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Rehabilitation R & D Progress Reports 1990

XV. Spinal Cord Injury

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XV. Spinal Cord Injury

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A. General

[495] Accelerometric Body Segment Motion Analysis During Spinal Injury Patient Handling: A Pilot Study

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Sponsor: VA Rehabilitation Research and Development Service (Pilot Project #B967-PA)

Purpose—To meet the need for more precise methods of quantifying the dynamic performance of devices for immobilizing, moving, and maintaining traction on cervical spinal cord injury (SCI) patients, we developed a method for measuring relative head-to-trunk motion using accelerometers. We tested installation and simulated patient handling of 8 types of backboards and cervical collars using 14 able-bodied subjects. Alignment and traction stability on the kinetic bed were measured with seven able-bodied and two acute SCI patients.

Methodology—Measurements were made using 3-axis ± 5 G silicon accelerometers on the front and right side of the head and chest. A 50-lb range cable tension transducer indicated traction force. Signals were amplified, digitized, and stored by an IBM PC-XT.

In order to test the ability of the lateral supports of the kinetic bed to maintain spinal alignment and the constancy of traction force, we measured relative head-to-body acceleration during placement and rotation of able-bodied postacute and acute SCI subjects on the kinetic bed. We also measured traction force versus rotation angle of three different traction devices (the sheathed steel cable normally supplied with the kinetic bed, a 9-spring constant-force traction unit, and a cord on a swiveling pulley). Continuation of cervical collar installation and function consisted of testing of the Olympic Medical "Vac-Pac" conformable splint.

Results—Evaluated prehospital support devices include: the traction, alignment, cervical immobilization, and transport (TACIT) device (a short spine board with width-adjustable foam-padded shells for applying non-invasive traction); the Miller backboard; the Dixie backboard; and the Rehabilitation Research and Development Center's composite backboard.

Three types of rigid cervical collars (Philadelphia, Malibu, and StifNeck) were evaluated using normal volunteers. Manual and automatic operation of the RotoRest kinetic bed, as well as lifting onto this bed, were tested at the Santa Clara Valley Medical Center, using normal volunteers and post-acute SCI patients.

Traction force versus rotation angle without complications due to movement of a patient on the bed showed that force output for the sheathed cable varied four times as much as the constant-force unit. With able-bodied subjects, the sheathed-cable method ranged from 3.15 to 4.3 lbs and the constant-force unit produced 2.6 to 2.85 lbs during a rotation cycle, confirming published observations of variation with angular position. Traction force for one SCI patient ranged from 4.4 to 13.5 lb; the other varied from 6 to 14.5 lb. Torsional head-to-body motion between the sensor sites totaled 2.9 degrees in both the able-bodied and SCI subjects during a complete rotation cycle.

Data for backboards and collars were examined to identify activities associated with higher-than-background risk of unintentional neck displacement, including:

closure of fasteners during installation; head elevation while installing posterior components of collars; ineffectiveness of a collar's occipital restraint in extension; jostling as the attendant's hands grasp a backboard; contact of backboard edges with floor for log-rolling; slipping of the subject's trunk, or less frequently leg, if straps were not adequately tightened; and, progressive loosening of Velcro head-restraint attachments. Such findings may be useful to equipment designers attempting to minimize motion, and they may coincide with avoidable neck pain in patients.

Future Plans—Testing of traction force on the RotoRest bed confirmed published observations of variation with angular position; changes in traction force and relative head-body torsion angle were demonstrable during routine activities such as suctioning a tracheotomy tube

and shifting a patient lower on the bed. The possibility of improving spinal stability on beds and similar equipment has led to discussions of future collaboration with potential local manufacturers of traction devices and with the manufacturer of the RotoRest bed (Kinetic Concepts, San Antonio, TX). A proposal has also been submitted to NASA for testing of spinal stabilization during helicopter aeromedical transportation.

Recent Publications Resulting from This Research

Effectiveness of Cervical Spine Stabilization Devices: Accelerometric Identification of Risk Factors During Installation and Use. Sabelman EE, Sumchai AP, Martino JM, in Proceedings of the 12th Annual RESNA Conference, New Orleans, 125-126, 1989.

Dynamic Traction Force and Neck Stability on the Kinetic Bed. Sabelman EE et al., in Proceedings of the 13th Annual RESNA Conference, Washington, DC, 175-176, 1990.

[496] Factors Influencing Joint Compliance and Reflex Mechanisms Following Spinal Cord Injury

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Sponsor: VA Rehabilitation Research and Development Service (Project #B446-RA)

Purpose—Electrical stimulation of muscle has been proposed as a technique to restore function to paralyzed muscles. But, from a control standpoint, little is known about how such artificial activation interacts with the still intact spinal reflex loops. We have developed instrumentation to measure and compare ankle compliance and muscle electromyographic (EMG) activity when the ankle is subjected to perturbations in torque or angular position from bias positions that are achieved volitionally or via electrical muscle stimulation. We also use this instrumentation to quantify the effect of anti-spasmodic pharmaceuticals, since objective measures of spasticity are hard to obtain clinically.

Methodology—We have developed instrumentation and analytical techniques that we use for quantitative measurements of joint compliance in individuals with spinal cord injury and in the neurologically intact. Essentially, the instrumentation consists of a high-powered torque motor that rotates the joint under test over a few degrees, with the resultant torque, position, and acceleration

changes measured. Joint compliance is the incremental relationship between angular displacement and torque, after the effects of acceleration are excluded, and is the inverse of joint stiffness.

We deliver precise torque or position perturbations (step, ramp, sinusoidal, random) to the ankle via a pivoting footplate driven by a computer-controlled torque motor. Angular displacement, torque, acceleration, and two to four channels of EMG data are collected on analog (VHS) tape and simultaneously digitized and stored. Torque or position biases away from normal ankle equilibrium position are applied volitionally (for the neurologically intact or impaired) or via electrical stimulation of the gastroc/soleus or the tibialis anterior muscle (for either the neurologically intact, impaired, or paralyzed). A special stimulator/recording amplifier permits the recording of EMG signals from the muscle being stimulated. An overview of the features and response characteristics of the perturbation system and a comparison from preliminary studies of responses at different biases achieved volitionally versus those achieved by

stimulation are listed in Recent Publications Resulting from This Research.

Results—In the last 6 months, we have studied 17 individuals, approximately half with spinal cord injury. We found that in general the mechanical response of the ankle is quite different under the two types of bias. The joint is far less compliant under volitional bias than under stimulated bias. This is possibly due to subjects with volitional control co-activating the soleus and tibialis anterior. The EMG response shows differences in the evoked stretch reflex. Under volitional bias there was very little, if any, evoked response in the tibialis anterior when the ankle was plantarflexed, while there was significant response in the stimulated bias condition.

In the relaxed state, preliminary results indicate that the ankle stiffness of neurologically intact individuals falls within a much narrower range than that obtained from those with spinal cord injury. We are currently analyzing these data to see if the variability seen in the spinal cord injured population can be attributed to factors like time-since-injury, completeness

of injury, extent of antispasmodics prescribed, and other variables.

Future Plans—We are now extending these observations to the knee, because control of the knee plays a much more important role in the ultimate functional use of electrical muscle stimulation than was previously thought.

Recent Publications Resulting from This Research

Biomechanical Responses to Ankle Perturbations During Electrical Stimulation of Muscle. Robinson CJ et al., in *Advances in External Control of Human Extremities*, D.B. Popovic (Ed.), 10:145-158, 1990.

A Comparison in Neurologically Intact and Spinal Cord Injured of Ankle Joint Compliance and Reflex Activity to Angular Perturbations Using Volitional and Electrically Stimulated Biases (Abstract). Flaherty B et al., in *Proceedings of the Annual Meeting of the Society for Neuroscience*, 16:1316, 1990.

Reflex Responses to Ankle Perturbations During Electrical Stimulation of Muscle. Robinson CJ et al., in *Proceedings of the Rocky Mountain Bioengineering Symposium*, Denver, 1990.

Responses to Ankle Perturbations During Electrical Stimulation of Muscle: Interaction Between Ankle Compliance and Timing of Stimulation. Robinson CJ et al., in *Proceedings of the Annual International Conference of the IEEE/Engineering in Medicine and Biology Society*, 11, 1990.

[497] The Corticospinal System

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Purpose—The purpose of our studies is to identify corticospinal systems which may be important in the recovery of motor function following spinal cord or cortical injuries. Our current studies focus on the corticospinal projections from the primary motor cortex and the premotor areas in the frontal lobe. Classically, the premotor cortex has been viewed as functionally distinct from the primary motor cortex and as a center for the integration of complex skilled movements. Premotor cortex was thought to participate in the generation and control of distal movement only through its projections to the primary motor cortex (area 4). On the other hand, there is a remarkable recovery of motor function that follows lesions of the primary motor cortex. Several studies have suggested that this recovery may depend on the integrity of output pathways from the premotor cortex. We have proposed that the premotor areas contribute to the corticospinal system and, as a result, have output pathways

which are independent of the primary motor cortex. The goal of our experiments is to define the organization of descending projections from the premotor areas and then compare this organization with that of projections from the primary motor cortex.

Methodology—We have examined the topographic organization of corticospinal projections to cervical segments of the spinal cord. In macaques, one fluorescent tracer was injected into upper cervical segments (C2-4) of the spinal cord. Then, in the same animals, a second fluorescent tracer was injected into lower cervical segments (C7-T1). Retrograde transport of these tracers was used to define the origin of corticospinal projections to each segmental level.

Results—Previously, we demonstrated that a substantial portion of the corticospinal system from the frontal lobe

originates from six premotor areas, as well as from the primary motor cortex. Our present experiments indicate that five of the six premotor areas have corticospinal projections to both upper and lower segments of cervical spinal cord. Most of the corticospinal neurons in these areas terminated selectively in either upper or lower cervical segments; only 5% of the sample sent branches to both levels. Only the arcuate premotor area, which is located on the caudal bank of the arcuate sulcus, had a segmental termination that was limited almost entirely to upper cervical segments. These observations suggest that lesions of the spinal cord which selectively affect lower cervical segments would leave a large system of corticospinal projections to upper cervical segments intact.

In the premotor areas, as well as in the primary motor cortex, regions which project to upper cervical segments overlapped those which project to lower cervical segments. However, in each cortical area, the peak densities of corticospinal neurons projecting to the different segmental levels were spatially separate. These results suggest that the topographic organization of arm representation in five of the six premotor areas is similar to that in the primary motor cortex.

The maps of arm representation generated by our studies differ from the classical maps of Woolsey et al. (1952) in at least two striking respects. We found two "lower cervical only" bands of corticospinal neurons in the region of primary motor cortex where Woolsey's map located a single arm representation. Furthermore, we found dense corticospinal projections to lower cervical segments in the region of the supplementary motor area (SMA) where Woolsey's map located the leg representation. These observations suggest that the maps of body representation in the primary motor cortex and the SMA should be reevaluated.

Recent Publications Resulting from This Research

- Corticospinal Projections from the Motor Areas in the Frontal Lobe. Dum RP, Strick PL, in Taniguchi Symposia on Brain Sciences No. 12: Neural Programming, 49-63, M. Ito (Ed.). Tokyo: Japan Scientific Societies Press, 1989.
- Premotor Areas on the Medial Wall of the Hemisphere: Corticospinal Projections to the Cervical and Lumbosacral Cord. He SQ, Dum RP, Strick PL, Soc Neurosci Abstr 15:282, 1989.
- Premotor Areas: Nodal Points for Parallel Efferent Systems Involved in the Central Control of Movement. Dum RP, Strick PL, in Proceedings of the Dahlem Workshop on Motor Control: Concepts and Issues (in press).

[498] Colorado Comprehensive Spinal Cord Injury Surveillance Program

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Sponsor: *Colorado Department of Health; Rocky Mountain Regional Spinal Injury System; National Institute on Disability and Rehabilitation Research; Centers for Disease Control*

Purpose—The Early Notification System (ENS) conducts comprehensive, population-based spinal cord injury surveillance, assesses changing trends in injury demographics, etiologies and outcomes, and identifies risk factors, enabling the implementation of primary and secondary prevention efforts. This particular program is conducted in collaboration with the Colorado Department of Health and is funded both by the National Institute on Disability and Rehabilitation Research and by a cooperative agreement from the Centers for Disease Control for the prevention of disabilities. Its purpose is the identification and development of strategies of prevention and control of secondary disabilities of spinal cord injury.

Methodology—The collection of ongoing secondary disability, medical complications, and cost surveillance data

will be added to existing surveillance information. In addition, tools that measure physical and societal functioning will be used in annual patient interviews. During 1991, a one-time study of ongoing care costs among a sample of 60 clients will be conducted. Established cost determination methodologies will be used, which identify all providers of medical services (including physicians, hospitals, clinics, pharmacies, equipment vendors, attendants, etc.) over a 1-year period. Detailed billing for those services to clients in the sample will be obtained.

Progress—Over 400 patients have been identified since January 1, 1986, and continue to be tracked.

Future Plans—Medical complication and secondary disability data will be analyzed, and preventable conditions amenable to intervention will be identified. Cost data will

also be analyzed to document the costs of ongoing SCI care, the total cost of spinal cord injury in Colorado, the proportion of SCI expenditures attributable to preventable

secondary complications and disabilities, and the economic impact of primary and secondary prevention. Appropriate interventions will be designed.

[499] Psychosocial Adjustment of Persons with Combined Spinal Cord Injury and Traumatic Brain Injury: A Longitudinal Investigation

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Sponsor: *National Institute on Disability and Rehabilitation Research*

Purpose—Spinal cord injury (SCI) is often the result of a rapid deceleration event and/or a direct impact to the head, neck, or trunk. Therefore, in some cases, an associated traumatic brain injury (TBI) is sustained in addition to the SCI. While evidence of a concomitant traumatic brain injury is at times quite apparent, at other times, “softer” signs of a TBI may not be so apparent and may be overlooked. This project is an attempt to determine whether persons with concomitant TBI in addition to SCI: 1) experience more marital/familial distress post-discharge than a matched group of patients with SCI only; 2) achieve less progress educationally and/or vocationally post-discharge than a matched group of patients with SCI only; 3) experience more psychological/behavioral distress post-discharge than a matched group of patients with SCI only; and, 4) experience more social maladjustment post-discharge than a matched group of patients with SCI only.

Methodology—The social, vocational, psychological, and familial adjustment over time, of a cohort of persons

with SCI and concomitant TBI, and a matched control group of persons with SCI only, have been compared through a battery of well-validated psychometric measures administered via mail.

Results—This study has now been completed. We found that most of the head injuries we identified in this population were mild or moderate and had no important prognostic impact on long-term adjustment. There was a relationship, however, between the more severe injuries and long-term adjustment.

Recent Publications Resulting from This Research

Spinal Cord Injury and Traumatic Brain Injury: Results of a Controlled Follow-up Study. Richards JS, Jaworski TA, Reeder K, ASIA Abstracts Digest 15, 18, 1989.

Spinal Cord Injury and Traumatic Brain Injury: Results of a Controlled Follow-up Study. Richards JS, Jaworski TA, Reeder K, Paraplegia (in press).

[500] A Longitudinal and Cross-Sectional Analysis of Well-Being in Persons with Spinal Cord Injury and Their Caregivers

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Purpose—Recent clinical and empirical studies suggest there may be an increasing toll in terms of coping and feelings of well-being for persons who live with spinal cord injury (SCI) for 10, 20, and 30 years. Moreover, this toll is more quickly taken when the initial injury occurs at a more advanced chronological age. This study will examine the quality of life of both the person with SCI and his/her caregiver at several intervals postinjury. We

propose to study the patient/caregiver interaction both cross-sectionally and longitudinally to determine whether changes in well-being occur over time, and if so, what factors account for that change, and whether the same factors affect changes in well-being at different times postinjury. The project is an attempt to: 1) examine the relationships between factors of well-being in persons with SCI and their caregivers measured at preselected

times postinjury; 2) determine the association between physical and psychosocial characteristics of the person with SCI and the feelings-of-burden variables in caregiver(s) at preselected times postinjury; 3) determine the interrelationships between feelings of well-being of the person with SCI and his caregiver(s) in different cohorts over time; and, 4) determine the interrelationships between physical and psychosocial characteristics of the person with SCI and feelings-of-burden in the caregiver(s) over time.

Methodology—Persons with SCI and their caregivers will be studied during the short-term (1-2 years), mid-term (4-7 years), and long term (9-13 years) postinjury periods. Yoked SCI/caregiver pairs, both of whom agree

to participate, will be included in the study. We will include 80-120 pairs for each of these three cohorts. Data will be collected representing four hypothesized constructs. The first two constructs will be caregiver and patient well-being, which will be assessed by collecting data on the physical health, mental health, finances, and social activities of both the patient and caregiver. The third construct will be the caregiver's feelings-of-burden, which will likely be composed of measures of social support, the Zarit scale, the Robinson Caregiver Strain Index, the short form of the Beck Depression Inventory, and the State-Trait Inventory. The fourth construct will be patient status, including measures of functional independence, psychosocial status, incidence and prevalence of medical complications, and perceptions of pain.

[501] Long-Term Costs of Spinal Cord Injury

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Purpose—The purpose of this study is to: 1) develop predictive models to estimate lifetime expenditures for individuals who have spinal cord injuries; 2) estimate the effect of spinal cord injuries on the earning potential of these persons; 3) estimate the aggregate costs of spinal cord injury to society; and, 4) estimate the proportion of lifetime services provided by NIDRR-sponsored model spinal cord injury care systems.

Methodology—A random sample of 651 patients injured 1 to 16 years ago was selected from the National Spinal Cord Injury Statistical Center (NSCISC) database. An additional 300 newly injured patients were also randomly selected for inclusion in the study at the time of admission to any of the 13 currently funded model systems. For each study subject, data are being collected prospectively using standardized forms and instructions on all charges incurred and wages earned during the next one year period. All information required for submission to the NSCISC database is also being collected at this time.

Multiple linear regressions analysis will be used to develop predictive models for annual expenditures, with first-year costs being analyzed separately from those sub-

sequent years. When possible, cost categories (hospital charges, physician fees, attendant care, medications, supplies, etc.) will also be analyzed separately. These annual cost estimates combined with projections of life expectancies developed from our previous research will result in estimates of lifetime direct costs of care.

Indirect costs will be estimated using the human capital approach by comparing wages before and after spinal cord injury, and previously reported estimates of the incidence of spinal cord injury will be used to assess the aggregate costs to society. Sensitivity analysis will be conducted to assess the effects of the models' underlying assumptions. Finally, an assessment will be made of the proportion of services provided by the system of care and the proportion of services provided elsewhere.

Preliminary Results—Patient enrollment is complete and data collection is ongoing. Preliminary analyses of data have not been conducted at this time.

Future Plans—Data collection terminated September 30, 1990, and data analysis is scheduled for completion by September 30, 1991.

[502] Aging in Relation to Spinal Cord Injury

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Sponsor: *National Institute on Disability and Rehabilitation Research*

Purpose—Under the auspices of the Rehabilitation Research and Training Center in Community-Oriented Services for Persons with Spinal Cord Injury, a study is being conducted of age-related changes in persons with spinal cord injury. The study is based upon a $2 \times 2 \times 2$ prospective, longitudinal design that involves 100 participants. The three independent variables are: 1) duration of injury; 2) age when injured; and, 3) measurement of Occasion 1 versus Occasion 2. Three years will intervene between the two measurement occasions. Dependent variables are being assessed in six different life domains (physical well-being, psychological well-being, social integration, independence, productivity, and economic self-sufficiency), and with respect to five moderating factors (social support, health beliefs and practices, environmental supports, perceived control, and mobility). Threats to physical well-being that are being documented include bacteriuria, kidney or bladder calculi, renal insufficiency, pulmonary insufficiency, coronary heart disease, hypertension, spinal arthritis, heterotopic ossification, neuromuscular pain or progressive fatigability, lipid abnormalities, and pressure sores. The psycho-

logical well-being of participants is being compared with norms for the general population in terms of life satisfaction, depression, and perceived psychological stress.

Progress/Methodology—Participants were chosen on a random basis from a cohort of more than 640 persons with spinal cord injury who reside in a 13-county area in southeast Texas that includes the cities of Houston and Galveston. Following a home visit that includes an interview and completion of multiple self-administered instruments, participants undergo a day-long assessment at The Institute for Rehabilitation and Research that includes a physical examination, clinical laboratory assessments, X-rays, a renal scan, and provocative cardiopulmonary evaluation.

Future Plans/Implications—Results of this study will contribute to the identification of risk factors for a number of the age-related problems of persons with spinal cord injury, and to the anticipation of service needs that emerge as these persons grow older. The first wave of data acquisition has been completed, and the second wave will begin in September, 1991.

[503] Life Status Study of Persons with Spinal Cord Injury

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Purpose—Under the auspices of the Rehabilitation Research and Training Center in Community-Oriented Services for Persons with Spinal Cord Injury, this study is being conducted of the life status and service needs of persons with long-term injury of the spinal cord. Life status is being assessed in six domains: physical well-being, psychological well-being, social integration, independence, productivity, and economic self-sufficiency. Variance in each life domain is being explored as a func-

tion of individual difference variables particular to spinal cord injury (e.g., level and duration of injury to the spinal cord) and variables that apply to the general population (e.g., educational attainment and gender). Measures are also being obtained on five variables that are posited to moderate the relationship between the individual difference variables and the life domains. The moderating variables are social support, health beliefs and practices, environmental supports, perceived control of one's life,

and mobility. Where possible, measures have been chosen for which norms are available for the general population so that comparisons can be made.

Progress/Methodology—A cohort was established of persons with spinal cord injury who reside in a 13-county area in southeast Texas that includes the cities of Houston and Galveston. A random sample of 140 persons was drawn from the cohort of more than 640 individuals. Following a home visit that included an interview and completion of multiple self-administered instruments, participants underwent a day-long assessment at The Institute for Rehabilitation and Research that included a physical examination, clinical laboratory assessments, X-rays, a renal scan, and provocative cardiopulmonary evaluation.

Threats to physical well-being that were documented include bacteriuria, kidney or bladder calculi, renal insufficiency, pulmonary insufficiency, coronary heart disease, hypertension, spinal arthritis, heterotopic ossifi-

cation, neuromuscular pain or progressive fatigability, lipid abnormalities, and pressure sores. The psychological well-being of participants will be compared with norms for the general population in terms of life satisfaction, depression, and perceived psychological stress.

Other comparative data concerning social integration, functional independence, productivity, and economic self-sufficiency should contribute to the knowledge base necessary to anticipate the service needs of persons with long-term spinal cord injury.

Future Plans/Implications—This study is based upon a representative sample from a cross-section of persons with long-term spinal cord injury rather than a convenience sample of persons known to a particular service program. Consequently, reasonable estimates can be made of the prevalence of various problems and service needs of persons with long-term spinal cord injury. Data acquisition has been completed and analyses of the data are in progress.

[504] Comparative Rehabilitation Outcomes for Women and Men as Reflected by the National Spinal Cord Injury Database

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Purpose—Under the auspices of the Texas Model Spinal Cord Injury System, outcomes are being compared of men and women whose rehabilitation was provided by model spinal cord injury systems. As a complement to a companion study which has a prospective, longitudinal design, this study consists of retrospective analyses of information in the National Spinal Cord Injury Database. Gender-related differences will be assessed in rehabilitation outcomes that exist 12 months following injury at a time when these persons have resumed their lives in the community. The principal dependent variables are at the levels of handicap (occupational/educational status, marital status, and place of residence [nursing home or otherwise]), disability (attendant care utilization), secondary complications, and unplanned service utilization (number of admission days in system and non-system hospitals).

Progress/Methodology—All women who were enrolled in the database between 1984 and 1986 will be included who were age 16 or older at the time of injury, who were admitted for inpatient rehabilitation no more than 60 days following injury, and whose records contain data on the variables described above. These subjects will be matched with an equal number of males in terms of the level and completeness of the spinal cord injury, age at injury, and preinjury occupational/educational status.

Future Plans/Implications—The goal of this project is to evaluate the effectiveness of services of the model spinal cord injury systems in terms of comparative outcomes for women and men at their first anniversary postinjury. Data analyses began in October, 1990.

[505] A Comparative Longitudinal Study of Rehabilitation Outcomes for Women and Men with Spinal Cord Injury

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Purpose—Conducted under the auspices of the Texas Model Spinal Cord Injury System, this study addresses the acknowledged void of scientifically validated information about the rehabilitation-related needs and outcomes that distinguish men and women who incur spinal cord injury. Using a prospective longitudinal design, similarities and differences between women and men undergoing inpatient rehabilitation and follow-up services will be documented in terms of functional recovery, prevalence and severity of secondary complications, psychological well-being, and utilization of services. Variables to be monitored that are distinctive to women will include selective aspects of social role performance, sexuality, and obstetrical and gynecological status. A related objective is to identify similarities and differences between women and men in their preinjury characteristics, and characteristics of their inpatient rehabilitation experience that forecast postdischarge health status, degree

of disability, social role performance, as well as the kinds and extent of service utilization.

Progress/Methodology—A minimum of 30 females who are admitted for rehabilitation into the Texas Model Spinal Cord Injury System will be matched with the same number of male patients in terms of level and completeness of spinal cord injury, age at injury, and preinjury vocational/educational status. In addition to data that reflect participants' inpatient rehabilitation experience, follow-up data will be obtained at 6-, 12-, and 24-months postinjury.

Future Plans/Implications—The resulting data will serve to evaluate the comparative effectiveness of model spinal cord injury system services in terms of interim and post-rehabilitation outcomes for men and women. Data acquisition began in November, 1990.

[506] Collaboration Between Model Spinal Cord Injury Systems and Independent Living Centers in Facilitating Independent Living by Persons with Recently Incurred Spinal Cord Injury

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Sponsor: *National Institute on Disability and Rehabilitation Research*

Purpose—Under the auspices of the Texas Model Spinal Cord Injury System, a project is being conducted to develop, implement, and systematically evaluate a cooperative, model reentry program involving a medical rehabilitation program and an independent living center. Building upon the experience of the University of Michigan spinal cord injury system, this project will assess the expectation that by providing coordinated community living reentry services by a medical rehabilitation program and an independent living center during the post-discharge period, life-adjustment will be enhanced during that period and, in turn, long-term adjustment will be enhanced as well. Life-adjustment will be evaluated in

terms of the individual's physical and subjective well-being, psychological and functional independence, productivity, social integration, and intensity of health services utilization, both planned and unplanned.

Progress/Methodology—A cycled treatment and comparison group design will be used. Specifically, for one 4-month period, all eligible spinal cord injury inpatients will participate in the model reentry program. For the succeeding 4-month period, all eligible patients will receive conventional reentry services. Over the two-year period during which patients are enrolled in the study, 50 patients will be enrolled in the model reentry program,

and 50 patients will be enrolled in the conventional program. The experience of participants in both programs will be tracked over a 2-year period following discharge from the spinal cord injury center.

Future Plans/Implications—This project represents an attempt to confirm the expectation that by providing

coordinated community living reentry services by a medical rehabilitation program and an independent living center during the post-discharge period, life adjustment will be enhanced during that period and, in turn, long-term adjustment will be enhanced as well. Data acquisition began in January, 1991.

[507] Direct Approach to Synaptic Organization of Nociception

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

Purpose—This project was devised with the specific aim of clarifying whether spinal modulation of nociceptive sensory information, transmitted by peptidergic sensory fibers, occurs at a pre- or post-synaptic site. Our hypothesis, based on the available evidence, is that both sensory fibers containing substance P and enkephalinergic spinal neurons act postsynaptically on glomerular or non-glomerular dendrites of nociception-driven dorsal horn neurons. For that purpose, a unique combination of ultrastructural immunocytochemistry with intracellular recordings and injections of nociception-driven neurons will be used. This type of labeling is the only one that can provide a direct answer to the hypothesis outlined above, and has never been used before in a systematic way.

Methodology—All the experiments will be carried out in adult cats under α -chloralose anesthesia. Nociception-driven neurons of lamina I of the lumbar spinal cord will be injected intracellularly with horseradish peroxidase

(HRP). The animals will be fixed by vascular perfusion and the relevant segments of the spinal cord sectioned in a vibratome and processed for the demonstration of peroxidase. The slices containing intracellularly injected cells will be further processed for the simultaneous demonstration of substance P and enkephalin immunoreactivities at the electron microscopic level. The sensory origin of the substance P fibers will be assessed in some animals by injections of tritiated amino acids in the dorsal root ganglia, and by combining immunoreactivities for calcitonin gene-related peptide, γ -Aminobutyric acid, serotonin, choline acetyltransferase, and somatostatin, in combination with radioimmunocytochemistry for substance P or enkephalin, and electrophysiology will also be carried out.

Implications—This research is expected to bring important new information on the modulation of pain in the spinal cord.

[508] Spinal Somesthetic Pathways (Monkeys)

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

Purpose—This project has three major goals. The first goal is the improvement of neurological diagnosis of spinal cord injury by defining the sensory capacities that depend critically upon transmission along the dorsal spinal columns. This major somatosensory pathway has been investigated thoroughly by anatomical and physiological techniques, but psychophysical investigations are

needed to determine the functional significance of organizational features that have been described.

The second goal is an analysis of the mechanical factors that determine the sensitivities of cutaneous receptors that can be described by application of video analysis techniques to microscopic views of the skin during indentation. This analysis will focus on the

non-hairy (glabrous) skin of primates that is specialized for exquisite tactile sensitivity.

Goal three is to improve understanding of the participation of spinal cord circuitries in the control of pain; therefore, pharmacological compounds will be introduced directly on the spinal cord (intrathecally), and both sensory and motor capacities will be evaluated thoroughly. By comparing the effectiveness of a variety of opiate agonists in modulating pain reactions without producing other effects, improved methods of pain therapy can be suggested.

Methodology—The proposed studies will be conducted with monkeys, because the spinal pathways are quite similar among primates, but differ considerably between primates and other mammals. The stimuli utilized in these are brief, noninjurious, and easily tolerated by monkeys and humans. This is a multidisciplinary approach within the neurosciences, involving direct correlations of anatomical and physiological data with highly quantitative evaluations of sensory thresholds and motor reactions to precisely controlled somatosensory stimuli.

[509] Rehabilitation Technology Needs Assessment of Farmers and Ranchers with Spinal Cord Injuries

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Sponsor: *Paralyzed Veterans of America, Spinal Cord Research Foundation*

Purpose—The objective of the project is to increase the benefits of appropriate assistive technology to farmers, ranchers, and agricultural workers with spinal cord injury, and members of their families. The project has two basic goals: 1) to develop an estimate of the number of individuals with spinal cord injury who live and/or work on American farms and ranches, or who are involved in some aspect of agricultural production; and, 2) to complete a rehabilitation technology needs assessment, with a special emphasis on agricultural worksite accessibility of individuals with spinal cord injury.

Methodology—Rural and farm population data will be extrapolated to estimate the number of persons with spinal cord injury involved in agriculture. Site visits will be made to farmers with spinal cord injury in 10 states.

A survey for needs assessment for agricultural workers with spinal cord injury will be developed and field-tested.

Progress—The needs assessment survey has been distributed to 225 farmers with spinal cord injury. The response rate for completing the survey was 51% as of June 1990.

Results—A mailing list of farmers with spinal cord injury has been developed. Photographs of worksite modifications have been obtained and descriptions written.

Future Plans/Implications—Analysis of the needs assessment survey will be conducted. A general technology needs assessment will be developed. During the second year of the project resource material for farmers with spinal cord injury will be prepared.

[510] Physiological Mechanisms of Spinal Cord Plasticity

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Sponsor: *Paralyzed Veterans of America, Spinal Cord Research Foundation*

Purpose—The purpose of this project is to identify sites where plasticity of the spinal cord can occur, and the ways in which it can affect spinal cord function.

Methodology—In most experimental studies of spinal cord plasticity, spinal cord trauma is mechanically

induced, with the result that complex and diffuse changes are initiated, making study of subsequent plasticity difficult. In the present study, a nontraumatic method of eliciting spinal cord plasticity has been used. Animals are trained in a task for which they are rewarded for changing the size of a simple spinal reflex. Over the course of

several weeks, animals are able to increase or decrease the size of this reflex, depending on the requirements of the task.

Progress—Modification of the strength or the organization of neuronal connections is being studied by examining the intrinsic properties of individual neurons comprising this spinal reflex pathway and the strength of their synaptic influences on each other.

Results—Changes in reflex behavior appear to be long-lasting. The site of plasticity has been identified to be within the spinal cord itself.

Future Plans/Implications—These studies should localize and define the changes elicited in the spinal cord by the reflex modification task and should begin to reveal the mechanisms that create these changes. The work may

help to trigger efforts to develop new therapeutic techniques for promoting recovery of useful function after spinal cord injury. This work is significant in that it represents the development of an simple animal model to study memory traces.

Recent Publications Resulting from This Research

Memory Traces in Spinal Cord. Wolpaw JR, Carp JS, Trends in Neurosciences 13(4):137-142, 1990.

Operant Conditioning of H-Reflex in Freely Moving Monkeys. Wolpaw JR, Herchenroder PA, J Neurosci Methods 31:145-152, 1990.

Motoneuron Physiology After H-Reflex Operant Conditioning: Initial Studies. Carp JS, Wolpaw JR, Neurosci Abstr (in press).

Operant Conditioning of Triceps Surae H-Reflex: The First Days. Wolpaw JR, Neurosci Abstr (in press).

Triceps Surae Motoneurons and Ia Afferent Connections: Further Anatomical Studies. Lee CL, Carp JS, Wolpaw JR, Neurosci Abstr (in press).

[511] Electrophysiological Basis for Contraction in the Bladder

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Sponsor: *Paralyzed Veterans of America, Spinal Cord Research Foundation*

Purpose—The purpose of this study was to characterize the activity of interstitial cells of Cajal (ICC), which are hypothesized to be pacemaker cells, and which are found in colonic and bladder muscles. Additionally, the study will determine the effects of various drugs on the rhythmic electrical activity of ICC, which are essential for normal motor functioning of the colon and bladder.

Progress/Methodology—Interstitial cells of Cajal from colon segments and bladder in dogs were identified through morphological examination. Excitability of these cells was studied using a whole-cell patch clamp technique. Experiments were performed to determine whether isolated ICC were capable of spontaneous rhythmic activity. In addition, whole bladder electrophysiological studies were conducted using standard

electrophysiological techniques to record intracellular membrane potential.

Results—Electrical recording from ICC cells indicated that they were indeed electrically active, producing a series of rhythmic electrical events. Excitatory input in the whole bladder appeared to be largely cholinergic; however, it appeared that a noncholinergic excitatory transmitter was also released upon stimulation.

Future Plans/Implications—Further work will characterize the role of ICC in generating electrical activity and the development of specific probes for ICC cells. The results of this project should provide a scientific rationale for the development of new drugs to help patients with functional motor problems of the colon and bladder.

[512] Intrathecal Baclofen for Intractable Spinal Spasticity

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Sponsor: *Physicians' Services Incorporated Foundation*

Purpose—Reports indicate that intrathecal baclofen has effectively and safely reduced spasticity, as opposed to conventional therapeutic measures. It has been embraced as a treatment outside Canada, although a careful evaluation of its efficacy is lacking. Such treatment requires permanent implantation of a costly drug administration device similar to the insulin pumps currently in use, and therefore requires careful appraisal. This preliminary study is to demonstrate whether there is a significant treatment effect that can be reproduced and maintained without serious side effects.

Progress/Methodology—Facilities in the Rehabilitation Engineering Department of the Rehabilitation Centre were set up to record electromyograms of the lower limbs. Software was developed to record the data

and a special device was built to induce a reflex in the leg.

Subjects are recruited from the spinal cord rehabilitation unit at the Rehabilitation Centre and the Multiple Sclerosis Clinic at Ottawa General Hospital. They are admitted to the neurological intensive care unit at the Ottawa General Hospital where a percutaneous lumbar subarachnoid catheter is introduced under local anaesthesia. Baclofen is administered through the catheter. Outcome measurements include: muscle tone, bladder function, overall motor function, and self care. Evaluations include self-assessment by the subjects, clinical examinations, and physiological recordings.

Future Plans—Recruitment and treatment should be completed in 1991.

[513] Health and Functional Status of Aging SCI Persons

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Sponsor: *Rocky Mountain Regional Spinal Injury System; National Institute on Disability and Rehabilitation Research*

Purpose—This two-pronged collaborative study is designed to identify and evaluate secondary complications and disabilities which occur in people living many years with spinal cord injury (SCI). Objectives of this effort include: 1) determining causative factors of complications that are amenable to intervention; and, 2) developing intervention methodologies to prevent and minimize the severity of these secondary disabilities.

Methodology—Craig Hospital is collaborating with the National Spinal Injury Centre in Aylesbury, England, and the Regional Spinal Injury Centre in Southport, England, both of which have a 45-year history of providing comprehensive rehabilitation and follow-up services to the military and civilian SCI persons in the United Kingdom. An unbiased sample of SCI cases that were traumatically injured more than 20 years ago in a specified geographic region in proximity to the two SCI centers and admitted within one year for treatment, is being used. Nine

hundred and thirty four persons, of whom 394 are surviving, meet the narrow study criteria. In addition to thorough analysis of the medical records of all study cases, surviving individuals will be located to obtain a current medical assessment and to complete a comprehensive interview regarding medical and psychosocial history.

Progress—Approximately 300 individuals completed the comprehensive medical assessment and interview by January 1, 1991. In addition, Craig Hospital is leading five other federally designated United States model spinal injury treatment centers in collaborative research to document the nature and extent of medical complications, functional losses, and psychosocial effects which accompany aging with SCI. A companion study will focus on Craig Hospital clients injured more than 20 years ago.

Implications—Data from the 300 individual participants in the British collaborative study will be analyzed and

compared with normative data from longitudinal gerontological studies in order to determine the relative rate of health and functional decline of spinal cord injured individuals in comparison with the able-bodied population. As indicated by the data, specific future studies may be conducted to further examine particular aging issues and to test the effectiveness of the proposed treatments, preventive techniques, or interventions, and to explore new models of service provision.

Future Plans—A computerized summary medical record to aid in lifetime care and research will be developed. Also, a prospective longitudinal database which comprehensively describes the aging of organ systems, the incidence and prevalence of medical complications, and associated functional decline occurring throughout the

lifetimes of people with spinal cord injuries will be established. Valid and reliable measures of disability, handicap, and quality of life will be developed and used to document changes over time. This database will facilitate comparison of the aging of individuals with SCI with the aging of able-bodied persons. It will allow for analysis of the interactive impact of chronological age and duration of spinal cord injury. The differential impact of aging for males and females, and those who sustained their spinal cord injuries in youth versus those who were injured later in life, also will be examined.

Finally, Craig Hospital is planning a national consensus conference to disseminate the latest knowledge in aging with spinal cord injury and to establish research and long-term care goals for the future.

[514] Shepherd Spinal Center's Leisure Education Program: An Evaluation

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Sponsor: *Shepherd Spinal Center Research Review Committee*

Purpose—Social integration following spinal cord injury (SCI) has become a topic of interest and concern in recent years. It has been found to be the most significant determining factor in survival versus death after spinal cord injury. A marked decrease in the number of social contacts, frequency of entering the community, and number of roles played in the community following SCI has been noted with concern. Work on intervention strategies that increase the function of persons with spinal injury in interpersonal, vocational, and community activities has been called for.

Progress—Since 1981, the Therapeutic Recreation Department has implemented a Leisure Education Program (LEP) in an effort to facilitate social integration postdischarge. The goals of the program are: 1) to locate community resources; 2) discover personal leisure attitudes and values; 3) assess pre-injury lifestyle patterns and changes that will occur; 4) explore new lifestyle options and begin to develop new skills; 5) develop skills related to leisure, such as

assertiveness, problem-solving, and social skills; and, 6) develop and finalize a discharge leisure plan. This research study was designed to evaluate the effectiveness of the LEP. In doing so, four major questions were addressed with 60 experimental subjects: 1) Are the outcomes congruent with the program's intended objectives? (as measured by a knowledge exam); 2) What effect does participation have on participants intended future involvement in leisure activities? (as measured by the Leisure Activities Blank); 3) Does participation in the LEP have an effect on social integration patterns postdischarge? (as measured by phone interview 6 to 8 months postdischarge); and, 4) What are the correlations between the demographic variables (age, sex, level of injury, and amount of time in rehabilitation program) and the LEP outcomes?

Recent Publications Resulting from This Research

A Survey of Post-Acute Spinal Cord Patients: Medical, Physiological and Social Characteristics. Anson C, Shepherd C, Trends: Research News from Shepherd Spinal Center, March, 1990.

B. Treatment and Rehabilitation

[515] Development and Testing of New Spinal Implant Systems

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Sponsor: VA Rehabilitation Research and Development Service (Project #B365-2RA)

Purpose—The overall purpose of this grant is to better define the dynamic biomechanical properties of retrieved laboratory animal spines, to conduct cyclic testing on surgical implant systems *in vitro*, and to evaluate new implant systems *in vivo* in primates for functional safety and efficacy. The data would then be used to design, test, and apply new devices useful for surgical reconstructions and rehabilitation within veteran patient populations.

Progress/Methodology—Laboratory model analyses have been extended to include preliminary biomechanical models and test systems on the MTS Bionix 858 dynamic testing system. Dynamic fatigue compression, torsion, and combined compression-torsion testing systems have been established, quantified, and applied to swine and primate spines. A three-dimensional TV and computer-based methodology has been further defined and calibrated for motion analyses of whole spines and adjacent vertebral bodies. One PhD dissertation (R. Moeini) and one MS thesis (G. O'Connell) in Biomedical Engineering are being coordinated within the VA Medical Center project activities. Dr. Lemons is serving as committee chairman for both students. An anterior implant has been redesigned to include titanium alloy and a final shape to accommodate fabrication and clinical placement. Baboon cages have been obtained and the surgical placements of the implants in primates or swine were initiated in 1990.

The *in vivo* baboon studies have been significantly delayed because of changes in animal welfare requirements, the closure of primate facilities at Wright-Patterson Air Force Base necessitating a move to the University of Alabama at Birmingham, and the requirement to procure adequate caging facilities. Testing on pedicle-based spinal fixation systems has been completed and the results presented at a national meeting. These studies showed that spinal pedicle-based rod and plate systems applied to a vertebrectomy model loaded under axial compression and torsional fatigue conditions did not provide stability of fixation. The spinal implants in this model system exhibited loosening and mechanical damage during testing.

Future Plans—The current plan is to extend the *in vitro* biomechanical testing to include: new and current posterior systems, the new anterior spinal implant, and retrieved spines containing the previously implanted anterior spinal device. *In vitro* and *in vivo* phases of the program should be completed in 1991. The affiliated graduate student research programs should be completed during the third year of this grant period. Since several of the proposed posterior systems and composites could not be studied within this grant period, a new grant proposal for continuing the investigation will be submitted during 1991.

[516] Management of the Musculoskeletal Complications of Spinal Cord Injury

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Sponsor: VA Rehabilitation Research and Development Service (Project B576-RA)

Purpose—This project is designed to develop and apply newly discovered, bone cell-specific serum markers to clinical studies of musculoskeletal assessment in patients with trauma and illness involving the spinal cord. The

methods to be used involve new immunoassay procedures with increased sensitivity and defined specificity for classical skeletal markers such as bone alkaline phosphatase (BAP) and bone acid phosphatase (BAP) and new

skeletal markers such as bone Gla protein (BGP, osteocalcin) and its derived peptides. It is our hypothesis that these procedures will assist in the design and evaluation of treatment regimens for patients with spinal cord injury and disease. We should be able to identify those regimens that are beneficial (or deleterious) for optimal rehabilitation of the patient.

In accord with the recommendations of the Review Panel on Spinal Cord Injury, we are focusing on the development and validation of these serum markers and are not yet conducting clinical studies.

Progress/Methodology—We have made considerable progress in each component of our proposal during the first 5 months of the project. For BAP measurements, we have developed a protocol two-site radioimmuno-metric assay specific for this protein. To confer specificity for BAP, the assay utilizes one immobilized antibody and another radiolabeled antibody to the enzyme. In validation studies, we were able to demonstrate that BAP was elevated in patients with Paget's disease, 365 U/ml, but indistinguishable from normal in patients with liver disease. In these validating studies, BAP correlated with total alkaline phosphatase (TAP) ($r=0.96$), and less so with BGP ($r=0.60$). The corresponding correlation between BGP and TAP was 0.57. Our results demonstrate both similarities and differences of BAP with other skeletal indices. This assay for BAP will thus be uniquely useful in the assessment of patients with calcium and skeletal disorders. It distinguishes BAP from liver alkaline phosphatase and should provide a new clinical tool for studying bone metabolism in patients with spinal cord injury. For bone Gla protein (BGP, osteocalcin), we have initiated a program to identify monoclonal antibodies specific to different sequences of the molecule that are compatible with a two-site assay format.

For BAcP, we have developed a purification scheme for the protein that should permit antibody development. Pieces of cleaned human bone are ground in a stainless steel blender. Two volumes (ml/g) of 50 mM tris-acetate with pH 7.8, 100 mM NaCl, 0.1% Triton X-100, 1 mM PMSF are used to homogenize the bone powder. Bone extract is then subjected to cation-exchange chromatography (ZetaChrom SP sulfopropyl chemistry). Cationic proteins are eluted with 500 mM NaCl. Eluted fractions high in tartrate-resistant acid phosphatase activity are pooled and chromatographed by SDS-PAGE. Samples are solubilized in sample buffer and run under non-reducing conditions on BioRad 7.5% Tris-HCl ReadyGels. Immediately following electrophoresis, gels are developed at 37 degrees C for tartrate-resistant acid phosphatase activity in 120 mM acetate buffer, pH 5.4 containing 10 mM l-tartaric acid and 1 mg/ml 1-naphthyl phosphate as substrate. Reaction product is visualized by conjugation with 0.2 mg/ml Fast Garnet GBC in the reaction solution. This purification scheme has allowed us to identify candidate species of BAcP for assay development.

Preliminary Results/Implications—The first 5 months of this project has resulted in significant advances in all stages of our proposed research. The above-described progress will support our goal to develop methods that will ultimately assist in the clinical management of patients with spinal cord injury.

Recent Publications Resulting from This Research

A Two-Site Immunoradiometric Assay Specific for Human Bone Alkaline Phosphatase Correlates with Other Indices of Osteoblast Function. Deftos LJ, Weisman MG, Hill CS, J Bone Min Res 55:A642, 1990.

[517] Compression and Ischemia As It Affects Spinal Cord Injury

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Sponsor: VA Rehabilitation Research and Development Service (Project #B535-RA)

Purpose—The pathophysiology of the injuries to the spinal cord and cauda equina is poorly understood. Injury due to mechanical compression and ischemia is common, but not well delineated. The purpose of this project is to gain increased knowledge of the effects of various insults to the spinal cord and nerve roots.

Progress—Our progress in the past year has been to complete the examination of the effects of hypotension during compression and recovery, and hypotension during compression with normotensive recovery at the level of the cauda equina. These results were compared with our past work, the effects of normotension with compression.

A two-level coccygeal laminectomy was performed on 20 mini-pigs weighing 40 ± 6 kg. A polyethylene balloon was placed between the cauda equina nerve roots and a rigidly secured plexiglass plate. Electrodes were positioned proximal and distal (control) to the compression device, and electrodes were placed in the tail to allow electrophysiologic monitoring. Blood pressure was reduced to a mean of 60 mmHg (normotensive mean 94 ± 5 mmHg) using sodium nitroprusside. The spinal nerve roots were then compressed at 0 (sham), 50, 100, or 200 mmHg for 2 hours followed by a 90-minute recovery period. Results were compared to compression in normotensive animals to assess the effect of hypotension and compression on nerve root function. The experiment was then repeated, but using normotension during the recovery period. Results were then compared to compression with hypotension throughout to assess the effects of hypotension and compression with a normotensive recovery period on nerve root function.

Results—*Hypotension during compression and a hypotensive recovery period.* This study demonstrated an independent effect of hypotension on cauda equina nerve roots undergoing acute graded compression. Compressive injury represents a combination of ischemic and direct mechanical damage. Our data suggest that hypotension has its major impact on nerve root function at lower levels of compression. At higher compression levels (above the mean arterial pressure), ischemia is complete and the effect of hypotension is seen predominantly during the recovery period.

Hypotension during compression and a normotensive recovery period. This study demonstrated a significant improvement in nerve root recovery with normotensive recovery conditions following a combined hypotensive and compressive nerve root insult. Sensory

(afferent) fibers are more sensitive to hypotensive effects in the recovery period.

Future Plans—Our future plans are to continue to examine the effects of hypertension with compression, hypoxia with compression, and complete vascular ischemia at the level of the cauda equina, after which we plan to repeat the same series of experiments at the level of the conus medullaris, and then at the level of the thoracic spinal cord. This is in an effort to gain increased knowledge concerning the underlying causes of injuries to the spinal cord and spinal nerve roots.

Recent Publications Resulting from This Research

- Differential Recovery of Motor and Sensory Nerve Root Conduction Following 2 or 4 Hours of Graded Compression of the Pig Cauda Equina (Abstract). Pedowitz RA et al., International Society for the Study of the Lumbar Spine, Kyoto, Japan, 17-18, 1989.
- The Effects of Magnitude and Duration of Acute Compression Upon Impulse Conduction in the Pig Cauda Equina: Differential Recovery of Sensory and Motor Nerve Roots (Abstract). Pedowitz, RA et al., in Transactions of the 35th Annual Meeting, Orthopaedic Research Society, Las Vegas, 14:428, 1989.
- Graded Compression of the Pig Cauda Equina: Differential Recovery of Efferent and Afferent Spinal Nerve Root Conduction (Abstract). Pedowitz RA et al., North American Spine Society, Quebec City, Canada, 68-69, 1989.
- The Effect of Hypotension and Acute Graded Compression on Cauda Equina Nerve Root Function (Abstract). Cohen MS et al., in Transactions of the 36th Annual Meeting, Orthopaedic Research Society, New Orleans, 15 (Sect 1):122, 1990.
- The Effect of Hypotension and Acute Graded Compression on Cauda Equina Nerve Root Function (Abstract). Garfin SR et al., American Spinal Injury Association, Orlando, 35; International Society for the Study of the Lumbar Spine, Boston, 23; and, North American Spine Society, Monterey, CA 43, 1990.
- Changes in Spinal Nerve Root Impulse Conduction Induced by Acute Graded Compression of the Pig Cauda Equina. Rydevik BL et al., Spine (in press).
- Nerve Roots of the Cauda Equina: The Effects of Hypotension and Acute Graded Compression on Cauda Equina Nerve Root Function. Garfin SR et al., J Bone Joint Surg (in press).

[518] Electric Field Distribution in Experimentally Injured Spinal Cord: Improved Function After Electrical Stimulation of Injured Spinal Cord

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Sponsor: VA Rehabilitation Research and Development Service (Project #B423-RA)

Purpose—This study evaluates the effect of electrical stimulation upon the functional status of injured spinal cord.

Progress/Methodology—A contusion model of injury is being investigated. To ensure that both stimulated and

control animals are injured to the same degree, the trauma device has been further refined and standardized, incorporating features of designs described in the literature. This includes an adjustable magnetic vertebral stabilizer, an in-line computer-interfaced strain gauge, and an independent, pre-positionable Teflon impounder head. Our findings suggest that the resulting injury is more controlled and reproducible, making conclusions regarding improvement after treatment more significant.

Six cats weighing from 2 to 2.5 kg were anesthetized with an intramuscular injection of ketamine and xylazine. A laminectomy was performed at T8-T10 and the spinal cord was subjected to a contusion injury at the T9 level using a modified weight drop method which delivers an impact force of 75 to 85 newtons to the spinal cord. These animals received daily postoperative care in accord with the American Association for Accreditation of Laboratory Animal Care (AAALC) guidelines. Of these six cats, three received platinum disc electrodes which were inserted 2 cm above and below the level of the lesion and connected to an implantable pulse stimulator.

The cathode and anode were placed caudally and rostrally, respectively, to the injury site. The electrodes were placed epidurally with the anode on the dorsal surface and the cathode on the ventral surface of the spinal cord. The electrical stimulation consisted of 20 μ A peak current of 0.5 ms duration with a frequency of 10 Hz.

Preliminary Results—For 6 to 7 months, the animals were examined for behavioral performances using a wide range of tests. At the end of the test period, the two cats with stimulators displayed tactile placing responses and

partial weightbearing in the hindlimbs. One of the three electrically stimulated cats walked or pushed on its “knuckles” while keeping its knees close to the ground. The second cat appeared to be voluntarily pushing slightly with its hindlimb. None of the cats in the control non-stimulated group showed any tactile placing responses or any weightbearing in the hindlimb.

Electrophysiological recordings showed the absence of somatosensory and spinal evoked responses in all animals after trauma following stimulation of the tibial nerve. However, in the stimulated cat showing the most behavioral recovery, responses were present at 120 days post-trauma while absent at 60 and 90 days post-trauma.

Future Plans—Further studies are planned using controlled injury and electrical stimulation methods as well as objective assessment techniques to determine whether or not there is a clear functional benefit of applied electric fields in spinal cord injury.

Recent Publications Resulting from This Research

- Electrical Stimulation in the Treatment of Experimental Traumatic Spinal Cord Injury. Khan T, Myklebust J, International Symposium on Biomagnetism, Magnetobiology and Magnetotherapy, Newport, 1989.
- Improved Micturition with Direct Current Stimulation of the Spinal Cord in the Spinal Cat (Abstract). Khan T et al., Soc Neurosci 15:630, 1989.
- Current Distribution in Normal and Injured Cat Spinal Cord. Zaug CA et al., in Proceedings of the 10th Annual Meeting of the Bioelectrical Repair and Growth Society, 1990.
- Effects of Two Electrode Configurations on Current Distribution in Cat Spinal Cord. Zaug CA et al., in Proceedings of the 10th Annual Meeting of the Bioelectrical Repair and Growth Society, 1990.

[519] Wheelchair Graded Exercise Test for Patients with Lower Limb Disabilities

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Sponsor: VA Rehabilitation Research and Development Service (Project #B398-RA); Vaughan Chapter of the Paralyzed Veterans of America

Purpose—The primary purpose of this 2-year study was to develop improved methods for the objective evaluation of the cardiorespiratory health and fitness of spinal cord injured (SCI) and other patients with lower limb disabilities. These evaluations will provide baseline data useful in judging the effectiveness of patient rehabilitation, cardiorespiratory training programs, and in charting any

progressive deterioration of health resulting from disability-imposed inactivity. Our objectives were to: 1) establish standardized maximal and submaximal wheelchair graded exercise tests to accurately measure the cardiorespiratory fitness of patients restricted to the manual wheelchair; 2) evaluate the sensitivity of the testing system for detecting abnormal cardiovascular and

pulmonary responses to exercise stress in SCI and other persons with lower limb disabilities; and, 3) compare data resulting from the experimental wheelchair testing protocol with data obtained from conventional arm crank ergometry.

Progress—Fifty-one males (17-69 years old) with tetraplegia, paraplegia, amputations, and other lower limb disabilities completed one continuous and one discontinuous maximal wheelchair graded exercise stress test on the Wheelchair Aerobic Fitness Trainer (WAFT) and one continuous test on the arm crank ergometer (AC). Subjects with complete or incomplete SCI were assigned to three experimental groups: upper-level injury (ULI), C₅-T₃ (n=12); mid-level injury (MLI) T₄-T₁₀ (n=19); and, lower-level injury (LLI) below T₁₀ and persons with lower limb fractures (n=20). Stages were 3 minutes with power output increments of 16 watts per stage for the AC and 7 for the WAFT. Significant between-group mean differences were found in peak measures of heart rate (HR), oxygen uptake ($\dot{V}O_2$) and minute ventilation (\dot{V}_E) for all experimental conditions. Peak measures of HR, $\dot{V}O_2$ and \dot{V}_E during AC and WAFT exercise tests were significantly correlated ($p < 0.001$). Correlation coefficients for continuous and discontinuous WAFT tests at the peak of exercise for the same parameters were also significant ($p < 0.001$). Correlation coefficients showed a strong relationship between differentiated ratings of perceived exertion for AC and WAFT continuous exercise ($r = 0.94$). It was concluded that the WAFT provides a valid method for evaluating the cardiorespiratory fitness of persons with SCI and other lower limb disabilities.

A comparison of maximal arm crank and continuous wheelchair exercise performance of lower limb disabled veterans from this study and subjects from previously published research demonstrates that the veterans in the MLI and LLI groups produced consistently lower power outputs and metabolic values for both arm crank and wheelchair ergometry. This observation may not be

considered remarkable given the low level of chronic physical activity of these subjects and that the majority of comparison data has been collected from individuals who are a decade younger and regularly involved in wheelchair sports. However, there is reason for concern regarding the cardiorespiratory health of the aging middle-aged sedentary person with lower limb disabilities.

We continue to gather data to demonstrate that a wheelchair graded exercise test will provide a sufficient challenge to the cardiovascular and pulmonary systems of lower limb disabled patients with suspected coronary artery disease (CAD). The need for a noninvasive upper body exercise stress test with an acceptable degree of sensitivity and specificity for the detection of CAD in persons with lower limb disabilities is increasing; the WAFT and test protocol may meet this need. Seventeen lower limb disabled veterans (44-81 years old) with suspected CAD were referred to our laboratory for wheelchair stress testing; eight had true positive ECGs substantiated by either cardiac catheterization or echocardiography. No patients had a false positive test, seven patients had true negative and two patients false negative tests. The two false negative findings were attributable to the influence of drugs used to regulate the inotropic and chronotropic states of the heart. We are currently developing new standardized procedures for combining stress echocardiography with wheelchair ergometry.

Recent Publications Resulting from This Research

- Interactive Video Games and Real Time Displays for the Wheelchair Aerobic Fitness Trainer. Flaherty BP, Robinson CJ, Langbein WE, in Proceedings of the IEEE/Engineering in Medicine and Biology 11th Annual Conference, Seattle, 1989.
- Speed-Torque Calibration of the MAGTURBOtm and Wheelchair Aerobic Fitness Trainer. Langbein WE, Robinson CJ, Kynast LT, in Proceedings of the IEEE/Engineering in Medicine and Biology 11th Annual Conference, Seattle, 1989.
- Validation of a New Ergometer for Graded Exercise Testing of Persons with Lower Limb Disabilities. Langbein WE et al., in Proceedings of the American Heart Association 62nd Scientific Sessions—Medical Research, Nursing Research, New Orleans, 1989.

[520] Interactive Videodisk Training for Self-Care Skills

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Sponsor: VA Rehabilitation Research and Development Service (Project #B45I-RA)

Purpose—Between one-third and one-half of people with spinal cord injuries are rehospitalized in any given follow-up year. The average annual cost for each rehospitalization can range from \$6,700, if surgery is not required, to \$20,000, if surgery is required. The incidence of rehospitalization due to preventable complications can be decreased with appropriate instruction in self-care skills. Such instruction can also hasten people's progress toward adaptation to their disability and personal independence.

Traditional methods of health-care education such as personalized instruction by a health-care professional, self-instruction from written or audiovisual materials, participation in learning groups, or interaction with other disabled persons are often ineffective. The success of such programs may be influenced by factors such as the person's psychosocial, economic, or educational status; the extent of involvement by health-care professionals; and the instructional material or methods. Although some of these factors can be controlled and improved, others cannot. Accordingly, health-care institutions are faced with the difficult problem of teaching valuable skills to people with diverse socioeconomic backgrounds, attitudes, and skills, using staff who may have little time to teach them.

We believe that this problem may be resolved by augmenting traditional education programs with interactive learning technology. Technologies such as computer-

assisted instruction (CAI) or interactive-videodisk instruction (IVI) have several advantages as adjuncts to traditional educational methods. People with diverse socioeconomic and educational backgrounds can learn at their own pace. The novelty of interacting with a computer may provide motivation for learning. CAI or IVI may also be more effective than personalized instruction for teaching difficult or emotion-laden subjects, since they are impersonal and nonthreatening. Interactive learning technologies also free staff to give personalized instruction to people who need it.

Progress/Future Plans—We have developed a menu-driven authoring package for IBM-compatible personal computers that allows someone with marginal computer skills to develop highly interactive instructional material. The authoring system provides the user with interfaces to routines for creating graphics, computer-generated speech, menus, two- or four-alternative questions, and routines for controlling commercial videodisk players. It also provides the user with the ability to establish the sequence of instructional material, thus providing him or her with the ability to create complex scenarios with feedback to the student.

We have developed an instructional series on skin care and will soon be testing its efficacy as an adjunct to traditional instructional methods for self-care skills in a population of persons with spinal cord injuries.

[521] Urinary Bladder Stimulation Following Spinal Cord Injury

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Sponsor: VA Rehabilitation Research and Development Service (Project #B44I-2RA)

Purpose—After spinal cord injury, control of bladder function is usually lost. This project's goal is to learn more about the mechanism of bladder dysfunction following spinal trauma and to use this knowledge

to develop ways to manage urinary functions following injury. Methods of stimulating sacral nerves, the pelvic floor, and the bladder directly are under investigation.

Progress—In the anesthetized spinal cord injured cat (T-1), we have compared direct bladder stimulation to sacral nerve stimulation. During terminal procedures, 10 weeks post-spinal cord injury, direct bladder stimulation was conducted with four teflon-coated, “single knot” electrodes inserted in the wall with a needle above the ureters (Cooner wire). Sacral nerve stimulation was conducted with previously implanted needle electrodes inserted into the sacrum (Pisces Quad, Medtronics). In the four male cats investigated, direct bladder stimulation was superior to sacral nerve stimulation because it induced voiding both during and after stimulation, whereas sacral nerve stimulation only induced voiding after stimulation. Voiding rates were also higher with direct bladder stimulation than with sacral nerve stimulation when similar peak bladder pressures were induced. These results show that in the anesthetized animal, direct bladder stimulation can induce effective bladder contractions and does not increase urethral resistance as much as sacral nerve stimulation. We are currently developing an instrumented cat model for chronic recording in the unrestrained animal. This instrumentation will allow us to compare direct bladder stimulation to sacral nerve stimulation in the unanesthetized animal.

Repetitive, spontaneous bladder contractions occurred when the bladder was full in the unanesthetized spinal cat, 4 to 10 weeks after injury. Both sacral nerve and pelvic floor stimulation techniques were investigated to

inhibit the contractions. Stimulating currents that induced pelvic floor and anal contractions were generally effective for inhibiting the bladder. Pudendal nerve stimulation may be more specific than sacral nerve stimulation for bladder inhibition because fewer side effects, such as leg spasms, were noted.

Future Plans—We plan to evaluate a multichannel implantable simulator for micturition control, bladder stimulation for voiding, and pelvic floor stimulation for preventing incontinence. Such systems have been or are being developed at Case Western University and Rancho Rehabilitation Engineering Center.

Recent Publications Resulting from This Research

- Comparison of Sacral and Pudendal Nerve Stimulation for Bladder Inhibition in the Spinal Cat. Walter JS et al., Soc Neurosci 15:630, 1989.
- Effects of Filling Volume on Detrusor Contractility. Walter JS, in Proceedings of the 11th Annual Urodynamics Society, 11-12, 1989.
- Role of the Urethral Emptying Reflex in High Urethral Resistance Following Spinal Cord Injury. Walter JS et al., in Proceedings of the Thirty-Fifth Annual Meeting of the American Paraplegia Society, 24, 1989.
- Surface Stimulation Techniques for Bladder Management in the Spinal Dog. Walter JS et al., J Urol 141:161-165, 1989.
- Urethral Reflexes in Spinal Cord Injured Cats. Walter JS et al., J Urol 141:569A, 1989.
- Urethral Responses to Sacral Stimulation in the Chronic Spinal Dog. Walter JS et al., Am J Physiol 257:R284-R291, 1989.

[522] Effect of Exercise on Upper Extremity Recovery Following Quadriplegia

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Sponsor: VA Rehabilitation Research and Development Service (Project #B320-2RA)

Purpose—Acute quadriplegia is commonly followed by some recovery of function in one to two spinal segments at the level of the cord injury. For example, a patient with C4 quadriplegia often recovers some C5 function, allowing use of the upper extremities for operating a power wheelchair and for feeding oneself. This upper extremity recovery likely results from several mechanisms, including: 1) resolution of a transient conduction block in descending motor pathways of the spinal cord or in lower motoneurons or roots; 2) motor axon sprouting by spared motoneurons to reinnervate denervated muscle fibers; and, 3) muscle fiber hypertrophy in spared motor units. This study attempts to identify the mechanisms mediating

the various stages of the recovery process and to explore the role of exercise in facilitating these individual recovery mechanisms.

Methodology—Weak upper extremity muscles in patients with recent traumatic quadriplegia are examined using a battery of electrophysiologic tests. One weak muscle is randomly assigned to receive standard twice-daily strengthening; the other weak muscle receives strengthening three times per week. Subsequently, both muscles receive standard twice-daily strengthening. The battery of electrophysiologic tests are repeated monthly to monitor the patterns of recovery and the effects of differential strengthening.

Results/Future Plans—Several distinct types of weakness have been distinguished by comparing compound muscle action potential amplitudes (M amplitudes) as a percent of normal and maximal motor-unit firing rates. Some weak muscles have relatively spared M amplitudes but slow firing rates; others show very low M amplitudes but fast motor-unit firing rates. These findings are consistent with upper and lower motoneuron type weakness respectively. The former is often seen two or more segments rostral or caudal to the cord level, corresponding to the level of a spine fracture in motor-incomplete

quadriplegia. Current work addresses the temporal patterns of recovery and the effects of exercise on this recovery.

Recent Publications Resulting from This Research

Electromyographic Evidence for Motor Axon Sprouting in Recovering Upper Extremities of Acute Quadriplegics. Little JW et al., J Am Para Soc 13:16, 1990.

Patterns of Upper Extremity Weakness and Recovery in Quadriplegia. Little JW, Powers R, Moore D, presented at the Annual Meeting of the American Paraplegia Society, Las Vegas, 1990.

[523] Control of Perioperative Hemodynamic Instability in Quadriplegia

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Sponsor: VA Rehabilitation Research and Development Service (Project #B516-RA)

Purpose—Complete injury to the cervical spinal cord effectively removes all sympathetic outflow from higher centers while parasympathetic control remains largely intact. As the cardiovascular system is highly dependent upon autonomic influences, it is logical that this injury pattern might interface with the complex mechanisms involved in hemodynamic stabilization. We have previously shown that acute cervical injury in man results in a variety of cardiovascular abnormalities, including bradycardia, hypotension, tachyarrhythmias, and cardiac arrest. Fortunately, these autonomic disturbances resolve spontaneously from 2 to 6 weeks after injury via an unknown mechanism. Although this adaptive response is obviously beneficial to the rehabilitative goals of the quadriplegic patient, the chronic stage of cervical spinal cord injury is marked by its own set of cardiovascular abnormalities.

Chief among these is autonomic dysreflexia. This condition, found in more than 85% of quadriplegics, is characterized by transient episodes of profound hypertension, diaphoresis, piloerection, headache, seizures, and even death. To date, the mechanism of this apparent mass sympathetic reflex has not been established, and no satisfactory treatment has been discovered.

During rehabilitation, patients at risk learn proper techniques of bowel and bladder manipulation to minimize the likelihood of triggering a dysreflexic episode. However, the barrage of afferent nervous activity that regularly accompanies surgery represents a potent stimulus of dysreflexia. This phenomenon, combined with

baseline vasodilation and hypotension, makes intraoperative hemodynamic control in quadriplegia extremely difficult. Indeed, systolic arterial pressure swings of over 100 mmHg are commonly encountered during surgery. Surprisingly, there have been no prospective studies published to date that well characterize the magnitude of this problem.

There is considerable controversy as to the ideal anesthetic and pharmacologic approach to take with these individuals. Each technique tried in the past has intrinsic limitations that precludes widespread applicability. On both theoretic and empiric grounds, the transdermal administration of the α -agonist clonidine may effectively blunt both extremes of blood pressure variation during surgery when given prophylactically. Preliminary data from our laboratory strengthen this concept, and support the need for a large scale investigation.

We propose to study this new technique of perioperative hemodynamic control via a randomized, double-blind, placebo-controlled trial. Transdermal clonidine or a matching placebo will be administered to 60 patients with chronic, complete quadriplegia undergoing surgery. Several physiologic parameters will be monitored non-invasively during the procedure to assess autonomic and hemodynamic function, including arterial pressure, electrocardiographic ST segment height, tissue oxygen tension in areas below the level of injury, and sympathetic neurohormonal release. Finally, subjective sensations will be quantitated in awake patients using strictly defined criteria. In addition to intraoperative assessment, blood

pressure and heart rate will be monitored in the immediate postoperative period using a portable measuring device.

The facilities for this research are being provided by the Seattle VA Medical Center: initiation of patient enrollment was in Fall 1990.

[524] Evaluation of Virginia Regional Spinal Cord Injury System Follow-up Care

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Sponsor: *National Institute on Disability and Rehabilitation Research*

Purpose—The purpose of this study was to evaluate the follow-up care provided to patients in the Virginia Regional Spinal Cord Injury System (VRSCIS). In the VRSCIS, follow-up care is delivered through three centers to accommodate patients from different geographic areas. Patients may be recalled to clinics at Woodrow Wilson Rehabilitation Center (WWRC), the University of Virginia Medical Center, or to an outreach clinic at Abingdon in Southwest Virginia. In addition, patients may receive a home visit from the WWRC project staff at one and two years after discharge, and at least an annual phone call thereafter.

Methodology/Results—A total of 446 clients in the VRSCIS who met specified criteria were identified as being eligible for inclusion in the study. A representative sample of 200 clients, stratified by geographic region, was randomly selected.

Eligible subjects were contacted by letter inviting their participation in the study. One hundred and forty-three subjects were interviewed to obtain the answers to 12 research questions. The subjects had been discharged from our Center an average of 8.5 years.

Data are currently being analyzed. However, some preliminary findings are as follows: it appears that about 20% of our patients use follow-up care as their primary health care. These patients will initiate follow-up visits rather than wait for contact from the VRSCIS. Forty percent do not have regular follow-up; they elect to wait until something is wrong. This attitude is not particularly surprising in view of the attitude of the general public toward preventive health care.

Pain is an ongoing problem for many people with SCI. Seventy three (51.7%) persons complained of chronic pain. Further, most of these people found that medication did not help. People with incomplete lesions were somewhat more likely to suffer pain. However, this was not statistically significant.

Reimbursement for supplies and durable medical equipment is a major problem for people with SCI. Medicare will, in fact, pay for most supplies but it is extremely difficult to get the information needed to make this happen. Attendant care is difficult to find and most subjects who needed it found paying for it a major problem.

This project was terminated in September 1990.

[525] Pathologic Effects of Recurrent Bacteriuria in Patients with Spinal Cord Dysfunction

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Sponsor: *National Institute on Disability and Rehabilitation Research*

Purpose—Urinary tract infections (UTIs) are a serious source of morbidity for spinal cord injury (SCI) patients. Recurrent hospitalizations and out-patient services required for treatment of acute and chronic UTIs are extremely expensive and may impede both the rehabilitation process

and vocational pursuits. In addition, UTIs may lead to grave urologic complications and, in some cases, eventual renal failure. There is a need to prevent these infections and their sequelae; this would improve the overall rehabilitation potential and quality of life for SCI patients.

Objectives of this study include: 1) determination of the incidence of clinically significant urinary tract complications coincident with the major bacterial species; 2) determination if aggressive treatment of most pathogenic organisms results in fewer long-term secondary urinary tract complications; 3) determine if patients with certain human leukocyte antigen (HLA) combinations are at unusually high or low risk for developing long-term secondary urinary tract complications; 4) determine if the phagocytic activity of human leukocytes correlates with the incidence of clinically significant UTIs and long-term secondary complications; 5) determine if the degree of bacterial adherence to the urothelium correlates with the incidence of clinically significant UTIs and specific HLA combinations; and, 6) determine the prevalence of *Mycoplasma hominis* and *Ureaplasma urealyticum* in lower and upper urinary tract (where possible in selected patients with SCI), and the association of these organisms with various pathologic conditions, with particular emphasis on upper urinary tract disease and calculi.

Methodology—Records of SCI patients evaluated in the outpatient clinics at Spain Rehabilitation Center are being evaluated to determine the presence of UTI, the species of organisms involved, and type(s) of urologic complications which occur over time. The incidence and severity of urinary tract complications secondary to chronic or repeated infections is documented in successive follow-up visits in a group of SCI patients who are either newly injured or are within 2 years of the initial injury. This group is followed at quarterly intervals and treated aggressively for infection. These patients will be compared to those who are evaluated only once each year.

Also, a group of patients (subjects) who are chronically infected and have diminished renal function, and a

separate group (controls) who have consistently sterile urine or whose sole complicating diagnosis is bacteriuria, have been identified from our patient database. Fifty patients from each of these two groups will have tests performed at the time of their annual urologic evaluation to determine the phagocytic abilities of their peripheral blood neutrophils, the degree of adherence of bacteria to the urinary bladder epithelial cells in those who are infected, and for the determination of HLA haplotypes. Leukocyte phagocytic activity and bacterial adherence will be correlated with incidence of clinically significant urinary tract complications and with particular HLA combinations. Finally, the prevalence of mycoplasma in urine specimens from SCI patients will be determined.

Preliminary Results—Neutrophil phagocytosis assays have been performed on 14 patients from the experimental group, and 11 from the control group, for a total of 25 since August 1988. Numbers are still too small to predict outcomes, although no apparent difference in the phagocytic activity in the two groups has been observed thus far.

HLA antigens have been determined on leukocytes from 23 patients in an attempt to determine whether an association exists between a particular HLA haplotype and predisposition to urologic complications following SCI. The results will be evaluated when a sufficient number of persons have been tested.

Urine screening for mycoplasmas has been performed on 793 specimens with positive cultures identified in 103. Repeated positive cultures over time have been observed in some patients. The distribution of positive cultures, the presence or absence of concomitant bacterial species, and possible clinical implications of these microbiological results are being evaluated.

[526] A Comprehensive Approach to Management of Infertility in Males with Spinal Cord Injury

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Sponsor: National Institute on Disability and Rehabilitation Research

Purpose—Infertility is a major problem among male spinal cord injury (SCI) patients. This study seeks to: 1) determine optimal conditions for producing seminal emission via electrical stimulation of the pelvic sympathetic nerves; 2) compare electrical stimulation with strong vibratory stimulation of the genitalia in eliciting

seminal emission in male SCI patients; 3) determine if repeated stimulation improves semen quality (sperm count, motility, and morphology); 4) determine if intermittent testicular cooling improves semen quality; 5) relate success or failure of seminal emission production to neurologic level and extent of spinal lesion,

urodynamic assessment of lower urinary tract function and incidence of recurrent urinary tract infection; and, 6) artificially inseminate a male SCI patient's female partner who has been unable to be impregnated since the patient's injury.

Methodology—Male SCI patients voluntarily participating in the study will be assigned to a 2 to 3 month trial in the vibratory stimulation group. Seminal emissions will be acquired and sperm counted and examined for viability. Patients failing to produce viable sperm will be entered into the electrical stimulation group if they wish to proceed. Patients who continue to fail to produce adequate numbers of viable sperm will undergo stimulation with testicular cooling. Caffeine stimulation will be performed on selected specimens to evaluate its effectiveness on improving sperm motility.

If these techniques produce no improvement in semen quality, the patient will be given the opportunity to participate in a study of direct aspiration of sperm from the surgically-exposed vas deferens. Viability of sperm produced will be determined. The concomitant success or failure of seminal emission production will be assessed statistically. Female partners of patients with satisfactory sperm production will be evaluated physically and if in good health, artificially inseminated.

Preliminary Results—Twenty-nine patients have been entered in the study. A total of 13 patients have attempted vibratory stimulation techniques. Fourteen patients have undergone electroejaculation. One patient has undergone a vas deferens aspiration of spermatozoa.

Of the 13 patients who have used the vibrator regularly, only two have reported consistent ejaculations. One

of these patients has since had poor success and has not been able to produce an ejaculation for semen analysis. The other patient, identified in the previous progress report as having a normal specimen, was referred to a fertility specialist for evaluation of his spouse and possible insemination trials.

No further progress has been made in improving semen quality using intermittent testicular cooling or caffeine stimulation techniques. Motility continues to be suboptimal for specimens collected during this period.

One specimen has been collected using the vas deferens aspiration technique. The results were somewhat encouraging. This patient underwent 9 trials of electroejaculation. On the first trial, he produced a specimen with a sperm count of 303 million cells/ml with 45% motility and 60% normal cells. Subsequent trials only showed a decrease in sperm quality over a period of approximately one year with the last specimen obtained having no motile sperm. Morphology and count were not reported. A very small specimen (0.2 ml) was collected by vas deferens aspiration. This specimen showed a count of less than one million/ml with motility of 50%. Morphology was not reported. Artificial insemination was attempted using this specimen, but no pregnancy was achieved. To date, artificial insemination has not been attempted using specimens collected by vibratory stimulation. Patient compliance using the vibrator and cooling devices has improved some, but is still poor.

Future Plans—Patients who are unsuccessful with both types of stimulation will be offered the opportunity to participate in a study of direct aspiration of sperm from the surgically-exposed proximal vas deferens.

[527] Medical and Psychological Considerations Regarding the Surgical or Pharmacological Treatment of Impotence in Males with Spinal Cord Injury

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Sponsor: *National Institute on Disability and Rehabilitation Research*

Purpose—Erectile dysfunction is prevalent in the spinal cord injury (SCI) populations as well as in other males with various forms of spinal cord dysfunction. For the last 15 years, various penile implants have been developed and utilized for erectile dysfunction; recently, pharmacological interventions have become available as well. Much of the existing literature concerning both of these procedures,

particularly as it relates to SCI, has been focused on medical and/or physical complications, with very little attention paid to the impact of these procedures on sexual behavior, sexual satisfaction and/or relationships. This study will prospectively evaluate the impact of both implant and injection procedures on sexual behavior, sexual satisfaction, and relationships in the SCI population.

Methodology—All couples are screened for evidence of relationship stability and desire to comply with the study protocol. In addition, they are assessed for psychological and physical health, including evidence of drug and/or alcohol abuse, prominent depression, and marital discord. Individuals showing evidence of any of these problems are referred to appropriate counseling or other treatment before beginning either the implant or injection procedure.

Once screening has been completed, the couple is assigned on a randomized basis to either the immediate treatment or delayed treatment group. Those in the immediate treatment group complete a battery of sexual behavior and satisfaction scales before the intervention (implant or injection) is initiated. Three months after the procedure has been completed, the couple repeats the same battery of forms.

In the delayed treatment group, a similar sequence occurs, except the battery is given 3 months prior to the intervention, and is followed with a second administration of the battery immediately prior to intervention. The battery is administered a third time 3 months post-intervention. This sequence of tests controls for spontaneous changes in sexual behavior and/or satisfaction which may occur simply as a function of time or idiosyncratic events.

Preliminary Results—Over the past grant year we identified, on average, two potential participants per month. However, many of these persons are excluded from the study for various reasons, including: 1) the absence of a

regular partner; 2) inadequate reading ability; and, 3) poor physical and/or emotional health. Only a few candidates who have agreed to an implant or injection have refused to participate.

To date, eight couples have completed the immediate intervention protocol, and three more are in the process of completing it. Four couples have completed the delayed intervention, and one more has yet to complete the study. Unfortunately, several couples have dropped out of this group: two couples ended their relationship during the course of the study and two participants experienced complications from the injection procedure.

We have advertised the availability of this screening process and study in our consumer newsletter, *Pushin' On*, and anticipate a continuing supply of potential candidates. Very preliminary results suggest that these interventions do not appear to make a major impact on sexual behaviors and/or frequency, but sexual self-esteem scales do seem to reflect improvement, more for SCI males than for their partners.

Future Plans—We will continue to recruit SCI men and their partners for both the implant and injection treatments and collect data from participants pre- and post-treatment.

Recent Publications Resulting from This Research

Sexual and Marital Satisfaction Following Penile Implant/Injection.
Jaworski TA, Richards JS, Lloyd LK, ASIA Abstracts Digest
15:114, 1989.

Intravenous Injection for Management of Erectile Dysfunction in
Spinal Cord Injury. Paraplegia (accepted for publication).

[528] Influence of Age on Rehabilitation Outcome of Persons with Spinal Cord Injury

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Purpose—As the median age of the U.S. population has increased, special attention is now being given to the health care needs of older persons. Even though most people with spinal cord injury (SCI) are relatively young, the health care needs of the subpopulation of older people with SCI may vary enough from their younger counterparts to suggest a need for alternative treatment modalities.

The purpose of this study is twofold: Phase I will examine the influence of age at the time of SCI on various

demographic, process-oriented, and short-term outcome factors. Phase II will examine the longer-term impact on the health care delivery system of an aging population with SCI.

Methodology—All patients enrolled in the National SCI database will be included in this study. During Phase I, all patients will be divided into six age groups in 15-year intervals. Demographic, process-oriented, and short-term outcome factors will be compared for each age

group, either by calculating the percentage of patients with each factor in each age group and then using the Chi-square test, or by calculating the arithmetic mean for each variable in each age group and then using Student's *t*-test. Multivariate techniques, such as analysis of variance, multiple linear, and logistic regression will be used to control for the possible confounding effects of appropriate covariates such as neurologic level and extent of lesion.

Phase II will be a cross-sectional study comparing current age with outcomes during the current follow-up year. The data will be analyzed in essentially the same manner as in Phase I.

Preliminary Results—The Phase I data set has been created and includes 12,418 patients. Preliminary findings show that patients in the oldest age group are most likely to be white females with motor functional quadriplegia whose injuries resulted from falls. More than one-third

were widowed, slightly over one-half were high school graduates, and very few were still employed in the competitive labor market at the time of their injury. These findings were all highly statistically significant ($p < 0.0001$). There was also a statistically significant decrease in both the mean days from injury to system admission, and the mean total days hospitalized for patients in the oldest age group relative to all other age groups ($p < 0.001$). Patients in the oldest age group were also far more likely to be discharged to nursing homes and to be ventilator-dependent at discharge than their younger counterparts ($p < 0.0001$). In addition, patients in this age group are the least likely to improve neurologically. Not surprisingly, few patients are employed 2 years post-injury.

Future Plans—All Phase I activities have been completed. Completion of Phase II and dissemination activities are underway.

[529] Ultrasound for Urinary Tract Surveillance of Persons with Spinal Cord Injury

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Purpose—Since renal ultrasound examinations (RUSE) are easily performed, completely noninvasive, well-tolerated, and relatively inexpensive, RUSE could prove to be an ideal method for the periodic routine long-term surveillance of the upper urinary tract. This surveillance would help considerably in detecting and managing some of the most serious secondary complications of SCI.

This study seeks to: 1) determine the role of RUSE in the periodic routine long-term upper urinary tract surveillance of persons with SCI; 2) determine whether RUSE of the upper urinary tract is sufficiently sensitive to detect abnormalities identified by excretory urography (EXU) or comprehensive renal scintigraphy (CRSP); and, 3) determine in what instances RUSE could be substituted for either EXU or CRSP in the routine screening for secondary urologic complications among persons with SCI.

Methodology—Investigators have previously shown the utility of CRSP for long-term urinary tract screening in lieu of the more traditional EXU and serum creatinine or creatinine clearance. Building on that experience and other recent studies of ultrasound, this project will compare the results of RUSE with those obtained via EXU and CRSP for approximately 200 persons with SCI. In most instances, the tests will be performed on the same day, and in no instances will they be performed more than two weeks apart.

Progress—The study began June 1, 1990. Data collection has begun. First year efforts will concentrate on the development of data collection instruments and an accompanying syllabus. CRSP, EXU, and RUSE will be performed and evaluated.

[530] A Clinically-Derived Protocol for Changing Condom Catheters in Males with Spinal Cord Injury

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Sponsor: *National Institute on Disability and Rehabilitation Research*

Purpose—While meticulous hygiene and observation of the condom catheter and penis is consistently advocated, a disagreement exists on how often the condom catheter needs to be routinely changed. Recommendations range from changing it twice a day to changing it every few days. In fact, several of the most highly regarded nursing texts make no recommendation on how frequently it should be changed. Failure to reach a consensus on this issue is undoubtedly the result of the lack of any meaningful data upon which to base this clinically important decision.

The objectives of this randomized controlled clinical trial are: 1) to determine the incidence of urinary tract and penile skin complications for male patients with spinal cord injury (SCI) whose condom catheters are changed daily, every other day, or every third day; and, 2) to develop a protocol for routine changing of those catheters.

Methodology—The study population will include all male patients with SCI admitted to our hospital who use condom catheter urinary collection devices, are asymptomatic for urinary tract infection for at least 48 hours, and are free from other urinary tract and penile skin complications at the time of entry into the study.

Subjects will be randomly assigned to one of three groups: 1) patients whose condom catheters are changed

every day (Group I); 2) changed every other day (Group II); and, 3) every third day (Group III). Routine inspection of the penile skin will occur whenever the catheter is changed regardless of study group assignment. Total study population will be 87 patients. The duration of the study will be 30 days for each patient. A single brand of condom catheter has been selected and will be used for all study subjects. Patients having numerous accidents related to an improperly fitting catheter will be dropped from the study. At the conclusion of the study, a protocol will be developed for routine changing of these catheters.

Preliminary Results—During the past year, there has been a continuing problem in obtaining patients to be study subjects, the 30-day time factor being the major obstacle (many patients are discharged before they can complete the study). It was decided to delete the third study group and include only patients in the first two groups. In addition, to increase the sample size, patients from the SCI outpatient department will be included. The nurse clinician in the clinic will assess dependability and obtain patient consent to participate. Currently, 14 patients have participated in the inpatient component of the study.

Future Plans—Plans are to continue enrolling patients.

[531] Histopathology of Denervated Skin Following Spinal Cord Injury

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Purpose—Skin complications represent a leading source of morbidity in the spinal cord injured population, yet relatively little is known about the histopathology of denervated skin. In order to improve the clinical management of these complications, and ultimately to prevent them, we are conducting a study to increase the understanding of precisely what happens at the cellular and tissue level when the body's largest organ, the skin, is denervated.

The objectives of this study are to: 1) describe and establish the histopathology of denervated skin in patients with spinal cord injury (SCI) using appropriate laboratory and electron-microscopic techniques; 2) establish the pathogenesis and natural history of skin changes following SCI; 3) determine the nature of the relationship between the neurologic level and extent of SCI and the occurrence of specific skin changes; and, 4) determine whether there is a meaningful correlation between the

severity of post-SCI skin complications and possible covariates such as the histopathologic changes observed, the neurologic level, and extent of lesion.

Methodology—Skin punch biopsies are obtained from patients with SCI who have injuries that are neurologically complete, sensory sparing only, or motor nonfunctional. Study patients are divided into three groups by level of injury; 1) T6 and above; 2) T7-T11 with sacral reflexes present and upper motor neuron evidence to legs; and, 3) T12 and below with absence of sacral reflexes and lower motor neuron loss to legs. Biopsy specimens are obtained from a group of patients who have chronic SCI, more than one year post-injury, as well as a prospective group of patients who were injured less than two months prior to the time the skin biopsy was obtained. Skin biopsies will be examined by a dermatopathologist using histopathologic methods of examination. In addition, a subset of the biopsies will be studied by electron microscopy.

Preliminary Results—Considerable time is required to review records and select patients who are appropriate to the study. Consent must also be obtained, a sometimes difficult task in the prospective group of patients when it is explained that a second biopsy will be required in 2 years. The prospective study has almost been completed (Groups 2 and 3 need two more patients each). It is extremely difficult to find complete injuries in these categories. The electron microscopy study has had all the specimens collected and findings are being summarized. Since this is a controlled study, the dermatopathologist is blinded; however, the principal investigator received the reports. Some preliminary analyses of the findings will be initiated later in this project year.

Future Plans—Studies of biopsy specimens in the chronic group will continue. We will also start to evaluate early results from these biopsy specimens to see if the histopathologic findings are related to the level of injury.

[532] Natural History and Clinical Course of Skin Complications (Excluding Pressure Ulcers) in Persons with Spinal Cord Injury

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Sponsor: *National Institute on Disability and Rehabilitation Research*

Purpose—Persons with spinal cord injury (SCI) frequently develop an array of potentially serious skin complications in addition to the more dramatic pressure ulcer typically associated with spinal paralysis. Examples include superficial and deep bacterial and/or fungal infections, furuncles, abscesses, dermal fibrosis, paronychia, and a host of related changes affecting the nail plate, bed, and wall. Our experience is that nonpressure ulcer skin complications represent a more significant and serious source of morbidity in this population than generally acknowledged.

The objectives of this study are to: 1) establish a clinically useful method to document the occurrence, etiology, definitive characteristics, management, and treatment outcome(s) of all nonpressure ulcer skin lesions occurring in a series of patients with SCI; 2) determine the nature of the relationship(s), if any, between nonpressure ulcer skin lesions in patients with SCI and specific characteristics of the spinal injury itself (e.g., neurologic level and extent of lesion, time post-injury, etc.); and, 3) develop, print, and distribute a clinically-oriented, teaching/training monograph devoted

to the photographic documentation and description of nonpressure ulcer skin lesions in patients with SCI.

Methodology—A data collection instrument has been developed, refined, and field-tested to document non-pressure ulcer skin complications in patients with SCI. A history is obtained and a physical examination is performed at the patient's annual follow-up examination. A clinical nurse specialist examines the patient's skin and completes the data collection forms. Data are obtained by actual observation of the patient. When possible, a diagnosis of the skin lesion(s) is made. Skin lesions are documented by photographs. When appropriate, bacterial and/or fungal cultures are acquired and appropriate treatment is given.

The analysis will be stratified by potential risk factors such as neurologic level and extent of lesion, age group, sex, and time post-injury. A high quality, clinically-oriented monograph will be produced by the project team.

Preliminary Results—Data have been collected on 360 patient visits. Fifty-two patients were seen at two successive

annual visits so that there are now 308 patients total. These numbers are fairly close to the projected number of patients to be studied. The compliance meter which was used initially to obtain a more objective measure of the amount of skin thickening was discontinued. After a thorough evaluation of the measurements using the compliance meter and comparing those measurements to the clinical assessment of skin thickening, it became obvious that the correlation was very poor; of even more concern was the fact that the compliance meter did not give consistent readings in the same subjects.

[533] Natural History and Clinical Course of Urinary Tract Complications in Patients with Spinal Cord Dysfunction

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Purpose—Appropriate clinical management of patients with neurogenic bladders resulting from spinal cord dysfunction requires: 1) knowledge of the natural history or clinical course of urinary tract complications in this group; and, 2) data from which to determine if urinary complications in this group are predictable from early post injury urinary tract status and method of early bladder drainage management. The objectives of this study include: 1) to document the natural history and clinical course of urinary tract complications in persons with spinal cord injury (SCI) by continuing to build a urology database; 2) to answer specific research questions addressing the effects of *a*) various bladder drainage management methods; *b*) various bacterial pathogens; and, *c*) various demographic factors (including age, sex, etc.) on long-term renal function, measured by effective renal plasma flow (ERPF), and the development of urologic complications including orchitis and/or epididymitis, penoscrotal abscess, penoscrotal fistula, ureterectasis, pyelocaliectasis, and calculi in a population with SCI; and, 3) to develop, refine, and offer for extramural acquisition a transportable urologic complication data collection protocol and its associated database. One of the specific research questions is addressed: "What is the incidence of clinically significant urologic complications in females with spinal cord injury?"

Methodology—Data are collected for each patient admitted to the University of Alabama—Spinal Cord Injury Care System (UAB-SCICS) at admission, discharge, and

We are continuing to take photographs of interesting skin lesions which may be used for the monograph at the end of the study.

It is still too early to analyze the data in depth. However, we are starting to look at trends in the data, especially the clinical grades of dermal thickening.

Future Plans—The goal is to obtain data on 250 to 400 patients annually. As additional data become available, preliminary analyses will be made to evaluate the progress of the study.

annually thereafter. In addition, data have been collected retrospectively on 596 patients admitted to the UAB-SCICS between 1970 and 1979; prospective data are collected on these patients as they return for their annual follow-up examinations.

In our study of the incidence of urologic complications in females, patients were stratified by known risk factors (including method of bladder drainage management and neurologic level, and extent of lesion). The incidence of each urologic complication was then calculated for both females and males.

Preliminary Results—Complete studies have been performed and data recorded on 327 patients from a retrospective study group and 876 patients from a prospective group, thus yielding 1,203 completed studies to date.

In a study of 110 females injured between 1973 and 1985, multiple linear regression was used to assess the effects of neurologic classification method of bladder management and renal complications on renal functions at discharge and up to 10 years post-injury. However, bladder management methods and neurologic classification showed no statistically significant effect on renal function. Conclusively, the method of bladder management in females does not adversely effect long-term renal function.

A second study compared 42 females with 186 males injured between 1973 and 1984 according to age, race, neurologic level and extent of lesion, method of bladder management, and incidence of secondary urologic

complications during the first 4 years post-injury. No statistically significant differences between males and females were found when multivariate statistical techniques were used to control for the possible confounding effects of age, race, bladder drainage management, neurologic level and extent of lesion.

Future Plans—Five additional research questions have been included: 1) What are the effects of various bladder drainage management methods on long-term renal func-

tion in persons with SCI? 2) When are persons with SCI at greatest risk for developing clinically significant urologic complications? 3) What is the optimal schedule for routine urologic follow-up of persons who have experienced a spinal cord injury? 4) What is the effect of external sphincterotomy on long-term urologic function in persons with spinal cord injury? and, 5) Are the consequences of renal calculi more serious in older than younger persons with SCI? The first question will be addressed during the next year.

[534] Disuse Osteoporosis in Spinal Cord Injured Patients

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Sponsor: *National Institute on Disability and Rehabilitation Research*

Purpose—Our research project had three goals: 1) to describe the natural history of bone loss with acute paralysis in newly injured spinal cord injured patients; 2) to assess the degree of osteoporosis and associated fracture risk in patients with spinal cord injury of long duration; and 3) to examine the efficacy of two intervention modalities, functional electric stimulation (FES), and upright stance on a tilt table, to prevent or reverse bone loss.

Progress/Methodology—We studied 30 newly injured patients prospectively for up to 2 years postinjury. The chronic response was investigated in a retrospective study of individuals with duration of injury between 1 and 33 years. Data collection included bone mineral density measurements of the lumbar spine and proximal femur (by dual photon absorptiometry), and biochemical assays of bone metabolism. The two studies are considered together as representing the early and later stages of a continuum of responses.

Results—Different responses were observed in the proximal femur than in the spine. In the femur, where mechanical loads had been greatly reduced or eliminated, the immediate response to acute paralysis was increased bone remodeling resulting in rapid loss. The rate of bone loss was approximately 1% per month, with an indication of more rapid loss in the first 4 to 5 months (2.1%), and slower loss thereafter (0.9%). Bone turnover was elevated above normal, and increases were observed in both resorption and formation markers, presumably, with resorption rate greater than formation.

With chronic paralysis, there appeared to be a stabilization of this response. This is reflected both by normal levels of metabolic markers, and no evidence of continued loss over time (that is, lack of correlation between duration of paralysis and bone mass). However, mean femoral bone mass in this group was decreased below predicted normal values by 28%.

The specificity of this response was examined in a study of 21 polio survivors who had different levels of ambulation, and differing lower extremity muscle strength. Subjects were grouped by ambulation type: wheelchair use, ambulation with assistive device or abnormal gait, and normal ambulation. Mean femur bone mineral density of all subjects (not grouped) was significantly below predicted normal values (92%). However, if subjects were separated by ambulation status, the normally ambulating subjects were not different from predicted normal values (101%), while those who used assistive devices and those who used wheelchairs had femur bone mineral density significantly below normal (84% and 83%, respectively). There was no significant difference between these latter mean values. This may be due to several factors, such as: several wheelchair users were semi-ambulant and/or recently in wheelchairs, others had variable muscle strength and distribution of paralysis/paresis regardless of whether they were able to ambulate.

No decline was observed in the lumbar spine either with acute or chronic paralysis. It is suggested that weight-bearing of the upper body during sitting provides sufficient loading of the vertebrae to maintain skeletal integrity.

Studies of two intervention modalities were initiated. Six subjects participated in a study of the application of FES to the quadriceps femoris muscle, 3 times per week, 50-60 minutes per session, over 8 months. No significant changes were observed in either muscle strength (while stimulated) or bone mineral density. The lack of response may be due to several factors. The duration of injury for all subjects was greater than 2 years (and up to 25 years), so that they may have had a reduced physiological capacity to respond to the treatment, and the stimulation parameters may have been inadequate (100 milliamps, surface electrodes). We were unable to complete the study of upright stance because of low recruitment and poor compliance among participants.

Implications—The results indicate that the skeleton responds rapidly and locally to immobilization, but that

this response may stabilize within a few years after the injury. We were unable to demonstrate a response to electrical stimulation in patients with chronic spinal cord injury. The implication of these data, taken together, is that therapeutic modalities (such as medications to suppress bone loss or physical interventions) should begin within the first year in order to maximize effectiveness.

Recent Publications Resulting from This Research

Effects of Chronic Immobilization (Paralysis) on Vertebral and Femoral Bone Mineral Density. Kiratli BJ, Agre JC, Smith EL, J Bone Miner Res 4:S173, 1989.
Femoral Bone Mineral Density in Polio Survivors. Kiratli BJ et al., Arch Phys Med Rehabil 70:A16, 1989.
Reduction in Femoral Neck Strength with Disuse. Kiratli BJ et al., Am J Phys Anthropol 81:251, 1990.

[535] Standard Versus Low Molecular Weight Heparin in the Prevention of Thromboembolism in Spinal Cord Injury

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Purpose—The purpose of this study is to determine whether LMW (Logiparin) is as safe and effective as standard heparin in the prevention of thromboembolism in patients with complete motor paralysis due to spinal cord injury (SCI).

Methodology—After informed consent is obtained, patients are randomized within 72 hours of injury to receive either Logiparin, 3500 u subcutaneously once daily; or standard heparin, 5000 u subcutaneously every 8 hours for an 8-week period. Activated partial thromboplastin times, platelet counts, hemoglobin, and hematocrit are obtained at baseline and twice weekly. Venous flow studies, including impedance plethysmography, Doppler examination, and in selected cases compression ultrasound, are obtained at baseline and twice weekly for the first 2 weeks, once weekly for the next 2 weeks, and biweekly for the last 4 weeks. Positive results on venous flow studies are confirmed with venography. The study is discontinued if a patient has a thromboembolic event or bleeds.

Results—In the first part of this investigation, 41 consecutive patients were randomized within 72 hours of

injury to receive either Logiparin or standard heparin. The age, sex distribution, location of spinal injury, and baseline activated partial thromboplastin time were very similar for both groups. Of the 20 patients randomized to Logiparin, 16 completed the 8 weeks without incident. Two were transferred to other institutions 4 to 29 days after initiation of therapy; none of these patients experienced thrombosis or bleeding. An additional two patients had to be switched to standard heparin at day 22 and 23 because of a temporary shortage of the Logiparin. None of the low molecular weight heparin-treated patients had thrombosis or bleeding (95% confidence interval, 0% to 14%).

Of the 21 patients randomized to standard heparin, 7 experienced bleeding or thrombotic events, giving a cumulative event rate of 34.7% (95% confidence interval, 13.7% to 55.2%). Two patients had bleeding severe enough to require discontinuation of the heparin; in both, the activated partial thromboplastin time was considerably prolonged. Three patients had deep vein thrombosis documented by abnormal venous flow studies; in two, the diagnosis was confirmed by venography, and in the third, the flow study 5 days earlier had been normal and at the time of the abnormal flow study the affected leg was

swollen. This patient was treated with full-dose anticoagulation and a follow-up flow study showed resolution of the thrombus. Two patients, aged 22 and 52, suddenly expired while being turned in bed on days 38 and 21 after admission. Both had been considered to be making excellent progress and had no other medical illness. In both patients, post-mortem diagnosis was massive pulmonary embolism. The remaining 12 patients completed the 8 weeks without incident.

None of the patients on Logiparin had a hemorrhage or thrombosis, whereas seven subjects assigned to stan-

dard heparin had such events. This difference in event rate is statistically significant ($p=0.006$). Examining the frequency of thrombosis alone also yielded a significant difference ($p=0.020$). Because there was a statistically significant increase in event rate in the standard heparin group, and because two patients in this group had fatal thrombosis, the trial was terminated.

Recent Publications Resulting from This Research

Low Molecular Weight Heparin in the Prevention of Thromboembolism After Spinal Cord Injury. Green D et al., *Ann Intern Med* (in press).

[536] Managing Urinary Tract Infection in Spinal Cord Injury

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Purpose—In this project we are investigating the techniques and procedures that will improve the prevention and treatment of urinary tract infection. Our objectives are to: 1) increase patient involvement and responsibility in monitoring, prevention, and management of urinary tract infection; 2) develop a systematic approach in identifying the presence of infection, localizing the site of infection, and controlling the infection with simple steps; and, 3) identify a safe management method for resistant bacteriuria.

Methodology—*Self-monitoring bacteriuria at home.* The Dip-Slide method used in this project to detect the presence or absence of bacteriuria appeared to be easy for the patients to learn and perform. Before discharge, patients were instructed in the procedure for using Dip-Slides, followed by an actual performance of the test and interpretation of the results by the patient. With this technique, the Dip-Slide with culture medium on each side was dipped into a fresh urine specimen, then placed in a warm location for 24 hours. The test results were incorporated into the bladder management at the first outpatient visit. The colonies that grew on the Dip-Slide were easily identified. Patients had no difficulty determining the colony density on the Dip-Slide. It is an effective, convenient, and less expensive screening procedure for home use. Once able to monitor bacteriuria, the patient was instructed in the proper steps to take when asymptomatic bacteriuria is found. Emphasis was placed on the need to increase the frequency of bladder emptying.

Progress/Preliminary Results—There are 35 patients participating in the study. Seven of the 35 did not perform the assigned testing at home. The seven indicated that the main reason for not performing the self-monitoring was that there were too many things to do after discharge. More than half of the studied patients indicated interest in continuing the test for self-monitoring. Six patients had significant bacteriuria, and 12 had sterile urine culture as detected by the Dip-Slide method.

Localizing the site of urinary infection prior to anti-bacterial therapy. In a previous study, we found that the Fairley Bladder Washout test could be simplified for use as a clinical screening procedure to localize the site of infection and sometimes achieve therapeutic results.

The total number of patients involved is now 28. Among the 20 patients who had bladder irrigation with diluted Betadine solution (30 ml), 4 patients experienced bladder spasm. Of all the patients tested, half achieved complete or near-complete bladder preparation in that the post-irrigation specimen had none or few colonies in the Dip-Slide. Preliminary results indicated that one-third (10) of the 28 subjects appeared to have a lower tract infection, 8 appeared to have an upper tract infection, and the rest were indeterminate.

Managing lower tract infection with resistant organisms. To date, three patients have been studied. All patients have shown conversion of a highly resistant organism to a different organism. One converted to a different highly resistant organism, one converted to a highly sensitive organism, and the other had sterile urine after irrigation procedures.

[537] Expiratory Muscle Training in Spinal Cord Injury: A Randomized Controlled Clinical Trial

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Purpose—This study has been designed to determine whether a simple expiratory muscle training program will be effective in improving expiratory force, increasing endurance, and reducing complications in individuals with spinal cord injury (SCI).

Methodology—Approximately 60 patients who have had a cervical or upper thoracic SCI no longer than 6 months prior to evaluation and who meet study criteria are to be studied. At initial evaluation, the patient undergoes a comprehensive medical history, physical examination, and pulmonary function testing. Each patient is instructed in the proper use of an expiratory resistive breathing training device, through which the patient performs 10 expiratory maneuvers twice a day, for 30 days. Patients are monitored by physician-investigators while performing the expiratory maneuvers. Patients are randomly assigned into one of two groups: 1) the Expiratory Training Group which performs the program with a closed-end resistive breathing device; and, 2) the Control Group

which uses the device with an open gauge without respiratory resistance. At the end of 30 days of respiratory muscle training, each patient undergoes an exit evaluation of history, physical exam, and pulmonary function testing. The same procedure is performed at follow-up. Comparisons of results between training groups and between time periods is then conducted.

Progress—Twenty-seven SCI patients have completed their participation in the project, and five are actively involved with the clinical trial. Of the total 32 subjects, 9 underwent initial clinical and pulmonary function testing and then withdrew from the study. The remaining 23 subjects consist of 14 patients randomized to the Expiratory Resistance Training Group (including 1 currently enrolled) and 9 randomized to the Control Training Group (including 4 currently enrolled). Additional subject recruitment and data collection are planned. Preliminary data analysis is in progress and preparation for presentation of the technique and preliminary data is underway.

[538] Treatment of Spasticity with Electrical Stimulation in Spinal Cord Injured Men and Women

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Sponsor: *National Institute on Disability and Rehabilitation Research*

Purpose—Spasticity, common in spinal cord injury (SCI), frequently interferes with an individual's work, sleep, self-care, and recreational activities, and can contribute to increased morbidity. Fertility studies at the National Rehabilitation Hospital have shown that SCI men receiving rectal probe electrostimulation (RPES) for ejaculation experience significant improvement in their spasticity for up to 6 or 8 hours and occasionally longer. This 3-year study will determine the technical factors associated with modifying spasticity and what subject characteristics affect the ability to modify spasticity using RPES.

Methodology—During the first year, 10 healthy SCI men will be tested twice a month. The testing includes assessment of subjects' spasticity before RPES and day-long monitoring by an independent team of assessors. Subjects are also asked to rate any changes in their spasticity and performance of self-care activities. The study will include five additional SCI men and five SCI women in both the second and third years. Data will be analyzed to determine what factors most strongly modify spasticity.

Implications—RPES may become an effective alternative to other modalities, which often have undesirable side effects.

Recent Publications Resulting from This Research

The Effects on Spasticity of Rectal Probe Electrostimulation. Halstead LS, Seager SWJ, in Proceedings of the American Spinal Injury Association, 1989.

[539] Voice-Augmented Telephone Access for Quadriplegics

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Sponsor: *National Institute of Child Health and Human Development, National Institutes of Health*

Purpose—Spinal cord injury causes dramatic changes in a person's ability to function in society. With proper rehabilitation, many paraplegics and some quadriplegics are able to live and function with a high degree of independence. Those with C-5 and above paralysis currently must depend on family, medical

personnel, and a variety of assistive devices to accomplish the most basic activities of daily life. This project proposes to use automatic speech recognition to enhance telephone use by quadriplegics. It also proposes to examine use of the same system for note-taking and note retrieval.

[540] Treatment of Infertility Among Spinal Cord Injured Males Using Vibratory Stimulation

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Sponsor: *National Institute on Disability and Rehabilitation Research*

Purpose—The objective of this project is to evaluate serial changes in hormonal levels, semen analysis findings, and clinical course using repeated vibratory stimulation of the penis in spinal cord injured (SCI) men. By determining relationships between external stimulation, serial hormonal changes, and serial semen analysis results, this study is expected to provide new insights into mechanisms of infertility and their management in SCI patients.

Methodology—Twenty-five male patients between the ages of 18 and 45 years with acute traumatic SCI of 6 months duration or longer and no associated injury or illness who agree to participate, and their partners will be studied. Following a detailed explanation of procedures, risks, and benefits, informed consent is

obtained from each patient. Strict confidentiality is maintained.

Progress—A consent form has been developed and revised, and Institutional Review Board approval obtained. The actual procedure for vibratory stimulation was developed. Pilot information was obtained from several patients concerning the use of vibratory stimulation. The procedures were refined by the Northwestern Memorial Hospital Reproductive Endocrinology Laboratory and the Andrology Laboratory, where hormone and semen studies, respectively, will be performed.

To date, one subject with high thoracic paraplegia has given informed consent, been formally enrolled, undergone vibratory stimulation, and is actively participating in the project. Additional data collection is planned.

[541] Neuromuscular Plasticity: Recovery After Spinalization

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

Purpose—Our emphasis is on the plasticity of the neuromuscular system in response to spinal lesions and the consequences of the plasticity or lack of it, to locomotor capabilities.

Methodology—The experimental models to be used in addition to normal cats are: low thoracic complete spinalization, surgical isolation of the lumbar cord, partial deafferentation, partial denervation of muscle, self-reinnervation of muscle, and surgical removal of synergistic muscles. Variations of these models include three forms of training, passive hindlimb oscillation and static posture maintenance of spinalized cats, and hindlimb oscillation of spinally isolated cats. The plasticity of

movement control will be studied at the systemic level by carefully assessing force, velocity, length, and electromyographic pattern of individual muscles. Cellular responses of and within motor units and of muscles, will be studied in an effort to define mechanisms that might play a role in the induction of the neuromuscular adaptations.

Implications—These studies should provide further data suggesting that the clinical benefits of optimizing post-neural lesion care can be significant. Further, these studies should provide important data which identifies the features of the rehabilitation procedures that are particularly effective.

[542] Movement Deficits Following Spinal Cord Lesions (Macaques)

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Purpose—Motor disorders have long been known to follow damage to the dorsal columns. However, following extensive postoperative training, the only enduring deficits are those involving the grasping and manipulation of objects with the fingers. These results have indicated that the dorsal columns provide specialized sensory information that is critical to the execution of the precise finger movements involved in active touch. As a source of feedback to the motor cortex, the dorsal columns may provide information that is critical for digital fractionation, involving precisely timed and directed sequences of movement of individual digits.

Methodology—The proposed experiments test this hypothesis with a methodology that permits direct challenges and measurements of digital motor acts. We have developed two paradigms which evaluate the ability of monkeys to make independent finger movements or track moving stimuli with the finger. The experiments will evaluate in detail the deficits in individual finger movements that result from DC lesions, and the animals will be retrained to maximal capacity with specialized

shaping procedures. The contributions of separate populations of joint and cutaneous receptors to digital fractionation and tracking will be evaluated, and the role of dorsolateral sensory pathways in recovery of digital dexterity will be determined. Because the corticospinal pathway is regarded as the afferent pathway of control over motoneurons involved in digital fractionation of primates, the consequences of dorsal column and corticospinal tract section will be compared directly.

Results—We have previously demonstrated that many of the initially debilitating motor effects of DC lesions recover with training. Fine movements of the hands have been an exception to this, but training procedures are critically important for providing full opportunity for recovery. The stepwise shaping procedures for the finger movement tasks are appropriate to test the limits of functional plasticity of the spinal cord following well-defined damage.

Implications—A major goal of this work is to provide information of direct relevance to clinical neurology and

neurosurgery. A better understanding of spinal tract function is fundamental for accurate diagnosis of central nervous system pathology affecting the somatosensory system. Also, an accurate description of the functional

contributions of the different spinal inputs to these regions is fundamental to an understanding of somatosensory coding mechanisms at thalamic and cortical levels.

[543] Fundamental Studies in Spinal Cord Injury

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Purpose/Methodology—In order to provide a scientific basis for a possible therapeutic approach to human spinal cord injury, animal (rat) trials are being conducted with multiple classifications of agents, including calcium-entry blockers, steroids, hyperbaric oxygen, and antioxidants. In addition, therapeutic trials with phosphate and other buffers will be continued. Therapeutic trials will, at the same time, test various hypotheses concerning primary and secondary injury factors in the production of necrosis following traumatic injury. These include calcium toxicity, ischemia, and free radical injury. Lactic acid myelopathy *in vivo* that developed earlier will be evaluated, using pH electrodes and a chemical microsensor, to

determine the extracellular pHs in the spinal cord required to produce myelopathic changes. Studies will be completed that were previously initiated on secondary changes in the rat spinal cord following Wallerian degeneration and postmortem autolysis, which are being compared with the primary traumatic events, and are critical to the interpretation of the latter.

Future Plans—Future studies are anticipated which will determine the role of calcium in these secondary events which are present in the traumatized spinal cord. In addition, freeze-fracture membrane pathological evaluation of spinal cord trauma will be initiated.

[544] Clinical Research Center for Acute Spinal Cord Injuries

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

Purpose—This proposal is for a continuation of the Clinical Research Center for Acute Spinal Cord Injuries at New York University. The underlying theme of this proposal is to intensively study experimental spinal cord injury at a basic pathophysiologic level as a model for clinical spinal cord injury. Major emphasis will be placed on studying the effects of trauma to the spinal cord beyond the acute period following the injury.

Methodology—Changes in the distribution of ions (such as calcium, sodium, and potassium) within the cord, neurophysiologic studies of ascending and descending pathways, and the role of cellular inflammatory response as a cause of progressive damage to the spinal cord in the weeks following the trauma, will be used to test the hypothesis that the injury to the spinal cord is progressive beyond the first 12-24 hours. This will provide important

information about treatment regimens which may have to be utilized for extended periods if any recovery is to be achieved. In addition to determining these pathophysiologic changes in the spinal cord, the effect of different treatment modalities on these parameters will be tested.

The clinical studies will examine the efficacy of opioid antagonists and corticosteroids in the amelioration of spinal cord injury as part of a multi-center randomized trial. Alternate therapies will also be tested in pilot studies. Experimental treatment will test the hypothesis that the opioid receptors play a role in spinal cord injury and that this therapy and corticosteroids are effective even when administered more than 1 hour after injury. The evaluation of therapy on the recovery of injured animals will include neurologic, physiologic, and morphologic outcome parameters. This will provide a

comprehensive picture of the experimentally injured spinal cord and the response to therapy that will provide a rational basis for selecting clinical therapies.

Implications—The goal of a Center for Spinal Cord Injury will be realized by the close integration of the component projects of this proposal.

[545] Evaluation of Neural Implantation for Recovery from Spinal Injury

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Purpose/Methodology—The object of this project is to use implanted neural tissue and cells to facilitate functional recovery after contusion injury to the spinal cord. Survival of implants and integration of the implants into host tissue will be investigated at set intervals using light

and electron microscopy and immunocytochemistry. Behavioral deficits resulting from spinal cord contusion and changes to these parameters due to tissue implant will be regularly assessed. All evaluations will include both acute and chronic preparations.

[546] Microstimulation of the Sacral Spinal Cord

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Purpose—The objective of this research is to determine the feasibility of using microstimulation of the sacral spinal cord with arrays of ultraminiature electrodes to restore control of genito-urinary functions in individuals with spinal cord lesions.

Preliminary Results—The location of cell bodies of external urethral sphincter neurons and terminal connections of penile afferents in the sacral spinal cord have been determined in the cat.

[547] Microstimulation of the Sacral Spinal Cord

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Purpose—The objective of this research is to determine the feasibility of utilizing microstimulation of the sacral spinal cord as part of a neural prosthesis for controlling micturition and sexual function in spinal cord injury victims.

Progress—Wheat germ agglutinin-horseradish peroxidase-labeled neurons have been identified in

sacral spinal cord sections after injection of the tracer in the external urethral sphincter. The tracer path was clearly visible in both afferent and efferent neurons from the pudendal nerve, but no interneurons could be detected.

[548] The Role of Weightbearing and FES-Induced Exercises on Bone Loss After Acute Spinal Cord Injury

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Sponsor: Paralyzed Veterans of America, Spinal Cord Research Foundation

Purpose—Prominent among the metabolic changes after a spinal cord injury (SCI) is the abnormal calcium metabolism that ultimately results in disuse osteoporosis with significant bone loss occurring below the level of injury. The objectives of this study are to: 1) determine if bone resorption can be prevented by exercises which place mechanical stresses across muscle and bone; 2) investigate the reversibility of disuse osteoporosis with vigorous remobilization; and, 3) determine the most effective exercise program in preventing disuse osteoporosis.

Methodology—A group of chronic spinal cord injured patients will be placed on a cycling exercise program powered by functional electrical stimulation (FES-CE). The reversibility of disuse osteoporosis with vigorous remobilization will be investigated in this group. A group of acute spinal cord injured patients will be placed in one of three exercise programs aimed at studying the most effective means to prevent disuse osteoporosis. These exercise programs will include weightbearing through quiet standing, FES-induced isometric exercises, and FES-induced bicycle ergometry. The effects of these exercises on bone loss will be monitored by biochemical methods and by measurements of bone density.

Progress—Progress has been made in determining the effect of muscle contraction versus weightbearing on the reversal of neurogenic osteopenia following SCI. Active recruitment and early data gathering is ongoing in the control group and isometric FES portion of the study.

Results—Of the 10 subjects involved in the chronic SCI study, 8 subjects have completed 9 months of training. All subjects had evidence of significant osteopenia; however, normal parameters of calcium metabolism

reflected the stimulation of bone formation. Measurements of regional bone mass revealed no significant changes. Concomitant endocrine studies revealed a significant increase in parathyroid hormone and vitamin D. These data suggest that although lower extremity FES-CE increases osteoblastic activity, it is followed by secondary hyperparathyroidism which may negate anticipated increments in bone mineral density.

To date, 13 subjects have been enrolled in the acute SCI study of FES-CE. After 12 weeks of training, bone mineral density at the lumbar spine increased slightly, while losses in bone masses were noted at all other sites. There were no significant changes in serum calcium, phosphate, alkaline phosphatase, or osteocalcin with training. However, urine calcium decreased significantly. These preliminary results suggest that FES-CE appears to have no significant effect on preventing osteopenia, but is associated with a dramatic decline in urine calcium excretion.

Future Plans/Implications—Studies will be conducted to determine if secondary hyperparathyroidism observed in chronic subjects is reversible.

Recent Publications Resulting from This Research

Can Functional Electrical Stimulation Cycle Ergometry Reverse Disuse Osteopenia in Chronic Spinal Cord Injury? (Abstract). Bloomfield SA et al., in American Society for Bone and Mineral Research, 1990.

Changes in Regional Bone Mineral Density with Immobilization Due to Spinal Cord Injury (Abstract). Bloomfield SA, Mysiw WJ, Jackson RD, Med Sci Sports Exer 22(2):S76, 1990.

Effect of Functional Electrical Stimulation Calcium and Bone Metabolism in Chronic Spinal Cord Injury (Abstract). Jackson RD, Mysiw WJ, Bloomfield SA, Arch Phys Med Rehabil 71(10):786, 1990.

Hypercalciuria But Not Bone Loss is Prevented by Functional Electrical Stimulation (Abstract). Mysiw WJ, Jackson RD, Bloomfield SA, Arch Phys Med Rehabil 71(10):795, 1990.

[549] Bladder Reinnervation by Anastomosis of L4 VR to L6 VR While Leaving Intact L4 DR as Starter of Micturition

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Sponsor: *Paralyzed Veterans of America, Spinal Cord Research Foundation*

Purpose—The objective of this project is to establish an alternative reflex pathway “skin-CNS-bladder” for micturition. In most spinal cord injured patients, the normal reflex pathway “bladder-CNS-bladder” has been severely damaged. A new pathway would provide a means to bring micturition under voluntary control with the patient initiating voiding by scratching the skin.

Methodology—In rats, the motor nerve of a normal reflex arc above the injury (L4 VR) will be connected to the motor nerve leading to the bladder below the injury (L6 VR), while leaving the intact L4 DR (sensory root) as a starter of micturition. After three months of regeneration, the new pathway will be studied electrophysiologically and by HRP neural tracing. Signals from the skin and muscles remain intact and are used to activate the new micturition reflex pathway.

Progress—The new reflex pathway has been successfully established in terms of histology and is functionally effective.

Results—The results demonstrated that the motor root above the spinal micturition center can be used to reinnervate the bladder, and that the axons can regenerate to at least as far as pelvic ganglia.

Future Plans/Implications—These results have strong potential for clinical application in patients with neuro-pathic bladders. It may be observed that since impulses from efferent neurons of a somatic reflex arc have been utilized to initiate response of an autonomic effector, it may be possible for similar pathways to be developed for other applications to problems caused by disease or injury to the spinal cord.

[550] Prophylaxis for Deep Vein Thrombosis in Acute Spinal Cord Injury Comparing Two Doses of Low Molecular Weight Heparinoid in Combination with External Pneumatic Compression

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Sponsor: *Paralyzed Veterans of America, Spinal Cord Research Foundation; National Institute on Disability and Rehabilitation Research*

Purpose—The evaluation of various methods of prophylaxis for deep vein thrombosis (DVT) in acute spinal cord injury remains an important focus of research. Adjusted dose heparin and either low dose heparin or aspirin/dipyridamole in combination with external pneumatic compression have all demonstrated a reduction in the incidence of DVT. A low molecular weight heparinoid (ORG 10172) has been developed which possesses more rapid subcutaneous absorption, a prolonged duration of action, selective inhibition of factors Xa and IIa, and no reported effect on platelets. We conducted a pilot study to evaluate two doses of ORG 10172 in combination with external pneumatic compression (EPC) for the prevention of DVT in the first two weeks following acute spinal injury.

Progress/Methodology—Forty-five patients with C2 through T12 motor complete or motor nonfunctional injury were randomized to receive either ORG 10172, 750 units SC every 12 hours with EPC (Group A), or ORG 10172, 1250 units, SC, every 24 hours with EPC (Group B). The dose of ORG 10172 was blinded to the investigators. All patients underwent daily surveillance with ¹²⁵I fibrinogen scanning and a venous duplex scan on Day 14. Venography was performed on all patients with positive ¹²⁵I fibrinogen or venous duplex scanning. Nineteen patients were randomized into Group A with 16 completing the study. DVT developed in three of the 16 patients (18%). Two of the three DVTS were proximal and the third distal. These developed on Days 6, 8, and 14, respectively. Twenty-six of 30 patients entered into

Group B completed the study. DVT developed in 2 of the 26 (7%). These were isolated calf thrombi developing on Days 7 and 9. The difference between Groups A and B was not significant. The excluded patients in the groups listed above were dropped secondary to medical or physical inability to complete the protocol.

Implications—This analysis indicates that ORG 10172 may be an effective agent for combination prophylaxis in this high risk group of acute spinal cord injured patients and warrants further study.

[551] Spinal Cord Monitoring Using Adaptive Matched Filters

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Sponsor: *Vancouver Foundation, Rick Hansen Man-in-Motion Legacy Fund*

Purpose—During spinal cord surgery, a dedicated system for monitoring spinal evoked potentials is becoming increasingly important for maintaining spinal cord integrity. Thus, the proposed research project is to design and develop a practical spinal cord monitoring instrument which is suitable for use in an operating room environment.

Progress—The proposed approach is that of evoked somatosensory potential measurement. This will utilize dedicated signal processing technology (TMS320) to

provide rapid indication of any changes in the propagation characteristics of the spinal cord.

The signal processing techniques shall consist of a signal-averaging stage, followed by an adaptive matched filter approach containing a generic template. The filter should be able to adapt to the patient's own evoked response, thus able to track any changes that occur, and as well, to eliminate the presurgical time required to obtain the initial template by a nonadaptable matched filter implementation.

[552] Magnetic Resonance Imaging (MRI) Changes Associated with Chronic Post-Traumatic Myelopathy

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Sponsor: *Rocky Mountain Regional Spinal Injury System; National Institute on Disability and Rehabilitation Research*

Purpose—The development of progressive post-traumatic cystic myelopathy is a significant late complication of spinal cord injury and is a common cause of additional late neurologic deterioration. It occurs in from 0.9% to 3.2% of patients with spinal cord injury. Because the predisposing factors and mechanisms which result in cystic extension are poorly understood, a longitudinal prospective study was begun in 1987 to establish the actual incidence, natural history, and MRI correlates of cystic changes in the spinal cord.

Methodology—Specific objectives of the research are to define the incidence and natural history of both the focal form of post-traumatic cystic myelopathy and the progressive form of cystic myelopathy, and identify the MRI correlates of progressive post-traumatic cystic myelopathy

which will identify those individuals at higher risk for this complication.

Progress—Baseline MRIs have been conducted on 100 consecutive cases with the following criteria: traumatic cervical or thoracic spinal cord injury; date of injury between January 1, 1987, and January 1, 1990; Frankel classification A, B, or C upon admission; admitted to Craig within one year of injury; residence at time of injury in Colorado or Wyoming, or regular long-term follow-up planned at Craig; MRI not contraindicated (e.g., substantial internal fixation devices that would interfere with adequate imaging, presence of bullet fragments, pacemakers, etc.). Followup MRIs are being obtained at years 1, 3, and 5.

Preliminary Results—Preliminary analysis of the baseline MRI studies indicate that 32 of 100 cases appear to be completely normal; 50 show minor abnormalities such as cystic degeneration, myelomalacia, or microcystic changes; and 18 demonstrate clear cystic myelopathy. None of the latter showed associated clinical symptoms.

Future Plans—All cases will be followed. At the conclusion of the study, recommendations will be made for further research, programmatic development, and patient follow-up.

[553] Comparative Long-Term Evaluation of Urologic Management Methods

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Purpose—The prevailing opinion appears to be that indwelling catheter methods of bladder management are associated with a higher incidence of complications, such as upper urinary tract deterioration, urinary tract stones, pyelonephritis, and bladder cancer. However, the urological clinicians at Craig Hospital have felt that with an active management approach, the risk of complications is lowered considerably. Craig Hospital therefore has begun a prospective longitudinal urinary management study to provide new data that can assist patients and clinicians in determining the relative merits of the variety of bladder management options available.

Methodology—One hundred and eighteen males admitted consecutively after January 1, 1986, were tested to determine their early postinjury bladder and kidney status utilizing various bladder management techniques. They were followed to assess the frequency of urinary complications including clinically significant urinary tract infections for each method. Analysis of differences in outcomes of renal function between individuals utilizing the various methods of bladder management were performed. Specific tests studied included renal plasma flow

values from isotope renographic studies, excretory urogram or intravenous pyelogram studies, number of episodes of chills and fever associated with urinary tract infection, and the presence and location of renal, ureteral, and/or other urinary tract calculi. Data were utilized to compare outcomes in persons using different methods of bladder management. Social and other nonmedical issues relating to bladder management options were also examined.

Progress—Baseline testing is complete on all 118 men, and follow-up studies are scheduled for years 3 and 5 postinjury.

Preliminary Results—Of the 118 cases, 54 are using suprapubic cystostomy, 45 use intermittent catheterization, and 19 are using other methods. Preliminary analysis of baseline testing reveals that 98 of the 118 cases had normal renal function, 9 cases had slight abnormalities, and 11 cases demonstrated abnormal renal function (including 2 cases with associated trauma to the kidneys, 1 with pre-existing renal disease, 1 with acute renal disease, and 3 with significant medication interactions). All will be followed for 5 years.

[554] Comparative Effectiveness of Two Methods of Weaning Quadriplegics From a Ventilator

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Purpose—This study has been designed and implemented to compare the relative effectiveness of weaning persons with quadriplegia from the ventilator. The two current

methods used for weaning include: 1) Synchronized Intermittent Mandatory Ventilation (SIMV); and, 2) Progressive Ventilator Free Breathing (PVFB). Because

Craig Hospital has had clinical success with PVFB, while many other hospitals attempt to wean persons with quadriplegia from the ventilator using SIMV, a prospective study comparing these two methods is being conducted.

Methodology—A randomized control group who meet the study selection criteria and agree to participate in the study will be randomly assigned to one of the two weaning protocols. Criteria includes patients who are less than 65 years old and have injuries below the C-3 level and are otherwise medically stable; absence of significant head injury; no major respiratory problems such as active asthma, pneumonia, atelectasis above stage one, or acute respiratory disease; existence of at least one volitional diaphragm and a vital capacity of greater than 50 cc; and physician's agreement that the patient is ready to wean and patient's willingness to participate. Random assign-

ment to the two conditions will be made within three strata of initial vital capacities (under 500 cc, 500-1000 cc, and over 1000 cc), which are assumed to have different likelihoods of successful weaning.

Progress—All protocols have been designed and the study is currently underway.

Implications—In patients with quadriplegia who are ventilator-dependent, it has been observed that a certain number, in whom SIMV is utilized, will progress to a certain point and then stall in the weaning at that point. By comparatively testing the effectiveness of these two approaches, criteria can be established as to whether one method is safer, faster, and/or more successful than the other ventilator weaning method, and whether or not one method results in fewer complications and fewer indications of stress than the other.

C. Spinal Cord Regeneration

[555] Toward Better Methods of Nerve Repair and Evaluation

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Purpose—The goal of this research is to provide a means for repair of nerve function. This includes cases of nerve injury within intact limbs, connection of nerves in an amputation stump to a prosthetic limb, and functional neuromuscular stimulation (FNS) applications in spinal cord injury. It is felt that all of these modes of nerve repair can be achieved using a general-purpose neural interface, capable of recording from and stimulating small groups of axons that have regenerated through holes in the device.

Methodology—To verify the basic design concepts, passive neural interfaces were implanted in the peroneal nerves of 12 Sprague-Dawley rats to be evaluated 1-year postoperatively. To optimize the designs in terms of nerve regeneration, a second study using 30 rats is underway. A new surgical coupler design is being used to implant several different "via hole" designs, geometries, and densities (varying the total percentage of nerve cross-sectional area available for regeneration). The results will

be evaluated using extraneural stimulation and compound action potential recording to assess the degree of nerve regeneration for each implant (controls are fully occluded and fully open silicon devices). In addition, work is progressing on technology development for active versions of the neural interfaces, including amplifiers and related circuitry.

Progress—There has been considerable progress in functional demonstration and refinement of the neural interface technology. Early devices with laser-drilled holes through the silicon were made using fabrication technology that was not compatible with inclusion of the microelectronic devices required for future versions. Active circuit compatible fabrication processes were developed that led to the realization of passive microelectrode arrays with thin-film iridium microelectrodes, silicon nitride passivation (insulation) layers, and plasma-etched via holes. The basic stimulation and recording properties of these passive neural interfaces

have been examined *in vivo*. This information is being used to refine the designs of the devices. Progress has also been made in the area of development of interconnect technology (to allow the neural interfaces to be wired to external electronics), improvement of the fabrication technology, and the implementation of active circuits to be included with the neural interfaces.

Results—Electrophysiological tests on the first group of passive neural interface implants demonstrated regeneration of the axons through the holes and the ability to both stimulate with and record from the neural interfaces. Test devices for the second study have been successfully fabricated and are being implanted, with results expected in 1991. New surgical couplers (to overcome limitations of those used for the early work with laser-drilled devices), preliminary Teflon-coated wire interconnects to the neural interfaces, fabrication improvements, and computer simulations of the new active microcircuits have yielded encouraging results.

Future Plans—In order to successfully realize directly interfaced limb prostheses as our first clinical milestone, we must implement an advanced version of the neural interface with on-chip amplifiers for recording, current sources for stimulation, and associated circuitry. A prototype of this device for *in vitro* experiments, which has already been designed and tested, will be modified to

meet these requirements. These modifications would entail the inclusion of new active microcircuits, through-chip via holes and the passivation coating required to protect the microcircuits from body fluids. This work is currently underway.

Recent Publications Resulting from This Research

Fabrication Techniques for Directly Implantable Microelectronic Neural Interfaces. Kovacs GTA et al., in Proceedings of the 12th Annual RESNA Conference, New Orleans, LA, 292-293, 1989.

Accurate Small-Signal Characterization of Microelectrodes. Kovacs GTA et al., in Proceedings of the 13th Annual RESNA Conference, Washington, DC, 381-382, 1990.

Development of a Neural Network Interface for Direct Central Nervous Control of a Prosthetic Limb. Wan EA et al., in Proceedings of the International Joint Conference on Neural Networks, Washington, DC, 1990.

Technology Development for a Chronic Neural Interface. Kovacs GTA, PhD diss., Technical Report No. E073-1, Stanford University, 1990.

A Method for Evaluating the Selectivity of Electrodes Implanted for Nerve Stimulation. Liang DH et al., in Proceedings of the IEEE Engineering in Medicine and Biology Society (in press). Nerve Repair at the Axon Level: Long Term Regeneration of Axons in Rats and Primates Through Laser-Drilled Holes in Silicon Chips. Rosen JM, Grosser M, Hentz VR, J Reconstr Neurol (in press).

Awards

The Peter J. Gingrass Memorial Award of the Plastic Surgery Research Council was given to Gregory Kovacs for his presentation of this research.

[556] Axonal Regeneration in Artificial Nerve Graft Model

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Sponsor: VA Rehabilitation Research and Development Service (Project #B387-2RA)

Purpose—Indications for nerve grafting vary from gaps of 1 cm to greater than 5 cm or more before a graft would replace an end-to-end repair under tension. Where a graft is indicated, autografts are the preferred method at the present time. The autograft fulfills three major requirements for an ideal nerve graft: 1) it acts as a *passive* conduit for axonal regeneration; 2) it is a *natural* substitute which is immunologically acceptable; and, 3) it is vascularized by the recipient bed as a free graft. The major limitation of the autografts is the requirement of a donor nerve. Homografts and heterografts have been evaluated as an alternative to autografts, but have been found to be immunologically unacceptable. Therefore,

the development of an artificial nerve graft is necessary to solve both problems of availability and rejection by the immune system.

The purpose of this study is to examine the regeneration of the peripheral nervous system through an artificial nerve graft composed of a synthetic conduit of collagen and fibrin filled with a collagen type I matrix.

Methodology—Five monkeys had experimental gaps of 30 mm created in six nerves in each animal (two each of dorsal branch of ulnar, dorsal branch of radial, and the palmar cutaneous branch of the median nerve). These gaps were repaired with one of three possible methods:

1) sutured autograft; 2) collagen/fibrin tube filled with collagen type I; or, 3) collagen/fibrin tube filled with heparinized saline. Ten repairs of each method were performed. Nerve repairs will be evaluated at 9 months by histological, physiological, and end organ evaluations (sensory).

Progress—The long-term study has been set up in five primates. These animals will be evaluated after 9 months.

[557] Artificial Nerve Graft: Union of Cellular and Noncellular Components

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Sponsor: VA Rehabilitation Research and Development Service (Project #B588-2RA)

Purpose—Injuries to peripheral nerves may result in a significant loss of tissue which requires a graft to bridge the gap between the transected ends. Presently these gaps are reconstructed using autografts. However, the autograft causes morbidity at the donor site, and in cases of major nerve loss there may not be sufficient donor nerve available to span the clinical nerve gap. In this study, an artificial nerve graft composed of viable cultured Schwann cells, oriented collagen type I, and a synthetic conduit will be employed to study regeneration across a 10 mm gap in the rat peroneal nerve.

Methodology—The protocol is divided into four phases during the proposed 3-year study. The first phase concerns itself with the isolation and purification of Schwann cells in culture. The second phase involves the preparation of the graft. This phase consists of the orientation of collagen type I fibers with added cultured Schwann cells and insertion into a glycolide trimethylene carbonate (GTMC) conduit. Phase III moves to the *in vivo* aspect of the study where the artificial nerve graft will be compared to autografts, collagen-filled GTMC tubes, and empty GTMC tubes in the regeneration of peripheral nerves. The final phase covers the evaluation of the nerve repairs with the various grafts. Short-term (3 months) animals will be evaluated by qualitative histology only, while long-term (12 months) animals will be evaluated

Implications—The results of this study should provide us with direction toward a larger mixed nerve primate study before proceeding to clinical trials.

Recent Publications Resulting from This Research

Artificial Nerve Graft Compared to Autograft in a Rat Model.

Rosen J et al., J Rehabil Res Dev 26(1):1-14, 1989.

Artificial Nerve Graft Using Collagen as an Extracellular Matrix for Nerve Repair Compared to Sutured Autograft in a Rat Model. Rosen J et al., Ann Plast Surg (in press).

noninvasively every 2 months via toe-spread analysis (functional test) during the regenerative period, and with qualitative histology, transmission electron microscopy, fiber diameter histograms (quantitative histology), electrophysiology, and twitch-tension analysis (functional test) at the end of the regenerative period.

Progress—The study is currently at Phase III, with the use of the collagen type I/Schwann cell/GTMC grafts for the repairs of 10 mm gaps in the rat peroneal nerve. Controls have been set up using matched pairs and consist of empty GTMC tubes, sutured autografts, and collagen-filled GTMC tubes. Within 2 months, an evaluation (Phase IV) of the short-term animals will begin.

Results—We have demonstrated that the Schwann cells survive in the graft *in vitro*. We have also now begun to isolate glial growth factor, a potent mitogen for Schwann cell growth *in vitro*.

Future Plans—The combination of cellular and non-cellular components should provide an ideal environment for regeneration. Our initial studies in the rat model should lead to follow-up studies with longer gaps in a primate model. The long-term goal of this project is to improve the clinical results of peripheral nerve graft reconstructions.

[558] Regeneration and Functional Recovery in Neural Tissue**Mary B. Bunge**

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Purpose—The overall goals of this project are to increase the fundamental knowledge of factors that govern peripheral nervous system (PNS) and central nervous system (CNS) nerve fiber growth and maintenance, as well as survival of the parent neuronal cell body, and to better understand mechanisms involved in the development of connections and adaptation and behavioral plasticity in different areas of the CNS.

The individual projects will investigate: 1) non-neuronal cell secretory products (both soluble and insoluble) that promote CNS neurite growth and neuronal survival in the animal and in culture; 2) regenerative potential of cultured CNS growth cones under differing environmental conditions to better understand differences in growth capacity; 3) distribution and molecular associations of myosin, actin, and several actin-associated proteins in cultured growth cones, to clarify mechanisms responsible for oriented growth of neuronal processes;

4) improving functional recovery following nerve repair by ameliorating the response of sensory neurons to injury with the administration of nerve growth factor; 5) the role of synaptic transmitters in visual cortex development; 6) physiological and morphological substrata for the process of adaptation of the vestibulo-ocular reflex; 7) response properties and connections of surviving somatic sensory cortex that receive cortical lesions in infants versus adults, to search for the basis of observed behavioral recovery in the infant; and, 8) cerebellar unit and spindle afferent firing, reflex electromyographic changes, and stiffness and damping of the monkey's wrist during prevention of oscillations produced by novel loads through adaptive (plastic) control of movement behavior.

Implications—The results will facilitate progress toward better understanding basic mechanisms of regeneration and useful plasticity.

[559] Recovery and Regeneration After Spinal Neuron Injury**Edward R. Perl**

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Purpose—This program is a continuing investigation of the effects of injury to spinal nerves or to spinal cord tracts upon the functional organization of vertebrate spinal neurons. The overall goal of this program is to provide data on the degree to which functionally effective regeneration or reorganization of spinal neurons and their connections can take place in immature or mature vertebrate nervous systems. Each of the projects has its counterpart or point of departure in deficits suffered by human beings after disease or traumatic injury of the spinal cord and/or of the nervous processes of spinal neurons.

Methodology—The approaches are interdisciplinary and employ animal models, in which combinations of physiological, morphological, biochemical, and behavioral measures are combined in various ways to test for exam-

ples of: 1) regeneration or reorganization of spinal pathways in vertebrates; 2) changes in the organization of spinal reflexes involving the kidney and bladder after spinal cord injury; 3) conditions favoring functionally effective reinnervation of the urinary bladder by foreign nerves; 4) factors associated with the specificity of reinnervation and regeneration after injury of sympathetic preganglionic neurons; 5) changes in utilization of amino acids and associated modification in cytoskeletal protein synthesis by motoneuron cell bodies after injury of their axons; 6) modifications of the projections into the spinal cord of thin afferent fibers after injury of dorsal roots and associated alterations in functional properties of neurons in laminae I and II; and, 7) modifications in the distribution of chemical markers for primary afferent fibers, such as peptides in the spinal gray matter, after injury of ascending spinal pathways.

[560] Center for Acute Spinal Cord Injury

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Purpose—Injury to the spinal cord initiates a complex cascade of events, the net effect of which is a behaviorally limiting neurological deficit. Innumerable investigations of spinal cord injury have led to the realization that in order to improve the neurological outcome of patients, we must first understand the basic mechanisms that promote differentiation and growth in the developing nervous system and regeneration and repair in the adult. This program is designed as a coordinated effort to identify basic cellular mechanisms influencing degeneration and regeneration in the central nervous system (CNS) following injury. The goal of the program is to develop a body of knowledge sufficient for identifying and understanding basic mechanisms which may be susceptible to intervention strategies leading to an improvement in neurological outcome.

The program is divided into six major areas: 1) a core facility providing for electron microscopy studies; 2) a core facility providing for administrative support;

3) studies focused on trophic factors and membrane components that may influence regeneration; 4) analyses of mechanisms influencing sprouting and reactive synaptogenesis; 5) characterization of functional capacities of regenerating neurons, including the activity of voltage-dependent channels; and, 6) cytochemical and genetic mechanisms underlying regeneration and the role of the genome in reactivating specific developmental genes potentially important in regenerative responses.

Implications—These studies will fill critical gaps in our current understanding of regenerative responses in the developing and adult CNS. This knowledge is crucial for the development of successful strategies for treating spinal cord injury, injuries elsewhere in the CNS, and disease processes involving the progressive loss of populations of neurons, such as that which occurs in Alzheimer's dementia.

[561] Spinal Cord Injury Research Center

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Purpose—Spinal cord injury and its eventual outcome is a product of the cellular and molecular mechanisms of degeneration, growth, and regeneration. These processes may be understood best by a combination of studies which examine the acute and chronic mechanisms of degenerative phenomena. In addition, since the capacity to regenerate spinal neurons is limited in the adult spinal cord, an attempt to examine regenerative phenomena during development, when such phenomena are enhanced, is an important part of this research.

Methodology—The specific aspects of these phenomena to be explored include an examination of the biochemical pathophysiology of degeneration, and the physiology, biochemistry, and anatomical characterization of reorganization of nervous tissue subsequent to nerve trauma. The further development and evaluation of a new injury device is an important step toward the control of injury

as an independent variable. Alterations in lipids, membrane integrity and recovery, and the ability to induce changes in the metabolic (PO_2) or ionic (Ca^{++}) micro-environment will be studied to assess the effects of ischemia or impact injury to the spinal cord. Interventions into this pathological process will also be attempted with naloxone to improve tissue oxygenation and spinal hypocalcemia. The degree to which such interventions are successful will also be assessed chronically by behavioral or morphometric analysis.

Mechanisms of axolemmal synthesis will be studied by assessing ganglioside contributions to peripheral nerve trauma. Reorganization and regenerative phenomena will be assessed in the cat and developing frog, respectively, using horseradish peroxidase (HRP) histochemistry, intracellular neurophysiological techniques, and electron microscopy. The role of nerves in the regenerative plasticity involved in limb regeneration will also be assessed.

Implications—Only by studying acute alterations in spinal pathophysiology and attempting to reverse them chronically can we begin to effect changes in the capacity

of the central nervous system to use the inherent mechanisms of regeneration that it initially had, but may have lost during development.

[562] Mechanisms of Recovery After Spinal Cord Injury

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Purpose—We propose to investigate the mechanisms accounting for, limiting, and encouraging the recovery of function after spinal cord damage. Recovery from the level of the neuron to that of the whole animal's behavior will be examined. We wish to determine which aspects of neuronal plasticity, including sprouting and regeneration, may contribute to recovery. A clearer understanding of the nature, extent, and regulation of neuronal plasticity should lead to rational strategies for enhancing the extent and quality of recovery from spinal cord injury. Our long-range goal is to find methods that can enhance recovery mechanisms, and determine if those methods improve functional recovery after damage to the spinal cord.

Methodology—Our experimental models are the cat and rat spinal cords. Our experimental approach is multidisciplinary, including intra- and extra-cellular recording from axotomized and deafferented neurons; regulation of synthesis of mRNA coding for proteins in axotomized neurons; the use of neural transplants to enhance regenerative potential; morphological examination of regeneration and sprouting in spinal neurons; and behavioral examination of recovery of motor function following spinal cord damage. Correlative studies include electron

microscopic and physiological studies of reinnervation of partially denervated neurons; metabolic and morphological studies of recovery of damaged neurons; morphological, biochemical, and physiological studies of the determinants of regeneration; and morphological and behavioral studies of recovery of function.

In projects 1 and 2, investigations of physiological and morphological correlates of axotomy and regeneration of spinal and brain stem motoneurons are proposed; the differences in gene expression between regenerating and nonregenerating neurons will be explored in project 3; the increased potential for CNS regeneration elicited by embryonic transplants will be examined in project 4, including an investigation of synapse formation by the regenerating axons. In project 5, light microscopic-electron microscopic correlates of sprouting of spinal systems will be examined quantitatively to learn the rules that determine successful reinnervation; project 6 uses Clarke's nucleus as a model for studying morphological and physiological correlates of recovery of deafferented or axotomized neurons (including physiological consequences of reinnervation and metabolic determinants of survival of damaged cells); and, in project 7, behavioral and anatomical correlates of recovery of function and lesion-induced sprouting will be explored.

[563] Recovery of Function After Spinal Cord Injury

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

Purpose—A number of studies have shown that embryonic transplants can ameliorate some deficits or mediate recovery of function following central nervous system (CNS) damage. Often these effects are due to diffuse release of hormones or transmitters and are independent of the formation of specific connections that replace the

damaged pathways. We intend to test the hypothesis that after spinal cord damage at birth, embryonic spinal cord transplants mediate recovery/sparing of specific motor functions by permitting the anatomical elongation of specific damaged supraspinal pathways into spinal motor centers.

We have shown that after spinal cord injury at birth, spinal cord transplants prevent the retrograde cell death of immature axotomized neurons and support the growth of certain populations of axons across the site of a neonatal spinal cord transection. Recent preliminary work in this laboratory indicates that such transplants enhance the development and recovery of motor function. The aim of the current project is to determine the extent to which, and the mechanisms by which, the transplants mediate recovery of function following spinal cord injury.

Methodology—We will examine four representative pathways which are at different stages of development at the time the lesion is made: corticospinal, raphe-spinal, coeruleso-spinal, and dorsal root afferents. We will use neuroanatomical and neuropharmacological techniques to assess the influence of these pathways on recovery of function following spinal cord damage at birth, and we will examine how the response of the immature spinal

cord changes during development to produce the more restricted response to injury which is characteristic of that observed in the mature spinal cord.

Motor function will be measured by qualitative and quantitative assessment of the animal's ability to perform a battery of reflex and locomotor tests which are designed to evaluate specific components of the animal's sensorimotor capacity.

Results/Implications—If the pathways that grow through the transplant are individually ablated and specific functions are disrupted, that would support the hypothesis that the anatomical reorganization of these specific pathways mediate the recovery of motor function.

We hope to gain a better understanding of the mechanisms of recovery of function and anatomical reorganization in this animal model of spinal cord injury, in the hope that improved therapeutic approaches in human spinal cord injury can be identified.

[564] Spinal Cord Injury and Repair

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Purpose—This program on spinal cord injury represents a blending of interdisciplinary approaches to explore the potential for restoring function in the injured spinal cord. With this long-term objective in mind, various anatomical, behavioral, electrophysiological, neurophysiological, and microsurgical methods will be used to achieve the following immediate goals: 1) to examine the capacity of fetal central nervous system (CNS) and peripheral nervous system (PNS) grafts to mediate anatomical and functional repair in acute and chronic injuries; 2) to develop models that will ultimately permit definitive correlative analyses of therapeutic strategies aimed at restoring sensory, motor, and/or autonomic function; 3) to test new approaches that may permit in-depth studies of behavior and cellular neurophysiology; and, 4) to demonstrate fundamental events underlying functional recovery in the amphibian spinal cord.

Methodology—The program is divided into eight project areas. Project 1 will examine the ability of fetal CNS grafts to establish host-graft synaptic interactions in the chronically injured spinal cord, as well as the capacity of

these grafts to prevent the death of certain spinal neurons following cord damage in the adult rodent; methods will also be developed for intraspinal transplantation into the adult cat in conjunction with our Core laboratory.

Project 2 will utilize electrophysiological methods to document changes in segmental and descending such post-injury alterations.

Project 3 focuses on the problem of spasticity, as manifested in the cat, and seeks to establish approaches that will permit direct correlations between non-invasive physiological evaluations and electrophysiological recordings.

Project 4 will test the efficacy of PNS grafts in restoring somatosensation and segmental reflex activity in the cat and primate.

Project 5 will study the neurophysiology and synaptic organization of the cat sacrocaudal cord—a region which may serve as a novel model for studies of spinal cord plasticity and regeneration.

Project 6 will explore sensory physiology and the ascending pathways that subserve cortical perception of respiration in various animal models, as well as in humans with spinal cord injuries.

Project 7 addresses the afferent component of the penile reflex pathways in the rat.

Project 8 will examine some of the variables that influence plasticity, regeneration, and functional repair in the amphibian spinal cord.

Implications—Collectively, these subprojects will provide a comprehensive and interactive investigation of various aspects of spinal cord motor, sensory, and autonomic function that are of fundamental scientific and clinical interest.

[565] Novel Cell Lines for Spinal Cord Transplantation

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Purpose—To optimize central nervous system (CNS) graft survival, fetal donor tissue is essential. Given the ethical and logistical constraints of obtaining human fetal tissue to replace damaged CNS tissue, one alternative strategy is the development of CNS cell lines whose mitotic activity and differentiation *in vivo* can be regulated. The goal of this research is to develop such cell lines, characterize their differentiation *in vitro*, and begin to address their potential as replacement for damaged CNS neurons and oligodendrocytes.

Methodology—Immortal, temperature-sensitive (ts) cell lines will be developed by infecting neuroepithelial precursor cells with a retrovirus encoding the ts-mutant of the SV40 large T transforming protein. The rationale for this strategy is that cells transformed with this construct are mitotically active at permissive temperatures (33 degrees C). At 39 degrees C the thermolabile oncogenic protein is inactive, the cells stop dividing and resume differentiation, presumably in the direction that was interrupted at the time of viral infection. The ts-cell lines will be developed from E13 medullary raphe nucleus

(RN), in an attempt to generate oligodendrocytic, serotonergic and GABAergic tsRN cell lines.

Isolated tsRN cell lines will be grown under differentiating conditions and characterized for the expression of astrocytic-, oligodendrocytic-, and neuronal-specific antigens. Oligodendrocytic-differentiating tsRN cell lines (oligo-tsRN) will be screened for the ability to myelinate dorsal root ganglion neurons *in vitro*. Myelinating oligo-tsRN cell lines will be transplanted into the spinal cord of the myelin-deficient rat and myelin formation *in vivo* assessed.

Neuronal tsRN cell lines will be further analyzed for the ability to synthesize and release 5-HT and GABA. Positive cells will be transplanted into a 5,7-DHT lesioned spinal cord and biochemically and immunohistochemically assessed for the ability to replace denervated 5-HT fibers. If GABAergic tsRN cells are not obtained, one neuronal, nonserotonergic tsRN cell line will be transfected with the glutamic acid decarboxylase (GAD) cDNA and a GABA-tsRN cell line isolated. The tsRN TGAD cell line will then be transplanted into adult ventral spinal cord and assayed for the ability to secrete GABA *in vivo*.

[566] Repair of Injured Nervous Tissue with Foreign Grafts

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Purpose—A short gap in a peripheral nerve can be repaired with a living nerve graft, dead tissue that contains basement membrane tubes (e.g., a frozen nerve graft), or an artificial tube (e.g., a silicone tube) that is initially filled with a fibrin gel. We are analyzing these methods of repair in rats using electron microscopical

and histochemical techniques to ascertain how regeneration occurs in each, and whether aspects of nerve function are restored. The perineurial-nerve barrier (PNB) and the blood-nerve barrier (BNB) regulate the movement of macromolecules into the endoneurium from around the nerve and from endoneurial blood vessels respectively.

In previous studies, the PNB and BNB were restored in living nerve grafts, whereas in nerve segments formed in silicone tubes, the PNB developed, but the BNB did not.

Methodology/Results—To better understand barrier formation, we performed a developmental study using the barrier tracer horseradish (HRP). The results indicated that the nerve barriers matured at different times. The PNB kept HRP out of the endoneurium for 2 weeks, but for a time it leaked out of the BNB (i.e., from endoneurial blood vessels). The BNB did not retain intravenously-injected HRP until 6 to 8 weeks postnatally. In contrast to the blood-brain barrier (in which certain enzymes appear), the endothelial cells of the endoneurial blood vessels did not develop any gamma glutamyl transpeptidase

activity, and alkaline phosphatase appeared long before the BNB became intact. In an analysis of cellular events occurring in silicone tubes, we found that the cable within it could form in the absence of axons present in the proximal nerve stump. Indeed, this type of cable could support axonal growth through it later on, after a normal nerve end was joined to it. Because the nerve segment formed in a tube is not morphologically normal, we injured it to determine whether this cable would undergo Wallerian degeneration and support axonal regeneration again. As expected, a crush injury of an axonal-containing cable formed at 4 months paralyzed the leg of the rat. After 8 weeks, the leg recovered movement and the nerve cable contained regenerated axons in various stages of remyelination.

[567] Muscle Function Recovery After Peripheral Nerve Injury Enhanced by Chronic Direct Current Stimulation

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Purpose—Using an animal model, we will determine the optimal direct current stimulation parameters for enhancing nerve regeneration and muscle function recovery after nerve crush injury. Understanding the mechanisms involved in weak chronic DC stimulation will enable further study which could benefit patients with peripheral nerve and spinal cord injury.

Progress—We have developed and tested a simple *in vivo* quantitative method for measuring changes in muscle function during denervation and reinnervation of plantar flexor muscle of rats. An implantable DC stimulator with wick electrodes was also designed. We studied muscle function recovery after nerve crush under the influence of DC currents. The animals were randomly divided into three groups: CA (cathode distally to the site of axotomy); AN (anode distally); and, SH (with sham implants, identical in size, shape, and weight to the real one, battery replaced by a piece of noncorrosive metal). Isometric contraction of plantar flexors was recorded during reinnervation, as a measure of muscle function

state. The force of tetanic contraction was assessed in a period of six consecutive weeks, once weekly.

Results—Muscle force returned to the control value during the fourth week in cathode-stimulated rats, and in the fifth week in anode and sham group. The differences are statistically significant (two-tailed, unpaired Student *t*-test).

To facilitate our understanding about how the cell translates the electrical signal into a functional answer, as well as future studies of the complex changes during *in vivo* nerve regeneration and possible beneficial effects of DC, we united the relevant current knowledge with our assumptions into a simplified qualitative model of peripheral nerve regeneration after crush lesion.

Recent Publications Resulting from This Research

Nerve Regeneration and Externally Applied Electric Field. Ribaric S, Stefanovska A, Bresjanac M, in *Advances in External Control of Human Extremities*, D.B. Popovic (Ed.), Nauka, Yugoslavia, 497-507, 1990.