Abstracts

SCIENTIFIC SESSION A
Cerebrovascular Disease, Behavior, and Pathophysiology

A1. The Retina as a Possible Model for Gray Matter Vasculopathy
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If, as is generally held, the inner layers of the retina are comparable to gray matter of the brain, the eye provides a unique opportunity to study certain neuropathological processes unobscured by associative myelin reactions. Study of microvascular accidents is especially opportune since the retinal vessels may be prepared as whole mounts by trypsin digestion and visualized with conventional dyes. These mounts may then be correlated with the preceding ophthalmoscopic observations and with subsequent ultrastructural changes. The present report will document the vascular morphology of the retina and the consequences of occlusive vascular disease, with the implication that similar changes may be expected in the microcirculation of the brain's gray matter.

A2. Correlation of Retinal and Cerebral Vascular Disease: Concurrence of Retinal and Cerebral Stroke
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Despite increasing interest in the risk of cerebral stroke among patients with central retinal artery occlusion (CRAO), reliable data are meager. In an effort to develop statistics for the concurrence of retinal and cerebral stroke, we retrospectively analyzed 85 patients with either CRAO or central retinal artery branch occlusion (CRABO) seen between 1970 and 1980. Demographic characteristics and clinical profile of the patient population, including signs of extracranial atherosclerosis, incidence of atherosclerosis risk factors, and angiographic findings, will be presented. Based on these data, the patients were assigned to one of three diagnostic categories: (1) intracranial and extracranial atherosclerosis, (2) nonatherosclerotic cause, and (3) diagnosis unknown. With the use of these diagnostic categories, the incidence of cerebral transient ischemic attacks (TIAs) and stroke will be discussed and compared to their incidence in the total retinal stroke population. The data showed a 15% incidence of cerebral stroke and 13% incidence of cerebral TIAs in the total retinal stroke population. Within specific diagnostic categories, we found a cerebral stroke incidence of 17% for CRAO and 20% for CRABO when the basis was atherosclerosis. For cerebral TIAs the incidence was 13% and 16%, respectively. In contrast, no cerebral TIAs or stroke occurred in patients with retinal strokes (both CRAO and CRABO) of nonatherosclerotic origin. In the unknown diagnostic category, the frequency of cerebral stroke and TIA mirrored the atherosclerotic incidence for CRAO and the nonatherosclerotic incidence for CRABO. Recognizing this risk incidence, we will present recommendations for an algorithm of retinal stroke evaluation.

A3. Venous Malformations of the Thalamus with Normal Angiograms
Karyl A. Norcross, Ivan S. Ciric, Michael A. Mikhael, and Nicholas A. Vick, Evanston, IL

We have cared for two patients with fatal vascular malformations involving the thalamus who we thought had gliomas. A third patient, still alive, has a similar-appearing lesion. All three experienced progressive neurological impairment with subacute onset as adults; one had had neurologic symptoms earlier that might have been related to extension of his lesion into the brainstem. Computed tomographic (CT) scans in all three patients showed large mass lesions of increased density without noteworthy contrast enhancement. All had normal cerebral angiograms. In the two patients who died, serial CT scans had shown expanding mass lesions. Without biopsy, they were treated with radiation to no avail. The third patient, who presented at age 59 years with intermittent sensory symptoms on the right side, was found by CT to have a left thalamic mass. A stereotactic biopsy of his lesion showed only gliosis and caused an intracerebral hemorrhage with right hemiparesis. Despite the ominous appearance of his left thalamic lesion, his sensory symptoms have improved and his hemiparesis has cleared without specific treatment. Moreover, serial CT scans have documented regression in the size of his lesion. We believe he has an angiographically negative venous malformation of the thalamus, as did the two patients who died and whose brains were examined. It appears that some of these lesions may steadily expand and mimic true neoplasms. Radiotherapy certainly was ineffective for our two patients who died; whether it played a role in their decline is not easy to know. Cases such as these point out the problem of proceeding with radiotherapy without a tissue diagnosis. The third case illustrates the potential for trouble if one tries to establish a tissue diagnosis of a deeply placed lesion during life, as well as the possibility of a benign course.

A4. Hypoglycemia Masquerading as Cerebrovascular Disease (Hemiplegic Hypoglycemia)
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Hypoglycemia caused recurrent hemiplegia in 15 patients initially suspected of having a stroke. Clinical examination, cerebral angiography, computed tomography, and in a single case necropsy failed to demonstrate cerebrovascular or focal brain disease. All the patients had conventional hypoglycemic attacks as well as recurrent hemiplegia, but when they were hemiplegic the usual features of hypoglycemia were absent. Thirteen were diabetics taking hypoglycemic agents, and they usually exhibited hemiplegia in the morning. Two had insulinomas and showed a more random pattern. Hypoglycemia was recognized as a cause of hemiplegia in 14 patients, and correction of the hypoglycemia led to complete and rapid recovery as well as freedom from future attacks. One patient died during a prolonged attack of hypoglycemia. The hemiplegia was exclusively right-sided in 8 patients, left-sided in 5, and alternating in 4. The hemiplegia lasted from 30 minutes to 24 hours. Insulin infusion reproduced the hemiplegia in only 1 of 5 patients. Neither undetected brain disease nor selective neuronal vulnerability adequately explains all the features of this disorder. Hemiplegic hypoglycemia deserves a place in the
differential diagnosis of cerebrovascular disease. When the syndrome is recognized and successfully corrected, aggressive neurological investigations are usually unnecessary.

A5. Outcome in Spontaneous Dissections of the Internal Carotid Arteries

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Thirty-six patients with spontaneous dissection of the internal carotid arteries were followed from 3 to 140 months (mean, 39 months). Twenty patients, with 24 vessels involved, had follow-up arteriograms within 1 to 45 months (mean, 11 months) following the initial study. Nine vessels had returned to normal, in 5 the narrowing had lessened, and in 6 there were residual aneurysms but the luminal narrowing had either resolved or markedly improved. Three vessels showed no change. One vessel had completely occluded following direct surgical intervention. Superficial temporal artery-middle cerebral artery bypass was carried out in 7 patients. The stenotic lesions had resolved in all 6 patients who had subsequent arteriograms. Seven patients received 3 to 6 months of anticoagulant therapy and 13 received antiplatelet agents. Clinically, 75% of the patients achieved complete resolution of symptoms with 15 demonstrating only slight residual miosis or ptosis. Headaches resolved within 3 months in three-quarters of the patients. Eight patients had residual neurological deficits including hemiparesis, sensory deficits, and dysphasia, none severe. All patients were ambulatory and independent. One patient has continued with severe, although diminishing, headache after five years. Despite their often disconcerting angiographic appearance, spontaneous dissections of the internal carotid arteries carry a good prognosis in most cases. The arterial stenoses often resolve spontaneously.

A6. Anticoagulant-induced Hemorrhage in Acute Cerebral Embolism

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The role of anticoagulants in the treatment of acute nonseptic cerebral embolism of cardiac origin remains controversial. The central issue is whether the benefit of anticoagulants in reducing the risk of early recurrent embolism outweighs their risk of inducing hemorrhage into the infarcted area. We reviewed a series of 28 patients with nonseptic cerebral embolism of cardiac origin treated with anticoagulants and report 5 in whom early anticoagulant treatment resulted in clinical deterioration or death from frank hemorrhage into the acute infarct. In each case, an initial computed tomographic scan excluded the presence of cerebral hemorrhage and a second scan, after clinical deterioration had occurred, documented frank hemorrhage into the infarcted zone. Four patients were hypertensive, and all had large infarctions in a middle cerebral artery territory. Four patients received heparin within 36 hours of their stroke, and 1 was taking warfarin at the time of embolism. Clinical deterioration occurred after intervals of several hours (2 cases), 5 days (2 cases), and 30 days (1 case). Three patients died as a result of the hemorrhage. These cases emphasize that caution should be exercised regarding the early anticoagulation therapy of patients with acute cerebral embolism, particularly in the setting of hypertension and large infarctions.

A7. Glucose Utilization Changes in Cerebral Cortex and Cerebellum Associated with Brain Tumors

Giovanni Di Chiro, Nicholas J. Patronas, Robert L. DeLaPaz, Barry H. Smith, Henry Milam, Rodney A. Brooks, and Paul L. Kornblith, Bethesda, MD

We used positron emission tomography (PET) with 18F-deoxyglucose in 54 patients with cerebral tumors to study metabolic changes in cerebral tissues not directly involved in the lesion. Thirty patients had biopsy-proved high-grade gliomas (grade III or IV), and 20 were diagnosed by either biopsy or multiple clinical and computed tomographic (CT) criteria as having low-grade gliomas (grade I or II). The remaining cases included 3 meningiomas and 1 cerebral metastasis. We found that in 90% of our patients, the cerebral cortex adjacent to the tumor was metabolically suppressed by 11 to 60% compared with the opposite hemisphere. The CT studies in the majority of these cases showed that suppressed cortex was hypodense due to spread of edema, but in about 30% of the patients the suppressed cortex appeared normal. In 10 cases hypometabolism was also seen in remote regions neuronally connected to the tumor area. Furthermore, in 12 out of 24 patients in whom satisfactory PET sections of the posterior fossa were available, metabolic suppression of the cerebellum on the side opposite to the cerebral tumor was observed. These cortical metabolic abnormalities in patients with brain tumors often may explain clinical symptoms which cannot be fully accounted for by the presence of the neoplasm alone. The relationship of our PET observations to the phenomenon of "diaschisis" described by von Monakow will be discussed.

A8. Aphasia: Clinico-pathological Correlations and Brain Mechanisms

Harold B. Schiff, Michael P. Alexander, Margaret A. Naeser, and Albert Galaburda, Boston, MA

The syndrome of aphasia has been lost in terminological arguments for the past 120 years. The syndrome is, however, a clinically distinctive one and is the only syndrome among the anterior aphasias in which early prognostication is possible. The theoretical implications of this syndrome, in which disorders of speech and language intersect, are important for comprehending the cerebral mechanisms for language, yet understanding of the anatomical basis for the syndrome has not progressed since the arguments of Dejerine and Pierre Marie. Four new cases of aphasia will be presented, 2 with cortical and 2 with deep white matter lesions. We will review the speech and language abnormalities and clinical course of these patients as well as the 32 adequately described cases from the literature. The clinical syndrome of aphasia will be described and the tomographology correlated with anatomic data from computed tomographic scans (personal cases) and autopsy reports (literature). We propose an anatomical basis for this predominantly dysarthric syndrome. Within the framework of the anterior aphasias, an understanding of the pathogenesis of aphasia may well cast light on the brain mechanisms for speech and language.
A9. Nuclear Magnetic Resonance Imaging in Patients with Definite Multiple Sclerosis
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Ten patients with clinically definite multiple sclerosis were examined with both high-resolution computed tomography (CT) and a high-resolution nuclear magnetic resonance (NMR) unit using a superconducting 3.5 kilogauss magnet. The NMR images were generated using both inversion-recovery and spin-echo techniques. The spin-echo images were generated using a variety of time intervals between application of the radiofrequency pulse and signal acquisition. The NMR images demonstrated many discrete areas of white matter abnormality in all patients, while in most cases both precontrast and postcontrast CT scans were normal. In addition, in most patients the NMR images demonstrated periventricular areas of discrete high signal intensity corresponding to the known pathological distribution of demyelination. None of the patients studied were experiencing an acute flare-up of their disease at the time of the studies, but all had a residual neurological deficit. The number and distribution of high-intensity areas far exceeded that which could explain the patients' neurological deficit. It therefore appears that NMR can readily demonstrate lesions which are clinically silent. The inversion-recovery images appear to provide the best spatial detail, while spin-echo images give the best density resolution and resolve the largest number of abnormal areas. The longer the interval between the application of radiofrequency pulse and signal acquisition, the better the density-resolving capabilities in this disease.

A10. A Histological Substrate for Speech-related Cortical Asymmetry
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Little is known about relevant microhistological substrates for cerebral hemispheric asymmetry and lateralization of function. We performed a quantitative study of neuronal dendritic patterns in the premotor speech-related frontal region of the left hemisphere (Broca area) compared with its homologous cortical zone (right) and with ipsilateral and contralateral Rolandic (motor) regions located directly posterior. One hundred ninety-two Golgi-stained cells from these four regions from eight males (seven of known handedness) were analyzed to compare dendrite lengths and segmental patterns. We found that: (1) the total length of basilar dendrites of premotor neurons was greater by 20% than that of motor neurons; (2) the basilar dendrite systems of the left and right premotor cortices differed, not in total dendrite length but in relative distribution, between lower-order (1 through 3) and higher-order (4 through 6) dendrite segments, the latter predominating on the left; and (3) the only instance in which total length of higher-order dendrites was greater in the right premotor region occurred in a non-right-handed patient. The time course of sequential patterns of dendritic growth is known (Conel), fourth- to sixth-order dendrites appearing during the second to fourth years of life. Our findings, indicating a predominance of higher-order segments on the left, suggest the presence of a structural analogue of the later-maturing language function. (Supported by Grant NS 13871-1-3 from the US Public Health Service.)

A11. Computed Tomographic Scan Predictors of Recovery of Auditory Comprehension in Aphasia
David S. Knopman, Ola A. Selnes, and Alan B. Rubens, Minneapolis, MN

Lesion location and volume as determined by computed tomography (CT) were analyzed as predictors of recovery of auditory comprehension following ischemic stroke of the left hemisphere in 39 consecutive patients. The patients, aged 44 to 75 years, were right-handed native English speakers with no previous central nervous system disease. Auditory comprehension was assessed initially and then monthly for six months using the token test, a series of commands of increasing complexity. CT scans obtained five months postonset were used for lesion localization and volume determination. In 14 patients without initial deficit in auditory comprehension, the lesion volume was small (mean volume, 21 cm$^3$) and the posterior superior temporal region was spared in 12. A severe initial deficit in auditory comprehension with no improvement was seen in 9 patients; all had large lesions (mean volume, 123 cm$^3$) including the posterior superior temporal region. Poor initial auditory comprehension was also present in the remaining 16 patients, all of whom showed some recovery over six months, but in only 8 of the 16 was the recovery complete. Of the fully recovered patients, 6 of 8 had no lesions of the posterior superior temporal area, while the 8 who achieved partial recovery had lesions in that region. These two groups of patients, one fully and the other partially recovered, differed only in involvement of the posterior superior temporal region but not in mean lesion volume (52 versus 60 cm$^3$, respectively), initial deficit, or lesions elsewhere. Thus, lesions of the posterior superior temporal region were highly reliable but not perfect predictors of recovery of auditory comprehension by six months after stroke. Neither lesion volume nor severity of the initial deficit in auditory comprehension were as useful as predictors.

A12. A New Syndrome of Delusional Misidentification
Joseph M. Foley and Lawrence Breslin, Cleveland, OH

Syndromes of delusional misidentification, long considered to be part of major psychoses of a“nonorganic”variety, are now being recognized in dementing illnesses associated with structural lesions of the brain. These include the syndromes of reduplicative paramnesia and the syndrome of Capgras. We report a syndrome of delusional misidentification which we believe has not been recognized previously. We have observed it in seven patients and studied it in detail in three. The patient fails to recognize his or her own image in a mirror while recognizing and properly identifying the images of other people in the mirror. Generally, but not always, the patient’s self-image is regarded as undesirable, as a person intending harm to the patient, and is associated with other evidences of paranoid behavior. All the patients were demented, probably suffering from Alzheimer disease. Prospagnosia was not present. Phenothiazines and haloperidol reduced the intensity of the reaction in two patients but did not entirely suppress it. Behavioral changes previously unexplained became understandable and, to a degree, manageable when the mirror phenomenon was identified as part of the overall disturbance.
Neuromuscular Disease, Neuropharmacology, and Miscellaneous Disorders

B1. Cerebellar Cortical Degeneration Caused by High-Dose Systemic Therapy with Cytosine Arabinoside
Marc D. Winkelman and John H. Hines, Cleveland, OH

Four patients developed cerebellar cortical degeneration in relation to a course of high-dose systemic cytosome arabinoside (3 gm per square meter of body surface area given intravenously twice daily for six days) administered as induction therapy for acute leukemia. Ataxia of stance and gait and of limb movements, scanning dysarthria, and nystagmus began three to six days after the first dose and reached their peak of severity in six to eight days, after which they stabilized and then incompletely abated over a period of days to weeks. Alcoholism and weight loss were not factors. Survival after the onset of cerebellar signs ranged from three weeks to six months. Complete postmortem examinations, performed in all four patients, showed a diffuse but patchy degeneration of the cerebellar cortex affecting mainly the Purkinje cell and molecular layers. Remaining neurons, examined by phase microscopy, were normal. The clinical features correlated closely with the pathological changes, and both differed from those of cerebellar degeneration of the malnourished alcoholic. The stereotyped onset of symptoms in close temporal relationship to administration of high-dose systemic cytosome arabinoside, and the improvement following cessation of therapy, indicate that the cerebellar cortical degeneration was not paraneoplastic in nature but was due to direct toxic effects of the drug.

B2. Cauda Equina Syndrome Secondary to Longstanding Ankylosing Spondylitis
J. D. Bartelson, M. D. Cohen, T. M. Harrington, and W. W. Ginsburg, Rochester, MN

We report 13 patients with cauda equina syndrome secondary to longstanding ankylosing spondylitis. The mean age at onset of the spondylitis was 22.5 years. Symptoms of cauda equina syndrome began at a mean age of 56 years. Only 4 patients had received radiation therapy to the spine. Five of the 13 patients presented with sensory loss, 3 with pain, 2 with simultaneous cutaneous sensory and urinary sphincter disturbances, 2 with bladder complaints, and 1 with difficulty evacuating stool. In time, 6 patients experienced pain, 3 in the leg and 3 in the rectum. Two patients developed painless neurotrophic skin ulcerations in both heels. Sensory loss was found in the distribution of the fifth lumbar or sacral nerve roots (or both) on one or both sides in every patient. Mild to moderate weakness in a similar distribution was noted in 7 of the 13 patients, but all were ambulatory. Every patient had urinary sphincter problems, including overflow incontinence, difficulty emptying, and decreased sensation. There was prominent loss of rectal sphincter tone, and most had bowel complaints; half had incontinence of stool. Electromyographic abnormalities, sometimes minimal, were consistent with multiple lumbar-sacral radiculopathies. Myelography, surgical exploration, and computed tomography, when performed, showed a normal or enlarged caudal dural sac and occasional dorsal arachnoid diverticula. The course of the patient's cauda equina syndrome was slowly progressive. Recognition of this syndrome may allow one to omit myelography, which is difficult to perform owing to the associated spinal abnormalities. Surgical intervention should be avoided.

B3. Successful Treatment of Myotonic Dystrophy with Imipramine
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Myotonic dystrophy (dystrophia myotonica, myotonia atrophica, Steinert disease) is a common neuromuscular disorder (incidence, 13.5 per 100,000) characterized by clinical myotonia and progressive, mainly distal, muscle weakness. There are associated multiple systemic disturbances, including abnormal esophageal, gastrointestinal and gallbladder motility; glucose intolerance; defective cardiac conduction and contraction; extrathyroidal hypometabolism; and intellectual impairment. We found that patients with myotonic dystrophy also characteristically fulfill the American Psychiatric Association DSM III criteria for major depression (Med Hypotheses 7:1059, 1981). While receiving tricyclic antidepressants to treat this depression, 35 patients with myotonic dystrophy who were evaluated before and during treatment also showed: (1) reduced clinical myotonia; (2) significant measurable increases in muscle strength testing; (3) improvement in gastrointestinal function (including cessation of cyclic diarrhea and constipation); (4) measurable improvement in cognitive function (by neuropsychological testing); and (5) reduction in frequency or disappearance of electrocardiographically recordable cardiac arrhythmias. These improvements, including better strength, were observed in 30 patients receiving imipramine in doses of 100 to 150 mg per day (blood levels of 100 to 200 ng/ml). Five patients treated with comparable amitriptyline doses showed similar improvement.

B4. Mechanism of Ataxia in Fisher Syndrome
Bhagwan T. Shahani and Allan H. Ropper, Boston, MA

Since the original description by Fisher, many reports have appeared of a Guillain-Barré syndrome variant with ophthalmoplegia, areflexia, and an ataxia that has a "cerebellar" rather than "sensory" appearance. We performed detailed clinical and electrophysiological studies to elucidate the mechanism of ataxia in a 43-year-old man with Fisher syndrome. In addition to the typical findings, sensory examination demonstrated relative preservation of pinprick, light touch, and vibration sensations. However, joint movements of similar velocity were perceived better distally than proximally; approximately 5 to 10 degrees in finger and wrist joints, 30 degrees at the elbows, and 60 degrees at the shoulders (normal, 5, 10, and 15 degrees, respectively). In contrast, silent periods, produced by carefully adjusted electrical stimuli to study proprioceptive function, were present in proximal but absent in distal muscles. Surface electromyographic recording from antagonist muscles and accelerometric tracing during voluntary activity of the arm had features indistinguishable from those of cerebellar ataxia. F-responses were abnormal and H-reflexes were absent. The findings of diminished joint position sense and preserved proprioceptive function proximally, and the opposite distally, suggest that cerebellar-like ataxia in peripheral neuropathy may be due to unbalanced inputs from muscle spindles and joint capsule receptors, both of which are responsible for signaling limb position.
B5. A Double-Blind Controlled Trial of Leucine in Duchenne Muscular Dystrophy
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Ninety-six patients with Duchenne muscular dystrophy were evaluated using a protocol that measures strength, joint contractures, functional grade and activity, and pulmonary function test (Muscle Nerve 4:186, 1981). The patients were initially followed at regular intervals for one year, during which they were given a placebo capsule; this was done to determine the natural history of the disease in the study population. After one year, the group was randomized and placed on either placebo (consisting mostly of cellulose filler with a few milligrams of quinine) or leucine (0.2 gm per kilogram of body weight). One month after initiation of the leucine phase there was a significant difference (p < 0.01) in the strength of the two groups, the treated group being stronger than the placebo group. This difference persisted for two months and then gradually disappeared over the rest of the year’s treatment. When the results were compared to those obtained during the preceding “natural history” year when all patients were given placebo, the difference was found to be due to an unexplained worsening in the placebo group rather than a beneficial result in the treatment group. There was no change in any of the laboratory findings. Without the availability of an initial year’s study on placebo, these results would probably have been misinterpreted as being due to a beneficial response to leucine.

B6. Acute Pandysautonomia
P. A. Low, P. J. Dyck, E. H. Lambert, W. S. Brimijoin, J. C. Trautmann, and J. R. Malagelada, Rochester, MN

Acute pandysautonomia is characterized by severe sympathetic and parasympathetic impairment with relative or complete preservation of somatic motor and sensory function. Sural nerve biopsies have been reported in two cases (Young RR et al, Brain 98:613-636, 1969; Appenzeller and Kornfeld, Arch Neurol 29:334-339, 1973) and have been normal or have shown only mild abnormalities. We report two patients, one of whom has been extensively studied over five years with excellent correlation between dysautonomia and special studies. The extensively studied patient was a 46-year-old woman who had the sudden onset of abdominal colic followed by severe impairment of blood pressure control, retention of urine, blurred vision, and anhidrosis. Sural nerve biopsy showed selective loss of small myelinated fibers; density of unmyelinated fibers was reduced to 15,000/mm²; a C potential was absent in the in vitro compound muscle action potential; dopamine-β-hydroxylase was unmeasurable. On autonomic testing the patient had severe postural hypotension and marked impairment of vasomotor, sudomotor, pupillographic, and bladder function. Gastrointestinal motility studies were markedly deranged. When autonomic tests were repeated five years later there was only partial return of autonomic function. (Supported in part by Grant NS 14304 from the National Institutes of Health and by grants from the Muscular Dystrophy Association and the Mayo Foundation.)

B7. Morphometric Confirmation of Axonal Atrophy and Secondary Segmental Demyelination in Hereditary Motor-Sensory Neuropathy Type I
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From our previous studies it is known that axonal atrophy leads to secondary segmental demyelination in chronic neuronal (axonal) degeneration. To test whether atrophy precedes degeneration and plays a role in segmental demyelination of hereditary motor-sensory neuropathy type I (HMSN-I), transverse semithin sections of sural nerve were morphometrically assessed using imaging and as corrected by electron microscopy. Values for 10 nerves from symptomatic patients with HMSN-I were compared to values for 41 nerves from age-matched controls (Karnes, Nukada, and Dyck, 1982). Although the means of the median myelinated fiber diameters were not significantly different between disease and control nerves, the axon area was significantly smaller for the disease than for the control group (5.06 and 7.42 µm², respectively; 0.001 < p < 0.005). The mean of the median myelin area of myelinated fibers was slightly greater in disease than in control nerves (0.01 < p < 0.02), which was interpreted as due to myelin wrinkling. The slopes of regression lines relating axonal area or index of circularity (IC = πD²/p) to myelin thickness (MT) or number of myelin lamellae were significantly less steep for myelinated fibers in HMSN-I than in control nerves. The mean values of the axonal areas for the 0.5 µm MT point on the regression lines were not different (1.1 and 1.1 ln µm²; p > 0.05) for disease and control nerves, respectively. Comparable values for 1.5, 2.5, and 3.5 µm MT were: 1.6 and 2.3 ln µm² (p < 0.0005), 1.9 and 3.5 ln µm² (p < 0.0005), and 2.2 and 4.4 ln µm² (p < 0.0005). These results provide unequivocal evidence for axonal atrophy in HMSN-I. Axonal atrophy therefore appears to be involved in the segmental demyelination, onion bulb formation, and axon loss of HMSN-I.

B8. Inherited Plexus Neuropathy and Inherited Tendency to Pressure Palsy Are Different Disorders
Anthony J. Windebank, Jasper R. Daube, and Peter James Dyck, Rochester, MN

Kinships with focal recurrent neuropathies may constitute a spectrum of disease or several distinct disorders. We prospectively studied 16 patients from seven families who presented with subacute focal neuropathy and had a family history of the disorder. They were examined clinically, genetically, electrophysiologically, and pathologically and by computer-assisted sensory examination (CASE). Additional information was gathered on 21 affected and 36 unaffected family members. Autosomal dominant inheritance was universal, but there was segregation by family into two distinct groups: those who presented with recurrent painful plexus neuropathies—four families with inherited plexus neuropathy (IPN); and those with recurrent painless pressure palsies—three families with inherited tendency to pressure palsy (ITPP). Among the patients with ITPP, 4 had clinical and electromyographic evidence of diffuse sensorimotor neuropathy. Symptomatic involvement at pressure points was characterized by conduction slowing or block. Two patients examined by CASE showed generalized sensory involvement. Brachial plexus fascicular biopsy in 1 case showed focal thickening of the myelin sheath (tomaculous neuropathy). In all 12 patients with IPN, clini-
of and electromyographic evidence of generalized neuropathy was absent. In 4 cases studied acutely, electromyography suggested axonal destruction within the plexus. In 8 cases studied by CASE, no generalized sensory changes were found. Brachial plexus biopsy from 1 patient did not show any myelin abnormality. It appears that two phenotypically distinct, genetically determined disorders occur within this class of disease. Complete functional recovery from acute episodes was the rule, although in 2 patients with TTPP the features of progressive distal neuropathy persisted in later life.

B9. Abnormal Aspartate/Malate Metabolism in a Dominantly Inherited Olivopontocerebellar Degeneration

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Nondominant olivopontocerebellar atrophy (OPCA) has been shown to be associated with a systemic defect in glutamate/a-ketoglutarate metabolism (Plaitakis et al, Science 261:193, 1982). Though this defect is not present in the dominant form of OPCA, an alternate but similar metabolic abnormality may exist. To explore this possibility, we measured various amino acids and Krebs cycle substrates in plasma of 8 fasting patients from a dominant OPCA kindred. Aspartate levels were selectively reduced in the plasma of these patients (3.99 ± 0.48, mean ± SD) when compared to age- and sex-matched healthy family members not at risk (5.07 ± 0.51; p < 0.001) as well as 49 unrelated normal and disease controls (5.03 ± 0.68; p < 0.001). Fasting plasma aspartate concentrations showed a bimodal distribution pattern in 16 family members who were at risk for developing the disease, suggesting that changes in plasma aspartate may precede the onset of the illness. Oral glutamate loading (60 mg per kilogram of body weight of monosodium glutamate) in affected patients resulted in a normal rise in plasma aspartate, indicating an intact transamination pathway. Oral glucose loading, however, induced significant increases in plasma malate after one hour (by 70%, p < 0.001) and two hours (by 59%, p < 0.001) together with significant reductions in the plasma aspartate/malate ratio in patients compared with controls. These data suggest decreased aspartate formation from malate, which may result from defective mitochondrial transport or oxidation of malate. Abnormal metabolism of neuroexcitatory amino acids may underly the various OPCAs.

B10. Monoclonal Antibody Analysis of the Mononuclear Cell in Muscle Biopsy

Kichi Arahata and Andrew G. Engel, Rochester, MN

Except for macrophages, the importance of mononuclear cells in muscle myopathies has been unclear. Monoclonal antibodies recognizing all peripheral T cells (Lyt 3), suppressor/cytotoxic T cells (OKT8), inducer/helper T cells (OKT4), B cells, macrophages, and activated T cells (Ia-positive cells) were used to type mononuclear cells by the immunoperoxidase method in 75 biopsies (normal, 9; inflammatory myopathies, 56; Duchenne dystrophy, 10). Sparse Ia-positive cells and T cells were found in normal muscle. In all diseases, Ia-positive macrophages invaded necrotic fibers. In all inflammatory myopathies a mixed exudate of OKT8-, OKT4-, and Ia-positive cells was observed. This was predominantly perivascular in scleroderma and dermatomyositis but was also present in perimysial areas and between muscle fibers in pure polymyositis. In inclusion body myositis, OKT4 cells were uncommon. In 13 of 14 cases of inclusion body myositis and 8 of 18 of polymyositis, OKT8-positive cells focally surrounded and invaded nonnecrotic muscle fibers. Rare fibers in Duchenne dystrophy were similarly affected. Electron microscopy revealed lymphocytic cells with spike-like projections penetrating deeply into the fibers under attack, and immunoelectron microscopy confirmed that the invading cells were of the OKT8 subset. We infer that: (1) T cell-mediated muscle fiber injury plays a role in polymyositis and inclusion body myositis; (2) T-T and T-B cell cooperation is likely to exist in effector responses in muscle; and (3) T cell-mediated cell injury can also occur in a nonautoimmune disease such as Duchenne dystrophy.

B11. Flier Syndrome: Muscle Cramps, Acanthosis Nigricans, Acral Hypertrophy, and Insulin Resistance

William Kingston, Richard T. Moxley, Robert C. Grigg, Zachary Freedman, and Richard Levy. Rochester, NY

We studied a 29-year-old woman with the syndrome described by Flier et al (N Engl J Med 303:970, 1980). The patient presented with disabling muscle pain accompanied by a 10- to 20-fold elevation in creatine kinase. Other features included enlargement of the hands and feet, acanthosis nigricans, and hirsutism. Endocrine evaluation showed severe insulin resistance. The successful treatment of previous cases with phenytoin (Flier, unpublished results) led us to study the effect of this agent on the patient's clinical and laboratory findings. Whole-body insulin sensitivity and muscle clearance were studied with the insulin clamp technique (80 mU/m2/min) and compared to the results in 16 normal controls (Flier et al, Diabetes 31:132, 1982). Insulin receptors were studied using 125I-insulin binding to freshly isolated monocytes. The patient's glucose disposal rate was markedly reduced (2.99 versus 8.65 ± 0.38 mg/kg/min). Her insulin clearance rate was also decreased (311 versus 510 ± 74 mL/min). Monocyte insulin binding capacity was diminished but affinity was normal. Phenytoin administration controlled the patient's muscle pain but did not result in a significant change in whole-body insulin sensitivity or monocyte insulin binding characteristics. Flier syndrome is associated with resistance of target cells to insulin and decreased insulin binding and clearance. Phenytoin alleviates the neuromuscular symptoms without correcting these abnormalities.

B12. Comparison of Embryonic Stages of Spina Bifida and Anencephaly

Michael T. Smith and Lawrence R. Wood, Bethesda, MD

Scanning electron microscopy (SEM) was used to compare the surface modifications of the neural tube during successively developing embryonic stages of spina bifida and anencephaly. Pregnant 180 gm Sprague-Dawley rats were given either a 1 ml subcutaneous injection of 1% trypan blue on days 7 or 8 or intragastric administration of 75,000 units of vitamin A on days 8 through 10 to consistently produce embryos with spina bifida or anencephaly, respectively. Controls were given vehicle only. SEM examination at 9 days revealed no morphological differences between experimental and control embryos. Cilia developed on
neural epithelium by gestational day 10, differentiating it from cutaneous epithelium. Lamellodipia and blebs were specialization observed at the epithelial border marking the site of neural tube closure. However, on day 11, progressive widening of the rostral or caudal neural tube of experimental embryos was observed with a subsequent increase in lamellodipia and blebs, whereas control neural tubes continued to close, followed by disappearance of those structures. Enlargement of nonclosed neural folds occurred until spontaneous necrosis of the maldeveloped tissue resulted in the classic appearance of spina bifida or anencephaly. Thus, it appears that antenatal development of the two abnormalities is essentially identical.

**SCIENTIFIC SESSION C**

**Viral Infections, Demyelinating Disorders, and Extrapyramidal Disorders**

**C1. Neurological Complications of Gay-related Immunodeficiency Disorder**

*Sandra L. Horowitz, D. Frank Benson, Michael S. Gottlieb, Irene Davos, and John R. Benton,* Los Angeles, CA

Gay-related immunodeficiency (GRID) is a recently described syndrome that primarily affects previously healthy male homosexuals. It features a specific T cell dysfunction that renders the patient susceptible to both common and rare pathogens. These include *Candida albicans*, cytomegalovirus, herpesvirus, *P. carinii*, *Toxoplasma gondii*, cryptosporidium, and *Mycobacterium avium*. Kaposi sarcoma may also be present. We have seen nine patients with GRID, all with retinopathy and seven with severe neurological involvement that contributed directly to death in the three patients who had autopsy examinations of the brain. Pathological findings were acute necrotizing encephalitis with vasculitis due to cytomegalovirus, multifocal necrotizing toxoplasmosis, and multifocal cerebritis with viral inclusions in the median eminence. Of the three surviving patients, one was treated successfully for central nervous system toxoplasmosis and one is recovering from Guillain-Barré syndrome. Clinical patterns of central nervous system involvement are emerging that include early mental status changes and seizures. The most frequent finding on computed tomography is cerebral atrophy, but in *T. gondii* infections the scan shows focal lesions. The cause of GRID with its neurological complications is obscure, but this increasingly common syndrome is a life-threatening disorder that requires early recognition and treatment.

**C2. Neurological Complications of the Gay Immunosuppressed Syndrome: Clinical and Pathological Features**

*C. B. Britton, M. D. Marquardt, B. Koppel, G. Garvey, and J. R. Miller,* New York, NY

Acquired deficiency of cell-mediated immunity associated with multiple opportunistic infections, especially viral, occurs in homosexual men (gay immunosuppressed syndrome). Neurological complications, however, have not been described. We report neurological abnormalities in four patients with the gay immunosuppressed syndrome. Three patients had organic psychosis characterized by paranoia, hostility, delusions, and agitation. One of them also had quadriplegia (muscle weakness), resting tremor, rigidity, dystonia, and transiently elevated creatine phosphokinase levels. All had generalized seizures when metabolic problems were severe. At autopsy, pathological abnormalities similar to those reported in adult cytomegalovirus encephalitis were found. There were microglial nodules in two cases and Alzheimer type II cells in one. Two patients had proved cytomegalovirus infection not involving the central nervous system. In one case, brain culture was suspicious for cytomegalovirus. The fourth patient, with progressive multifocal leukoencephalopathy (PML) due to papovavirus at biopsy, had progressive cerebellar pontine dysfunction and blood cultures positive for cytomegalovirus. Two patients received antiviral treatment (ara-A, acyclovir) without benefit. Abnormal findings in each of these patients suggest that central nervous system involvement in the gay immunosuppressed syndrome may not be rare. Except in the case of PML, evidence for viral invasion is circumstantial. Brain biopsy is unlikely to be diagnostic except when herpes simplex or PML is suspected.

**C3. Central Nervous System Complications of Bone Marrow Transplantation: A Clinical and Pathological Study**

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The clinical and complete autopsy findings in 77 patients who died after bone marrow transplantation were reviewed. The average age was 23.5 years (range, 3 to 49). Pretransplant diagnoses were leukemia in 57 patients, aplastic anemia in 14, and other malignancies in 6. Central nervous system (CNS) complications after bone marrow transplantation were seen in 48 patients. Altered mental status (43 patients) was the most common problem; its causes included: metabolic/hypoxic encephalopathies in 24 patients, CNS infections in 6, infarcts in 3, hemorrhage in 1, and undetermined causes in 9. Neurological complications in the 5 patients without altered mental status were seizures in 3, malignant cells in the cerebrospinal fluid in 1, and torticollis in 1. The CNS infections were due to aspergillus in 3 patients, herpes simplex virus in 2, and *Listeria monocyto genes* in 1. None of the aspergillus infections was diagnosed before death. Five cases of nonbacterial thrombotic endocarditis and 1 of acute bacterial endocarditis were present; none was diagnosed antemortem. All major infects (3 patients) were associated with endocarditis, 2 nonbacterial thrombotic and 1 acute bacterial. CNS complications related directly to antineoplastic therapy were myelopathy and multifocal micronecrosis, which occurred in 1 patient each. Malignant cells in the cerebrospinal fluid (19 patients) and focal findings (10 patients) before the transplant did not predispose patients to CNS complications afterward. Findings noteworthy by their rarity were residual (or recurrent) CNS leukemia (2 patients), bacterial infection of the CNS (1 patient), and marked intracranial hemorrhage. Metabolic, vascular, and infectious disorders were the most important CNS complications following bone marrow transplantation.

**C4. Clinical Syndromes of Spinal Cord Atrophy**

*Michael R. Fetell and Michel E. Masud,* New York, NY

Enlargement of the spinal cord may be effectively demonstrated with contrast myelography. Criteria for diagnosis of spinal cord atrophy are not established, however, and the diagnosis is rarely made premortem. We used computed...
tomography augmented with intrathecal metrizamide to study patients with cervical myelopathy. Thirty patients with spinal cord atrophy were identified. Chiari malformation and intramedullary cysts were excluded in all of them. In 15 cases, intrinsic cord atrophy was identified by widening and deepening of the normal sulci and fissures (particularly the ventromedial fissure) and beaking of the lateral funiculi. Both multiple sclerosis and motor neuron disease were found to cause intrinsic cord atrophy, but cases with prominent sensory signs showed flattening of the dorsal aspect in addition to flattening of the ventral surface. Clinically atypical multiple sclerosis with cord atrophy was identified by evoked responses and by oligoclonal bands in the cerebrospinal fluid. Five cases of motor neuron disease affecting one arm (monomelic motor neuron disease) or asymmetrical spinal muscular atrophy showed a striking pattern of ipsilateral cord hemiatrophy. In 15 other cases, extrinsic cord compression by spondylolisthesis also resulted in cord atrophy, but sulci and fissures were not accentuated; localized cord atrophy and distortion predominated. The cord sometimes assumed the shape of a kidney bean indented by a central osteophyte. Studies of this kind may resolve a perpetual dilemma: that of separating spondylotic myelopathy from motor neuron disease with incidental spondylolisthesis.

C6. Distribution of Interferon in Cerebrospinal Fluid after Systemic, Intrathecal, and Intraventricular Administration

Richard A. Smith, David Kingsbury, John Alksne, Hector James, and Kari Cantell, San Diego, CA, San Francisco, CA, and Helsinki, Finland

Intrathecal administration of interferon has been proposed as the treatment of choice for neurological diseases in which the blood-brain barrier is intact, because interferon does not readily reach the nervous system after systemic injection. Recently, intralumbar administration has been reported to reduce the frequency of relapses in multiple sclerosis, and intraventricular administration has been used to treat acute viral encephalitis. Since data from pharmacokinetic studies should help in the design of clinical trials with interferon, we studied the distribution pattern in the cerebrospinal fluid of single doses of interferon administered systemically, intrathecally, and intraventricularly in patients with amyotrophic lateral sclerosis. Serial sampling of ventricular fluid over a period of 48 hours showed interferon activity amounting to less than 5 IU/ml after subcutaneous and intravenous administration of up to 6 × 10^6 IU of partially purified human leukocyte interferon (PIF). In contrast, ventricular administration of 2.5 × 10^6 to 1 × 10^6 IU of PIF achieved high cerebrospinal fluid titers of interferon (up to 3,500 IU/ml), and interferon was detected in lumbar cerebrospinal fluid for up to 24 hours. We found no interferon activity in serial ventricular cerebrospinal fluid samples after intralumbar injection of 1 × 10^6 IU of PIF. Ventricular injections of interferon caused fatigue, chills, fever, headache, nausea, and anorexia, which resolved over 24 hours. Repeated ventricular administration caused a sterile pleocytosis in one patient accompanied by anorexia, fatigue, and malaise. Full recovery occurred after injections were stopped.

C7. The Lymphoproliferative Response to Measles Virus in Twins with Multiple Sclerosis

J. I. Greenstein, D. E. McFarland, and H. F. McFarland, Bethesda, MD

Previous studies have demonstrated that the normal proliferative response to measles virus is considerably lower than that to mumps or vaccinia virus, and that patients with stable multiple sclerosis (MS) do not differ from the norm. The proliferative response to these viruses was investigated in thirty sets of twins who were both concordant and discordant for MS. Normal responses to mumps and vaccinia occurred in all. Three sets (two dizygotic and one monozygotic), all discordant for MS, were identified in which one twin had a persistently elevated response to measles virus while the other had a normal response, all high responders being the affected twin. While these findings are limited to three twin sets, the correlation between high response and disease is striking. The parameters of cellular responsiveness to measles virus were examined in these individuals. The specificity of the response resides in a T cell subpopulation, and its expression is dependent on adherent cells. The addition of various low-responder cell populations to high-responder cells has not identified an
active suppressor cell in nonresponders. Responsiveness correlates with production of interleukin-2. These findings suggest the presence of a clonally expanded T cell population and have potential relevance to understanding immune regulation in MS.

C8. Lisuride and Bromocriptine in Patients with Advanced Parkinson Disease
Abraham N. Lieberman, Govindan Gopinathan, Andreas Neophytides, Russell Walker, and Emil Hiesiger, New York, NY

Treatment with lisuride was compared to bromocriptine therapy in 25 patients in whom the response to levodopa had diminished. Nineteen patients were experiencing "on-off" phenomena. At the time bromocriptine was added to levodopa, the mean age of the patients was 62.7 years, mean duration of disease was 8.9 years, and mean duration of levodopa treatment was 6.2 years. For the group, disability as determined in both the "on" and the "off" period decreased significantly (p ≤ 0.05) and the number of hours in which patients were "on" increased from 9.6 to 12.8. Bromocriptine was discontinued in 11 patients because of adverse effects, and in the remaining 14 because of decreased efficacy. The mean dose of bromocriptine was 55 mg (range, 20 to 100 mg). At the time lisuride was substituted for bromocriptine, the patients were 3 years older and were more disabled. Nonetheless, disability decreased significantly (p ≤ 0.05) in both the "on" and the "off" period, and the number of hours in which patients were "on" increased from 3.9 to 8.9. The mean dose of lisuride was 2.8 mg (range, 0.6 to 5.0 mg). Lisuride was discontinued in 8 patients because of adverse effects. Although both bromocriptine and lisuride are useful in patients with advanced Parkinson disease, lisuride, because its activity (unlike bromocriptine's) is independent of presynaptic dopamine synthesis, may be the more useful in those patients with farther advanced disease.

C9. Edentulous Oro dyskinesia
William C. Koller, Chicago, IL

 Orofacial chorea is a common type of involuntary facial movement and may be disease related or drug induced, as occurs with tardive dyskinesia. Choreatric movements of the facial area are said to occur spontaneously in the elderly and to result from edentulousness. However, these entities are poorly defined. Seventy-five consecutive patients who had had removal of some or all of their teeth and 75 elderly patients (average age, 68.6 years) without tooth extraction were examined for facial dyskinesias. Movements were scored using the AIM scale and were filmed. Twelve (16%) of the edentulous patients had orofacial dyskinesias consisting of smacking and pursing of the lips, lateral deviation and protrusion of the tongue, and occasional lateral deviation of the jaw. Abnormal movements of the upper face and limbs were absent. Ability to sustain tongue protrusion and tests of oral proprioception were normal. Tooth extraction preceded the onset of movements by an average of 12 years. Dentures were not being used by half the dyskinetic patients and 9.5% of the edentulous patients without dyskinesia. None of the 75 elderly patients without tooth extraction had oral dyskinesias. Videotapes of patients' movements will be shown, and differentiation of edentulous dyskinesia from disease-related, drug-induced, and spontaneous dyskinesia will be discussed.

C10. Dystonia: Therapy with Dopaminergic Ergot Derivatives
Richard P. Newman, Peter A. LeWitt, Marc I. Rapaport, Norman L. Foster, Donald B. Calne, and Thomas N. Chase, Bethesda, MD

Although the pathological features of dystonia do not reveal its causes, there is evidence that the symptoms arise from impaired carbocholaminergic function. A therapeutic trial was undertaken with dopaminergic ergots since this therapy may be effective against dystonic and other features of parkinsonism. Eleven patients with a variety of dystonic syndromes (autosomal dominant and recessive, "delayed-onset," sporadic onset, spasmodic torticollic, Meige syndrome) were treated with gradually increasing doses of bromocriptine over several weeks in a double-blind, placebo-drug study. Patients were assessed by several observers using standardized rating scales and videotape recordings. Bromocriptine was administered concurrently with other medications that some patients had already been receiving (e.g., clonazepam, diazepam), and the dosage was increased until maximal clinical effect or intolerable adverse symptoms occurred. Improvement in physical signs and functional capabilities was observed in six patients, whose diagnoses included generalized dystonia and Meige syndrome. The mean maximum dose in responders was 110 mg per day (range, 45 to 150). Two other patients (Meige syndrome, spasmodic torticollic) had transient functional improvement. No patient worsened with therapy. Two patients also responded to lisuride, another dopaminergic ergot. Although it is difficult to assess what factors permitted successful outcomes in this survey of various dystonic syndromes, high-dose bromocriptine or lisuride may be effective against dystonic symptoms.

C11. Levodopa Favorably Influences the Natural History of Parkinson Disease
Howard I. Hurtig, Ruben C. Gur, and Ken Pearson, Philadelphia, PA, and New York, NY

Levodopa effectively controls the symptoms of Parkinson disease, although the majority of patients eventually show signs of progression. Levodopa's long-term effect on the natural history of Parkinson disease has been highlighted by two recent contradictory reports. Fahn (Neurology, 1979) warned that levodopa has a finite period of usefulness, whereas Markham (Neurology, 1981) found no such limitation. Neither report fully considered the highly variable rate of progression among parkinsonian patients, as shown in the classic paper by Hoehn and Yahr (Neurology, 1967) published before levodopa became available. We evaluated an unselected series of 41 parkinsonian patients treated for an average of eight years at the Hospital of the University of Pennsylvania. Patients were subdivided into three groups according to duration of disease before levodopa therapy was started: Group A, less than 2 years; Group B, 2 to 5 years; and Group C, more than 5 years. Neurological deterioration was assessed by the Hoehn and Yahr index (stage per year). Group A had the steepest slope of progression, whereas Groups B and C progressed more slowly. Treatment with levodopa significantly (p < 0.001) changed the slope of progression for the better in every group. These findings support the hypothesis that levodopa moderates the natural history of Parkinson disease, although the outcome may still depend on the intrinsic rate of progression for any individual victim.
The vascular changes of migraine have been well documented, but no satisfactory explanation has yet been advanced for the predominantly unilateral nature of migraine headache. Recent studies in our laboratory demonstrated that stimulation of the locus ceruleus in monkeys increases ipsilateral cerebral vascular resistance while decreasing resistance in the external carotid circulation, both constrictor and dilator responses persisting after cervical vagotomy. Complementary experiments in cats showed that a similar carotid vasodilator response can be obtained from stimulation of the trigeminal nerve as well as from the locus ceruleus, and that the response is mediated by the greater superficial petrosal branch of the facial nerve. We postulate that the ipsilateral cerebral vasconstrictor response is mediated by direct noradrenergic projections from locus ceruleus to the cortical microcirculation which, together with known serotoninergic projections from raphe nuclei, may be responsible for the oligemic phase of classic migraine in addition to contributing to the increased extracranial blood flow of the headache phase. Since noradrenergic and serotoninergic bulbo spinal tracts also control afferent input in spinal and trigeminal pain pathways, cyclical variation in their activity could account for the association of unilateral pain and vascular changes in migraine.

P1. Does Migraine Increase the Risk of Cerebral Ischemic Events in Persons with Mitral Valve Prolapse?
John P. Conomy, Maurice R. Hanson, and David McFarling, Cleveland, OH, and San Antonio, TX
Cerebral ischemic events occur in only a small subset of individuals with mitral valve prolapse (MVP). The clinical, physiological, and biochemical hallmarks that set these individuals apart from their neurologically asymptomatic counterparts is unknown, but the incidence rate for cerebral events in individuals with MVP has been shown to be about four times greater than the rate of cerebrovascular events in non-MVP populations. Loisy et al in France hypothesized a correlation between migraine, particularly the ophthalmic form, and MVP. Steele et al in the United States suggested that individuals with MVP and neurological events demonstrate abnormal platelet function. We studied three patients with various forms of migraine, brain ischemic syndromes, and MVP. They included two young men and a young woman who had a clear history of infrequent but severe classic migraine with prominent visual prodromes, all of whom experienced hemispheric brain infarctions outside the setting of their migrainous attacks. Both men were treated with antplatelet drugs, and neither experienced subsequent stroke or headache over 24 months. A 21-year-old woman with frequent basilar migraine incurred numerous syncopal episodes and was found to have MVP. This same cardioneurological syndrome occurred in five other members of her family over three generations. Patients with MVP and complex forms of migraine may bear an increased risk for cerebral ischemic episodes. The relationship merits further study since both the embolic propensity of MVP and the clinical expression of migraine may involve platelet dysfunction.

P2. Transient Behavioral Syndrome Associated with Reversible Vascular Lesions of the Fusiform-Calcarine Region in Humans
John P. Conomy, Robert Laurore, and Walid Massarweh, Cleveland, OH, and Washington, DC
A fixed neurological syndrome consisting of mental disturbance, memory defect, and hemianopia or cortical blindness occurs in patients with infarctions involving the fusiform gyrus and calcarine regions of the human brain (Horenstein, Chamberlain, and Conomy, Trans Am Neurol Assoc, 1967). The mental aspects of the syndrome are seen with unilateral or bilateral lesions and take the form of agitated delirium, global disorientation, and memory disturbance. Visual defects may be unilateral or bilateral depending upon the vascular beds involved. Previously reported patients displaying this syndrome have been those with large, irreversible lesions and permanent mental and behavioral defects. Recently we have encountered patients in whom the neurobehavioral syndrome of fusiform-calcarine infarction was evident, the site of lesion confirmed by clinical and neuroradiological studies, but the neurological disturbance was transient. The first, a 58-year-old man, developed agitated behavior, disorientation, continuous profane speech, and cortical blindness. Thirty-six hours later he had recovered completely and was amnesic for his neurological episodes. The second, a 38-year-old hypertensive man, was thought to be suffering from delirium tremens but was found to be hemianopic. Computed tomography showed brain hemorrhage occupying the right fusiform-calcarine region. His symptoms and signs resolved in 72 hours. We suggest that, as in the case of better known and more frequently recognized vascular brain impairments, the fusiform-calcarine syndrome can occur in either reversible or irreversible forms and that it is seen in reversible brain events such as transient ischemia of the posterior circulation or parenchymal hemorrhage with recovery.

P3. Arteriographically Diagnosed Cerebral Arteritis: Clinical Spectrum and Outcome
G. A. Donnan, H. L. Baker, and R. G. Siekert, Rochester, MN
Studies of arteritis have been restricted to isolated case reports, and hence no adequate information is available about the outcome of the spectrum of diseases in which arteriography disclosed changes which have been termed “arteritis.” Arteriograms from 1972 to 1982 with a diagnosis of “cerebral arteritis” were reviewed. Those showing mass lesions or subarachnoid hemorrhage were excluded. Eleven cases were found not to adhere strictly to established roentgenographic criteria of arteritic change and were excluded. In the remaining 26 patients, the site, extent, and nature of arterial involvement were correlated with clinical and laboratory findings such that two groups could be recognized: Group A—the arteriographic findings were incidental to the clinical findings (3 patients); Group B—clinical, laboratory, and arteriographic findings correlated well (21 patients). No relevant laboratory abnormalities were found in Group A. Laboratory findings contributed to the diagnosis in 10 cases in Group B. The extent of arterial involvement correlated with the neurological presentation.
and outcome. Follow-up (6 months to 10 years) was obtained by review of charts, letter, or telephone contact.

No neurological sequelae developed in Group A during follow-up. In Group B, 19 patients presented with cerebral ischemic disease (infarct, transient ischemic attacks), 1 with dementia, and 1 with seizures. Follow-up revealed recurrent transient ischemic attacks or cerebral infarction in 11 cases, 3 of which were fatal. Arteriographically diagnosed "cerebral arteritis" is nonspecific. It is of importance only when accompanied by major clinical abnormalities.

P4. Lacunes in the NINCDS Pilot Stroke Data Bank
J. P. Mohr, C. S. Kase, P. A. Wolf, T. A. Price, A. Heyman, J. H. Dambrosia, and S. Kuntz, Mobile, AL, Boston, MA, Baltimore, MD, Durham, NC, and Bethesda, MD

During a 20-month period, 100 of 933 hospitalized patients with stroke at Boston, Duke, Maryland, and South Alabama were classified as having lacunes. It was the stroke subtype most commonly associated with hypertension (67%) and diabetes (32%). The functional prognosis was not influenced by the mode of onset in these patients, including the 20% whose stroke developed gradually. Despite smooth worsening in 20%, clinical improvement occurred in fully one-third of cases within 24 hours from onset. Patients with lacunes showed the best functional prognosis and the least mortality (5%) of any stroke subtype. Among 88 patients with motor stroke, severe hemiparesis developed in 9 of 42 with positive CT scans but in only 2 of 36 with negative scans (p < 0.1). Substantial functional improvement occurred within a month in 85% of cases with incomplete hemiparesis. Patterns of face-arm-leg paresis did not exactly conform to traditional formulations of a "homunculus" in the internal capsule. In sensory stroke, involvement of the trunk plus the face and limbs was present in 9 of 12 cases of thalamic lacune, but the value of truncal hypesthesia as a thalamic sign was minimized by its presence in 59 of 88 patients with hemispheral ischemic infarcts.

P5. Spontaneous Dissection of the Internal Carotid Arteries: Clinical Presentation and Angiographic Features
Bahram Mokri, O. Wayne House, Thoralf M. Sundt, Jr, and David G. Piepgras, Rochester, MN

Of 36 patients with spontaneous dissection of the internal carotid arteries, 21 were women and 15 were men. Their ages ranged from 21 to 63 years: 75% were between 30 and 50 years of age. Headache or neck pain was present in 34. A unilateral headache, usually orbital, periorbital, and frontal, was the initial symptom in 25 patients. Oculosynthetic palsy was present in 13. In 13 patients, hemianopia and oculosynthetic palsy with or without bruit were the only clinical manifestations. Subjective bruit, or frank transient, was reported by 14, and objective bruits were detected in 10. Ten patients reported light-headedness and 4 had syncopal spells. Symptoms of ischemia were noted in 24: transient ischemic attacks in 14, stroke in 13, and the two combined in 3 patients. Thirteen patients were hypertensive, 17 were smokers, 5 were taking oral contraceptives, 4 were migraine sufferers, and 5 had fibromuscular disease of the carotid or renal arteries. The dissection was bilateral in 9 patients. Forty-five internal carotid arteries, 29 right and 20 left, were involved. Major angiographic changes consisted of one or more of the following: long, usually irregular and tapered narrowing of the lumen, often extending to the base of the skull (71%); fairly abrupt reconstitution of the narrowed lumen at the carotid canal (49%); dissecting aneurysm (33%); tapered occlusion (16%); and intimal flaps.

P6. Recovery from Acute Stroke and Changes in Cerebral Blood Flow
Allan Barke, Donald Younkin, Michael Kashner, John Gordon, Lisa Pistone, Harry Shapiro, and Martin Reivich, Philadelphia, PA

To assess the correlation between regional cerebral blood flow (rCBF) and recovery from stroke, ten patients with acute stroke underwent four 133Xe inhalation flow studies over one month. Scored serial neurological and neuropsychological examinations were performed. All patients had acute ischemic infarctions of the anterior circulation with residual function on the involved side. Patients with lacunes or coma were omitted. In four patients, statistically significant increases in rCBF (p < 8%) occurred simultaneously with clinical improvement. The only patient taking anticoagulants showed increases in rCBF but no improvement on either examination. In the remaining five patients, clinical improvement developed one week after acute stroke, when rCBF was lowest; rCBF subsequently increased. The initial rCBF value did not correlate with clinical outcome in this group of ten patients (r = 0.27). We conclude that rCBF is not predictive of clinical outcome in patients with acute stroke who remain conscious and have some residual function on the involved side. Increases in rCBF appear to be not a cause of neurological improvement but rather a result of recovery of neuronal function with improved cerebral metabolism, which secondarily influences rCBF. In addition to maintaining flow, stroke therapy directed at cerebral metabolism may provide greater efficacy in salvaging ischemic neurons. (Supported by Program Project Grant NS-20939-10 from the US Public Health Service.)

P7. Clinical Benefit of Steroids in Early Postischemic Disruption of the Blood-Brain Barrier
Jacob I. Sage and Robert L. Van Uitert, Piscataway, NJ, and Williamstown, MA

The relative importance of many factors involved in postischemic edema changes with time after the ictus and may influence the efficacy of any one therapy. Most postischemic cerebral edema peaks approximately 72 hours after the insult, but edema occurring early (<48 hours) after cortical infarction can be a serious complication of stroke. We administered high-dose dexamethasone (100 mg per day) to seven patients in whom increasing hemiparesis and decreasing levels of consciousness suggested early postischemic edema and computed tomography (CT) confirmed brain swelling. 99mTc brain scans were performed in all seven patients within 12 hours after onset of edema and immediately prior to dexamethasone treatment. Once started, steroids were continued for five days. Scans of three patients showed blood-brain barrier breakdown to 99mTc. These patients all improved clinically on steroid therapy; five days later, repeat CT showed resolving edema and 99mTc scans had reverted toward normal. The other four patients initially had normal 99mTc scans; after five days of steroid treatment, no clinical improvement had oc-
curred and cerebral edema persisted on repeat CT. Preliminary experience from these seven patients suggests that there may be two types of early postischemic brain edema. High-dose dexamethasone therapy reduces early postischemic edema in areas of abnormal permeability to $^{99m}$Tc ("vasogenic" edema) but does not affect edema unassociated with blood-brain barrier breakdown to $^{99m}$Tc. This may explain why previous studies on the efficacy of steroid treatment after stroke have been inconclusive.

P8. Early Changes in Blood-Brain Barrier Permeability to Small Molecules after Transient Cerebral Ischemia: A Possible Role in Postischemic Edema
Jacob I. Sage and Robert L. Van Uitert, Piscataway, NJ, and Williamstown, MA

The blood-brain barrier appears to be intact after cerebral ischemia when tested with conventional indicators. Edema during this period is therefore considered to be related to swelling of brain cellular elements (cytotoxicity). This explanation does not preclude a multifactorial cause for postischemic edema, however. One factor may be breakdown of the blood-brain barrier to small molecules that are detectable only with more refined techniques than have previously been used. Brain unidirectional extraction and flux of leucine were measured simultaneously with cerebral blood flow (CBF) at various times after transient global cerebral ischemia in 31 rats. The results permit an evaluation of blood-brain barrier permeability in the postischemic period independent of alterations in CBF at the time of measurement. Leucine extraction was higher ($p < 0.001$) than that of CBF-matched controls at 15 minutes and 6 hours after 30 minutes of global cerebral ischemia but did not differ from control values at 30 minutes and 1 hour after ischemia. Leucine flux into brain was increased only at 15 minutes after reperfusion of the brain. Cerebral edema occurs 15 to 30 minutes after reperfusion in this ischemia model, but the permeability of the blood-brain barrier to large molecules is unaltered during this period (Petito et al, Ann Neurol 8:91, 1980). Increased barrier permeability to small molecules such as leucine may contribute to the production of this early postischemic edema.

P9. Reduplication of Transient Symptoms with Recurrences of Carotid Stenosis
C. M. Fisher and R. G. Ojemann, Boston, MA

Carotid stenosis occasionally recurs after endarterectomy. Four cases were studied in which the tendency to rather exact reduplication of the original transient ischemic attacks (TIAs) challenges the idea that TIAs result from haphazard dislodgement of embolic particles from a plaque, and favors instead an anatomicphysiologically predisposed hemodynamic failure. One patient had two recurrences in the same carotid artery, one had a recurrence in each carotid artery, and two had a single recurrence in one carotid artery. In each instance there was a bruit, angiography showed a lumen of 1 mm or less, and endarterectomy was performed. Patient 1 experienced one 2-minute episode of tingling of the right middle finger spreading to the index finger and thumb. The first recurrence was 6 years later and involved tingling of the middle and index fingers for several seconds. A second recurrence 3 years later consisted of 1 minute of numbness in the distal middle finger. Patient 2 had three 5-minute spells of grayness in the lower half of the visual field of the left eye. Recurrence 9 years later consisted of eight spells of grayness in the same location. Patient 3 experienced three 5-minute spells of cloudiness in the lower half of the right visual field. Recurrence 3½ years later consisted of an identical spell. Patient 4 had three 2-minute episodes of weakness of the right hand. Four years later this patient had two episodes of numbness in the right hand lasting 3 minutes.

P10. Prognosis in Patients with Asymptomatic Carotid Bruits due to Nonstenotic Lesions
J. Grotta, W. S. Fields, and K. Kuve, Houston, TX

Twenty-six patients who had 30 arteries with asymptomatic bruits were followed prospectively over two years for the development of cerebral ischemia. All patients had carotid arteriography, and none had greater than 50% stenosis of the internal carotid artery. Fifteen arteries were normal or only slightly irregular, 4 had less than 50% stenosis without ulceration, and 11 had less than 50% stenosis with ulceration. All but 4 patients were treated with aspirin, dipyridamole, or both. Three transient ischemic attacks (TIAs) occurred (incidence, 9% per year) and one stroke (incidence, 2% per year) referable to the arteries in question. This compares with a 0 to 3.5% yearly incidence of TIA and 0 to 1% of stroke in the few other published studies of patients with asymptomatic bruits without marked stenosis. Two of the patients with TIA and the one with an infarct were among the four patients not treated with platelet antiaggregant drugs. Patients with nonstenotic internal carotid artery lesions may have carotid bruits which on physical examination are similar to those caused by stenotic lesions. The incidence of TIA and stroke related to these lesions is low, and it is unlikely that the prognosis could be improved by surgical intervention.

P11. Transient Global Amnesia: A Case-Control Study
M. Kushner, C. Anderson, and W. A. Hauser, Philadelphia, PA, and New York, NY

The relationship between transient global amnesia (TGA) and cerebral vascular disease remains problematic. Follow-up studies of TGA patients report subsequent completed stroke in as few as 6% to as high as 100%. Over 60% of patients with TGA have been reported to have risk factors for cerebrovascular disease, but this proportion is difficult to interpret in a population over age 60 years. To further elucidate risk factors for TGA and to investigate the relationship between risk factors for cerebrovascular disease and occurrence of TGA, the medical histories of 18 patients with TGA admitted to the Neurological Institute and examined during ictus were compared to those of 84 age- and sex-matched patients admitted for either radicular back pain or extraxial lesions of the central nervous system. The case group demonstrated a higher frequency of prior transient ischemic attacks ($p < 0.02$), hypertension ($p < 0.02$), cardiac arrhythmia ($p < 0.001$), angina ($p < 0.01$), and carotid bruits ($p < 0.001$) when compared with controls. A higher proportion of cases demonstrated abnormalities on computed tomography, and in all cases those abnormalities were consistent with lesions in the distribu-
tion of the posterior cerebral circulation (thalamic or mesial temporal). On follow-up (mean, 2.5 years) 1 patient had experienced a repeat TGA and another, transient ischemic attacks, but none had suffered a completed stroke. Thus, some risk factors for TGA and cerebrovascular disease are similar. Clinical features of these well-documented cases as well as other differences between the case and control groups will be discussed.

P12. Cerebral Ischemia Damages Neurons Despite Lowered Brain Lactate Levels
W. A. Pulsinelli, J. French, D. Rawlinson, and F. Plum, New York, NY

Concentrations of lactic acid above 15 μmol/gm in brain appear greatly to enhance the severity of ischemic brain damage. Although it is known that lactate concentrations below this level leave ischemia-exposed endothelial cells and astrocytes unscathed, it is not evident whether lactic acid levels over a continuum of lower values proportionately affect survival of neurons. Cerebral lactic acidosis during ischemia varies with the brain's glucose concentration. Accordingly, we tested whether insulin-induced hypoglycemia, induced prior to cerebral ischemia, would reduce the ensuing brain damage. Adult rats were fasted for 24 hours and then injected with insulin or saline solution. Forty-five minutes later severe forebrain ischemia was induced by the method of four-vessel occlusion. In half the animals, cerebral blood flow was restored after 30 minutes and three days later the animals' brains were perfusion-fixed. Morphological damage was evaluated with the light microscope. The brains of the remaining animals were frozen in situ with liquid nitrogen at the end of ischemia, and lactate was measured in neocortex, striatum, and hippocampus. Insulin pretreatment lowered the blood glucose concentration from 6.4 ± 0.3 mM to 2 to 3 mM and reduced the accumulation of brain lactate during ischemia from 11.2 ± 1.6 μmol/gm to 5.7 ± 1.4 μmol/gm. No significant difference was observed in the degree or extent of morphological brain damage between normoglycemic and hypoglycemic animals. These findings suggest that low concentrations of lactic acid are not a critical mechanism of ischemic injury to selectively vulnerable neurons in the brain.

P13. Cranial Nerve Paralysis following Carotid Endarterectomy
E. Wayne Massey, Albert Heyman, James Fuchs, Carol Utley, and Carol Haynes, Durham, NC

Among 347 patients with focal transient cerebral ischemia seen at Duke University Medical Center in the past seven years, 158 underwent carotid endarterectomy. In 24 (15%) of the surgically treated patients, 26 distal cranial nerve paralyses appeared as a complication of endarterectomy. These included paralyses of the hypoglossal nerve (13 patients), the cervical branch of the facial nerve (5 patients), and the vocal cord (8 patients). This frequency of occurrence is similar to that (12.4%) described in a recent report of the complications of carotid surgery. Residual deficits were present at one year in 2 patients with facial nerve injury and 4 with hypoglossal palsy. No patient experienced residual hoarseness. Dysarthria and altered ability to move food in the mouth were usual symptoms in hypoglossal dysfunction. Even though these complications of carotid endarterectomy are generally benign, they can be avoided if careful attention is given to anatomical localization of these cranial nerves during surgery.

P14. Cerebrovascular Disease and Serum Prostacyclin Binding Capacity
Robert W. Stein, William J. Weiner, and Kenneth Wu, Chicago, IL

Prostacyclin is a powerful vasodilator and inhibitor of platelet aggregation that has been implicated to play an important role in cerebrovascular disease. Prostacyclin is unstable in aqueous solution and stabilized in serum. Our previous studies showed that prostacyclin may be stabilized by binding to an unidentified serum protein as measured by gel filtration (Lancet 1:460, 1982). In 11 patients with cerebrovascular disease, prostacyclin binding capacity was measured to determine if any alteration is present. 3H-labeled PGI2 (10 nM) was incubated with 0.35 ml of serum at room temperature for 3 minutes and applied to a Sephadex G25 column. PGI2 binding capacity was expressed as the percentage of total radioactivity present in the binding peak. Patients with cerebrovascular disease had a binding capacity of 26.4% ± 6.3% compared to a control value of 35.5% ± 4.4% (p = 0.133). However, 4 of these patients showed a marked reduction in prostacyclin binding capacity (19.5% ± 2.0%). Although serum albumin has been thought to metabolize PGI2, serum prostacyclin binding capacity correlated poorly with serum albumin concentrations (N = 0.569, p = 0.065). Some patients with cerebrovascular disease exhibited decreased prostacyclin binding capacity not related to serum albumin concentration. Decreased serum prostacyclin binding capacity may allow accelerated degradation of prostacyclin, thereby increasing susceptibility to stroke. Further studies in specific stroke syndromes with sequential measurement of prostacyclin binding capacity are in progress.

P15. Autonomic Dysfunction in Pontomedullary Stroke
Rameeh K. Khurana, Baltimore, MD

Previous reports of autonomic dysfunction in pontomedullary infarction are limited to the description of Horner syndrome, Ondine's curse, hiccup, dysphagia, and vomiting. This study documents, for the first time, widespread autonomic involvement of cardiovascular, respiratory, gastrointestinal, thermoregulatory, ocular, and urinary systems in five patients with pontomedullary strokes. Four of these patients had bilateral pontomedullary dysfunction, and autonomic evaluation showed persistent tachycardia, orthostatic hypotension without cardiac acceleration, episodic bradycardia, cardiorespiratory arrest, Ondine's curse, vomiting, intermittent hiccups, dysphagia with or without criopharyngeus muscle spasm, apneustic esophagus, gastrointestinal reflex, gastric retention, recurrent unexplained fever, Horner syndrome, and urinary retention. The fifth patient, who had unilateral medullary dysfunction, died of central hypoventilation, episodic supine hypotension, and profound bradycardia. A microscopic study of sections through the hindbrain of this last patient revealed unilateral Wallenberg syndrome. This study demonstrates the extensive autonomic manifestations of pontomedullary strokes. It is important to recognize that early evaluation of the autonomic system in all such patients can reduce morbidity and mortality.
P16. Intravenous Digital Subtraction Angiography of the Head and Neck
Anthony J. Farlan, Michael T. Modic, Meredith A. Weinstein, Judith Capraro, William Pavlicek, and John R. Little, Cleveland, OH

Recent improvements in image tube-TV camera systems as well as computerized high-speed digital acquisition have permitted the evolution of real-time angiographic examinations performed by means of intravenous injections of contrast material. Compared to conventional arteriography, digital subtraction angiography (DSA) is a safer, less expensive alternative that can be performed on an outpatient basis for selected cerebrovascular problems. Conventional angiography and DSA were used to examine the common carotid artery bifurcation in 100 patients with clinically suspected arteriosclerotic disease. When the carotid bifurcation was well visualized (currently 85% of the time), there was excellent correlation (97%) of DSA with conventional angiography. Intracranial vessels were examined in 55 patients with both conventional angiography and DSA. The DSA examination was as diagnostic as the conventional angiogram in 65% of these patients. The accuracy, normal anatomy, and variations of the intracranial dural sinuses and veins have been studied in 100 patients. Intraarterial DSA compensates for the problems of intravenous DSA and appears more cost effective than film-screen arteriography. Experimental work using DSA to estimate arterial blood flow will be illustrated, and the physical principles and technological advances responsible for DSA's ability to produce clinically useful images from intravenous injections will be demonstrated.

P17. Positron Computed Tomography in Glycogen Storage Disease Type I
John C. Mazziozzo, Michael E. Phelps, Randall Hawkins, and Michel Philippart, Los Angeles, CA

Glycogen storage disease type I (GSD-I) is characterized by a functional deficit in glucose-6-phosphatase, which normally hydrolyzes glucose-6-phosphate to glucose. This enzyme is primarily found in the liver, kidney, and muscle but is also present in brain. It appears to participate in the regulation of cerebral tissue glucose through a cycle of phosphorylation with hexokinase and dephosphorylation with phosphatase. Since most neurological symptoms in GSD-I patients are attributed to repeated bouts of systemic hypoglycemia, previous reports have not examined possible deficiencies in phosphatase activity in the brain. We used positron computed tomography, 18F-labeled 2-fluoro-2-deoxyglucose, and a tracer kinetic model for 2-fluoro-2-deoxyglucose to measure the cortical/tissue forward and reverse transport, phosphorylation and dephosphorylation rate constants, tissue/plasma concentration gradient, and tissue concentration turnover rate for this competitive glucose analogue, and the cortical metabolic rates for glucose. Studies were carried out in age-matched normal subjects (N = 13) and one GSD-I patient. The dephosphorylation rate constant in the GSD-I patient was one-tenth the normal value, indicating a low level of cerebral phosphatase activity. The other measured variables were within normal limits except for the rate of glucose phosphorylation, which reflected a cortical glucose metabolic rate one-half the normal value. Since glucose transport and tissue glucose concentration were normal, the reduced glucose metabolism probably resulted from the use of alternate substrates (β-hydroxybutyrate and acetoacetate) which are consistently elevated in the plasma of GSD-I patients. Such studies demonstrate the feasibility of using positron computed tomography to examine inborn biochemical deficits using kinetic data measured noninvasively.

P18. Senile Gait: Correlation with Computed Tomographic Scans
W. C. Koller, S. C. Glatt, R. S. Wilson, M. Huckman, and J. H. Fox, Chicago, IL

Gait difficulties unrelated to clinically obvious neurological or systemic disease but associated with aging are referred to as "senile gait." The anatomical basis of the disorder is unknown. Degeneration of the frontal lobes, basal ganglia, or cerebellum as well as hydrocephalus have been proposed. We examined computed tomographic scans of 16 patients with senile gait (mean age, 73 years) and of 59 subjects with normal gait who were group matched for age. Dementia was present in approximately half of each group. Senile gait consisted of a small-stepped, wide-based, slowed gait with poor postural stability and tandem ability. Fourteen supratentorial and infratentorial tomographic scan measurements were taken. No differences in infratentorial measures were found. Two-way analyses of variance of the supratentorial measures with diagnosis (dementia versus control) and gait (normal versus abnormal) as the factors indicated that senile gait is associated with increased bifrontal (p < 0.0001), bicaudate (p < 0.002), and third ventricle (p = 0.02) to skull ratios but not with enlargement of the cerebral sulci. These findings are independent of the presence or absence of dementia. The data suggest that ventriculomegaly, particularly of the frontal horns of the lateral ventricle, is correlated with the presence of senile gait abnormalities.

P19. A Comparison of Oculoplethysmography and the Nuclear Cerebral Angiography in the Evaluation of Extracranial Carotid Occlusive Vascular Disease
W. Craig Clark and Jon H. Robertson, Memphis, TN

From 1978 to 1981, 1,000 oculoplethysmographic (OPG, Karrchener/McRae) examinations were performed in patients clinically suspected of having extracranial carotid occlusive disease. A retrospective review of these cases revealed 72 patients who had been evaluated using OPG, nuclear cerebral angiography (NCA), and conventional contrast angiography. With conventional contrast angiography as the standard of comparison, both OPG and NCA were evaluated regarding their respective diagnostic accuracies. McNemar's test for correlated proportions yielded a test statistic significant at p < 0.01. It was concluded that in the noninvasive evaluation of extracranial carotid occlusive disease, OPG produced diagnostic results more often in agreement with contrast angiography than did NCA. Furthermore, an analysis of percentage data indicated that OPG alone agreed with contrast angiography in 79.2% of cases, compared with 58.3% of cases in agreement with the NCA. When NCA and OPG were used together in the evaluation of extracranial carotid occlusive disease, the percentage of agreement increased to 89%.
P20. Correlational Differences of Regional Glucose Metabolism in Huntington, Parkinson, and Alzheimer Diseases

E. Jeffrey Metter, Walter H. Riege, Motonobu Kameyama, Michael E. Phelps, and David E. Kuhl, Sepulveda and Los Angeles, CA, and Sendai, Japan

18F-fluorodeoxyglucose positron computed tomography studies have evaluated local cerebral metabolic rates for glucose (LCMRglc) in Alzheimer (AD), Parkinson (PD), and Huntington (HD) diseases, but comparisons are difficult because of different regional mapping techniques. LCMRglc values were uniformly determined for thirteen regions in each hemisphere for 8 AD, 7 PD, and 12 HD patients and 31 normal volunteers (aged 27 to 78 years). As compared to normal subjects, LCMRglc was markedly lower in all regions in AD patients and mildly lower in PD with only the caudate low in HD patients. Expressing regions as a ratio of local to mean CMRglc, the high-normal intercorrelations between all hemispheric mirror regions disappeared in each patient group; however, HD and PD lost only cortical correlations while both cortical and subcortical correlations were lost in AD. The number of significant regional correlations ($p < 0.02$) decreased from 52 in normal subjects and 48 in AD to 29 in HD and 16 in PD with a loss primarily of cortical-to-cortical correlations in HD and PD, suggesting a loss in focusing of cortical activity that may relate to abnormalities of the basal ganglia. In AD, frontal-to-frontal and negative temporal-to-frontal correlations were increased, suggesting a reorganization of regional metabolic interactions secondary to cortical lesions. These observations demonstrate that LCMRglc differences and area-to-area relationships are distinct in these diseases and differ from findings in normal subjects.

P21. Comparison of Nuclear Magnetic Resonance and Computed Tomographic Findings in Patients with Extrapyramidal Movement Disorders

S. A. Lukes, M. J. Aminoff, C. Mills, D. Norman, and T. H. Newton, San Francisco, CA

We undertook a study to determine if nuclear magnetic resonance imaging (NMR) would have any useful role in the investigation of selected gray matter degenerative disease characterized by abnormal movements. Four patients with Huntington's chorea, five with parkinsonism, two with Wilson disease, and two with focal dystonia were examined with high-resolution computed tomography (CT) and with a high-resolution NMR unit using a 3.5 kilogauss superconducting magnet. The NMR images were generated using both inversion-recovery and spin-echo techniques. Preliminary evaluation indicated that NMR and CT show similar findings in both Huntington's chorea and parkinsonism and that NMR imaging provides no additional or complementary information. The anatomicopathological basis for focal dystonia is presumably in the basal ganglia, but neither CT nor NMR has thus far identified any abnormality. In Wilson disease, the CT findings of low density and occasional calcification of the basal ganglia have been well described in the literature; in the spin-echo NMR images, high signal intensity is identified in the basal ganglia and the red nucleus. Thus it appears that NMR provides complementary as well as additional information in this disorder. Our survey suggests that NMR may be helpful in the evaluation of patients with Wilson disease, and thus far provides no additional information in patients with Huntington's chorea, parkinsonism, or focal dystonia.

P22. Computed Tomographic Correlates of Hemiparesis following Ischemic Stroke, and Prognosis for Recovery

John J. Witek, David S. Knopman, and Alan B. Rubens, Minneapolis, MN

The prognosis for recovery from right hemiparesis following cerebral infarction was related to lesion localization on computed tomographic (CT) scans obtained five months postonset in a consecutive series of 35 previously neurologically healthy, right-handed, aphasic patients aged 44 to 75 years. The patients had neurological examinations three weeks postonset and monthly for six to twelve months. CT localization was done without knowledge of the neurological findings. Comparisons were made between internal capsule, upper rolandic, lower rolandic, and corona radiata lesions. Ten patients had involvement of the posterior limb of the internal capsule with or without other lesions. Initially 9 had severe plegia and 1 had moderate paresis involving arm and leg equally. No recovery occurred in 8, and partial proximal recovery in 2. Of 12 patients with upper rolandic involvement (above the level of the lateral ventricle) without internal capsule lesions, 1 had no initial paresis, 5 recovered completely, and 3 partially recovered arm and leg function. Two of the 3 patients with no or limited proximal recovery in the arm and leg had subcortical extension. Of 5 patients with lower rolandic lesions (without lesions of the internal capsule or upper rolandic area), none had persistent paresis. Only 1 of 7 patients with central corona radiata lesions (without lesions of the internal capsule or the upper or lower rolandic region) had persistent paresis. In summary, in stroke, the pattern of weakness and prognosis for recovery are predicted by lesion localization on CT scan. Internal capsule lesions imply a poor prognosis and upper rolandic lesions an intermediate prognosis; lower rolandic or corona radiata lesions generally do not result in a persistent hemiparesis.

P23. Contralateral Cerebellar Hypometabolism following Cerebral Hemispheric Insult: A Positron Emission Tomographic Study

Michael Kushner, Martin Revitch, Abass Alavi, Robert Dann, Howard Hurtig, and Joel Greenberg, Philadelphia, PA

Abnormal metabolism in the cerebellum was noted in studies of unilateral supratentorial lesions using positron emission tomography (PET). PET was performed in 9 patients with acute ischemia of the anterior circulation, 2 with initially presenting astrocytoma, and 8 normal controls. Images of local brain metabolism were obtained using 18F-fluorodeoxyglucose. Local metabolic rates for glucose were calculated in the cerebellum, and these data were used to express a left-to-right metabolic ratio for the cerebellar hemispheres ($0.99 \pm 0.05$ in controls). Within the lesion group this ratio showed a significant asymmetry (10% or greater difference) in 5 cases (3 strokes, 2 tumors); in each case, the lower metabolic rate lay in the cerebellar hemisphere contralateral to the cerebral lesion ($p < 0.05$ by sign test). Although this ratio was not significantly asymmetrical in the other 6 patients with lesions, the lesser metabolism also lay contralateral to the cerebral lesion. When com-
pared to control values, the lesion ratios showed significantly greater asymmetry ($p < 0.02$ by Mann-Whitney U test). A cerebellar abnormality tended to occur when the PET images showed widespread depression of cerebral metabolism. The presence of a cerebellar abnormality on PET did not appear to be influenced by either the degree of motor weakness or the presence of a cerebellar syndrome. These data indicate that a mechanism exists whereby unilateral cerebellar dysfunction may influence contralateral cerebellar metabolism, possibly by disruption of descending tracts that are destined to modulate activity in the cerebellum.

**P24. Macular and Peripheral Visual Field Representation in the Striate Cortex Demonstrated by Positron Emission Tomography**

Michael Kushner, Alan Rosenquist, Abs Alavi, Martin Reivich, Joel Greenberg, and Walter Cobb, Philadelphia, PA

Using positron emission tomography (PET), we previously showed that patterned stimulation of either visual hemifield causes significant increases in glucose metabolism in the contralateral striate cortex. We now report the results of restricting the spatial extent of the visual stimulus to the central 20 degrees (macular region) of the left hemifield and the peripheral 60 degrees of the right hemifield in four normal subjects aged 19 to 25 years. Subjects were positioned at the center of curvature of a plastic hemisphere (radius, ~45.5 cm) onto which was rear-projected a black-and-white check pattern, each check subtending 3 degrees of arc. The check pattern was reversed at rates of 5 and 10 Hz in two subjects each. Central fixation was assured by monitoring the subject's response to dimmings of a central light-emitting diode. Images of local cerebral metabolism during stimulation were obtained using 18F-fluorodeoxyglucose. Data were expressed as ratios of metabolic rates in the left and right anterior striate cortices and the left and right posterior striate cortices ($L/R - MR = 0.99 \pm 0.05$ for both comparisons in eight unstimulated controls). In all subjects the right posterior striate cortex (macular vision) showed significantly higher metabolism ($L/R - MR = 0.81, 0.82, 0.79$, and $0.85$). The left anterior striate cortex (peripheral stimulation) showed significantly higher metabolism in two subjects and tended to be higher in a third ($L/R - MR = 1.15, 1.12, \text{and} 1.07$); no effect was noted in one case. These results show that PET may be useful in mapping the representation of the retina upon the striate and extrastriate cortices in humans.

**P25. Cerebral Mapping of Apraxia by Positron Emission Tomography in Alzheimer Disease**

N. L. Foster, T. N. Chait, N. J. Patronas, R. L. Brooks, G. Di Chiro, and P. Fedio, Bethesda, MD

In an attempt to shed light on the cerebral localization of apraxic dysfunction, eleven right-handed patients with Alzheimer disease were evaluated clinically and by positron emission tomography (PET) using fluorodeoxyglucose. All were free of motor or sensory deficits; comprehension of spoken commands was not impaired. Each patient was scored on a battery of 75 motor acts to verbal command. Computerized analysis of PET scans (Ortec ECAT II) provided peak metabolic rates for glucose in 164 standardized voxels ($3 \times 15 \times 20 \text{mm}$) of cerebral cortex. Cortical localization patterns of voxels evidencing a close correlation between apraxia task performance and glucose metabolism varied considerably from one type of task to another. For example, scores on tasks of whole-body praxis (e.g., the demonstration of standing up or squatting) appeared to be associated mainly with metabolism in the left frontotemporal lobe, while competency on tests of nonrepresentational apraxia (i.e., placing the hand under the chin, touching the index finger to the ear, and so on) were largely localized to frontoparietal voxels in the right cerebral hemisphere. Performance on psychometric tests with similar localization correlated with these apraxia scores. Total apraxia scores were significantly related to tests of global intellectual function.

**P26. Nuclear Magnetic Resonance Imaging in Stroke: Regional in Vivo Measurements of $T_1$ and $T_2$ Relaxation Times and Mobile Proton Density**

Ferdinando S. Buonanno, J. Philip Kistler, Ian L. Pykett, Thomas J. Brady, Kenneth R. Davis, Mark R. Goldman, and Gerald M. Pobost, Boston, MA

True three-dimensional proton ($^1H$) nuclear magnetic resonance (NMR) imaging produces tomographic sections, in any selected angle, of mobile proton distribution ($p$) modified by the spin-lattice ($T_1$) and spin-spin ($T_2$) relaxation times in a way that depends on the particular pulse sequence used. It is possible to image and measure, in vivo and with a high degree of spatial resolution, each of the three NMR parameters ($p$, $T_1$, $T_2$), and thus characterize various cerebral lesions. We previously reported prolonged $T_1$ and $T_2$ values in bulk in vitro samples of gerbil brains symptomatic after ipsilateral cortical carotid ligature. We now present our clinical experience with quantitative in vivo proton spin density ($p$) $T_1$ and $T_2$ mapping in cases of human stroke. NMR imaging using pulse sequences that emphasize relaxation times (e.g., inversion recovery) appear to have a lesion-detecting sensitivity equal or superior to that of x-ray computed tomography. It remains unclear whether the additional information gleaned from spin-density or $T_2$ mapping adds specificity to the procedure and permits differentiation of ischemic from infarcted tissue, while pulse sequences with lower $T_1$ weighting (such as saturation recovery) possess lower sensitivity, notwithstanding their higher spatial resolution.

**P27. Proton Nuclear Magnetic Resonance Imaging of Human Brain**

Ferdinando S. Buonanno, Ian L. Pykett, Thomas J. Brady, Paul F. J. New, Kenneth R. Davis, Mark R. Goldman, Gerald M. Pobost, and J. Philip Kistler, Boston, MA

Proton nuclear magnetic resonance (NMR) imaging produces tomographic sections of mobile proton distribution as modified by the spin-lattice ($T_1$) and spin-spin ($T_2$) relaxation times. Available imaging techniques emphasize, in subtly different ways, the contribution of the various NMR parameters to the resultant image. We exhibit a sampling of inversion-recovery and saturation-recovery NMR imaging results in normal subjects and in various examples of human cerebral disorders. NMR imaging using the inversion-recovery pulse sequence appears to have a sensitivity equal or superior to that of x-ray computed tomography; however, since all lesions appear as areas of decreased signal intensity, characterization of pathological processes will require additional information (such as in vivo $T_1$ or $T_2$ mea-
P28. A Quantitative Model for the Measurement of
Brain Receptor Binding and Number in Vivo with
Positron Emission Tomography
M. Mintun, G. F. Wooten, and M. E. Raichle, St. Louis, MO

Almost from the time of its introduction the claim has been
made that positron emission tomography (PET) will pro-
vide a means by which receptor function and distribution can be quantitatively evaluated in vivo. Despite this claim, no quantitative method has emerged that permits assess-
ment of receptor function and distribution with PET. We
present the first in vivo method for use with PET scanning that results in a quantitative determination of regional dopamin receptor concentration (Bmax) and receptor affinity (Kd) using radiolabeled spiperone. The data are analyzed using a mathematical model that describes the behavior of spiperone in the brain. The procedure was tested in rats using [3H]-spiperone, multiple animals, and brain dissection to produce data sets (tissue and blood) that simulate the sequential PET scanning that will be done in human subjects when an appropriately labeled form of this ligand becomes available (e.g., [18F]-spiperone). From these data the following estimates were obtained: brain permea-
bility of spiperone, 8.6 x 10^-5 cm/sec (assuming a capil-
лаry surface area of 100 cm²/gm); Bmax = 2.3 pmol/gm protein; and Kd = 2 pM. To our knowledge, these data are the first quantitative evidence that PET can be used to measure, locally and in vivo, both the function (i.e., bind-
ing affinity) and number of receptors in human brain. The remaining step necessary for implementation of this tech-
nique in humans is the development of high specific ac-
tivity [18F]-spiperone.

P29. Real-Time Ultrasound Imaging of the Brain
George J. Dohrmann and Jonathan M. Rubin, Chicago, IL

Since most intracranial lesions occur subcortically or beneath the brain, a method to visualize them in the operat-
ing room would be very useful. In a sense, it would allow the neurosurgeon to explore the brain before operating on it. The surgeon could locate the lesion and chart the best approach to it before opening the dura or the brain itself. Real-time ultrasound scans (called that because the rapid frame rate gives an effect similar to fluoroscopy and physi-
ological motion is visualized as it happens) were performed on 150 patients during operative procedures for suprat-
entorial (100 patients) and infratentorial (50 patients) lesions. The scan head contained transducer elements of three frequencies (3, 5, and 7.5 MHz). After the scan head was placed in a sterile plastic bag, scanning was done through a burr hole, craniectomy, or craniotomy, with the dura in-
tact. Normal and pathological intracranial anatomy could be demonstrated. Lesions such as neoplasms, cysts, and abscesses were visualized. The scans were recorded on videotape; an image was frozen on the screen, and the distance to the lesion as well as the dimensions of the lesion were calculated by computer. By moving the scan head over the dura and changing the angle of the scan head, an optimal approach to each lesion was planned. Ultrasound was of particular use in the localization of small cerebral neoplasms, vascular malformations, or hematomas and in the localization and drainage of abscesses, cysts, or cystic portions of neoplasms. Biopsy of deep tumors was accomplished; the biopsy probe could be guided directly to the mass and tissue obtained from a given area of the tumor. Aneurysms were identified and thrombosis of all or part of them could be shown. Bone fragments or foreign bodies were accurately visualized intraoperatively using ultra-
sound; ventricular catheters were guided into optimal posi-
tion using ultrasound during the procedure. In summary, intraoperative real-time ultrasound is very useful in intra-
cranial neurosurgical operations and can provide informa-
tion unobtainable by other means. With further refine-
ments, the ultrasound scanner may well be considered a surgical instrument and become a valued part of the
neurosurgical operating room.

P30. Use of Real-Time Ultrasound Scanning in
Neurosurgical Operations
Jonathan M. Rubin and George J. Dohrmann, Chicago, IL

Real-time ultrasound scanning in the neurosurgical oper-
ating room allows the intracranial contents to be viewed dynamically. We will demonstrate the techniques and ap-
lications of ultrasound in neurosurgical procedures. The exhibit will show the equipment used, the techniques em-
ployed in scanning during surgery, and the types of lesions that can be detected. In particular, we will show examples of tumors, cysts, hematomas, foreign bodies, and abscesses that were localized by ultrasound. We have biopsied intra-
cranial lesions and placed catheters under ultrasonic guidance, and these methods will also be shown. A video-
tape recorder/monitor is incorporated into the display in order to show the power of the dynamic capabilities of the technique.

P31. Regional Cerebral Blood Flow in Humans by
Positron Emission Tomography: Unique
Determination by an in Vivo Autoradiographic
Method
Myron D. Ginsberg, Bernard E. Howard, Alan H. Lockwood,
and Philip Freed, Miami, FL

We have developed an in vivo autoradiographic strategy for determining regional cerebral blood flow (rCBF) by positron emission tomography (PET). With this method, an inert diffusible indicator (15O-labeled water) is adminis-
tered intravenously, multiple arterial blood samples are drawn to define the resulting activity curve of the arterial tracer, and a cerebral image is accumulated by the tomo-
graph over a time interval T1 to T2. rCBF is calculated from knowledge of the accumulated regional cerebral activity and the arterial concentration curve. In a previous study (J Cer Blood Flow Metab 2:89–98, 1982), the in vivo paradigm was validated against the classic autoradiographic strategy of Kety in a series of rats, and excellent agreement was obtained. We report the successful application of this method to PET studies of rCBF in humans. In three normal subjects, a bolus intravenous infusion of 20 to 30 mCi of tracer was employed and a 90-second PET image was ob-
tained. This strategy maximized cumulative cerebral activity (C) while preserving a monotonic relationship between C and rCBF (f) over the physiological range of rCBF (i.e.,
was performed over 60 to 90 seconds in order to analyze TI and TZ, and theorems were derived that establish conditions under which the unique determination of $\gamma$ is guaranteed. Our results support the practicability and sensitivity of this method for the reliable estimate of rCBF in humans.

P32. Metabolic Rates Using $^{18}$F-Deoxyglucose Obtained by Dynamic Positron Emission Tomographic Scanning
R. A. Brooks, G. Di Chiro, R. L. DeLaPaz, N. J. Patronas, B. J. Shatzman, and G. H. Weiss, Bethesda, MD

We have done dynamic positron emission tomographic (PET) scanning on 20 patients who were injected with up to 5 mCi of $^{18}$F-deoxyglucose. The studies consisted of twelve 2½ minute scans beginning immediately after the injection. We used both fast (30-second) and slow (5- to 10-minute) injections but found better results with the slow ones. We then calculated rate constants $k_1$, $k_2$, and $k_3$ by curve-fitting the uptake data to the model equation. This method permits accurate determination of metabolic rate; however, the rate constants determined by curve fitting were less accurate. Metabolic rates were obtained by this method which correlated well with the values determined by the more usual method of waiting 45 minutes before scanning. An error analysis has also been performed which compares the statistical accuracy of this technique with that of the usual method. The use of dynamic scanning with $^{18}$F-deoxyglucose can greatly reduce the time spent on each patient study. However, if multiple scanning levels are desired, the method requires a multislice scanner.

P33. Measurements of Glucose-6-Phosphatase in Normal and Tumoral Brain Tissue
Rodney A. Brooks, Giovanni Di Chiro, Ann A. Tran, Nicholas J. Patronas, and Robert L. DeLaPaz, Bethesda, MD

The basis of the deoxyglucose technique for determining metabolic rate is that deoxyglucose, like glucose, is phosphorylated by hexokinase but, unlike glucose, becomes metabolically trapped because it is not a suitable substrate for phophoglucoisomerase. Trapping of deoxyglucose-6-phosphate, however, can be reversed by the enzyme glucose-6-phosphatase (and possibly other enzymes), which can lead to escape of the tracer material. To correct for the phosphatase effect, the rate constant $k_4$ has been incorporated into the operational equation. However, questions have been raised about the value of $k_4$ in normal and pathological tissue. We studied the rate constant $k_4$ in a group of 20 glioma patients scanned with positron emission tomography following injections of $^{18}$F-deoxyglucose. By comparing metabolic rates calculated from early scans (25 to 30 minutes after injection), normal scans (about 60 minutes after injection), and late scans (2 to 3 hours after injection), we obtained information on $k_4$, and hence on phosphatase activity. We found that for normal gray matter, the $k_4$ constant is in agreement with information reported by Huang et al (Am J Physiol 238:E69–E82, 1980). Furthermore, values in tumoral tissue, on the average, did not differ significantly from normal values.

P34. Phosphorus 31 Nuclear Magnetic Resonance Analysis of Huntington and Control Brain
J. Pettigrew, N. Minshew, T. Glonek, S. Kopp, and M. Cohen, Dallas, TX, and Chicago, IL

Phosphorus nuclear magnetic resonance ($^{31}$P NMR) is an established method for studying phosphorus metabolism in vitro and in vivo. We present the first reported application of $^{31}$P NMR to human brain in a genetic neurological disorder, in this case Huntington disease (HD). Coded human brain samples were obtained through the Brain Tissue Resource Center from a 39-year-old man with HD and a 45-year-old male control. Samples were obtained from each brain from Brodmann's area 9, caudate, and cerebellum, and $^{31}$P NMR analysis was performed on perchloric acid extracts from these samples. The readily identifiable signals were $\alpha$-glycerol phosphate, ribose 5'-phosphate, choline phosphate, inorganic orthophosphate, glycerol 3-phosphorylethanolamine, and glycerol 3-phosphorylcholine. HD brain exhibited elevations in $\alpha$-glycerol phosphate, glycerol 3-phosphorylethanolamine, and glycerol 3-phosphorylcholine commensurate with the degree of neuropathological involvement (i.e., caudate > frontal cortex > cerebellum). This finding was considered to reflect non-specific degenerative changes. The most striking finding was an almost twofold increase in ribose 5'-phosphate (HD = 10.44 ± 1.35%, control = 5.58 ± 0.46% of total phosphate signal) in all sampled areas of HD brain. Since we previously demonstrated levels of ribose 5'-phosphate to be unaltered by ischemia or hypoxia (Glonek et al, J Neurochem, in press), we postulate that the elevation is secondary to antemortem alterations in HD ribonucleo-proteins. This finding may correlate with reported electron microscopic alterations in nucleoprotein structures in HD cortical biopsies (Roizin et al, Adv Neurol 23:95–122, 1979). This $^{31}$P NMR finding may provide helpful insights into the molecular pathology of HD.

P35. Multifocal Computed Tomographic Enhancement in Multiple Sclerosis
G. C. Ebers, F. Vinuela, and T. E. Feasby, London, Ont, Canada

A review was made of 116 computed tomographic (CT) scans of 106 patients with multiple sclerosis. Of the scans done during an acute relapse, 50% (29/58) showed enhancing lesions, characteristically in areas other than those suspected to be active by clinical criteria. Enhancing lesions were seen in 37.8% (14/37) of the scans done during an "active stage" of disease (i.e., progression or relapse within three months), while only 14.3% (3/21) showed enhancement during clinically inactive periods. High-volume delayed scans increased the number of enhancing lesions seen (24/39, or 61.5%, of the scans done during acute relapse). In the total group, 34.5% (40/116) of all scans showed low-density lesions; 17 of these scans also showed enhancement. Although some of the lesions had been suggested by clinical symptoms, the majority were unsuspected. Multiple enhancing lesions were seen in 1 patient in whom 5 scans had been done over a year. At autopsy the brain was serially sectioned to correspond to the CT slices. Typical plaques were found where transitory enhancement had been seen. This study suggests that enhancing CT lesions in multiple sclerosis reflect biological activity and are most likely to be seen during acute, clinically active relapses.
The findings concord with the clinical impression that acute relapses are commonly multifocal and mediated by bloodborne factors.

P36. Metabolic Changes during Regeneration of the Rat Hypoglossal Nerve
C. B. Smith, A. M. Crane, M. Kaederow, M. Rendel, B. Agranoff, and L. Sokoloff, Bethesda, MD

Section or injury to a nerve results in characteristic morphological changes in the cell bodies of origin. These changes are followed by regeneration of axons and restoration of function if the nerve is peripheral to the central nervous system. Neurons with axons contained entirely within the central nervous system have a limited reaction that generally ends in cell death. Investigation of the biochemical changes which accompany the cell reaction to axotomy are important for fully understanding the process of regeneration and perhaps why it fails to occur in the central nervous system. We studied the response of the rat hypoglossal nucleus to unilateral section of the twelfth nerve, and we determined the time course of changes in the rates of protein synthesis and glucose utilization with two recently developed quantitative autoradiographic methods. Our results showed that both processes increase in the nucleus ipsilateral to the sectioned nerve. The large increase in glucose utilization of 300 nmol per gram of tissue per minute precedes the increase in protein synthesis of 1 to 2 nmol of leucine incorporated per gram per minute, and both persist even after functional innervation of the tongue returns. It is clear from these studies that while increases in both biochemical reactions are involved in the process of neural regeneration, the changes in the energetics of the system must be associated with neural functions in addition to protein synthesis.

P37. Imaging of Local Cerebral Blood Flow Derived by the Stable Xenon/Computed Tomographic Technique
S. K. Wolfson, Jr, H. Yonas, E. E. Cook, D. Gur, L. Shabason, W. F. Good, D. M. Miller, R. E. Latchaw, and M. Boench, Pittsburgh, PA

Xenon-enhanced computerized tomography (CT) is a useful technique for definition of cerebral blood flow in vivo. Utilizing a fast scanner in the dynamic mode, blood flow determinations at multiple brain levels have been made during inhalation studies lasting from four to six minutes in the nonhuman primate and in human subjects. A computer technique has been devised to simultaneously determine the partition coefficient and blood flow constants, and in turn generate a cerebral blood flow determination for preselected CT volumes (voxels). Color maps of blood flow have been generated with a high degree of anatomical specificity (full width half maximum, 4 mm in each direction). Manipulation of arterial carbon dioxide tension caused an increase in gray matter flow of 6%/torr and in white matter flow of 4%/torr. Blood flow values were 60 ml/100 gm/min in normal gray matter, 18 ml/100 gm/min in normal white matter, and below 5 ml/100 gm/min in areas of known infarction. Blood flow maps were derived using 35% xenon/65% oxygen in awake patients and 60% xenon/40% oxygen in intubated, brain-injured patients. The method offers an equally high degree of resolution at the surface and deep within the brain substance. It is possible to construct three-dimensional images of flow from a series of adjacent flow maps (slices). The three-dimensional numerical matrix from which this volume is constructed contains the information needed to "cut" planes or slices at any angle to reveal flow patterns of internal structures. This will be visually demonstrated.

POSTER PRESENTATION:
EPILEPSY AND NEUROPHARMACOLOGY

P38. Minor Motor Anticonvulsants Selectively Depress Benzodiazepine Receptor Binding in Cultures of Mouse Cerebral Cortex
Phyllis K. Sherr, Elaine A. Neale, and Phillip G. Nelson, Bethesda, MD

Valproic acid (VPA), ethosuximide, and diazepam are widely used for the chronic treatment of minor motor seizures, yet no definitive mechanism of action for these drugs is known. To evaluate possible mechanisms as well as drug toxicity, we studied the effects of each anticonvulsant on mouse cerebral cortical cell cultures at twice the high therapeutic serum concentration (VPA, 200 µg/ml; ethosuximide, 200 µg/ml; diazepam, 5 µg/ml). The drugs were added on day 9 in culture and maintained for 10 days. At the end of this period the cultures were assayed for 125I-tetanus toxin labeling, high-affinity uptakes of 3H-labeled y-aminobutyric acid (GABA) and 3H-β-alanine, choline acetyltransferase activity, 3H-benzodiazepine binding, clonazepam-displaceable (neuronal) benzodiazepine binding, total protein, and neuronal cell counts. Our results show that: (1) there is mild (75 to 85% of control), generalized toxicity for VPA and diazepam but none for ethosuximide as determined by neuronal cell counts; (2) VPA causes a specific reduction in β-alanine uptake, possibly related to toxic effects on nonneuronal elements; and (3) all three drugs selectively depress both markers of benzodiazepine binding: specific benzodiazepine binding is not detectable in diazepam-treated cultures, is 44 ± 2% of control for VPA, and is 72 ± 4% for ethosuximide; clonazepam-displaceable binding is also not detectable for diazepam; it is 47 ± 4% for VPA and 79 ± 4% for ethosuximide. Studies on diazepam and VPA suggest that these effects are recoverable to the general toxicity level of each drug. Acutely, benzodiazepines have been shown to augment GABA inhibition. Our results suggest that decreased benzodiazepine receptor binding after chronic exposure to these anticonvulsants might effect an overall reduction of GABA inhibition in this seizure type. These data lend support to the notion that excessive inhibition may be implicated in the pathophysiology of absence seizures.

P39. How Often Does Cerebrospinal Fluid Pleocytosis Occur after Generalized Seizures?
J. W. Schmidtley, R. Edwards, and R. P. Simon, San Francisco, CA

We recently called attention to postictal pleocytosis, a transient and otherwise unexplained cerebrospinal fluid (CSF) pleocytosis following repetitive major motor convulsions (Ann Neurol 9:81, 1981). To determine the frequency of postictal pleocytosis, we prospectively reviewed CSF obtained within 72 hours of a seizure or seizures. Seventy-five episodes of seizures in 71 patients aged 19 to 88 years were studied. There were 19 episodes of a single seizure and 36 of multiple seizures (2 to 12 seizures). The most common causes of seizures were alcohol withdrawal and posttraumatic epilepsy, which together accounted for 60% of
admissions. In 11 patients, failure to take anticonvulsants regularly contributed to the seizures. Seventy-three CSF samples in 69 patients contained 4 or fewer white blood cells per cubic millimeter. We found a transient postictal pleocytosis in 2 patients (2.7% of our series). A 43-year-old man with posttraumatic epilepsy had 12 white cells per cubic millimeter of CSF 24 hours following 6 generalized convulsions; 19 hours later the CSF contained only 2 white cells. A 44-year-old man with posttraumatic epilepsy had 70 white cells per cubic millimeter of CSF 18 hours after a single prolonged seizure; two and four days later the CSF contained 10 and 3 white cells, respectively. Bacteriologic studies on CSF were negative; antibiotics were not given. The timing and course of the pleocytosis in these 2 patients was identical to that in our 6 previously reported cases. We conclude that postictal pleocytosis is uncommon and that it may follow a single prolonged seizure as well as repetitive seizures.

P40. Endocrinological Changes following a Single Generalized Seizure in Humans
M. J. Aminoff and R. P. Simon, San Francisco, CA

We measured the plasma concentrations of various hormones over a 24-hour period following a single generalized tonic-clonic seizure in 21 patients in order to determine whether the changes relate to activation of specific pathways, as suggested by some, or merely reflect a nonspecific activation of neurohormonal mechanisms. The seizures related to alcohol withdrawal in 13 cases and were of diverse cause in the remainder. Epinephrine, norepinephrine, prolactin, growth hormone, B-lipotropin, B-endorphin, adrenocorticotropic hormone (ACTH), cortisol, and vasopressin were each found to be elevated within 30 minutes of seizure onset, returning to baseline values over a variable period depending on the hormone. Plasma renin values did not change significantly in the period under study. These results suggest that: (1) these hormonal responses are a nonspecific consequence of a generalized seizure; (2) the close parallelism in the time course of ACTH, B-endorphin, and B-lipotropin changes reflects the common origin of these substances; (3) the time course of the cortisol response to a seizure is that predicted by the ACTH response; and (4) the time course of the B-endorphin response is not incompatible with the theory of others that endogenous opioids released during seizures may play a role in postictal depressive states.

P41. Local Cerebral Glucose Utilization and Electroencephalographic Alterations in Enkephalin-induced Seizures
Harry T. Chugani, Diane C. Chugani, Robert F. Ackermann, and Jerome Engel, Jr, Los Angeles, CA

Animal studies have demonstrated epileptogenic properties of opioid peptides. We studied the effects of D-Ala2-methionine-enkephalin (D-Ala), a long-acting form of methionine-enkephalin, on local cerebral glucose utilization (ICGU) in rats using the 2-deoxyglucose method. Male Sprague-Dawley rats received 100 mg of D-Ala in 10 ml of saline instilled into a lateral ventricle through previously implanted cannulas, while control animals received only saline. Another group of rats received 20 mg of naloxone per kilogram of body weight intravenously in addition to either D-Ala or saline. Surface and depth electroencephalograms (EEGs) were recorded. Immediately after D-Ala infusion, the EEGs showed intermittent bursts of high-voltage spike and polyspike activity lasting over 45 minutes. Animals were awake but in a state of stupor. Intravenous naloxone injections reversed the stupor and normalized the EEG. Quantitative autoradiography revealed a two- to threefold increase in ICGU in the lateral septal nucleus and CA1 hippocampal region on the side of injection as compared to the contralateral side. Decreases in ICGU were found in several cortical and subcortical sensory structures. Animals treated with both D-Ala and naloxone showed marked attenuation of these changes. No changes were seen in saline- and naloxone-treated controls. These results support the notion that the hippocampus and lateral septal nucleus play a major role in opioid-induced absence-like seizures.

P42. Changes in Plasma Epinephrine and Norepinephrine Concentrations following Generalized Tonic-Clonic Seizures in Humans
R. P. Simon, M. J. Aminoff, and N. L. Benowitz, San Francisco, CA

We measured plasma concentrations of norepinephrine and epinephrine at frequent intervals over 24 hours following single generalized tonic-clonic seizures of diverse cause in 12 patients. Both norepinephrine and epinephrine were maximally elevated during the first 10 minutes; levels then fell rapidly so that by 3 hours the values were similar to those measured after 24 hours. Peak norepinephrine concentrations averaged 1,059 ± 184 (SE) pg/ml compared with 465 ± 85 at 24 hours, whereas epinephrine peak concentrations averaged 154 ± 30 pg/ml compared to 50 ± 7 pg/ml at 24 hours. Comparison of plasma catecholamine concentrations following alcohol withdrawal seizures and seizures from other causes revealed no difference except at 24 hours, when patients with alcohol withdrawal seizures (N = 7) had values approximately twice normal, while patients with other seizure types (N = 5) had values within the normal range (norepinephrine, 218 ± 17; epinephrine, 20 ± 2). The rise in plasma norepinephrine concentrations immediately following seizures presumably reflects generalized sympathetic neural activation; for most patients the maximal norepinephrine concentrations achieved were insufficient to produce marked cardiovascular effects. The rise in plasma epinephrine indicates adrenal activation; circulatory increases of the magnitude we observed could have profound cardiovascular and metabolic consequences (e.g., arrhythmias, hyperglycemia, and lactic acidosis).

P43. Dopamine Receptor Supersensitivity and Tolerance Induced by Haloperidol Is Not Inhibited by Prophylactic Lithium Administration
A. Reches, H. R. Wagner, V. Jackson, and S. Fabon, New York, NY

Prophylactic treatment with lithium was reported to prevent haloperidol-induced dopamine (DA) receptor supersensitivity. If such an effect exists, lithium may be useful in the prevention of tardive dyskinesia, which is probably related to DA hyperfunction. Chronic lithium feeding (0.2% w/w in the diet) in rats induced plasma lithium levels of 0.97 ± 0.06 mEq/L but failed to modify the haloperidol-induced supersensitivity of presynaptic DA receptors in both the nigrostriatal and mesolimbic DA terminals. Supersensitivity was reflected in the increased ability of
apomorphine to inhibit DA synthesis. Similarly, prophylactic treatment with lithium failed to block haloperidol-induced increases in \(^3\)H-spiroperone binding sites in the striatum, which reflect postsynaptic receptors. The acute administration of haloperidol (0.5 mg · kg\(^{-1}\) induced 2- to 3.1-fold increases in DOPAC (dihydroxyphenyl acetic acid) and homovanillic acid concentrations in the striatum and nucleus accumbens. Prophylactic treatment with lithium had no attenuating effect on this increase in DA turnover. Lithium also had no effect on the biochemical tolerance that developed in the striatum and accumbens after prolonged administration of haloperidol (2.0 mg · kg\(^{-1}\) for 21 days). We conclude that lithium does not prevent the presynaptic and postsynaptic DA receptor supersensitivity induced by haloperidol, nor does it modify the acute and chronic changes in DA metabolism induced by the drug in either the striatum or the accumbens.

P44. Tetrabenazine Blocks Dopaminergic Receptors in Rat Brain
A. Reches, R. E. Burke, C. Kuhn, M. Hassan, V. Jackson, and S. Fabn, New York, NY
Tetrabenazine (TBZ) is used in the treatment of hyperkinetic movement disorders. Its effect is thought to be mediated only by depletion of presynaptic dopamine (DA) stores. We studied other possible mechanisms of action of this drug. TBZ decreased DA concentration in the rat striatum and nucleus accumbens in a dose-dependent manner with an IC\(_{50}\) of approximately 1.2 mg · kg\(^{-1}\). Maximal depletion was obtained within 30 minutes, with only partial recovery at 8 hours. At 40 mg · kg\(^{-1}\), TBZ induced five- to eightfold increases in DOPAC (dihydroxyphenyl acetic acid) and homovanillic acid concentrations in both regions. Unlike reserpine, TBZ completely abolished the apomorphine-induced inhibition of DA synthesis under conditions in which this effect is mediated only by presynaptic DA receptors. TBZ also inhibited \(^3\)H-spiroperone binding in the striatum, with \(K_c = 2.1 \times 10^{-6}\) M. In rats, after unilateral destruction of the nigrostriatal pathway by 6-hydroxydopamine, pretreatment with TBZ (5 mg · kg\(^{-1}\)) significantly reduced, while pretreatment with reserpine (0.5 mg · kg\(^{-1}\)) significantly increased, the number of rotations induced by apomorphine compared with the number of rotations obtained in the same rats treated with apomorphine only. Both TBZ (5 mg · kg\(^{-1}\)) and reserpine (5 mg · kg\(^{-1}\)) depleted striatal DA content by approximately 90% at 1 hour. However, TBZ, but not reserpine, significantly stimulated in vivo tyrosine hydroxylase activity. Finally, in rats treated with TBZ (5 mg · kg\(^{-1}\) ), prolactin levels had increased at 30 minutes from 4.2 ± 0.7 to 167.9 ± 23.1 ng/ml plasma. TBZ, but not reserpine, blocked apomorphine inhibition of prolactin secretion. It is suggested that in addition to depleting monoamines, TBZ also blocks DA receptors in rat brain.

P45. Pharmacokinetics of Trihexyphenidyl after Acute and Chronic Administration
Robert E. Burke and Stanley Fabn, New York, NY
Trihexyphenidyl (THP) has long been used to treat Parkinson disease, and we recently showed that it is also beneficial for torsion dystonia (Neurology 32(2):A112, 1982). In spite of the clinical usefulness of the agent, little is known about its clinical pharmacology because sensitive phy- sicochemical methods for assay of serum levels are not available. Recently it has been shown that radioreceptor methods can be used to measure serum anticholinergic activity, and we have used THP displacement of the muscarinic ligand \(^3\)H-quinuclidinyl benzilate to measure serum THP levels and to study its pharmacokinetics. Standard curves of THP displacement of \(^3\)H-QNB binding show an IC\(_{50}\) of 45 ± 0.4 nM in the presence of serum, with a lower limit of detection of 7 ± 0.6 nmol of THP per deciliter of serum. Because an intravenous preparation of THP is not available, we studied the half-life (TV\(_{1/2}\)) for elimination by administering the drug orally and performing a linear regression analysis of the final portion of a ln (THP) versus time curve. We found that normal volunteers (N = 8; age, 31 ± 2 years) had a TV\(_{1/2}\) of 1.7 ± 0.2 hours. Dystonic patients treated chronically with high-dose THP (N = 6; age, 18 ± 5 years) had a TV\(_{1/2}\) of 3.7 ± 0.3 hours. This difference did not appear to be age related, as there was no correlation between age and TV\(_{1/2}\). Among volunteers, cerebral side effects (lethargy, confusion) were more closely related to age than to peak serum levels; those with moderate symptoms (N = 3) were 35 ± 2 years old and had serum levels of 24 ± 4 nmol/dl; those with mild symptoms (N = 6) were aged 28 ± 2 years and had levels of 21 ± 3 nmol/dl.

P46. Diazepam Inhibits Kindling and Calcium- and Calmodulin-stimulated Phosphorylation of Synaptic Membrane Proteins
Debora Farber and Claude G. Wasterlain, Los Angeles, CA
The second messengers calcium and calmodulin stimulate phosphorylation of several proteins in synaptic plasma membranes, and this may alter synaptic function (DeLorenzo, Cell Calcium 2:365, 1981). The stimulation is reduced in the hippocampus of septal-kindled rats but not in stimulated controls (Wasterlain and Farber, Ann Neurol, in press). We examined the effect of anticonvulsants on kindling and on in vitro phosphorylation of hippocampal synaptic plasma membranes. Diazepam (20 mg/kg 15 minutes before stimulation) completely blocked the development of kindled seizures from medial septal stimulation (400 \(\mu\)A, 60 Hz, 1 sec). In vitro, diazepam (10 \(\mu\)M to 1 mM) inhibited the calcium- and calmodulin-dependent stimulation of phosphorylation of three proteins of 50K, 54K, and 56K daltons in hippocampal synaptic plasma membranes without affecting the calcium- and calmodulin-dependent phosphorylation of proteins of higher molecular weight in the same preparation. The effective diazepam concentration in vitro and the effective dose in vivo both suggest an action through the low-affinity benzodiazepine receptors. These results raise the possibility that the blockage of kindling by anticonvulsants may be related to their ability to modify the phosphorylation of synaptic membrane proteins. (Supported by the Research Service of the Veterans Administration.)

P47. Calcium and Calmodulin: Second Messengers in the Kindled Hippocampus?
Claude G. Wasterlain and Debora Farber, Los Angeles, CA
Stimulation of the medial septum induced prominent hippocampal afterdischarges and kindled seizures and inhibited the magnesium-stimulated phosphorylation of hippocampal synaptic plasma membrane proteins in vitro (Wasterlain and Farber, Neurology 32(2):A93, 1982). This phosphorylation was unaffected by cyclic 3',5'-AMP, cyclic
3',5'-GMP, calcium, or calmodulin alone, but the combination of calcium and calmodulin together markedly stimulated incorporation of 32P into synaptic plasma membrane proteins of 50K, 54K, 56K, 98K, 106K, and 115K daltons. This stimulation was significantly less in kindled rats than in controls untreated or stimulated on a rapid schedule that did not lead to kindling. Calcium- and calmodulin-dependent phosphorylation was maximal within 30 seconds, suggesting that the role of protein phosphatases may have been minor. Similar results were found in cortex, basal ganglia, the amygdaloid region, brainstem, cerebellum, and spinal cord. However, differences between kindled and control animals were less striking in cortex, basal ganglia, and brainstem and were absent in spinal cord and were absent.

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P48. Regional Alterations in γ-Aminobutyric Acid Binding Produced by Cerebrospinal Fluid
Walter B. Eisman, Donald Blair, Morton Nathanson, and Eric J. Eisman, New York, NY

Receptor sites for γ-aminobutyric acid (GABA) in the brain have been altered by changes in seizure status. We examined the effect of protein-free cerebrospinal fluid (CSF) on isolated presynaptic and postsynaptic membranes associated with kindling. Significant (p < 0.01) inhibition of GABA binding occurred in the presence of CSF from patients with active, untreated seizure disorders at both presynaptic and postsynaptic sites of the cerebral cortex (59% and 79%) and diencephalon (29% and 72%), but not the cerebellum. CSF from patients with treated seizure disorders significantly (p < 0.05) reduced the number of GABA binding sites only on postsynaptic membranes from the rat cerebral cortex (47%) and diencephalon (50%). Postsynaptic sites from cerebellar cortex (mosaic fiber endings) were unaffected by any of the protein-free CSF samples. GABA levels did not differ in concentration (1.03 ± 0.04 μmol/ml), and all CSF samples were initially normal for protein concentration. These data suggest that CSF from patients with active, untreated seizures can alter GABA binding to its receptors in rat brain. Also, CSF from treated patients with seizure disorders reduces GABA binding to postsynaptic sites, though by a lesser degree.

P49. Nasopharyngeal Electrodes: Are They Worth the Trouble?
Ann Louis, James C. White, and J. William Langston, San Jose, CA

The exact role of nasopharyngeal (NP) electrodes in the electroencephalographic evaluation of patients with seizures remains controversial despite more than thirty years of experience since their introduction in 1949. In order to determine the risk of missing epileptic activity if NP electrodes are not routinely used, we prospectively evaluated 656 consecutive sleep electroencephalograms utilizing NP leads. These were obtained on patients referred to our laboratory for evaluation of seizures between the years 1977 and 1981. Seventy-one records (11%) contained pathological spikes. In only 1 tracing (1.4%) were the spikes confined solely to NP-derived leads. In 3 records (4.2%), epileptic activity apparent on the surface recording might easily have been missed without the use of NP electrodes. All records containing pathological spikes from the NP electrodes also showed abnormalities on the surface recording. Benign epileptiform transients of sleep were seen in 21% of the recordings, confirming a previous study (White, Langston, and Pedley, 1979). We conclude that the risk of missing pathological spikes if NP electrodes are not routinely used is remarkably small (1.4%). No patient with a completely normal awake and asleep surface recording demonstrated abnormalities in the NP-derived leads alone. However, NP electrodes are helpful in clarifying and localizing suspicious surface potentials.

P50. Semantic Agraphia
David P. Roeltgen, Leslie Rothi, and Kenneth M. Heilman, Hershey, PA, and Gainesville, FL

Spelling is thought to occur via two separate pathways. The phonological route uses sound to grapheme correspondence rules to write regular words, and the lexical-semantic route utilizes visual word images and meaning to write irregularly spelled words. We have seen four patients who demonstrate that the lexical route can be dissociated from semantic processing. All the patients had a comprehension deficit but correctly spelled irregular words. To learn if they could spell words they could not comprehend, we gave these patients a homophone test. We dictated sentences with homophones and asked the patients to spell each homophone using the context of the sentence. Although the patients spelled the homophones correctly, they frequently spelled the semantically incorrect one (e.g., "spell not, as in 'He is not here'"; a typical reply was "k-n-o-t"). All patients spelled low-frequency irregular words relatively more frequently than high-frequency irregular words. Therefore, they were correct relatively more often when asked to spell low-frequency words such as knight than when asked to spell night. These results suggest that lexical writing may be dissociable from semantic influence. Also, low-frequency irregular words may be better encoded within the lexical system, while high-frequency words are dependent upon semantic influence.

P51. Stroke Mechanism and Aphasia Type
Elizabeth Zarate-Yoo, Louti R. Caplan, and Daniel B. Hir, Chicago, IL

The mechanism of stroke was analyzed in 103 cases of aphasia identified in 256 consecutively examined strokes of the anterior (carotid) circulation. The most common stroke mechanism producing aphasia was embolism of intracranial or cardiac origin (52% of patients), followed by large-vessel thrombosis (32%) and hemorrhage (7%). Miscellaneous causes (such as aneurysm) accounted for 9% of the aphasias. Consistent with prior studies, Wernicke aphasia was commonly due to embolism (67% of patients) and rarely due to thrombosis (7% of patients). Both thrombosis (37%) and embolism (58%) were common mecha-
isms underlying Broca aphasia. None of the cases of Broca aphasia were due to hemorrhage. In Broca aphasia with rapid recovery, embolism was the predominant mechanism (78% of patients). Embolism was the most common mechanism underlying Broca, Wernicke, transcortical, and mixed aphasia, whereas thrombosis was the most common cause of strokes producing either conduction or anomic aphasia. Although hemorrhage was uncommon among the aphasic patients as a group (7%), the incidence was considerably higher among the patients with transcortical aphasia (25%). Embolism is the most common stroke mechanism underlying aphasia, probably reflecting the tendency of emboli to lodge in the middle cerebral stem and its branches, thus injuring superficial cortical structures relevant to language. Embolism should be especially suspected in cases of Wernicke or Broca aphasia with rapid recovery.

P52. Association of Visual Agnosia and Transcortical Sensory Aphasia
Andrew Kertesz, London, Ont, Canada

Transcortical sensory aphasia (TSA) is a recognized, albeit controversial clinical syndrome of fluent speech with poor comprehension but good repetition. In a series of 31 cases of TSA we found 7 patients with anatomical localization who also had striking visual agnosia (VA). The latter is often considered not to involve language disturbance. The neurological features and language and cognitive behavior on standardized tests were tabulated. In addition to TSA and VA, right homonymous hemianopia occurred in 7 patients, tactile agnosia in 5, alexia with agraphia in 4, constructional apraxia in 3, and “optic ataxia” in 3. Alexia without agraphia and semantic jargon also occurred in some patients. Isotope scan was available in 5 patients, computed tomographic localization in 5, and autopsy in 1. Anatomical analysis indicates that the occipitotemporal and inferior parietal regions of the dominant hemisphere are involved when TSA and VA are both seen. The callosal disconnection that is an essential feature of visual agnosia in unilateral left-sided lesions may be accomplished by larger subcortical infarcts in the territory of the posterior cerebral artery. This was the case in all but 1 patient, who had an arteriogenous malformation in the same region. The association of the two syndromes is more than coincidental and appears to be related to the anatomical proximity of the areas that are crucial for visual recognition and semantic associations of auditory and visual language.

P53. Pseudoneglect in a Callosally Disconnected Patient
Kenneth M. Heilman, Dawn Bowers, and Robert T. Watson, Gainesville, FL

It has been proposed that each hemisphere not only processes contralateral afferent stimuli and controls motor processes of the contralateral extremities, but also mediates attention and intention in contralateral hemispace. Hemispace is defined by the body and head midline and is independent of the sensory field or extremity used. If each hemisphere mediates activities in contralateral hemispace independent of the sensory field or extremity used, then each extremity therefore should gravitate to its own hemispace. To test this hypothesis, we examined a patient who had callosal disconnection secondary to an infarction and compared her performance with that of controls. In trying visually to bisect lines with her left hand in right hemispace, the patient made systematic errors to the left (mean, 1.7 cm to left; p < 0.05); in bisecting lines in left hemispace with her right hand, she made systematic errors to the right (mean, 0.6 cm to the right; p < 0.05). Performance of the control group was almost flawless. The patient made similar errors on a somesthelic line-bisection task. These results support the hypothesis that each hemisphere mediates activities in contralateral hemispace independent of the sensory field or extremity used.

POSTER PRESENTATION:
EXTRAPYRAMIDAL DISORDERS

P54. Lisuride in Parkinson Disease
Abraham N. Lieberman, Govindan Gopinathan, Andreas Neophytides, Morton Leibowitz, Russell Walker, and Emil Hieti, New York, NY

Lisuride was administered to 63 patients with advanced Parkinson disease who were no longer satisfactorily responding to levodopa. The group included 40 patients with “on-off” phenomena. Lisuride alone (13 patients) or combined with levodopa (50 patients) resulted in a 54% decrease in parkinsonian disability as assessed in the “on” period, a 16% decrease in disability as assessed in the “off” period, and a 96% increase in the number of hours in which patients were “on” (from 5.3 to 10.8 hours). Thirty-seven patients (59%) improved at least one stage. All these changes were significant (p = 0.001). Mean dose of lisuride was 2.6 mg (range, 0.2 to 5.0 mg), and duration of treatment was 5.0 months (range, 2 weeks to 26 months). The major adverse effect limiting treatment was the occurrence of an organic confusional syndrome. This was related in part to the presence of an underlying dementia in some patients. Lisuride is an important new drug, and, when combined with levodopa, its effects may be synergistic.

P55. Neuron Loss in the Nucleus Basalis of Meynert in Paralysis Agitans and Parkinsonism-Dementia Complex of Guam
Imahari Nakano and Asao Hirano, New York, NY

The nucleus basalis of Meynert (nbM) was investigated in 12 cases of paralysis agitans (PA) (parkinsonism; loss of pigmented neurons and presence of Lewy bodies in the brainstem), 2 cases of Guamanian parkinsonism-dementia complex (PDC), and 14 age-matched control cases in which the most representative level of the nbM was available. In a 10 μm Nissl-stained section from this level, areas showing the maximal density of large nbM neurons were selected and the number of neurons within ten different frames, each measuring 320 × 220 μm, was counted. Cell density was expressed as the average number of cells per frame. The total number of nbM neurons in the Nissl-stained section was counted directly. The cell density and total number of cells (mean ± SEM) were, respectively: 9.5 ± 1.0 and 273 ± 44.8 for PA (p = 0.01 versus controls by the Mann-Whitney U test), 2.5 and 45.5 for PDC (p ≤ 0.01 versus controls by the Mann-Whitney U test), and 19.5 ± 0.9 and 618.1 ± 45.5 for controls. Recent investigations have shown that nbM neurons send diffuse cholinergic
fibers to the cerebral neocortex. The neuron loss reported here suggests the possibility of damage to this cholinergic system in some cases of PA and PDC.

P56. Electroencephalographic Triphasic Waves in Parkinson Disease
Russell H. Glantz, Donna C. Bergen, and Elizabeth S. Kessler, Chicago, IL

Asterixis, which is seen in hepatic or other metabolic dysfunction, has also been described as a component of the toxic encephalopathy associated with chronic levodopa therapy for Parkinson disease. Electroencephalographic (EEG) triphasic waves may also commonly be seen in states of metabolic dysfunction, but they have not previously been reported in levodopa-treated parkinsonian patients. We describe 12 patients (age range, 58 to 88 years) with idiopathic Parkinson disease and triphasic waves on the EEG. None had evidence of any other cause of metabolic encephalopathy. Liver function and metabolic tests were normal in all. In most patients, the triphasic waves were sharply contoured and were always seen against a slow background consisting of 6 to 7 Hz theta activity with admixed delta waves. Six of the patients had asterixis, and all had some degree of cognitive dysfunction. Five patients underwent multiple EEGs. In 2 of these 5 patients the levodopa was discontinued because of severe encephalopathy; in 1 of them, an EEG fourteen days later (after the patient was restarted on levodopa) did not show triphasic waves even though the background rhythm remained slow. This corresponded to improvement in cognitive function and disappearance of asterixis. The other patient remained confused, and serial EEGs over the following five weeks confirmed the presence of triphasic waves even though levodopa was not restarted. EEG triphasic waves may be seen in levodopa-treated parkinsonian patients in the absence of metabolic dysfunction. The sign is sometimes associated with asterixis but is always seen in the presence of cognitive dysfunction. Triphasic waves do not necessarily disappear with discontinuation of levodopa.

P57. Frontal Release (Primitive Reflex) Signs and Dementia in Parkinson Disease
Russell H. Glantz, Linas A. Bieliauskas, and Harold L. Klawans, Chicago, IL

Patients with Parkinson disease have generally been thought to have a higher incidence of dementia than non-parkinsonian patients. Clinicians have often used the presence of frontal release signs to support the diagnosis of dementia. More recently it has been suggested that the presence of these primitive reflexes is age related in normal subjects and does not necessarily relate to dementia in Parkinson disease. However, such studies have frequently employed global ratings of dementia that were not determined independently of ratings of frontal release signs. We undertook a study in which a neurological examination including evaluation of the grasp, glabellar, snout, palmomental, and jaw jerk reflexes were done independently of a comprehensive neuropsychological evaluation in 18 sequentially examined patients with idiopathic Parkinsonism. Seven of these patients were rated as exhibiting cognitive deficits characteristic of dementia; 11 did not show signs of dementia. Of the frontal release signs, none correlated with the presence of dementia except for the jaw jerk. When the correlation with age was partialied out, the jaw jerk no longer correlated significantly with dementia. These results support the lack of relationship between frontal release signs and dementia in patients with Parkinson disease.

P58. Parkinsonism and On-Off Fluctuations: Long-term Effects of Pergolide Therapy
Ira Shoulson, Charlyne Miller, Roger Karlan, Robert Levy, Bernard Mack, and Robert Hamill, Rochester, NY

Pergolide is a potent and long-acting dopamine agonist that produces clear-cut antiparkinsonian effects. We report on the long-term results of pergolide therapy in patients with advanced Parkinson disease who experience disabling on-off motor fluctuations. Seven patients with idiopathic Parkinson disease and levodopa-related on-off effects were treated with pergolide to a daily maintenance dose of 2.2 ± 0.6 mg (mean ± SD). Parkinsonian features, functional capacities, and the severity of on-off effects were rated at monthly intervals. At one month, pergolide therapy resulted in an average 50% reduction in on-off fluctuations, a 42% reduction in the dosage of levodopa, and a uniform improvement in functional performance. After six months of maintenance therapy, patients lost most of their initial benefits. A partial restoration of therapeutic efficacy was observed in four patients who were switched to an alternate-day dosing schedule of pergolide. These observations confirm that pergolide is an effective antiparkinsonian agent that reduces on-off effects in severely disabled patients. The declining efficacy of pergolide appears related to a reversible down-regulation of dopamine receptors. Alternate-day pergolide therapy may prevent excessive stimulation of dopamine receptors and produce more enduring benefits.

P59. Biochemical Characteristics of an Animal Model for Huntington's Chorea with Spontaneous and Irreversible Abnormal Movements
Bruce I. Diamond, Ana Hitri, and Richard L. Borison, Augusta, GA

Previously we described an animal model in which 7-day administration of β-i-nitropropionitrile (IDPN) to rats, mice, hamsters, and rabbits induced head and neck choreiform movements that occurred spontaneously and were irreversible. These movements were blocked by dopamine antagonists and exacerbated by dopamine agonists. In our present studies, IDPN (75 mg per kilogram of body weight intraperitoneally for 7 days) induced choreatic behavior that was quantified over a three-month period in rats. After sacrifice, the striata were removed and assayed for dopamine receptor changes using radioligand binding studies with 3H-spiroperidol. The tissue was also analyzed spectrofluorometrically for levels of dopamine and its metabolites 3-methoxytyramine (3MT), 3, 4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA). The number of spiroperidol-labeled striatal receptors was decreased in the high-affinity binding site (1.08 fmol/mg tissue versus 14.9 in control); whereas the affinity was increased (70.3 pmol versus 103.5 in control); IDPN entirely eliminated the low-affinity binding site. The levels of dopamine, 3MT, DOPAC, and HVA were all decreased; however, total dopamine turnover rate was increased. These results show biochemical evidence for a striatal degeneration with a compensatory increase in dopamine turnover and receptor sensitivity. These data, together with the behavioral pharmacology of this model,
mimic the biochemistry and pharmacology of Huntington's chorea. It is hoped that this model for spontaneous dyskinesias will provide a more accurate pharmacological model with which to find more specific antidyskinetic medications.

P60. The Role of Cholecystokinin in the Striatum: Implications in Parkinson Disease
Bruce I. Diamond, Ana Hitri, Richard L. Borison, and Giulio Passinetti, Augusta, GA, and Milan, Italy

It is now well established that neuropeptides play a role in the central nervous system, either as neuromodulators or as cotransmitters. Cholecystokinin (CCK 26–33) is highly localized within the extrapyramidal system, and electrophysiological and biochemical evidence exists for the interaction of CCK with dopamine in this system and with CCK receptors in the neostriatum. To study the role of CCK within this system, male Sprague-Dawley rats (200 to 250 gm) that were given reserpine (10 mg/kg, 24 and 2 hours) or else had cannulas placed bilaterally in the caudate nucleus were used. CCK (500 ng) locally administered to the striatum produced behavior identical to that of dopamine (10 µg), which included contralateral turning to the side of the injection, stereotyped sniffing, grooming, and gnawing at the cage grid. Reserpine-treated animals exhibited rigidity, akinesia, tremor, and ptosis, which were reversed by the striatal administration of CCK. Moreover, when animals were treated with α-methyl-p-tyrosine (250 mg/kg, 4 hours) and reserpine, the effects of CCK were diminished but not abolished. Furthermore, these effects of CCK were potentiated in animals whose dopamine receptors were sensitized by chronic haloperidol treatment (0.5 mg/kg, 14 days). These results suggest that CCK modulates the release of dopamine in the extrapyramidal system and that in Parkinson disease, in which there is a deficit of dopamine, analogues of CCK may have future therapeutic significance.

POSTER PRESENTATION:
AGING, DEMENTIA, AND HYDROCEPHALUS

P61. High-Resolution CT Blood Flows in Senile Dementia of the Alzheimer Type Differ from Those in Normal Aging
John S. Meyer, Terry Shaw, Takabiro Amano, Takashi Okabe, and Kari Mortel, Houston, TX

Neurochemical markers for catecholaminergic systems in samples of basal ganglia are reported to show declines in both normal aging and senile dementia of the Alzheimer type (SDAT), while in SDAT disease-specific declines in cholinergic systems occur which are reportedly absent in elderly controls (Davies, 1977; Carlsson, 1981). Declines in cholinergic activity in SDAT patients were measured in gray matter samples from frontal, temporal, parietal, and hippocampal regions. Local cerebral blood flow (ICBF) may be used as an index of functional activity and neuronal metabolism in vivo, since normally they are tightly coupled. ICBF and partition coefficients were measured during 35% Xe inhalation by serial CT scanning (Meyer et al, Gur et al, 1981) in 13 normal healthy volunteers (10 men, 3 women) age-graded between 20 and 80 years (mean age, 49.3) to establish normal age-related CBF changes. Results were compared with measurements in 8 patients (7 men, 1 woman; mean age, 67.5) with mild to moderate SDAT. Diagnoses of SDAT were supported by Mayer-Gross scales, impaired memory and cognition, and neurological signs of diffuse cortical release. Seven of the normal group (5 men, 2 women) were selected for age-matched controls (mean age, 64) for direct comparison with SDAT. Normal volunteers showed age-related declines in ICBF for all hemispheric regions examined, including cortex, white matter, basal ganglia, and thalamus. There were no age-related changes in partition coefficients. Compared to age-matched normal subjects, SDAT patients showed no ICBF reductions in basal ganglia or white matter but there were reduced ICBF values in frontal, temporal (p < 0.01), lateral occipital (p < 0.02), parietal, and thalamic gray matter, with greatest reductions in temporal regions (−21.5%). Partition coefficients were normal in SDAT, validating comparable concurrent 133Xe measurements. Patterns of excessive cortical ICBF reductions in SDAT differ from the mild, diffuse effects of normal aging and reflect their separate biochemical and pathological causes.

P62. The Dense Microsphere Hypothesis of Senile Plaque Formation in Alzheimer Disease
Paul Averback, Montreal, Que, Canada

The dense microsphere is a solitary, parasympathetic, intraneuronal, spherical, membrane-bound, electron-dense, homogeneous body 1 to 10 µ in diameter that is found randomly distributed in normal postinfancy gray matter neuropil chiefly in cerebral cortex, hippocampus, amygdala, and hypothalamus (Arch Pathol Lab Med, in press, 1981; Fed Proc, in press, 1982). Dense microspheres are hypothesized to be precursors of senile plaques because the two structures are found in the same location, with the plaques appearing when dense microspheres disappear, in quantitative balance. A dynamic scheme of this hypothetical process was constructed from photomicrographs (N = 1,280) of postmortem sections from Alzheimer disease brain (N = 42; mean age, 74 years), each representing a single time point sample. The photomicrographs were enlarged (×1,280), rotated in the plane according to goodness of fit, and collated in sequences of 6 to 26 frames. The results of this study indicate that within the context of the sequences just described, over 70% of senile plaques in Alzheimer disease could be accounted for, and second, the diameter of the plaques was significantly smaller when they were associated with less spatially dispersed fragmentation and degeneration of dense microspheres. The latter result is emphasized because of its potential importance as a basis for therapeutic investigation.

P63. Correlation of Measurements of Senile Plaques and Dense Microspheres in the Cerebral Cortex and Hippocampus in Alzheimer Disease
Paul Averback, Montreal, Que, Canada

The dense microsphere is a solitary parasympathetic intraneuronal, spherical, membrane-bound, electron-dense, homogeneous body 1 to 10 µ in diameter that is found randomly distributed in normal postinfancy gray matter neuropil chiefly in cerebral cortex, hippocampus, amygdala, and hypothalamus (Arch Pathol Lab Med, in press, 1981; Fed Proc, in press, 1982). Dense microspheres are hypothesized to be precursors of senile plaques because the two structures are found in the same location, the plaques appearing when the microspheres disappear, in quantitative balance. Although numerous morphometric studies have been done of Alzheimer disease brain, no data have been published on the size or geometry of senile plaques appearing when dense microspheres disappear, in quantitative balance. Although numerous morphometric studies have been done of Alzheimer disease brain, no data have been published on the size or geometry of senile plaques appearing when dense microspheres disappear, in quantitative balance.
plaques were consecutively measured by optical micrometer (×100 to ×650; N = 50) in postmortem sections of cerebral cortex and hippocampus from Alzheimer patients (N = 42; mean age, 74 years) and normal subjects (N = 80; age range, 1 to 90 years). Mean normal volume of hippocampal dense microspheres is 13.9 μ3 at 1 to 10 years of age, 27.4 μ3 at 20 to 30 years, and 65.5 μ3 at 65 to 90 years. Corresponding volumes of dense microspheres in the cerebral cortex are 7.2, 12.4, and 28.5 μ3. The ratio of hippocampal to cerebral cortical dense microsphere volumes at these intervals is stable (1.91, 2.21, 2.30). Mean diameter of senile plaques in the hippocampus is 61.8 μ; in the cerebral cortex, 34.1 μ. The hippocampal/cortical ratio of senile plaque diameters is 1.75; 5.36 for their volumes (calculated as 4/3πr3). The data indicate a nearly equivalent topographical size gradient for dense microspheres and senile plaques in these areas (p < 0.001 by chi-square test) with essentially no overlap between the distributions, suggesting that the size of the two structures is significantly correlated.

P64. Axodendritic Alterations in the Cerebral Cortex of Aging Rat: Implications for Human Aging
S. T. DeKosky, S. W. Scheff, C. Hackney, and N. H. Bass, Lexington, KY
Characterization of age-related changes in human brain have led to introduction of the aging processes of several infrahuman species as models for the human condition, the major model being the rat. In an effort to define the nature of cerebral cortical changes in rat brain in senescence, we assessed changes in structural neurochemical components in freeze-dried sections of somatosensory isocortex of the Fischer 344 rat at 3, 16, and 28 months of age. All animals were screened for electrolyte imbalance, renal failure, and hematological abnormalities. Cortical thickness and dry weight per unit volume of cortex did not change over the lifespan, nor did DNA per dry weight (cell packing density) change between 3 and 28 months. Ganglioside sialic acid, a neuronal membrane marker, decreased significantly per dry weight between 3 and 16 months with no significant change thereafter, indicating loss of axodendritic expanse. However, galactocerebrosides, a quantitative index of myelin, rose significantly between 3 and 16 months. This increase in myelin was accompanied by a decrease in protein per dry weight, which is normally lower in myelin-enriched areas. Thus, the aging rat brain manifests a loss of dendritic proliferation similar to that seen in human brain. The continuous accumulation of myelin suggests that different metabolic factors may be operative in the rat, considering the age-related atrophy and loss of myelin components reported in human aging. (Supported by the Medical Research Service of the Veterans Administration and by Grants NS 00444 and 16981 from the National Institutes of Health.)

P65. Dementia Pugilistica: Loss of Basal Forebrain Cholinergic Neurons and Cortical Cholinergic Markers
G. R. Uhl, M. McKinney, J. C. Hedreen, C. L. White III, J. T. Coyle, P. J. Whitehouse, and D. L. Price, Baltimore, MD
A substantial part of cortical cholinergic innervation arises from neurons in the basal forebrain. Recent studies from our laboratory have documented loss of neurons in the nucleus basalis of Meynert (nbM) in several dementias including Alzheimer disease, Pick disease, and the dementia associated with Parkinson disease, while this population appears to be spared in Huntington disease. In Alzheimer disease, loss of nbM cells is accompanied by a reduction in the cortical presynaptic cholinergic marker choline acetyltransferase. To assess the role of the cholinergic nbM system in another type of dementia associated with neurofibrillary abnormalities, we examined the pathological and neurochemical changes in the brain of a 52-year-old former boxer with well-documented dementia pugilistica. The brain weighed 1,200 gm. Neurofibrillary tangles were present in the cortex and were numerous in the nbM. Senile plaques were not visualized. Quantitative cell counts revealed a significant reduction (by about 40%) in nbM neurons in this case of dementia pugilistica as compared to age-matched controls. Measurement of choline acetyltransferase activity in the nbM and in several regions of the cerebral cortex disclosed values significantly lower than control values. These findings in traumatic dementia will be discussed in light of the emerging association of changes in these basal forebrain–cortical cholinergic systems with dementia.

P66. Response to Shunting Procedure in Idiopathic Normal Pressure Hydrocephalus
Ronald C. Petersen, Babram Makri, and Edward R. Laws, Jr, Rochester, MN
Forty-six patients (24 men and 22 women) with idiopathic normal pressure hydrocephalus, who had been treated with shunting procedures in our institution during the years 1966 to 1981, were reviewed. Their ages ranged from 56 to 84 years (mean, 68 years for both men and women), and the mean follow-up period was 31.5 months (range, 10 to 157 months). The majority of the patients (25 of 46) manifested the entire symptom complex of a gait disturbance, dementia, and incontinence. Thirty-four of 46 patients (74%) showed at least mild improvement using a functional activity scale. The mean duration from onset of first symptom to surgery for the patients who improved was 25 months and for those who did not improve, 39.5 months. Computed tomography was the leading laboratory test used in diagnosis, but neither the change in size of the ventricles nor the degree of atrophy correlated well with response to shunt. Favorable response to the shunting procedure appeared to correlate best with careful selection of patients displaying the typical triad of symptoms.

POSTER PRESENTATION: NEOPLASIA

P67. Evaluation of Patients with Brain Metastasis of Unknown Primary Origin
Howard D. Weiss and Enrique Sajor, Baltimore, MD
Neurologists occasionally encounter patients with radiological evidence of cerebral metastasis in whom there is no prior history of cancer. Complete physical examination and simple laboratory tests (urinalysis, chest roentgenogram, stool guaiac) often give important clues to the source of the primary tumor. At times, however, the results of these
routine screening procedures are entirely normal, and the physician faces a dilemma regarding further diagnostic evaluation and therapy. In the past two years we have seen five patients (all men, aged 61 to 90 years) with solitary (two cases) or multiple (three cases) central nervous system tumors having characteristics suggesting metastasis on computed tomography. None of these patients were known to have cancer, and initial physical examination, chest roentgenogram, urinalysis, and routine blood work revealed no abnormality to indicate systemic neoplasia. In 4 of these cases, whole-lung tomography, computed tomography of the thorax, or both, revealed an occult pulmonary neoplasm near the hilus. Reevaluation of the initial chest roentgenograms of these patients did not show the neoplasm, even in retrospect. The fifth patient had multiple central nervous system tumors on brain scan, but extensive evaluation failed to reveal the underlying primary tumor. All five patients smoked cigarettes. Metastatic parenchymal brain tumors reach the central nervous system hematogenously, and the lung should be involved (either as the primary tumor or secondarily) in most cases. This series confirms that it is appropriate to proceed directly with lung tomography, computed tomography of the thorax, or both, in patients with suspected cerebral metastasis of unknown primary origin, even when the initial chest roentgenogram is "normal." This approach can reduce the number of radiological procedures necessary to make the proper diagnosis and can help avert the need for craniotomy to make a tissue diagnosis.

P68. Intraarterial BCNU Chemotherapy for Malignant Astrocytomas

Harry S. Greenberg, William D. Ensminger, James Knake, William F. Chandler, and Timothy W. Phillips, Ann Arbor, MI

Grades III and IV astrocytomas are rapidly fatal with current treatment. The isolated arterial supply makes intraarterial chemotherapy attractive. BCNU (N,N-bis[2-chloroethyl]-N-nitrosourea) was given every six weeks to 23 patients by either transfemoral selective internal carotid artery catheterization or through a new, fully implantable intracarotid drug delivery system, beginning with a dose of 200 mg per square meter of body surface area. Ten patients were treated after partial resection of tumor without prior radiation therapy. After two to five cycles of chemotherapy, 10 patients showed a decrease in tumor size and surrounding edema on contrast computed tomographic scan. Median duration of chemotherapy response and survival after irradiation was 6.5+ months (range, 2 to 9+ months) and 11+ months (range, 5 to 28+ months), respectively. Three patients, the first of whom did not have irradiation, are alive at 12, 12, and 28 months. Two patients received intraarterial BCNU and radiation therapy concomitantly without response and are dead at 5 and 8 months. Eleven patients, 8 with grade III or IV astrocytomas and 3 with Grade I or II astrocytomas who had unsuccessful partial resection and irradiation, received two to seven courses of intraarterial BCNU therapy. Eight were improved or stable for a median of 5.5 months (range, 3 to 15+ months). The catheterization procedure is safe, with no immediate complications in 77 infusions of BCNU. A delayed side effect in 9 patients has been unilateral loss of vision secondary to intraretinal vasculitis. Visual loss has not occurred since we decreased the ethanol diluent to 1 ml per 100 mg of BCNU.

P69. A New Implantable Intracarotid Drug Delivery System for Continuous and Intermittent Treatment of Malignant Astrocytomas

Harry S. Greenberg, Timothy W. Phillips, William F. Chandler, Glenn Kindt, and William D. Ensminger, Ann Arbor, MI

A totally implantable intracarotid chemotherapy system has been developed that allows continuous and intermittent bolus delivery of drugs through the carotid arterial tree into the vascular bed of an astrocytoma. A Silastic catheter is introduced and advanced retrograde down the external carotid artery to the carotid bifurcation, where it is tied into position. Distally, the external carotid artery is ligated and the proximal catheter is threaded subcutaneously along the lateral neck and connected to an Infusaid Model 400 pump (Metal Bellows Company, Sharon, MA), which is placed in a subcutaneous pocket inferior to the ipsilateral clavicle. The pump consists of two chambers separated by a mobile diaphragm. The upper drug chamber has a 50 ml capacity and flows constantly at 2.5 ml per day to permit continuous infusion of cell cycle specific agents or radiosensitizers. It can be percutaneously refilled with chemotherapeutic agents and heparin using a deflected point needle. Pressure upon filling the drug chamber converts Freon gas in the charging chamber to a liquid form. The Freon reverts to gas at body temperature, driving the pump. The upper chamber contains an auxiliary injection system (side port), bypassing the pump, for intermittent bolus administrations of chemotherapeutic agents. Six patients and two monkeys have had the system implanted for up to nine months without vascular complications.

P70. Primary Leptomeningeal Lymphoma

David R. Macdonald, Kurt Jaeckle, and Jerome B. Posner, New York, NY

Primary lymphoma of the brain is well described, but primary lymphoma of the meninges has rarely been reported and no recent description of the disorder exists. We have seen three men and two women, aged 33 to 58 years (median, 39), with primary leptomeningeal lymphoma. Symptoms of leptomeningeal disease were spinal root or cranial nerve (or both) dysfunction or else hydrocephalus, and began 1 to 22 months (median, 4 months) before diagnosis. Diagnosis was by myelography (intradural nodules or arachnoiditis, confirmed by biopsy or cerebrospinal fluid cytology) in three patients and by abnormal findings on cerebrospinal fluid cytology in two. Cerebrospinal fluid cytology was often difficult to interpret. There was no evidence of cerebral or systemic lymphoma at diagnosis, but two patients developed tumor spread outside the central nervous system 4 and 6 months later. Radiation therapy improved all patients for 1 to 12 months (median, 5 months). Intrathecal methotrexate improved four of them for 1 to 20 months (median, 6 months). Three died of meningeal lymphoma 6 to 32 months (median, 14 months) from diagnosis. Two are alive with progressive disease 14 and 28 months from diagnosis. Immunocytochemical study of cerebrospinal fluid cells suggests a monoclonal B cell lymphoma. Primary leptomeningeal lymphoma should be considered in the differential diagnosis of chronic lymphocytic meningitis.
Plasma melatonin levels may be useful as a marker for neoplasms of the pineal gland. Melatonin-producing tumors conceivably could be monitored systemically; other types of tumors that invade pineal tissue might also be monitored. Plasma melatonin levels were measured in a patient before and after excision of a pineal tumor using a recently developed, highly accurate and sensitive mass spectrometric assay for plasma melatonin (Lewy and Markey, Science 201:741, 1978). The patient was a 17-year-old white boy who presented with headaches and Parinaud syndrome and was found at surgery to have a well-encapsulated tumor of mixed histological type (low-grade astrocytoma and pineoblastoma). Preoperative plasma melatonin levels obtained every 2 hours revealed a normal circadian secretory rhythm, with levels rising during the night to 70 pg/ml and falling during the day to between 1.5 and 10 pg/ml. Six weeks later, plasma melatonin levels were again evaluated every 2 hours over a 24-hour period: at no time could melatonin be identified in the plasma (minimal detectable concentration for this assay was less than 1 pg/ml plasma). The patient was on the same drug regimen (Dilantin) during both study periods and was not treated with radiation until after the second study. This is the first demonstration of exclusive pineal derivation of plasma melatonin in a human being. We previously showed with the mass spectral assay that pineallectomy completely abolishes plasma melatonin in the rat (Lewy et al, J Clin Endocrinol Metab 50:204, 1980). Plasma melatonin levels may be a means of assessing whether removal (surgical or otherwise) of the pineal gland is complete, and may be of benefit in the diagnosis and treatment of patients with pineal tumors.

Microgliomas (primary central nervous system lymphomas) are rather uncommon central nervous system (CNS) neoplasms which, unlike other lymphomas, have a very limited sustained responsiveness to radiation therapy. They have also shown very limited responsiveness to standard chemotherapeutic agents. In a recent review by Barry and Simpson of 21 patients with microgliomas treated with radiation therapy, the overall survival one year from diagnosis was 47%. Although there has been a single case report of the successful use of high-dose methotrexate to treat CNS lymphoma recurrent after radiation therapy, McIntosh et al, in a recent review of 105 patients with CNS lymphoma (primary and secondary), were not able to calculate any statistically significant trends in their large series treated with high-dose intravenous methotrexate. We recently treated 2 patients with multicentric microgliomas who had 80 to 90% regression of their tumors after only three courses of chemotherapy. These patients were treated with 1 to 1.5 gm of intraarterial methotrexate following osmotic disruption of the blood-brain barrier on day 1, intravenous cytoxan (15 mg/kg) on days 2 and 3, and procarbazine, 150 mg orally on days 2 through 15. Although this experience represents only 2 patients in whom follow-up continues, the dramatic response in both cases, in contrast to clinical studies reported in the literature, offers cautious optimism on the use of this modality to treat microgliomas. It is certainly promising that the response was obtained without radiation therapy.

Adrenocorticotropic hormone (ACTH) gel in a dose of 100 units was given intramuscularly twice a day for three weeks to four male patients 39 to 60 years of age with clinically definite chronic progressive multiple sclerosis (MS) whose course had been stable for at least six months. ACTH was then tapered to 0 over 10 days, and 100 mg of prednisone was started orally every other day. Marked increases were seen in white blood cells and polymorphonuclear leukocytes, while the lymphocyte count was reduced. There were no consistent changes in the percentages of T cells, B cells, and cells bearing the Fc receptor. However, T cell response to phytohemagglutinin and killer activity were markedly reduced in all four patients. Activity of natural killer cells was also reduced in three of the four cases. Preliminary results in two patients show a decrease in lymphocytes typed by the Leu 2 or OKT8 antibodies. IgG synthesis rate within the blood-brain barrier was reduced by greater than 50% in all four patients, reaching normal levels of synthesis in one. Oligoclonal bands were also reduced, but there was no change in the pattern or disappearance of bands. Clinically the patients were unchanged. Leu 2 and OKT8 antibodies label a T cell subpopulation associated with suppressor cell activity. Despite the observation that reduction in the cells labeled by this antibody appears to correlate with clinical relapse of MS (Rheinherz et al, 1980), we found no alteration in clinical activity with pharmacologically induced reduction of suppressor T cells. This is the first time ACTH, an FDA-sanctioned treatment for MS, has been shown to produce a significant reduction of peripheral blood suppressor T cells in MS. Is this reduction related to the cause of the remarkable reduction of IgG synthesis within the blood-brain barrier? On the other hand, the relationship of the pathogenesis of reduction of peripheral blood suppressor T cells to MS is not a simple matter, since a reduction has been reported to be associated with relapses by Rheinherz et al (1980) and with the chronic progressive course but not relapses by Paty et al (1982).

Cyclophosphamide, CCNU, and 5-Fluorouracil in Patients with Multiple Sclerosis
R. W. Baumber, W. H. Shih, W. W. Taurelott, P. Shapshak, S. Staugaitis, A. R. Potvin, K. Syndulko, and J. L. Fabey, Los Angeles, CA, and Arlington, TX
Cyclophosphamide, CCNU (1-[2-chloroethyl]-3-cylohexyl-1-nitrosourea), and 5-fluorouracil were given in single-course schedules to 13 men 28 to 59 years of age with

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clinically definite chronic progressive multiple sclerosis (MS) whose course had been stable for at least six months. Selective reduction in natural killer cell activity was observed with cyclophosphamide and 5-fluorouracil, while no significant alteration was seen in percentage of FC receptor cells or killer activity. Cyclophosphamide reduced the lymphocyte count and B cell percentage. 5-Fluorouracil had a selective effect on T cells, reducing their percentage while the lymphocyte count remained unchanged. CCNU for the first time was shown to have definite immunosuppressive effects in human patients, reducing the lymphocyte count and T cell proliferative response to phytohemagglutinin. In addition, CCNU caused a mild but significant reduction in IgG synthesis rate within the blood-brain barrier. The effect of 5-fluorouracil in this regard was questionable, and no change was observed with cyclophosphamide. Cerebrospinal fluid oligoclonal patterns were not altered by any of the three drugs. Clinically, the patients were unchanged or continued to progress in their disability. This study supports our previous results showing that the MS immune reaction compartmentalized within the blood-brain barrier, manifested by IgG synthesis within the barrier, is remarkably persistent even when powerful cytotoxic drugs produce profound suppression of the peripheral immune system. The ability of drugs to penetrate the blood-brain barrier may be important in the selection of putative immunosuppressive treatments for MS.

P75. [Withdrawn]

P76. Immunological Studies of Optic Neuritis
V. Calabrese, M. Irivainen, P. Leinikki, W. Wallen, I. Shekarchi, J. Selhorst, E. Waybright, J. Harkin, R. Selbit, D. Madden, and J. Seer, Richmond, VA, and Bethesda, MD

Immunoglobulins and antibodies were measured in 35 patients with optic neuritis, 25 with multiple sclerosis, and 34 control patients. Immunoglobulin studies consisted of cerebrospinal fluid (CSF) IgG/albumin ratio, IgG index, and sodium dodecysulfate/polyacrylamide-gel electrophoresis of the CSF. Among the patients with multiple sclerosis, 81% showed both abnormal IgG and oligoclonal banding, 14% showed only banding, and 5% showed neither. In the optic neuritis group less than 55 years old, 37% showed both abnormal IgG and bands, 26% showed only bands, 15% showed only an abnormal IgG, and 22% showed neither. The electrophoretic patterns of the optic neuritis and multiple sclerosis patients were similar. Antibody to rubeola, rubella, vaccinia, coronavirus, and purified myelin were measured by ELISA and recorded as the ratio of optical density (OD) of a given sample dilution to the OD of standard serum. Good correlation was noted between the OD and either hemagglutination inhibition titers or end-point titer (ELISA). Despite great overlap, there was a trend for multiple sclerosis and optic neuritis patients to have a lower serum/CSF ratio than controls. Eight patients had either another neurological sign or an unverifiable history of another neurological symptom, and were therefore classified as having probable MS. With a follow-up of two to four years, 3 have progressed to definite MS. Only 1 had an abnormal IgG, but 2 had banding. Of the 5 cases that remain probable, 2 patients had both tests abnormal and the other 3 had one.

P77. Antinerve Antibodies and Circulating Immune Complexes in Cold Agglutinin-positive Chronic Inflammatory Polyradiculoneuropathy
P. K. Coyle, Steven E. Schutzer, Arnold B. Sterm, Cheryl Hamilton, and Fred Miller, Stony Brook, NY

A 43-year-old man with inactive sarcoid presented with elevated cold agglutinins and a clinical picture consistent with chronic inflammatory polyradiculoneuropathy. Nerve conduction velocities were markedly slowed; sural nerve biopsy showed axon loss, demyelination, focal inflammatory infiltrates, and onion bulb formation. Teased fibers showed extensive segmental demyelination and remyelination. Electron microscopy revealed minute axons with large myelin sheaths, Schwann cell sequestration of axons, and frequent evidence of loss of unmethylated fibers. Antinerve antibodies were found in serum (IgM and IgG) and cerebrospinal fluid (IgG) by indirect immunofluorescence study. Direct immunofluorescence showed IgM and complement components linearly deposited along the external Schwann cell plasmalemma, while IgG diffusely stained internal axons. At 4°C, 40% of peripheral lymphocytes had surface-bound antibody; when the sample was run at 37°C this fell to 25%, suggesting a cold-reactive antibody directed against a lymphocyte subset. The patient’s condition worsened as the cold agglutinin titer fell. Steroid therapy and plasmapheresis were instituted with a good clinical response and disappearance of the antinerve antibodies, circulating immune complexes, and cold-reactive antibodies. We conclude that in certain patients with chronic inflammatory polyradiculoneuropathy, antibodies directed against axonal components may play a role in the disease pathogenesis.

P78. Disparate Results of Experimental Thymectomy for Chronic Progressive versus Relapsing-Remitting Multiple Sclerosis: A Preliminary Trial
John L. Trutter, Thomas F. Ferguson, David B. Cliford, and Erwin B. Montgomery, St. Louis, MO

Thirty-five patients with multiple sclerosis (MS) were followed after experimental thymectomy. Nineteen of them had 12 months of azathioprine treatment immediately following thymectomy. These patients were compared over a two-year period with 19 controls matched for age, sex, disability status scale (Kurtzke), functional group (Kurtzke), and exacerbations. Significant p < 0.02) improvement occurred in pyramidal signs and symptoms, but not in other systems, during the follow-up period. There was also significant improvement (p < 0.05) in disability status scale for the patients with relapsing-remitting disease, while a suggestive (p < 0.10) worsening occurred in those with chronic-progressive MS compared with controls. The treated and control groups showed no significant difference in change in the rate of exacerbations. One-year follow-up of the 16 MS patients treated by thymectomy alone revealed no significant differences between treated and control patients for functional group score, exacerbations, or disability status scale. We conclude that the clinical therapeutic response to treatment in patients with chronic progressive MS differs from that in patients with relapsing-remitting disease. At present we cannot demonstrate a synergistic effect of thymectomy and azathioprine therapy compared to azathioprine alone; however, as in myasthenia gravis, it may take up to five years for the full immunosuppressive effect of thymectomy to be realized.
P79. Δ⁴-Tetrahydrocannabinol for Tremor in Multiple Sclerosis
David B. Clifford, St. Louis, MO

Δ⁴-Tetrahydrocannabinol (THC) was studied for its effect on tremor and ataxia in eight patients with definite multiple sclerosis. Oral doses of increasing size were administered while mental status, truncal stability, hand and foot ataxia, speech, station and gait, and activities of daily living such as use of spoon and toothbrush were monitored. The patient population consisted of four men and four women with Kurtzke Disability Status Scale scores of 5, 6, 6, 6, 7, 7, 9, and 9. Their ages ranged from 21 to 49 years. Half of the patients had previously used marijuana, and two were regular users. With THC therapy all patients eventually had a subjective “high.” In two, this was a dysphoric experience. Two patients had subjective and objective improvement with THC. Five patients had mild subjective improvement without objective signs. One improved patient had titubation of the head and neck reminiscent of a coarse essential tremor, which was completely suppressed at 30 to 60 minutes following 5 mg oral THC and remained absent for 5 to 6 hours. Placebo did not reproduce this effect. Another patient, who had severe ataxia involving the hands and had been unable to write for four years, was able to print legibly after 15 mg of THC, but not after 5 mg, 10 mg, or placebo doses. Cannabinoids appear to have potential in suppressing tremor and possibly in improving ataxia, although this effect was seen in only 25% of severely debilitated multiple sclerosis patients. The strongest effect was on a tremor reminiscent of an essential tremor. As less toxic cannabinoid derivatives are developed, they should be screened for action against tremor.

P80. Is Paraneoplastic Cerebellar Degeneration an Immune-mediated Condition? Detection of Circulating Antibodies to Purkinje Cells in a Patient with the Disorder
John E. Greenlee, Charlottesville, VA

Paraneoplastic cerebellar degeneration is a rare disorder characterized by severe ataxia, nystagmus, dysarthria, and vertigo. Affected brains show depletion of Purkinje cells, variable loss of granule cells, and perivascular and meningeal lymphocytic infiltrates. The inflammatory infiltrates observed in sections of cerebellum and the frequent presence in the cerebrospinal fluid of pleocytosis and elevated immunoglobulins suggest an infectious or immunological basis for the disorder. We have studied serum from a patient with pathologically confirmed ovarian carcinoma and cerebellar degeneration for the presence of antibodies to Purkinje cells or other cerebellar constituents. Sections of normal human cerebellum obtained at autopsy were overlaid with serial dilutions of the patient’s serum and reacted with FITC-conjugated antihuman globulin. Bright immunofluorescent labeling of Purkinje cells was observed with the patient’s serum through a dilution of 1:640 but was not seen with control sera. Review of the literature reveals one other report of anti-Purkinje cell antibodies in a patient with clinically diagnosed paraneoplastic cerebellar degeneration, but pathological verification of the diagnosis was not obtained in that case. The present study confirms the presence of circulating antibodies to Purkinje cells in paraneoplastic cerebellar degeneration. Experiments are in progress to determine the role of antibody in the pathogenesis of the disorder.

P81. Inhibition of Concanavalin A–inducible Suppressor Cell Function in Multiple Sclerosis by Adrenocorticotropic Hormone
William Sheremata, Alexander J. Rzepelia, Joseph Berger, Alan Sazant, and Albert Castro, Miami, FL

Adrenocorticotropic hormone (ACTH) is commonly used to treat multiple sclerosis (MS) despite the unpredictability of the cortisol response in that disorder. However, the regular inhibition of mixed lymphocyte responses in MS produced by ACTH (Birnbaum et al) suggests an effect not dependent on cortisol. Preliminary results in our laboratory suggested that ACTH, but not exogenous steroids or other drugs, enhanced suppressor cell activity. Therefore we serially studied 8 ACTH-treated patients, 4 in acute exacerbation and 4 with moderately severe, progressive disability of two to four years’ duration. The assay described by Antel was modified so that only autologous responder cells were used. A group of 15 normal subjects gave 52 ± 3.1% suppression, whereas 8 others in acute exacerbation had a mean of 15 ± 3.8%. Prior to ACTH treatment, 4 patients with acute MS gave values of 0 to 8% and the 4 with progressive MS, 30 to 43%. All 8 had increased suppressor cell responses (52 to 193%) after 1 to 14 days of intravenous ACTH therapy. One to 25 days after treatment the values declined to 24 to 66%. Increased suppressor cell activity did not correlate with changes in plasma cortisol. Enhanced suppressor cell function therefore probably explains the reduction of mixed lymphocyte responses after ACTH and may, in part, explain the clinical response to such treatment.

P82. Serial Evaluation of Peripheral Blood T-lymphocyte Subsets in Patients with Relapsing-Remitting Multiple Sclerosis
L. F. Kastrukoff and D. W. Paty, Vancouver, BC, Canada

A serial study of 12 patients with multiple sclerosis and 3 controls is in progress to correlate peripheral blood T-lymphocyte subsets and disease activity over a one-year period. Lymphocytes are obtained weekly and labeled with monoclonal antibodies. Analysis is by a dual laser fluorescence-activated cell sorter (FACS IV). Results are available over 13 weeks. One relapse has occurred, and the number of suppressor cells has remained normal. Marked fluctuations of suppressor lymphocyte numbers have occurred in all subjects, unrelated to clinical activity. Controls follow a similar pattern. Although lymphocytes labeled with anti-Leu 2A, OKT5, and OKT8 have shown parallel fluctuations in most cases, there have been occasions when one monoclonal antibody has identified significantly fewer cells than the others. This is most common with OKT5 and may be explained by antigen modulation. Double labeling experiments using anti-Leu 2A and OKT5 with dual laser analysis suggest that under these conditions two subpopulations may exist, one expressing both antigens (15%) and the other expressing only Leu 2A (5%). The number of cells expressing Leu 3A and OKT4 has been much more stable. The meaning of these findings is not clear. Perhaps functional changes in the suppressor T cell population are accompanied by modulation of antigenic expression.
P83. The Predictive Value of Cerebrospinal Fluid Electrophoresis in “Possible” Multiple Sclerosis
D. W. Moulin, D. W. Paty, and G. C. Ebers, London, Ont, and Vancouver, BC, Canada
The presence of oligoclonal banding in the cerebrospinal fluid has been well established in patients with clinically definite multiple sclerosis (MS). However, demonstration of oligoclonal bands is mainly of value in the clinical situation in which the diagnosis of MS is in doubt. We reviewed 185 patients with “possible” MS in whom cerebrospinal fluid electrophoresis had been performed at the initial diagnostic evaluation (in most cases). All patients had objective evidence of neurological disease, and the majority presented with a chronic myelopathy, optic neuritis, or brainstem disease. Of 102 patients without oligoclonal bands, who were followed for a mean of 28 months, 8 (8%) developed clinically definite MS. Of 83 patients with oligoclonal banding, followed for a mean of 29 months, 13 (16%) converted. This difference was significant (p = 0.05). Evoked response testing showed evidence of dissemination in 39 of 62 patients (63%) with oligoclonal banding and in 36 of 79 (46%) without bands (p < 0.10). The results indicate that patients with monosymptomatic demyelination who show monoclonal banding are about twice as likely as those without banding to develop clinically disseminated disease over the follow-up period of this study.

P84. Multiple Sclerosis: Flow Cytometry with Simultaneous Detection of Surface Antigen and Cell Cycle Phase Reveals That Activated Cells in Cerebrospinal Fluid in Acute Attacks Are Not OKT8 Positive
Avertoano Noronha, Gillis R. Otten, David P. Richman, and Barry G. W. Arnason, Chicago, IL
We previously reported the presence of activated cells in the cerebrospinal fluid (CSF) of patients with multiple sclerosis as detected by acridine orange staining followed by flow cytometry. To characterize the activated cells further, we have now developed a staining procedure for flow cytometric analysis that simultaneously assesses lymphocyte surface antigens and cell cycle phase. Indirect immunofluorescence with monoclonal antibodies OKT4 (marker for helper cells) and OKT8 (marker for suppressor/cytotoxic cells) was used to measure surface antigen density, and propidium iodide was used to determine DNA or RNA content. When this method was applied to mitogen-activated peripheral blood lymphocytes, calculated cell cycle phase percentages were consistent with cell cycle analysis by the acridine orange procedure. When CSF cells from three patients experiencing an acute attack of multiple sclerosis were analyzed by this method, the results showed that (1) OKT8-positive cells were found only in the quiescent phase; (2) OKT4-positive cells were distributed between quiescent and activated phases; and (3) there was good correlation with acridine orange data in two of the three MS patients. When the number of activated cells is few, as was the case in the third patient, they are better detected with the acridine orange procedure. These findings suggest that in acute multiple sclerosis, OKT8 cells are not found in the activated cell population in the CSF. In contrast, OKT4 cells occur in both the quiescent and activated populations.

P85. Indirect Hemagglutination Titer in Cerebral Cysticercosis
Patricio F. Reyes, Timothy Sheely, Victor Suidivar, and Walter Buell, San Antonio, TX
The clinical picture of central nervous system cysticercosis frequently presents a diagnostic challenge. Recent investigators have shown that an antibody response to naturally acquired cysticercus antigens occurs in only 50% of affected patients. Other investigators have reported the indirect hemagglutination titer to be positive in 87.5% and false positive in 13.0% of cases. Previous United States series described single serum titers in 13 cases, and 3 did not have actual values. We collected 20 clinically diagnosed cases of cerebral cysticercosis including 2 with histopathological studies. Serum indirect hemagglutination titers obtained in 10 patients were positive in 7. Three of these patients had repeated titers because of either exacerbation or progression of their neurological deficits. In all 3 cases, the second titer was significantly elevated. Highest values were observed in 2 patients with clinical and pathological evidence of leptomeningeal cysticercosis. Although the humoral or cellular immune mechanisms (or both) involved in human cysticercosis remain to be investigated, it is possible that antibodies to cysticercus persist for a limited period in the systemic circulation, accounting for the marked variability in patients' immunological response. Serial indirect hemagglutination titers are therefore an important laboratory tool to confirm the presence of active cerebral cysticercosis.

P86. The Genetic Basis for Viral Injury to Specific Neuronal Populations
Kenneth L. Tyler, Roderick T. Bronson, Karen Byers, and Bernard N. Fields, Boston, MA
Neurotropic viruses including rabies, polio, herpes, and reovirus III are able to replicate within and damage specific cell populations in the central nervous system. A unique feature of the reovirus is the capability to determine the molecular and genetic basis of these properties using recombinants with specific combinations of genes from reovirus types I and III. The behavior of these recombinants can be compared with the parent strains and the importance of individual genes and their protein products established. Using this approach, we previously demonstrated that the viral hemagglutinin, a product of the S1 gene, is the component responsible for the ability of type III reovirus to infect neurons and type I ependymal cells. We now report that type III and type I reovirus injure different components of the retina. After intracerebral inoculation of type III, virus rapidly appears in both eyes. Viral titer increases 10,000-fold during the next several days, and histological studies show frequent eosinophilic cytoplasmic inclusions in retinal ganglion cells. By contrast, type I does not show evidence of replication in eyes and does not produce histological injury to retinal ganglion cells. Preliminary evidence using type I and III recombinants supports the hypothesis that the S1 gene may be responsible for the ability of virus to replicate in and subsequently damage retinal ganglion cells. This work indicates that reovirus can serve as a powerful probe to specifically
injure certain neuronal populations in both brain and retina.

P87. Herpes Simplex Encephalitis in Immune-compromised Hosts
Allen J. Aksamit, Jr. and Babram Mokri, Rochester, MN

Of seventeen autopsy-proved cases of herpes simplex encephalitis seen in our institution in a 10-year period (1972–1981), five patients (29%) were significantly immune compromised. In three, the diagnosis of herpes simplex encephalitis had remained unsuspected ante-mortem. One of these patients had a glioma, was taking high doses of corticosteroids, and had recently finished a course of whole-brain irradiation. The second patient had lymphoma with spinal cord compression. He also was being given high doses of corticosteroids and had received radiation therapy to the spine. The third patient had unsuspected multiple sclerosis and had been treated with high doses of corticosteroids for 10 months. Of the two patients in whom the diagnosis was suspected before death, one had pemphigus vulgaris and was taking high doses of corticosteroids plus azathioprine. The other had chronic lymphocytic leukemia and was receiving chemotherapy. The increased frequency of herpesvirus group infection in immune-compromised hosts has been well established. This correlation, however, has not been documented in herpes simplex encephalitis. Although the cases reported here might represent a sample of herpesvirus group infection in immune-compromised patients, the high percentage of immune-compromised patients was surprising. Herpes simplex encephalitis may occur with higher frequency in immune-suppressed patients.

P88. Persistent Infection of Oligodendrocytes in Theiler Virus–induced Encephalomyelitis
Moses Rodriguez, Julian Leibowitz, and Peter W. Lampert, La Jolla, CA

Theiler murine encephalomyelitis virus (TMEV) causes a chronic demyelinating disease in susceptible mice. There is evidence indicating that the mechanism of demyelination is immune mediated. To determine the localization of viral antigens in infected cells of the spinal cord, we used ultrastructural immunoperoxidase techniques to study SJL/J mice intracerebrally infected with TMEV. Viral antigens were expressed in the cytoplasm of a few neurons and astrocytes 4 and 11 days after infection. At 28 days, many macrophages, astrocytes, and occasional oligodendrocytes showed viral antigen in their cytoplasm. At 45 and 83 days the great majority of infected cells were oligodendrocytes, as revealed by immune peroxidase–positive staining of prominent oligodendroglial loops, that connected with myelin lamellae. Some of these sheaths also showed Schmidt–Lanterman incisures that stained for viral antigens. At 270 and 360 days after infection only a few scattered cells, all of which were identified by electron microscopy as oligodendroglia or astrocytes, were infected. These findings suggest that chronic relapsing demyelination in Theiler virus–induced encephalomyelitis may be the result of an immune-mediated response directed against persistently infected oligodendroglia. (Supported by Grants NS 07078, NS 00418, and NMSS RG1288A1 from the National Institutes of Health.)

P89. Studies of Infectious and Inactivated Influenza B Virus in the Experimental Model of Reye Syndrome
Larry E. Davis, Linda L. Cole, and Steven J. Lockwood, Albuquerque, NM

Infectious influenza B/Lee virus intravenously injected into mice reproduced many clinical, biochemical, and pathological features of Reye syndrome. One to three days after injection with 6,400 hemagglutinin units (HAU) of infectious virus, 50% of Balb/c mice developed lethargy and seizures and died. The cerebrospinal fluid was normal. Serum glutamic oxaloacetic transaminase levels increased 1,900% and plasma ammonia levels were elevated 259% over control values. Serum bilirubin levels remained normal. Microvesicular fatty metamorphosis developed in the liver, while the brain showed mild cerebral edema without inflammatory changes. Viral propagation did not occur in the liver or brain, but viral hemagglutinin, neuraminidase, and nucleoprotein antigens were produced in hepatocytes. Heat-inactivated (56°C) influenza B virus produced a similar clinical syndrome (median lethal dose, 52,000 HAU) but with less striking biochemical and pathological changes. No viral antigen was detected in hepatocytes. Virus inactivation by ultraviolet light, Triton X-100 and octylglucoside detergents, formalin, bromelain, acetone, β-propiolactone, and monoclonal hemagglutinin antibody possessed no toxicity in mice even at concentrations up to 500,000 HAU. These observations demonstrate the importance of infectious virus in the experimental model and suggest that it may also play an etiological role in those cases of Reye syndrome associated with influenza B infection.

P90. Quantitative Autoradiographic Mapping of Focal Herpes Simplex Virus Encephalitis in Rats Using a Radiolabeled Antiviral Drug
Y. Saito, R. W. Price, D. A. Ruttenberg, J. J. Fox, T. L. Su, K. A. Watanabe, and F. S. Philips, New York, NY

We predicted that 14C-labeled FMAU (2′-fluoro-5-methyl-1-β-D-arabinosyluracil), a potent new antiviral drug that is selectively phosphorylated by viral thymidine kinase, could be used to image, by quantitative autoradiography, herpes simplex virus (HSV) infected regions of brain by virtue of metabolic "trapping" of its phosphorylated metabolites within infected cells. Focal encephalitis was produced in the rat by unilateral intraocular inoculation of HSV type 1, and the animals were studied five or six days later. 14C-FMAU (specific activity, 47.5 μCi/mg), 5 mg per kilogram of body weight, was injected intravenously 6 hours before the animals were sacrificed and their brains frozen. Regional isotope concentration, quantitatively assessed in digitized autoradiograms of brain sections, correlated closely with viral antigen distribution as defined by immunoperoxidase staining. Activity within infected brain regions ranged between 2 and 15 times that of background activity in uninfected brain, visceral organs, and blood. Our results indicate the utility of quantitative autoradiography in evaluating local metabolism of antiviral drugs that have a mechanism of action involving phosphorylation by viral thymidine kinase. These results enhance the prospect of using radiolabeled antiviral drugs for diagnostic purposes. Just as autoradiography can be used for quantitative mapping of infected brain in our animal model, we would hope that contemporary neuroimaging methods could be used in
conjunction with radiolabeled drug to detect human HSV encephalitis.

POSTER PRESENTATION: NEUROMUSCULAR DISORDERS AND NEUROBIOLOGY

P91. Survival in Amyotrophic Lateral Sclerosis
James T. Carasco, William Ford Calhoun, James Zistein, Harry Fisch, and Melvin D. Yahr, New York, NY

Previous studies of survival in amyotrophic lateral sclerosis (ALS) have been based on small numbers of patients and retrospective collection of data. The result is controversy about longevity in this disease. In an effort to assess this factor, we used the technique of survival analysis on data collected prospectively from 328 patients. Median survival for all patients was 5 years. To evaluate the prognostic value of clinical manifestation of the disease, patients were divided into 264 cases of classic ALS, 32 of progressive bulbar palsy, 25 of progressive muscular atrophy, and 7 of primary lateral sclerosis. Median survival for ALS was 4.3 years and for progressive bulbar palsy, 4.8 years. Median survival for progressive muscular atrophy and primary lateral sclerosis could not be calculated because of insufficient data. Survival was, however, longer in these clinical forms. Although there were few deaths in the progressive bulbar palsy group, no statistically significant difference in survival was found between ALS and progressive bulbar palsy, contrary to most previous reports in which the latter is accorded a worse prognosis. Age of onset was a significant prognosticator, shorter survivals occurring with increasing age of onset. Preliminary analysis also indicates that patients with a history of allergies had a worse prognosis.

P92. Sweat Gland Dysfunction in Diabetic Neuropathy
William R. Kennedy and Manabu Sakuta, Minneapolis, MN

Sweating was studied in diabetic patients with autonomic neuropathy using methods that provide accurate counts of the active sweat glands and a continuous record of sweat volume. Thirty-five normal subjects and 100 diabetics were studied. Sweating was activated by iontophoresis of 1% pilocarpine on the dorsal foot. Emerging sweat droplets made spherical indentations in silicone-elastic material applied to the skin. These were magnified and counted. Sweat volume was a function of water evaporation measured by relative humidity sensors located at two levels above the skin. In normal controls, the rate of sweating was always over 100 gm/m²/hr 15 minutes after the pilocarpine stimulation. After 60 minutes a gradual decline began. In diabetic neuropathy, the rate of sweating declined substantially before 20 minutes. In conclusion, the number of active sweat glands was normal in patients with mild diabetes but was significantly decreased in severe cases. Many diabetics have a sweating defect manifested by inability to maintain a steady level of sweat output after stimulation with pilocarpine. In severe cases, even the number of active sweat glands was significantly decreased. Motor conduction velocity and the severity of sensory neuropathy correlated with the degree of sweat gland dysfunction.

P93. Actin Localization in Schwann Cells of Myelinated Nerve Fibers
Albert J. Wong and John W. Griffin, Baltimore, MD

Actin is an abundant component of peripheral nerve, but its localization within mature nerve fibers is incompletely known. We used NBD-phallacidin, a recently described probe for F-actin, to investigate the distribution of staining in rat sciatic nerve fibers. Both teased and fresh or formaldehyde-fixed nerves (cut longitudinally or in cross section) were examined. The teased fibers or sections were stained with NBD-phallacidin (courtesy of Dr. L. Barak) and examined by fluorescent and bright-field microscopy. In myelinated fibers the Schwann cells were stained in a distinct structure and consistent pattern. In the internodes the Schwann cell of myelinated fibers. The prominence of staining in the Schmidt-Lanterman clefts could reflect a system of intracytoplasmic transport through the myelin sheath. NBD-phallacidin staining affords an opportunity to examine changes in cytoskeletal organization in peripheral nerve disease.

P94. Immunoregulatory T and B Cells in Patients with IgM Paraproteinemic Polyneuropathy
Marinos C. Dalakas, David L. Madden, Aurella A. Krezlewicz, and John L. Sever, Bethesda, MD

There is evidence that some patients with monoclonal IgM paraproteinemic polyneuropathy (PP) have antibodies to peripheral nerve myelin. The immunoregulatory mechanisms that control production of the monoclonal antibody are unknown. We studied lymphocyte subsets in 4 patients with PP (3 with IgM, 1 with IgG) and 11 others with non-PP. The following monoclonal antibodies identifying surface membrane markers were used: OKT3 for mature T cells, OKT4 for helper/inducer T cells, OKT8 for suppressor/cytotoxic T cells, IgM for B cells, and OKIal for B cells/monocytes. Reactive cells stained with FITC-conjugated antimouse IgG were analyzed in a flow cytometer. In all patients, the absolute number and percentage of OKT3-positive cells were normal. The patients with IgM PP had a significant, up to 2½-fold elevation, of OKT8-positive cells; the OKT4-positive cells were diminished in 2 IgM patients but normal in the rest. The ratio of OKT4/OKT8-positive cells (normal, 2:1) was severely abnormal in the 3 IgM patients (ratios, 0.27:1, 0.39:1, 1.07:1) but normal in the rest. The IgM-positive and OKIal-positive cells were elevated 2-fold in IgM patients. These findings indicate that patients with IgM PP have abnormal immunoregulation involving both B and T cells. The marked elevation of cells with OKT8-positive markers may represent: (1) cytotoxic cells for nerve components, (2) true suppressors overcompensating for active T helper subsets, or (3) cells expressing abnormal surface phenotypes without specific functional activity. Because high OKT8-positive cells are predominantly found in certain infections associated with IgM-specific antibodies (i.e.,
cytomegalovirus, Epstein-Barr virus, or toxoplasma infections), the possibility of a persistent infection in patients with IgM PP is under investigation.

P95. Heterogeneity of Neuropathies Accompanying Monoclonal Gammapathies
Kari Stefansson, Linda Marton, R. P. Rooth, C. Helgason, Riley Yu, J. P. Antel, and B. G. W. Arnason, Chicago, IL

Immunohistochemistry, immunoblots, and tissue cultures were used to study two patients with monoclonal gammapathies and neuropathy. Results differed between the two cases. The first patient had biopsy-proved demyelinating neuropathy and monoclonal IgM, directed against human myelin sheath in both peripheral and central nervous system (by immunohistochemistry) and to two nervous system antigens with molecular weights of 90K and 75K daltons (by immunoblots). This IgM did not react with any tissues in other species we have looked at. Serum from Patient 1 did not damage myelinated cultures of rat dorsal root ganglia, as might have been expected from the species restriction of the reactivity of the IgM. The second patient had clinically severe neuropathy, very slow nerve conduction velocities, and monoclonal IgM, directed against axons of human and rat peripheral but not central nervous system (by immunohistochemistry) and to three nervous system antigens with molecular weights of 20K, 25K, and 30K daltons (by immunoblots). Serum from Patient 2 completely demyelinated cultures of rat dorsal root ganglia in two days. When the serum was removed, the cultures became remyelinated over three weeks. These two cases demonstrate immunological heterogeneity of neuropathies accompanying monoclonal gammapathies and provide some justification for vigorous attempts to reduce the concentration of paraproteins in these patients.

P96. Peripheral Sympathetic Nerves Grow into Guinea Pig Hippocampus after Septal Lesions
James N. Davis and Patterson McKinnon, Durham, NC

Peripheral sympathetic nerves grow into various regions of rat brain after interruption of their central cholinergic inputs. This sympathetic ingrowth has been most extensively studied in the rat hippocampus, where it occurs following lesions of the septohippocampal pathway. Sympathetic ingrowth appears to be initiated by a factor produced in the mossy fibers of dentate granule cells in the hippocampal formation. In order to determine if sympathetic ingrowth occurred in other species, we carried out septal lesions in 15 male guinea pigs. Sympathetic fibers were found in guinea pig hippocampal formation beginning at 6 to 8 weeks and reaching a maximum by seven months after the lesion. These fibers had a distinctly different pattern of ingrowth compared to that seen in the rat. Fibers were noted in the CA1 region in the guinea pig, where they are not seen in the rat. More striking was the dense innervation of sympathetic fibers around the pyramidal cell bodies in the hippocampal gyrus, whereas these fibers tend to innervate the apical dendrites of these neurons in the rat. These data show that: (1) sympathetic ingrowth in response to cholinergic denervation occurs in other animals besides the rat, (2) this sympathetic ingrowth takes much longer to develop in the guinea pig than in the rat, and (3) the pattern of ingrowth is distinctly different in the guinea pig, suggesting a different source for a putative trophic factor in this species. The observation that sympathetic ingrowth takes place in other animals besides the rat suggests that it may also occur in human beings. Since central cholinergic de- nervation is part of stroke, brain injury, and Alzheimer disease, sympathetic ingrowth may have important implications in the understanding of dementia or brain injury in patients.

P97. Decreased Cyclic Nucleotides in the Spinal Cord in Motor Neuron Disease Induced by Murine Neurotropic Retrovirus
Benjamin Rix Brooks and W. David Lust, Madison, WI, and Bethesda, MD

Motor neuron disease induced by murine neurotropic retrovirus is a naturally occurring, late-onset, noninflammatory degeneration of motor neurons. Our previous studies of a naturally occurring genetic spinal muscular atrophy (wobbler mutant) of mice have shown decreased concentrations of cyclic nucleotides, particularly cyclic guanosine monophosphate (cGMP), in the spinal cord of affected homozygous mice. We have extended our investigations to the virus-induced model of motor neuron disease. Glucose, glycogen, adenosine triphosphate and diphosphate, phosphocreatine, γ-aminobutyric acid, cyclic adenosine monophosphate (cAMP), and cGMP were measured by standard techniques in cerebral cortex, cerebellar wedge, and spinal cord of paralyzed and nonparalyzed virus-infected animals, and were compared to these chemical intermediates in uninfected control animals and controls infected with a nonneurotropic retrovirus. Spinal cord sections were dissected into dorsal white matter, dorsal horn, and ventral horn portions. No alterations in cyclic nucleotides were noted in the cerebral cortex among virus-infected, paralyzed or nonparalyzed mice or controls. cGMP was decreased 49% in the cerebellum of paralyzed mice compared to controls, as was found in wobbler mice. cAMP was decreased 43% and cGMP 12 to 49% in the spinal cord of paralyzed animals. These changes were localized exclusively to the ventral horn and were not found in the dorsal horn or white matter. The chemical changes described here that occurred in two murine models of motor neuron disease suggest that reduced tissue levels of cyclic nucleotides might be the basis for the decreased cyclic nucleotide turnover in the central nervous system that we have observed in human motor neuron disease, and suggest a common chemical pathogenesis for motor neuron disease.

P98. Pyridoxine Megavitaminosis Produces Sensory Neuropathy (Neuronopathy) in Humans
Herbert Schaumburg, Jerry Kaplan, Steven Rasmus, and Nicholas Vick, Bronx, NY, and Evanston, IL

We report a man and a woman in good health who developed distal symmetrical sensory loss in the limbs following megavitamin doses of pyridoxine. The man, aged 25 years, consumed 3 gm of pyridoxine daily in addition to a well-balanced diet for 3 months before symptoms appeared; the woman, aged 37, followed an 11-month regimen of increasing daily dose until a level of 2 gm was followed by symptoms. The recommended daily requirement of pyridoxine is 2.5 mg per day. Both individuals initially experienced numbness in the feet, which steadily ascended the legs and subsequently developed in the hands. Neither had
dysesthiasis, facial involvement, or weakness. Examination revealed moderately diminished sensation to pinprick, temperature, and touch sensation and severe loss of vibration sense in a stocking-and-glove distribution. Distal tendon reflexes were absent; strength was normal. Motor nerve conduction studies and electromyograms were normal; no sural nerve potentials were elicited, and medial nerve sensory action potentials were markedly diminished. Neither patient has improved in the year following discontinuation of pyridoxine, and thorough evaluations have revealed no other cause for neuropathy. We propose that the sensory neuropathy (neuronopathy) in these individuals may reflect pyridoxine-induced dysfunction in sensory neurons, analogous to the degeneration in dorsal root ganglion cells recently described in dogs maintained at megalavitamin levels (Krinke et al, Neurotoxicology 2:13, 1981).

**P09.** Distribution of Protein Components of the Sarcoplasmic Reticulum in Normal and Abnormal Human Muscles

F. J. Samaha and B. Nagy, Cincinnati, OH

Sarcoplasmic reticulum (SR) membrane proteins were studied by sodium dodecyl sulfate/polyacrylamide-gel electrophoresis. SR fractions were obtained from normal and diseased human muscles and were purified by extraction with potassium chloride and ultracentrifugation. The quantity of the three major protein bands of SR at 100K, 55K, and 44K dalton range were measured densitometrically after Coomassie blue staining. These were compared as percentage contribution to the total proteins present in SR and were normalized to the distribution found in normal human samples. The studies included samples of 11 normal, 11 Duchenne dystrophy, 5 myotonic dystrophy, 5 polymyositis, 3 glycogen storage disease, and 4 miscellaneous muscular disorders (genetically determined muscular dystrophy, Duchenne carrier, carnitine deficiency, and spinal muscular atrophy). The percentage distribution of the three protein bands in the order just presented for the groups studied are: 55:15:30; 14:18:12; 53:27:20; 13:7:8; 37:35:28; and (0.83:17, 20:38:42, 31:31:38, 31:27:43). The almost total absence of 100K dalton protein in the genetically determined muscular dystrophy is a special case. The noteworthy alterations were in Duchenne SR with low content of 100K dalton protein and a 44K/55K dalton protein ratio of 0.7. We propose the hypothesis that the decrease in calcium–adenosine triphosphatase activity in the SR of patients with Duchenne dystrophy may be due to the increased neutral protease activity recently reported by several investigators. (Supported by the Muscular Dystrophy Association.)

**P100.** In Vitro Model for Altered Sarcoplasmic Reticulum Proteins in Duchenne Dystrophy

Bela Nagy and F. J. Samaha, Cincinnati, OH

The protein gel electrophoretic pattern of the sarcoplasmic reticulum (SR) of Duchenne dystrophic muscle was found to differ from normal. The 100K dalton protein was 40% of that found in normal SR. The ratio of 44K/55K dalton protein in normal human SR was 1.7; in Duchenne SR it was 0.9. The decrease in 100K dalton protein is consistent with previous findings that the calcium–adenosine triphosphatase (ATPase) activity and calcium uptake of Duchenne SR are lower than that of normal human muscle (N Engl J Med 280:184, 1969). Assuming that the decrease in 100K dalton protein is due to endogenous protease activity in Duchenne muscles, we used trypsin digestion of rabbit SR as an in vitro model. In the presence of ATP and pCa 6.5, inorganic phosphate release showed an initial increase, then a decrease to zero ATPase activity within 40 minutes. The calcium uptake, measured by chlorotetracycline fluorescence, showed complete overlap with ATPase activity. The remaining protein pattern in the SR, at time intervals after addition of trypsin inhibitor and separation by sedimentation in a Beckman Airfuge, showed a decrease in 100K dalton protein and increases in 55K and 44K dalton bands. At 60% reduction in 100K dalton protein, the ATPase and calcium uptake together with the electrophoretic protein pattern was similar to that found in Duchenne SR. These results are consistent with our hypothesis that increased protease activity observed in Duchenne muscles can affect not only structural proteins but membrane proteins as well, and alter their normal functional values. (Supported by the Muscular Dystrophy Association.)

**P101.** Biochemistry and Morphology of Duchenne Dystrophic Muscle in Culture

F. J. Samaha, S. T. Iannarcone, B. Nagy, and C. Johnson, Cincinnati, OH

In the past we have used the Askanas and Engel method to grow large quantities of normal human muscle cells in culture. We have provided evidence that these cultures are free of fibroblasts, monitored the myogenesis over 36 days, and established normal standards for some biochemical markers of cell differentiation. Muscle cultured from six patients with Duchenne dystrophy has been studied morphologically and compared biochemically to similar cultures from eight normal patients. Over a 36-day time study, the rate of total protein and myosin heavy chain synthesis was similar to that of normal muscle cultures. Pyruvate kinase activity was not different from that in normal cultures with the use of total protein and myosin as reference bases. A significant decrease in creatine kinase activity was noted in Duchenne dystrophy cultures with reference to total protein and myosin with each day of development, although phase micrographs showed development of multinucleated myotubes as in normal cultures. Given our methodology and the lack of full maturation of normal muscle cells in culture, it appears that lowered creatine kinase activity is a consistent finding in cultured Duchenne cells. (Supported by the Muscular Dystrophy Association.)

**P102.** Familial Dystrophy Associated with Periodic Paralysis and a Unique Deficit of the Major Protein of Sarcoplasmic Reticulum

S. T. Iannarcone, K. Bove, B. Nagy, and F. J. Samaha, Cincinnati, OH

Two brothers, aged 11 and 5 years, with a unique neuromuscular syndrome were evaluated. Both had nearly identical histories and physical findings: normal perinatal course, delayed motor development with progressive proximal weakness apparent after 12 months of age, episodes of flaccid quadriplegia from ages 1 through 4 years, pseudohypertrophy of the calves, and hyperactive deep tendon reflexes with Babinski responses. Each experienced four or five episodes of paralysis during warm summer months after a prodrome of mild febrile illness, requiring three
weeks for recovery to baseline strength. The younger brother appeared to be weaker than the elder at a comparable age. Both patients had markedly elevated creatine phosphokinase, myopathic electromyograms, and abnormal muscle biopsies that demonstrated central nuclei, mild fibrosis, many atrophic fibers, and type grouping. Sarcolemmal reticulum was isolated from fresh muscle at the time of biopsies. Both patients showed nearly identical electrophoretic patterns, with absence of the 100K dalton protein in the weaker patient and near absence in the other. These patterns are remarkably different from those obtained in normal subjects and in patients with Duchenne muscular dystrophy and other myopathies. Such a deficit in the calcium transport mechanism could explain the periods of paralysis superimposed on progressive proximal weakness. (Supported by the Muscular Dystrophy Association.)

P103. Myoclonus and Mitochondrial Myopathy: A Clinical, Muscle Pathology, and Electrophysiological Study of a Pedigree Including Three Generations with a Dominantly Inherited Brain and Muscle Disorder
Howard S. Rosing, Linton C. Hopkins, and Charles M. Epstein, Atlanta, GA

This is a report of the largest pedigree presented thus far with dominantly inherited myoclonus associated with mitochondrial myopathy. The proband is a 19-year-old girl who presented with progressive multifocal myoclonus, sensorineural hearing loss, hypoventilation, and dementia over several years. The clinical findings associated with her mild muscle weakness were more indicative of upper motor neuron disease than of myopathy. Muscle and skin biopsies, done to investigate the possibility of Lafora disease, showed numerous ragged-red fibers which on electron microscopy were shown to be due to an increased number of abnormal mitochondria. Investigation of her family uncovered a pedigree with dominantly inherited myoclonus, mitochondrial myopathy, and sensorineural hearing loss with variation of expression in family members. The proband’s mother and grandmother both have mitochondrial myopathy, hearing loss, and electroencephalographic abnormalities but have had no myoclonus, while other family members have had myoclonus as the major expression. Increased amplitude of photic driving on conventional electroencephalograms was the most sensitive electrophysiological marker, but high amplitude of the pattern-shift visual evoked response was also noted. The electromyogram was mildly myopathic in the proband, normal in her mother and grandmother.

P104. Augmented Anti-Acetylcholine Receptor Response following Chronic D-Penicillamine Administration
Christopher T. Bever, Jr., B. J. Fowlkes, Richard Asofky, Hai W. Chung, and Andrey Penn, Bethesda, MD, and New York, NY

Because of the association of D-penicillamine (Pen) therapy with myasthenia gravis, we studied chronic Pen treatment of six inbred strains of mice: A/J, AKR, BALB/c, C3H/HeJ, and DBA/1. Mice were injected intraperitoneally with saline alone. Through the end of the six-month treatment period, the mice remained clinically normal and had no measurable anti-acetylcholine receptor (AChR) antibody response. Seven days after the end of Pen treatment, all mice were challenged with 10 μg of purified AChR from Torpedo californica in complete Freund’s adjuvant by intraperitoneal injection. Anti-AChR titers were measured ten days after the challenge. A comparison of the mean titers of Pen-treated mice with controls showed a difference only in B6 mice. In these animals the mean titer among those treated with Pen was 44 nM/ml, significantly higher (p < 0.001) than the 28 nM/ml seen in the control group. An isotype-specific anti-AChR assay showed that most of the response was IgM. A second, larger group of similarly treated B6 mice was prepared. Pen treatment was again found to lead to an augmented anti-AChR response. The response to an unrelated T-dependent antigen (sheep red blood cells) was found not to be changed by Pen treatment. This result suggests that the alteration in anti-AChR response may not be part of a generalized alteration in T-dependent antigen responses.

P105. Treatment of Myasthenia Gravis: Extension of Data on Prednisone and Adjunctive Thymectomy, Antimetabolites, and Plasmapheresis
Robert M. Pascuzzi, H. Branch Coslett, and T. R. Johns, Charlottesville, VA

 Favorable results were obtained in 93 of 127 patients with myasthenia gravis treated initially with high daily doses of prednisone and subsequently maintained on lower doses for several months to fifteen years. Either remission or marked improvement occurred in 73% of all cases. In 9 patients it was possible to discontinue prednisone one year or more after thymectomy. One hundred ninety-eight consecutive patients were reviewed to determine the efficacy of treatment with cholinesterase inhibitors, thymectomy (81 patients), adrenocorticotropic hormone, prednisone, antimetabolites, and plasmapheresis (32 patients). Complications and inadequate therapeutic responses will be emphasized. Comparison of the various therapeutic regimens will be made, and results of prednisone therapy will be compared to earlier published data (Mann, Johns, and Campa, Neurology 26:729–740, 1976).

POSTER PRESENTATION:
PATHOPHYSIOLOGY AND NEUROPATHOLOGY

P106. Neurological Complications of Hemoglobin SC Disease
Roderic H. Fabian and Bruce Peters, Galveston, TX

Hemoglobin SC disease (HgSCD) is a doubly heterozygous sickling hemoglobinopathy. We reviewed the medical records of 68 patients with HgSCD (mean age, 30 years; age range, 3 months to 72 years) for major neurological complications, and compared them to an age- and sex-matched group of black patients without hemoglobinopathies. A significant increase in the incidence of retinopathy (11 patients), seizures (3 patients), and stupor or coma or both (4 patients) was noted in the HgSCD group. In addition, 2 young adult patients with HgSCD presented with hemiplegia. Our results are similar to those reported previously except that stupor and coma as a presenting symptom was more common in our series. HgSCD as a cause of stupor and coma may go undiagnosed in older patients without obvious manifestations of a sickling hemoglobinopathy. Exchange transfusion has been advo-
cated for patients with sickling hemoglobinopathies and cerebrovascular syndromes. HgSCD should be considered in black patients with coma or stupor of uncertain cause, even in elderly patients. Alcohol or drug abuse, infection, fever, dehydration, and hypoxemia are known to precipitate sickling crises and the associated neurological problems, and should be avoided in these patients, especially those undergoing surgery or parturition.

P107. Neurological Aspects of the Hemolytic-Uremic Syndrome
Arnold H. Greenhouse and Edward Adickes, Omaha, NE

The hemolytic-uremic syndrome, which was first described in 1955, is a serious, not uncommon disorder originally thought to occur only in children. Characteristic features include hemolytic anemia, thrombocytopenia, renal failure, and intravascular coagulopathy. Adults also are affected, a relatively unknown fact. The disease may follow respiratory or gastrointestinal symptoms, but often there is no apparent previous illness. This condition, which frequently appears with seizures, altered consciousness, and other indications of a cerebral disturbance, is rarely mentioned in the neurological literature. The brain dysfunction has been attributed to metabolic factors or to a microangiopathy resembling that found in the kidneys. To date, almost no in-depth neuropathological studies have been published, whereas the renal changes are well documented. This report reviews the clinical course of one child and two adults with hemolytic uremia; gives the first detailed histological findings on the central nervous system, studied in one of these cases; and discusses the cause and treatment of this increasingly important entity. The neurological picture may have several causes, but most often it appears to result from the effects of an acute nephropathy. New therapies for the latter are emerging, but management at present is directed to rapid and effective support of renal function, thereby preventing brain injury.

P108. Hypoglycemia: Causes, Neurological Manifestations, and Outcome
Rene Malouf and John C. M. Brust, New York, NY

In a twelve-month prospective study, 125 consecutive Harlem Hospital Emergency Room patients were treated for symptomatic hypoglycemia. Thirty-nine were comatose; 26 were obtunded; 38 were confused or had bizarre behavior; 10 were dizzy, tremulous, or diffusely weak; 9 had seizures; and 3 were hemiparetic but alert. The cause was excessive insulin or oral hypoglycemic agents in 48; ethanol abuse in 35; both diabetes mellitus and ethanol in 20; and miscellaneous problems, including sepsis, terminal cancer, fasting, and myxedema, in 22. Among 32 comatose patients in whom no other disease appeared to be contributing to altered consciousness, the average serum glucose level was 15 mg/dl (range, 2 to 38); 21 similarly selected patients with obtundation had an average serum glucose of 33 mg/dl (range, 8 to 59); there was no difference in the reported duration of symptoms between comatose and obtunded patients. All 9 patients with seizures were either alcoholic or epileptic, so the contribution of hypoglycemia (average, 27 mg/dl; range, 6 to 54) was uncertain. Although 14 patients died, in only 2 was death directly attributable to hypoglycemia. Lasting neurological sequelae were similarly infrequent, consisting of hemiparesis or reflex asymmetry in 5 patients, of whom were initially considered to have had a stroke.

P109. Cerebral Injury and Blood-Brain Barrier Disruption Induced by Arachidonic Acid: Histopathological Features
N. A. Martin, S. W. Schmidley, S. L. Wissig, R. A. Fishman, and P. H. Chan, San Francisco, CA

Our laboratory previously demonstrated induction of brain edema in rat cortical slices by polyunsaturated fatty acids, which are present in injured and ischemic brain. Further studies showed that these compounds, particularly arachidonic acid (C20:4), also cause cerebral edema in vivo. We studied the histopathological changes and effects on the blood-brain barrier resulting from exposure of rat brain to arachidonic acid in vivo. Rats anesthetized with pentobarbital were subjected to ventriculocisternal perfusion with either Krebs-Ringer or Krebs/Ringer/fatty acid solution (800 μl over 60 minutes). Rats were sacrificed and their brains fixed by perfusion at various times after treatment; the animals were injected with Evans blue dye 15 minutes before being sacrificed. Ventricleocisternal perfusion with 5 mM arachidonic acid (N = 10) produced a characteristic acute lesion consisting of ependymal disruption, subependymal edema, and local disruption of the blood-brain barrier as evidenced by leakage of Evans blue from periventricular capillaries (identified on fluorescence microscopy). Ventricleocisternal perfusion with Krebs-Ringer solution (N = 4) or with 5 mM nonanoic acid (C9:0) (N = 4) caused no apparent periventricular injury. Rats surviving 7 to 14 days (N = 4) after exposure to arachidonic acid uniformly developed hydrocephalus due to aqueductal stenosis. These rats had periventricular gliosis without edema and no leakage of Evans blue. This study identified the histopathological lesions resulting from exposure of cerebral tissue to arachidonic acid. Our findings support the conclusion of previous biochemical studies that arachidonic acid induces membrane changes responsible for vasogenic and cytotoxic brain edema.

P110. Chronic Subdural Hematoma Presenting as Transient Neurological Deficits: Review of 13 Cases
Mark L. Master, David Johnston, and Oscar M. Reinmuth, Pittsburgh, PA

A new transient ischemic attack (TIA) often demands an urgent therapeutic decision on whether to start immediate anticoagulation therapy. Transient neurological symptoms are known to appear in the course of chronic subdural hematoma but the frequency of this occurrence is not widely appreciated, allowing a potentially dangerous error in management to be made. After encountering 4 patients with TIA due to chronic subdural hematoma in one year, we reviewed hospital records from 1976 to 1980 and detected 130 patients with chronic subdural hematoma of whom 13 presented with symptoms of TIA that were initially considered to be ischemic vascular disease. Clinical features included no headache in 4 patients; no history of head injury in 8 and only mild injuries in the remainder; aphasia as a prominent feature in 7; chronic subdural hematoma visible on computed tomographic scan in 13, though not correctly identified in all of them at first; and recurrent transient symptoms in the first month after surgical evacuation of hematoma in 4 patients but none thereafter. TIA occurs in as many as 10% of patients with chronic subdural hematoma, while approximately 2% of patients with TIA are estimated to have chronic subdural hematoma. This important possibility must be kept in mind, especially when high-resolution computed tomography is not available on an emergency basis.
P111. Quantitative Computed Tomographic Assessment of Furosemide- and Mannitol-induced Changes in Brain Water Content

T. Cascino, J. Baglivo, J. Conti, J. Szewczykowski, and D. A. Rottenberg, New York, NY

We studied the effects of two commonly employed antiedema agents, mannitol and furosemide, on brain density determined by computed tomography (CT) in patients with primary and metastatic tumors. Noncontrast CT scans were performed before and after intravenous infusions of furosemide (60 to 160 mg, 4 patients) and mannitol (1.15 to 2.70 gm per kilogram of body weight, 4 patients); 5 patients studied before and after repositioning (J Comput Assist Tomogr 6:417-421, 1982) served as controls. Co-planar brain slices were scanned before and after antiedema treatment, and serial blood samples were analyzed for osmolality. Computer-generated frequency histograms of CT numbers from 'before-and-after' brain slices were compared using quantile-quantile (QQ) plots and the chi-square statistic. Following the mannitol instillation, a progressive increase in mean CT density occurred that corresponded to an upward shift in the QQ plot over the range of 0 to 70 Hounsfield units. For all 4 patients, an analysis of proportions revealed significant differences between baseline and treatment histograms (in each case, p < 0.001) that coincided with peak serum osmolality. A diminution in mean CT number, which occurred in 3 of the 4 mannitol-treated patients by 60 minutes, was associated with appropriate changes in the QQ plot. No statistically significant effects were observed in the furosemide group despite maximal diuresis (1,250 to 2,100 ml/hr). The relative magnitude of the quantitative changes observed after furosemide and mannitol administration are consistent with anticipated changes in brain water content. These results indicate that our CT methods are sufficiently sensitive to monitor regional effects of antiedema therapy.

P112. A New Protein Band in Normal Human Cerebrospinal Fluid

Nicholas M. Papadopoulos, Peter A. LaWitt, Richard P. Newman, Marc I. Raphaelson, and Thomas N. Chase, Bethesda, MD

An improved high-resolution agarose gel zone electrophoretic technique has consistently demonstrated, in the cerebrospinal fluid (CSF) of 20 normal subjects, a single protein band in the gamma globulin region in 16 subjects and multiple bands in the others. Our survey of various neurological disorders, including cerebellar degeneration, progressive supranuclear palsy, Parkinson disease, and dystonia, has also shown the frequent occurrence of one or, rarely, more protein bands. In contrast, a diffuse gamma globulin zone was evident in central nervous system infections, while multiple sclerosis and central nervous system malignancy showed oligoclonal patterns. The possibility that the single band is a methodological artifact is unlikely for several reasons: the same technique demonstrated a diffuse gamma globulin zone in 95% of normal human serum samples; the band disappeared with storage of CSF at room temperature or 4°C for more than three days; and diffuse gamma globulin zones have been observed in a few patients. We attempted to identify the new protein band by immunofixation electrophoresis using monospecific antisera against human heavy- and light-chain immunoglobulins as well as against other normal serum proteins, including C-reactive protein, haptoglobin, α2-macroglobulin, transferrin, and ceruloplasmin. None of these antisera produced a precipitation reaction with the CSF protein band. We conclude that the protein band in the gamma globulin region consistently detected by this electrophoretic technique is a normally occurring protein unique to the CSF.

P113. Monozygotic Twins with Tourette Syndrome: Evidence for a Genetic Factor?

Richard L. Borison, William Hamilton, and Bruce I. Diamond, Augusta, GA

Gilles de la Tourette syndrome is a relatively rare illness that may be genetically transmitted with variable penetrance. Previous genetic studies have suffered from unrepresentative study populations and lack of data on concordance in twins. We report Tourette syndrome in monozygotic twin girls. The gestation period and birth of these girls were unremarkable, and they are now 18 years old. The onset of symptoms started at age 8, when eye blinking and coughing noises appeared. Both girls have since experienced head, neck, arm, truncal, and leg tics. Vocal tics have included screaming and grunting; only one twin has had coprolalia. Obsessive-compulsive traits have manifested themselves as echolalia, echopraxia, and compulsive touching, sniffing, and licking behaviors. The nature of the clinical presentation in these two girls has been virtually identical with the exception that only one demonstrates coprolalia. At age 14 both were diagnosed as having Tourette syndrome and were treated with haloperidol. After two years of therapy with similar doses, one twin developed a persistent (duration more than two years) lingual tardive dyskinesia that interferes with speech and swallowing. The concordance of Tourette syndrome in identical twins further supports the genetic aspect of the disorder; however, the presence of tardive dyskinesia in only one twin would suggest that this iatrogenic illness requires more than a genetic susceptibility to the neurotoxicity of neuroleptics.

P114. Inability to Simultaneously Breathe and Sleep in a Patient with Chronic Paralytic Poliomyelitis

Michael J. Thorpy and Elliot D. Weitzman, New York, NY

Medullary or upper cervical cord lesions may produce inability to breathe while asleep. Unless ventilation is assisted, death can result. The inability to breathe and sleep simultaneously was unequivocally demonstrated in a 55-year-old man. He had had acute poliomyelitis at age 26 and required a tank respirator for six months. Thirty years later he presented with a ten-year history of progressive daytime sleepiness. Bulbar function was intact, but there was weakness of the arms and total paralysis below T5. Awake breathing was dependent upon accessory muscles. Transdiaphragmatic pressures were minimal, and phrenic nerve stimulation produced no discernible contraction. Lung volumes were reduced but maximal voluntary ventilation was normal. Hypercapnia, hypoxemia, and polycythemia were present. Polysomnography was performed during six sleep periods. All respiratory movements stopped and oxygen saturation (SaO2) fell when sleep other than stage 1 occurred. Spontaneous arousals and at least three breaths then occurred and the SaO2 rose. The longest apnea (88 seconds) and lowest SaO2 (<40%) occurred in REM sleep. Despite the lack of assisted ventilation, this pattern persisted unchanged for more than three years. Daytime sleepiness, blood gas levels, and polycythemia improved with nightly low-flow oxygen therapy. The inability to simultaneously breathe and sleep is not incompatible with life.
Multiple experimental studies have indicated that destruction of the ventromedial hypothalamic nuclei causes obesity. In this regard, the best clinicopathological correlation available has been provided by tumor cases. We describe a 35-year-old man who suffered a syndrome of finicky hyperphagia, hypersomnia, and recent memory loss following viral encephalitis. In an eight-month period he gained 45.5 kg. Methylphenidate hydrochloride reduced his hyperphagia. At autopsy one and a half years after the encephalitis, two symmetrical, slit-like areas of necrosis were found to involve the ventromedial portion of the hypothalamus from the suprachiasmatic area through the level of the mammillary body. The lateral hypothalamic nuclei were spared. With its more selective pathological localization, this case confirms previous observations on the important role of the medial hypothalamus in regulation of food intake. It also provides an example of recent memory loss with a lesion restricted to the hypothalamus.

The measurement of P1 changes induced by adding filters to an eye with an optic neuropathy was not an effective provocative test for optic nerve disease. The afferent pupillary defect and P2 latency increases observed in normal subjects were possibly due to delayed retinal recruitment of the light stimulus.

Observation of eye movements induced by head rotation is an important part of evaluation of the unconscious patient. We have quantitated this "doll's-head response" by measuring horizontal eye movements using DC electro-oculography. An approximate calibration of the apparatus was made by inducing a full horizontal deviation of the eyes (about 90 degrees). Head movements were recorded using a helmet to which a potentiometer was attached. Two unconscious patients (one with hepatic encephalopathy, one with probable viral encephalitis) and one patient who was in a persistent vegetative state following Japanese B encephalitis were studied. With position-step head rotation, all three patients showed prompt, compensatory deviation of their eyes that was not sustained; the eyes drifted back, exponentially, to the primary position with a time constant of 1 to 2 seconds (normal, 25 seconds). This centrifugal drift reflected impaired gaze-holding mechanisms. Quick phases of nystagmus could be induced only in the vegetative patient. The peak velocity/ amplitude relationships of these quick phases were estimated to be similar to those of saccades from normal, alert subjects, suggesting that this patient's brainstem saccadic generator was intact. Quantification of the doll's-head response may increase the value of this reflex in evaluating coma.

Cerebral potentials related to gaze in three patients with congenital paralysis of horizontal saccades, pursuit, and vestibular eye movements, signifying brainstem involvement. Gaze shifts were achieved exclusively by head saccades. Results were compared with previously studied potentials before saccades with the head fixed and before combined eye and head refixations in ten normal subjects. Each epoch (N = 70 to 100) was triggered by the onset of self-paced gaze shifts to a target, or in darkness. Potentials were averaged from frontal and parietal scalp leads, referenced to linked ears, and from cervical electromyographic electrodes. Head saccades, both to targets and in darkness, were preceded by a negative readiness potential for up to 1 second. An inconstant premotion positive wave (+9 ± 6 μV) occurred just before head saccades. These potentials may represent cerebral motor programs that command gaze. They provide electrophysiological evidence of the level of brain involvement in gaze palsy. In these patients, they signified integrity of cerebral motor activity preceding gaze and indicated that surface activity preceding head saccades is identical to that preceding normal eye saccades.
P119. Frequency of Acute Confusional States with Lesions of the Right Hemisphere

Norman Geschwind, Boston, MA
William Mullally, Kenneth Huff, Michael Ronthal, and Michael Ronthal, and
P119. Frequency of Acute Confusional States with abnormalities not primarily within the central nervous system, as a result of lesions in the right middle cerebral artery distribution (Mesulam et al, J Neurol Neurosurg Psychiatry 39:84–89, 1976), or with lesions in either the right or left occipital lobe. We reviewed all inpatient neurological consultations over a three-month period at our institution.

Acute confusional state was diagnosed when the mental examination revealed failure to maintain a coherent stream of speech or action, inattention, and distractibility. Of 308 patients seen in consultation, 60 fulfilled the criteria for diagnosis of acute confusional state. In 24 of these, systemic causes were believed to be present. The remaining 36 patients had focal lesions consistent with pathology on the basis of either definite computed tomographic findings (26 patients) or definite clinical signs alone (10 patients). Thirteen had lesions in the right parietal lobe, 4 had right temporal lesions without elementary physical signs, and 2 had changes in the left occipital lobe. Focal lesions in the right hemisphere or left occipital lobe are therefore a frequent cause of the syndrome of acute confusional state, sometimes with relatively minor or absent elementary signs.

P120. Papilledema following Acute Head Injury

John B. Selhorst, Steven K. Gudeman, John F. Butterworth, John W. Harbison, J. Douglas Miller, and Donald P. Bicker, Richmond, VA

A study of the incidence, evolution, and diagnosis of papilledema and of its association with raised intracranial pressure (ICP) was made from 426 consecutive patients undergoing serial ophthalmoscopy who had neurological deficits following acute head injury. Papilledema occurred in 15 patients (3.5%), which contrasts with the presence of choked discs in 50 to 75% of patients with chronically increased ICP from brain tumors or subdural hematomas. The low incidence is attributable to the brief, controllable form of raised ICP, and a favorable prognosis, the magnitude of the head injury among patients with papilledema was not as severe as in the overall group. The delayed causes of raised ICP following head injury and the explanation for the absence of papilledema in 6 patients with severe, uncontrollable ICP (> 60 mm Hg) for three days or longer needs further study.

P121. Role of the Striate Cortex in Generation of Smooth Pursuit Eye Movements

M. E. Goldberg, C. J. Bruce, L. Ungerleider, and M. Mishkin, Bethesda, MD

To clarify the role of striate cortex in the generation of smooth pursuit eye movements, we first studied three monkeys trained one year after unilateral striate lesions to make visual fixations, smooth pursuit eye movements, and saccades. The monkeys successfully pursued stimuli moving in any direction at velocities up to 30 degrees per second using the strategy of keeping the stimulus always in the intact hemifield. We then examined smooth pursuit of stimuli confined to the visual hemifield contralateral to the lesion. First, eye position was fed by computer back to a mirror galvanometer controlling stimulus position to keep the stimulus on one retinal locus. Loci in the intact hemifield generated a mixture of saccades and smooth pursuit movements as the monkey attempted to capture the stimulus. Loci in the impaired hemifield generated only saccades. Second, monkeys fixated a spot that jumped and then made a ramp movement. Steps into the intact hemifield generated a smooth pursuit movement before the fixation saccade. Steps into the impaired field never generated smooth pursuit until the saccade brought the stimulus out of the impaired field. Therefore, unilaterally destruete monkeys can generate smooth pursuit eye movements only from targets in their intact visual hemifield.

P122. Bilateral Transection of the Angular Bundle Retards Development of Amygdala Kindling

James O. McNamara, Lewis C. Rigsher, and Helmer Pedersen, Durham, NC

Kindling is an animal model of epilepsy induced by periodic electrical stimulation of the brain. The cellular and molecular basis of the phenomenon is unknown. Elucidation of the underlying mechanisms would be facilitated by understanding the location of the network of altered neural circuits responsible for kindling. We found that amygdala kindled seizures result in increased numbers of benzodiazepine receptors in the rat hippocampal formation. We localized these increases to a specific neuronal population, the dentate granule cells. We therefore hypothesized that the granule cells are part of the network of neural circuits responsible for development of amygdala kindling. We then found that destruction of dentate granule cells by microinjection of colchicine retarded the development of amygdala kindling. In the present experiments, we found that bilateral knife cuts of the principal excitatory afferents to the granule cells (axons from entorhinal cortex coursing through the angular bundle) also slowed development of amygdala kindling by 69%: number of stimulation-induced afterdischarges to third generalized kindled motor seizure (mean ± SEM)—control, 24.7 ± 3.2 (N = 14), experimental, 41.8 ± 2.4 (N = 18); p < 0.001 by two-tailed Student t test. These data strengthen the conclusion that dentate granule cells and their afferents play a key role in the development of kindling from the amygdala. We suggest that benzodiazepine receptor alterations may serve as
a marker for the network of altered neural circuits responsible for kindling.

P123. Vasogenic Brain Edema: Blood-Brain Barrier Breakdown Is Mediated by Enhanced Polyamine Synthesis in Cerebral Microvessels

Harold Koenig, Alfred D. Goldstone, and Chung Y. Lu, Chicago, IL

Blood-brain barrier breakdown is characterized by enhanced endocytosis and vesicular transport in the microvascular endothelium. A preliminary study (Koenig et al, J Cell Biol 97:420a, 1982; Neurology 32(2):A109, 1982) showed that cryoinjury rapidly raised ornithine decarboxylase (ODC) and polyamine levels in rat cerebral; the ODC inhibitor α-difluoromethylornithine (DFMO), 250 mg per kilogram of body weight subcutaneously, suppressed the increase in ODC polyamines and blood-brain barrier breakdown. In the present study, polyamine concentrations were 1.5- to 2-fold greater in microvascular fractions than in parenchyma. Three hours after unilateral cryoinjury a 65 to 80% increase in microvascular and parenchymal polyamines and an 8-fold rise in fluorescein uptake had occurred in injured hemisphere, with one-half these increases in uninjured hemisphere. DFMO attenuated the increment in polyamine levels and fluorescein uptake by 60 to 70%. Putrescine, 0.5 mg subcutaneously, overcame DFMO inhibition, restoring the increase of microvascular (and parenchymal) polyamines and fluorescein uptake. Thus, increased polyamine synthesis in cerebral microvessels (and brain cells) occurs shortly after cryoinjury and appears to be essential for breakdown of the blood-brain barrier. Polyamines may stimulate endocytosis and membrane transport (also other calcium-dependent processes) by interacting with calcium depots (mitochondria, microsomes, plasma membrane) and increasing free cytosolic calcium. (Supported by the Research Service of the Veterans Administration and by Grants NS 14700 and NS 18047 from the National Institute of Health.)

P124. Selective Effects of Ammonia on Regional Brain Glucose Metabolism

Alan H. Lockwood, Myron D. Ginsberg, Cathy M. Butler, and Maria T. Gutierrez, Miami, FL

Unknown mechanisms cause ammonia intoxication to play a central role in the pathogenesis of hepatic encephalopathy. We evaluated the effect of unilateral infusions of ammonium acetate on the local cerebral metabolic rate for glucose (ICMRG). Rats were anesthetized with nitrous oxide, paralyzed, and ventilated. Catheters were placed in the femoral artery and vein and at the bifurcation of the carotid artery via the external carotid artery. Ammonium acetate or saline, each 200 mM, was infused via the carotid catheter at 20 μl/min for 15 minutes before an intravenous bolus of 11C-deoxyglucose was given. Arterial blood samples were collected over the next 45 minutes while the infusion was continued. The animal was then killed and the brain processed for autoradiography. Values for ICMRG were calculated from microdensitometer readings using standard techniques. The uniformity of hemispheric ammonia delivery was assured in parallel studies using intracarotid infusions of 15N-ammonia. On the side of the ammonia infusion, ICMRG was increased in multiple nuclear areas of the thalamus, the hypothalamus, and most strikingly in the substantia nigra. The ICMRG in the overlying lateral cerebral cortex was reduced compared to values measured in contralateral homotypic cortex. Ammonia appears to exert metabolic effects that are specific for various nuclei, with patterns that suggest suppression of metabolic activity in some areas of the cerebral cortex. Selective activation and inhibition of cerebral glucose metabolism may be a factor in the pathogenesis of early ammonia intoxication.

P125. Ultrasensitive Detection of IgG in Unconcentrated Cerebrospinal Fluid Utilizing Silver Nitrate Staining after Isoelectric Focusing and Immunofixation

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Patients with multiple sclerosis show abnormal bands, denoted oligoclonal IgG, on isoelectric focusing/polyacrylamide-gel electrophoresis (IEF-PAGE) in cerebrospinal fluid (CSF). These bands generally occur between pH 7.0 and 10.0, most often above pH 8.2. IEF-PAGE with Coomassie blue staining requires IgG concentrations of 200 mg/dl. Therefore, concentration techniques are utilized to concentrate CSF for these analyses. Silver nitrate staining (Oakley et al, 1980; Merrill et al, 1980) increases the sensitivity of protein detection. We have used immunofixation to increase the sensitivity of the subsequent silver nitrate staining step as well as to confirm that the bands seen are IgG on IEF-PAGE and are able to detect oligoclonal IgG in unconcentrated CSF. We determine the maximum sensitivity of our technique by analyzing serial dilutions of a standard CSF pool (#3299). Matched CSF and serum samples from controls and from patients with multiple sclerosis, subacute sclerosing panencephalitis, and other neurological diseases were also analyzed. The optimum volume of application was 10 μl, though up to 30 μl may be used. Under these conditions, 0.5 to 1 μg of IgG can be reproducibly detected. Satisfactory results can be obtained within 5 hours after IEF. For optimum staining after IEF and immunofixation, the procedure takes 20 to 30 hours. Gels 0.5 mm thick give better and faster results than 1 mm gels. Silver stain enhanced by immunofixation permits analysis of unconcentrated CSF having 2 mg/dl IgG and thus is practical for research and diagnostic use.

P126. Adrenoleukodystrophy: A Wide Spectrum of Clinical Disorders

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A 36-year-old man died after a 25-year history of a progressive neurological illness characterized by frequent seizures, blindness, and insidious spastic quadriaparesis. Extensive clinical evaluation, including a computed tomographic scan and brain biopsy late in the course, yielded no specific diagnosis. Autopsy examination of the brain revealed diffuse demyelination characteristic of adrenoleukodystrophy (ALD); biochemical analysis of white matter confirmed the typical accumulation of long-chain fatty acids in cholesterol esters, and light and electron microscopy demonstrated pathognomonic cytoplasmic inclusions in adrenal cortex. To our knowledge, previous reports of cases of ALD with pathological documentation have described survival of no more than 9 years after the onset of illness. The slow progression of disease, long survival, and prominence of seizures in our patient are exceptional for ALD. This case,
considered together with other reported clinical variants of ALD, e.g., patients with total remissions, connatal onset, late-adult onset, or primary spinal cord and peripheral nerve involvement (so-called adrenomyeloneuropathy), indicates that ALD represents a wide spectrum of clinical disorders that share certain histopathological and biochemical features. Assays of plasma long-chain fatty acids and baseline adrenocorticotrophic hormone stimulation tests should be performed routinely in patients who have undiagnosed degenerative neurological disorders with clinical features of blindness, long-tract involvement, or peripheral neuropathy.

P127. Autonomic Symptoms and Hypersensitivity to β-adrenergic Blockade in Chronic Paroxysmal Vestibular Disease

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Two patients with chronic paroxysmal vestibular disease developed autonomic phenomena during attacks, and each experienced exacerbation of symptoms when given low doses of propranolol. A woman with dominantly inherited paroxysmal ataxia precipitated by visual pursuit movements developed flushing, sweating, and bradycardia in the initial phase of her attacks, which included: ataxia, vertigo, nystagmus, dysmetria, dysarthria, and electroencephalographic abnormalities. Acetazolamide and anticonvulsants were without effect. Attacks could be precipitated with propranolol (30 mg) and immediately aborted with isoproterenol. Spontaneous attacks also responded to isoproterenol.

Another woman, with Meniere’s disease, developed biphasic autonomic responses during attacks: bradycardia at the onset, followed by tachycardia, flushing, and hypertension. Section of the vestibular nerve eliminated vertigo from the attacks, and prazosin, an α-adrenergic blocker, modified the hypertensive phase, but neither reduced the frequency of attacks. Attacks could be induced with propranolol (10 mg), but nadolol, a beta blocker without major central effects, was well tolerated. In contrast, two patients with Friedreich and one with Marie ataxia tolerated over 100 mg of propranolol daily without adverse experiences. These observations in patients with chronic paroxysmal vestibular disease suggest alterations in the responsiveness of noradrenergic pathways from brainstem to cerebellum.

P128. Alcohol Produces Acute and Chronic Changes in Neural α-adrenergic Receptors

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Alcohol produces many effects on neural cell membranes. We investigated the consequences of this interaction on neuroreceptors in NG108-15, a murine neuroblastoma × glioma hybrid cell line. Opiate receptor binding and α2-adrenergic receptor binding increased 2.6 ± 0.6 fold in chronic ETOH cells compared to controls. Opiate receptor binding increased less consistently. Acute addition of ETOH to cells grown chronically in alcohol had less effect on α2-adrenergic binding than in control cells. Sensitivity of opiate receptor binding to ETOH was unaffected by chronic ETOH. Thus, while acute ETOH strikingly reduced α2-adrenergic receptor binding in NG108-15, chronic ETOH produced compensatory increases in that binding with tolerance to the acute effects of ETOH. This model system will be of value in studying the development of alcohol tolerance in neural cells.

P129. Infantile Orthochromatic Leukodystrophy with Multisystem Lipid Storage

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Over the years, the classification of the leukodystrophies characterized by “normal” myelin breakdown products has been particularly confusing. Much of this confusion has resulted from the variation in clinical, genetic, and neuropathological alterations described. At least one specific entity, X-linked juvenile adrenoleukodystrophy, has been recognized. In the past three years we have had the opportunity to study 5 affected infants born into four different families. Clinical symptoms, present at or shortly after birth, were characterized by severe hypotonia, including lack of head control and poor feeding. Developmentally the infants showed failure to thrive, severe psychomotor retardation, seizures, spontaneous nystagmoid eye movements, blindness, deafness, and death at a very early age. Neuropathologically there was a great deal of variation from individual to individual, but each demonstrated evidence of a leukodystrophy with severe gliosis of the white matter and rare foci of collections of lipid-laden macrophages and perivascular infiltrates. Ultrastructural examination of the thymus, liver, adrenal glands, and lymph nodes demonstrated crystalline inclusions. Biochemically, the cholesterol ester fraction extracted from brain demonstrated a fatty acid pattern similar to that found in juvenile adrenoleukodystrophy. It is our opinion that this infantile leukodystrophy is a distinct entity and most likely inherited as an autosomal recessive disorder.

P130. Somatosensory Cortical Evoked Potential Monitoring: Measurement of Ordinary Variability

Marc R. Nuwer and Edgar C. Dawson, Los Angeles, CA

During evoked potential (EP) monitoring in the operating room or intensive care unit, prompt identification of significant EP change is crucial. We measured variability of cortical somatosensory EPs to lower extremity stimulation in 20 neurologically normal patients undergoing placement of a Harrington rod. Before and during general anesthesia, amplitudes and latencies were measured for peaks 20 to 60 msec after the stimulus at three different frequency bands (1 to 1,000, 15 to 3,000, 75 to 8,000) from various scalp locations. Between 8 and 20 samples were taken for each setting over two to four hours. Minimum variability was often found at the earliest peaks recorded with the high bandpass over the scalp ipsilateral to the leg stimulated. Those peaks generally showed latency variability of less than 1 msec and amplitude variability of less than 30% during clinically stable periods. Some patients showed less variability at other scalp locations or at the middle bandpass (especially when high bandpass peaks had relatively low
amplitude). Careful attention to the morphology of peaks was needed with some patients to avoid varying the part of a peak used to obtain measurements. Optimal bandpass and electrode placement strategy needed to be empirically determined for each patient. Such baseline determinations appear clearly superior to preselected limits of variability deduced from other patients.

P131. Relationship between Spinal Injury and Upper Limb Motor Function in Patients with Cervical Central Cord Syndrome

Dominic Foo and Alain B. Rosier, Boston, MA

Six patients with cervical spinal cord syndrome are presented. They were admitted within 2 to 40 days after injury (mean, 18 days). A comprehensive muscle test was performed at admission, and motor power was graded from zero (absent) to 5 (normal). The patients were divided into four groups according to the level of vertebral injury: (A) C2-3 (1 patient), (B) C3-4 (1 patient), (C) C4-5 (3 patients), and (D) C5-6 (1 patient). Other subjects with no bony lesion or with more than one level of spinal injury were excluded. The percentages of muscles graded zero in the various myotomes were as follows: 10% in C5-6 myotomes, 50% in C6-7, 62.5% in C7-8, and 100% in C8-T1 in the patient from Group A; 0% in C5-6, 40% in C6-7, 62.5% in C7-8, and 90% in C8-T1 in the subject from Group B; 0 to 10% (mean, 3.3%) in C5-6, 25 to 62.5% (mean, 42.5%) in C6-7, 37.5 to 81.3% (mean, 62.5%) in C7-8, and 62.5 to 90% (mean, 74.2%) in C8-T1 in the patients from Group C; and 0% in C5-6, 30% in C6-7, 75% in C7-8, and 100% in C8-T1 in the subject from Group D. Our findings show that the level of maximal muscle weakness occurs several segments below the site of injury to the spine in patients with central cord syndrome, and that a gradient of motor deficits exists within the cervical spinal cord. These can be explained by secondary involvement of the blood supply of the cervical cord.

P132. Brown-Séquard Syndrome with Paralysis of Head Turning

Anthony M. Iannone and Arthur M. Gerber, Toledo, OH

A 24-year-old man suffered a laceration of the right side of the spinal cord at the C1 level, confirmed at surgical exploration. Brown-Séquard syndrome was produced with the following findings: sensory—absent position sense on the right side, and loss of pinprick sensation on the left to the level of C2, up to the vertex; motor—complete flaccid paralysis of all muscles of the right side of the body except for the right sternocleidomastoid muscle (SCM), which could exert a normal force in turning the head to the left. The left side had normal strength except for paralysis of the left SCM on right head turning. Flexion of the neck produced strong contraction of both SCM muscles in spite of paralysis of the left muscle for head turning. These findings directly contradict the idea of uncrossed innervation of the SCM (Balagura S, Katz RG: Ann Neurol 7:84-85, 1980) because in that case the right-sided lesion would produce paralysis of the right SCM. They support the descriptions of Beevor (Paralysis of movements of the trunk in hemiplegia, Br Med J 1:881, 1909) and make Geschwind’s arguments in favor of a double decussation of the upper motor neuron fibers the most tenable hypothesis (Geschwind N: Ann Neurol 10:495, 1981). The second decussation in our patient must be below C1. Intraneuronal neurons in the upper cervical cord to motor neurons on both sides probably mediate this movement.

P133. Axonal Abnormalities in the Central Nervous System of a Dysmyelinating Rat Mutant

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The Wistar rat mutant, md, totally lacks central nervous system myelin (Citza and de Lahunta, 1979). The earliest ultrastructural change is in oligodendrocytes, which show, with increasing frequency after the third postnatal day, dilatation and disruption of the nuclear envelope and rough endoplasmic reticulum. Since pathological changes occur in axons in similar dysmyelinating murine mutants, and since axons are crucial to both myelination and oligodendroglial maturation, a search for axonal alterations was undertaken in md rats. Axonal balloons measuring up to 15 μm in widest dimension occur in md rats in optic nerves, corpus callosum, and spinal cord after 17 days of postnatal age and are packed with mitochondria, various forms of dense bodies, vacuoles, neurofilaments, and microtubules. Some axonal enlargements fold back upon and enfold thin axons of origin. Cerebellar mossy fiber termini contain vacuoles and large accumulations of glycogen. Similar mossy fibers are present in normal developing rat brain but may persist longer in the mutant. Morphometric observations on optic nerve axons in 19-day control and md rats indicate that axoplasmic areas and mitochondriall density and volume composition in the two groups are similar. Axonal changes probably are not primary to the oligodendroglial and myelin abnormalities in md rats. (Supported by the Veterans Administration and by the National Multiple Sclerosis Society.)

P134. Neuropathological Features of Murine Lupus

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The pathogenetic mechanisms underlying neurological manifestations of systemic lupus erythematosus (SLE) are poorly understood. We undertook a light and electron microscopic study of the central nervous system in female New Zealand Black/White F1 hybrid (NZB/W) mice, an animal model of SLE. NZB/W mice were studied at 3, 5, 8, 12, and 14 months of age, and female C57BL/6J mice were studied as aged controls. Viscera from 3- and 14-month-old NZB/W mice were also examined. A lymphoproliferative process was identified in the central nervous system of 41% of the 8- to 12-month-old NZB/W mice and in all 14-month-old NZB/W mice. The extent of involvement was greatest in 14-month-old mice. Infiltrates composed of lymphocytes, plasma cells, and plasmacytoid lymphocytes were seen in subarachnoid, choroid plexus interstitial, and Virchow-Robin spaces. Lymphoid cells occasionally infiltrated brain parenchyma or accumulated as nodular masses. Concomitant visceral involvement in lymph nodes, spleen, liver, lung, and kidney was noted in 14-month-old mice. Dense deposits were seen ultrastructurally in brain parenchymal vascular basement membranes in 14-month-old NZB/W mice. These dense deposits had an appearance similar to that of immune complexes described in glomerular basement membrane, and appeared at a time when an advanced lupus-like glomerulopathy was evident. Similar deposits were not observed in choroid plexus. A lymphoproliferative process, such as described in these mice, may be relevant to the clinical syndrome of aseptic meningitis.
occasionally seen in human SLE. Dense deposits may represent deposition of immune complexes and may play a role in the pathogenesis of some neurological syndromes in human SLE.

P135. Meningocortical Angiopathy in Sturge-Weber-Dimitri Syndrome: A Multidisciplinary Study Including Electron Microscopy
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A clinicopathological study was made of 13 patients of both sexes ranging from 3 years 4 months to 57 years 11 months old, with 4 complete autopsies. The outstanding clinical findings included port-wine nevi, buphthalmos, glaucoma, and vascular and atrophic changes of the fundi; epileptic seizures with abnormal electroencephalograms; motor and sensory disturbances, deafness, and blindness; atrophic changes and pathological reflexes; low IQ, emotional instability, and behavioral disorders; and heterogeneous anomalies. Laboratory examinations (urine, hematology, blood chemistry, and cerebrospinal fluid) were not contributory. Roentgenograms of the skull revealed cerebral hemiatrophy with characteristic gyriform radiographic contours. Pneumoencephalograms showed ventricular enlargement on the involved side. Postmortem studies focused principally on the involved leptomeninges and subjacent vessels of the central nervous system. Histological, histochemical, and electron microscopic examinations revealed an angiopathy characterized by anomalous, dystrophic and degenerative vessels of variable caliber and permeability, intertwined with pleomorphic capillary networks. Concomitantly, vascular walls and surrounding tissue showed various stages, patterns, and degrees of calcification and siderosis. The pathogenesis of the described angiopathy is traceable to a morphogenetic defect or disorder occurring at the stage of metamorphosis or differentiation of the embryonal "primary vascular plexus" into the venous, arterial, and capillary systems.

P136. Cavernous Optic Atrophy with Compressive Lesions of the Anterior Visual Pathway
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Cavernous degeneration of the optic nerve, classically a sign of glaucoma, was demonstrated in 31 eyes of 16 patients with lesions compressing the anterior visual pathway. None of the patients had marked elevation in intraocular pressure, and 7 had normal tonography. However, glaucoma was initially diagnosed in 5 cases because of cupping of the optic nerves. Color-contrast determinations of the cup to disc ratio demonstrated a ratio of 0.6 or greater bilaterally in 10 patients and unilaterally in the other 6. Further evaluation of the optic nerves by stereobiomicroscopy showed cavernous degeneration by contour changes, but cup to disc ratios were less than those found by color determinations. In contrast, true glaucomatous cupping is greater when contour defects are evaluated. Other signs of glaucoma, such as saucierization of the cup temporally (16 eyes) and baring of circumlinear arterioles (14 eyes), were found. Analysis of visual fields was the most important study other than computerized tomography in distinguishing our patients from those with glaucoma. Most demonstrated the classic bitemporal defects found with compression of the chiasm. None had fields with arcuate or paracentral scotomas, nasal steps, or baring of the blind spots typical of glaucoma. In addition, most of our patients had severe loss of visual acuity (Snellen), out of proportion to the extent of optic disc cupping. This study indicates that diseases other than glaucoma can cause cavernous degeneration of the optic nerves. Detailed evaluation of the disc changes and the visual fields will prevent confusion between compression of the anterior visual pathway and glaucoma, leading to early definitive therapy.

P137. Hypothalamic Obesity in the Human
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In 1939, Hetherington and Ranson first demonstrated that ablation of the ventromedian hypothalamic nuclei in the rat will result in profound obesity. Many case reports in the literature have suggested that this same phenomenon occurs in human beings, but most cases were caused by progressive or rather ill defined processes. We wish to report a remarkable patient who virtually ate herself to death over four years after a transient neurological illness. Neuropathological examination revealed bilateral localized infarcts within the hypothalamus with virtual destruction of both ventromedian nuclei. In addition, the lateral hypothalamic nuclei were severely damaged; only the far-lateral portion of the left nucleus was spared. This area corresponds almost exactly to the far-lateral hypothalamic feeding center originally described by Anand and Brobeck in 1951, providing evidence for the first time about the exact location of such a center in human beings. Because the lesions were well defined and static, our case represents an exceptional opportunity to demonstrate the effects of discrete hypothalamic lesions in humans. The experimental literature will be reviewed and correlated with detailed anatomical demonstration of our patient's lesions. In addition, a mechanism whereby ventromedial lesions may cause hyperphagia, which is dependent on preservation of the far-lateral portion of the lateral hypothalamic nuclei, will be presented.

P138. National Neurological Research Bank
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The purposes of the National Neurological Research Bank (NNRB) are to recruit donor members and to collect, cryopreserve, and distribute human tissue specimens such as antemortem serum, cerebrospinal fluid, leukocytes, and autopsy tissue from normal individuals and from patients with multiple sclerosis, subacute sclerosing panencephalitis, Huntington disease, Parkinson disease, amyotrophic lateral sclerosis, hereditary ataxia, Tourette syndrome, tardive dyskinesia, dementia, mental retardation, schizophrenia, or manic-depressive disease as well as suicides and drug abusers. Cerebrospinal fluid, blood, and tissue can be obtained before freezing upon request. The tissue specimens are available to investigators who desire to try their standardized techniques to unravel the chemical, immunological, or virological pathology of the listed incurable diseases. Persons interested in requesting specimens from the NNRB should write to W. W. Tourtellotte, MD, PhD, VA Wadsworth Medical Center, Los Angeles, CA 90073, or telephone (213) 824-4307. For persons interested in becoming a donor member of the NNRB or assisting in the recruitment of donor members, a brochure is available at the booth or on request.