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Platform Session Abstracts

1 MECHANISMS OF NEURONAL CELL DEATH AND RECOVERY IN THE CENTRAL NERVOUS SYSTEM

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Recent progress has significantly advanced our understanding of mechanisms leading to neuronal cell death, or apoptosis, in the central nervous system (CNS). Evidence for apoptotic cell death has now been demonstrated in many neurodegenerative diseases as well as after ischemic damage, traumatic brain and spinal cord injury. In many of these disorders, similarities can be demonstrated in the time course and molecular cascades of apoptotic cell death. However, despite these advances, translating this knowledge into effective neuroprotective therapies has been far from successful. This is due, in part, to a lack of understanding about specific cell death pathways in neurons and other cell types, as well as recent evidence suggesting that the CNS may have several types of cell death that are poorly defined. Cell death in the CNS can be grouped by various intracellular triggering mechanisms that include mitochondrial dysfunction with formation of reactive oxygen species, aberrant cell cycle activation and DNA damage, and abnormalities of the ubiquitin-proteasome system, all of which lead to the activation of proapoptotic proteins. These mechanisms will be discussed with particular focus on spinal cord injury, following which extensive glial cell apoptosis also occurs.

2 CORTICAL PLASTICITY FOLLOWING SPINAL CORD INJURY

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Cortical reorganization can occur after loss of a limb, but the extent of cortical reorganization after spinal cord injury (SCI) is unknown. The timing, extent, and nature of the reorganization of the sensorimotor pathways play a crucial role in possible reconnection or neuroprosthetic rehabilitation. Functional MRI, EEG, and other neuroimaging techniques have been used to examine whether SCI survivors show a different pattern of cortical activation for active movement and passive stimulation than would age-matched controls. There is evidence that the motor networks controlling the hand, foot, and tongue are all affected, regardless of the level of injury. The relationship between cortical reorganization and dysaesthetic pain following differentiation is also a current question. There is some evidence that the amount and nature of the reorganization may be related to the pain, and other evidence arguing that the primary sensory and motor cortex are not the fundamental sites that lead to dysaesthetic pain and other sensory abnormalities. The distinction between reorganization due to central nervous system injury and reorganization due to peripheral nervous system injury cannot be overlooked and limits the generalizability of cortical reorganization theories based on findings in amputees.

3 REVIEW OF RECENT REPAIR STRATEGIES

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Reestablishing neural function after spinal cord injury (SCI) requires transplantation techniques to set up a cellular bridge at the point of injury to allow damaged axons to regenerate over the injury gap and reestablish connection of nerve circuits. After SCI, neurons and pathways located within the injury site undergo several changes that contribute to obstacles against regeneration and functional recovery. Neuronal loss caused by necrosis and apoptosis also impede regeneration. Functional recovery for a patient with SCI can be classified into three strategies: rescuing neurons from death, including methods to prevent local neuron pool loss; reconnection and recovery of normal function in the neural pathway involving reactivation of dysfunctional pathways; and replacement of cells after neuronal death. The major goal of neuroprotective therapy is to prevent secondary cell death from occurring within hours, days, or even weeks following injury. Neuroprotective effects can be provided in several ways. The application of corticosteroids, antioxidative agents, intracellular signaling manipulators, and trophic factors are beneficial. Neurotrophic factors may play an increasingly significant role in increasing the cell survival rate after axotomy. The strategy of reconnection and recovery of pathways is based on reinsertion of peripheral nerves into gray matter as opposed to white matter. Rerouting pathways from nonpermissive white to permissive gray matter was chosen as a major strategy to evade oligodendroglial proteins that inhibit axon regeneration. The positive effects of rerouting have been further enhanced by the addition of trophic factors, primarily acidic fibroblast growth factor (aFGF) containing fibrin glue. Additionally, much work has been done with neural supportive Schwann cells, including transplants, and olfactory ensheathing glia (OEG) are now being tested in injury sites to observe regeneration in the central nervous system (CNS). OEGs could promote long-distance axonal regeneration after transplantation to partial or complete spinal cord lesions. Recently, stem cells have been touted in the media as a panacea for many diseases, including SCI. Our work has focused on bone marrow stem cells, which have greater functional plasticity than previously suspected and may have the potential to differentiate into functional neuronal cells. Current observations indicate that bone marrow stem cells can differentiate into cells that express several neural proteins, including the neuron precursor marker (nestin), immature neuron markers (NeuN, TuJ-l), and more mature neuron markers (NF-H). This holds great promise for future spinal cord repair strategies.

4 PHARMACOLOGICAL CHANGES OF THE SPINAL CORD ASSOCIATED WITH LEARNING A MOTOR TASK

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Three important properties of the spinal cord will be discussed that provide the possibility of using activity-dependent rehabilitative strategies to regain the ability to stand and to step following spinal cord injury (SCI). First, the spinal cord can receive and interpret the sensory information from the lower limbs that is associated with weight-bearing standing and stepping. Therefore, when the body is placed in a weight-bearing posture, the spinal cord will respond by generating the appropriate activation signals necessary to execute successful standing and stepping. In essence, the spinal cord itself is capable of generating the appropriate activation patterns for standing and stepping. The second important property to be discussed will be the ability to improve the functionality of these spinal circuits by practicing a specific motor task. Evidence will be presented that demonstrates the ability of mice, rats, and cats to learn to stand and to step following a complete mid-thoracic spinal cord transection. It is clear that the glycinergic and GABAergic inhibitory systems within the spinal cord are modulated (both pharmacologically and by training) by SCI and

by training. The ability of the complete SCI subject to regain standing and stepping capabilities is a function of the manner and degree to which these two systems are modulated. The third important property is the responsiveness of the lumbosacral spinal cord to a combination of administration of a 5 HT agonist in combination with step training to facilitate learning to step. These studies in general demonstrate an extensive capability of the neuromotor circuitry within the spinal cord to be modulated in a controlled manner so that successful standing and stepping can be achieved with minimal or no input from the brain.

5 FUNCTIONAL MAGNETIC STIMULATION FOR PATIENTS WITH SPINAL CORD INJURY/ DISORDERS (SCI/D)

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This presentation reviews a relatively novel technology, functional magnetic stimulation (FMS), and provides experimental findings on several clinical studies that applied FMS in animals and in humans, including in patients with SCI/D. FMS can be defined as a technology that applies a time-varying magnetic field to produce functional movement in paralyzed muscles. Using a magnetic stimulator and placing the coil along the lower cervical and upper thoracic region, significant inspired volume and pressure can be achieved in animals with high cord transection. By placing the coil in the lower thoracic region, significant expiratory muscle activation was achieved. With a 4-week conditioning protocol, FMS resulted in significant improvement in expiratory muscle function in patients with SCI/D. By placing the coil in the lumbar region, FMS also demonstrated efficacy in improving gastric emptying and colonic transit time in patients with SCI/D. FMS of the detrusor muscle was also observed by FMS that facilitated voiding function in several subjects tested. Furthermore, placing the magnetic coil at the popliteal region and activating the calf muscles demonstrated significant improvement in fibrinolysis in both normal subjects and in patients with SCI/D. FMS is painless and can be applied externally over clothes and should be considered an emerging therapeutic tool for patients with SCI/D.

6 BIONs*—HISTORY AND POTENTIAL

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The concept of an injectable BIONic Neuron arose circa 1987 during the development of similarly injectable RF transponders now in widespread use to identify animals. The glass-encapsulated BION1 (2 mm diameter × 16 mm long) that we have been testing in patients since 1999 receives power and individually addresses digital command signals from an externally worn inductive coil. It generates precise and reproducible stimulus current pulses (0 mA–30 mA, 2 µs–512 µs) that activate the terminal branches of motoneurons, resulting in synaptic activation of paralyzed or paretic muscles. This has proven useful in preventing and reversing disuse atrophy in stroke and osteoarthritis patients. We are working on BION2 technology, which will include sensors and back-telemetry of command and feedback signals required to produce functional reanimation of paralyzed limbs.

*BION® is a registered trademark of Advanced Bionics Corporation (Valencia, CA), covering a family of implantable neuromuscular microstimulators that are being developed in cooperation with a consortium of academic and affiliated research organizations.

7 BION®: FUTURE STUDIES AND NEXT GENERATION SELF-POWERED DEVICES

Joe Schulman, PhD; Ross Davis, MD

President, Alfred Mann Foundation; Medical Consultant, Alfred Mann Foundation, Santa Clarita, CA

Injectable BION microstimulators may be used for a variety of therapeutic and functional applications that would benefit spinal cord

injury patients. Examples include treatments to restore grasp or diaphragm function, alleviation of obstructive sleep apnea, and prevention of pressure sores. The current generation of RF BION devices are powered by an external magnetic field and are programmable through user-friendly software, allowing the clinician to efficiently modify stimulation parameters as patient needs change. Depending on the application, BION microstimulators may be injected during an office visit, allowing the patient to avoid major surgery and general anesthesia. Animal studies and biocompatibility tests have shown that the implants can remain in situ, without migration and with no adverse effects, even when stimulation is no longer required. A battery-powered BION should be ready for animal studies by the end of 2004. These "FES BION" devices will contain inductively rechargeable batteries and will be able to intercommunicate via a Master Control Unit. Such improvements will eliminate the need for a coil to be worn during use, making the system more clinically acceptable and tolerable to patients. These new FES BION devices will be designed with sensing capabilities that will allow measurement of limb angles, pressure, biopotentials, and other physiological parameters.

8 ADVANCES IN UROLOGICAL MANAGEMENT

Inder Perkash, MD

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Earliest historical review in Edwin Smithe papyrus of the neuropathic bladder is from the 17th century B.C. when for the first time attention was given to the patients with spinal cord trauma. Suprapubic bladder massaging and credè was reported in l9l6–l7 following World War I. Foley indwelling catheter was first available for use in l930. The first I.V. urography was reported in l929. Critical objective management started with the understanding of bladder physiology through urodynamics by Langworthy, Kolb, and Monro in l936. Authors' contributions, including emphasis on urodynamics, diagnosis of detrusor sphincter dyssynergia (DSD), association of autonomic dysreflexia and DSD, and use of linear array sonography during urodynamics, will be presented. First, Laser Transurethral sphincterotomy (TURS) was reported by the author in l99l. Follow-up successful results were reported in 78% patients (for a mean period of 7 years) on the first 99 patients after TURS. Clean technique intermittent catheterization, secondary bladder neck obstruction, and false passages in the urethra are some of the many publications that have been reported by this author. They will be reevaluated.and presented. Critical review on bladder augmentation, bladder substitution, sensory nerve stimulation, and other therapies including use of botulinum toxins, capsaicin for neurogenic bladder rehabilitation will be discussed.

9 SARS UPDATE

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The newly recognized Severe Acute Respiratory Syndrome (SARS) has generated a great interest among healthcare providers of all types and in various locations. Although it initially originated in and was limited to Southeast Asia, this syndrome has become a transcontinental problem. Caused by a newly recognized Coronavirus that probably originated from close human contacts with certain animal hosts in China, SARS can spread by face-to-face contact and possibly via airborne, fomite, and fecal oral routes. Although the transmission of SARS has been slowed down by isolation and quarantine measures, relaxed epidemiological interventions can lead to resurgence, as was recently observed in Toronto, Canada. At the present time, a travel advisory (deferral of nonessential travel) exists for China, Hong Kong, and Taiwan, whereas a travel alert (heads-up) exists for Toronto, Hanoi, and Singapore. Although dozens of probable cases of SARS have been reported in the United States, particularly in California, no associated deaths have been documented. The potential future impact of SARS in the United States is still unclear and may not be determined until later this year.

10 MANAGEMENT OF PULMONARY INFECTIONS AND SEPSIS IN PATIENTS WITH SPINAL CORD INJURY

Rabih O. Darouiche, MD

Department of Veterans Affairs Medical Center and Baylor College of Medicine, Houston, TX

Although less than 10% of infections in patients with spinal cord injury (SCI) affect the respiratory tract, the high mortality associated with pneumonia makes it the leading cause of mortality in this population. Pneumonia is the most common pulmonary complication in the immediate postinjury period and is particularly prevalent during the first few months after cervical or high thoracic SCI and among quadriplegics and older persons. In patients with aspirated gastric contents, infections by gram-negative bacilli are most common. Staphylococcus aureus (including MRSA) and gram-negative bacilli (particularly Pseudomonas aeruginosa) commonly cause pneumonia or tracheitis in mechanically ventilated patients and in those with tracheostomy. In the absence of aspiration and indwelling respiratory devices, community-acquired respiratory infections due to typical bacteria such as Streptococcus pneumonia, haemophilus influenza, and Branhamella catarrhalis, or atypical organisms such as Mycoplasma and Legionella species predominate. In cases where identification of the infecting organisms and their antimicrobial susceptibilities are pending, empirical treatment of pulmonary infections in patients with SCI should be guided by the patient-specific predisposing conditions and the hospital-specific antimicrobial profiles.

11 SURVEY OF PREVALENCE OF DYSLIPIDEMIA IN PATIENTS WITH SPINAL CORD INJURY

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Background: Premature coronary heart disease (CHD) is the leading cause of morbidity and mortality in persons with chronic spinal cord injury (SCI). We examined the prevalence of risk factors, specifically dyslipidemia, in a large cohort of SCI patients and assessed the degree of undertreatment. Methods: A cohort of SCI patients from the Long Beach Department of Veterans Affairs Medical Center were selected, and the following risk factors were obtained from a retrospective chart review: lipid profile, hypertension, diabetes, prior CHD, and proportion on cholesterol-lowering medications. Results: In an interim analysis of 50 patients with SCI, low HDL-C was the major CHD risk factor identified, with over 50% of the patients with this abnormality. In addition, 34% of the SCI patients had hypertension, 22% had diabetes, and 10% had preexisting CHD. Additional data from ongoing analyses will be presented. Conclusions: SCI patients, due to their immobility, have a disportionate risk of CHD due to a higher prevalence of low HDL-C, hypertension, and diabetes. Efforts to reduce known risk factors would improve morbidity and mortality from CHD in this population.

12 CARDIOVASCULAR DYSFUNCTION IN SPINAL CORD DISORDERS

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SCI Director, Veterans Integrated Service Network 1 (VISN 1)

Cardiovascular dysfunction occurs in all phases of spinal cord injury (SCI) and is an important cause of morbidity and mortality. Autonomic pathways are impaired as a result of the spinal cord lesion, especially in cervical and high thoracic injuries. There is loss of supraspinal regulatory control of the sympathetic nervous system resulting in reduced overall sympathetic activity below the level of injury. Morphological changes associated with peripheral alpha-adrenergic hyper-responsiveness may occur distal to the injury. In addition to autonomic abnormalities, there are indirect effects of immobility and other SCI related conditions on cardiovascular function. Cardiovascular concerns in the acute phase of SCI include bradycardia, cardiac arrest, and hypotension. In the first few months after injury, there is a propensity for venous thromboembolism and orthostatic hypotension. Ongoing cardiovascular

issues include autonomic dysreflexia, low baseline blood pressure, reduced cardiovascular fitness and exercise capacity, and drug-related cardiovascular side effects. With aging of individuals with SCI, comorbidities such as coronary artery disease and peripheral vascular disease are encountered, often with atypical presentations and special diagnostic and therapeutic considerations. This presentation summarizes the pathophysiology, clinical manifestations, and management of cardiovascular dysfunction encountered throughout the continuum of SCI care.

13 RECENT ADVANCES IN THE MANAGEMENT OF MULTIPLE SCLEROSIS

Michael J. Olek, MD

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Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system, affecting young adults with a female predilection. The disease is characterized by inflammation that leads to myelin destruction causing sensory, motor, and cognitive dysfunction. Recent advances include the establishment of new diagnostic criteria (McDonald), updated from the 1983 Poser criteria, which places greater emphasis on MRI and includes clinically isolated syndromes. A newer measure of clinical function has also been introduced for use in clinical trials named the MSFC (Multiple Sclerosis Functional Composite) scale, which includes the 9-hole peg test, timed 25-foot walk, and the paced auditory serial addition test (PASAT). In addition to routine MRI measures, new techniques such as brain atrophy and 3D/4D computerized models have enhanced diagnosis and drug monitoring. A better understanding of the immunologic mechanisms involved in MS has produced more targeted therapeutics. Currently, there are 48 compounds involved in individual trials and several compounds in combination. Current treatments are only partially effective and their efficacy can be reduced with the development of neutralizing antibodies. Results of a few of the combination trials will be presented.

14 THE IMMUNE SYSTEM AND INFLAMMATORY RESPONSE IN PERSONS WITH SPINAL CORD INJURY

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Mortality from sepsis accounts for the highest ratio of actual to expected deaths after spinal cord injury (SCI). Multiple alterations in the immune system have been documented after SCI, which may interrupt the response to tissue invasion by foreign pathogens. In addition, virtually all of the deleterious systemic phenomena known to be associated with chronic inflammation (e.g., cachexia, anemia, hormone disturbances) are seen in persons with longstanding SCI. Laboratory assays now provide the ability to easily identify the presence of an inflammatory response and are leading to the development of a number of promising therapeutic agents. For one to assess the immune deficits in persons with SCI, the key elements of the normal immunologic response to invasion by foreign antigens are identified for laboratory study. Several studies published in the literature describe the components of the inflammatory and immunologic response that can be measured in SCI. Many of these studies have detailed laboratory abnormalities present in SCI, but the clinical significance of these findings is still undetermined. Multiple new therapies that manipulate cytokine and acute phase protein physiology have become available for clinical use. Employing these agents in persons with SCI must be done with an acknowledgment of the unique characteristics of the immune response in this group of patients.

15 BASIC NEURAL MECHANISMS FOR CONTROL OF BREATHING

Jack L. Feldman, PhD

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Breathing is relentless, reliable, and robust, yet labile to behavioral and physiological demands, like exercise, hypoxia, speech, or sleep. The site(s) and mechanisms of respiratory rhythm

generation in mammals are being revealed at levels from molecules to cells to networks. Site(s): Approximately 600 neurons expressing the neurokinin 1 receptor—which essentially define the pre-Bötzinger Complex in the rostroventrolateral medulla—are essential for generation of breathing rhythm. Destruction of >75% of these neurons permanently disrupts normal breathing in adult rats. Preinspiratory neurons, located rostral to the pre-Bötzinger Complex also appear to play a role in generation of respiratory pattern. The interaction of the pre-Bötzinger Complex and preinspiratory neurons is revealed by "quantal," i.e., discontinuous, slowing of breathing under pharmacological conditions that weaken coupling between these rhythmogenic sites. We hypothesize that there are two distinct oscillators that have distinct evolutionary origins, with the pre-Bötzinger Complex critical for generation of diaphragmatic inspiratory activity. Mechanisms: Voltage-dependent pacemaker neurons are hypothesized to be the kernel for respiratory rhythm. Yet, respiratory-related rhythm persists in slices in the absence of apparent voltage-dependent pacemaker neuron activity. Since postsynaptic inhibition also does not appear to be essential to respiratory rhythm generation, we are investigating mechanisms that require neither voltage-dependent pacemaker activity nor postsynaptic inhibition.

16 PULMONARY FUNCTION TESTING AND EVALUATION FOR PATIENTS WITH SPINAL CORD INJURY/DISORDER

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Marvin Lesser, MD

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Spinal cord injury (SCI) results in varying degrees of respiratory muscle paralysis and pulmonary autonomic nervous system dysfunction. The severity of this effect depends upon the level and completeness of injury: the higher and more complete the SCI, the greater the degree of pulmonary function compromise. Initial clinical evaluation should identify any respiratory symptoms; the most commonly reported are breathlessness, cough, phlegm, and wheeze. The presence of symptoms provoked by airborne irritants should be determined. In 180 subjects with SCI, 68% reported one or more respiratory symptom with breathlessness being the most prevalent complaint (Spungen et al., 1997). Airflow and lung volumes are likely to be compromised in individuals with SCI relative to the level of lesion. Airflow is measured by spirometry. Lung volumes are measured by nitrogen or helium washout techniques or whole body plethysmography. Many studies have been performed describing airflow limitations and lung volume reductions in this population. One study using a logistic regression model demonstrated that breathlessness significantly correlated with level of injury, cough combined with phlegm and/or wheeze (CPWZ), total lung capacity percent of predicted, and expiratory reserve volume (Spungen et al., 2001). Significant independent associations with CPWZ included current smoking, breathlessness, and forced expired volume in 1 second (FEV_1). Maximal static inspiratory and expiratory mouth pressures (MIP and MEP) are surrogate measures of respiratory muscle strength. In a double-blind placebo controlled trial of 1-month duration, administration of an inhaled β_2 agonist, salmeterol, was associated with significant improvement in MIP and MEP in persons with tetraplegia (Lesser et al., 2001). Inspiratory muscle strength may also be measured by sniff nasal inspiratory pressure (SNIP). Airway resistance (R_{aw}) is a measure of the opposition to airflow provided by all the airways between the atmosphere and the gas exchange units of the lung (Dubois, 1956). It is measured by a pressurized whole body plethysmograph in which the patient sits in an enclosed pressurized box and performs various breathing and panting maneuvers. This method is considered to be the gold standard for R_{aw}. Difficulties with this method include transferring of patients to the box and cooperation with panting maneuvers. Another measurement of airway resistance is performed by use of a high-frequency impulse oscillation system (IOS). IOS has been demonstrated to be sensitive to pre- and postbronchoprovocation changes, but may not be as accurate for baseline assessments as is plethysmography. IOS technology does have the advantage of being performed during normal tidal breathing

with patients in their wheelchair. Airway hyperreactivity is a term used to describe an amplified bronchoconstrictive response of the airways to a noxious stimulus. Airway hyperreactivity is measured by bronchoprovocation testing with agents such as methacholine, histamine, or ultrasonically nebulized distilled water. Patients with cervical lesions have been demonstrated to have an increased prevalence of a positive response to provocation.

17 EPIDEMIOLOGY OF RESPIRATORY DYSFUNCTION IN SPINAL CORD INJURY

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Death in chronic spinal cord injury (SCI) is commonly due to respiratory diseases, yet the natural history of respiratory dysfunction following SCI remains ill-defined. Understanding the causal pathway and the recognition of treatable risk factors will be important in improving survival as persons with SCI age. Since 1994, 476 subjects >1 year after SCI have been enrolled to assess cross-sectional and longitudinal predictors of pulmonary function, chest illness, and mortality. Subjects complete a respiratory health questionnaire and undergo standardized pulmonary function testing and neurological exam In cross-sectional analyses, subjects with complete cervical injury were more likely to report wheeze than others with SCI, but heart disease and cigarette smoking were greater risk factors. Chest illness resulting in time off from work, staying indoors, or staying in bed in the 3 years prior to questionnaire completion was significantly associated with wheeze and cervical injury, but heart disease and cigarette smoking accounted for most of the risk. Mortality through 2000 was not related to SCI, but was attributable to age, diabetes (RR = 2.8; 95% CI 1.3–6.2), heart disease (RR = 3.9; 95% CI 1.7–8.6), cigarette smoking, and reductions in FEV_1. These results suggest that recognition and treatment of comorbid medical conditions and smoking cessation in SCI may reduce mortality previously attributed only to SCI.

18 ASSESSMENT OF AIRWAY DYNAMICS AND MECHANISMS OF BRONCHOCONSTRICTION IN TETRAPLEGIA

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Previous spirometric studies of subjects with spinal cord injury demonstrated that between 40% and 50% of subjects with tetraplegia experienced significant improvement in forced expiratory volume in 1 second (FEV_1) following inhalation of ipratropium bromide (IB), an anticholinergic agent, or metaproterenol sulfate, a short-acting beta-2 agonist. These findings introduced the possibility that subjects with tetraplegia were also hyperresponsive to bronchoconstricting agents. Accordingly, studies were performed using aerosolized methacholine, histamine, and ultrasonically nebulized distilled water, which revealed that most subjects with tetraplegia, but not those with paraplegia, displayed airway hyperreactivity similar to that found in mild asthma. Further, among 32 subjects with tetraplegia challenged with histamine, low baseline FEV_1 correlated with greater responsiveness to the agent, suggesting that low baseline airway caliber may contribute to hyperresponsiveness among these individuals. Reduced airway caliber, with associated increase in airway resistance, may play a pivotal role in airway hyperresponsiveness based upon the mathematical theorem that resistance of laminar gas flow is inversely related to the fourth power of the radius. Therefore, with narrow airways, a given degree of further narrowing caused by a bronchoconstricting agent will be associated with greater measured obstruction to flow than the same degree of narrowing occurring at normal patency. To further evaluate baseline airway caliber in tetraplegia, body plethysmographic measurements of airway resistance (R_{aw}) and specific airway conductance (sGaw, L/s/cmH_2O/L) were performed before and after aerosol administration of IB. Total respiratory resistance at 5 (R5) and 20 (R20) Hz were also measured using an impulse oscillation system (IOS). R5 is a measure of total pulmonary resistance, and R20 is more reflective of large airway resistance. We found that sGaw was significantly lower in tetraplegia

(0.14 ± 0.03) compared to high paraplegia (0.19 ± 0.05), low paraplegia (0.19 ± 0.04), and able-bodied individuals (0.23 ± 0.06). Baseline R5 and R20 values did not differ significantly among the four groups. The sGaw findings clearly demonstrate that baseline airway caliber is reduced in tetraplegia. Following IB, sGaw increased by 77% in tetraplegia compared to 19% in high paraplegia, 13% in low paraplegia, and 17% in able-bodied individuals. R5 decreased by 31%, 11%, 12%, and 14%, respectively. R20 decreased by 27%, 7%, 12%, and 15%, respectively. The changes for all three measurements were highly significant for tetraplegia compared to those found for the other three groups. These dramatic responses to IB in tetraplegia reveal that baseline airway caliber is reduced in these individuals because of amplified vagal tone, presumably due to loss of sympathetic innervation of the lungs and/or low circulating epinephrine levels. In an additional study in those with tetraplegia, responsiveness to IB was compared with that for albuterol (ALB), a short-acting beta-2 agonist. sGaw increased 79% following IB compared to 52% following ALB. R5 decreased 31% following IB compared to 19% for ALB. R20 decreased 26% for IB compared to 9% for ALB. These findings indicate that IB induced bronchodilation by acting throughout the bronchial system, whereas ALB acted more peripherally. Cumulatively, these studies demonstrate that baseline airway caliber is low in tetraplegia because of increased vagal tone and suggest that reduced airway caliber contributes to airway hyperreactivity. Studies are currently underway to determine if administration of an anticholinergic agent regularly to subjects with tetraplegia reduces dyspnea and improves quality of life.

19 ELECTRODIAGNOSTIC EVALUATION IN THE CRITICAL CARE ENVIRONMENT

Shu Huang, MD

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Electrodiagnosis is an essential tool in assessing patients with difficulty in weaning off respirator and unexplained weakness. Technical difficulty includes excessive swelling of the surface area, presence of intravenous lines, multiple monitor devices, and lack of volitional effort. Better machines, accessories, and experience can overcome these. The electrodiagnostic repertories include sensory and motor conduction, late responses such as F waves, H reflexes, study of cranial nerves, blink reflexes, and repetitive study. The degree of workup is dictated by the clinical suspicion. Critical illness axonal polyneuropathy accounts up to one-third of these patients with multiple organ failure. It should always be considered. In patients with neuromuscular blockage, not only can the use of such blockage result in myopathy that is often self-limiting, diffuse axonal polyneuropathy with much worse prognosis still accounts for majority of such weakness. Small sensory and motor-evoked responses with mildly slowed velocities and prolonged late responses are the key findings with diffuse presence of wallerian degeneration seen on needling examination. Other diagnoses to be discussed are acute axonal or demyelinating Guillian-Barre syndrome, myasthenia gravis, myasthenic syndrome, myelopathy, encephalopathy, other drug-induced neuromyopathy, pan fascicular muscle fiber necrosis, and catabolic myopathy.

20 CRITICAL CARE FOR PATIENTS WITH CHRONIC SPINAL CORD INJURY

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The major causes for death in chronic SCI are due to pulmonary complications. Specifically, these include acute respiratory failure due to atelectasis, pneumonia, COPD, lung cancer, and thromboembolism as well as the acute respiratory distress syndrome due to sepsis. Sepsis is frequently caused by pneumonia, decubitus ulcers, or urinary tract infections. The SCI compromises the muscles used to cough. Consequent inadequate secretion clearance can lead to atelectasis and pneumonia. Meticulous attention to bronchial hygiene as well as to prevention of decubitus ulcers and urinary tract infections

may decrease ICU admissions for sepsis. Once sepsis occurs, antibiotic therapy needs to be directed at the source. Early recognition of sepsis is particularly important, since early aggressive goal-directed therapy of severe sepsis will decrease mortality (from 46% to 30%). Goal-directed therapy consists of maintenance of adequate central venous pressure, mean arterial pressure, and venous oxygen saturation with fluids, vasopressors, and blood transfusions. Similarly, administration of drotrecogin alpha-activated (an anti-inflammatory, antithrombotic, and profibrinolytic drug) decreases mortality in severe sepsis. Mortality may be further decreased by tight glycemic control as well as the administration of low-dose steroids in septic patients with adrenal dysfunction. Lastly, low tidal volume ventilation may decrease mortality in ARDS.

21 CRITICAL CARE NURSING FOR PATIENTS WITH SPINAL CORD INJURY/DISORDER

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The intensive care unit (ICU) nursing needs of the patient with SCI are diverse and complex. Most traumatic SCIs in the United States result from motor vehicle crashes (47.7%), followed by falls and falling objects (20.8%), acts of violence such as gunshot wounds and stabbings (14.6%) and sports activities, especially diving, football, and skiing (14.2%). Nursing management of SCI requires a comprehensive, holistic approach to care. Some of the most common diagnosis admitted to the ICU is pneumonia, UTI, ilius, and decubitus ulcer infections. Critical nursing interventions include careful surveillance for deterioration of neurological status or development of adverse symptoms, indicating physiological deterioration or complication, administration and evaluation of medical interventions to maintain physiological homeostasis and prevent complications, and psychosocial support and ongoing communication with the patient and family regarding the treatment regimen. Additional interventions in the ICU setting may include NG tube, foley catheter insertion, NPO status, and SQ heparin to prevent venous stasis complications. Because of the enormous number of individual variables and circumstances surrounding the SCI, no two cases of SCI will be exactly the same.

22 ANEMIA AND BLOOD TRANSFUSION IN CRITICALLY ILL

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Critically ill patients receive an extraordinarily large number of blood transfusions. We have found that over 50% of all patients admitted to the ICU receive at least 1 unit of RBCs during their ICU admission. In the patients with a prolonged ICU length of stay (greater than 1 week), 85% receive a transfusion of at least one unit of RBC. These transfusions are not restricted to the early ICU course; rather these patients tend to be transfused at a constant rate of 2 to 3 units per week. This same phenomenon is seen in ICUs across the country; over 14% of patients in critical care units are transfused on any given day (ranging from 4% in CCUs to 27% in SICUs). More recent data from both the United States and Europe confirm that transfusion practice is little changed over the last decade. Between 40% and 50% of all patients admitted to ICUs receive at least 1 RBC unit and average close to 5 RBC units during their ICU admission. In these patients, extent of anemia is associated with poorer clinical outcomes. However, RBC transfusion not only does not improve clinical outcomes but also is associated with increased mortality. The anemia of critical illness is a distinct clinical entity characterized by a blunted EPO production and abnormalities in iron metabolism identical to what is commonly referred to as the anemia of chronic disease. There is little evidence that “routine” transfusion of stored allogeneic RBCs is beneficial to critically ill patients. It is clear that most critically ill patients can tolerate hemoglobin levels as low as 7 mg/dL, and therefore, a more conservative approach to RBC transfusion is warranted. Strategies to minimize loss of blood and increase the production of RBCs are also important in the management of all critically ill patients.

23 REACTIVE AIRWAY DISEASES

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Asthma affects 10% of the population in the United States, and its prevalence has continued to increase over the last 20 years. This disease encompasses a wide range of clinical manifestations, presenting from early infancy through adult life. Predisposition to reactive airway diseases involves genetic, environmental exposure, and postviral factors. The pathophysiology of asthma includes smooth muscle hypertrophy, epithelial cell desquamation, and inflammatory cell infiltration and mucous hypersecretion. The trigger of symptoms may include allergic and nonallergic stimuli. Diagnosis is based upon a thorough medical history, supplemented by a number of objective tests. The National Asthma Education and Prevention Program (NAEPP), in its recent Executive Summary, has outlined classification of asthma severity. Treatment strategies target the reactive airway response with bronchodilator medications and preventive anti-inflammatory therapies. Special concerns in spinal cord injury patients include bronchial hyperresponsiveness, impaired mucociliary clearance, and mucous hypersecretion and alterations in respiratory mechanics that make diagnosis and treatment more difficult.

24 MECHANICAL VENTILATION IN SPINAL CORD INJURY/DISORDER

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Ventilatory insufficiency and impaired airway secretion clearance are common complications of spinal cord injury. These compli-cations can lead to respiratory failure, which is the leading cause of death in both acute and chronic stages. Eighty-four percent of patients with C1–C4, and sixty percent of patients with C5–C8 had serious pulmonary complications after the acute injury. A large percentage of these patients will require intubation within the first 24 hours after the injury. Mechanical ventilation is aimed at providing adequate gas exchange and comfort. Positive end-expiratory airway pressure (PEEP) is usually applied to improve oxygenation as a result of pneumonia or atelectasis. The inspiratory flow setting should be tailored to the patients' comfort. Too low or too high inspiratory flow settings result in discomfort and should be avoided. A large percentage of patients with cord injury at C4 or below can be successfully weaned, although it takes more than 2 weeks before weaning from mechanical ventilation can begin in more than one-half of the patients. Although a systematic study on the application of noninvasive mechanical ventilation in patients with acute cervical cord injury is sparse, successful application has been reported provided that the patient is cooperative and medically stable.

25 DEEP VENOUS THROMBOSIS (DVT) AND PULMONARY EMBOLISM (PE) IN SPINAL CORD INJURY

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Patients with neurologic impairment accompanied by extremity paresis or plegia secondary to spinal cord injury (SCI) have a very high incidence of DVT, especially during the acute-case stage (up to 80% by venography). It has been recognized for decades that PE represents a common cause of death following SCI and that the prevalence of PE is increased in patients dying with paraplegia or quadriplegia. Thromboprophylaxis for a minimum of 3 months and possibly through the rehabilitation phase has become a routine strategy in management of these patients. Although there are limited well-controlled comparative studies of the different strategies for DVT prophylaxis following SCI, a number of available principles should be considered from the small number of studies available. Management constructs for the prophylaxis, diagnosis, and treatment of DVT/PE applicable for this high-risk group of patients will be discussed.

26 NEURAL PROSTHESES IN THE RESPIRATORY SYSTEM

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Patients with spinal cord injury often suffer from respiratory failure due to paralysis of their inspiratory muscles and an increased incidence or respiratory tract infections due to paralysis of their expiratory muscles and lack of an effective cough mechanism. In patients with bilateral phrenic nerve function, diaphragm pacing has been used successfully to maintain patients off mechanical ventilatory support. Diaphragm pacing affords patients marked improvements in life quality and offers significant advantages compared to mechanical ventilation. Unfortunately, many patients cannot be offered this modality because of injury to the phrenic nerve or the phrenic motoneurons in the spinal cord. Preliminary studies in four patients, however, suggest that in patients with a single functioning phrenic nerve, combined intercostal and diaphragm pacing can also maintain ventilatory support for prolonged time periods. The intercostal muscles can be activated by epidural stimulation applied at the T2 spinal cord level. This technique can provide patients with many of the same benefits as bilateral diaphragm pacing. Preliminary studies in animals indicate that epidural stimulation applied over the lower thoracic spinal cord level results in marked activation of the expiratory muscles. This technique holds promise to restore an effective cough mechanism and potentially reduce the morbidity and mortality of respiratory complications in patients with spinal cord injury.

27 THE ELECTRODIAGNOSTIC EVALUATION OF THE UPPER LIMB IN PATIENTS WITH SPINAL CORD INJURY/DISORDERS

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The basic electrodiagnostic (EDX) examination the nerve conduction studies (NCS), motor and sensory, and the needle electrode examination (NEE) can help in assessing patients with cervical spinal cord injuries (SCIs) as follows: (1) Sensory nerve action potentials (SNAPs) usually are unaffected, because the cell bodies of the axons being studied are in the dorsal root ganglia, which are located in or near the ostium of the intervertebral foramina, rather than in the spinal cord (SC) itself. (2) Compound muscle action potentials (CMAPs) are of low amplitude or unelicitable whenever the SC segments that supply the recorded muscle are damaged, because the axons evaluated arise from anterior horn cells (AHCs) located in the SC. Thus, the ulnar motor NCS amplitudes, recording hypothenar, are affected with lesions of the C8 SC segment, but not with lesions involving segments superior or inferior to it. (3) On NEE, fibrillation potentials are seen in muscles supplied by the injured SC segment, while two types of motor unit potential (MUP) firing abnormalities are observed, one in muscles innervated by the injured segment, the other in muscles innervated by all segments inferior to it. Utilizing the above, many aspects of the focal SC lesion can be documented, including its (1) exact level, (2) longitudinal extent, and (3) symmetry or asymmetry from side to side.

28 MANAGEMENT OF UPPER LIMB SPASTICITY

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Three cardinal disabling features affect patients with spastic paralysis: motor weakness, muscle shortening, and muscle overactivity. None of these mechanisms of impairment are evenly distributed throughout the muscles, and across joints, there is usually imbalance between less hyperactive and weaker agonists, and more hyperactive and shorter antagonists. Therapy targeting overactivity in specific muscles (local treatments) may therefore be preferable to systemic approaches (oral or intrathecal medications). We review the local treatments of the three mechanisms of impairment in the spastic upper limb: stretch programs for the shorter muscles, training programs for the

weaker muscles, and injection of blocking agents for the more hyperactive muscles. For each patient, it should be determined whether the priority is to improve comfort and passive function (activities performed by the caregiver or by the other arm), or to improve active function of the paretic upper limb. Injection treatments are always possible, even in the more severely affected patients, and are useful for both passive and active function purposes. However, stretch and training programs require patient cooperation and are indispensable only to improve active function. Optimal treatment of the spastic upper limb should include (1) individualization of injection protocols (muscle selection, doses, dilution), (2) injection technique using exploratory stimulation, (3) inclusion of the shoulder muscles among target muscles, (4) stretch programs in the injected muscles, (5) training of the antagonists when feasible, and (6) electrical stimulation in both injected muscles and their antagonists. The combination of the latter three techniques with injections of blocking agents should improve functional outcome.

29 SHOULDER BIOMECHANICS: MUSCLES CONTRIBUTE TO DISLOCATION AS WELL AS JOINT STABILITY

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Joint instability is one of the most common human afflictions, affecting not only the hip, knee, and shoulder but also all joints of the body. Surgical repair of these joints are performed approximately 800,000 times a year in the United States of America. Unfortunately, it has not been able to consistently restore function. Pain, recurrence of instability, joint stiffness, muscle injury, and degenerative joint disease are common sequelae. We have directed our efforts to improve understanding of glenohumeral joint instability, since the shoulder is the most commonly dislocated joint. This study included not only the static (anteroinferior capsulolabral) restraints but also their important interplay with the dynamic (shoulder muscles) restraints. In this regard, we not only studied muscles known to stabilize the joint, but we also sought out those that may contribute to dislocation. An in vitro, cadaveric model that includes relevant shoulder muscles and a mechanism of dislocation similar to an in vivo mechanism was developed. The capsulolabral pathoanatomy that occurred after dislocation was studied. We hope to aid understanding of joint dislocation and improve functional results after both rehabilitation and surgical repair not only at the shoulder but also at all other human joints as well.

30 PAINFUL SHOULDERS

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Shoulder pain in individuals with spinal cord injury (SCI) has been a common and persistent problem. Recent research indicates as many as 30%–70% of the SCI population has new or chronic shoulder pain. The increased risk of developing shoulder pain with aging likely results from a combination of factors including the unusual functional demands on the shoulder, altered biomechanics of the joint, and age associated changes in shoulder structures. The impact of shoulder pain on functional activities in persons aging with SCI will be discussed and rationale for specific therapeutic interventions will be examined in this presentation. In addition, a randomized clinical trial currently investigating the effectiveness of a specific intervention of therapeutic exercise and movement optimization will be described.

31 SHOULDER IMPINGEMENT IN THE SPINAL CORD INJURY POPULATION

Amy Ladd, MD

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Shoulder impingement is endemic in the spinal cord injury (SCI) patient, both paraplegic and tetraplegic populations. We review the etiology, response to treatment and propose an outcome measurement based on the experience of

the Palo Alto Veterans Affairs Spinal Cord Injury Unit. Between 1990 and 2001, we examined 207 patients with shoulder problems (305 shoulders), including 88 tetraplegic and 119 paraplegic patients. We identified 101 patients (49%) with impingement symptoms, usually with positive imaging studies. Thirty-one cuff tears were suspected. All patients underwent home-based rotator cuff and scapular stabilizing exercises, stretching, and education; many were prescribed physical therapy and anti-inflammatory drug use. Eighty-nine patients improved or not deemed surgical decompression candidates. Twelve patients (15 shoulders) underwent subacromial decompression and glenohumeral debridement; three also had rotator cuff repairs. One underwent reoperation after injury. Two surgical and seventeen nonsurgical patients have died. Physical exam and a modified Constant score using standard muscle grading are currently used for assessment. Most patients improve with nonoperative measures, and selected few have benefited from surgical decompression. We propose a modified Disabilities of the Hands, Shoulder and Arm (DASH) outcome measurement specific for the SCI population to provide better assessment of patients' function, response to treatment, and quality of life.

32 SURGICAL MANAGEMENT OF SHOULDER DYSFUNCTIONS IN PATIENTS WITH SPINAL CORD INJURY/DISORDER

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The paraplegic shoulder is particularly susceptible to overuse injuries of the rotator cuff. While traditional teaching has stated that rotator cuff injuries are due to subacromial spurs, recent evidence has shown that the rotator cuff fails by primary intrinsic tendon degeneration, or tendinosis. The subacromial spur is reactive, and not a pathology-inducing lesion. As the majority of rotator cuff tears are asymptomatic and the majority of symptomatic rotator cuff tears are rendered asymptomatic by strengthening, the rotator cuff tear itself is not often a source of pain. The pain of rotator cuff pathology is due to the buildup of degenerative tendinosis tissue. While subacromial decompression may relieve pressure on a painful tendon, denervate the coracoacromial arch, or allow an opportunity for rest and proper rehabilitation, it fails to address the primary pathologic tendinosis lesion and is associated with a significant number of complications, including recalcitrant pain. Simple arthroscopic debridement is a lower morbidity procedure, with a greater efficacy and fewer complications. Furthermore, it avoids iatrogenic injury to the coracoacromial arch, which is an important secondary static stabilizer of the humeral head against superior migration.

33 UPPER LIMB EVALUATION AND THERAPIES FOR PATIENTS WITH SPINAL CORD IINJURY/ DISORDER

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There are many areas of assessment in the area of tetraplegia. Among the common areas are assessment of motor and sensory level using the ASIA classification and the International Classification for Surgery of the Hand in Tetraplegia (ICSHT); analysis of equipment including amount needed, effort, and ability to don and cosmesis; pain and pain syndromes; effort and spontaneity of activity and temporal aspects of activity performance, all of which are understudied and underestimated; comorbidities; spasticity; skin issues; and age. While most assessments concentrate on evaluation of SCI/D as a medical condition, the overall assessment requires the understanding of SCI/D as a cultural, political, social, and personal experience. Over the past four decades, disablement models have been proposed as a basis to understand disability beyond the medical condition. Most recently, the International Classification of Functioning, Disability and Health (ICF) has been presented as a means to understand the constituents of health. The goal of this lecture is threefold. First, medical conditions that are not typically part of the standard assessment in tetraplegia will be discussed. Second, case studies will be presented to illustrate the significance of nonmedical dimensions of disability. Last, the

Canadian Occupational Performance Measure (COPM) will be discussed as a way to assess performance of and satisfaction with client-directed activities. All children injured before skeletal maturity and half of those injured during or after adolescents will develop paralytic spine deformities. While paralytic spine deformities enable compensatory head-to-hand strategies and abilities in perianal care, many persons with tetraplegia will require surgical correction of the deformities to prevent pulmonary compromise and skin breakdown; correction of these deformities in the form of spinal fusion takes away these compensatory strategies. Assessment requires careful analysis of function. Proximal deformity, pain, and instability play a pivotal role in the success of upper-extremity (UE) therapies. Evaluation of static and dynamic sitting posture is another key to the overall assessment in tetraplegia. The inability to independently assume a variety of sitting postures throughout the day is one of the main reasons why persons with SCI\D depend on others for ADL as opposed to UE capacity. Many persons with SCI\D do not have the postural requirements for function. Determination of preinjury and postinjury hand and arm dominance is necessary, and the understanding of the implication of motor and sensory asymmetry in the UE completes the evaluation. The cultural, social, and personal dimensions of disability are influenced by political and economic factors. While they are the predominant dimensions influencing health and quality of life, they also foster medicalization and often negate the impact of positive medical results. The Canadian Occupational Performance Measure (COPM) is an assessment of patient's perception of performance and satisfaction with self-selected activities. The COPM provides useful information into abilities but also into the social, personal, and cultural dimensions of disability.

34 UNIQUE ASPECTS OF THE PEDIATRIC PATIENT WITH SPINAL CORD INJURY AND THE EFFECTS ON UPPER-LIMB MANAGEMENT

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This paper describes some unique aspects of the pediatric patient (<15 years old) with SCI and its effect on upper-limb management. Pediatric patients have a higher prevalence of upper cervical spine injuries (at the C7 level) as compared to the C5-6 level in adults. On prospective MRI scanning in children, 50% have a spinal cord syrinx, the same as adults. Scoliosis occurs in almost 100% of patients, with two-thirds requiring surgery if injured prior to skeletal maturity. Prophylactic bracing has been found to be effective in delaying or preventing a fusion; however, bracing can inhibit function. Standard spinal fusions with instrumentation from T2 to the pelvis can have an adverse effect on compensation strategies used by children, especially with hand-to-mouth function in patients with tetraplegia. Contouring the spinal rods during surgery can lessen that adverse effect. A therapy consultation prior to surgery can be extremely helpful in anticipating adverse effects. Upper-limb reconstruction surgery should be offered to most children with tetraplegia, as the outcomes have been shown to be extremely positive, and there are no adverse effects seen with growth. Animal and human investigations have shown that implanting an FES system in children can be feasible, safe, and efficacious for applying the same FES technologies available for adults.

35 UPPER-LIMB ORTHOSES

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The practice of prescribing upper-limb orthoses and splints for individuals with tetraplegia is widely accepted. Upper-limb orthoses are used to enhance function, prevent joint

deformities and overstretching of muscles, create adaptive shortening, and support the arm, wrist, and hand. The wide support of splinting the upper limb in tetraplegia is largely based on general physiological principles. Published studies on orthoses are scarce, and they are mostly based on practice surveys and not on controlled clinical trials, which examine the efficacy of one orthosis versus another. With such lack of data, it is more useful to describe the general splinting objectives rather than focus on the superiority of one particular orthosis. An exception to this paucity of objective data is the information published about the functional Wrist Driven Wrist Hand Orthoses (also called Tenodesis splint, flexor hinge splint, and the "Rancho" Splint). Innovations in the neuroprosthetic field far exceed the improvements in mechanical upper-limb orthoses. Some innovations in mechanical orthoses are described. For further information read: Atkins M, Clark D, Waters R. Upper limb orthoses. In: Lin VW, editor. Spinal cord medicine: Principles and practice. New York: Demos; 2003. p. 663–74.

36 TISSUE ENGINEERING NERVE CONDUITS

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Approximately 8,000,000 surgical procedures are performed annually in the United States to treat tissue and organ deficiencies. These associated medical costs exceed $400 billion annually. Tissue engineering has great potential in extending the quality of life and reducing the cost of healthcare. In 1997, operating expenses allocated to tissue engineering exceeded $450 million and funded the activities of nearly 2,500 scientists and support personnel. Peripheral nerve injuries can result from mechanical, thermal, chemical, congenital, or pathological etiologies. Failure to restore these damaged nerves can lead to the loss of muscle function, impaired sensation, and painful neuropathies. Current surgical strategies for repair of critical nerves involve the transfer of normal donor nerve from an uninjured body location. Frequently, however, these "gold standard" methods for tissue restoration are limited by tissue availability, risk of disease spread, secondary deformities, and potential differences in tissue structure and size. Our current technology for nerve repair using autologous nerve grafts is limited by the availability of donor tissue and its related morbidity. The utilization of allografts and immunosuppression as nerve grafts is an option; however, outcomes in nerve reconstruction with the use of allografts have not approached results obtained with autografts. Further, oncologic and traumatic considerations frequently preclude the use of allografts with immunosuppression. One possible alternative to autogenous tissue replacement is the development of engineered constructs to replace those elements necessary for axonal proliferation and to include a scaffold, support cells, induction factors, and extracellular matrices (ECMs). Tissue engineering holds promise in the treatment of verve defects following surgical ablation and injury by reducing the current limitations.