

# Journal of Rehabilitation Research and Development

## Rehabilitation R & D Progress Reports 1990

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### VI. Head Trauma and Stroke

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*For additional information on topics related to this category see the following Progress Reports: [86], [94], [95], [99], [102], [448], [458], [460], [461], [462], [463], [485], [499].*

## [176] Computer-Assisted Treatment of Hemi-Inattention in R-CVA Patients

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Sponsor: VA Rehabilitation Research and Development Service (Project #B610-RA)

**Purpose**—This project is designed to evaluate the efficacy of a computer-assisted training program in reducing the accident prone behaviors of R-CVA victims suffering neglect of left space.

Patients with strokes involving the right hemisphere (R-CVA) have more accidents than all other rehabilitation patients. Our previous work revealed that R-CVA patients with hemi-inattention (i.e., neglect, hemispacial neglect) to left space were more likely to have accidents than either our control subjects (including a group of L-CVAs) or R-CVA stroke victims without hemi-inattention. We also observed that falls during transfers and wheelchair navigation were the most common types of accidents reported for our hemi-inattending R-CVAs.

**Methodology**—We plan to develop a technique to train R-CVA subjects with hemi-inattention to compensate for hemi-inattention-related problems during simulated high accident risk activities (i.e., wheelchair propulsion, transfers) and evaluate the impact of training on incident reports, ratings of rehabilitation staff, and progress of the subjects during rehabilitation therapies. We also plan to assess the generalization of training to other neuropsychological measures and to a wheelchair obstacle course that we previously developed.

Our training will be initiated within the first 2 days of the subjects' admission to the rehabilitation service in order to maximize its impact on other rehabilitation

activities. The results of training will be compared with a control group which receives training to improve attention, but not to improve scanning or other skills deficient in the hemi-inattentive patient. We will train the experimental subjects to sit at true vertical, systematically scan into left space, and scan while performing computer simulations of risky activities, including propelling a wheelchair through a cluttered hallway, and parking a wheelchair for transferring to a bed. Computer simulation will be used so that training can begin even if the subject does not have the physical ability to transfer or drive a wheelchair initially. Most of our subjects will be wheelchair-bound at the beginning of therapy; however, some of these subjects will be ambulatory with or without assistive devices by discharge. Our experience is that training hemi-inattentive subjects to scan during wheelchair movement generalizes to scanning during walking; hence, we believe that our training will be beneficial even if the subject is ambulatory soon after admission. Our specific objectives are: 1) to investigate if training hemi-inattentive subjects to scan will reduce their accident proneness as indicated by ratings of rehabilitation staff and incident reports; 2) to investigate if training using computer simulation facilitates skill mastery on actual wheelchair mobility and transfers; and, 3) to investigate the degree of generalization of training to neuropsychological tests and to our wheelchair obstacle course.

## [177] Hemi-Neglect Syndrome: Visual Scanning and Reading Skills Retraining

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Sponsor: VA Rehabilitation Research and Development Service (Project #C552-RA)

**Purpose**—Patients with left hemi-neglect after right hemisphere stroke frequently receive perceptual or cognitive retraining as outpatients, after discharge from inpatient rehabilitation programs. In anticipation of conducting a controlled clinical trial of outpatient cognitive retraining, we studied the course of visual left hemi-neglect in patients who received no treatment beyond the standard inpatient rehabilitation during acute recovery.

**Methodology/Progress**—To date, we have tested 52 right hemisphere stroke patients (age range = 42 to 83; mean = 66.2 years) in the hospital within 4 weeks of the stroke, using confrontation testing and six paper-and-pencil tasks. Confrontation testing involved both unilateral and simultaneous bilateral visual stimulation. Paper-and-pencil tasks were: line crossing, line bisection, letter cancellation, the position preference index for the Raven's Colored Progressive Matrices Test, left-margin-indented paragraph reading, and drawing or copying pictures and designs. Our criterion for neglect was evidence of neglect on two or more of the six paper-and-pencil tasks. Subjects were retested 2 months, 3 months, and 6 months post-stroke if, and only if, they had met this criterion on the previous test session.

Thirty-six patients (69%) met the criterion for visual left hemi-neglect at initial testing. Eleven of these patients became unavailable for further study, and one has not yet been retested. Of the 24 who were tested, 15 met the criterion for neglect at 2 months (62.5%). Of these 15, 2 became unavailable, and 2 others have not yet been retested. Of the 11 who were tested, 7 met the criterion for neglect at 4 months (63.6%). Of these 7, 2 became unavailable, and one has not yet been retested. Of the 4 who were tested, all continued to meet the criterion for neglect at 6 months (100%).

The 15 subjects who dropped out of the study had become unavailable for the following reasons: 7 transferred to nursing homes, 3 moved away from the area,

4 died, and one refused to participate. On each test occasion, these subjects were similar in severity of neglect to the subjects who remained in the study; therefore, we estimated prevalence of persistent neglect among the 36 subjects who showed it initially using figures prorated from the rate of neglect among those actually tested on each occasion. We estimate that approximately 40% of those who initially met the criterion for neglect would continue to meet the criterion 6 months later, or that 60% would recover without outpatient treatment. These data suggest that much of the improvement described in the rehabilitation literature can be attributed to spontaneous recovery of function. When we have completed data collection on all subjects, we will use more sophisticated statistical techniques to estimate the rate of recovery from neglect.

We also obtained suggestive evidence that confrontation testing with simultaneous stimuli to both hemi-fields was more sensitive to hemi-neglect than were the paper-and-pencil measures. It may be that hemi-inattention deficits during parallel information processing tasks persist after deficits in serial information processing tasks have been resolved.

We are currently analyzing the data to identify early predictors of persistent neglect, to determine the relative sensitivity of various measures of neglect, and to evaluate the possibility of "confound" with educational level.

**Future Plans**—During the next year, we will address the following questions: 1) Is perceptual retraining effective in ameliorating the perceptual deficits in patients who continue to demonstrate hemi-neglect on paper-and-pencil tests one year post-stroke? 2) Is it effective in reducing the prevalence of persistent neglect in high-risk patients? 3) What proportion of patients with right hemisphere stroke manifest suppression during bilateral stimulation one year post-stroke? and, 4) What are the mechanisms underlying suppression during bilateral stimulation?

## [178] Expanding Loose Training Alternatives with Response Elaboration Training

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Sponsor: VA Rehabilitation Research and Development Service (Project #C384-RA)

**Purpose**—The primary purpose of this proposal is to develop and evaluate computerized versions of an aphasia treatment program (Response Elaboration Training [RET]) so that we can conduct controlled evaluations of stimulus and response parameters that affect generalization.

The following experimental questions will be investigated: What is the relative efficacy of RET and a didactic aphasia treatment program for facilitating an increase in the number of content words and novel content words produced by mildly to moderately impaired aphasic patients?

Will improvements generalize to and be maintained on: 1) untrained stimuli; 2) standard probes conducted with familiar individuals and untrained settings; 3) spontaneous speech; and, 4) standardized language measures?

What is the relative effectiveness of RET's minimal context presentation as compared to a contextual-animated stimulus presentation for facilitating generalized improvements in the verbal elaboration abilities of aphasic patients?

Does an RET format that restricts stimuli and patient response options to a controlled set of semantic relations (e.g., agent, action, etc.) facilitate generalized improvements in verbal elaboration abilities for aphasic patients?

**Progress**—Previous results have demonstrated that RET facilitates an increase in the amount and variety of informational content (e.g., content words) produced by aphasic patients. A moderate degree of generalization to stimuli, settings, and individuals has also occurred.

Extensive time series data have been collected and analyzed for 15 aphasic patients and social validation data have been collected for 10 matched normals. In an attempt to further examine the efficacy of RET, intervention was initiated to facilitate acquisition of an elaborated drawing system as a means of functional communication for nonverbal, aphasic-apraxic subjects. Subjects acquired the ability to spontaneously produce elaborate drawings in response to training stimuli and functional generalization probes.

**Methodology**—The effectiveness and generality of RET is being examined using single case experimental design. Variations of RET have served as the primary independent

variables and measures of informational content have been used as the primary dependent variables. The computerized variations of the RET protocol allow us to systematically alter stimulus parameters (e.g., context, auditory input, etc.), and response options (e.g., limited versus extensive choices).

**Preliminary Results**—For the present project, we have developed computerized RET animated treatment programs. The programs incorporate semiautomatic data collection for response accuracy and reaction time for patients' ability to name the treatment stimuli. Pilot data are being collected while the programs are being refined.

The results from four subjects provide preliminary data on the relative efficacy of RET and didactic aphasia programs. Across subjects, RET facilitates a greater amount of content than convergent, didactic programs for three of four sets of training items. Results of qualitative analysis of novel content also provide data supporting the relative benefits of RET in encouraging response variety. Maintenance of treatment effects is relatively equivalent for the two treatment types.

**Future Plans/Implications**—Computer analogues of RET will enhance our ability to manipulate stimulus and response parameters, permit examination of the effect of parameter changes on generalization, and facilitate comparisons of RET and traditional didactic aphasia treatment programs. In addition, computerization of the programs will facilitate the development and testing of RET treatment options for a wide range of aphasic patients and clinical problems. Future research will also examine the effect of "cognitive styles" of subjects on generalization and determine if targeting response variety and flexibility as a goal of intervention is more powerful than providing an opportunity for flexible responding.

### Recent Publications Resulting from This Research

Aphasia Complicated by Severe Visual Deficits. Kearns KP, Yedor K, in *Difficult Diagnoses in Adult Communication Disorders*, 101-113, N. Helm-Estabrooks, J. Aten (Eds.). Boston: College-Hill Press, Inc., 1989.

Methodologies for Studying Generalization. Kearns K, in *Generalization Strategies in the Treatment of Communication Disorders*, 13-30, J. Spradlin, L.V. McReynolds (Eds.). Toronto: B.C. Decker, Inc., 1989.

Broca's Aphasia. Kearns KP, in *Aphasia and Related Neurogenic Language Disorders*, 1-37, L.L. LaPointe (Ed.). New York: Thieme Medical Publishers, Inc., 1990.

An Alternating Treatments Comparison of Loose Training and A Convergent Treatment Strategy. Kearns KP, Yedor K, in *Clinical Aphasiology*. T.E. Prescott (Ed.). San Diego: College-Hill Press, Inc. (in press).

A Qualitative Analysis of Response Elaboration Training Effects. Gaddie A, Kearns KP, Yedor K, *Clinical Aphasiology*. San Diego: College-Hill Press, Inc. (in press).

## [179] Demonstrating the Efficacy of Memory Training

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**Sponsor:** VA Rehabilitation Research and Development Service (Project #F471-RA)

**Purpose**—This project is divided into two components, one involving development of a prosthetic memory device for individuals with severe organic amnesia, and the other for development of memory training computer-based instruction for individuals with milder forms of neurologically caused loss of ability to remember.

The specific purpose of the first component is to design, construct, and field-test a prosthetic memory device. The device will be programmable and portable, and will contain information regarding orientation, safety, and various activities of daily living (ADLs). The device is meant for patients with severe amnesia who have little if any recall of recent events. The subjects for the field-testing will be patients with organic amnesic disorder (Korsakoff's syndrome). The field trials will involve training these patients to use the device, and evaluating its utilization in daily living situations.

The second component involves development and testing of a series of training methods for improvement of memory. The three methods to be tested involve recall of lengthy lists of information, learning the names of new acquaintances, and recalling tasks. The methods will be computer-based and will largely involve imagery as a mnemonic aid. Subjects will be individuals with histories of closed head injury resulting in persistent amnesia.

**Progress**—The program has only recently been funded and initiated. The first year of its 3-year plan is devoted to development of instrumentation and software. These activities are in progress, and several preliminary programs have been written. "Mock-ups" of the prosthesis have been produced.

**Methodology**—The prosthesis will be developed based upon concepts derived from cognitive theory. The design of the instrument, its keyboard, its capability of analyz-

ing input and synthesizing output, and the manner in which the information is organized will be compatible with such theory and with what is known about the neuropsychology of patients with amnesia. The steps in the development process are: 1) design and synthesis of a prototype; 2) field trials with expert consultants and normal individuals for "debugging" purposes; and, 3) modifications and clinical trials with patients. There are two parts to this process, one to see if we can teach patients to remember to use the device, and the other to evaluate the extent of its use in natural environments.

The programs for the head-injury subjects are being written for a personal computer. They are based upon previous studies done in our laboratory, partly in non-computerized versions and partly on a newly designed program. Following preparation of the necessary materials, trials will commence with head-injured patients who are having persistent memory difficulties. Following a pretraining assessment, the patients are scheduled for a number of training sessions followed by a posttraining evaluation. There are three criteria for success: improvement during the course of the training, improvement on the posttraining evaluation (which utilizes different materials from those used in the training), and application of the training to ADLs in natural environments. The latter criterion will be accomplished through the application of functional assessments done by the trainees themselves and informants.

**Future Plans/Implications**—Data collection is planned for late in the second year and during the third year of the project. It would be premature to speculate on implications in the absence of data. However, if the prosthesis development is successful, it may be useful to substantially larger populations of individuals with memory problems, notably individuals with the dementing illnesses of old age.

## [180] Effects of Thermal Stimulation on Dysphagia After Stroke

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**Sponsor:** VA Rehabilitation Research and Development Service (Project #C485-RA)

**Purpose**—This project was designed to measure the effects of thermal stimulation on impaired swallowing following multiple strokes.

**Methodology**—Medically stable patients with clinical and imaging evidence of multiple cerebral vascular accidents (CVAs) and delay in the initiation of the pharyngeal response during liquid swallows, as confirmed by videofluoroscopy, were enrolled in this study. We used a modified withdrawal design with matched-subject pairs and replication across 20 subjects. After baseline neurologic and swallowing examinations, subjects were randomly assigned to either an ABAB or BABA pattern. "A" refers to a 5-day no-thermal stimulation phase. "B" refers to a 5-day thermal stimulation phase. Follow-up testing was done one month after subjects were discharged from the study.

Videofluoroscopic data were analyzed traditionally, and with a visual image processing program (Swallowing/Speech Interactive Image Processing Program (SIP). Inter- and intrajudge reliability were determined, and the clinical significance of changes in dependent variables were established by visual inspection of data displays.

**Results**—Twenty subjects have completed the experimental protocol. Data from the first seven subjects have been analyzed. Two of three judges agree that two of these seven subjects demonstrated decreased "duration of stage transition" with no change in aspiration or penetration. Overall, the data from all seven subjects fail to provide strong evidence that alternating patterns of thermal stimulation/no-thermal stimulation improve dysphagia following multiple strokes. Multiple replications are needed, and data from the next 13 subjects are being analyzed.

## [181] An Interactive Computer Program to Assess and Facilitate Cognitive Function in Head-Injured Young People

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**Sponsor:** Easter Seal Research Institute of Ontario; Apple Canada Ltd.; Hospital for Sick Children Foundation

**Purpose**—Our purpose was to develop and evaluate a microcomputer-based program for assessing and training language skills in cognitively impaired young people. Specific objectives include: 1) developing an interactive computer program for the assessment and remediation of cognitive-related language deficits in head-injured patients; and, 2) evaluating the effectiveness of this program for remediating the skill areas of attention, comprehension, memory and word retrieval, organization, and reasoning/problem-solving.

**Methodology**—Software was developed based on an "adventure-type" format. It incorporates the challenge, fantasy, and curiosity elements considered essential for motivated instruction. The software was developed on the Macintosh in HyperCard and utilized scanned artwork, animation, sound and voice output, and voice

input, using the Voice Navigator speech recognition system.

The program consists of two packages: a screening module, and a remediation module. The screening module was designed to provide an admission criteria for the program, and measure the progress (test/retest) achieved through the remediation program. The results are collected in a data file which includes information on whether the response is correct/incorrect, type of response given, number of cues required for task completion, response time per task, and the total time taken to complete the entire module. The response time information added to the quantitative results, and provides insight into the efficiency of cognitive processing.

There are four linked remediation modules: Shipwreck (attention); Fantasy (reasoning/problem-solving); Poser (comprehension/organization); and Cave-In

(memory/word retrieval). Each module focuses primarily on one skill area, although several tasks require the integration of more than one skill. Although the story line differs, the tasks from the remediation modules were designed to complement those in the assessment module. Each task has a database which contains five equivalent problems at three levels of difficulty. This means that no two games are alike, as a different task is presented in succeeding games. Clinical input was used to determine the appropriate difficulty level for each student through the initial set-up menu options. Similar data was collected as in the screening module.

During the second year of the project, the program was to be pilot-tested with adolescents who are recovering from closed head injury accidents. An A, A', B within-subject design was employed so that subjects were their own controls. A standardized assessment battery was administered to establish a baseline measure. The battery was readministered 12 weeks later to measure the extent of spontaneous recovery. Results from the standardized assessment battery were compared with those obtained from the screening module of the software. A 12-week remediation program followed. Upon completion of the remediation program, a third test session was employed to evaluate the effectiveness of the training.

**Results**—The software was evaluated with three closed head-injured adolescents who were between 4-6 months

postinjury. Subject rankings were obtained from the screening module and compared to the standardized assessment battery. Rankings for subjects were identical, indicating that the program has preliminary face validity. Subjects' initial screening assessment results ranged from 25 to 55% correct, which indicates that task difficulty is appropriate, showing neither floor or ceiling effects. Responses were designed to minimize correct choices made by chance selection.

All three subjects reported that the program was both interesting and challenging. Preliminary results indicate that the remediation program was effective when validated by the standardized tests. One of the most sensitive indicators of recovery was processing time. The screening module demonstrated that processing time had decreased substantially following the computer-based remediation.

**Future Plans**—A future study with larger numbers of adolescents who have had head injuries is planned to assist with further development of the program.

#### **Recent Publications Resulting from This Research**

An Interactive Computer Program to Assess and Facilitate Cognitive Function in Young People with Head-Injuries. Johnson PC, Thomas-Stonell N, in Proceedings of the 3rd Annual Conference on Cognitive Rehabilitation, Clearwater, FL, 454, 1989.  
Computer-Based Assessment and Training of Cognitive Skills in Young People with Head-Injuries. Johnson P et al., Minds in Motion (in press).

### **[182] Substance Abuse Prevention Programming for Patients Incurring Traumatic Injury**

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**Sponsor:** *J.M. Foundation*

**Purpose**—A training program for rehabilitation staff on substance abuse prevention will be established as a service to the Rehabilitation Institute of Chicago's traumatic brain injury (TBI) and spinal cord injury (SCI) program, and curricula will be developed for dissemination to other rehabilitation programs. With the assistance of the Illinois Prevention Resource Center,

a non-profit, state-funded alcohol and drug abuse prevention center, this program will develop staff training materials regarding substance abuse prevention services to patients. These services will include curriculum development, patient and family education, staff training, and information dissemination to other care providers.

## [183] Quantification of Motor Coordination of the Lower Limb in Normal and Hemiparetic Subjects

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Sponsor: Medical Research Council of Canada; Fonds de la Recherche en Santé du Québec; Department of Health and Welfare, Canada

**Purpose**—A dynamometer measuring static torques exerted simultaneously in different planes of motion at the hip and at the knee (flexion/extension, abduction/adduction, internal/external rotation, and flexion/extension respectively) was developed. To date, we have used this apparatus in a task-control situation with 22 normal subjects and 14 hemiparetic subjects to quantify and compare torque and muscle activation patterns occurring at the lower extremity.

**Methodology**—Subjects are seated with their lower limbs secured to two dynamometers. Strain gauges on the dynamometers are interfaced with a desktop computer used to calculate torque in real-time and to collect data. A video monitor is used to display the direction and magnitude of the subject's effort. During the experiment, hemiparetic subjects are asked to successively perform specific efforts (flexion and extension of the hip and the knee), and combined efforts (flexion/abduction, flexion/adduction, extension/abduction, and extension/adduction of the hip with or without feedback regarding torques in internal/external rotation of the hip) at approximately 2.5, 5, 10 and 15% of their maximal voluntary contraction (MVC). For normal subjects, efforts were exerted at 5, 10, 15 and 30% of the MVC. Associated torque at the hip and knee joints were measured during each effort. Electromyographic activities in different muscles of the lower limb (vastus lateralis, rectus femoris, biceps femoris, gracilis, gluteus medius, gluteus maximus, tibialis anterior, and soleus) were recorded concurrently with surface electrodes. In addition, motor and functional performances of hemiparetic subjects were evaluated using different clinical tests.

**Progress**—The directional specificity of muscle activation was unchanged in the hemiparetic lower limb as compared to normals. However, the level of electromyographic activity of some muscle groups (e.g., erector femoris), was greater in the hemiparetic subjects. These results differ with the changes observed in directional specificity reported for paretic muscles of the upper limb, suggesting that weakness tends to be more pronounced in the lower limbs of hemiparetic subjects.

**Future Plans**—The apparatus developed can now be used in different electromyographic, biomechanical, and clinical studies. Eventually, it will be possible to evaluate the described methodology as an evaluation tool or as a treatment modality in clinical studies of stroke patients.

### Recent Publications Resulting from This Research

- Abnormal Patterns of Elbow Muscle Activation in Hemiparetic Subjects. Bourbonnais D et al., *Brain* 112:85-102, 1989.
- Ipsilateral Associated Torques Measured During Static Effort at a Single Joint of the Lower Limb in Normal Subjects (Abstract). Bourbonnais D et al., presented at the Annual Meeting of the Society for Neuroscience, 1989.
- A Reliability and Validity Study of a Multi-Directional Dynamometer (Abstract). Gauthier J et al., presented at the 6th Biennial Conference of the Canadian Society for Biomechanics, 1989.
- Quantification of Electromyographic Activities Using Circular Statistics (Abstract). Bourbonnais D et al., presented at the Annual Meeting of the Society for Neuroscience, 1990.
- A Dynamometer Measuring Torques Exerted Statically at the Hip and Knee (Abstract). Bourbonnais D et al., presented at the 13th Annual Meeting of the American Society for Biomechanics (in press).

**[184] Pediatric Trauma Registry**

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*Sponsor: National Institute on Disability and Rehabilitation Research*

**Purpose**—The National Pediatric Trauma Registry (NPTR) is a multi-institutional database managed by the Department of Rehabilitation Medicine at Tufts/New England Medical Center in Boston. The NPTR's emphasis is on how circumstances of traumatic events and acute management of the injured patient affect resulting morbidity and mortality.

**Progress**—With the support of the American Pediatric Surgical Association Trauma Committee, 53 national centers for pediatric trauma care participate in the data collection effort. Phase 1 (1985-1988) of the PTR contains over 14,000 cases. Phase 2 (October 1988 to present) currently contains over 9,000 cases. By merging Phase 1 and Phase 2 databanks, the project is in charge of one of the most extensive data collection efforts on pediatric injuries in the country. The yearly rate of accumulation is in the order of 6,000 to 7,000 cases, and is expected to increase with the increased demand for participation.

This database allows conduction of several studies designed to evaluate the efficacy of medical and rehabilitative intervention while also accumulating information needed to develop injury prevention programs and activities. The findings from these studies are used to recommend clinical strategies for health professionals and to provide information to policy makers and organizations advocating injury prevention.

**Methodology**—All injuries to children up to 20 years of age that are traffic-related (i.e., motor vehicle, pedestrian, bicycle, motorcycle, and all-terrain-vehicle), gun-related, caused by falls, stabbing, beating, child abuse, etc., that are treated at the 53 participating institutions are included

in the Registry with the following exceptions: 1) children pronounced dead at the scene, since they are brought directly to the morgue; and, 2) children seen in the emergency room and treated thereafter on an out-patient basis.

The NPTR data collection form is completed by a Trauma Coordinator at the participating institution. These forms are then forwarded to the Department of Rehabilitation Medicine at Tufts/New England Medical Center for coding, verification, and data entry.

**Results**—Twice a year, in April and October, the Registry generates statistical and graphical reports about the entire data collection, and about data contributed by each institution, for the participants and other interested professionals. Retrieval of information and statistical analyses are also performed upon request.

Falls are the single most common cause of injury in children. However, when combined, traffic-related injuries are the most common cause of injury, especially in the 16-20 year age group.

#### **Recent Publications Resulting from This Research**

- Inter-Rater Reliability of the Injury Severity Score as Applied to the Pediatric Trauma Patient. Tepas JJ et al., Proceedings of the American Association for the Advancement of Automotive Medicine, 1989.
- National Pediatric Trauma Registry. Tepas JJ et al., J Pediatr Surg 24(1), 1989.
- Mortality of Head Injury: The Pediatric Perspective. Tepas JJ et al., J Pediatr Surg 25(1), 1990.
- Utilization of Inpatient Rehabilitation Services Among Traumatically Injured Children Discharged from Pediatric Trauma Centers. Osberg S, DiScala C, Gans B, Am J Phys Med Rehabil 69(2):67-72, 1990.

## [185] Trauma Center Impact on the Disability Outcomes of Brain and Spinal Cord Injured Survivors

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*Sponsor: National Institute on Disability and Rehabilitation Research*

**Purpose**—This study examines the extent to which trauma centers are altering the severity and prevalence of disability from traumatic brain and spinal cord injury, and how these changes affect the need for medical rehabilitation and various long-term care services. The study involves about 400 traumatic injury survivors from three level-1 trauma centers, located at the Washington Hospital Center in Washington, DC; the University of California, San Diego; and the University of California, Davis, in Sacramento.

The study will: 1) determine how the probability of survival has changed over time; 2) ascertain the long-term outcomes (up to 5 years) of trauma center survivors; 3) determine the extent of rehabilitation utilization; and, 4) evaluate how injury acuity (e.g., as measured by the Revised Trauma Score) relates to long-term outcome (e.g., as measured by various components of the Sickness Impact Profile).

**Methodology**—In this study, patients in three major trauma centers who experienced serious head and spinal cord injury during the period 1984-1988 were mailed questionnaires which solicited information on their physical status, rehabilitation experience, and general outcomes since their injury. These data have been combined with trauma data for each patient from the Major Trauma Outcome Study (MTOS), a multi-institutional trauma database sponsored by the American College of Surgeons. Combining these two data sources for the same patients

enables linking trauma acuity data with long-term outcome data for each patient.

**Progress**—To date, approximately 1,542 letters were mailed to potential respondents. Of this number, 466 persons consented to participate in the study. Questionnaires were mailed to these persons, and 376 questionnaires have been returned to date. Data from the questionnaires have been entered into the study database, and the process of merging questionnaire data and data from MTOS is ongoing. The data-merging process was completed during the Fall of 1990.

**Future Plans**—The data will be analyzed, focusing on the interrelationship between injury severity, use of rehabilitation services, and functional outcome. This analysis will include an assessment of how injury severity and the receipt of rehabilitation services affect long-term outcomes. The study will also investigate the ability of three injury severity measures (the revised trauma score, the injury severity score, and the trauma score) to predict receipt of rehabilitation, and to predict functional outcome.

**Implications**—The results of this study will have implications for: 1) knowing how injury severity maps into long-term functional status; 2) identifying appropriate candidates for rehabilitation; and, 3) understanding the impact of trauma care on the need for rehabilitation and other long-term care services.

## [186] Studies of Spasticity in Brain Injured Patients

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose/Methodology**—The goal of the proposed grant is to objectively test the effectiveness of intrathecal baclofen for spasticity. Patients with spasticity that significantly interferes with motor function or causes painful spasms will be screened with injections of intrathecal baclofen. If they respond, a programmable drug pump

will be implanted to give the medicine chronically. The dose levels needed to control painful spasms, clonus, and rigidity will be determined. Voluntary control, if present, will be tested in the Motor Control Laboratory. Once the optimal dosage has been selected, the patient will receive the drug continuously. Quantitative studies of motor

function, as well as activities of daily living, will be assessed at regular intervals. The prospective study will provide information about the long-term efficacy, as well as the risks of the procedure.

A secondary goal will be to relate decreases in rigidity, hyperactive reflexes, and clonus to voluntary

control. The basic question is whether a reduction in the signs of spasticity necessarily means that voluntary control will improve. If voluntary control does improve, what signs are most predictive, and can these measurements be used to select patients who will respond best to treatment?

### [187] Functional Recovery After Focal Cortical Injury (Monkeys)

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**Sponsor:** *National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—Using recently described quantitative techniques, we documented severe metabolic brain dysfunction far distant from surgically placed lesions in the association cortex of monkeys. Two (frontal and parietal) hemisensory neglect syndromes were documented using behavioral testing. Symptoms correlated in time with metabolic anatomically intact foci of glucose hypometabolism, not structural damage *per se*. Further, neglect animals' behavioral data point to moment-to-moment neural activity changes related to conditions of stimulus presentation. A definitive explanation for neglect symptoms is thus offered for the first time.

**Methodology**—We propose to further test and expand our original findings using methods previously validated in this laboratory, including: 1)  $^{14}\text{C}$ -2-deoxyglucose autoradiography (2DG) to determine quantitative local cerebral glucose utilization (LGU), as an indicator of regional neural activity; 2) operative unilateral lesions that reproducibly induce neglect and other symptoms; and, 3) quantitative behavioral measures of neglect symptoms and their recovery. We will add computer-assisted densitometry and image analysis to improve accuracy of

the LGU measure and computer control of behavioral tests to allow a measurement of orienting efficiency. These methods will be used in experiments to: 1) vary neglect symptoms *vis-a-vis* distant metabolic dysfunction in frontal and parietal animals (e.g., neglect animals infused with 2DG while performing symmetrical motor activity will be sacrificed and the distribution of label compared with the distribution in previously studied nonperforming operated animals); and, 2) determine if other operative lesions outside frontal and parietal association cortex are accompanied by distant metabolic effects and if there are behavioral changes that correlate with them (e.g., we will make unilateral superior colliculus (SC) lesions, and sacrifice with 2DG acutely, and after spontaneous recovery in resting alert monkeys).

**Implications**—These primate model studies will advance understanding of the distant metabolic effects of focal cerebral damage, and will provide direct correlates for diagnosis and management of human stroke patients, in whom recovery is often impeded by neglect and other higher cortical function deficits.

### [188] Cognitive-Linguistic Mechanisms in Writing Disorders

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**Sponsor:** *National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—The long-term objective of this project is to characterize the cognitive and linguistic mechanisms that underlie the spelling (writing) process, and the ways in which this process may be disrupted as a consequence of brain damage. The specific aims of the project are to:

1) evaluate the hypothesis that specific forms of spelling dysfunction (dysgraphia) result from damage to distinct components of the spelling process; and, 2) characterize in detail the internal structure of the components assumed to comprise the spelling system, thereby providing a basis

for a deeper understanding of the various forms of spelling disorders found in brain-damaged patients.

**Methodology**—These aims will be accomplished through a two-phase program of research. In the first phase, a large number of patients with focal brain damage will be tested with a spelling test battery specially designed to distinguish among various types of spelling disorders. Patients' performance on the test battery will be used to: 1) evaluate models of the spelling process; and, 2) define subgroups of patients with selective deficits to various components of the spelling process. In the second phase, patients with selective deficit to particular processing components (e.g., the component that stores knowledge of the orthographic structure of words) will be tested with sets of experimental tasks designed to probe in considerable detail the structure of the various components involved in spelling. Information generated from the detailed analyses in this phase of the project will be used to: 1) revise the test battery to better discriminate among

different types of spelling disorders; and, 2) evaluate specific hypotheses about the internal structure of particular components of processing.

Another major component of the proposed research involves the use of computational modeling techniques. This aspect of the proposed research will allow the formulation of a computationally explicit model of the spelling process, and the stimulation of spelling disorders by the "experimental lesioning" of the implemented model. Finally, the detailed characterization of spelling disorders in terms of damage to specific components of the cognitive/linguistic mechanisms that underlie spelling will be used to explore correlations between locus of brain damage and type of functional disorder.

**Implications**—The results of the proposed studies will contribute to a deeper understanding of the basis for spelling disorders in brain-damaged patients—an indispensable foundation for the diagnosis and remediation of dysgraphia.

## [189] Stroke Clinical Center

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—The major thrust of this project (primarily demographic in nature), is to assess the community profile of strokes for the state of Oregon. Our investigations emphasize therapies focused upon stroke patients in three broad areas of importance: 1) preventive therapy; 2) acute medical treatments; and, 3) rehabilitation intervention for higher cortical impairment.

**Methodology**—Preventive therapies are designed to assess various risk and prognostic factors in stroke patients to develop better molecular handles on both acute therapy and prevention. Factors which may yield to

better identification and therapy of risks are: mononuclear cell cholesterol ester hydrolase activity; glycosylated hemoglobin; cholesterol turnover in arteromatous plaques; and physicochemical bases for platelet behavior in stroke. Acute medical treatments focus initially upon the potentially beneficial assessment of prostacyclin infusion. In addition, staged, sequential evaluation of aminophylline/barbiturate and vasopressors will be continued in a prospective, randomized fashion. Rehabilitative intervention for higher cortical impairment deals with neuropsychological and language impairments with compensatory learning strategies.

## [190] Hemispheric Specialization in Stroke Patients (Human)

**Dahlia W. Zaidel**

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose/Methodology**—Five experiments are proposed to investigate the hemispheric nature of long-term semantic

memory (LTSM). The experiments are designed for three subject populations: 1) stroke patients with unilateral

focal lesions; 2) (complete) commissurotomy patients; and, 3) normal subjects. The stimuli are pictorial and the responses are also nonverbal. The experiments measure the semantics of complex pictorial scenes, pictures of individual natural objects, artificial pictorial concepts, and logically defined concepts, as follows: 1) test memory for scenes, when the scenes have normal organization with respect to everyday life, such as familiar schemata (organized), lack organization, such as randomly juxtaposed objects (unorganized), or violate coherence by portraying parts of two conflicting schemata in the same picture (incongruous); 2) determine "mental distances" among concepts of natural superordinate categories with typicality levels of common objects serving as the guideposts; 3) study formation of "prototypical" concepts with the use of artificial (random-dot patterns) categories; 4) investigate the validity of the hypothesis

that the left hemisphere uses a logic-bound classificatory system, and that the right uses an experience-bound system for all concepts alike by the use of logically defined categories (e.g., odd number). Characterizing the mechanisms of functional asymmetries in the human brain is important for both basic scientific research and medical practice. Unilateral stroke, tumor, or missile wounds can cause devastating language, cognitive and memory disorders, and treatment for such impairments can improve only with increased understanding of hemispheric specialization.

**Implications**—The experiments proposed here should help gain direct insight into hemispheric mechanisms of a fundamental central processing module, namely, the conceptual system, LTSM, which plays a central role in modern cognitive scientific research.

## [191] Treatment of Affective Deficits in Stroke Rehabilitation

**Wayne A. Gordon**

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—Poststroke affective disturbances are pervasive (i.e., they affect anywhere from 40 to 65% of stroke patients). The diagnosis and treatment of these disturbances in stroke patients is a major untreated problem facing the medical rehabilitation community. Traditional approaches to diagnosis which have relied exclusively on verbal self-report or nonverbal expressions of depression have not adequately addressed either the communication difficulties of aphasics or some of the other cognitive disturbances (i.e., aprosody, minimization, concrete thinking), which limit the cognitive capacities of stroke patients. Furthermore, the effectiveness of various approaches to treatment has not been systematically studied in this population.

The aims of this study are twofold. The first aim is to validate a comprehensive diagnostic battery which permits an accurate examination of the affective disorders following stroke; the second is to evaluate the effectiveness of two approaches to treatment: antidepressants and cognitive therapy, when administered singly or in combination.

**Implications**—It is expected that greater accuracy in diagnosis and more aggressive treatment will significantly improve the quality of life of this subgroup of older Americans.

## [192] Neural Basis of Motor Behavior

**Howard Poizner**

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—This proposal investigates the nature of the neural basis of motor behavior as a special window into higher brain functions. In this investigation, we link

sophisticated three-dimensional (3-D) computergraphic analyses of movement with experiments that allow us to infer underlying motor control processes performed

under conditions of failure of specific motor systems. All of the experiments that follow proceed from this unique vantage point and should mark a significant advance in our understanding of brain function for motor behavior.

**Methodology**—Five experiments are proposed that investigate performance of patients with damage to three central motor systems of the brain. *Neural Basis of Motor Planning and Control Experiments 1-3* study the neural basis of motor planning and control, beginning with the possible breakdown of a motor law, moving to the spatial control of hand trajectories, and finally to underlying brain processes for complex movements. *Neural Basis of*

*Motor Equivalence Experiment 4* investigates the neural basis of a process of motor control integral to the production of speech as well as control of the limbs, that of motor equivalence. *Interplay Between Linguistic and Motor Behavior Experiment 5* begins the investigation of the interplay between neural control processes for linguistic and for motor behavior, from the study of a motor disorder in deaf signers.

**Implications**—These 3-D computergraphic analyses of movement should not only advance our understanding of the neural basis of motor behavior, but should also serve as a useful tool in evaluating diseases which affect the motor systems of the brain.

### [193] Reduced CNS Injury and Improved Recovery with Gangliosides

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**Sponsor:** *National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose/Preliminary Results**—This proposal focuses studies on the acute effects of GM<sub>1</sub> ganglioside on central nervous system (CNS) injury processes in stroke. We have already found that ganglioside injections can decrease functional deficits and reduce mortality within 24 to 48 hours in rats that sustained substantial brain ablations. Subsequently, we found that ganglioside treatment limited cerebral edema, and reduced associated losses of CNS membrane, Na,K-ATPase activity, and intracellular K<sup>+</sup> following cerebral trauma, as well as after denervation of subcortical regions. We have hypothesized that gangliosides reduce the extent of local CNS damage at the time of injury by preventing membrane failure, subsequent cell loss, and fiber degeneration. By limiting the extent of CNS tissue damage at the time of injury, conditions may be optimized for CNS regeneration and functional recovery. Most recently, we have begun studying the effects of ganglioside treatment on ischemia. Completed studies show that, after 48 hours, ganglioside treatment of gerbils with global ischemia results in a 48% decrease in mortality and protection from associated losses of membrane Na,K-ATPase activity. Using the rat model of focal cerebral ischemia (MCAo), this study examines in greater detail the

phenomena and molecular mechanisms by which gangliosides reduce pathological membrane events associated with CNS injury, and whether such acute effects result in reduced functional losses. In order to determine whether ganglioside treatment reduces functional losses immediately (1-72 hours) after the induction of ischemia, rats will be assessed on behavioral tests sensitive to cortical parietal damage (locus of primary infarct). Using light microscopy and tissue analyses, *in vivo* localization of (H3)GM<sub>1</sub> ganglioside will provide morphological evidence indicating where the CNS locus of action for these injected glycolipids might be. *In vivo* analyses of membrane components (ATPases and membrane fatty acids), and ions, which undergo changes during ischemia, will be assayed to focus on processes in the pathophysiology of membrane events associated with stroke and how these are affected by GM<sub>1</sub> treatment.

**Implications**—Studying these membrane events as a function of time will indicate whether the treatment prevents further spread of the ischemic damage. Aside from the therapeutic clinical implications, this study will provide insight into ischemic injury processes and the mechanisms by which ganglioside treatment is effective.

**[194] Information Extraction from Peripheral Nerves**

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—This work is directed toward providing better rehabilitation for people suffering from somatosensory loss and paralysis due to spinal cord injury, head trauma, or stroke. The goal of this project is to demonstrate that information suitable for controlling prosthetic devices, modulating functional electrical stimulation of muscle, and providing a sense of touch and position from areas of the body suffering sensory loss can be extracted, on-line and in real time, from recordings of sensory activity in peripheral nerves.

**Methodology**—This will be done by developing software that digitizes action potentials from multiunit recordings of peripheral nerve activity made with implanted intrafascicular electrodes; creating templates of the measured characteristics for identified single units; generating a decision tree that allows rapid

assignment of an action potential to one of the templates or to a “not identified” category; and measuring the distribution of activity among the set of identified units from recordings made during natural stimulation. Once this is completed, a prototype hardware system that can perform this analysis on-line in real time will be built.

**Implications**—While the thrust of this work is directed toward developing a microprocessor-based instrument capable of providing sensory feedback for controlling movement of hands and limbs in paralyzed patients, or for controlling stimulation of intact sensory systems to provide proprioceptive and tactile sensations from insensate regions, such a system would also be useful in research on the encoding and processing of sensory information by the nervous system.

**[195] Brain-Injury Memory Disorders Research Center**

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—This program proposal seeks support for a Memory Disorders Research Center dedicated to the study of the information-processing deficits underlying memory disturbances of individuals suffering brain injury or disease. These investigations will utilize contemporary research techniques and instrumentation to explore the on-line processing impairments of amnesic patients. This will permit greater understanding of the memory process, and will provide a basis for differential assessment and therapy.

**Methodology**—Four independent, yet interrelated projects are proposed. The first (Issues) focuses on unresolved issues of amnesia including an analysis of the relative contributions of episodic and semantic memory to implicit priming; compilation and organizational aspects of procedural learning; reconstruction and familiarity as aspects of contextual learning; and finally, factors underlying remote memory disturbances. The

second component (Case Studies) seeks to describe unique individual cases of amnesia both from a clinical and issue-driven experimental point of view. Alcoholic Korsakoff, postencephalitic, anoxic, bilateral temporal, retrosplenial, and selective stroke patients will be assessed for their dissociative memory abilities and disabilities. The third component (Neuroanatomy) explores the neuroanatomy of amnesia using neuroimaging techniques such as MRI and CAT scans. This will culminate in a greater understanding of the neural systems underlying memory and information processing. The fourth component (Assessment and Therapy) will develop an assessment battery to permit the differential diagnosis of amnesic patients along many of the dimensions explored in the Issues Component of this proposal. This assessment will then provide a basis for therapeutic attempts with some of these amnesic individuals.

The entire Center will be administered, organized, and monitored through the development of a Core

administration depicted in the fifth, and final component of this program project; including administrative assistance, secretarial support, consults, and educational opportunities. The entire program will thus

bring together research from otherwise diverse, and often disparate areas of investigation to explore the behavioral, cognitive, and neural underpinnings of amnesia.

## [196] Ultra-Early Evaluation of Intracerebral Hemorrhage

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—Spontaneous intracerebral hemorrhage (ICH) is a major public health problem, involving approximately 31,500 Americans yearly and resulting in more than 15,000 deaths. Approximately 1 of 10 strokes is an ICH. Benefit has not been established for any specific medical or surgical therapy. In an ongoing study of hyperacute therapy for cerebral infarction using tissue plasminogen activator, 20% of the patients arriving for care within 60 minutes of symptom onset have been excluded because of ICH. Active intracerebral bleeding was documented for two of these patients; for one patient, the active bleeding preceded clinical deterioration. These two cases, plus three other cases of documented active bleeding, prompted the investigators to review prior studies regarding the temporal profile of continued bleeding in the setting of spontaneous intracerebral hemorrhage.

Unfortunately, this question has not been appropriately addressed. If active bleeding continues for 1 to 6 hours following onset of spontaneous intracerebral hemorrhage, there may exist a “therapeutic window” during which therapeutic maneuvers such as blood pressure adjustment, administration of antifibrino-

lytic therapy, or ultra-early surgical evaluation may hold promise.

The primary study objectives are to determine: 1) the percentage of patients with ICH who have computerized tomography (CT) evidence of continued bleeding during the first hours after onset; and, 2) whether CT evidence of continued bleeding correlates with early clinical deterioration.

**Methodology**—We propose performing hyperacute evaluation of all stroke patients with CT within 3 hours of symptom onset. They will be examined at that time with a standard neurological examination. The CT scan will be repeated twice: once immediately after the first is completed, and again at 24 hours after initial symptom onset. The neurological examination will also be repeated at those times. Data will be gathered on each blood pressure measurement. Fifty-two patients will be studied over a 30-month period. Patients who expire will be examined at postmortem to determine the primary diagnosis and to determine, if possible, the reason for hemorrhage growth (if active in-hospital bleeding has been documented prior to death).

## [197] Individualized Memory Prosthetic Device

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—Approximately 500,000 persons suffer a traumatic brain injury (TBI) each year, with total annual costs estimated to reach \$4 billion. A large portion of TBI patients are left with permanent memory or other neurobehavioral deficits. The “Individualized Memory Prosthetic Device” (IMPD) will provide both rehabilitative treatment and long-term

cognitive support functions for patients who have experienced a TBI.

**Methodology/Implications**—The IMPD is based on a hand-held computer which prompts the patient in real time for the initiation and completion of tasks. The IMPD software is flexibly “data-driven” by a downloaded

therapist's prescription, and contains clock, calendar, alarm, and two-way communication functions to support cueing, monitoring, and reinforcement of patient behaviors. Therapist desktop software has been designed for the assessment and programming of the patient's IMPD-assisted therapy.

The perfected IMPD system will have immediate and direct applicability to other large clinical populations

suffering cognitive deficits induced by stroke, Alzheimer's disease, and other dementias. Additionally, the IMPD could be employed in normal populations for time management, habit training, other forms of behavior therapy, and as a "people meter," for use in both medical and marketing research.

## [198] Reversible Focal Cerebral Ischemia

**Warren Richard Selman**

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—Reperfusion of ischemic tissues is presently thought to be potentially useful in the treatment of focal stroke. Pharmacologically- or surgically-induced reflow, however, might trigger another series of events more deleterious than those for persisting ischemia. The overall objective of this proposal is to determine the benefits of reperfusion as a function of ischemic duration and proximity of the tissue to the ischemic focus.

**Methodology**—The rat model of temporary middle cerebral artery (MCA) occlusion emulates the clinical manifestations of focal stroke, and is amenable to studies which will evaluate the viability of the focal and perifocal regions during reperfusion, after increasing periods of ischemia. Such studies will delineate the time threshold for irreversible damage not only in the ischemic core, but also in the perifocal region.

The focus of these studies is to evaluate the metabolic viability of the affected regions after varying periods of ischemia. Experience has shown that the different regions of the brain affected by MCA occlusion are relatively small. Microquantitative histochemistry resolves this problem by increasing our sampling precision of the

perifocal, focal, and normal tissue regions. Such a strategy, however, requires supporting techniques to identify the regions of interest, and to that end, autoradiograms from quantitative cerebral blood flow measurements are a guide to dissection of lyophilized tissue. Administration of C-2-deoxyglucose during ischemia delineates the site of the original ischemic focus. Routine histological studies are planned and electrophysiology performed when required to complement the metabolic data.

**Preliminary Results/Implications**—Preliminary studies with proton magnetic resonance imaging indicate that this noninvasive procedure provides a natural history of edema formation and resolution, and the metabolic correlates to these changes will be determined. The clinical management of an acute ischemic insult to the brain remains problematic. Until the events leading up to death or infarction are established in focal ischemia, little insight can be gained on how to improve therapy.

The proposed study will provide new information on the recovery process in the focal and perifocal regions, if they differ, and whether unique forms of intervention should be tried to improve the safety of reperfusion.

## [199] Quantitative Histopathology of Multifocal Cerebral Ischemia

**Patrick Lyden**

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—Stroke is the third leading cause of death in the United States, and the primary cause of neurologic morbidity. Vascular causes of dementia are the second

most common cause of dementia in elderly Americans. No specific therapy currently exists for either stroke or cerebral vascular dementia. The failure to develop

effective therapy for these diseases may be partially the result of the absence of a reproducible animal model of this type of cerebral vascular disease.

**Methodology/Implications**—We have developed new animal models that allow for the rapid and inexpensive testing of new drugs that may be effective in the treatment of cerebral vascular disease. We propose to extend our previous observations by refining a method for the quantitative analysis of the histopathologic consequences of

multifocal cerebral ischemia on behavior (learning). We hypothesize that learning behavior will change in a measurable way depending on the topographic distributions of lesions following ischemia, and that these observations will be altered by pharmacologic therapy.

These methods will allow us to screen new drugs for their potential benefit in the treatment of victims of stroke or vascular dementia, and will provide insights into the mechanisms underlying the dementia apparent in many patients with vascular lesions.

## [200] Neurotransmitter Release: Role in Ischemic Injury

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**Sponsor:** *National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—The major goal of this project is to explore the role of dopamine (DA) in the development of ischemic neuronal damage in the dorsolateral striatum. We hypothesize that ischemia-induced release of specific neurotransmitters and/or neuromodulators (i.e., DA) to the extracellular fluid is essential for the development of ischemic neuronal damage in vulnerable brain regions (i.e., striatum). The protective effect of substantia nigra (SN) lesion might be associated with the inhibition of DA release during ischemia.

**Methodology/Implications**—Using the microdialysis technique, we will document the effects of specific striatal deafferentation, and a nonspecific lesion near the SN on extracellular levels of DA in the medioventral and dorsolateral striatum, during and after transient global ischemia. We will then determine whether attenuation of ischemia-induced neuronal injury in the dorsolateral striatum is specific to dopaminergic deafferentation, or can be reproduced by other lesions. Since the susceptibility of the striatum may be associated with post-ischemic uncoupling of blood flow and metabolism, we will evaluate, by autoradiographic strategies, changes in local cerebral blood flow and glucose metabolism induced by transient global ischemia, and determine

whether they can be affected by specific and nonspecific pathway lesions.

Further studies will be performed to characterize the specificity of the protective effect of the SN lesions by evaluating its time-course, and its effects on glial cell activity in the striatum. In attempting to develop a novel pharmacological paradigm for treatment of stroke, we will evaluate whether post-ischemic neuronal injury can be attenuated by pharmacological modulation directed toward: 1) the depletion of DA; or, 2) inhibiting specific DA receptor.

We hypothesize that such a pharmacological modifier might attenuate ischemic damage, and could lead to an appropriate therapeutic strategy in the treatment of brain ischemia. A related issue stems from our recent finding demonstrating that acute and massive release of extracellular norepinephrine (NE) occurs in the hippocampus during ischemia. We will explore the role of NE in the development of delayed neuronal damage in the hippocampus by evaluating the effects of locus coeruleus lesions and pharmacological modulation of NE activity on the development of morphological and biochemical measures of ischemia in the hippocampus. We hypothesize that increasing NE activity may prove to be beneficial in delaying or ameliorating hippocampal neuronal damage.

**[201] 1989 Gordon Research Conference on Neural Plasticity****Carla Shatz**

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—The Gordon Research Conference on Neural Plasticity has been held every alternate year since 1977 at Brewster Academy, Wolfeboro, NH. Gordon Research Conferences (GRC) were established to stimulate ideas in an informal setting. Uninhibited discussion is fostered by GRC strictures on the publications, proceedings, or indeed the citation of presentations.

The format has proved particularly useful in the Conference on Neural Plasticity—a highly interdisciplinary meeting in which the subject of modifiability of the nervous system is examined at the molecular, cellular, and systems levels, and in which the participants come from broadly different backgrounds (biochemical, pharmacological, anatomical, electrophysiological, and behavioral). One evening is set aside for a keynote speaker

and poster session. The remaining eight sessions will focus on specific issues, with three or four scheduled speakers, so that significant time is preserved for discussion. The discussion tends to continue informally during the afternoon, when no formal sessions are scheduled.

It is the experience of participants that these informal interactions are often more fruitful than the extended sessions characteristic of other meetings. The formal program includes sessions on: cellular and molecular models of learning, learning in the adult cerebral cortex, genetic and hormonal models of neural development and plasticity, regulation of neuronal receptors, oncogenes and neural plasticity, neural grafting, NMDA receptors and long-term potentiation, and the role of ion channels in neural plasticity.

**[202] PET Study of Biochemistry and Metabolism of the CNS****David E. Kuhl**

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—A Positron Emission Tomography (PET) Facility has been established at the University of Michigan for the development of a new, noninvasive approach to human brain research utilizing positron-emitting metabolic and pharmacologic probes. A dedicated TCC CS-30 medical cyclotron, a TCC PCT-4600A tomographic scanner, the radiochemical/radiopharmaceutical facilities, and a small image-processing computer facility will be used in the performance of PET studies and complement the existing Nuclear Medicine facilities.

**Methodology**—Proposed studies involve the use of positron-emitting probes 15-0-C0, 15-0-H20, 15-0-02, 18-F-2-deoxyglucose, 11-C-BCNU, 68-Ga-EDTA, and 11-C-scopolamine to study cerebral blood volume, blood flow and partition coefficients, oxygen utilization,

glucose utilization, tumor uptake, blood-brain barrier integrity, and muscarinic receptors respectively. Patients with Huntington's disease, epilepsy, brain tumors, the hypotonic and hypertonic phases of paralysis associated with stroke, dystonia, olivopontocerebellar atrophy, and aging in the human brain will also be studied. Studies of the normal brain with several agents will continue. New positron-emitting radiopharmaceuticals will be synthesized, and new labeling techniques will be investigated. 11-C-scopolamine will be available for high specific activity *in vivo* receptor studies, and 11-C-amine cyclopentane carbocyclic acid (ACPC) will be developed for amino acid uptake studies. New physiological modeling techniques will be instituted for mapping receptor sites. Parameter estimation techniques will be developed to determine rate constants from dynamic PET studies of FDG metabolism.

### [203] Cerebral Ischemia, Viability and Oxidative Metabolism

**Myron Rosenthal**

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—Our overall goal is to utilize intracellular indicators of oxidative metabolic activity to assess the changes that occur during cerebral anoxia/ischemia, and to determine the factors most critical to overall tissue viability during and following periods of circulatory compromise.

**Methodology/Implications**—Noninvasive techniques of fluorometrically monitoring changes in the reduction/oxidation ration of intramitochondrial NAD, and the technique of reflection spectrophotometry to measure redox changes of cytochromes, together with changes in

hemoglobin oxygenation and local blood volume will be utilized. By relating parameters of metabolism and function, we will discern how the vulnerability of functional activity is associated with periods of ischemic insult.

We will continue efforts to define the relationships between energy metabolism and the functioning of the central nervous system to increase our understanding of how and why the brain uses oxygen, metabolic substrates and oxidative energy, and to determine how viability is threatened by the loss of oxygen and circulatory perfusion.

### [204] Head Injury Clinical and Laboratory Research Center

**Harold F. Young**

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—The main objective of this Head Injury Clinical and Laboratory Research Center is to establish a system whereby rational and improved therapies for patients with head injury can be defined, developed, and tested scientifically. To accomplish this objective, the proposed program will: 1) define the physiological, morphological, metabolic, and psychosocial sequelae of head injury in man; 2) collect, assemble, and analyze data from head-injured patients to formulate an accurate prognosis; and, 3) define in a well-controlled animal model the anatomical, physiological, and biochemical effects of injury on brain parenchyma and blood vessels, and on systemic function.

**Methodology**—The influence of systemic insults to the injured brain will be studied both in man and in animal models. Evaluations will be made in humans of therapy for brain acidosis, elevated intracranial pressure, ischemic and hyperemic cerebral blood flows, neurophysiological status, and posttraumatic mental depression. The role of iatrogenic hypocapnic alkalosis in the management of patients will be clarified. The unifying hypothesis to be

tested is that the brain parenchyma and its intrinsic vasculature can sustain reversible injury. These tissue elements can be rendered dysfunctional; yet, such dysfunction does not implicate irreversible disruption. The dysfunctional state may be temporary, and if the internal milieu is appropriate for healing, the cells can recover. Dysfunction may be represented by reduced, excessive, or aberrant metabolism.

An animal intensive care unit and a controlled brain injury model provide the experimental environment. Acute and chronic animal studies will be conducted on morphologic neural and vascular changes, brain glucose utilization, cerebral microcirculation, the brain arachidonic acid cascade, regional cerebral blood flow, and surface brain energy metabolism following controlled brain injury. Therapy will be tested by studying cerebral acidosis and treatment with THAM.

**Implications**—We seek to understand the fundamental basis of neuronal loss after injury, and by intervention, to reverse the process.

**[205] Center for Stroke Research****Kenneth M. Welch**

Department of Neurology, Henry Ford Hospital, Detroit, MI 48202

*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—Our objective is a better understanding of the pathophysiology of stroke. The program features an integration of the research activities of the Departments of Neurology, Neurosurgery, Neuropsychology, and Diagnostic Radiology in the study of cerebral vascular disease. The research emphasizes and explores the utility of 31-P Topical Nuclear Magnetic Resonance (TMR) proton spectroscopy, and proton NMR imaging in the study of brain anatomy, cerebral blood flow (CBF), and energy phosphate metabolism in clinical patients with stroke.

**Methodology**—Administrative, statistical, and methodological cores and four individual projects are proposed. The methodological cores describe the NMR facility, CBF laboratory, and neuropsychological laboratories.

Project 1 proposes early experiments toward the development of NMR methods for the eventual autoradiographic measurement of CBF. The second project

explores the dynamic changes in cerebral energy metabolism as measured by 31-P NMR and 1-H in cat models of global and focal cerebral ischemia.

Studies of the clinical patient with stroke begin in Project 3 with a proposal to improve and explore the utility of the <sup>133</sup>xenon inhalation technique for the measurement of CBF, and to establish abnormal CBF as a risk factor for stroke.

Project 4 proposes to apply 31-P and 1-H spectroscopy, together with NMR imaging, to the study of the clinical patient with diffuse hemispheric ischemia and focal ischemic infarction.

**Future Plans/Implications**—The eventual goals of this Program Project are to establish noninvasive techniques to identify hemodynamic and metabolic markers which permit the logical and safe therapy of acute and chronic ischemia in cerebrovascular disease by either medical or surgical means.

**[206] Reorganization in Brain and Spinal Cord After Injury****Sid Gilman**

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—The goal of this project is to continue our studies of the mechanisms underlying the responses of the central nervous system (CNS) to injury, and the basis for the partial recovery that can occur with time.

**Methodology**—Animal models of CNS lesions affecting adult humans will be created in mature animals with ablations of the cerebral cortex, and with kainic acid and 6-hydroxydopamine-induced lesions of the basal ganglia and thalamus. Animal models of CNS injury affecting immature humans will be produced in neonatal animals with ablations of the cerebral cortex and with cerebral

lesions induced by hypoxic-ischemic insults. A central focus concerns the immediate and long-term responses to injury of CNS neurotransmitter receptor systems, including glutamate, Gamma-aminobutyric acid/benzodiazepine, opiates, dopamine, and acetylcholine.

Investigations will be performed using awake-behaving animals, tissue from basal ganglia, thalamus, brainstem and spinal cord, and neuronal cell cultures. The experimental approaches include recordings of single neuronal unit activity, studies of neurotransmitter receptors, determinations of glucose metabolic activity, and investigation of ionic conductances in mammalian nerve cell membranes.

## [207] Precursors of Stroke Incidence and Prognosis (Human)

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—It is proposed to extend the prospective findings of the Framingham Study on stroke to 30 years of follow-up, including the age groups 75 to 84 years, and to examine a number of possible precursors for which there has been too little follow-up. These include the roles of: arrhythmias as determined by one-hour ECG monitoring; echocardiographic findings of valvular and myocardial dysfunction; lipid profiles including LDL and HDL cholesterol; physical activity status; menopausal status; psychosocial factors including Type A personality; carotid bruit; Ecolyzer-confirmed smoking histories; and, glucose tolerance based on a glucose load, among others.

**Future Plans/Implications**—Further studies of asymptomatic carotid bruits will be carried out by analyzing the continuous wave Doppler signal for its direction, mean frequency, and frequency content, as they are found at selected moments in the cardiac cycle, over the carotid arteries in the neck, and phonoangiography of carotid bruit in an attempt to identify those bruits which are true precursors of stroke. A more accurate delineation of the type of stroke will be accomplished using CT scan infor-

mation in addition to clinical findings. This should permit better definition of the frequency of different types of stroke and a more accurate determination of the epidemiologic features of each type.

The stroke, its precursors and disability, will be pursued, focusing particularly in the elderly. Functional assessment of the patient's activities of daily living will be made at the time of stroke, and 3, 6, and 12 months later. Scores on recently standardized tests, scales of activities of daily living (e.g., feeding, dressing, grooming, bathing, etc.); assessments of function in the home and in society; and, the use of aids and appliances following stroke will be obtained by a rehabilitation nurse. These data will permit detailed evaluation of disability following stroke in a general population sample.

An attempt will be made to devise a more powerful predictive stroke-risk profile using those ingredients identified above as independent contributors to stroke incidence. The decline in mortality rates from stroke has accelerated in recent years. Secular trends in incidence by stroke type will require more cases occurring over time and should be available as a by-product of this proposal.

## [208] Manipulation of Adenosine Metabolism and Control of Stroke

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*Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose/Methodology**—Stroke and cardiac arrest constitute two of the most frequent causes of death in the United States and even when patients survive it is frequently with some degree of neurological impairment. A massive release of the excitotoxic amino acids, glutamate and aspartate, occurs in the brain during ischemia, and these, together with calcium entry into depolarized nerve cells and the generation of toxic oxygen-derived free radicals, are considered to be major causes of ischemic cellular damage. Adenosine, which is also released in the ischemic brain, attenuates the release of these excitatory amino acids and acts as an antagonist at membrane

calcium channels. The adenosine metabolites hypoxanthine and xanthine are substrates for an enzyme, xanthine oxidase, which generates free radicals.

The first objective of this proposal is to use two potent inhibitors of adenosine deaminase, the enzyme which metabolizes adenosine to the inert product inosine, to elevate adenosine levels in the ischemic brain and to thus reduce excitatory amino acid release and membrane calcium permeability with the ensuing neuronal damage. Inhibition of adenosine deaminase also results in a decrease in hypoxanthine formation, thus depriving xanthine oxidase of its substrate, reducing free radical formation.

Secondly, inhibitors of xanthine oxidase will be used to reduce free radical formation. Neurochemical experiments on amino acid and purine release from the rat cerebral cortex will be coupled with studies on the degree of actual protection against stroke deficits conferred by treatment with adenosine deaminase or xanthine oxidase inhibitors.

**Implications**—The findings from these experiments could lead to the development of prophylactic and thera-

peutic uses of these enzyme inhibitors in individuals at risk for cardiac arrest or stroke. An obvious alternative approach for the use of purines in the treatment of cerebral ischemia would be direct administration of a stable adenosine analog. The disadvantage of this strategy, apart from the fact that these compounds may not cross the blood brain barrier, is that they also have potent hypotensive effects. Manipulation of the metabolism of endogenously released adenosine avoids these potential complications.

## [209] Microvascular Occlusions: Acute Focal Cerebral Ischemia

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**Purpose**—The overall objectives of this proposal are to examine the contribution of acute microvascular occlusions in the lenticulostriate territory to the extent of cerebral ischemia following acute middle cerebral artery stroke in a nonhuman primate model and to assess the mechanism by which those occlusions are generated. The hypotheses to be tested state: 1) that LSA microvascular occlusions are secondary to the adherence of (and vascular obstruction by) PMN leukocytes and/or tissue factor-mediated stasis thrombosis; and, 2) that established monoclonal antibodies against leukocyte adherence and TF activity will decrease occlusion numbers and infarction volume, and improve neurological outcome. The finding of occlusions containing blood elements in the microcirculation of the LSA territory following MCA occlusion and subsequent reperfusion in the primate acute stroke model suggests a pathogenesis for the “no-flow” phenomenon in focal cerebral ischemia. Measures which reduce the extent of this phenomenon in cerebral ischemia may reduce the region of focal cerebral ischemia and improve neurological recovery. Heretofore, this concept has not been testable.

**Methodology**—The mechanism of microvascular occlusion formation as defined by the ability of MoAb to inhibit occlusion formation, and the neurological consequences of these interventions will be developed in stages: 1) the presence of PMN leukocytes in the LSA microvasculature will be identified and quantitated by India ink/glutaraldehyde/light microscopy, and the vascular PMN leukocyte and platelet morphology will be defined by electron microscopy in short-term (5-hour) experiments; 2) the development of LSA microvascular occlusions will be monitored by vascular occlusion score and by in-platelet deposition in the ischemic corpora striata of intact formalin-fixed brain by g-camera imaging in short-term (5-hour) experiments; and, 3) the ability of microvascular occlusion inhibition by MoAb to decrease infarction volume and improve functional outcome will be assessed in long-term (14-day) experiments in the primate model.

**Implications**—This approach may have significant consequences for acute stroke patient management.

## [210] Biochemical Mechanisms of Brain Injury

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**Sponsor:** *National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—Previous experiments indicate that following experimental concussive brain injury, the oxygen-free

radicals produced during cyclooxygenase metabolism of arachidonic acid cause endothelial lesions, dilation,

reduced responsiveness to hypocapnia and abnormal responsiveness to acetylcholine and bradykinin, and may be responsible in part for stimulating arachidonic acid metabolism following injury. We therefore wish to test the following hypotheses. *Hypothesis 1:* Following concussive brain injury, receptor-mediated mechanisms contribute to an increased metabolism of polyunsaturated fatty acids and the production of oxygen radicals which cause cerebrovascular and brain dysfunction. *Hypothesis 2:* Pharmacologic inhibition of fatty acid metabolism, free radical production, or free radical action will reduce the cerebrovascular dysfunction caused by traumatic brain injury.

Our general aims are to understand: 1) factors responsible for initiation and regulation of fatty acid metabolism following injury; 2) the pathways and products of this metabolism; 3) the cerebrovascular consequences of increased fatty acid metabolism and radical

production; and, 4) how pharmacologic intervention can prevent, reduce, or reverse the injury process.

**Methodology**—To accomplish our aims, we will utilize microscopy and radioimmunoassay to correlate simultaneous *in vivo* arteriolar diameter responses, and *in vivo* cyclooxygenase and lipoxygenase synthetic responses. We will employ gas chromatography/mass spectrometry to identify and measure fatty acids and their metabolites.

**Implications**—Little is known about regulation of the changes in fatty acid metabolism, and the concomitant cerebrovascular consequences of increased oxygen radical production following brain injury. The proposed studies will address these problems and are consistent with our long-term goal of elucidating chemical mediators of, and therapeutic agents for, brain injury.

## [211] Treatment of Physiological Disturbances in Head Injury

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**Purpose**—Central nervous system injury is a dynamic process. The initial insult, resulting in primary neurological injury, sets into motion secondary pathological processes which compound the initial injury and adversely affect the outcome. These secondary processes include ischemia, hyperemia, edema, hypermetabolism, acidosis, inflammation, and delayed hematoma formation. To optimize neurological recovery, specific methods of monitoring for and treating each of these phenomena are needed. This program project represents an interdisciplinary research effort by the Departments of Neurosurgery, Neurology, Pediatrics, and Pathology of the Baylor College of Medicine. The aim of the project is two-fold: 1) to clinically test new therapies, and systems for continuous monitoring, that have recently been developed;

and, 2) in a laboratory setting, to devise new therapeutic strategies for the common secondary insults associated with head injury-ischemia, inflammation, and delayed hemorrhages.

**Methodology**—The project consists of six closely related scientific proposals and three supporting Core units: 1) treatment of the hypermetabolic response to CNS injury; 2) monitoring adequacy of cerebral perfusion in head-injured patients; 3) continuous monitoring of intracranial compliance by ICP waveform analysis; 4) characterization and treatment of the inflammatory response to CNS injury; 5) reduction in CNS injury by modification of ischemic energy metabolism; and, 6) prevention of hyperemia and hemorrhage in the newborn brain.

## [212] Epidemiologic Study of Stroke Outcome in Three Ethnic Groups

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**Sponsor:** *National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—Despite the reported decline in the incidence of stroke, there has not been a decline in stroke recurrence. Relatively little is known about whether ethnicity, independently or in conjunction with stroke risk factors, determines outcome after cerebral infarction. Most epidemiologic studies have been conducted in predominantly white populations. Less is known about black survivors of cerebral infarction, and few studies have been done in the growing Hispanic population. The study is designed to determine in whites, blacks, and Hispanics the risk of stroke recurrence, myocardial infarction, and death in 30-day survivors of cerebral infarction up to 10 years after an index event.

**Methodology**—Members of the cohort were admitted to the Neurological Institute of New York from 1983 to 1988. The majority are from northern Manhattan, a community with many black and Hispanic residents. Columbia-Presbyterian Medical Center is the main provider of ambulatory and hospital care for this community. Risk factors for stroke, infarct subtype, and findings on neurological examination and diagnostic studies,

identified at the time of the initial cerebral infarction, have already been collected on the systematically evaluated cohort.

Annual telephone follow-up of the patient or next of kin will be used to measure changes in risk factors, and to identify those with stroke recurrence, symptomatic myocardial infarction, or death. In-person follow-up interview and examination will be done on patients suspected of a subsequent event. Outcome after cerebral infarction will be analyzed by life table methods and Cox proportional hazards modeling. Stratification, or the addition of other collected variables to the models, are expected to show that the effect of ethnicity is not independent of other risk factors.

**Implications**—Besides gaining new epidemiologic information on the risk and determinants of stroke recurrence, myocardial infarction, and death after cerebral infarction in three ethnic groups, understanding the role of individual risk factors and their interactions with ethnicity will encourage more selective secondary prevention strategies.

## [213] Calcium Channel Activation in Models of Cerebral Ischemia

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**Sponsor:** *National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose/Methodology**—We used *in vivo* and *in vitro* autoradiography and  $^3\text{H}$ -nimodipine, a dehydropyridine calcium channel antagonist, to study rat brain at various intervals after focal cerebral ischemia. The severity of ischemia was graded by blood flow measurements performed at the same time in separate rats.

**Results/Implications**—We observed that *in vitro* autoradiography was inadequate as a means to study binding in focal cerebral ischemia, since the act of decapitation activated the cortical binding sites diffusely, and the preceding focal ischemia became unapparent. Conversely, *in vivo*, a very dynamic picture of both

regional and duration-dependent binding to nimodipine was evident.

Comparison to CBF data indicated that the most ischemic regions show the earliest activation of nimodipine binding. As these regions lost their activation, more moderately ischemic regions exhibit activated binding.

**Future Plans**—We therefore propose to test the hypothesis that loss of nimodipine binding in a previously activated region is associated with infarction, while slower but more persistent activation characterizes salvageable tissue.

We then propose to compare control ischemia to the results obtained when calcium channel or NMDA

receptor antagonists are administered after the onset of ischemia. Using positron-emitting  $^{11}\text{C}$ -nimodipine synthesized here, we propose to use PET to study the effect of

varying ischemic severity on nimodipine binding in baboon brain and, with the same techniques, investigate the natural history of nimodipine binding in stroke patients.

### [214] Modulation of Glucose Transporters in Brain Endothelium

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**Purpose**—The prime requirement for glucose, both as a fuel and as a source of growth by brain and nervous tissue, makes it especially important to understand the molecular events that govern glucose homeostasis in these tissues under normal as well as diseased conditions. The first step in cerebral metabolism of glucose is its transport into the tissue. The interface between blood and brain is comprised of a layer of endothelial cells which is the site of glucose transport. The long-term goals of this research are to characterize the molecular events whereby D-glucose is transported transcellularly from the plasma to the interstitial fluid of the brain. These goals include an understanding of where the transporters are located, and how transport activity is regulated.

**Methodology**—To investigate the brain endothelial cell glucose transporter, a polypeptide and the amino acid sequence of the C-terminal end of the glucose transporter will be synthesized, and antiserum against this peptide will be prepared. This antibody will be used to localize the glucose transporter on brain sections, and on cultured endothelial cells by light immunocytochemistry, and to determine the distribution and abundance of the glucose transporter on the luminal, abluminal, and subcellular

membranes of brain endothelial cells by ultrastructural immunocytochemistry.

Cultured dog brain endothelial cells will be used as a model of the blood-brain barrier to determine the abundance of glucose transporters under conditions of anoxia, hypoglycemia, and hyperglycemia, or exposure to phorbol ester and insulin. The Mongolian gerbil occlusion model will be used to determine the response of the brain endothelial cell glucose transporter to ischemia, and for up to 72 hours post-ischemia. An oligonucleotide probe complementary to the known mRNA sequence of the glucose transporter will be synthesized and labeled. This probe will be used to examine regulation of the glucose transporter at the transcriptional level by *in situ* hybridization of glucose transporter mRNA in the ischemic gerbil model, and in Northern blots of TNA derived from the cultured brain endothelial cell model.

**Implications**—Understanding the mechanisms by which glucose is transported across the blood-brain interface, and the alterations of this glucose transport system induced by abnormal conditions or by therapeutic agents, will have important bearing on human brain metabolism and brain function during and subsequent to strokes, cardiac arrest, and metabolic encephalopathies of diverse types.

### [215] Post-Ischemic Hyperexcitability: The Role of Adenosine

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**Sponsor:** *National Institute of Neurological Disorders and Stroke, National Institutes of Health*

**Purpose**—The factors which render certain cells sensitive to transient ischemia remain largely unknown. In the selectively vulnerable CAL region of the hippocampus, neuronal hyperexcitability has been implicated in the process of post-ischemic cell death. The reason for post-ischemic hyperexcitability in the CAL region is unknown,

but is likely to reside in a disturbance of one or more of the inhibitory or excitatory mechanisms which normally serve to control the output of these cells. This proposal will examine the specific hypothesis that a change in the efficacy of adenosine neuromodulation participates in the process of CAL cell loss by directly contributing

to post-ischemic hyperexcitability in this selectively vulnerable region.

Adenosine is among the strongest modulators of neuronal activity in the vulnerable CAL region of the hippocampus. This purine nucleoside is a potent inhibitor of neuronal discharge, and appears to function as an endogenous anticonvulsant in CAL. Specific membrane receptors mediate the inhibitory action of adenosine and the regional density (i.e., number) of these receptors is a critical factor in determining the strength of adenosine action. Following transient ischemia, these receptors are decreased in number in the vulnerable CAL region and this decrease is correlated temporally with the onset of post-ischemic hyperexcitability. These observations lead to the hypothesis that the post-ischemic reduction of adenosine receptors contributes to post-ischemic hyperexcitability by attenuating the strength of the endogenous, inhibitory action of adenosine. The studies proposed in

this application will: 1) elucidate the role of adenosine neuromodulation in post-ischemic hyperexcitability; 2) identify the cellular site of adenosine action impacted by transient ischemia; 3) establish a model system for the examination of vulnerable and nonvulnerable CAL pyramidal neurons; and, 4) examine the trigger mechanism for the post-ischemic loss of adenosine receptors.

**Implications**—The effects of transient ischemic episodes, such as occur in conjunction with cerebrovascular and cardiovascular disease, are often debilitating. Identification of the critical factors responsible for post-ischemic neuronal vulnerability will clearly aid in the development of appropriate strategies for treating or preventing these deficits. This proposal will play an important role in this process by providing direct information on the relation between post-ischemic cellular dysfunction, and the reduced efficacy of adenosine neuromodulation.

## [216] Role of Magnesium in the Pathophysiology of Brain Injury

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**Purpose/Methodology**—Head injuries pose a significant and unique health problem in the United States. Of people that survive head trauma, over 60,000 each year experience residual neurological dysfunction. These neurological deficits appear to be caused by direct mechanical disruption of neuronal pathways, and through secondary or delayed mechanisms that develop over a period of hours to days following the traumatic insult. Although part of the delayed damage to the central nervous system (CNS) after traumatic injury appears as a result from the release or activation of endogenous autodestructive factors, the fundamental mechanisms underlying secondary injury are poorly understood and current therapies are largely unsatisfactory.

Recent work from our laboratory suggests that decline of brain magnesium (Mg) may be a critical factor in the pathophysiological sequelae of traumatic brain injury. Because Mg is mandatory for all ATP-producing and ATP-consuming reactions, it regulates the cellular bioenergetic state and exerts considerable control over a large diversity of metabolic and ionic flux pathways. Changes in tissue Mg will therefore

be a common mechanism linking apparently unrelated CNS injury factors and the response to specific treatments.

The proposed studies will examine the pathophysiological role of Mg in secondary brain injury, using a model of fluid-percussion traumatic brain injury in the rat. Changes in total, extracellular, and intracellular free brain Mg concentrations after brain injury will be characterized and related to time course and injury severity. Magnesium changes will also be correlated with alterations in cellular bioenergetic state (31P NMR), mitochondrial respiratory function, as well as changes in other brain cation concentrations (Ca, Na, K, Zn), and tissue water content. The effect of Mg deficiency (dietary restriction) and Mg supplementation on neurochemical, histopathological, and neurobehavioral outcome after brain injury will be examined. To evaluate the role of the magnesium-gated excitatory amino acid (EAA) ion channel in brain injury, non-competitive EAA receptor antagonists MK-801 and CGS-19755 will be evaluated, with and without Mg supplementation, for their efficacy in the treatment of brain injury.

**Implications**—These studies will expand our understanding of the fundamental pathophysiological mechanisms that contribute to irreversible tissue damage after trau-

matic brain injury, and may lead to the development of effective new therapeutic approaches for the treatment of brain injury.

### [217] Biochemical Receptor Studies in Stroke (Rats, Rabbits)

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**Purpose**—Catecholaminergic systems have been implicated in both the pathogenesis of stroke and the recovery of function after ischemic injury. This proposal is designed to further elucidate the structure, regulation, and function of the  $\alpha_1$ -adrenergic receptor ( $\alpha_1$ -AR) for catecholamines. In the control of the cerebral circulation in man,  $\alpha_1$ -AR mediated events may play a role. In addition, the  $\alpha_1$ -AR may directly influence cellular metabolism through the putative second messengers inositol triphosphate and diacylglycerol. This may be important for the understanding of neuronal growth, plasticity and altered neurotransmission. The work has three specific aims: 1) to develop technologies for the purification of the necessary quantities of receptor protein; 2) to raise antibodies directed against the  $\alpha_1$ -AR; and, 3) to develop

a system for the reconstitution of the  $\alpha_1$ -AR into phospholipid vesicles.

**Methodology/Implications**—Purification of the receptor protein will be accomplished through sequential affinity chromatography, wheat germ agglutinin chromatography, and high performance steric-exclusion liquid chromatography. Purified receptor will then be employed to immunize rabbits for the production of antibodies. A reconstitution system will provide a means of assaying the activating function of the receptor and a way of studying the mechanisms by which the receptor-effector system is regulated. Combined with previous work, the availability of these biochemical tools will permit further study of the  $\alpha_1$ -adrenergic receptor at the molecular level.

### [218] Disorders of Spatial Behavior in Right Brain-Damaged Stroke Patients

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*Sponsor: Nijmegen Institute for Cognition Research and Information Technology*

**Purpose**—Adequate processing of spatial information is essential for the performance of sensorimotor tasks. Some specific defects concerning the processing of spatial information can be observed in stroke patients with a lesion in the right posterior cerebral cortex. These include a neglect for the contralateral space, under- and/or overshoots in reaching, and a visuomotor apraxia. Although these disorders are clinically well-documented, little is known about the way basic information processing systems are disturbed.

**Methodology**—A series of experiments were performed focusing on the understanding of neglect at a rather

fundamental level. In a first series of experiments, subjects had to react as quickly as possible to visual or auditory stimuli coming from right or left. In one condition, the subjects had to press a button, whereas in other conditions, they had to move toward (left or right) targets. The cognitive difficulty of the task was manipulated across conditions (compatible versus noncompatible task conditions).

**Future Plans**—In a second series of experiments, subjects will have to perform a sequence of reaching tasks toward static (nonmoving) and dynamic (moving) targets.

### [219] Long-Term Effects of Closed Head Injury: A Disability- and Handicap-Oriented Study

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Sponsor: WVC; NIZW

**Purpose**—The aim of the present project is to describe the epidemiology of traumatic brain injury in the Netherlands and to deliver information about the actual life situation of brain-injured subjects.

**Methodology**—One hundred and twenty-one subjects (and their relatives) were interviewed and neuropsychological checklists were utilized. People were studied in

their home situation, 3 to 7 years after the accident. At the time of the accident all subjects were between 15 and 30 years of age.

**Preliminary Results**—The preliminary results revealed that 65% of the subjects suffered from more or less serious behavioral problems (e.g., attentional deficits, memory problems, fatigue, and headache).

### [220] Development of a Multidisciplinary Measurement System for the Quantification of Deficits Following Traumatic Brain Injury

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Sponsor: Société de l'assurance automobile du Québec; Fonds de la Recherche en Santé du Québec

**Purpose**—The long-term objective of this project is to establish a multidisciplinary measurement system which will be used to quantify the deficits, impairments, and handicap following a traumatic brain injury (TBI). The computer-based system will provide the basis for an integrated multi-center data acquisition system which will track the progress of clients from their arrival at an acute care hospital via their rehabilitation up until the time of their return to the community.

**Progress**—The first three years of this 5-year project have been devoted to the selection and/or development of quantitative clinical tools which will form the basis of the measurement system. Appropriate clinical tools have been identified to measure deficits in the following domains: medical, neurophysical, psychological, activities of daily living, leisure, social, communication, and vocational. Present studies are investigating the validity and reliability of the various components. An integral part of the development of the measurement system has been the establishment of a longitudinal study which serves as a means for evaluating the clinical feasibility and sensitivity of the system components. The longitudinal study, which currently involves a neurosurgical unit and a

rehabilitation center, follows patients during the 2 years subsequent to their injury.

**Results**—To date, 68 severe (Glasgow Coma Score  $\leq 8$  or intracranial surgery) TBI patients who were involved in a vehicle-related accident have been followed as part of the longitudinal study. The data obtained from these patients have been entered into the system database.

**Future Plans**—Statistical analyses will be performed to reduce the number of variables and to isolate key descriptors of recuperation/rehabilitation. The final version of the measurement system will be computerized to permit optimum data management. The system, when completed, will be introduced into a number of hospitals and rehabilitation centers in order to provide a comprehensive understanding of the evaluation and evolution of the TBI patients and the impact of specific rehabilitation strategies.

#### Recent Publications Resulting from This Research

Motor Recovery Following Severe Traumatic Brain Injury. Sullivan SJ et al., in Proceedings of the S.M. Dinsdale International Conference in Rehabilitation, 1990.

An ADL Profile of the Adult with Severe Head Injury. Dutil E et al., Occupational Therapy and Health Care (in press).