near-
fluid was acellular with a protein of 141 mg/dl. The other distal vibration perception, and hyperpathia of hands and feet. Conventional nerve conduction studies demonstrated normal motor results in both patients, absent or reduced sensory amplitudes in the first patient, and normal sensory results in the second. Autonomic studies identified profound abnormalities in testing of sympathetic skin potentials, sinus arrhythmia, and Valsalva's ratio. In both cases, nerve biopsy was not performed for fear of exacerbating the patient's hyperpathia. Subsequent hemodynamic and electrophysiological testing showed improvement in autonomic function, paralleling the patients' clinical amelioration. Although uncommon, a painful, sensory and autonomic, partially reversible polyneuropathy may develop after the use of tri-methoprim-sulfamethoxazole.

P209. Serial Single-Fiber Electromyographic Studies in Patients With Focal Laryngeal Dystonia Following Botulinum A Toxin Injections

M. Kathleen Donovan, Mark C. Weissler, Stanley J. Martinskisky, and James F. Howard, Jr, Chapel Hill, NC

The remote effects of botulinum A toxin injections into vocalis muscles for treatment of focal laryngeal dystonia were investigated using single-fiber electromyography (SFEMG). Botulinum A toxin injections have been proven effective therapy for various dystonic disorders including focal laryngeal dystonia, blepharospasm, and torticollis. Previous SFEMG studies have demonstrated remote effects of the toxin in noninjected muscles after treatment for both blepharospasm and torticollis. These effects include an increase in fiber density, mean jitter (MCD), and percentage of fiber pairs with increased jitter. Other researchers have postulated that the distant effects of this toxin may be related in part to the dose of botulinum toxin injected. To investigate this hypothesis we have studied patients treated for focal laryngeal dystonia because the amounts of toxin required are 1/25th to 1/100th of the doses used to treat other dystonias. Using electromyographic (EMG) guidance, bilateral injections of 2.5 or 5.0 mouse units of botulinum A toxin were injected into each vocalis muscle of 11 patients. Each patient had significant improvement in phonotory function within 48 hours after injections and have been followed serially (usually within 3 weeks and again at 2 mo) after injections, with SFEMG recordings of the left extensor digitorum communis and sternocleidomastoid muscles. Five patients have had more than 1 series of injections over the 10 months since we began this study. SFEMG studies have revealed no significant change in the fiber density, mean MCD, or percent of fiber pairs with normal jitter in either muscle. In conclusion, our studies support the hypothesis that the presence of remote effects of botulinum toxin may be related, in part, to the amount of toxin used.

P210. Onset of Polymyositis and Dermatomyositis During Pregnancy: Report of 4 Cases

Carlos Otero and Martina C. Dalakas, Bethesda, MD

Four patients developed polymyositis (PM) or dermatomyositis (DM) during pregnancy or puerperium. Patient 1, a 35-year-old woman, developed severe muscle weakness, myoglobinuria, elevated serum creatine kinase (CK), and histological features of DM at the nineteenth week of gestation. Patient 2, a 25-year-old woman, developed slowly progressive muscle weakness, elevated CK, and histological features of PM 3 weeks after cesarean section. Patient 3, a 37-year-old woman who started with mild myopathic muscle weakness after delivery, developed a full-blown clinical and histological picture of DM within the next 3 months. Patient 4, a 25-year-old woman who had mild weakness 4 months before pregnancy, developed typical clinical and histological features of PM during the first trimester. All patients, followed for a mean period of 6 years from onset, had poor-to-mild response to various immunotherapies. Except for the relative refractoriness to therapy, no other clinical, histological, or laboratory finding distinguished these patients from the nonpregnancy-associated PM or DM. We conclude that PM or DM can begin or worsen during pregnancy or after delivery; thus, the immunosuppressive state associated with pregnancy may not always be sufficient to protect the immune factors that trigger the disease. Because of poor response to therapies, management of such cases with aggressive and potentially teratogenic immunotherapies may be reconsidered. PM and DM are autoimmune neuromuscular diseases associated with or aggravated by pregnancy.

P211. C57BL/6/Ola Axons Show Rapid Degeneration in a High-Calcium Environment

Jonathan D. Glass, Edwin B. George, and John W. Griffin, Baltimore, MD

The C57BL/6/Ola mouse exhibits the remarkable characteristic of prolonged survival of axons separated from their cell bodies (slow Wallerian degeneration). Previous work has demonstrated that the axon itself is responsible for the phenotype of prolonged survival. We investigated whether the lack of rapid axonal degeneration after axotomy in this substrain is due to an inability to break down cytoskeletal components, a process that is normally accomplished by activation of intrinsic calcium proteases. Segments of desheathed sciatic nerves from normal and Ola mice were incubated for 2 hours under conditions that disrupt the axolemma (freeze/thaw or in 1% triton x-100), allowing external calcium free access to axoplasm. Nerves were analyzed by Western blot for neurofilament (NF) proteins and by electron microscopy. In high-calcium media (1 mM CaCl2), NF immunoreactivity was lost and axoplasm was reduced to watery debris in both substrains, whereas in EGTA-buffered media, axoplasm was preserved. These results demonstrate that calcium-activated proteases are present and can be activated in Ola nerves. The defect in these mice that allows for prolonged survival of transected axons is likely in the mechanism for calcium entry into the distal stump.

P212. Effect of Cisplatinum and ACTH4-10 on Neural Transport in Cisplatinum-Induced Neurotoxicity

James W. Russell, Anthony J. Windebank, Daniel J. Brat, Mark A. McNiven, and W. Stephen Brimijoin, Rochester, MN

The mechanism by which the analogue of adrenocorticotropic hormone, ACTH4-10, prevents cisplatinum (CP) neurotoxicity is unknown. Murine N1E-115 neuroblastoma cells and neural crest-derived, squirrel fish erythrophore cells
have similar vesicular transport mechanisms to human neural cells. They were used to study the effects of CP and ACTH₄₋₉ on cellular transport. Differentiated N1E.115 cells were treated 1 hour prior to observation with serum-free media (SFM, control); SFM/CP 5 µg/ml or SFM/CP 5 µg/ml and 100 ng/ml ACTH₁₋₉. Organellar transport was studied (7 neurons and 100--140 organelles per condition) using computer-enhanced video microscopy. Mean fast anterograde (1.00 ± 0.7 µm sec⁻¹ vs 1.65 ± 0.7 µm sec⁻¹) and retrograde (0.67 ± 0.04 µm sec⁻¹ vs 1.19 ± 0.05 µm sec⁻¹) transport were decreased in CP-treated compared to control cells (p < 0.0001). In CP/ACTH₄₋₉-treated cells, mean anterograde (1.46 ± 0.07 µm sec⁻¹) and retrograde (1.13 ± 0.04 µm sec⁻¹) velocities were greater than in CP cells (p < 0.0001). Velocities in control and CP/ACTH₄₋₉ cells were not statistically different. Erythrophagocyte particle transport was observed in a blinded study, using similar techniques. Mean aggregation velocity was greater in control (1.99 ± 0.09 µm sec⁻¹) and CP/ACTH₄₋₉ (1.97 ± 0.07 µm sec⁻¹) treated cells compared to CP (1.43 ± 0.07 µm sec⁻¹) cells (p < 0.0001). Incubation with CP for 1 or 72 hours affected velocities equally, but acute exposure was more easily reversed by control or ACTH₄₋₉ containing media. There is striking inhibition by CP in cross-species models of organellar transport. This can be prevented by ACTH₄₋₉. Erythrophagocytes allow future study of individual transport components.

P213. A Consensus Secondary Structure in a Neurontrophin Receptor Monomer Involved in Neurite Growth

R. J. Roppelle, S. M. Myers, S. M. Dustaler, D. F. Weaver, and R. A. Murphy, Kingston, Ontario, and Montreal, Quebec, Canada

To investigate signal transduction pathways involved in neurite growth, the cytoplasmic regions of p75NGFR, the common neurotrophin receptor monomer, were searched for a motif analogous to the predicted secondary structure of the tetradecapeptide mastoparan. Potential sequences were modeled using a semi-empirical molecular mechanical force field approach. The sequence rat p75NGFR 367-379 represents a highly conserved amphiphilic domain predicted to be involved in neurotrophin signal transduction via G-protein mechanisms. To test this prediction, peptides containing sequences homologous to p75NGFR 367-379 were examined for effects on trophic factor-induced survival/differentiation responses of rat PC12 pheochromocytoma cells. Peptides mutated to alter cationic amino acid relationships or amphiphilicity were less effective than the peptide identical to p75NGFR 367-379. When the plasmid P0 promoter ligated to the reporter gene chloramphenicol acetyltransferase (CAT) was used in transient transfection assays, the combination of T antigen and the protooncogene c-jun downregulated CAT expression. In Schwann cells, T antigen also induces the expression of c-jun mRNA, and the two proteins T antigen and c-jun formed an immunoprecipitable complex. Using Hela cell extracts in an in vitro transcription assay followed by primer extensions analysis, the combination of T antigen and c-jun downregulated transcription from the P0 promoter. Furthermore, DNA binding analysis lead to the identification of the sequence on the P0 enhancer that bound purified T antigen. Antisense experiments and inactivation of the P0 gene by homologous recombinations by other investigators have shown that failure to express P0 protein leads to the failure of myelin formation. Thus, we believe that T antigen/c-jun complex by downregulating P0 expression causes the lack of myelin formation in the peripheral nervous system. (This work was supported by funding from the NIH and the National MS Society.)

P214. An Ongoing Signal Sustains Nerve Growth Factor Receptor Expression in Injured Motor Neurons

R. G. Wiley, D. M. Green, M. Meier, L. J. Moix, and D. M. Armstrong, Nashville, TN, and Washington, DC

Crushing the hypoglossal nerve causes hypoglossal motor neurons to decrease expression of choline acetyltransferase (ChAT) and begin expressing p75NGFR, the low-affinity NGF receptor. These changes are evident within 3 days after the injury and continue for several weeks. Inhibition of axonal transport by vincristine applied to uninjured nerves causes loss of ChAT expression without induction of p75NGFR. We sought to determine if topical vincristine would alter p75NGFR expression after nerve injury. Hypoglossal nerves were surgically exposed unilaterally in anesthetized rats and crushed. One week later, rats were reanesthetized and the same nerves were re-exposed. Vincristine or saline was applied at the crush sites by soaking a strip of cotonoid wrapped around the nerves. One week later, rats were anesthetized and perfused with aldehydes. Frozen sections from the brains were stained by indirect immunoperoxidase to demonstrate ChAT and p75NGFR were stained by indirect immunoperoxidase to demonstrate ChAT and p75NGFR, the low-affinity NGF receptor. There was a reduction in ChAT and p75NGFR in hypoglossal motor neurons ipsilateral to the crush injury. Vincristine-treated animals showed no ChAT and no p75NGFR. We interpret these results as indicating that a signal originating from the injury site maintains p75NGFR expression after nerve injury.

P215. Down-Regulation of Myelin P0 Protein by T Antigen

V. Bharrucha and G. Tennekoon, Ann Arbor, MI

T antigen is responsible for the human demyelinating disease progressive multifocal leukoencephalopathy as well as for experimental dysmyelination in rodents. Schwann cell lines, expressing large amounts of T antigen when co-cultured with dorsal root ganglia, recognized and segregated neurites but failed to form myelin, whereas cell lines expressing lower amounts of T antigen myelinated the neurites. Investigation of this observation showed that there was an inverse relationship between the amounts of T antigen and of P0 proteins. Thus, we believe that T antigen/c-jun complex by downregulating P0 expression causes the lack of myelin formation in the peripheral nervous system. (This work was supported by funding from the NIH and the National MS Society.)
P216. Catecholamine Toxicity to Cultured Oligodendrocytes Can Be Prevented by Cultulate and Astrocytes

Paul G. Noble, J. P. Anist, and V. W. Yong, Montreal, Quebec, Canada

Catecholamines have been reported to be toxic to embryonic-derived rat neurons and glia via the formation of reactive oxygen species (Rosenberg, 1988). We tried to determine whether oligodendrocytes (OL) from adult 6-month-old rat brain are similarly susceptible. Toxicity to OL was examined using light microscopy and galactocerebroside immunohistochemistry where the relative number of surviving OL and their extent of process formation were graded. Five days of exposure to norepinephrine (NE) and epinephrine (EPI) at 10 and 100 μM produced significant toxicity (p < 0.05, analysis of variance [ANOVA]) to adult rat OL; this toxicity was evident by 24 hours of exposure. Treatment with catalase (50 μg/ml), a free-radical scavenger enzyme, completely prevented the toxicity of catecholamines. To ascertain whether astrocytes, which have free-radical scavenging capacity, could prevent the catecholamine-induced injury to OL, rat OL were seeded on neonatal rat astrocytes. Under such conditions, the toxicity of NE and EPI was reduced significantly (p < 0.05, ANOVA). These findings suggest that impairment of this protective function of astrocytes may render OL and its myelin membrane susceptible to free-radical–mediated damage.

P217. Nicotinic Stimulation and Cation Influx Induce a Selective Increase in Immediate Early Gene mRNAs in Muscle Cells

Sawsan Abu-Shakra, Robert N. Adams, Andrew J. Cole, and Daniel B. Drachman, Baltimore, MD

Muscle acetylcholine receptor (AChR) synthesis is closely regulated by the state of neuromuscular activity. Denervation causes an increase in AChR subunit gene expression, while direct electrical stimulation of muscle downregulates AChR subunits. We have previously shown that carbachol (a cholinergic agonist) decreases AChR α-subunit message levels in primary rat muscle cultures 24 hours after treatment. However, the early genomic regulatory events induced by cholinergic treatment are unknown. Immediate early genes (IEGs), which encode transcription factors and are induced rapidly after cell-type stimulation, are candidates for such a role. We studied the expression of 4 IEGs (zif268, c-jun, nur77, and junB) in the mouse skeletal muscle cell line—C2—-that normally fuses and expresses AChRs. Treatment of C2 mouse skeletal muscle cells with carbachol induced increased zif268, c-jun, and nur77 mRNA levels 3 hours after treatment, while junB message levels showed no consistent change. This effect was blocked by α-bungarotoxin pretreatment. In addition, A23187 and Veratridine, which cause a cation influx of Ca2+ and Na+ ions, respectively, induced a similar pattern of IEG expression. This suggests a role for IEG expression in regulating skeletal muscle properties in response to neuromuscular activity.

P218. Detection of Borrelia burgdorferi DNA in the Cerebrospinal Fluid by Polymerase Chain Reaction: Sensitivity and Use of Nonradioactive Probes

Andrew R. Pachner, Nancy S. Ricalt, and Elizabeth Delaney, Washington, DC

Borrelia burgdorferi is an increasingly prevalent disorder, but the diagnosis generally has been indirect. Thus, the presence of other manifestations of the infection, consistent findings on neurological exam or lumbar puncture, or presence of CSF antibody have been used rather than direct isolation or identification of the organism from the CSF. We have previously developed polymerase chain reaction with hybridization (PCR/H) to identify Borrelia burgdorferi in the blood and organs of infected mice, and found that the assay was equivalent or, in some cases, preferable to culture (Ann Neurol 1991;30:302). The assay used for primers oligos derived from a sequence of genomic B. burgdorferi DNA expressed on a plasmid by Rosa and Schwart. A two-stage nested PCR was performed on CSF samples in which the DNA was isolated in a variety of ways. PCR products were subsequently hybridized with a digoxigenin-labeled internal probe by slot-blot hybridization. The sensitivity of the assay was excellent, being <0.1 fg of purified B. burgdorferi DNA/ml of CSF, and 1 to 10 spirochetes per ml of CSF when “spiked” CSF was tested. The assay then was applied to a battery of CSFs stored over the past 15 years in patients with definite, probable, and possible Lyme neuroborreliosis. The lack of PCR/H positivity in some patients with definite and probable disease signifies that the spirochete does not reside in the lumbar CSF in all patients with Lyme neuroborreliosis, and may be concentrated in the meninges or parenchyma.

P219. In Vivo Differentiation of v-myc-immortalized Progenitor Cell Line on Transplantation into the Adult Murine Brain

T. Kitaguchi, D.-H. Chui, and T. Tabira, Tokyo, Japan

Several multipotent neural cell lines were generated via retrovirus-mediated v-myc transfer into primary culture cells of the septum of embryonic murine brains (the retroviral vector, kindly provided by Dr. C. L. Cepko, Boston, MA). Two of those cell lines, when transplanted back into 6- to 8-week-old mice by stereotaxic operation, integrated into the septum in a nontransgenic manner. The implanted cells, which had been labeled with PKH26 dye, could be identified in animals up to at least 10 weeks after transplantation. Immunocytochemical analysis demonstrated that the transplanted cells were seen assuming a round morphology and no processes. They did not stain with any glial or neuronal markers except for A2B5 and HNK-1, in the same way as in vitro. Interestingly, after 10 weeks of implantation, the cells were located discretely in the transplanted site and displayed a small and round morphology with fine processes. Most of the transplanted cells showed immunoreactivity with monoclonal antibodies directed against neuronal markers such as neurofilament and MAP2. These data indicate that the immortalized cell lines might be useful in characterizing factors that regulate cell type differentiation in the mammalian nervous system. (Supported by a grant from the Science and Technology Agency of Japan.)

P220. Identification of a Novel Transcription Factor Related to Serum Response Factor in Human Brain and Muscle

Dana Leifer, Dimitri Krainc, Rachael Navs, Roger Breitkorth, Yir-Tah Yu, Bernardo Nachal-Giraud, and Stuart A. Lipton, Boston, MA

We have identified cDNA clones for a novel transcription factor that is expressed at high levels in human fetal brain and skeletal muscle, but not in a variety of other tissues, as demonstrated by Northern blotting. Sequence analysis indicates that the clones appear to have 2 alternatively spliced forms and have extensive homology with human serum re-
response factor (SRF) and a family of related transcription factors that has representatives throughout eukaryotic evolution in species from yeast to man. SRF is thought to have a role in regulation of immediate early genes and of muscle-specific genes. In gel mobility-shift assays, the SRF-like proteins coded for by our clones bind specifically to the myocyte-specific enhancer binding factor-2 (MEF-2) regulatory element, a DNA sequence that has so far been found to be functionally important in the promoter and enhancer regions of a variety of muscle-specific genes. Moreover, our SRF-like proteins specifically activate transcription of reporter genes containing the MEF-2 element. Given the abundant expression of our clones in human brain as well as in muscle, our results suggest that these proteins may have a significant role in development not only of muscle but also of brain.

P221. Computer Reading of the Human Clinical EEG
Robert Cohn and Russell W. Myers, Southampton, NY

A host of quantitative EEG studies, most of which employed variations of the fast-Fourier transform, have been made on isolated clinical entities such as the epilepsies, metabolic syndromes, and sleep with varying degrees of satisfactory correlations. Using a time domain wave-by-wave computer program that simulated the logical approach of the clinical electroencephalographer, we have studied more than 300 unselected routine neurological clinic and ward patients. The presenting problems ranged from headache to major cerebral involvement. Employing the dichotomy of normal and abnormal, the computer-read EEGs agreed with the routine EEG, the clinical manifestations (including imaging techniques), and neuropathological findings in 90% of all cases. This high level of correlation, which approached that achieved by well-trained EEGers reading the same records, was obtained by solely utilizing the background EEG activity. Such results became possible only when the computer program was so organized that the “raw” computed and original oscillograph records were made to match closely. The diagnosis, with topographically diagramed localization, was printed automatically as the final step of the program. Our data strongly suggest that routine computer reading of the human EEG is feasible, reliable, and potentially useful.

P222. Aluminum Salts Induce Amyloid Precursor Protein Accumulation in Damaged Neurites and Microglial Cells
Kazuo Shigenzatsu and Patrick L. McGeer, Vancouver, BC, Canada

Abnormal accumulation or abnormal processing of amyloid precursor protein (APP), or both, may be critical to the development of β-amyloid protein (BAP) deposits. However, Alzheimer’s disease (AD) has another pathological hallmark, which is the appearance of neurofibrillary tangles. The question is, therefore, to clarify the possible relationship between altered APP metabolism and neurofibrillary degeneration. One classic method for inducing neurofibrillary tangles is the administration of aluminum salts. Although these tangles are morphologically different than those seen in AD brain, this phenomenon has given rise to the hypothesis that aluminum might be an environmental factor in the causation of AD. This theory is controversial, but the animal aluminum model remains one of the few ways that long-lasting neuroskeletal changes can be induced. To explore the effects of aluminum salts on APP metabolism, we examined APP immunodistribution in rat brain injected intraventricularly or intrastriatally with AlCl3. We found a long-lasting accumulation of APP in affected neurites, as well as in activated microglia/macrophages. Abnormal neurites also showed argyrophilic changes, neurofilament accumulation, and Alz-50 immunoreactivity. The results support the hypothesis that interruption of axoplasmic flow by aluminum salts, as by other means, can lead to both APP accumulation and neuroskeletal alterations.

P223. Nondemyelinating Conduction Slowing of Myelinated Fibers Due to Inactivation of Na Channel
Takanori Yokota, Yukinobu Saito, and Tadashi Miyatake, Tokyo, Japan

In 4 patients with acute or chronic inflammatory demyelinating polyradiculoneuropathy, the marked improvement of motor-nerve conduction velocity without change of amplitude, configuration of the compound muscle action potentials (CMAPs) was observed in 3 days. To investigate the mechanism of this rapid recovery, we measured the difference in conduction velocity between the influence of Na channel blockade on nerve conduction was studied. In 4 healthy volunteers, the recovery of the CMAP and sensory nerve action potential (SNAP) of median nerve stimulation were recorded after the intravenous infusion of 100 mg of lidocaine. After the loading, CMAP and SNAP were reduced rapidly in amplitude and were slowed in latency. After the recovery of amplitude of CMAP and SNAP, the conduction velocities were improved gradually in 2 hours with the amplitudes and configurations of CMAP and SNAP unchanged. This indicated that myelinated nerve conduction velocity could be slowed by the inactivation of Na channels without demyelination or conduction block. The prolongation of rising time in depolarization of axonal membrane potential should be one of the mechanisms of this conduction slowing due to inactivation of Na channels.

POSTER PRESENTATION:
NEUROONCOLOGY

P224. The 52-kd Expression Product of Paraneoplastic Cerebellar Degeneration—17, a cDNA Cloned from Human Cerebellum, Is Uniformly Recognized by Sera and Cerebrospinal Fluids from Patients with Paraneoplastic Cerebellar Degeneration and Type I (“Anti-Yo”) Antibody Response
Koshibori Sakai, John E. Greenle, Kurt A. Jaechle, and Genjiro Hirose, Kanazawa, Japan, and Salt Lake City, UT

Paraneoplastic cerebellar degeneration (PCD) in gynecological and breast cancers frequently is accompanied by an autoantibody response (Type I or “anti-Yo”) reacting with 54- and 62-kd cytotoxicic antigens of cerebellar Purkinje cells. Sakai et al, using a cerebellar library (Stratagene), recently have isolated a cDNA clone expressing a 52-kd protein recognized by IgG from a patient with PCD and uterine carcinoma (Sakai et al, Ann Neurol 1990;28:692). This clone is believed to share some homology with the message encoding the 62-kd protein recognized by Type I sera. Because PCD17 was isolated using serum from a single patient, however, it is not known whether the expressed protein of PCD17 is recognized uniformly by all patients with Type I antibody response. E. coli strain XL1-Blue transformed with pWR590-2 containing the SnaBI/HindIII fragment of PCD17, pWR590-PCD17SN, was used for isopropylthiogalactoside. Bacterial lysates were electrophoresed on 10% SDS-PAGE gels and analyzed by Western immunoblot
methods using sera and CSF from patients with PCD associated with gynecological and breast malignancies who exhibited Type I antibody response. The 52-kd expression product was labeled by 8/8 sera and 4/4 CSF samples tested from antibody-positive patients but was not labeled by sera or CSFs from controls. Our studies demonstrate that the 52-kd protein expressed by PCD17 contains epitopes that are consistently recognized by both systemically and intrathecally produced antibodies from patients with PCD accompanying gynecological and breast malignancies.

P225. Taxol-Induced Neurotoxicity: Sensorimotor Neuropathy and Myopathy

V. Chaudhry, E. K. Rosensz, D. R. Cornblath, S. E. Sartorius, A. M. Corse, and R. C. Donehower, Baltimore, MD

Taxol is a novel antitumor drug that has demonstrated impressive clinical activity in breast, ovarian, and lung cancers. Although sensory neuropathy has been described secondary to both taxol and cisplatin-cisplatin combinations in clinical trials, detailed neurophysiological and pathological studies have not been described. Nineteen patients with solid tumors were treated with combinations of taxol (135–350 mg/m²), cisplatin (75–100 mg/m²), and granulocyte colony-stimulating factor (G-CSF) (5 μg/kg/day). Sequential neurological examinations, nerve conduction studies (NCS), and quantitative vibration testing (QST) were performed during and after treatment. Eighteen of 19 patients developed sensorimotor neuropathy and 3 developed myopathy. Thirteen were symptomatic with numbness or weakness and 17 had abnormal results on neuromuscular examination. NCS showed absent or prolonged H-reflexes (14), reduced peroneal motor amplitude (14), reduced sural sensory amplitude (13), and myopathic motor unit potentials in proximal muscles (3). QST results were abnormal in 9 of 15 tested patients. Muscle biopsy specimen in a patient with myopathy showed features of a toxic myopathy. The neuropathy was worse with higher cumulative dosages of taxol (>600 mg), with higher single doses of taxol (>300 mg/m²), or with a preexisting neuropathy. We conclude that sensorimotor neuropathy and myopathy are dose-limiting neurotoxicities of combined cisplatin and taxol use, now that neutropenia can be controlled with G-CSF.

P226. Retinoic Acid Decreases Proliferation and Hu Expression in Medulloblastoma Cells

Frank S. Lieberman, Diana Finzi, and John Ferro, New York, NY

All transretinoic acid (ATRA) inhibits proliferation and induces differentiation in a variety of neoplastic cell lines. We have studied the effects of ATRA on the human medulloblas- toma cell line D-283. On day 0, 2 × 10⁷ cells were placed into T-25 culture flasks containing MEM + 15% fetal calf serum and ATRA in concentrations ranging from 10⁻⁶ to 10⁻⁹ M or control media. Cell counting showed growth inhibition by day 4 for all ATRA concentrations. Changes in production or binding of transforming growth factor beta (TGF-β) are possible mechanisms for ATRA’s effects. Monoclonal antibody demonstrated TGF-β cell surface reactivity, before and after ATRA, which indicates that these cells were capable of binding TGF-β. We are currently studying the effects of ATRA on expression of specific TGF-β-binding proteins. Untreated D-283 cells expressed the neuronal nuclear marker Hu. Western blots of D-283 cells treated with 10⁻⁶ and 10⁻⁷ M ATRA for 7 days showed a dose-related decrement in Hu expression. ATRA inhibits proliferation of medulloblastoma cell line D-283. The concomitant decrease in Hu expression suggests the antiproliferative effect is not associated with differentiation along a neuronal pathway.

P227. Leptomeningeal Involvement in Primary Central Nervous System Lymphoma

Carilda Balmaceda and Lisa DeAngelis, New York, NY

Primary central nervous system lymphoma (PCNSL) is usually periventricular and may seed the CSF by direct growth through the ependyma. We reviewed the CSF profile of 83 non–acquired immunodeficiency syndrome (AIDS) patients (pts) with PCNSL. All pts had lumbar puncture (LP) and 46 had multiple samples from an Ommaya reservoir. Definite LM involvement was identified with a positive CSF cytology, lymphomatous LM infiltration on a surgical specimen, or MRI with gadolinium showing LM tumor. Probable LM lymphoma was diagnosed in pts with suspicious or atypical CSF cytology. There were 41 women and 42 men with a median age of 57 (range 20–81 yr). At diagnosis, mean white blood cell count was 49/mm³ (range 0–5,510); mean lumbar CSF protein was 103 mg/dl (range 3–1,893); and mean ventricular CSF protein was 32 mg/dl (range 4–265). Glucose was always normal. Nineteen of 57 pts sampled had oligoclonal bands, and 42/65 had elevated β₂ microglobulin. At diagnosis 43 (52%) had an abnormal CSF cytology: 22 positive, 16 suspicious, and 5 atypical. One pt had pathological infiltration of the LM and 1 had LM tumor on spine MRI for a total of 45 (54%) pts with definite or probable LM lymphoma. In 43 pts with abnormal cytology, the abnormality was found in 30/43 (70%) LPs and 32/55 (58%) of the Ommaya and ventricular specimens. In 8 pts the lumbar cytology was the only abnormal specimen despite multiple ventricular samples, and in 10 only the ventricular CSF was abnormal. Thirty-six of 83 (43%) pts developed recurrent tumor after treatment. Forty-two percent (13/36) of all patients with relapse had LM recurrence. LM recurrence was accompanied by brain recurrence in 9 pts, systemic in 1, ocular in 1, both systemic and ocular in 1, and isolated in 3. At diagnosis 59/83 patients received treatment directed against the LM. Of these, 8 (14%) had meningeal recurrence whereas 7 of the 24 (29%) patients who did not receive this treatment had LM recurrence. LM involvement by PCNSL is frequent, may be missed on a single CSF sample, and requires specific therapy at diagnosis.

P228. The Outcome of Single Brain Metastasis After Treatment with Irradiation Alone or Combined with Neurosurgery

H. Haaxma-Reiche, C. Vecht, G. Padberg, J. Voormolen, E. Noordzij, A. Wattendod, N. Lambooy, J. Metsaar, R. Brand, and J. Herman, Groningen, Rotterdam, Leiden, and Den Haag, The Netherlands

Sixty-three solid cancer patients with a single brain metastasis were prospectively randomized for neurosurgery and radiotherapy combined (Arm 1) or radiotherapy alone (Arm 2). They were stratified for lung or nonlung cancer and for active versus stable or absent extracranial disease. World Health Organization performance status was ≤2. Age, sex, performance status, and location of brain metastasis were divided evenly over both groups. One-month mortality was 9% in Arm 1 and 6% in Arm 2. Median survival of 11 months after combination therapy was significantly better compared to 6

286 Annals of Neurology Vol 32 No 2 August 1992
months after irradiation alone (p < .04). It made no difference whether they had lung or nonlung cancer. The largest difference between both treatment arms was observed in patients with stable or absent extracranial disease (12 vs 7 mo, p < .02). When systemic disease activity was present, median survival was 5 months irrespective of treatment arm. Functional independent survival was 1 to 2 months shorter than overall survival and was significantly better for patients with stable extracranial disease after combined therapy. Multivariate analysis showed that age was also an independent prognostic factor. Patients older than 60 years had a hazard ratio for dying of 2.8 (p .004).

P229. Neurological Complications of T-Cell Lymphoma
D. K. Kaufman, T. M. Habermann, P. J. Kurtin, and B. P. O'Neill, Rochester, MN
To determine the incidence of neurological complications, we reviewed the charts of 376 patients in whom T-cell lymphoma (TCL) was diagnosed between the years 1984 and 1990 (MRI era). Patients were classified as having metastatic (parenchymal, leptomeningeal, or epidural) or nonmetastatic (disease- or treatment-associated) disease. Pre-existing neurological conditions were excluded from this study. No patient had acquired immunodeficiency syndrome or had reactive human immunodeficiency virus or human T-lymphotropic virus type 1 serologies. The distribution of complications was as follows:

| Total | Metastatic | Nonmetastatic | Total |
|-------|------------|---------------|-------|
| Primary CNS TCL | 8 | . . | . . |
| Systemic TCL 197 | 14 (7.1%) | 21 (10.7%) | 35 (17.8%) |
| Cutaneous TCL* | 171 | 4 (2.3%) | 4 (2.3%) | 8 (4.7%) |
| 375 | 18 (4.8%) | 25 (6.6%) | 43 (11.4%) |

*Twenty-four patients subsequently developed systemic lymphoma; neurological complications were seen only in these patients.

We will detail the type and pattern of neurological complications in T-cell non-Hodgkin’s lymphoma (NHL), and review how they differ from those associated with B-cell NHL, and the lymphomagenic process. This study is the first step in a process to characterize these tumors to determine if special staging or CNS prophylaxis are indicated in any of the subtypes of T-cell lymphoma.

P230. Paraneoplastic Sensorimotor Neuropathy Associated with Breast Cancer
Kendra Petersen and Jerome B. Posner, New York, NY
We recently have encountered 5 women with breast cancer and an unusual sensorimotor neuropathy. The neuropathy was the major clinical problem. In 4 women the initial symptom was severe itching, 3 generalized and 1 first localized to the involved breast and then generalized. All developed distal extremity numbness and burning that very slowly progressed proximally, and in 2 became generalized. Four complained of painful muscle cramps in the extremities (4) and jaw (1). All had mild extremity weakness, distal (5) and proximal (1). Three women developed symptoms up to 21 months prior to cancer diagnosis, 1 shortly after diagnosis, and 1 5 years after diagnosis. Four women had disease confined to the breast and regional lymph nodes, and 1 had metastatic disease in remission. Although annoying, symptoms were generally not disabling. Three women stabilized or had slight improvement with cancer treatment, and 2 continue to gradually progress while in cancer remission; 1 required a cane to ambulate after 9 years due to sensory ataxia. One who developed cancer relapse had concurrent neurological relapse. One woman treated with high-dose immunoglobulin did not improve. None had significant weight loss. Laboratory abnormalities included elevated erythrocyte sedimentation rate (28–60) in 3, antinuclear antibody 1:40 in 1, CSF with lymphocytic pleocytosis (7–14 white blood cells/mm in 3/4 and elevated protein (51–97 mg/dl) in 4/4 available. EMG/NCV showed mild sensory-to-motor polyneuropathy in 3/4 available. None had detectable antibodies against peripheral nerve or dorsal root ganglia. The etiology of sensorimotor neuropathy in these patients is unknown, but it may represent a distinct paraneoplastic syndrome that can herald the onset of, and parallel the course of breast cancer.

P231. Seizures After Bone Marrow Transplant
Suwan C. Pannullo and Jerome B. Posner, New York, NY
A chart review was performed to determine the incidence and cause of seizures in 370 patients after bone marrow transplantation (BMT). Seizures were documented in 26, and were suspected in 3 others. Of the 26, 15 were male, and the mean age was 21 years. Seventeen patients had allogeneic transplants, and 9 had autologous transplants. Eleven patients had leukemia, 4 had lymphoma, 3 had aplastic anemia, 3 had immunodeficiency, and 5 had another illness. The patients received a variety of preparation regimens; 8 patients received CNS treatment or prophylaxis with intrathecal chemotherapy, cranial radiation therapy, or both. Four patients had a prior history of seizures. The interval between bone marrow infusion and seizure was 119 days (range 1–637 days). Five patients (20%) had seizures less than 1 week after BMT, and 13 patients (50%) had seizures more than 2 months after BMT. Nineteen had generalized seizures, 3 had focal seizures, and 3 had both (1 was not described). Five patients were febrile at the time of seizure. Postictal examination revealed altered mental status in 19 patients and localizing signs in 5. Twelve patients were neutropenic at the time of seizure, and 18 had platelet counts <50K. A probable cause was determined in 21/26 patients. Fourteen had a CNS disease: 8 had intracranial hemorrhage, 3 had CNS infection, 2 had meningeal leukemia, and 1 had multiple infarcts. Seven had systemic events, metabolic disturbance, or infection: 2 seizures after respiratory insufficiency, 2 after syncope; 1 was hypotensive, 1 was septic, and 1 had a seizure during benzodiazepine withdrawal. In 5 patients, no cause was found. Seizures occurred in 10 patients during an average length of patient follow-up of 151 days from initial seizure. There were 17 deaths; 9 were within 2 weeks of seizure. We conclude that seizures occur in approximately 8% of patients after BMT, often several months after infusion. In 20%, no cause of the seizure can be determined. More than one-third suffer recurrence of seizures.

P232. Ceramide Induces Changes of Differentiation in a Glioma Cell Line
Mark H. Werner, Aliza Bielauska, and Yaquf Hannun, Tampa, FL, and Durham, NC
Our objective was to determine whether ceramide induces differentiation of anaplastic glioma cells. Sphingomyelin hydrolysis resulting in ceramide production has been linked to differentiation of leukemia cells. T9 rat anaplastic glioma cells, seeded at 2 x 10^4 cells per well, were grown in serum-
processes longer than one cell body, and counted. C2 ceramide changed plump cells to flattened cells with many long processes: ceramide treatment increased the percentage of cells with processes from $22 \pm 4\%$ (SD) to $49 \pm 12\%$ ($n = 4, p < 0.01$). Control cells grew to $6.3 \times 10^5$ cells/well $\pm 0.6 \times 10^5$ cells; ceramide-treated cells grew to $1.6 \times 10^5 \pm 0.6 \times 10^5$ ($n = 4, p < 0.0005$). Although one ceramide analog reproduced the C2 ceramide-associated changes, the optical isomer of this analog did not, demonstrating stereospecificity. Ceramide did not decrease cell viability by trypan blue. Ceramide inhibits proliferation and induces process formation in a glioma cell line, causing it to assume a more differentiated phenotype. Ceramide or its analogs represent possible future therapeutic agents that would inhibit the growth and affect differentiation of anaplastic glomas.

P233. Stable Lytic Epstein-Barr Virus Infection of B Cells After Long-Term Passaging in Severe Combined Immunodeficient Mouse Brain
Rifaat Bashir, Kerry Kallweit, and Jana Luka, Omaha, NE

Primary brain lymphomas in acquired immunodeficiency syndrome (AIDS) patients contain the Epstein-Barr Virus (EBV) in latent and lytic forms (viral capsid antigen [VCA], in situ hybridization [Bashir, Mod Pathol 1990;3(4):429-434]). This is similar to the pattern seen in EBV-infected human B cells and unlike the uniform latent infection seen in Burkitt's lymphoma. We tested the hypothesis that long-term passaging of EBV-immortalized human B cells in immunodeficient mice leads to emergence of a uniform nonlytic pattern of EBV infection associated with appearance of the malignant profile. EBV-infected normal human B cells were serially passaged intracerebrally in severe combined immunodeficient CB17 mice ($5 \times 10^5$ cells per mouse, $5$ mice per passage for a total of $10$ passages). Frozen mouse brain sections from each passage were stained with VCA antibody (EBV lytic cycle) and hybridized with biotinylated BamH1-W sequence of EBV. All injected animals developed tumors as previously described (Bashir, Lab Invest 1991;65(6):702-709). Tumor cells continued to express VCA and showed latent and lytic hybridization patterns with BamH1-W after $10$ passages despite exhibiting monoclonality (surface immunoglobulins) and random chromosomal changes. Lytic infection of immortalized B cells with EBV is stable, resembling brain lymphomas in AIDS, and unlike the latent infection seen in Burkitt's lymphoma.

P234. A Novel Antineuronal Autoantibody Associated with Paraneoplastic Encephalomyeloneuritis
Edward J. Drobo and Walter Korfobetz, Birmingham, AL and Boston, MA

A previously healthy 73-year-old man developed diplopia and incapacitating, diffuse weakness over a period of 6 weeks. Examination showed a "one-and-a-half" syndrome of horizontal gaze paresis, patchy severe weakness with atrophy and fasciculations, absent tendon reflexes in the legs and right biceps, and decreased vibration sense in the feet. CSF contained a mild pleocytosis, elevated protein, and oligoclonal IgG bands. Electrophysiological testing indicated a generalized sensorimotor axonal neuropathy with diffuse denervation. Small-cell lung carcinoma was diagnosed by bronchoscopy. Prednisone produced mild subjective improvement. Chemotherapy was begun but the patient developed fatal septicemia. Serum was negative for anti-Hu or anti-GM1 antibodies. Serum and CSF contained high titers of IgG antibodies reacting specifically with a protein antigen of approximately 130 kD in immunoblots of human cerebral cortical neuronal nuclei or of human Purkinje cells. This pattern of autoantibody reactivity was not present in sera from any of 37 other patients with small-cell lung carcinoma, 17 of whom had paraneoplastic encephalomyeloneuritis and anti-Hu antibodies, nor was it present in many patients with other neurological disorders. The patient's serum has been used to probe a human cerebellum expression library and to isolate a cDNA clone that is being characterized.

P235. Acute Encephalopathy in Patients with Systemic Cancer
Rogerio Tuma and Lisa DeAngelis, New York, NY

Acute encephalopathy is the problem in 17% of neurology consultations reported at MSKCC. We studied 94 patients (51 prospectively and 43 retrospectively) to determine clinical findings, causes, and outcome. Fifty-five were women and 39 were men, and the average age was 63 years. All patients had cancer: lung (20%), gastrointestinal tract (19%), breast (12%), and others (49%). Forty-two patients (45%) were delirious on admission and delirium developed an average of 12 days later in 55%. Encephalopathy occurred postoperatively in 24%. Symptoms included confusion (92%), lethargy (59%), agitation (51%), hallucinations (29%), and seizures (10%). Signs included deficits in attention (44%), memory (38%), language (15%), lateralizing signs (50%), and ataxia (33%). The average Mini-Mental Status Test (MMST) score was 12 (30 = normal). A single cause for delirium was found in only 4% of patients with an average of 4 etiologies per patient. Metabolic abnormalities were found in 89% of patients, and were a primary cause in 44%; disseminated intravascular coagulation contributed to delirium in 11%. CNS metastases were found in 52% and were a major cause of delirium in all. Fifty-five percent of the patients had fever/systemic infection, but sepsis was present in only 4%; only 1 patient had CNS infection. Medication contributed to delirium in 97%; but was a primary cause in only 29%. The 30-day mortality rate was 31% and delirium improved in 68% (average MMST = 23). Patients with cancer have multiple, potentially treatable causes of delirium. Delirium is associated with a high death rate, though patients generally improve.

P236. Osteosarcoma of the Calvarium Following Radiation Therapy for Brain Tumors
D. W. Dodick, B. Mokri, K. K. Uusi, G. M. Miller, and E. G. Shaut, Rochester, MN

Osteosarcoma in a previously normal bone is a rare but recognized remote effect of radiation therapy. Any bone in the field of radiation can be affected. Involvement of cranial bones is exceedingly rare. We could identify only 4 patients (2 men and 2 women) with postirradiation osteosarcoma of the calvarium seen at the Mayo Clinic over a 50-year period, from 1931 to 1991. All had received radiation for brain tumor, osteosarcoma had appeared in the field of radiation in all, the interval from radiation therapy to the appearance of sarcoma ranged from 7 to 23 years, and diagnosis of sarcoma was confirmed histologically in all cases. The patients' age at the diagnosis of the bone tumor ranged from 18 to 41 years. The nature of the brain tumor was unverified in 2 cases, was a low-grade ependymoma in the third case, and a pilocytic astrocytoma in the fourth case. One patient is still alive 12...
months after the diagnosis of the sarcoma. She received che-
motherapy and subsequently underwent resection of the os-
teosarcoma. One patient died postoperatively after partial 
resection of the sarcoma. The other 2 patients died 7 months 
and 15 months after the diagnosis of the osteosarcoma de-
spite additional radiation therapy in the former and aggres-
itive chemotherapy in the latter.

P237. Evaluation of a Synapsin Regulatory 
Element-LacZ Fusion Gene as a Potential 
Marker of Neural Tumor Differentiation 
Lawrence Recht, Chiffon Wu, and Louis J. DeGennaro, 
Worcestor, MA

Inducing cancers to differentiate into more benign differenti-
ated tumors represents a novel oncological strategy. To estab-
lish a model that would permit assessment of this phenome-
non at a molecular level, we created and have partially 
characterized a murine neuroblastoma line that has been sta-
tably transfected with a synthetic fusion gene containing the 
promoter element of the rodent synapsin I gene (synapsin I 
regulatory element [SRE]). In vivo, this promoter directs the 
neuron-specific expression of the synapsin I gene in normal 
adults. The gene also is expressed in varying amounts in 
neuronal tumors including neuroblastoma. In the synthetic 
fusion gene, the SRE has been linked to the lacZ gene that 
encodes bacterial β-galactosidase. A simple histochemical 
assay for β-galactosidase therefore provides a specific marker 
of the expression of the fusion gene. Our preliminary experi-
ments as of this writing have shown that it is possible to 
detect β-galactosidase activity in the transfected neuro-
blastoma cells both in vitro and in transplanted tumors. It 
appears possible therefore that this transfected neuroblas-
toma cell line can provide a useful model system with which 
to assess the effects of differentiation therapies.

P238. Headaches in Patients with Brain Tumors: A 
Study of 111 Patients 
Peter Forsyth and Jerome B. Posner, New York, NY

One hundred eleven consecutive inpatients with brain tumor 
(BT) identified on CT or MRI were studied to characterize 
BT headaches (HAS). Median age was 44 years and 44 were 
men. Thirty-eight (34%) were primary tumors (12 GBMs, 
9 CNS lymphomas, 6 meningiomas, 4 anaplastic astrocy-
mas, and 7 other) and 76 metastatic (28 lung, 16 breast, 6 
melanoma, 4 NHL, 4 unknown primary, and 15 other) H As 
were present in 53 (48%), equally in primary (47%) and 
metastatic (49%) BTs. HAs were similar to tension-type 
HAs in 35 (66%), migraine in 3 (5%), and tension-
vascular in 6 (11%), and other types in 7 (14%). The typical 
HA was a tension-type HA described as "pressure," "ache," 
or "sinus" located bifrontally, worse ipsilaterally. It was inter-
mittent (62%) but progressive. The HA was mild to moder-
ate in severity; it was the worst symptom in only 24 (45%) 
and the first symptom in 32 (60%) patients. HAs were worse 
in the morning in 19 (36%) and interfered with sleep in 17 
(32%) patients. Unlike true tension-type HAs, BT HAs were 
worser with bending over in 17 (52%), with Vaalsava's 
maneuver in 12 (23%), and nausea or vomiting were present 
in 21 (40%) patients. An abnormal neurological exam was 
found in 38 (72%) patients with HAs and 43 (74%) patients 
without HAs. HAs were more common in patients with 
raised intracranial pressure (i.e., obstructive hydrocephalus, 
raised CSF opening pressure, Ca meningitis with hydroceph-
alus, or improvement after shunting), posterior fossa BTs, 
larger lesions (>18 cm³), and larger midline shifts (>4 mm). 
Twenty-eight of 36 (78%) patients with prior HAs had BT 
HAs compared to 25 of 75 (33%) patients without prior 
HAs. In 8 patients, their BT HA was similar to their previous 
HA but was more frequent or severe. We conclude that HAs 
in BT patients are common but usually not severe. Nausea, 
 vomiting, an abnormal neurological examination, or a change 
in prior headaches warrant further investigation.

P239. Oligodendrogliomas: CT Measurement of 
Transcapillary Permeability and Response to 
Vincristine Chemotherapy 
N. A. Paleologo, T. Zemrus; C. V. Allen, A. Ragin, 
A. Waldh, G. D. Lapin, D. R. Grotstue, and N. A. Vick, 
Evanston, IL

Cairncross and Macdonald showed that procarbazine, lomus-
tine, and vincristine (PCV) are effective for recurrent anaplas-
tic oligodendrogliomas (AO) (Ann Neurol 1988;23:360-
364). PCV now has a major role in management of all forms 
of oligodendrogliomas (O), but the biological basis for this 
response is unknown. To evaluate one subset of possibilities, 
we studied 14 patients (6 AO, 8 O) with a CT method that 
permits measurement of blood-to-tissue transport (Kt), 
tumor-to-blood transport (Kd), and vascular volume (Vv) 
(Ann Neurol 1991;30:581-587). PCV was used to treat 11 
of the 14 patients. Kt (μl gm⁻¹ min⁻¹) values were highly 
variable for whole tumor, ranging from 1.49 to 14.37 (mean 
4.87 ± 4.17) with no difference between AO and O. Kd and 
Vv were also highly variable. Kt of tumor-free brain was 1.40 
to 2.69 (mean 1.89 ± 0.50). In comparison to malignant 
astrocytomas, which have a mean Kt in the range of 21.0 
with some as high as 33.9, AO and O appear to be much 
less permeable. This suggests that the efficacy of PCV may 
be due to factors other than capillary transport, such as 
tumor-cell sensitivity.

P240. En Bloc Brain Tumor Resection Using 
Frameless Stereotactic Localizer 
Gene H. Barnett, Donald W. Kormos, and Charles P. Steiner, 
Cleveland, OH

Extent of tumor resection has been shown to correlate with 
prognosis in malignant gliomas. Although frame-based ste-
reotactic techniques can provide information regarding tu-
mor margin, they are often unwieldy and require expensive 
and elaborate computing systems. A frameless stereotactic 
nurosurgical localizing system was designed that overcomes 
these liabilities. This armless, frameless, stereotactic pointing 
device provides real-time three-dimensional localization in-
f ormation during operation. In addition to assisting in place-
ment of a trephine craniotomy, it allows volumetric resection 
of the tumor with virtually complete excision of even large 
irregularly shaped tumors. Mean error on localizing a point 
in space using this system has proven to be less than 2 mm. 
A technical description of the system as well as surgical re-
sults are presented.

P241. Age Influences Chemotherapy Response in 
Glioma Irrespective of Tumor Grade 
Robert Grant, Bertrand Liang, Michaelyn A. Page, 
Dawn C. Crane, Harry S. Greenberg, and Larry Junck, 
Ann Arbor, MI

To investigate the effect of age on response rate to chemo-
therapy and time to progression (TTP) in
patients with recurrent astrocytomas and malignant astrocytomas, we reviewed case records and scans of 143 patients who received chemotherapy at the University of Michigan with bischloroethyl nitrosourea or procarbazine. Three age groups were studied: (1) <39 yr (n = 64); (2) 40–60 yr (n = 56); (3) >60 yr (n = 23). Tumors were grouped as grade 2R+3 (recurrent grade 2 plus grade 3, n = 72) or grade 4 (n = 71). Serial computed tomographic or magnetic resonance scans were analyzed in a blinded fashion and graded as progressive disease (PD), stable disease (SD), or partial response (PR, >25% decrease in size). The PR rates for the 3 age groups were 58%/32%/0% for grade 2R+3 tumors and 36/31/24 weeks for grade 4. Median lTD was 31/23/6 weeks for grade 2R+3 and 22/16/10 weeks for grade 4. Median TTD was 53/48/19 weeks for grade 2R+3 and 36/31/24 weeks for grade 4. We conclude that age is an important prognostic factor with respect to likelihood of response to chemotherapy, duration of response, and survival irrespective of grade.

**P242. Intravascular Malignant Lymphomatosis: A Response with Plasmapheresis**

Cheryl P. Harris and Kurt A. Jaechle, Salt Lake City, UT

Intravascular malignant lymphomatosis (IML), a B-cell lymphoma confined to small venules and capillaries, often presents with neurological symptoms. This disease is uniformly fatal (5-month mean survival); no successful treatment has been identified. We observed marked reproducible neurological improvement after plasmapheresis in a 43-year-old woman with IML. Presenting with a cauda equina syndrome, she progressed over 1 year with neurological, hepatic, and hematological disease. Persistent laboratory abnormalities included a high sedimentation rate (140 mm/hr), coagulopathy, hemolytic anemia, and elevated liver enzymes. Extensive evaluations for infectious, autoimmune, and neoplastic processes, including bone marrow examination, were inconclusive. Because of neurological progression, empiric therapy with high-dose steroids followed by cyclophosphamide was initiated without response. Plasmapheresis (250 ml/kg in 6 exchanges) effected resolution of encephalopathy and normalization of the coagulopathy and sedimentation rate.Neurological progression recurred within 2 weeks of pheresis; 6 repetitive courses reproduced neurological response. Finally, progressive dementia ensued, and a decision was made to cease pheresis; the patient died 5 days later, 16 months after presentation. Autopsy disclosed diffuse intravascular CD-20 positive malignant lymphoma cells in small vessels of all organs. Although the mechanism is unknown, the serendipitous discovery of response to plasmapheresis in this patient warrants further consideration.

**POSTER PRESENTATION:**

**NEUROPHARMACOLOGY**

**P243. Morphine Synergy Between the Periaqueductal Gray and the Nucleus Raphe Magnus**

Grace C. Rossi, Richard J. Bodnar, and Garratt W. Pasternak, New York, NY

Morphine is an effective analgesic in the rat after injection into a number of discrete brainstem regions, including the periaqueductal gray (PAG), the locus coeruleus (LC), and the nucleus raphe magnus (NRM). Early work with morphine established the existence of synergy between the brainstem and the spinal cord in rats. More recently, studies from our laboratory revealed synergy between two brainstem structures, the PAG and the LC. In the current study, we explored the analgesic interactions between the PAG and the NRM using indwelling cannulae. First, we established morphine dose-response curves and calculated the ED₅₀ independently in the PAG (1.9 µg) and the NRM (2.5 µg). We then simultaneously injected various morphine doses into both regions. Injecting morphine at 1 µg into either the PAG or the NRM did not elevate tail flick latencies above baseline values. However, administered into both regions simultaneously, the 2 1-µg doses produced an 80% maximal response, corresponding to more than a threefold increase of baseline latencies. A fixed morphine dose of 1 µg in the PAG shifted the morphine dose-response curve fivefold in the NRM (ED₅₀ 0.5 µg), whereas a fixed NRM dose of 1 µg shifted morphine’s dose-response in the PAG approximately twofold. Together, these results clearly show synergistic interactions for morphine between the PAG and the NRM. The presence of synergistic interactions between brainstem nuclei as well as between the brainstem and the spinal cord underscores the complexity of opioid analgesic systems.

**P244. The Glutamate Uptake Inhibitor l-Trans-2,4-Pyridolyl Dicarboxylate Is Neurotoxic in Neonatal Rat Brain**

John D. E. Barks and Faye S. Silverstein, Ann Arbor, MI

important evidence of the neurotoxicity of endogenous glutamate (GLU) in mammalian brain was provided by the observation that DL-threo-3-hydroxyaspartate, a high-affinity glutamate uptake (HAGU) inhibitor, was neurotoxic in adult rodent striatum (J Neurochem 1985;44:247); however, the absence of neurotoxicity in neonatal brain was interpreted as evidence that immaturity of glutamatergic innervation limited the potential role of endogenous GLU as a neurotoxin in the immature brain. Yet, considerable data provide indirect support for the hypothesis that GLU can be neurotoxic at this stage. To resolve this issue, we assessed the neurotoxicity of a novel, selective HAGU inhibitor, l-trans-2,4-pyridyl dicarboxylate (l-PDC) (J Med Chem 1991;34:717), in postnatal day (PND) 7 rats (n = 8). l-PDC (pH 7.4) was stereotaxically injected into right anterior striatum (STR) (568 nmol, n = 2) or through dorsal hippocampus into posterior STR (568 nmol, n = 4; 150 nmol, n = 2). Animals were killed 5 days later, and neuropathology was assessed in cresyl violet-stained sections. After anterior injections, focal neuronal necrosis was evident in dorsal STR; high-dose posterior injections caused prominent hippocampal lesions with CA₂,3-pyramidal layer thinning and foci necrosis in dorsal thalamus, while 150 nmol produced small foci of pyramidal cell loss. In both groups, focal cortical necrosis and callosal cysts were apparent adjacent to the injection track. l-PDC-induced brain injury provides direct support for the hypothesis that endogenous GLU may be neurotoxic in the developing brain.

**P245. Safety and Efficacy of Naltrexone in the Treatment of Huntington’s Disease and Severe Oral-Lingual Dyskinesia**

Daniel S. Sax, Conan Kornetsky, Peter A. Mosbach, Richard S. Myers, and Robert G. Feldman, Boston, MA

Eight patients with hypotonic choreic Huntington’s disease (HD) showed improvement when receiving up to 250 milli-
grams per day of naltrexone, an opiate receptor antagonist (Sax et al, Ann Neurol 1991;30:311A). The signs and symptoms of 7 of these patients lessened for 12 to 22 months. Furthermore, a patient with a severe orofacial biting dyskinesia improved when taking doses up to 300 milligrams per day for 4 months. We noted no significant adverse reactions, although 4 patients had mild but labile elevations in SGOT and SGPT. One patient receiving opioid analgesics for pain inadvertently failed to discontinue the naltrexone but noted no reduction in the pain-alleviating effects of the analgesic. Although hyperkinesia, especially of midline functions, as well as quality of life improved for the HD patients, their cognitive deficits remained unaffected. These observations suggest that chronic naltrexone is a safe and effective agent to treat chorea, dysphagia, and oral dyskinesia in HD for periods longer than a year. Furthermore, they indicate that naltrexone can be effective in ameliorating oral-lingual biting tardive dyskinesia. These findings support our previous hypothesis that endogenous opioids play a role in the modulation of the dopamine system in hyperkinetic stereotypic movement disorders.

P246. Cholecystokinin-Neuroleptic Interactions
A. Jon Stoessl, Elizabeth Szwatkowski, and Hanna Frydrysak, London, Ontario, Canada

We previously have demonstrated (Psychopharmacology 1989;58:372-379) that intraperitoneally (IP) administered cholecystokinin (CCK-8S) suppresses vacuous chewing movements (VCMs, a putative model of tardive dyskinesia) in rats exposed to chronic neuroleptics. As CCK is not thought to cross the blood-brain barrier in significant amounts, its site of action in this paradigm is unclear. Other behavioral and neurochemical effects of IP CCK are blocked by vagotomy. Male Sprague-Dawley rats were administered fluphenazine decanoate (FLU; 25 mg/kg IM) or its vehicle every 3 weeks for approximately 20 weeks. CCK (10, 20, or 50 mg intracerebroventricularly) had no effect on neuroleptic-induced VCMs. Another group of neuroleptic-treated rats was subjected to bilateral subdiaphragmatic vagotomy or a sham procedure. CCK-8S (10, 20, or 50 μg/kg intraperitoneally) suppressed neuroleptic-induced VCMs in sham-operated animals, which confirmed our previous results. In vagotomized animals, chronic FLU failed to induce VCMs and CCK was without effect in vehicle- or neuroleptic-treated animals. These data suggest that the effects of CCK on FLU-induced VCMs may be mediated peripherally, and that vagal pathways may be important for generating this response. (Supported by the Ontario Mental Health Foundation and the Ontario Ministry of Health.)

P247. Excitotoxic Amino Acids Are Not Involved in Dopaminergic Neurotoxicity of MPTP
Eldad Melamed, Jutia Roenenthal, and Avisnou Reches, Petah Tiqva, Tel Aviv, and Jerusalem, Israel

The dopaminergic (DA) neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is mediated via its oxidation in CNS to MPP+, which enters DA neurons and poisons mitochondrial complex I. DA neuronal damage induced by direct nigral MPP+ injection is prevented by pretreatment with N-methyl-d-aspartate receptor antagonists, which suggests that excitatory amino acids are involved in MPTP toxicity. Since local MPP+ application may produce nonselective nigral damage, we examined whether excitotoxins have a role in toxicity of systemically administered MPTP. C57 black mice were injected intraperitoneally, once, with MPTP·HCl (40 mg/kg) and decapitated 5 days later. Groups of animals underwent the following pretreatments: (1) decortication 1 week prior to MPTP; (2) intracerebroventricular injections of the excitatory amino acid receptor antagonists 2-amino-phosphonoheptanoate and D-glutamyl-glycine; and (3) intraperitoneal injections of the calcium channel antagonists nimodipine, diltiazem, and flunarizine 30 minutes prior to MPTP. MPTP produced marked striatal DA depletions. Decortication, destroying glutamatergic corticostriatal projections, intracerebral amino acid receptor antagonists, and systemic calcium channel antagonists did not protect mice against MPTP toxicity; MPTP-induced striatal DA decreases were similar to those given the neurotoxin alone. This study suggests that excitotoxins are not involved in the mechanism of MPTP toxicity.

P248. High-Dose Thiamine Partially Reverses Scopolamine-Induced Cognitive Deficits
K. J. Meador, M. E. Allen, P. Franko, E. E. Moore, and D. W. Loring, Augusta, GA

A unique neurophysiological role for thiamine in cholinergic systems has been suggested. Total thiamine content in cholinergic nerve terminals is comparable to that of acetylcholine, and the phosphorylation state of thiamine changes with release of acetylcholine. Thiamine binds to nicotinic receptors and may exhibit anticholinesterase activity. Based on these observations, we investigated the effects of pharmacological doses of thiamine on the cognitive deficits induced by the anticholinergic scopolamine in 13 healthy young adults using a randomized, double-blind, placebo-controlled, double crossover design. Cognitive tests included the P3 event-related potential and free recall memory for a verbal paragraph. Conditions included baseline (BL), thiamine 5 mg by mouth and scopolamine .007 mg/kg intramuscularly (B1 + Scop), and lactose by mouth and scopolamine (Plac + Scop). Testing was performed 3 hours post thiamine or placebo, and 1.5 hours post scopolamine. Thiamine significantly reduced the adverse effects of scopolamine on P3 latency (F [1, 12] = 11.84, p <= .005) and percent recall memory (F [1, 12] = 10.62, p <= .007). Means (±SD) and P3 latency (ms) were BL = 335 (24), B1 + Scop = 360 (29), and Plac + Scop = 383 (39), and for percent recall memory were BL = 64 (23), B1 + Scop = 52 (22), and Plac + Scop = 36 (18). The results are consistent with a cholinomimetic effect of thiamine in the central nervous system.

P249. 4-Aminopyridine (EL-970)-Induced Visual Improvements in Multiple Sclerosis Closely Parallel Serum Levels Suggesting Rapid Central Nervous System Access
D. Stefoski, F. A. Davis, L. H. Rayman, and S. S. Laskin, Chicago, IL

Critical flicker fusion (CFF) is a sensitive and simple quantitative method for assessing optic nerve function as well as efficacy of 4-aminopyridine (EL-970) in multiple sclerosis (MS) (Davis et al, Ann Neurol 1990;27:186-192). We previously reported that CFF improved in 11 of 17 MS patients (65%) given EL-970 orally in divided daily doses ranging from 7.5 to 52.5 mg (Stefoski et al, Neurology 1991;41:1344-1348). Subsequent analysis revealed that in 14 of the 17 patients CFF improvements and reversals followed in a phase-locked trend the rising and falling serum concentrations of EL-970, including 3 patients whose changes remained below the 15%
increase needed to qualify for the improved category. These results resemble the phase-locked effects of temperature on neurological function in MS. The CFF changes, because they so closely reflect variations in serum concentration, suggest that EL-970 tissue levels closely follow those in serum and that EL-970 rapidly crosses the blood-brain barrier. Efficacy of EL-970 in MS is also predicted to have a close relationship to serum levels.

P250. Development of an Internal Standard Detectable by Proton and Phosphorus-31

W. E. Klunk, K. Panchalingam, R. J. McClure, and

J. W. Pettigrew, Pittsburgh, PA

Comparison of quantitative results from different analytical techniques can prove difficult due to the peculiarities of the particular techniques and the lack of a common standard applicable to all of the techniques. Recently, both in vivo and in vitro nuclear magnetic resonance (NMR) have been applied to the quantification of a large variety of metabolites. Although NMR can be applied to the study of living tissue, the question arises of how this technique compares with more traditional techniques such as high-pressure liquid chromatography (HPLC). Although this question can be addressed partly by studying perchloric acid (PCA) extracts, it is difficult to directly compare this in vitro NMR data with results from HPLC. To address this question, we have developed an internal standard that can be quantified directly by in vitro phosphorus-31 NMR, proton NMR, and by 9-fluoroenymethyl chloroforomate (FMOC) derivatization followed by separation by HPLC. A variety of aminophosphonic acids were studied by 31P NMR, 1H NMR, and HPLC. Promising compounds were added to PCA extracts of human brain. The optimal compound was found to be 3-amino-3-aminophosphonic acid (APP, HO3P-CH2-CH,-CH2-NH2). APP appears to be a useful internal standard in the study of phosphorus and amino acid metabolites by in vitro 31P NMR, 1H NMR, and HPLC.

POSTER PRESENTATION: BEHAVIORAL NEUROLOGY

P251. A PET Activation Study of Sentence Comprehension: Grammatical and Semantic Components Are Related to a Distributed Cerebral Network

Murray Grossman, Martin Reivich, Xin-Sheng Ding, Donald Morrison, Joel Karp, and Abass Alavi, Philadelphia, PA

Theories of sentence comprehension hypothesize at least a grammatical component that establishes the relationship among words in a sentence, and a semantic component that determines the meanings of these words. We used positron emission tomography (PET) to quantify regional cerebral blood flow (rCBF) in 12 neurologically intact subjects during their detection of a letter target, a grammatical target, or a semantic target in the same written sentences. A mixed-model analysis of variance (ANOVA) revealed significant main effects for region ($F_{[30, 210]} = 19.32; p < .001$), condition ($F_{[2, 14]} = 3.96; p < .05$), and a significant region times condition interaction ($F_{[60, 420]} = 1.46; p < .05$), but there were no differences between individual subjects. Subsequent ANOVAs revealed increased rCBF in a unique set of brain regions during the subjects' response to a grammatical probe when compared to their response to a letter probe of the same sentences. A unique distribution of rCBF also distinguished response to the semantic probe from response to the grammatical probe and the letter probe. Other brain regions apparently contributed to performance for several activation conditions. These findings support the hypothesized dissociation of specific linguistic components based on their unique cerebral topographical representation, and that a distributed network of brain regions subserves sentence comprehension.

P252. Topographical Brain Mapping Analysis of Cerebral Music Processing—A Comparison Study of Musically Trained and Naive Individuals

Louis S. Russo, Jr, Jacksonville, FL

We performed topographical mapping of brain electrical activity in 6 right-handed symphony musicians and 5 right-handed, musically naive individuals during various musical tasks; namely, listening to solo piano music, silent singing of familiar music, and silent reading of unfamiliar music. Fast-Fourier transform (FFT) of electrocortic activity was carried out during task performance and the eyes-open resting state. Data were analyzed using a computer-assisted model. Increases in regional beta activity of greater than 3 standard deviations from the resting state were considered significant of activation. During audition, the musicians showed activation in the right posterior parieto-temporal region; the naive showed no change from the resting state. During silent singing, the musicians showed bitemporal activation, $R > L$; the naive showed activation in the right mid- and posterior-temporal regions alone. During silent sight reading, the musicians showed a major activation in both temporal regions, $L > > R$; the naive showed only a marginal change in the posterior temporal-occipital regions. These data suggest that music processing is primarily a right cerebral function in untrained individuals and a bilateral function in musicians. Musicians, in contrast to the naive, show progressively more left brain activation as task complexity increases.

P253. Profiles of Language Impairment in Primary Progressive Aphasia

H. Karbe, A. Kertesz, and M. Polk, London, Ontario, Canada

The present study analyzes language profiles in 10 patients who presented with primary progressive aphasia (PPA) without global dementia for at least 2 years. Language and cognitive impairment were evaluated using the Western Aphasia Battery (WAB) and the Mattis Dementia Rating Scale (DRS). Expressive language disability with reduced speech fluency and anoma, but preserved language comprehension and nonverbal cognition, were typical features in early stages. Spontaneous speech was significantly more impaired in PPA than in anomic aphasia after left-hemisphere stroke and in language impairment in probable Alzheimer's disease (AD) ($p = 0.0004$). The profile of aphasia suggests that PPA tends to affect anterior parts of the language-dominant cortex first. Neuroimaging generally showed mild to moderate brain atrophy. In 2 patients atrophy involved especially the left frontal
cortex. Follow-up examinations that were done in 7 patients 1 or several years after the first assessment revealed continuous, most often rapid deterioration of language impairment. Two patients died 3 and 4 years after the onset of PPA. Neuropathological examination showed AD in 1 patient and Pick's disease in the other patient.

P254. Cognitive Changes with Chronic Vagal Nerve Stimulation in Man
Beaverley Clarke, Adrian Upton, Markad Kamath, and Helene Griff; Hamilton, Ontario, Canada

Eight patients implanted with a Cyberonics Neurocybernetic Prosthesis Model 100 to stimulate the vagus nerve were assessed for changes in cognitive performance. The patients had complex partial seizures for more than 10 years, with more than 6 per month. Patients were 34 years ± 7.8 SD old. Cognitive evaluation included response time to a randomized light signal appearing on a switch box (Test A); Test B, in which the signal appeared bilaterally; and Test C, in which a response to the signal was required while the patient simultaneously ignored a second signal. Data were collected and analyzed using an Apple II E computer and switch pad. All patients were taking therapeutic levels of 3 anticonvulsant medications and dosages were constant. Testing occurred 10 times during a day preoperatively (Day 1), 2 weeks postoperatively with the stimulator on (Day 2), and 3 months after turn-on (Day 3). Patients were randomized into high- and low-frequency stimulation groups (HFG and LFG). HFG parameters were 30 Hz, 500 msec pulse width (PW), and LFG 1 Hz, 130 msec PW. Examiners were blinded as to group. Student's t-test analyses of mean differences between groups and individual measurements showed a significant difference between HFG and LFG for Test C (p < 0.05). LFG showed a significant improvement for Tests A, B, C between Day 1 and 2, and for Test C between Day 2 and 3. No group effect was seen between Day 1 and 3 in the LFG. Individual measurements showed improvement for Test B (p < 0.05) for the HFG between Day 1 and 2, Test B (p < 0.05) between Day 2 and 3, and Tests A and B (p < 0.01) and (p < 0.05) Day 1 vs 1. The LFG group improved between Days 1 and 2 and 3. Between Day 1 and Day 3, the LFG showed improvement only for Test B (p < 0.001). Chronic stimulation of the vagus nerve improves cognitive function in epileptic patients and this improvement is more marked with low-frequency stimulation.

P255. Idiopathic Recurring Stupor: Association with an Endogenous Benzodiazepine Receptor Ligand (Endozepine)
P. Montagna, P. Tinuper, P. Cortelli, P. Avoni, G. Plazzi, E. Sforza, E. Lagares, A. Guidotti, and J. D. Rothstein, Bologna, Italy, Washington, DC, and Baltimore, MD

We reported idiopathic recurrent stupor (IRS) in a patient with stuporous episodes without known causes and reversed by flumazenil, a specific benzodiazepine (BZ) antagonist. Ictal plasma/cerebrospinal fluid (CSF) showed increased BZ-like activity (Ann Neurol, in press). Recently, an endogenous BZ-receptor ligand (endozepine [EZ]) has been purified from mammalian brain with properties similar to diazepam. It acts like diazepam to potentiate gamma-aminobutyric acid-mediated postsynaptic inhibition. We hypothesized that IRS might be due to an excess of this substance. IRS was diagnosed in 2 patients, 41 and 58 years old, who had recurring stupor or coma episodes lasting hours to days. Ictal brain CT/MRI, kidney, liver, heart, blood glucose, ammonia, and osmolality were normal. EEG showed fast 13-Hz background activity while the patients were unreactive to stimuli, reversed by flumazenil. Ictal serum or CSF revealed an enormous increase of the EZ in both patients, with levels as high as 400 nM, compared to 5 to 10 nM in control serum/CSF. Interictal CSF or serum in IRS contained EZ levels similar to control CSF and serum. IRS may be due to excess EZ. The cause for increased EZ is unknown.

P256. Language Comprehension Impairments in Parkinson's Disease: Evidence from Word Learning
Murray Grausman, Jennifer Nickanin, Barbara Schaefer, Kri Onishi, Matthew B. Stern, Steven Gollomp, and Howard Hurtig, Philadelphia, PA

Several reports have suggested that patients with Parkinson's disease (PD) have intellectual impairments in several domains such as memory, but few studies have explored difficulties in language processing. We investigated the ability of 20 nondemented PD patients with mild motor impairments to learn about the grammatical and semantic information represented in a new verb. The new verb was presented to patients in a sentence-picture matching context, and we probed their recall of the verb 10 minutes later. A sentence judgment task assessed grammatical knowledge by asking patients to judge the new verb, known verbs, and pseudowords used appropriately or incorrectly in a sentence. We found that 55% of PD patients were significantly impaired in their grammatical appreciation of the new verb (F [1, 33] = 17.03; p < 0.005). This was not related to their motor disorder or neuropsychological performance. A picture classification task used pictures illustrating specific aspects of the new word's meaning to evaluate semantic knowledge. PD patients were as accurate as controls at deciding whether a picture illustrated the meaning of the new verb (F [1, 33] = 0.10; p > 0.10). Only 1 PD patient (5%) had difficulty sorting pictures. Selective difficulty recalling only grammatical aspects of a new word suggests that the word learning impairment in PD cannot be entirely explained by poor memory. Instead, in agreement with other recent findings, PD patients may be impaired in some aspect of grammatical processing in language. We discuss the hypothesis that defects in the frontocaudate axis in PD underlie this impairment.

P257. Gender-Associated Cognitive Differences in Alzheimer's Disease
J. G. Buckwalter, Eugene Sobel, Marie Diz, and Victor W. Henderson, Los Angeles, CA

Neuropsychological performance on both verbal and nonverbal tasks is reported to differ between healthy men and women. Some of these cognitive differences are postulated to reflect differences in interhemispheric and intrahemispheric cerebral organization. Our preliminary study indicated that women with Alzheimer's disease (AD) performed worse than men on a composite neuropsychological battery, even after effects of potentially confounding variables were considered (Buckwalter et al, J Clin Exp Neuropsychol 1992;14:23). To explore further the nature of gender-associated differences in AD, we analyzed data from a verbal and a nonverbal task (the Boston Naming Test and drawings from the Spatial Quantitative Battery supplement to the Boston Diagnostic Aphasia Examination) for 22 men and 23 women who met NINCDS-ADRDA criteria for "probable" AD. Prior to ana-
lyzing the effects of gender, we used a hierarchical regression procedure to control for possible effects of subject age, education, age at onset of dementia symptoms, dementia duration, and family history of dementia. Significant gender effects were found for the verbal task (p < 0.005) (mean Boston Naming Test score of 21.4 for women and 34.4 for men), but not for the drawing task. We conclude that verbal abilities are more severely affected in women than in men with AD, a difference that may in part reflect premorbid gender-associated differences in cerebral hemispheric organization.

P258. A Paradoxical Hemispatial Effect in Chronic Neglect
Mark Monnemeyer, Steven Z. Rapsak, and Alan B. Rubens, Tucson, AZ

Hemispatial placement is known to affect line bisection in patients with neglect. Whereas placing stimuli in neglected space increases bisection error, placing stimuli in nonneglected space attenuates error. The effects of hemispatial placement on line bisection were examined in 4 patients with chronic neglect (over 5 months after stroke). All patients had large (frontotemporoparietal), unilateral, right-hemisphere lesions. Each patient bisected lines of different lengths (24, 26, 28, and 30 cm) in 3 hemispatial conditions (30 cm left of midline, midline, and 30 cm right of midline). Like previous reports, when patients bisected lines in left hemispace, a consistent (20/24 trials) left-sided neglect was observed (2.6 cm). However, when lines were bisected in center space, misbisections occurred on either side of the midline; and, unlike previous studies, when lines were bisected in right hemispace, a consistent (20/24 trials) right-sided neglect was observed (2.0 cm). The magnitude and directional consistency of line bisection errors were significant. Neither visual field defects nor limitations in reaching accounted for the results. Recovery in chronic neglect may involve a realignment of limited attentional resources favoring the body’s midline. Consequently, performance in both hemispatial fields can be biased toward midline, resulting in neglect of opposite directions.

P259. Depressive Symptoms Are Not Influenced by Severity of Multiple Sclerosis
Steven J. Huber, Robert A. Bernstein, and Kotstil W. Rammohan, Kansas City, KS, and Columbus, OH

Despite agreement that depression is the most common neuropsychiatric symptom associated with multiple sclerosis (MS), many aspects of this emotional change are unclear. One of the more controversial issues concerns the relationship between severity of MS and depression. This relationship is used to evaluate whether depression is an integral or reactive symptom of MS. Examination of this relationship is complicated by the presumed overlap between somatic features of depressive and neurological symptoms in MS. To clarify this situation, we examined the relationship between severity of MS and 4 categories of depressive symptoms using the Beck Depression Inventory (BDI). Eighty-nine patients and 47 normal controls were examined. For certain comparisons, patients were classified as mild (Extended Disability Status Scale of 0–2) or moderate/severe (3–8). Results indicated that total BDI scores and the depressive symptom categories (mood, self-reproach, vegetative, and somatic features) were elevated in patients with MS, but the extent of these elevations was not related to severity of disease. These results suggest that depression in MS is not a simple reaction to physical disability. Furthermore, clinical examination of depressive symptoms is straightforward and not confounded by severity of MS.

Poster Presentation: Other

P260. Neurological Involvement in Wegener's Granulomatosis: An Analysis of 324 Consecutive Patients
Hiroshi Nishimoto, Frank A. Rubino, Richard A. DeRemee, Jerry W. Swanson, and Joseph E. Parisi, Rochester, MN, and Jacksonville, FL

Neurological involvement in Wegener’s granulomatosis was studied in 324 consecutive patients diagnosed at the Mayo Clinic. One hundred and nine patients (34%) had neurological involvement. Peripheral neuropathy was seen in 53 (16.4%), cranial neuropathy in 21, external ophthalmoplegia in 16, cerebrovascular events in 13, seizures in 10, and miscellaneous involvement in 25. The mean age and sex ratio did not differ in those with or without neurological involvement. Among the patients with peripheral neuropathy, 42 had multiple mononeuropathy, 6 had distal symmetric polyneuropathy, and 5 had unclassified peripheral neuropathy. Multiple mononeuropathy was one of the major presenting symptoms in 8 patients. Kidney involvement was significantly higher in the patients with peripheral neuropathy compared to those without it (p < 0.001). Among the cranial nerves, the second, sixth, and seventh nerves were affected most frequently. Multiple cranial nerves were affected in 8 patients. Unusual neurological manifestations among the miscellaneous group included spastic paraparesis, temporal arteritis, Horner’s syndrome, and papilledema. This is the first comprehensive study on the frequency and distribution of neurological involvement in Wegener’s granulomatosis.

P261. Intravenous Immunoglobulin Treatment in Chronic Inflammatory Demyelinating Polyneuropathy: A Double-Blind Placebo-Controlled Crossover Study
Angela F. Hahn and Thomas E. Pearn, London, Ontario, and Calgary, Alberta, Canada

Treatment with high-dose intravenous human immunoglobulin (IVlg) has been reported to be beneficial in some patients with chronic inflammatory demyelinating polyneuropathy (CIDP), yet most observations have been not blinded. We examined the effect of IVlg therapy in 10 patients (6 men, 4 women) with CIDP in a double-blind, placebo-controlled crossover study. Disease was chronic progressive (n = 5) or chronic relapsing (n = 5) and of variable duration (4 mo to 21 yr). The diagnosis was confirmed by electrophysiological (10) and nerve biopsy (7) examinations. The trial consisted of two 28-day periods each. Patients were randomly treated with IVlg (0.4 mg/kg/day) or placebo on 5 consecutive days and followed. Function was assessed by a quantitative neurological disability score, functional grade, grip strength measurement, and electrophysiological nerve conduction studies at the beginning and end of each treatment period. With IVlg therapy, significant improvement was documented in 7/10 patients (improvement in neurological disability score mean 28 points [range 18–93], functional clinical grade 1 [1–6],
grip strength 9 kg (range 1.5–20 kg). The electrophysiological examination showed improvement with reversal of conduction block in 3 patients and was unchanged in 4. An apparent response to the placebo was seen in 3 patients. Improvement after IVIg therapy was maintained for variable durations (3–20 wk) and reoccurred with subsequent infusions. An equally effective response was documented after infusion of a single IVIg dose of 1 gm/kg. We conclude that IVIg therapy is effective in some patients with CIDP, even after long duration of illness. The best responses were observed in patients with recent relapse. A single high-dose treatment may be equally effective.

P262. Detection of *Borrelia burgdorferi* Antigen in Cerebrospinal Fluid from Neurological Lyme Disease Patients in the Absence of Anti-*B. burgdorferi* Antibodies

P. K. Coyle, Zhidian Deng, Lauren B. Krupp, Anita L. Belman, Jorge L. Benach, and Benjamin J. Luft, Stony Brook, NY

The object of this study was to examine whether *Borrelia burgdorferi* antigens could be detected in CSF in the absence of detectable antibodies to *B. burgdorferi* (the etiological agent of Lyme disease). Osp A is a 31-kd antigen that is specific for *B. burgdorferi*. Osp A was probed using Western (immuno) blot and specific mouse monoclonal antibodies. Polyclonal Lyme antibodies were detected in CSF using standard micro enzyme-linked immunosorbent assay. Seven patients had Osp A in CSF without detectable Lyme antibodies. There were 3 men and 4 women aged 20 to 58 years (mean 38 yr). Disease duration ranged from 2 weeks to 8 years. Neurological syndromes included confusion with acute flu-like illness, optic neuritis, hemiparesis with inflammatory brain lesion, encephalitis, headache with erythema migrans, bilateral facial nerve palsies, and encephalomyeloradiculitis. Three patients had CSF abnormalities. In 4 patients CSF parameters were otherwise completely normal. Possible explanations for undetectable CSF Lyme antibodies included early infection (3 patients), prior antibiotics (2 patients), and prior steroids plus antibiotics (1 patient). In 1 patient there was no obvious explanation. We conclude that Osp A, a specific antigen of *B. burgdorferi*, may be present in CSF without a detectable humoral response. The diagnosis of neurological infection with *B. burgdorferi* should not require a positive CSF serology.

P263. Herpes Simplex Type 2 in a Patient with Mollaret's Meningoitis: Demonstration by Polymerase Chain Reaction

Bruce A. Cohen and Anne Routley, Chicago, IL

A 29-year-old man was seen in September 1991 for his fourth episode of aseptic meningitis over a 4-year period. The episodes conformed to criteria for Mollaret's meningitis as published by Bruyn, Straathof, and Raymakers, and subsequently by others; they lasted about 1 week, and were characterized by fever, headache, meningismus, lymphocytic pleocytosis, elevated protein in cerebrospinal fluid (CSF), and spontaneous resolution without residua. Extensive prior evaluations had failed to uncover a cause. The patient was otherwise well and neither he nor his wife had any history of sexually transmitted diseases. Suspicion of herpes simplex virus (HSV) arose due to a single transient, raised skin rash several weeks earlier that failed to yield virus on culture. The patient was treated with acyclovir, which resulted in rapid resolution of symptoms. Though culture and immunological studies of CSF and blood again were unrevealing, polymerase chain reaction (PCR) studies of CSF confirmed the presence of HSV type 2. We suspect that herpes simplex virus is a more common cause of recurrent aseptic meningitis than current culture and immunological techniques would suggest. PCR offers increased diagnostic sensitivity for neurotropic viruses and should be considered in patients with recurrent meningitis of cryptic etiology.

P264. Inhibition of Astroglial-Induced Endothelial Differentiation by Inorganic Lead: A Role for Protein Kinase C

J. Laterra, J. P. Breisler, R. R. Indurthi, L. Belloni-Olivi, and G. W. Goldstein, Baltimore, MD

Microvascular endothelial function in developing brain is altered by inorganic lead. This may result from changes in protein kinase C (PKC) modulation. We examined the effects of inorganic lead on in vitro model of neural endothelial differentiation. Astroglial-induced endothelial differentiation into capillary-like structures was inhibited by lead acetate with 50% maximal inhibition occurring at 0.5 μM lead. Inhibition was independent of effects on cell viability or growth. We examined the effects of lead on cellular PKC pools under conditions that inhibited capillary-like structure formation. Membranous PKC increased in C6 astroglial and neural endothelial cells after exposure to lead acetate. Exposing C6 cells to 5 μM lead for 16 hours increased membranous PKC by 150% as determined by immunoblotting. Membranous PKC increased in response to as little as 50 nM lead and saturated at 1 μM. Phorbol esters were used to determine if PKC modulation was mechanistically related to lead’s inhibition of capillary-like structure formation. 12-Myristate 13-acetate (10 nM) inhibited endothelial differentiation by 65 ± 5%, whereas 4-alpha-phorbol 12,13-didecanoate was without effect. These findings demonstrate that inorganic lead may induce cerebral microvessel dysfunction by interfering with PKC modulation in microvascular endothelial or perivascular astroglial cells.

P265. Diaphragmatic Dysfunction in Multiple Sclerosis

W. F. Brown, B. V. Watson, J. Garland, G. C. Ebers, and N. Deat, London, Ontario, Canada

Gait difficulties in multiple sclerosis (MS) are commonly accompanied by fatigue and dyspnea. Possible explanations for the latter include weakness and/or dyssynergia of the respiratory muscles, including possible abnormalities in central pathways regulating respiration. This study examined central and peripheral motor conduction to the diaphragm in 15 MS patients whose gait was notably labored and accompanied by breathlessness. Peripheral conduction was assessed by measuring the latency and size of the surface-recorded diaphragmatic maximum M-potential responses to supramaximal stimulation of the phrenic nerve in the neck, and central motor conduction by comparable measurements in response to magnetoelectrical stimulation over the vertex. Peripheral motor conduction was normal. The most striking abnormalities were in central motor conduction. Cortical stimulus-evoked diaphragmatic responses were absent on both sides in 3 patients, and unilaterally in 1 patient, whereas in 5 others the latency of the cortical stimulus-evoked response was increased and the size clearly reduced and entirely normal in only 3 patients. These studies show that central conduction
Tuesday, October 20

to the diaphragm is commonly abnormal and may play a role in the fatigue and dyspnea experienced by MS patients.

P266. Coxiella-Associated Myelopathy
Y. M. Hwang, M. C. Lee, D. C. Sub, and W. Y. Lee,
Seoul, Korea

Six men (40–53 yr) developed myelopathy that progressed slowly over several months and was characterized by asymmetrical, incomplete spinal cord syndrome manifested at the sensory level at the trunk, mild spastic paraparesis, and urinary incontinence. The spinal cord lesions at appropriate levels were recognized by MRI as enhancing lesions in 4 of the men. Coxiella burnetii infection was confirmed in the blood of all patients by immunofluorescence microscopic assay (IFA) and transmission electron microscopy (TEM). In 2 patients, we detected C. burnetti by TEM and IFA using CSF of the patients inoculated onto fresh peripheral blood lymphocytes. Four patients who were treated with appropriate antibiotics responded with either partial resolution of symptoms or arrest of further neurological progression. In 3 patients the lesion was shown on MRI to have decreased in size. In summary, we report 6 cases of transverse myelopathy associated with C. burnetti infection. This is the first report, to our knowledge, of Coxiella-related chronic myelopathy.

P267. MRI of Sensorineural Hearing Loss:
New Observations
Alexander S. Mark and Dennis Fitzgerald, Washington, DC

We present a series of patients with different labyrinthine lesions diagnosed by MRI. Twelve patients with sensorineural hearing loss were studied by gadolinium-enhanced MRI, including 3-mm contiguous T1-weighted images through the labyrinth. Ten patients had enhancement of the cochlea or vestibule, or both. All patients with cochlear enhancement had severe neural sensory hearing loss. All patients with vestibular enhancement had severe vestibular symptoms. The patients’ final diagnosis included viral labyrinthitis (3 patients), syphilitic labyrinthitis (2 patients), bacterial labyrinthitis (1 patient), and vestibular neuromas (3 patients). One patient had an acoustic neuroma extending in the basal turn of the cochlea. The enhancement in patients with vestibular neuromas was brighter and there was slight mass effect in comparison with the patients with inflammatory labyrinthine lesions. One patient had hemorrhage within the vestibule from an adjacent temporal bone hemangioma. One patient with CT-proven cochlear otosclerosis had pericochlear areas of enhancement on gadolinium MRI. MRI can diagnose a variety of labyrinthine lesions that correlate very well with the patient’s clinical symptoms. Gadolinium should be used routinely in patients with suspected labyrinthine disease.

P268. Enhancement of the Endolymphatic Sac on Gadolinium-Enhanced MRI in Patients with Hearing Loss and Vertigo: A Possible Sign of Endolymphatic Hydrops
Alexander S. Mark, Sharon Seltzer, and Dennis Fitzgerald, Washington, DC, and Philadelphia, PA

The diagnosis of Meniere’s disease and endolymphatic hydrops remains a diagnosis of exclusion. Few radiographic findings have been correlated with the clinical symptoms of this entity. We describe 9 patients with symptoms of hearing loss or vertigo, or both, who demonstrated enhancement of the endolymphatic sac on gadolinium-enhanced MRI. No enhancement was noted in a series of 20 controls with no symptoms of hearing loss and vertigo. Enhancement in the brain correlates with inflammatory or neoplastic conditions. We thus can speculate that enhancement of the endolymphatic sac reflects an inflammatory process in this location that may interfere with the normal resorption of indulin and secondary hydrops. In addition to excluding an acoustic neuroma and a labyrinthine schwannoma (which clinically may be confused with Meniere’s disease), contrast-enhanced MRI may provide objective evidence in favor of labyrinthine hydrops.

*Note: The authors of posters 74, 116, 120, and 125 are recipients of the first annual Travel Fellowship Awards.

296 Annals of Neurology Vol 32 No 2 August 1992