Medical Education Systems, Inc.

Spinal Cord Injuries: An Overview

Medical Education Systems, Inc

TOLL FREE: 877-295-4719
LOCAL: 619-295-0284
FAX: 619- 295-0252
EMAIL:info@mededsys.com
WEBSITE: www.mededsys.com
P.O Box 81831 San Diego, CA 92138-3939.

Spinal Cord Injuries: An Overview

Learning Objectives

Upon successful completion of this course, you will be able to:

- Identify the tools for assessing spinal cord injury and repair
- Identify the outcome measurements used to assess injury and recovery
- Identify the steps involved in monitoring real-time progression of spinal cord injuries
- Identify the current therapeutic interventions

TOOLS FOR ASSESSING SPINAL CORD INJURY AND REPAIR

Because the spinal cord is encased in the protective armor of the vertebrae, investigation of the site of the injury or the effects of potential therapies has required the development of a diverse set of research tools. In the past 40 years the rapid progress in the technologies available to perform experiments has largely been responsible for the great strides that have been made in understanding the basic principles of neuroscience. Studies with animal models have been instrumental in the rapid development of neuroscience and understanding of the biology of the spinal cord. The advent of cell culture techniques has provided a means to isolate and grow cells. Researchers can now isolate specific molecules and proteins and examine their roles in neuronal injury and repair in laboratory animals that mimic human spinal cord injuries. Recent advances in imaging techniques and methods for investigation of the actions of genes have advanced the understanding of spinal cord injuries even further. They also provide researchers with the tools that they need to examine changes in the spinal cord at the molecular and structural levels, for example, improving knowledge of the inhibitory conditions that serve as barriers to neuronal regeneration.

This section describes the important genetic and in vitro tools that have been developed to advance spinal cord injury research; the key animal models that are used to mimic human spinal cord injuries and the major limitations of the existing animal models; and the outcome measures that have been developed to assess spinal cord injuries and the effectiveness of experimental therapies, including the development of imaging technologies.

MOLECULAR, GENETIC, AND IN VITRO TOOLS

Techniques have been developed that allow researchers to isolate and grow populations of neurons to investigate the effects of specific proteins and molecules on neuronal injury and repair. Neurons can be grown in isolation or with glial cells such as oligodendrocytes or Schwann cells to study the processes of axonal outgrowth and myelination. Investigators use molecular biology-based techniques, such as DNA or protein analysis, that can be used to easily visualize or analyze outcomes.

Demonstrating the power of a cell culture experiment, the simple growth-cone turning assay led to the discovery that altering various molecules inside the growing axon regulates protein and cyclic nucleotide activities, which, in turn, can convert an axon's response to a growth-inhibiting molecule from one of repulsion to one of attraction (Song et al., 1998). When this application is applied to regenerating axons in the rat spinal cord, investigators showed that the regrowth of transected neurons has the potential to be enhanced considerably (Neumann et al., 2002; Qiu et al., 2002). Furthermore, the recent elucidation of the signaling pathways responsible for this switch in response may lead to the discovery of a strategy for enhancing axon regeneration (Wen et al., 2004).

Often, in vitro assays can be used in experiments with animal models, thus allowing researchers to verify and examine the effects detected in vitro to be evaluated in a more complex system. For example, chondroitin sulfate proteoglycans were found to inhibit neurite outgrowth in in vitro experiments (Snow et al., 1990). Analysis with animal models demonstrated that the levels of these proteoglycans are enhanced, or up-regulated, during central nervous system (CNS) injury (Snow et al., 1990) and led to the development of a strategy to break down these substances and promote the regrowth of axons in the intact rat spinal cord after an injury (Bradbury et al., 2002).

Animal Models for Molecular and Genetic Studies

Models consisting of multiple-transgenic animals have been developed to investigate molecular mechanisms and to identify the molecules critical for specific processes (Table 3-1). These models provide a better understanding of the genetic and molecular basis by which spinal cord circuits, specific neuronal subtypes, and synapses are formed (Shirasaki and Pfaff, 2002; Lanuza et al., 2004). For example, by studying the development of the nervous system of the fruit fly (*Drosophila melanogaster*), researchers have identified numerous molecules that can regulate the growth of the axon and the formation of neuronal connections (Vaessin et al., 1991; Kidd et al., 1998; Kraut et al., 2001; Jin, 2002). This information should provide **TABLE 3-1** Animal Models Commonly Used to Identify Genes Involved in Axon Growth and Circuit Formation

Animal	Technique(s) Primary	Utility
Fruit fly	Transgenic	Identify and investigate molecular expression patterns; perform genetic experiments to identify the molecules involved in axon growth and guidance and the reformation of neuronal connections
Worm	Transgenic	Identify and investigate molecular expression patterns and perform genetic experiments
Fish	Transgenic, transection,	Examine motor control and the central pattern generator after transection of the spinal cord and investigate axonal regeneration models

Mouse Transgenic, imaging	Identify and investigate molecular expression patterns; perform genetic experiments to identify the molecules involved in axon growth and guidance and the reformation of neuronal connections; examine cellular and molecular basis of spinal cord circuits

The insights needed to reconstruct effective circuits once axonal regeneration has been achieved.

ANIMAL MODELS OF SPINAL CORD INJURY

Animal models allow in-depth investigation of the anatomical and molecular changes that occur in response to a spinal cord injury at a level of detail that would not be possible or ethical in studies with humans. These insights are critical for the design and interpretation of the results of studies with humans. Without the knowledge gleaned from studies with animals, the spinal cord would remain the equivalent of a black box and therapies aimed at restoring function would be limited. For example, experiments with rodents demonstrated that the neurons in the spinal cord are able to regenerate after an injury (Richardson et al., 1980; Xu et al., 1995).

Researchers have developed a variety of animal models that mimic different attributes associated with spinal cord injuries. Depending on the purpose of the study and the specific aspect of the injury to be investigated, researchers determine which animal model most closely replicates the injury in humans (Tables 3-2 and 3-3). In 2000, the International Spinal Research Trust published guidelines that describe four characteristics that are required for an optimal model of spinal cord injury (Ramer et al., 2000):

> The nature and the extent of the lesion should be precisely defined. If there is doubt about the extent of a lesion or whether axons have been spared, then interpretations of regeneration can be misleading.
>
> A histological method should be available to detect the growth of axons through the lesion.
>
> A method should be available to analyze the functional synaptic transmission beyond the lesion by measuring the electrical activity that neurons use to communicate with one another.
>
> A behavioral measure should be available that is capable of detecting restoration of known circuits.

It is important to examine therapies in a system that best mimics the condition of the individual with a spinal cord injury. For example, therapies designed for individuals with chronic conditions should not be tested in animal models immediately after the animal has received the injury but should be tested only after the animal is in the chronic stage of the injury (Kwon et al., 2002a; Houle and Tessler, 2003; Kleitman, 2004).

TABLE 3-2 Value of Animal Models for Spinal Cord Injury Research

Allows in-depth investigation of the anatomical changes that occur in response to an injury
Regeneration of axonal tracts between the brain and the spinal cord can be studied in detail
Individual components of the complex neural circuitry required for sensory perception and motor control can be examined
Factors that influence DNA and proteins can be characterized
Provides a means to examine the effects of specific genes
Provides a tool to identify and test the efficacies of potential therapeutic agents and targets
Identifies clinical end points that can be used to assess the efficacies of therapeutic agents

TABLE 3-3 Criteria for Choosing an Ideal Animal Model

Ability to match the behavioral complication to a morphology deficit
Similarities and differences between the anatomy and cellular composition of the animal and human spinal cord
Similarity of the whole injury process, including genetic changes and progression, to that observed in humans
Similarities and differences between the timing of the stages of injury and life cycle in animals and humans
Similarities and differences in the genetic backgrounds of the animal strains and species that may influence the response and recovery from a spinal cord injury
Economics of the model, including the costs of care and feeding, and regulations

SOURCE: Croft, 2002.

Furthermore, each type of spinal cord injury is different and presents its own set of challenges; therefore, each requires its own standard animal model that reliably mimics the complications experienced by individuals with that type of spinal cord injury.

A number of animal models have been developed, including models that mimic compression, contusion, and transection (Table 3-4). Blunt contusion injuries account for 30 to 40 percent of all human spinal cord injuries (Hulsebosch, 2002); thus, the contusion model provides an important tool that researchers can use to examine the neuropathology of the injury and to test the efficacies of different therapeutic agents.

In 1978, the clip compression technique was developed by researchers to simulate the continual pressure and displacement of the spinal cord common in spinal cord injuries, which is not reproduced in contusion injuries (Rivlin and Tator, 1978).

This procedure has provided researchers with a great deal of information about the pathophysiology of the spinal cord during the acute stages of the injury; the timing, necessity, and effectiveness of releasing the pressure from the spinal cord; and potential therapies (Kwon et al., 2002b). To target and eliminate particular groups of neurons, methods that generate microlesions (Magavi et al., 2000) and that leave the vast majority of the nervous system intact have been developed. Using this strategy, the functional consequences that result from losing the nerve groups can be systematically examined. Researchers are determining the neuronal populations responsible for specific spinal cord injury deficits, including the root causes of chronic pain (Gorman et al., 2001).

TABLE 3-4 Commonly Used Animal Models of Spinal Cord Injury

Animal and Injury Modeled	Primary Utility and Potential Issues
Primate transection	Test the safety and efficacies of therapies
	Determine the role of the central pattern generator in bipedal animals
	Ethical complications with the use of primates
	High cost of animal maintenance
	Limited number of animals that can be prepared for experimentation
	Spatial arrangement of the tracts differs from that in humans
Cat contusion, transection	Examine and define spinal cord circuitry and the central pattern generator
	Central pattern generator may have different amounts of brain regulation compared with that in humans
	Spatial arrangement of the tracts differs from that in humans
	Chromosomes and genes are organized differently from those in humans
Mouse contusion, compression, transection, transgenic, microlesion formation	Investigate molecular and anatomical changes that occur in response to injury; however, mice respond differently than humans to spinal cord injury
	Examine specific molecular targets for potential therapeutic targets
	Modify genes to test the effect on restoration or loss of function

	Difficult to assess upper extremity function
	Genetic variability in injury response, including scar formation
	Differences in scale size of spinal cord between mice and humans
	Spatial arrangement of the tracts differs between mice and humans
	Chromosomes and genes are organized differently from those in humans
Rat contusion, compression, transection, microlesion formation	Investigate molecular and anatomical changes that occur in response to injury
	Difficult to assess upper extremity function
	Differences in scale size of spinal cord in rats versus humans
	Chromosomes and genes are organized differently from those in humans

NOTE: Contusion refers to a bruising of the spinal cord. Transection models are used to simulate lacerations to the spinal cord. Transgenic refers to modification of the animal's genetic profile, which is done by deleting or modifying existing genes or introducing a novel gene.

Issues Regarding Animal Models

Mimicking Transection and Compression Injuries

To make certain that the results from transection experiments are correctly interpreted and to minimize the variability in results, it is important that transection methods be standardized and that control animals be prepared at the same time that the experimental animals are treated. For example, to ensure that the recovery of function is due to axonal regeneration and not spared spinal cord circuitry, researchers must precisely perform transections of the spinal cord and must be sure that the axons projecting from the neurons are completely severed. If not all of the axons are severed, sparing and sprouting from uninjured axons become issues.

It is important to note that damage to the dura mater as a result of a penetrating injury (including experimental transection) provides a route for the invasion of fibroblasts into the injury site (Zhang et al., 1996, 2004). Furthermore, in mice, there is extensive invasion of fibroblasts even without damage to the dura and the fibroblasts participate in the formation of a tissue matrix that is supportive for regeneration of at least some types of CNS axons. Following penetrating injuries, the potential contribution of fibroblasts (positive or negative) must be considered in evaluating experimental interventions to promote repair and functional recovery

By virtue of the means by which compression injuries occur, there is a large amount of variability in the severities of spinal cord injuries. However, when initial compression studies are performed, it is important to be able to study a large population of animals that have the exact same initial injury

characteristics before the experimental therapeutic intervention. Protocols have been developed to help minimize the variability in injury from animal to animal. Three impactors are widely accepted as standard methods for the delivery of contusion injuries to rodents: the Ohio State University (OSU) impactor, the Infinite Horizons device, and the Multicenter Animal Spinal Cord Injury Study (MASCIS) impactor (Bresnahan et al., 1987; Noyes, 1987; Kwo et al., 1989; Gruner, 1992; Young, 2002).

Genetic Variability Between and Among Species

Although it is important to test therapeutic interventions in animals before they can become established treatments in the clinic, genetic differences between animal species can potentially result in different responses to spinal cord injuries or treatments. For example, in response to injury, humans and rats develop a cavity in the spinal cord, but this does not occur in mice (although the precise cellular and molecular bases for this are not yet well understood). In amphibians, regeneration readily occurs directly through the glial scar.

BOX 3-1
The Story of Nogo-Knockout Mice: Cooperation, Collaboration, and Genetic Variability

Three groups of investigators recently used the gene-knockout strategy to examine whether Nogo, a potential inhibitor of axon growth, was responsible for preventing neuronal regeneration after an injury (Steward et al., 2003). Researchers coordinated their research efforts and published their findings in papers published in the same issue of the journal. Each group removed a specific part of a mouse's chromosome that is responsible for Nogo, with the hypothesis that if Nogo is responsible for inhibiting neurons from growing, then its removal would facilitate regeneration after a spinal cord injury. However, the experiments found contradictory results. One study reported that the loss of Nogo increased the extent of neuronal regeneration, as predicted (but only in young mice), and the second study reported a more modest enhancement; however, the third group did not find any significant difference (Kim et al., 2003; Simonen et al., 2003; Zheng et al., 2003). The various results could have been due to differences in the ages and the genetic backgrounds of the mice, the strategy used to delete the Nogo gene, and the compensatory changes in other genes. In order to better understand the differences in these results, two of the groups have set up a collaboration to share their mice and perform their own analyses. This example demonstrates the value of genetic techniques, the importance of consistency in experimental design, the need to replicate experimental results, and the value of collaborative and collegial interactions between research groups.

Different strains of the same animal species may respond differently to spinal cord trauma. For example, the nature and the extent of the secondary injury and wound healing vary in different strains of mice (Inman et al., 2002). Although these differences in responses between strains and species complicate comparison of the results of studies with different animal species, they may provide important insights about the specific genes that affect postinjury signaling cascades (Inman et al., 2002). Furthermore, the differences observed in experiments with the Nogo gene (Box 3-1) provide important lessons about the necessity to replicate experiments.

Scale

The human spinal cord is more than four times as long as the rat's entire CNS (brain and spinal cord). Figure 3-1 demonstrates the difference in size between the entire CNS of a rat and the caudal end of a human spinal cord.

FIGURE 3-1 Size discrepancy between the rat and the human spinal cords.

The human spinal cord is more than four times as long as the entire CNS of the rat. (A) A caudal segment of the human spinal cord, including the cauda equina. The human cauda equina is approximately the same length as the entire CNS of a rat, which includes its brain. (B) The diameter of the human spinal cord is also much larger than that of the rat spinal cord. Twenty slices of a rat spinal cord can fit inside one slice of a human cord.

Consequently, regeneration of nerve fibers over a few vertebral segments in a rat—which can result in the restoration of function—is equivalent to only a fraction of the distance that is needed to restore function in humans (Dobkin and Havton, 2004).

Furthermore, because neurons from both species demonstrate the same degree of spontaneous sprouting of their axons, approximately 2 millimeters (von Meyenburg et al., 1998), there are added complexities in promoting sufficient axon growth in humans (Dobkin and Havton, 2004). Although parts of the white matter of the human spinal cord are almost as large as the entire diameter of the rat spinal cord (Figure 3-1), there is no significant difference in the capacity for oligodendrocyte precursor cells to migrate to remyelinate axons in rats and humans.

One of the issues regarding the differences in scale between smaller laboratory animals and humans that has been discussed is the extent to which testing is needed in primate models. Depending on the treatment, it may be advisable to examine the efficacies of some cell therapies in primates. However, there are also limitations in the use of non-human primates for mimicking human responses. For example, some types of monkeys have specific antibodies that can attack and inhibit the survival of human cells. Additionally, the bioavailability and metabolism of anti-rejection drugs in non-human

primates and humans differ significantly. Therefore, rodents have frequently been used as the preferred model to study the efficacies of new immunosuppressive agents because of similarities in metabolism between rodents and humans. In addition, experiments are sometimes performed in rabbits and cats, which have larger spinal cords and are also less expensive and easier to maintain than primates. Furthermore, few tests have been developed to assess changes in spinal cord recovery in nonhuman primates. The committee believes that every therapy need not necessarily be tested in primates before clinical trials are performed with humans and that tests with primates be limited to those that will answer questions that are best explored only with non-human primate models.

Next Steps

The promise accorded by the methodical testing of therapies with animal models is beginning to pay off. Scientists have identified numerous inhibitory molecules and receptors that prevent the regeneration of neurons in the spinal cord and have clarified the pathways by which the inhibitory response can be modulated.

Additional resources and tools are still needed in some areas, however. Animal models need to be developed for solid spinal cord injuries, as they account for a significant portion of human spinal cord injuries (Hulsebosch, 2002). Primate models of contusion injury are particularly needed, as well as standard animal models for cervical spinal cord injuries. Furthermore, there is no standard laboratory animal model that spinal cord injury researchers can use to examine fine motor control of the upper extremities or the loss of the sensory modality proprioception, which is responsible for limb position and immediately varying the degree of muscle contraction in response to external stimuli. When individuals with spinal cord injuries lose their proprioception, they are unable to move freely and interact comfort-ably with the external environment (see Box 5-1). Therefore, the development of a standard animal model that mimics the loss of proprioception will facilitate the development of therapies in a timely fashion.

It is important that researchers use standardized animal models and that they use them consistently. The National Institute of Neurological Disorders and Stroke (NINDS), in recognition of the need to train researchers who work on spinal cord injuries, collaborated with Ohio State University to design a course that emphasizes competency in the technical approaches required for standard animal care and treatment and experimental design (Ohio State University, 2004). In addition, the University of California at Irvine has developed a similar course. These courses provide researchers with the opportunity to be trained to use the same standards for animal research.

By training multiple researchers to use standard techniques, consistent animal injury models can be implemented. These models will increase the extent to which research results can be compared and improve the extent to which animal models can be used to predict clinical outcomes in humans.

OUTCOME MEASURES USED TO ASSESS INJURY AND RECOVERY

Because of the variations in the severity and the nature of the outcomes that individuals with spinal cord injuries experience, it is often difficult for health care professionals and researchers to assess the success of a particular intervention. Similarly, it is difficult for preclinical researchers to consistently assess progress in laboratory animal experiments and to determine the amount of progress, if any, that results from natural recovery, drug therapy, surgical intervention, or rehabilitation.

Outcome Measures Used to Assess Spinal Cord Injury in Animal Models

Tests developed to examine the recovery of function in laboratory animals have been designed primarily to examine motor function (Table 3-5; Appendix D). However, to accelerate the translation of research in other areas, including sexual function, bladder and bowel control, and chronic pain relief, standard tests need to be developed to assess experimental therapies for each of these major complications (Widerstrom-Noga and Turk, 2003).

TABLE 3-5 Tools Used to Assess Spinal Cord Injuries in Laboratory Animals

Functional recovery

Basso, Beattie, and Bresnahan (BBB) scale, an open-field locomotor test for rats

- Is based on 5-point Tarlov scale
- Analyzes hind-limb movements of a rat in an open field
- Is a 21-point scale used to assess locomotor coordination
- Rates parameters such as joint movements, the ability for weight support, limb coordination, foot placement, and gait stability
- Small changes in tissue correlate to large changes on the scale
- Assesses walking, not other movements requiring coordinated spinal cord activity
- Does not assess pain, bowel, bladder, or sexual function

Basso Mouse Scale (BMS), an open-field locomotor test for mice

- Is an adaptation of rat BBB scale to examine the recovery of hind-limb locomotor function
- Assesses walking, not other movements requiring coordinated spinal cord activity
- Does not assess pain, bowel, bladder, or sexual function

Neuronal activity assessment by electrophysiology

- Assesses MEPs or SSEP
- Stimulates corresponding cortical areas of the brain and records response in target nerves to see if connections are still functional
- Correlates to impairment of locomotor activity
- Is noninvasive
- Neuronal activity may not correlate with functional changes
- Hard to assess subtle but critical improvements to circuitry

- Does not directly assess pain, bowel, bladder, or sexual function

Forepaw withdrawal

- Investigates recovery of heat perception
- The forepaw is placed on a heat block and the time that it takes for the animal to withdraw it is measured
- Forepaw withdrawal requires motor function
- Does not assess pain, bowel, bladder, or sexual function

Directed forepaw reaching

- Looks at coordinated limb and muscle movement
- Requires rats to reach under a barrier and pick up food with forepaws
- Limited scale for assessment
- Does not assess pain, bowel, bladder, or sexual function

Morphological assessment of recovery

Histology

- Is used to look at the morphology of axons and assess the degree of tissue sparing, injury, and recovery
  - Is used for anterograde and retrograde tracing of axons: a substance is injected above or below the location of the injury to determine if the neuron transports it up past the injury location
  - Uses electron microscopy to look at the morphology of the spinal cord at very high resolution
  - Uses antibody staining to determine the protein distribution in cells
  - Assessments cannot be made in real time
  - Cannot be performed with living animals

Real-time imaging of the spinal cord

- Uses MRI, CT, and PET, which are safe, noninvasive methods that provide detailed images of hard-to-view areas of the spine
- Resolution is not high enough to detect changes to individual cells

Genetically encoded reporter molecules

- Axon regrowth and formation of functional connections are visualized by use of genetically encoded reporter molecules in intact animal models or in isolated spinal cord preparations
- Requires a correlation to improvements in physiological function

NOTE: Abbreviations: BBB = Basso, Beattie, and Bresnahan; BMS = Basso Mouse Scale; CT = computed tomography; MEPs = motor evoked potential; MRI = magnetic resonance imaging; PET = positron emission tomography; SSEP = somatosensory evoked potential.

Researchers use a standard scale, the Basso, Beattie, and Bresnahan (BBB) scale, to assess the recovery of motor function in rats (Basso et al., 1995). The foundation of the BBB scale is the assessment of hind-limb movements in rats with spinal cord injuries. The 21-point BBB scale is sensitive enough that small gains in motor function are reflected in changes in the outcome score. However, the scale has several limitations as it assesses only the functional recovery of the hind limbs and not other elements of fine motor control that are required for coordinated activity regulated by the spinal cord; does not examine the recovery of sensory modalities, including pain and temperature sensations; does not assess other complications that arise as a result of spinal cord injuries, including bowel and bladder function, pain, or sexual capacity; and is not linear.

Outcome Measures Used to Assess Spinal Cord Injury in Humans

Clinicians have available more than 30 assessment tests and surveys that they can use to examine individuals with spinal cord injuries, including the American Spinal Injury Association (ASIA) scale and measures that assess all the major complications associated with spinal cord injuries. Each of these measures assesses a specific aspect of recovery from spinal cord injury or evaluates the individual's quality of life and is not designed to examine all the major complications that arise because of a spinal cord injury.

MONITORING REAL-TIME PROGRESSION OF SPINAL CORD INJURIES

Biomarkers

It is hoped that in the near future biomarkers will be available for diagnosis or prediction of the clinical course of an individual after a spinal cord injury; however, no biomarkers are currently available to identify the changes occurring in the cells in the living spinal cord, such as neurite outgrowth, cell death, or changes in gene expression. Researchers have identified a large number of potential biomarkers (Table 3-6) and are developing practical methods to assess changes to those markers that could be used in the clinical setting. Once biomarkers are available and validated, they could be used to aid researchers and clinicians with making a diagnosis and establishing a prognosis, monitoring changes over time, and evaluating therapeutic interventions.

Trauma to the spinal cord affects a large number of biochemical cascades and reactions, but specific details about the genes involved in these processes are not well understood. Most of these changes are reflected by changes in mRNA and protein levels (Table 3-7). Since mRNA is copied, or transcribed, from DNA and provides the transcript that the cell uses to synthesize new proteins, analysis of mRNA or protein levels could reveal information about changes in cellular events. Advances in microarray technologies over the last decade have made it possible for researchers to examine the expression patterns of hundreds, if not thousands, of genes at the same time by comparing changes in gene activity in spinal cord samples from healthy and injured individuals. Using biomarkers, microarrays, and other tools, investigators have started to assess the complexity of the biological response to spinal cord injury. The full potential uses of biomarkers for spinal cord injury research include the following:

Diagnosis and prognosis. The expression profile of a biomarker, especially proteins, could provide clinicians with information that aids in establishment of a diagnosis and a prognosis of a patient's injury. For instance, the progression of multiple sclerosis (MS) can be determined by examining the levels of a major myelin component, myelin basic protein, whose concentration increases in the cerebrospinal fluid in response to a demyelinating episode. Experiments with laboratory animals have identified similar gene expression fluctuations in response to spinal cord injuries. For example, the onset of the acute immune response is characterized by increases in the levels of the interleukin-6 protein (Segal et al., 1997; Carmel et al., 2001; Song et al., 2001; Nesic et al., 2002), whereas apoptosis, or the controlled death of cells that begins in the secondary stage of the injury, is regulated, in part, by changes in the levels of the Fas protein (Li et al., 2000; Casha et al., 2001). Thus, identification of specific fluctuations in the levels of proteins like interleukin-6 and Fas could inform clinicians about changes in an individual's level of injury.

TABLE 3-6 Criteria for Determining and Validating a Biomarker Used to Monitor Spinal Cord Injury Progression and Recovery of Function

Necessary properties of a progression marker	Describe a biological process that changes with the progression of the disease or recovery
	Correlate with clinical deterioration
Necessary properties of a progression indicator biomarker measure used as a	Objective (i.e., it should be amenable to a blinded or a centralized assessment)
	Reproducible (i.e., repeat measurements of the progression indicator for the same patient should be highly correlated)
	Specific to changes in progression indicator; otherwise, the effects of other changes in the biomarker (e.g., compensatory changes related to drugs used to treat the injury or to agent under study in a clinical trial) should be known so that suitable adjustments in the analysis of clinical trial data can be made
	Low signal-to-noise ratio for the biomarker measure
	Safe and tolerable and should not require maneuvers that could unblind the study

Other desirable properties of a biomarker measure used as a progression indicator	Relatively inexpensive and easy to use Capable of being used in repeated studies with a particular individual with a spinal cord injury
Data needed to support the use of progression indicator or biomarker measurement for application to a clinical trial for study of spinal cord injury	Data from longitudinal studies should be available for a sufficient number of individuals with spinal cord injuries to allow an informative assessment of the distributional properties (e.g., mean and variance) of the progression measure progression over periods of time pertinent to future clinical trials; such data are needed to allow calculation of the sample size and power for trials to evaluate the effects of specific treatments on spinal cord injury progression

NOTE: This table is based on recommendations for the development of biomarkers for use in monitoring the progression of Parkinson's disease.

SOURCE: Adapted from Brooks et al., 2003.

Treatment guidance. Analysis of gene expression during the course of the injury and recovery could provide clinicians with detailed informa-tion about the molecular events that are responsible for changes in spinal cord reorganization that occur over time. With this knowledge, physicians might be able to avoid preventable complications and specifically target ongoing events when they treat spinal cord injuries.

Outcomes assessment. Biological expression data that are correlated to functional improvement, such as increased locomotion, improved bowel function, or reduced spasticity, may provide helpful means of assessing beneficial or harmful changes to the spinal cord that may be missed when the primary clinical end points are behavioral.

The development of biomarkers that are specific for neuronal cell death, myelination, or nerve regeneration would be beneficial to both basic researchers and clinicians.

Potential therapeutic targets. The analysis of changes in specific gene products that are up- and down-regulated in response to a spinal cord injury could also provide researchers with a tool to identify specific targets that could be used for future drug development. Understanding of the molecular and cellular mechanisms involved in spinal cord injuries may permit identification of specific targets for therapeutic benefit.

Traditionally, biomarkers were identified by examining candidate genes involved in cellular events that occur as a result of a spinal cord injury and looking for other genes that were associated with the function of the candidate gene. This strategy led to the identification of many candidate genes, such as the Nogo gene and several of the interleukin genes, which have helped define the biological processes affected by a spinal cord injury. Although the individual process of identifying genes involved in a spinal cord injury has been critical for advancing the research, the process is also intrinsically biased and limited in its scope because of its dependence on previous detailed knowledge about the biological system under study. Another limitation is that changes in individual biomarkers may be induced by events other than spinal cord injuries. For example, the activities of the immediate-early genes c-fos and c-jun have been correlated to neurite outgrowth, but they are also involved in many other

processes, including cancer metastasis. Therefore, for a single biomarker to provide sufficient predictive value, it must be specific to spinal cord injuries and provide a sensitive measure for the assessment of the process being examined. Consequently, changes in multiple genes will need to be assessed to understand gene responses specifically related to spinal cord injuries as is true in assessing breast cancer (Hollon, 2002).

Protein Expression Profiles of Spinal Cord Injury

Because the body contains more than 1 million proteins that regulate metabolism and disease (Watkins, 2001), proteomic techniques that ana-**TABLE 3-7** Changes in Gene Expression After Spinal Cord Injury, by Stage of Injury

Gene Function	Primary Stage	Secondary Stage	Chronic Stage
Apoptosis	Caspases, c-jun, p53, Fas, FasL, CD95, rho	Caspases, c-jun, NF-κB, HSP70	None
Growth and differentiation	Vimentin, TGFβ, ANIA-6	Vimentin, TGF, VGF, BDNF, TrkB (–)	Vimentin, TrkB, BMPs
Inflammation	IL-6, IL-1β, IGFs, SOCS, MCP-1 (IESR-JE), ICAM-1, iNOS, GFAP, IL-4r, COX-2, IL-2Rα, HSP27	IL-6, IL-1, IGFs, SOCS, MCP-1 (IESR-JE), ICAM-1, iNOS, GFAP, TNF receptor, COX-3 (–), HSP27	IL-6, IL-1β, IGFs, HSP27
Regulation of ion transport	Ca^{2+} ATPase (–)	Ca^{2+} ATPase (–), K^+ channels, Na^+ channels (–), Na^+/K^+ ATPase (–)	Ca^{2+} ATPase (–)
Protection of neurons	None	Metallothionein I and II, survival motoneuron	Metallothionein I and II
Communication between neurons	SNAP-25 (–), syntaxins (–), glutamate receptors	SNAP-25 (–), syntaxins (–), synapsins (–), somatostatin (–), GABA transporters (–), glutamate receptors, GABA receptors (–), glutamate transporter	GABA receptors

lyze changes to individual or multiple proteins have the potential to provide investigators with information about cellular responses to spinal cord injuries. For example, Western blotting and immunohistochemistry allow investigators to examine modifications to a protein's structure that may change its activity and cellular distribution.

Protein arrays, like DNA arrays, allow researchers to screen simultaneously many proteins for changes in expression levels that result from the onset of a disease or a therapeutic approach. However, protein arrays are not as encompassing as DNA arrays. Current protein array technology only allows about 10 percent of a cell's total proteome to be represented on an array (2,000 to 3,000 proteins can be represented on a protein array, whereas 47,000 genes can be represented on a DNA array). Such arrays could be tailored to the specific aspect of spinal cord injury being studied. In addition, advances in mass spectrometry now make it possible to characterize the levels and even the phosphorylation state of many hundreds of proteins, allowing greater insights into the specific activities of proteins.

Gene Function	Primary Stage	Secondary Stage	Chronic Stage
Repair and regeneration of neurons and glia	Nestin, JAK, STAT, c-fos	Nestin, vimentin, dynamin (–), c-fos	Semaphorin, GAS-7, epithelins 1 and 2, platelet factor 4
Proteins that relay exterior information to the nucleus	PDE, CaM kinases (–)	PDE, MAP kinases, CaM kinases (–)	None
Proteins that generate and maintain cellular structure	None	MOG (–), neurofilaments, LAMP (–), MAP-2, tau (–)	None
Regulation of DNA synthesis	Fra-1, NGFI-A	Fra-1, NGFI-A	None

NOTE: Analysis of proteomic and DNA gene array studies identified significant changes in gene expression in response to a spinal cord injury. Classification of these genes into specific functions provides further insight into the processes that are changing. All genes are up-regulated unless a "(–)" notation is presented, in which case the gene is down-regulated.

SOURCES: Bregman et al., 1997; Segal et al., 1997; Li et al., 2000; Saito et al., 2000; Carmel et al., 2001; Casha et al., 2001; Fan et al., 2001; Song et al., 2001; Zurita et al., 2001; Bareyre et al., 2002; Nesic et al., 2002; Shibuya et al., 2002; Tachibana et al., 2002; Bareyre and Schwab, 2003; Di Giovanni et al., 2003; Dubreuil et al., 2003; Liu et al., 2003; Haberkorn et al., 2004.

Issues in Developing Biomarkers for Spinal Cord Injury

It is extremely difficult to obtain samples of mRNA or protein directly from spinal cord tissue without inducing further complications. The most practical sources of mRNA and protein are serum and cerebrospinal fluid.

However, a spinal tap—an invasive procedure, which requires the insertion of a special needle through the lumbar vertebral spine into the fluid space that surrounds the spinal cord—must be performed to obtain cerebrospinal fluid. Although serum is easier to collect by drawing blood samples, its analysis is complicated by the high concentration of several proteins (e.g., albumin, immunoglobulin G, and transferrin) that constitute approximately 80 percent of total serum proteins. These high background levels make it difficult to sieve through and detect changes in the levels of proteins that are present at low concentrations. Once a sample is obtained, issues about the usefulness of the contents remain. The mRNA derived from neurons and glia is not very abundant and degrades rapidly. Also, because serum and cerebrospinal fluid are indirect sources of spinal cord mRNA and proteins, the overall numbers of genes that are associated with spinal cord injuries are not well represented. Furthermore, the proteins that are present are typically restricted to those found on the exteriors of cells and the small intracellular concentrations of mRNA and proteins that are released when a cell dies, which further limits the pool of biomarkers that can be analyzed. Efforts are thus needed to improve the processes for detecting potential biomarkers.

Next Steps in Biomarker Development

Experimental therapies developed in the laboratory take as long as 7 to 15 years to enter into the clinic (Lakhani and Ashworth, 2001). To expedite this transition, spinal cord injury researchers should use strategies developed in other fields, including MS, Alzheimer's disease, and cancer biology. For example, clinical studies for MS and brain metastasis have been established to analyze changes in protein levels in the serum and cerebrospinal fluid. These trials could provide the framework for biomarker studies involving individuals with spinal cord injuries.

In 2000, the National Cancer Institute established the Early Detection Research Network (EDRN) to guide the process of biomarker discovery in an effort to produce a useful population-screening tool (Kutkat and Srivastava, 2001). This network consists of three laboratory components: biomarker discovery laboratories, biomarker validation laboratories, and clinical epidemiological centers. EDRN also helped to establish standards for the development and evaluation of biomarkers and guide the process of biomarker discovery related to cancer biology. Using EDRN as a model, the spinal cord injury community can transfer many of the recommendations and strategies developed to facilitate progress on cancer research for spinal cord injury research. In 2001 and 2004 NINDS issued two program announcements that focused on advancing proteome arrays and identifying clinical biomarkers (NINDS, 2001a, 2004); these are not specifically fo-cused on spinal cord injuries but do offer potential for advances in this area. Additionally, NINDS put out a request for proposals (NINDS, 2001b) for studies designed to define gene expression profiles following traumatic spinal cord injuries.

Because the technologies used to identify biological markers can detect small but significant changes in gene expression, they are sensitive to slight variations in protocol.

In fact, the gene profiles obtained from experimental studies are affected by differences in the instruments used to analyze the samples and by small changes in the ways in which samples are collected (e.g., the relative time after injury that tissue is collected, the location of the injury, and the quantity of the specimen) (Bareyre and Schwab, 2003). A standard set of methods is needed to minimize variability and maximize reproducibility (Bareyre and Schwab, 2003).

Visualizing the Living Spinal Cord

The spinal cord is embedded in bone and is surrounded by cerebrospinal fluid, which precludes direct visualization. The advent of neuroimaging techniques has allowed investigators to visualize the spinal cord so that they can begin to study the progression of spinal cord injuries. Magnetic resonance imaging (MRI) and computed tomography (CT) provide real-time information about the state of the injury and recovery. Moreover, imaging is noninvasive and the same region of the spinal cord can be repeatedly visualized to identify changes occurring over time. Imaging technologies, biomarkers, and molecular genetic technologies are being combined to provide researchers with powerful tools to monitor the progression of the injury and recovery through the visualization of specific molecular markers that define cellular events and functional changes.

MRI is a safe and noninvasive method of evaluating the spinal cord that provides detailed pictures of hard-to-view areas of the spine, including the spinal canal, vertebra, and soft tissue (Levitski et al., 1999). Clinicians use MRI after an individual has an acute spinal cord trauma to visualize the location and the extent of the spinal cord trauma and compressive lesions (e.g., blood clots) (AANS/CNS,

2002). It is superior to positron emission tomography (PET), CT, and other imaging technologies for the detection of abscesses or other masses near the spinal cord and is used to monitor patients with chronic compression injuries. However, imaging technologies have practical limits in the setting of acute spinal cord traumas, as a patient may not be stable enough to enter an MRI machine or may have other medical priorities that take precedence over receiving a detailed image of the spinal cord.

Functional MRI (fMRI) can provide second-by-second images of the brain to reveal changes in neuronal activity in response to different sensory

stimuli and mental tasks. It allows researchers and clinicians to study the changes in injured neuronal circuits. However, fMRI relies on the metabolic changes that occur in response to neural activity and the images obtained by fMRI are not a direct measure of neural activity. Therefore, caution should be placed on interpretation of the accuracies of the spatial maps generated by fMRI (Ugurbil et al., 2003). The National Institutes of Health has recommended that fMRI techniques be developed to assess the degree of loss and recovery of sensation in rodents with contusion injuries to their spinal cords (Hofstetter et al., 2003; NINDS, 2004).

Radiologists use CT scans as a standard procedure to clarify areas of clinical concern (Youmans, 1996; AANS/CNS, 2002). Although MRI is better suited for analyzing the soft tissue of the spinal cord, the strength of using CT scans is in investigating the bone structure and detecting fractures of the vertebrae (Figure 3-2). Helical CT scans offer advantages over traditional radiology X-rays due to their speed in accruing the images and increased accuracy (4.5 minutes and 98.5 percent, respectively, for helical CT compared with 25 minutes and 43 percent, respectively, for X-rays). Therefore, in conjunction with MRI, CT scans provide useful tools for emergency clinicians (Nunez et al., 1994).

FIGURE 3-2 MRI (A) and CT (B) of an injured spinal cord. Imaging of a spinal cord contusion injury by MRI and CT helps to reveal different aspects of the injury. The MRI image on the left reveals the soft spinal cord and bone, whereas the CT scan image on the right clearly delineates bone structures.

SOURCE: AANS, 1999.

Unlike MRI, fMRI, and CT scans, PET scans detect and localize specific naturally occurring proteins; molecules, such as sugars and water; and other substances, such as neurotransmitters, which have been modified to emit radioactive energy.

At present, PET scans are not commonly used in the clinic to assess spinal cord injuries. However, as discussed below, the technology has much potential to provide researchers and clinicians with a means by which to visualize changes in gene expression in the spinal cord.

Next Steps: Future Imaging Technologies

Imaging technologies provide clinicians with important tools to gauge the responses of patients to different therapies (Jacobs et al., 2003). The creation of sensitive assays that merge image-based technologies with biomarker research will allow investigators and clinicians to use specific tracers to localize molecular, genetic, and cellular processes in real time, thus providing further insight into the biological processes that affect the progression of the injury (Blasberg and Gelovani, 2002).

As of January 2005, no clinical studies in the United States were specifically examining the use of imaging marker technologies for the study of spinal cord injuries. In comparison, markers are used to assess the state of MS and Alzheimer's disease and imaging techniques are used to monitor the effects of different treatments for these conditions. For example, imaging assays are being developed to visualize specific neurotransmitter levels and to determine if they are involved in memory loss (Brown et al., 2003).

The Future of Magnetic Resonance Technology

In animals with syringomyelia, diffusion-weighted MRI, which is sensitive to the diffusion or random motion of water molecules in tissue, can detect cystic lesions in the gray matter of the spinal cord (Schwartz et al., 1999). The increased sensitivity offered by diffusion-weighted MRI will enable physicians to detect specific complications of spinal cord injuries sooner, thus increasing the potential for treatment.

Magnetic resonance technology can be adapted to provide more than diagnostic information about the structural changes occurring in response to a spinal cord injury. In 2001, Bulte and colleagues used magnetic resonance to track oligodendrocyte stem cells that were prelabeled with super paramagnetic iron oxide nanocomposites, which are small beads invisible to the naked eye that can be detected by MR technology (Bulte et al., 1999, 2001). Using this approach, the investigators were able to track the real-time migration and integration of these oligodendrocyte stem cells for up to 6 weeks in the same animal, which is important for distinguishing the efficacies of endogenous cells versus those of the exogenous transplanted stem cells.

The Future of PET Scans

PET scan technology is being developed to inform clinicians about whether drugs can bind to the appropriate targets. For example, clinicians are using PET scans to determine if treatments are effective by looking at the uptake of glucose, which tumors need to nourish their growth (Van den Abbeele and Badawi, 2002; Pollack, 2004). These effects can be observed before structural changes in the tumor can be detected.

Two caveats about the use of PET scans must be kept in mind. First, current technology does not have enough resolution to allow complete visualization through the entire diameter of the spinal cord. Furthermore, the current spatial resolution of commercial PET scanners is 4 mm but 2.5 mm resolution has been achieved in research instruments that use motion compensation. Second, information obtained from PET scans is based on metabolic events that correlate to neural activity and may not directly

correspond to the location where the changes in activity are occurring. Therefore, the images generated by PET scans could be misleading because they may not accurately represent the spatial specificities of the changes (Ugurbil et al., 2003). However, refinements to PET scans could provide important information about the cellular states of the injury, such as gene activation or suppression in response to the injury; this would provide physicians with the ability to quantify responses to different spinal cord injury treatments (Brooks et al., 2003) and to identify functional changes before the onset of structural changes identifiable by MRI (National PET Scan Management, LLC, 2004). PET ligands have been developed that can detect glucose metabolism, inflammation, and receptor abundance, including agents that track the *N*-methyl-D-aspartate (NMDA) receptor activity and proteases. PET measures very different process than does MRI whose spatial resolution is superior. However, PET contrast resolution for identification of proteins can be hundreds of times greater than MRI depending on the target. The potentials of PET for assessing the severity of injury and the responses to therapy await application of high resolution systems with recently developed radiopharmaceuticals.

Tracking Recovery with PET and Magnetic Resonance

Improvements to PET and MR technologies enable investigators to visualize the molecular signatures of damage and repair to the CNS. In an attempt to examine the activities of specific neuronal circuits, imaging markers that mimic neurotransmitters and receptors that are nonradioactive are being created, including the iron analog annexin V (Schellenberger et al., 2002), the fluorescent marker Cy5.5 (Petrovsky et al., 2003), and markers that do not become active until they reach their target. Future modification and adaptation of these technologies could be used to examine specific stages of regeneration, including those designed to detect neurite outgrowth, astrocyte scarring, oligodendrocyte myelination, and immunological response.

Transgenic Animals: Following the Labeled Cell

At present it is difficult to follow the path of cell transplants (such as stem cells, Schwann cells, and olfactory ensheathing cells) in the living spinal cord; therefore, it is difficult to draw conclusions about the efficacy of an experiment with such cells. Continued advancement of imaging techniques will provide a mechanism by which investigators and clinicians can assess the integration of grafted tissue or cells into the preexisting neuronal network or monitor the response to gene therapy by tracking the transgene location. Transgenic animal models have thus been developed. Specific populations of cells in these animals are genetically engineered to be fluorescent or to emit a fluorescent signal when they are functionally activated. Such approaches, which use two-photon confocal imaging to detect the signal, can be directly applied to spinal cord preparations in vitro and administered to intact mice and rats. With improvements in the current technology, the use and improvement of near-infrared markers might also provide researchers with a means to monitor the progression of a spinal cord injury and recovery in laboratory animals.

Multidisciplinary Research and Bringing Molecular Imaging to the Clinic

The promise of molecular imaging technologies can be realized only if the technologies can be successfully transferred to the clinical setting. The transfer of these technologies will require cross-

disciplinary collaborations and multidisciplinary research efforts among molecular and cellular biologists, imaging scientists, nanotechnologists, and clinicians. A review article by Massoud and Gambhir (2003) identified the following goals for the transfer of molecular imaging technologies from the research laboratory to the clinic:

> develop noninvasive in vivo imaging methods that detect specific cellular and molecular processes, such as gene expression and protein-protein interactions;
>
> monitor multiple molecular events in concert;
>
> monitor the trafficking and targeting of cells;
>
> optimize drug and gene therapies;
>
> image drug effects at the molecular and cellular levels; and
>
> assess the molecular pathology of disease progression.

Achieving these goals and translating those achievements into reliable clinical technologies will be critical steps toward the treatment and diagnosis of spinal cord injuries at the molecular level. To achieve these objectives, continued advances need to be made to overcome the challenges of biocompatibility, probe delivery, and high-resolution signal detection (Mahmood and Weissleder, 2002).

Cross-disciplinary collaboration and multidisciplinary research is needed to bring together molecular and cellular biologists, imaging scientists, nanotechnologists, and clinicians to reach these goals (Blasberg and Gelovani, 2002). Many of the imaging techniques used to examine the CNS were designed to visualize brain tumors or to assess Alzheimer's disease, Parkinson's disease, and MS. These resources and technologies can be applied or can provide models for spinal cord injury research. For instance, investigators are examining the utility of using multiphoton imaging techniques to monitor the progression of senile plaques in mice that model Alzheimer's disease (Christie et al., 2001). This technology could also be modified to assess and monitor the progression of the glial scar formation that results from spinal cord injuries.

The cancer research field not only has led the way in developing technologies but also has helped to establish research centers that have been critical in creating a means for translating imaging technologies into the clinic. In particular, the National Cancer Institute has developed two programs: the Small Animal Imaging Resources Program (SAIRP) and the In Vivo Cellular and Molecular Imaging Centers (ICMIC) Program. These programs, along with support mechanisms sponsored by the National Institute of Biomedical Imaging and Engineering, provide mechanisms and model systems that can be used to promote the cooperative development of new imaging systems for spinal cord injury research and treatment.

RECOMMENDATIONS

Recommendation 3.1: *Increase Training Efforts on Standardized Research Tools and Techniques*

Spinal cord injury researchers should receive training in the use of standardized animal models and evaluation techniques. Pre- and postdoctoral fellowship training programs focused on spinal cord injury research should require participation in courses designed to train investigators on the appropriate use of the available tools and techniques.

Recommendation 3.2: ***Improve and Standardize Research Tools and Assessment Techniques***

Preclinical research tools and animal models should be developed and refined to examine spinal cord injury progression and repair and assess the effectiveness of therapeutic interventions. These preclinical tools and assessment protocols should be standardized for each type and each stage of spinal cord injury. Particular emphasis should be placed on:

improving imaging technologies to allow real-time assessment of the current state and progression of the injury;

identifying biomarkers that can be used to monitor the progression of the injury and recovery;

developing additional animal models to explore the progression of spinal cord injury and repair;

establishing standardized sets of functional outcome measures for the evaluation of experimental therapies for each type and each stage of spinal cord injury in animal models; and

enhancing functional assessment techniques to examine motor function as well as secondary complications, including pain and depression of the immune system.

REFERENCES

AANS (American Association of Neurological Surgeons). 1999. *Spinal Cord*. [Online]. Available: http://www.neurosurgerytoday.org/what/patient_e/spinal.asp [accessed January 25, 2005].

AANS/CNS (American Association of Neurological Surgeons/Congress of Neurological Surgeons). 2002. Radiographic assessment of the cervical spine in symptomatic trauma patients. *Neurosurgery* 50(3 Suppl): S36-43.

Bareyre FM, Schwab ME. 2003. Inflammation, degeneration and regeneration in the injured spinal cord: Insights from DNA microarrays. *Trends in Neurosciences* 26(10): 555-563.

Bareyre FM, Haudenschild B, Schwab ME. 2002. Long-lasting sprouting and gene expression changes induced by the monoclonal antibody IN-1 in the adult spinal cord. *Journal of Neuroscience* 22(16): 7097-7110.

Basso DM, Beattie MS, Bresnahan JC. 1995. A sensitive and reliable locomotor rating scale for open field testing in rats. *Journal of Neurotrauma* 12(1): 1-21.

Blasberg RG, Gelovani J. 2002. Molecular-genetic imaging: A nuclear medicine-based perspective. *Molecular Imaging: Official Journal of the Society for Molecular Imaging* 1(3): 280-300.

Bradbury EJ, Moon LD, Popat RJ, King VR, Bennett GS, Patel PN, Fawcett JW, McMahon SB. 2002. Chondroitinase ABC promotes functional recovery after spinal cord injury. *Nature* 416(6881): 636-640.

Bregman BS, McAtee M, Dai HN, Kuhn PL. 1997. Neurotrophic factors increase axonal growth after spinal cord injury and transplantation in the adult rat. *Experimental Neurology* 148(2): 475-494.

Bresnahan JC, Beattie MS, Todd FD III, Noyes DH. 1987. A behavioral and anatomical analysis of spinal cord injury produced by a feedback-controlled impaction device. *Experimental Neurology* 95(3): 548-570.

Brooks DJ, Frey KA, Marek KL, Oakes D, Paty D, Prentice R, Shults CW, Stoessl AJ. 2003. Assessment of neuroimaging techniques as biomarkers of the progression of Parkinson's disease. *Experimental Neurology* 184(Suppl 1): S68-79.

Brown D, Chisholm JA, Owens J, Pimlott S, Patterson J, Wyper D. 2003. Acetylcholine muscarinic receptors and response to anti-cholinesterase therapy in patients with Alzheimer's disease. *European Journal of Nuclear Medicine & Molecular Imaging* 30(2): 296-300.

Bulte JW, Zhang S, van Gelderen P, Herynek V, Jordan EK, Duncan ID, Frank JA. 1999. Neurotransplantation of magnetically labeled oligodendrocyte progenitors: Magnetic resonance tracking of cell migration and myelination. *Proceedings of the National Academy of Sciences (U.S.A.)* 96(26): 15256-15261.

Bulte JW, Douglas T, Witwer B, Zhang SC, Strable E, Lewis BK, Zywicke H, Miller B, van Gelderen P, Moskowitz BM, Duncan ID, Frank JA. 2001. Magnetodendrimers allow endosomal magnetic labeling and in vivo tracking of stem cells. *Nature Biotechnology* 19(12): 1141-1147.

Carmel JB, Galante A, Soteropoulos P, Tolias P, Recce M, Young W, Hart RP. 2001. Gene expression profiling of acute spinal cord injury reveals spreading inflammatory signals and neuron loss. *Physiological Genomics* 7(2): 201-213.

Casha S, Yu WR, Fehlings MG. 2001. Oligodendroglial apoptosis occurs along degenerating axons and is associated with FAS and p75 expression following spinal cord injury in the rat. *Neuroscience* 103(1): 203-218.

Christie RH, Bacskai BJ, Zipfel WR, Williams RM, Kajdasz ST, Webb WW, Hyman BT. 2001. Growth arrest of individual senile plaques in a model of Alzheimer's disease observed by in vivo multiphoton microscopy. *Journal of Neuroscience* 21(3): 858-864.

Croft BY. 2002. Animal models for imaging. *Disease Markers* 18(5-6): 365-374.

Di Giovanni S, Knoblach SM, Brandoli C, Aden SA, Hoffman EP, Faden AI. 2003. Gene profiling in spinal cord injury shows role of cell cycle in neuronal death. *Annals of Neurology* 53(4): 454-468.

Dobkin BH, Havton LA. 2004. Basic advances and new avenues in therapy of spinal cord injury. *Annual Review of Medicine* 55: 255-282.

Dubreuil CI, Winton MJ, McKerracher L. 2003. Rho activation patterns after spinal cord injury and the role of activated Rho in apoptosis in the central nervous system. *Journal of Cell Biology* 162(2): 233-243.

Fan M, Mi R, Yew DT, Chan WY. 2001. Analysis of gene expression following sciatic nerve crush and spinal cord hemisection in the mouse by microarray expression profiling. *Cellular and Molecular Neurobiology* 21(5): 497-508.

Gorman AL, Yu CG, Ruenes GR, Daniels L, Yezierski RP. 2001. Conditions affecting the onset, severity, and progression of a spontaneous pain-like behavior after excitotoxic spinal cord injury. *Journal of Pain* 2(4): 229-240.

Gruner JA. 1992. A monitored contusion model of spinal cord injury in the rat. *Journal of Neurotrauma* 9(2): 123-126.

Haberkorn U, Altmann A, Mier W, Eisenhut M. 2004. Impact of functional genomics and proteomics on radionuclide imaging. *Seminars in Nuclear Medicine* 34(1): 4-22.

Hofstetter CP, Schweinhardt P, Klason T, Olson L, Spenger C. 2003. Numb rats walk—A behavioural and fMRI comparison of mild and moderate spinal cord injury. *European Journal of Neuroscience* 18(11): 3061-3068.

Hollon T. 2002. Classifying breast cancer models. *The Scientist* 16(17): 20-24.

Houle JD, Tessler A. 2003. Repair of chronic spinal cord injury. *Experimental Neurology* 182(2): 247-260.

Hulsebosch CE. 2002. Recent advances in pathophysiology and treatment of spinal cord injury. *Advances in Physiology Education* 26(1-4): 238-255.

Inman D, Guth L, Steward O. 2002. Genetic influences on secondary degeneration and wound healing following spinal cord injury in various strains of mice. *Journal of Comparative Neurology* 451(3): 225-235.

Jacobs AH, Li H, Winkeler A, Hilker R, Knoess C, Ruger A, Galldiks N, Schaller B, Sobesky J, Kracht L, Monfared P, Klein M, Vollmar S, Bauer B, Wagner R, Graf R, Wienhard K, Herholz K, Heiss WD. 2003. PET-based molecular imaging in neuroscience. *European Journal of Nuclear Medicine & Molecular Imaging* 30(7): 1051-1065.

Jin Y. 2002. Synaptogenesis: Insights from worm and fly. *Current Opinion in Neurobiology* 12(1): 71-79.

Kidd T, Brose K, Mitchell KJ, Fetter RD, Tessier-Lavigne M, Goodman CS, Tear G. 1998. Roundabout controls axon crossing of the CNS midline and defines a novel subfamily of evolutionarily conserved guidance receptors. *Cell* 92(2): 205-215.

Kim JE, Li S, GrandPre T, Qiu D, Strittmatter SM. 2003. Axon regeneration in young adult mice lacking Nogo-a/B. *Neuron* 38(2): 187-199.

Kleitman N. 2004. Keeping promises: Translating basic research into new spinal cord injury therapies. *Journal of Spinal Cord Medicine* 27(4): 311-318.

Kraut R, Menon K, Zinn K. 2001. A gain-of-function screen for genes controlling motor axon guidance and synaptogenesis in *Drosophila*. *Current Biology* 11(6): 417-430.

Kutkat L, Srivastava S. 2001. The early detection research network: A platform for communication and collaboration. *Disease Markers* 17(1): 3-4.

Kwo S, Young W, Decrescito V. 1989. Spinal cord sodium, potassium, calcium, and water concentration changes in rats after graded contusion injury. *Journal of Neurotrauma* 6(1): 13-24.

Kwon BK, Liu J, Messerer C, Kobayashi NR, McGraw J, Oschipok L, Tetzlaff W. 2002a. Survival and regeneration of rubrospinal neurons 1 year after spinal cord injury. *Proceedings of the National Academy of Sciences (U.S.A.)* 99(5): 3246-3251.

Kwon BK, Oxland TR, Tetzlaff W. 2002b. Animal models used in spinal cord regeneration research. *Spine* 27(14): 1504-1510.

Lakhani SR, Ashworth A. 2001. Microarray and histopathological analysis of tumours: The future and the past?. *Nature Reviews—Cancer* 1(2): 151-157.

Lanuza GM, Gosgnach S, Pierani A, Jessell TM, Goulding M. 2004. Genetic identification of spinal interneurons that coordinate left-right locomotor activity necessary for walking movements. *Neuron* 42(3): 375-386.

Levitski RE, Lipsitz D, Chauvet AE. 1999. Magnetic resonance imaging of the cervical spine in 27 dogs. *Veterinary Radiology & Ultrasound* 40(4): 332-341.

Li GL, Farooque M, Olsson Y. 2000. Changes of Fas and Fas ligand immunoreactivity after compression trauma to rat spinal cord. *Acta Neuropathologica* 100(1): 75-81.

Liu CL, Jin AM, Tong BH. 2003. Detection of gene expression pattern in the early stage after spinal cord injury by gene chip. *Chinese Journal of Traumatology* 6(1): 18-22.

Magavi SS, Leavitt BR, Macklis JD. 2000. Induction of neurogenesis in the neocortex of adult mice. *Nature* 405(6789): 951-955.

Mahmood U, Weissleder R. 2002. Some tools for molecular imaging. *Academic Radiology* 9(6): 629-631.

Massoud TF, Gambhir SS. 2003. Molecular imaging in living subjects: Seeing fundamental biological processes in a new light. *Genes & Development* 17(5): 545-580.

Metz GA, Curt A, van de Meent H, Klusman I, Schwab ME, Dietz V. 2000. Validation of the weight-drop contusion model in rats: A comparative study of human spinal cord injury. *Journal of Neurotrauma* 17(1): 1-17.

National PET Scan Management, LLC. 2004. *How Does PET Compare with Other Imaging Modalities?* [Online]. Available: http://www.nationalpetscan.com/petovew.htm [accessed November 11, 2004].

Nesic O, Svrakic NM, Xu GY, McAdoo D, Westlund KN, Hulsebosch CE, Ye Z, Galante A, Soteropoulos P, Tolias P, Young W, Hart RP, Perez-Polo JR. 2002. DNA microarray analysis of the contused spinal cord: Effect of NMDA receptor inhibition. *Journal of Neuroscience Research* 68(4): 406-423.

Neumann S, Bradke F, Tessier-Lavigne M, Basbaum AI. 2002. Regeneration of sensory axons within the injured spinal cord induced by intraganglionic cAMP elevation. *Neuron* 34(6): 885-893.

NINDS (National Institute of Neurological Disorders and Stroke). 2001a. *Biomarkers and Clinical Endpoints in Pediatric Clinical Trials*. [Online]. Available: http://grants.nih.gov/grants/guide/pa-files/PA-01-043.html [accessed November 11, 2004].

NINDS. 2001b. *Gene Expression Profiling in the Nervous System Following Traumatic Spinal Cord Injury*. [Online]. Available: http://www.ninds.nih.gov/funding/2rfp_01_03.pdf [accessed October 4, 2004].

NINDS. 2004. *Functional and Dysfunctional Spinal Circuitry: Role for Rehabilitation and Neural Prostheses*. [Online]. Available: http://www.ninds.nih.gov/news_and_events/proceedings/spinalcircuitrywkshp_pr.htm [accessed November 11, 2004].

Noyes DH. 1987. Correlation between parameters of spinal cord impact and resultant injury. *Experimental Neurology* 95(3): 535-557.

Nunez DB, Ahmed AA, Coin C, et al. 1994. Clearing the cervical spine in multiple trauma victims: A time-effective protocol using helical computed tomography. *Emergency Radiology* 1(6): 273-278.

Ohio State University. 2004. *Spinal Cord Injury: A Comprehensive Course*. [Online]. Available: http://medicine.osu.edu/sci/Main.htm [accessed November 11, 2004].

Petrovsky A, Schellenberger E, Josephson L, Weissleder R, Bogdanov A Jr. 2003. Near-infrared fluorescent imaging of tumor apoptosis. *Cancer Research* 63(8): 1936-1942.

Pollack A. 2004, August 4. In drug research, some guinea pigs are now human. *The New York Times*. p. A2.

Qiu J, Cai D, Filbin MT. 2002. A role for cAMP in regeneration during development and after injury. *Progress in Brain Research* 137: 381-387.

Ramer MS, Harper GP, Bradbury EJ. 2000. Progress in spinal cord research: A refined strategy for the International Spinal Research Trust. *Spinal Cord* 38(8): 449-472.

Richardson PM, McGuinness UM, Aguayo AJ. 1980. Axons from CNS neurons regenerate into PNS grafts. *Nature* 284(5753): 264-265.

Rivlin AS, Tator CH. 1978. Effect of duration of acute spinal cord compression in a new acute cord injury model in the rat. *Surgical Neurology* 10(1): 38-43.

Saito N, Yamamoto T, Watanabe T, Abe Y, Kumagai T. 2000. Implications of p53 protein expression in experimental spinal cord injury. *Journal of Neurotrauma* 17(2): 173-182.

Schellenberger EA, Hogemann D, Josephson L, Weissleder R. 2002. Annexin V-Clio: A nanoparticle for detecting apoptosis by MRI. *Academic Radiology* 9(Suppl 2): S310-311.

Schwartz ED, Yezierski RP, Pattany PM, Quencer RM, Weaver RG. 1999. Diffusion-weighted MR imaging in a rat model of syringomyelia after excitotoxic spinal cord injury. *American Journal of Neuroradiology* 20(8): 1422-1428.

Segal JL, Gonzales E, Yousefi S, Jamshidipour L, Brunnemann SR. 1997. Circulating levels of IL-2R, ICAM-1, and IL-6 in spinal cord injuries. *Archives of Physical Medicine and Rehabilitation* 78(1): 44-47.

Shibuya S, Miyamoto O, Auer RN, Itano T, Mori S, Norimatsu H. 2002. Embryonic intermediate filament, nestin, expression following traumatic spinal cord injury in adult rats. *Neuroscience* 114(4): 905-916.

Shirasaki R, Pfaff SL. 2002. Transcriptional codes and the control of neuronal identity. *Annual Review of Neuroscience* 25: 251-281.

Simonen M, Pedersen V, Weinmann O, Schnell L, Buss A, Ledermann B, Christ F, Sansig G, van der Putten H, Schwab ME. 2003. Systemic deletion of the myelin-associated outgrowth inhibitor Nogo-A improves regenerative and plastic responses after spinal cord injury. *Neuron* 38(2): 201-211.

Snow DM, Lemmon V, Carrino DA, Caplan AI, Silver J. 1990. Sulfated proteoglycans in astroglial barriers inhibit neurite outgrowth in vitro. *Experimental Neurology* 109(1): 111-130.

Song G, Cechvala C, Resnick DK, Dempsey RJ, Rao VL. 2001. GeneChip analysis after acute spinal cord injury in rat. *Journal of Neurochemistry* 79(4): 804-815.

Song H, Ming G, He Z, Lehmann M, McKerracher L, Tessier-Lavigne M, Poo M. 1998. Conversion of neuronal growth cone responses from repulsion to attraction by cyclic nucleotides. *Science* 281(5382): 1515-1518.

Steward O, Zheng B, Tessier-Lavigne M. 2003. False resurrections: Distinguishing regenerated from spared axons in the injured central nervous system. *Journal of Comparative Neurology* 459(1): 1-8.

Tachibana T, Noguchi K, Ruda MA. 2002. Analysis of gene expression following spinal cord injury in rat using complementary DNA microarray. *Neuroscience Letters* 327(2): 133-137.

Ugurbil K, Toth L, Kim DS. 2003. How accurate is magnetic resonance imaging of brain function? *Trends in Neurosciences* 26(2): 108-114.

Vaessin H, Grell E, Wolff E, Bier E, Jan LY, Jan YN. 1991. Prospero is expressed in neuronal precursors and encodes a nuclear protein that is involved in the control of axonal outgrowth in *Drosophila*. *Cell* 67(5): 941-953.

Van den Abbeele AD, Badawi RD. 2002. Use of positron emission tomography in oncology and its potential role to assess response to imatinib mesylate therapy in gastrointestinal stromal tumors (GISTs). *European Journal of Cancer* 38(Suppl 5): S60-65.

von Meyenburg J, Brosamle C, Metz GA, Schwab ME. 1998. Regeneration and sprouting of chronically injured corticospinal tract fibers in adult rats promoted by NT-3 and the mAb IN-1, which neutralizes myelin-associated neurite growth inhibitors. *Experimental Neurology* 154(2): 583-594.

Watkins K. 2001. Making sense of information mined from the human genome is a massive undertaking for the fledgling industry. *Chemical & Engineering News* 79(8): 26-45.

Wen Z, Guirland C, Ming GL, Zheng JQ. 2004. A CaMKII/calcineurin switch controls the direction of Ca^{2+}-dependent growth cone guidance. *Neuron* 43(6): 835-846.

Widerstrom-Noga EG, Turk DC. 2003. Types and effectiveness of treatments used by people with chronic pain associated with spinal cord injuries: Influence of pain and psychosocial characteristics. *Spinal Cord* 41(11): 600-609.

Xu XM, Guenard V, Kleitman N, Bunge MB. 1995. Axonal regeneration into Schwann cell-seeded guidance channels grafted into transected adult rat spinal cord. *Journal of Comparative Neurology* 351(1): 145-160.

Youmans JR, ed. 1996. *Neurological Surgery: A Comprehensive Reference Guide to the Diagnosis and Management of Neurological Problems*. Philadelphia: W. B. Saunders.

Young W. 2002. Spinal cord contusion models. *Progress in Brain Research* 137: 231-255.

Zhang YP, Iannotti C, Shields LB, Han Y, Burke DA, Xu XM, Shields CB. 2004. Dural closure, cord approximation, and clot removal: Enhancement of tissue sparing in a novel laceration spinal cord injury model. *Journal of Neurosurgery: Spine* 100(4): 343-352.

Zhang Z, Fujiki M, Guth L, Steward O. 1996. Genetic influences on cellular reactions to spinal cord injury: A wound-healing response present in normal mice is impaired in mice carrying a mutation (Wld(s)) that causes delayed Wallerian degeneration. *Journal of Comparative Neurology* 371(3): 485-495.

Zheng B, Ho C, Li S, Keirstead H, Steward O, Tessier-Lavigne M. 2003. Lack of enhanced spinal regeneration in Nogo-deficient mice. *Neuron* 38(2): 213-224.

Zurita M, Vaquero J, Zurita I. 2001. Presence and significance of CD-95 (Fas/APO1) expression after spinal cord injury. *Journal of Neurosurgery* 94(2 Suppl): 257-264.

CURRENT THERAPEUTIC INTERVENTIONS

As a result of recent advances in science and technology, individuals with a spinal cord injury have improved survival rates, increased opportunities for independent living, and longer life spans—all difficult to imagine possible even a few decades ago. Beginning at the accident scene, immobilization of the spine prevents or reduces the severity of a spinal cord injury, and advances in emergency response have improved the medical care for other urgent and life-threatening problems often associated with spinal cord injuries, including significant blood loss, blocked respiratory pathways, major head or body system trauma, and a dramatic drop in blood pressure. Improvements in rehabilitative care and treatment options have also provided significant functional enhancement and improved daily function.

Organized according to the stage of the injury and the targets for therapeutic intervention, this section describes the current standards of care and the treatment options for reducing the sequelae and secondary complications associated with spinal cord injuries, including improving sexual, bowel, and bladder functions; minimizing pulmonary embolisms, depression, and spasticity; alleviating pain; and enhancing function. The following material provides details of the progress that is being made in neuronal repair and regeneration and discusses the committee's recommendations for moving forward in developing therapeutic interventions.

CURRENT STANDARDS OF CARE

Clinical practice guidelines are used in all areas of medicine to promote the best available treatments backed by scientific evidence. Given the complexity of spinal cord injuries, only a limited number of guidelines have been developed or are under development. Clinical practice guidelines for spinal cord injuries have come largely from two professional groups, both of which rated the evidence by similar criteria to arrive at formal treatment recommendations. Guidelines from the American Association of Neurological Surgeons and the Congress of Neurological Surgeons (AANS/CNS) deal with acute care, and those developed by the Consortium for Spinal Cord Medicine deal with acute and chronic care (Table 4-1) (PVA, 2002). Other groups have developed additional evidence-based clinical guidelines (AHRQ, 1998). Panels accord the greatest weight to evidence from randomized, prospective, controlled clinical trials and the least weight to evidence from case reports describing one or more patients who improved with treatment. A lack of clinical guidelines for a particular treatment does not mean that the treatment is ineffective; rather, some treatments have not been entered into clinical trials to examine efficacy.

TABLE 4-1 Clinical Practice Guidelines for Treatment of Spinal Cord Injury

Current Guidelines

Acute Care

- Acute management of autonomic dysreflexia: Individuals with spinal cord injury presenting to health care facilities (1997, 2001)[a]
- Pressure ulcer prevention and treatment following spinal cord injury: A clinical practice guideline for health-care professionals (2000)[a]
- Diagnosis of occipital condyle fractures by computed tomography (CT) imaging[b]
- Isolated fractures of the axis in adults[b]
- Management of pediatric cervical spinal injuries[b]

Chronic Care

- Neurogenic bowel management in adults with spinal cord injury (1998)[a]
- Depression following spinal cord injury: A clinical practice guideline for primary care physicians (1998)[a]
- Outcomes following traumatic spinal cord injury: Clinical practice guidelines for health-care professionals (1999)[a]
- Prevention of thromboembolism in spinal cord injury (1997[a], 2002[b])

Guidelines Under Development

- Respiratory management[a]
- Preservation of the upper extremity function[a]
- Bladder management[a]
- Acute management of spinal cord injury[a]
- Sexuality and reproductive health[a]
- Treatment of spasticity[a]

[a]Consortium for Spinal Cord Medicine.

[b]American Association of Neurological Surgeons and the Congress of Neurological Surgeons.

SOURCES: Apuzzo, 2002; PVA, 1998, 2000, 2001, 2002.

THERAPIES FOR ACUTE INJURIES

Acute care begins at the scene of an injury, continues through transport of the patient, and ends with early evaluation and care at a trauma center. The complex medical challenges faced in treating patients who suffer a spinal cord injury begin at the injury scene where often the patient not only needs to be immobilized because of concerns about a spinal cord injury but also requires immediate attention for other urgent and life-threatening problems: significant blood loss, blocked respiratory pathways, major head or body system trauma, or a dramatic drop in blood pressure. One indicator of the progress that has been made in acute care is that patients increasingly arrive at the emergency department with less severe injuries. Most patients (55 percent) in the 1970s came to regional centers with complete spinal cord injuries, whereas today approximately 39 percent arrive with complete injuries (AANS/CNS, 2002a). The transformation to less severe injury is most likely the result of improved emergency medical services (EMS) at the accident scene and more careful handling and patient care during transport (Garfin et al., 1989). Apart from immobilization at the accident scene, few therapies for acute spinal cord injuries have been proven to be effective and safe.

Immobilization at the Scene and Transport to Acute Care

At the scene of the injury, the primary considerations related to the spinal cord injury are to stabilize the spine and to ensure rapid transport to the nearest acute-care facility. These goals are vital to preventing further injury, considering that it has been estimated that in the past between 3 and 25 percent of spinal cord injuries took place after the initial trauma, either during transport or early in the course of patient evaluation (Hachen, 1974). In the United States, the practice of immobilizing the neck and spine of all trauma patients at the scene has become nearly universal. Immobilization at the scene is supported by clinical experience and by biomechanical evidence that it reduces the pathological motion of the spinal column.

A major improvement in EMS arrival and transport times has led in recent decades to striking decreases in rates of mortality, injury severity, complications, and lengths of hospital stays (Hachen, 1974; Tator et al., 1993). In the mid-1990s, a large clinical trial conducted in multiple states noted the rapid times of EMS arrival at the scene (e.g., 4 minutes for 25 percent of cases) and arrival to the first emergency department in about 1 hour (Geisler et al., 2001). The elapsed time from the injury to the arrival at a specialized trauma center averaged 6.2 hours. Also, the quality of the care administered during transport has improved. Before 1968, many deaths took place in transit as a result of inadequate respiratory or cardiovascular support. Current treatment guidelines call for rapid transport to the closest facility with the capacity to evaluate and treat spinal cord injuries (AANS/CNS, 2002c).

Despite the progress in care at the scene of the injury, there are as yet no demonstrably effective pharmacological therapies that can be administered at the scene or during transport. Further attention needs to be given to the development of acute-care therapeutic interventions and to evaluation of other emergency response efforts that might improve patient outcomes, such as methods to relieve compression of the spinal cord and prevent further cell death, edema, and ischemia.

Decompression of the Spinal Cord

Decompression of the spinal cord, if it is performed during the appropriate time window, may provide a benefit to individuals with spinal cord injuries. In many patients, surgery is performed soon after the injury to remove the tissue debris, bone, disc, and fluid that compress the spinal cord.

The goal is to alleviate pressure and to improve the circulation of blood and cerebrospinal fluid, particularly for those with central cervical spinal cord injuries (Dobkin and Havton, 2004). Yet there are many unknowns about the value and timing of this procedure. Studies of decompression in rodents after a spinal cord injury demonstrate that the longer compression of the spinal cord exists, the worse the prognosis for neurological recovery (Dimar et al., 1999).

A meta-analysis found that although decompression clearly improves neurological recovery in animal models, the findings for humans are less impressive (Fehlings et al., 2001). Studies favoring decompression have mostly been case studies, which are less robust types of analyses than randomized controlled trials. No prospective clinical trials of the benefits and risks of decompression have been conducted. Furthermore, in the studies that have already been completed, the timing of surgery was not uniform, so the optimal timing remains unknown. Nevertheless, the best indication about timing comes from a large case series that found that the greatest benefits were obtained when decompression was performed within 6 hours of the injury (Aebi et al., 1986). Some evidence, on the other hand, indicates that decompression of the spinal cord may be harmful and is best avoided, as long as the individuals are provided with nonsurgical therapies (Fehlings et al., 2001). Weighing the evidence as a whole, two professional groups adopted the position that decompression does not constitute the standard of care but should remain an option (Silber and Vaccaro, 2001; AANS/CNS, 2002c). The Christopher Reeve Paralysis Foundation is in the process of developing an international clinical trials network and is examining the feasibility of performing a clinical trial to examine the optimal timing for spinal cord decompression.

Neuroprotection

Several human clinical trials of potential neuroprotective therapies after spinal cord injury were conducted in the 1980s and 1990s (Mirza and Chapman, 2001); however, none of these conclusively demonstrated a benefit for increasing function after a spinal cord injury. The most high profile clinical trials were of the medications methylprednisolone and the ganglioside GM-1. After careful review of the results by two separate panels, neither of the two medications received endorsement as a standard of care (Fehlings and Spine Focus Panel, 2001; AANS/CNS, 2002c).

The three clinical trials of methylprednisolone, a corticosteroid, were sponsored by the National Acute Spinal Cord Injury Study (NASCIS) (Bracken et al., 1984, 1990, 1997). The trials were launched after it was reported that methylprednisolone preserved neurological function in animal models by inhibiting ischemia, axon degeneration, and inflammation, among other effects. The first human clinical trial in the early 1980s compared high- versus low-dose methylprednisolone (Bracken et al., 1984); the second clinical trial compared the effects of methylprednisolone with those of another agent and a placebo (Bracken et al., 1990); and the third clinical trial compared the timing of methylprednisolone treatment (Bracken et al., 1997). Concerns have been raised about the robustness of the statistical analyses and the heterogeneity of the populations with spinal cord injuries used in the studies, which made it difficult to compare due to differences in the baseline characteristics of the study populations (Bracken and Holford, 2002). Consequently, it has been stated that the data describing improved recovery from methylprednisolone treatment are weak and that the improvements observed may represent random events (Hurlbert, 2000). In some cases the trials documented serious side effects, the most prominent of which were higher infection rates, respiratory complications, and gastrointestinal hemorrhage.

Another pharmacological therapy, the ganglioside GM-1, a lipid that is abundant in mammalian central nervous system membranes, was also reported to show improvement in animal models but has not

been found to be useful in humans. Its potential therapeutic value was suggested by its ability to prevent apoptosis and to induce neuronal sprouting in animal models. However, the findings from a large-scale clinical trial were negative when the results for the treated group were compared with individuals who received placebo (AANS/CNS, 2002c).

Similarly, experiments with rodents (Behrmann et al., 1994) and cats (Faden et al., 1981) have demonstrated that thyrotropin-releasing hormone (TRH) can significantly improve long-term motor recovery after a spinal cord injury. However, a large-scale randomized clinical trial designed to examine the effects of TRH analogs in individuals with acute spinal cord injuries was not fully completed (Pitts et al., 1995), and such an evaluation has not been revisited.

TREATING COMPLICATIONS OF SPINAL CORD INJURIES

Prevention or Elimination of Chronic Pain

Chronic pain, one of the most common sequelae of spinal cord injuries, is not adequately controlled by currently available treatments. Inadequately controlled pain not only erodes quality of life, functioning, and mood but also can lead to depression and, most tragically, suicide (Hulsebosch, 2003; Finnerup and Jensen, 2004). Some clinicians have been slow to recognize that chronic pain is real, has serious consequences, and should not be dismissed as grounds for psychiatric referral (Hulsebosch, 2003).

To assist with the development of treatments for the chronic pain associated with spinal cord injuries, an International Association for the Study of Pain task force was formed to define distinct categories and sources of pain (Vierck et al., 2000). Two categories were defined: at-level neuropathic pain and below-level neuropathic pain. At-level neuropathic pain is correlated to the amount of damage to the gray matter above and below the primary injury site (Yezierski, 2000) and the amount of secondary cellular damage caused by the release of neurotransmitters (glutamate and *N*-methyl-D-aspartate [NMDA]) (Tator and Fehlings, 1991) and inflammatory cytokines (Bethea et al., 1998; Vierck et al., 2000). Below-level neuropathic pain is associated with axonal disruption, loss, or damage along the spinothalamic tract (Bowsher, 1996).

Experts in spinal cord injury-associated pain consider the development of pain therapies to be a major and feasible research priority, considering the body of research that has been amassed over the past 10 years about pain mechanisms in individuals with spinal cord injuries, as well as related research on other forms of neuropathic pain. Neuropathic pain results from direct damage to neural tissue, whereas nociceptive pain is caused by damage to nonneural tissues (bone, muscles, and ligaments). Nociceptive pain is what most healthy people are familiar with, and it is more treatable and controllable with standard pain therapies like anti-inflammatory agents and analgesics. Neuropathic pain is often treated with antidepressants and anticonvulsants, but their efficacies specifically for the treatment of spinal cord injury-associated pain are weak (Finnerup and Jensen, 2004).

Few randomized controlled clinical trials of pain therapies for individuals with spinal cord injuries have been published in the medical literature, and none of the trials that have been conducted found commonly used pain therapies to be highly effective (Table 4-2) (Finnerup and Jensen, 2004). Explicit guidelines for the treatment of both pain and spasticity (see the next section) for clinicians and caregivers are lacking.

However, evidence is accumulating that opioid agents given in combination with other agents may have therapeutic value (Mao et al., 1995; Wiesenfeld-Hallin et al., 1997; von Heijne et al., 2000).

The use of some therapies that encourage axonal elongation may be inadvisable because they could also cause chronic pain. For example, in addition to promoting axon regrowth, brain-derived neurotrophic factor has been found to elicit pain (Kerr et al., 1999), likely by enhancing synaptic input into the superficial dorsal horn, where nociceptive pain processing takes place (Garraway et al., 2003).

TABLE 4-2 Randomized Controlled Trials of Pharmacological Treatments for Pain in Individuals with Spinal Cord Injuries

Active Drug	Number of Patients Tested	Outcome	Reference
Valproate	20	No effect	Drewes et al., 1994
Gabapentin	7	No effect	Tai et al., 2002
Lamotrigine	22	No effect	Finnerup et al., 2002
Amitriptyline	84	No effect	Cardenas et al., 2002
Trazodone hydrochloride	18	No effect	Davidoff et al., 1987
Lidocaine	21	Better than placebo	Loubser and Donovan, 1991
Lidocaine	10	Better than placebo	Attal et al., 2000
Mexiletine	11	No effect	Chiou-Tan et al., 1999
Morphine	9	No effect	Attal et al., 2002
Morphine	15	No effect	Sidall et al., 2000
Clonidine	15	No effect	Sidall et al., 2000
Morphine and clonidine	15	Better than placebo	Sidall et al., 2000
Ketamine	9	Better than placebo	Eide et al., 1995
Alfentanil	9	Better than placebo	Eide et al., 1995
Propofol	8	Better than placebo	Canavero et al., 1995
Baclofen	7	Better than placebo	Herman et al., 1992

SOURCE: Adapted from Finnerup and Jensen, 2004.

Primary sensory neurons (also known as primary afferents) in the spinal cord convey pain information from the primary sensory neuron to the brain. After a spinal cord injury, these neurons become hyperexcitable; namely, they fire more readily than before the injury. To explain hyperexcitability, a

recent study with animals revealed that projection neurons possess more sodium channels of a particular type ($Na_v1.3$) (Hains et al., 2003). Strategies to reduce the formation of this sodium channel may reduce hyperexcitability and pain. Furthermore, suppression of the activation of a key enzyme, known as MAP kinase, which aids the transmission of signals from the projection neuron's membrane to its nucleus (Kawasaki et al., 2004), may prevent the onset of pain.

Relief of Spasticity

Spasticity refers to the debilitating muscle spasms and other types of increased muscle tone that occur after a spinal cord injury. Spasticity is similar to pain in that both are highly common after spinal cord injuries and have multiple possible mechanisms that might account for their onset. The key difference between them is that spasticity results from the heightened activity of reflex pathways (proprioceptive sensory neurons and motor neurons), whereas pain reflects the heightened activities of pain pathways.

Spasticity affects, to various degrees, the vast majority of people with spinal cord injury (Kaplan et al., 1991). Treatment begins with stretching and other rehabilitation techniques. If it remains uncontrolled, drug interventions are used, and if it is severe, the treatment is surgery and administration of the drug baclofen by implanted pumps (Kirshblum, 1999). Baclofen and tizanidine have inhibitory effects on motor neurons because their actions mimic that of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). No treatment for spasticity is uniformly successful or provides a complete cure, most likely because of spasticity's multiple underlying causes, but it can be controlled in many individuals (Burchiel and Hsu, 2001). The drug fampridine, a potassium channel blocker, appears to alleviate some degree of spasticity and is being evaluated in clinical trials. One of the issues in the development of drugs used to control spasticity is that they may have the undesirable effect of inhibiting spontaneous activity that might be necessary for axon regrowth (McDonald and Becker, 2003) and may deprive patients of useful muscle contraction.

Thromboembolism

Thromboembolism is a potentially life-threatening condition frequently encountered in the early weeks after a spinal cord injury. Deep vein thromboses (DVTs) are blood clots that form deep within the veins, usually in the legs and thighs, and result from slowed or halted blood flow (venous stasis) in immobilized individuals with spinal cord injuries. The most feared complication of DVT is pulmonary embolism, which can bring sudden death. Pulmonary embolism occurs when a blood clot within a deep vein dislodges and travels to the pulmonary artery, where it obstructs the passage of oxygenated blood to the rest of the body. Widespread adoption of preventive regimens in the early 1990s decreased the incidence of DVT in individuals with spinal cord injuries in acute care or rehabilitation from 14 to 9.8 percent and the incidence of pulmonary embolism from nearly 4 to 2.6 percent (Chen et al., 1999).

Today, the incidences of both DVTs and pulmonary embolism have declined because of greater awareness of the conditions and several controlled clinical trials that found that combination strategies are effective in preventing DVT and pulmonary embolism. A panel rating the quality of evidence found several treatment modalities that warranted designation as a standard of care because they had been found to be effective in controlled clinical trials (AANS/CNS, 2002b).

The standards for preventing DVT call for prophylactic treatment with low-molecular-weight heparins (an anticoagulant) or adjusted-dose heparin, the use of rotating beds, or a combination of these modalities. Low-dose heparin, in combination with compression stockings or electrical stimulation, is also recommended as a standard of care. High doses of heparin have been found to lead to higher

incidence of bleeding. Several other preventive treatments were also listed as options for care (AANS/CNS, 2002c).

Bladder Dysfunction

Bladder dysfunction affects virtually all individuals with spinal cord injuries. Its treatment depends on the site and the type of injury, including the extent of sacral injury. Three types of bladder problems are common after a spinal cord injury. The first, flaccid bladder, results from injury to the sacral cord, which controls reflexive contraction of the bladder. The injury leaves the bladder's detrusor muscle incapable of being contracted and thus causes urine to back up in the kidneys. The treatment is intermittent catheterization, in which a tube is inserted into the bladder to permit passive drainage at regularly scheduled intervals to prevent urine from overfilling the bladder. Bladder overfill causes damage to the bladder wall and heightens the risk of infection (Burns et al., 2001). In order to reduce the incidence of urinary tract infections, intermittent catheterization should be performed by the patient (Cardenas and Mayo, 1987).

The other two types of dysfunction are detrusor hyperreflexia and detrusor-sphincter dyssynergia. The goal of treating detrusor hyperreflexia is to prevent incontinence. Treatment of detrusor-sphincter dyssynergia is aimed at ensuring adequate drainage, low-pressure storage, and low-pressure voiding. Both of these bladder conditions can be treated with anticholinergic or other types of medications that suppress contraction of the detrusor muscles. However, in many cases these medications do not suppress contractions. Bladder augmentation (augmentation cystoplasty) is often recommended for patients who have destrusor hyperreflexia or reduced compliance that fails to respond to anticholinergics (Sidi et al., 1990). New treatments have been introduced for these conditions, including pharmacological therapies to reduce the hyperactivity of the detrusor muscle (such as botulinum toxin or capsaicin) and functional electrical stimulation (see below). For example, a Food and Drug Administration (FDA)-approved device, known as the Vocare bladder system, uses surgically implanted electrodes to stimulate the sacral nerves controlling bladder function. The patient manually controls the stimulator using an external transmitting device. The benefits of these therapies have yet to be fully investigated (Burns et al., 2001). In another strategy, male patients may undergo sphincterotomy or stent placement to use the hyperreflexia to empty the bladder. The Consortium for Spinal Cord Medicine will soon be describing the strength of the evidence in a clinical practice guideline under development.

Neurogenic Bowel Treatment

Neurogenic bowel, the absence of voluntary control over stool elimination, affects the vast majority of individuals with spinal cord injuries. Some studies have found that as many as 95 percent of individuals with spinal cord injuries require at least one therapeutic procedure so that they can defecate (Glickman and Kamm, 1996). The majority of individuals with spinal cord injuries rate bowel dysfunction as a major life-limiting problem (Kirk et al., 1997). Before they leave the hospital, most patients are taught how to care for neurogenic bowel. Care is designed to regularize bowel movements and prevent constipation, incontinence, other gastrointestinal symptoms, and serious complications from impacted bowels (see the section on autonomic dysreflexia below).

It consists of a program with several components that are individualized to patients with one of two types of neurogenic bowel: reflexic bowel and areflexic bowel. Both types require dietary fiber and fluid intake, oral medications, and rectal suppositories. Treatments help to stimulate the transport of stool through the bowels and hold moisture within the stool. Key differences in treating reflexive bowel versus areflexic bowel include the type of rectal stimulant, the consistency of the stool, and the

frequency of bowel care. Clinical practice guidelines for the management of neurogenic bowel were developed in 1998 (Spinal Cord Medicine Consortium, 1998).

Autonomic Dysreflexia

Autonomic dysreflexia is a potentially lethal complication of a spinal cord injury that affects people with injuries at or above the thoracic level (usually T6 or above). The condition is manifest by severe headache (caused by an abrupt elevation of blood pressure), hypertension, profuse sweating, and activation of other autonomic reflexes. Symptoms come from overactivity of the autonomic (involuntary) nervous system cells in the spinal cord because of the blocked nerve impulses from the brain that normally keep these cells under restraint. The most frequent triggers of autonomic dysreflexia are an impacted bowel or an overfull bladder. The overactive sympathetic nerve and its branches cause a narrowing of the blood vessels, which, in turn, dramatically elevates blood pressure. Death from seizures, stroke, and abnormal heart beat rhythm can ensue if autonomic dysreflexia is not urgently treated.

Because autonomic dysreflexia is most often set off by bladder distention or bowel impaction, many individuals with spinal cord injuries have learned means of self-care to avoid emergency treatment by sitting upright to check urinary drainage or empty their bowel. An array of nonpharmacological and pharmacological agents are also available for emergency medical treatment (PVA, 2001).

Pressure Ulcers

Pressure ulcers are a highly frequent and serious complication of a spinal cord injury that affect physical, psychological, and social functioning. Ulcers are lesions caused by unrelieved pressure (if the force is perpendicular) or shear (if the force is tangential) to the tissue surface. The constant pressure can also interfere with the pressure in the capillaries and can therefore affect the exchange and elimination of nutrients and metabolites. Prolonged circulatory interference ultimately leads to cell death. In severe cases, individuals can develop a severe internal infection (septic shock), which can lead to organ failure. Stage I lesions are marked by discoloration and changes in tissue consistency on the skin surface, whereas the most serious lesions, stage IV lesions, are marked by extensive tissue necrosis and damage to muscle, bone, or supporting structures. About 32 percent of individuals with spinal cord injuries admitted to specialized care centers have been reported to develop pressure ulcers during the acute care stage, and at 2 years of follow-up the prevalence of pressure ulcers was 8.9 percent (Yarkony and Heinemann, 1995). The Consortium for Spinal Cord Medicine's clinical practice guideline advocates a range of prevention strategies, including the avoidance of prolonged positional immobilization, use of support devices on beds and wheelchairs, and dietary changes. Treat-ments include a range of cleansing strategies, debridement, and surgery for deep stage III or stage IV ulcers. The use of electrical stimulation to enhance healing of stage III or stage IV pressure ulcers is also recommended, on the basis of data from three randomized controlled clinical trials (PVA, 2000).

Treatment of Sexual Dysfunction and Fertility

Male Sexual Dysfunction and Fertility

Treatment research has largely focused on erectile dysfunction rather than the other two components of male sexual function, ejaculation and orgasm. The greatest strides have been with oral medications for erectile dysfunction. Although most men with spinal cord injuries have erections, their quality is often

not sufficient to sustain intercourse. Sildenafil (Viagra), which has been available since 1998, has been shown to have a high degree of efficacy, with up to 94 percent of men with spinal cord injuries in one study reporting improved erections and intercourse (Derry et al., 2002). Other new drugs with pharmacological and side effect profiles somewhat different from those of sildenafil have also become available (Anderson et al., 2004). Oral medications are now considered the first line of therapy and have largely supplanted less safe, more cumbersome, and costly treatments, such as penile prostheses (Benevento and Sipski, 2002). Local erectogenic neurotransmitters administered by injection, topical, or urethal forms are in development (Elliot, 2002).

Fertility problems, which are common in men with spinal cord injuries, result from poor sperm quality or ejaculatory dysfunction. Much progress has been made in enhancing male fertility through the development of penile vibratory stimulation, which has become routine for men with spinal cord injuries who wish to have children (Benevento and Sipski, 2002). Vibratory stimulation is considered preferable to another treatment, electroejaculation, because it is less invasive and may be performed at home or in a clinic setting. Studies have shown that nearly all men given one of these two treatments successfully ejaculate, after which approximately one-third of the couples achieved pregnancies (Sonksen et al., 1997). However, this success rate is still largely dependent on overcoming the low sperm quality in men with spinal cord injuries, which often requires very invasive forms of assisted reproduction, ranging from artificial insemination to in vitro fertilization and intracytoplasmic sperm injection.

Female Sexual Dysfunction and Fertility

Sexual dysfunction in women with spinal cord injuries received scant attention until the 1990s. The problems include insufficient vaginal secretions and failure to reach orgasm (especially in women with sacral injuries) (Benevento and Sipski, 2002). Women with spinal cord injuries benefit from sildenafil, which promotes increased subjective arousal (Sipski et al., 2000). In the trial, the drug worked most effectively when it was combined with manual or visual stimulation, and there were few adverse effects.

Fertility is generally preserved in women with spinal cord injuries (Charlifue et al., 1992), primarily because it does not rely on spinal circuits. Rather, fertility is controlled by the hypothalamic release of hormones that stimulate the ovaries. Pregnant women with spinal cord injuries tend to have babies with lower birth weights and tend to have more complications during pregnancy and delivery, including bladder and bowel problems, autonomic hyperreflexia, decubitus ulcers, urinary tract infections, edema, anemia, spotting, fatigue, cardiac irregularity, and preeclampsia (Charlifue et al., 1992; Jackson and Wadley, 1999).

Treatment of Bone Disorders

The reduced mobility and other pathological changes that occur in individuals with spinal cord injuries often lead to decreases in bone density (hence, a greater risk of bone fractures) and heterotopic ossification. The latter refers to the formation of bone in soft tissues near paralyzed joints. Bone density loss, particularly in the lower limbs, occurs during the first 6 months after the injury and then plateaus over the next 12 to 16 months (Demirel et al., 1998). The drug alendronate (Fosamax) has recently been found in a 2-year clinical trial to stop bone density loss at all bone sites at which measurements were taken (Zehnder et al., 2004). The drug, a bisphosphonate, works by inhibiting bone resorption by osteoclasts.

Heterotopic ossification can range from an incidental finding on an X-ray to massive bone formation surrounding a joint, producing total ankylosis. The most common location is the hips. Heterotopic ossification is treated with range-of-motion exercises, the drug etidronate, nonsteroidal anti-inflammatory drugs (NSAIDs), and irradiation. The use of NSAIDs, especially within the first 2 months of an injury, has been found to reduce the incidence of heterotopic ossification by a factor of 2 to 3 (Banovac et al., 2004). Severe cases are treated surgically, and the chance of recurrence may be reduced by the use of the nonsurgical therapies listed above.

Depression

Depression after a spinal cord injury is common and disabling. A key longitudinal study was conducted to track more than 100 individuals with spinal cord injuries for 2 years after discharge from the hospital (Kennedy and Rogers, 2000). It found that nearly 30 percent of the individuals were depressed at the time of discharge; the rate of depression then dropped, before climbing over the next 6 months. Rates peaked at 60 percent by year's end and then declined to 16 percent by the end of the second year. The treatment of depression in any group of individuals with a chronic physical illness, particularly those with spinal cord injuries, is expected to reduce unnecessary suffering and disability and to motivate adherence to complex programs of self-care, rehabilitation, and treatment.

Effective treatments are available for depression (APA, 1994). In 1998, the Consortium for Spinal Cord Medicine published a clinical practice guideline detailing specific steps for assessment, diagnosis, and treatment of depression (PVA, 1998).

RETRAINING AND RELEARNING MOTOR TASKS

The plasticity of the nervous system, or the nervous system's ability to adapt and reorganize itself, sometimes allows the body to partially recover some of the motor function lost as a result of a spinal cord injury. As described throughout this report, a great deal of the research and clinical effort has been focused on restoring lost motor function through pharmacological or surgical methods. However, physical training and rehabilitation techniques and neuroprostheses also provide individuals with additional tools that they can use to recover from a spinal cord injury.

Body Weight Support Training

It is important that patients do not overcompensate with motor function that has been spared, thus limiting the capacity of the nervous system to adapt (Barbeau, 2003). Therefore, body weight support techniques have been developed that assist in locomotion, while minimizing compensation. One therapy that is used to improve walking in individuals in both the acute and the chronic stages of their injuries is body weight-supported treadmill training. During this therapy, individuals are placed in a harness to unload between 0 and 50 percent of their weight and are then put on a treadmill to simulate walking (Wernig et al., 1995, 1998; Protas et al., 2001; Dobkin et al., 2003a). Therapists then systematically reduce the amount of weight support, while training patients to walk on the treadmill at faster speeds.

Although this technique is promising, it is still unclear how effective body weight support treadmill training is at improving function in individuals with incomplete chronic spinal cord injuries. It is

believed that body weight-supported training enhances the relearning of motor skills in the presence of spared pathways and facilitates the remaining pathways to relearn to interpret the complex sensory information associated with walking (Wernig et al., 1995; Harkema et al., 1997; Hulsebosch, 2002; Dietz and Harkema, 2004; Edgerton et al., 2004). These therapies produce a wide range of biochemical and physiological changes in the nervous system and musculature. Long term improvement in electromyogram (EMG) activity in paralytic legs has been observed (Wirz et al., 2001), which has been correlated to functional reorganization of neuronal centers in both the brain (Dobkin, 2000) and residual pathways in the spinal cord (Dietz and Harkema, 2004). Levels of neurotransmitters also change their levels in response to body weight support training (Edgerton et al., 2001). However, it is not clear if the observed physiological changes correlate with improvements in muscle control and function. To confirm these preliminary findings, an ongoing prospective large scale randomized clinical trial (The Spinal Cord Injury Locomotor Trial) has been designed to evaluate body weight-supported treadmill training and to compare that therapy with conventional physical therapy (Dobkin et al., 2003a,b). This study consists of two groups of patients, an experimental group that received body weight support and gait training, and a control group that received conventional standing and mobility training. Results from this study have not yet been published in a peer review journal; however, preliminary findings suggest that the treatment group was not associated with any improvement in the outcome measures compared to the "standard of care" gait training provided to the control group (Dobkin et al., 2003b, 2004). Three additional clinical trials are under way (NIH, 2004). Preliminary results from one of these phase II studies suggest that aggressive treadmill training may facilitate functional improvements, but this trial has not been completed and these results have yet to be published in a peer-reviewed journal (Hulsebosch, 2002).

A major difficulty with body weight support treadmill training is the effort required by therapists to guide the movements of individuals' legs (Hesse, 1999). Therefore, a number of approaches have been developed to assist, including robotic-assistive stepping devices such as the Lokomat (Hocoma AG, Volketswil Germany), in which the movements of an individual's legs are controlled by a preprogrammed physiological gait pattern. Other rhythmic leg exercises can be achieved with modified exercise bicycles.

A related approach is to incorporate functional electrical stimulation (see below) in combination with body weight-supported walking in individuals with incomplete injuries (ASIA C) (Postans et al., 2004). One study has demonstrated improvements in interlimb coordination with the use of afferent electrical stimulation during treadmill training (Field-Fote, 2001).
Individuals with spinal cord injuries will likely receive the greatest benefit by combining body weight-supported treadmill training with other approaches, such as robotic devices (Dobkin and Havton, 2004), drugs, and surgery.

Functional Electrical Stimulation

Functional electrical stimulation (FES) is the approach most commonly used to artificially improve muscle function. FES devices have two key components: a control unit and stimulating electrodes. The control unit translates commands from voluntary movements or sensors into signals that are sent to the stimulating electrodes, which are taped onto the skin or surgically positioned near the specific nerves that innervate muscle groups (Bhadra et al., 2001). The stimulating electrodes provide mild shocks to muscle groups, causing them to contract (Barbeau et al., 2002). These contractions help maintain muscle mass and can initiate muscle movements, such as controlling movements of the hands or legs (Peckham et al., 2002). Modulating the magnitude of the stimulus parameters affects the strength of the

muscle contraction and coordinated functional movements can be generated by controlling the relative stimulation strengths of collections of muscles (Dobkin and Havton, 2004).

FES is used in multiple ways to improve function, including cardiovascular conditioning, improving gait control and speed, restoring hand control and breathing, and controlling bowel and bladder function. FDA has approved neuroprostheses for the restoration of hand function, bowel and bladder control, and breathing, and clinicians at many spinal cord injury centers are trained in their use. In addition, an FDA-approved walking system uses a nonimplanted FES and an FES cycle ergometric device that allow periodic exercise of paralyzed leg muscles.

As noted earlier, electrical stimulation for bladder function control involves a neuroprosthesis sold in the United States as Vocare. It is an FDA-approved medical device that provides the user with the ability to void upon demand as a result of the stimulation provided by the implanted device. Electrodes are placed on the sacral roots either intradurally (which is the most popular location in Europe) or extradurally (which is the location used more frequently in the United States). Voiding of the bladder is controlled by an implanted radio receiver controlled by an external device that delivers energy and control to the implant. This system allows individuals with spinal cord injuries to manage difficult bladder problems and drain many urine management devices (catheters and condoms). It also reduces the incidence of bladder infections. The device has been implanted in more than 1,500 patients around the world, and 90 percent of those with the implant reportedly used it 4 to 6 days per week. Thus, the cost of the device compared with that of conventional care is recovered in about 7 years (Creasey and Dahlberg, 2001).

FDA has approved a neuroprosthesis for hand control, called Freehand, which provides two grasping patterns to individuals with C5 or C6 tetraplegia. It consists of a stimulator-receiver implanted in the chest and eight electrodes implanted at the motor points of hand and forearm muscles. Shoulder movement is used to proportionally control the degree of hand opening and closing. Fifty-one individuals with C5 or C6 tetraplegia were enrolled in a multicenter clinical study of the safety, effectiveness, and clinical impact of the Freehand system (Peckham et al., 2001). The results showed that the neuroprosthesis increased the pinch force of every subject, and it enabled 98 percent of the participants to grasp and move more objects in a standardized grasp-release test. An advanced system is under clinical investigation. This advanced system provides greater upper limb function and incorporates implanted control methods, thereby eliminating the need for the external shoulder sensor.

Tendon transfer surgery is often used either alone or in conjunction with neural prostheses (Kirshblum, 2004) for upper-extremity locomotion. This surgical procedure involves transferring one or more tendons of muscles with retained voluntary function to restore lost movements. The procedure is reversible and generally restores function equivalent to that provided by one or two spinal roots. Enhanced function is provided through additional stimulation channels, which are used to activate the muscles of the hand for fine control, elbow extension, and hand rotation. This system has been implanted in seven subjects (Peckham et al., 2002). An advanced neuroprosthesis that uses an implantable controller for restoration of hand and upper-arm control has been demonstrated to improve finger control in a group of individuals and has improved their performance of activities of daily living (Hobby et al., 2001). Recently, one participant received implants in both arms to further improve function.

For respiratory control, electrical stimulation can be used to stimulate the phrenic nerve, which controls the contractions of the diaphragm muscles. This technique, known as phrenic nerve pacing, was introduced in the 1960s (Escher et al., 1966). Phrenic pacing systems have allowed users to decrease or even discontinue the use of mechanical respirators and enable more normal breathing. The

technique has been applied to more than 1,000 patients worldwide and has become a clinically accepted intervention in selected individuals (DiMarco, 1999). An alternative to direct stimulation of the phrenic nerve has also been developed. It is less invasive, as electrodes are implanted laparoscopically into the diaphragm (DiMarco et al., 2002; Onders et al., 2004). To date, 10 individuals have received the implant, and 9 of these individuals have been able to comfortably tolerate extended periods (hours) of respirator-free pacing. If the utility of the device is confirmed in additional individuals, diaphragm pacing with intramuscular electrodes placed by laparoscopic surgery may provide a less invasive and less costly alternative to conventional phrenic nerve pacing.

The objective of some lower-extremity FES systems is to enable individuals with paraplegia to stand and transfer themselves. The functional goals associated with standing include reaching for high objects, having face-to-face interactions with other people, and transferring between surfaces independently or with minimal assistance. At present there are no commercial or FDA-approved systems for FES-aided standing; however, one implantable system has reached the multicenter clinical trial stage of development (Davis et al., 2001).

The only FDA-approved FES system for ambulation available is a surface stimulation system (Parastep). Individuals with paraplegia wear a microprocessor-stimulator unit at the waist and use a walker with controls built into the handles. This system allows these individuals to stand and walk with a reciprocal gait for limited distances. Use of the system has additional medical benefits, such as providing increased blood flow to the lower extremities, a lower heart rate at subpeak work intensities, increased muscle mass, and reduced spasticity and also has psychological benefits (Klose et al., 1997; Graupe and Kohn, 1998).

FES devices can also be used to maintain an individual's muscle fitness and potentially encourage the recovery of function. Decreased muscle mass is a secondary condition that, if left untreated, can diminish the potential for complete recovery. A common cause of muscle atrophy is the loss of motor neurons in the spinal cord that drive muscle contraction. Other, usually less severe but more widespread atrophy occurs over time because of the disuse of paralyzed but still innervated muscles. FES can help reverse disuse atrophy by stimulating muscle activity, but it relies on intact nerve-muscle connections and cannot easily be used to stimulate denervated muscles.

FES devices have received a mixed reception from both clinicians and individuals with spinal cord injuries. Originally, the controllers and stimulating electrodes were large and cumbersome and did not provide very fine control; however, technological advances are leading to reductions in the sizes of these devices and reductions in the numbers of surgical procedures required for implementation. In addition, the implanted electrodes have improved reliabilities and longevities. Some individuals with spinal cord injuries and their clinicians are dissuaded from using FES devices because of the surgical procedures required to implant the systems and, in the case of Vocare, the additional damage to the nervous system that results from the requirement to transect some of the sensory nerves that enter the spinal cord (Creasey et al., 2001). However, the potential benefit to an individual's quality of life and the decreased health care costs over the lifetime of the individual likely offset the large initial expense of FES devices (Creasey et al., 2000).

Considerable research and development have been invested in the development of computer-controlled FES devices (Taylor et al., 2002), and future advances are likely to be linked to advances in technologies and their appropriate application to individuals with spinal cord injuries. For example, numerous electrode interfaces that provide more selective activation of nerves will provide finer movements. Others use physiological principles to block neural firing and will be used to block pain

and suppress spasticity. Additionally, smaller stimulators are being developed. These will provide individuals with devices that can be fully implanted.

There is also a considerable effort to develop brain-computer interfaces that can be used to convert thoughts into electrical signals that can control and stimulate muscles (Friehs et al., 2004). These interfaces are most likely to initially have impact on the most severely disabled individuals who have lost other communication channels, but retain the ability to control their cortical firing. Cortical control may be used for control of the environment and for communication by such individuals, and may also be used as an interface for robotic manipulators and FES systems. Current approaches include, from least invasive to most, extracting control information from the electroencephalogram (Keirn and Aunon, 1990; Wolpaw and McFarland, 2004), placing electrodes subcranially over the brain, or placing electrodes into the brain. Research on all approaches is ongoing both in animal models and in patients, and two-dimensional control of cursors on a monitor screen has been demonstrated. Additional technologies are being developed to assist individuals with spinal cord injuries that severely restrict their movements, including an eyeglass-type infrared-controlled computer interface (Chen et al., 1999) and a wireless environmental control system using Morse code (Yang et al., 2003).

The overall acceptance of implantable neuroprostheses in upper extremity functional restoration has been very good, with over 80 percent of patients achieving regular use of the devices (Peckham et al., 2001). In addition, more than 95 percent of those who received implants reported satisfaction with the neuroprosthesis (Polacek et al., 1999). Neuroprothesis devices, such as the Freehand system, also have the potential to reduce the overall cost of care for spinal cord injured people (Creasey et al., 2000). Although it has been a difficult challenge, some insurance companies and the U.S. Department of Veterans Affairs reimburse individuals for associated costs. Ensuring that such benefits become available to individuals with spinal cord injuries in the future will require an effective delivery model, which requires collaboration between various clinical specialties (physical medicine and rehabilitation physicians, hand surgeons, and therapists) to identify individuals who would benefit from neuroprotheses, as well as greater knowledge within the spinal cord injury community of the availability and benefits of neuroprotheses. However, the development of FES products, like pharmaceuticals, presents a financial challenge to companies, and this challenge may constrain the future development of such systems (Cavuoto, 2002; Dobkin and Havton, 2004).

REFERENCES

AANS/CNS (American Association of Neurological Surgeons/Congress of Neurological Surgeons). 2002a. Cervical spine immobilization before admission to the hospital. *Neurosurgery* 50(3 Suppl): S7-17.

AANS/CNS. 2002b. Deep venous thrombosis and thromboembolism in patients with cervical spinal cord injuries. *Neurosurgery* 50(3 Suppl): S73-80.

AANS/CNS. 2002c. Guidelines for management of acute cervical spinal injuries. Introduction. *Neurosurgery* 50(3 Suppl): S1.

Aebi M, Mohler J, Zach GA, Morscher E. 1986. Indication, surgical technique, and results of 100 surgically-treated fractures and fracture-dislocations of the cervical spine. *Clinical Orthopaedics and Related Research* (203): 244-257.

AHRQ (Agency for Healthcare Research and Quality). 1998. *National Guideline Clearinghouse*. [Online]. Available: http://www.guideline.gov/ [accessed January 10, 2005].

Anderson PCB, Gommersall L, Hayne D, Arya M, Patel HRH. 2004. New phosphodiesterase inhibitors in the treatment of erectile dysfunction. *Expert Opinion on Pharmacotherapy* 5(11): 2241-2249.

APA (American Psychiatric Association). 1994. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. Washington, DC: American Psychiatric Association.

Apuzzo MLJ, ed. 2002. Guidelines for the management of acute cervical spine and spinal cord injuries. *Neurosurgery* 50(3 Suppl).

Attal N, Gaude V, Brasseur L, Dupuy M, Guirimand F, Parker F, Bouhassira D. 2000. Intravenous lidocaine in central pain: A double-blind, placebo-controlled, psychophysical study. *Neurology* 54(3): 564-574.

Attal N, Guirimand F, Brasseur L, Gaude V, Chauvin M, Bouhassira D. 2002. Effects of IV morphine in central pain: A randomized placebo-controlled study. *Neurology* 58(4): 554-563.

Banovac K, Sherman AL, Estores IM, Banovac F. 2004. Prevention and treatment of heterotopic ossification after spinal cord injury. *Journal of Spinal Cord Medicine* 27(4): 376-382.

Barbeau H. 2003. Locomotor training in neurorehabilitation: Emerging rehabilitation concepts. *Neurorehabilitation & Neural Repair* 17(1): 3-11.

Barbeau H, Ladouceur M, Mirbagheri MM, Kearney RE. 2002. The effect of locomotor training combined with functional electrical stimulation in chronic spinal cord injured subjects: Walking and reflex studies. *Brain Research–Brain Research Reviews* 40(1-3): 274-291.

Behrmann DL, Bresnahan JC, Beattie MS. 1994. Modeling of acute spinal cord injury in the rat: Neuroprotection and enhanced recovery with methylprednisolone, U-74006f and YM-14673. *Experimental Neurology* 126(1): 61-75.

Benevento BT, Sipski ML. 2002. Neurogenic bladder, neurogenic bowel, and sexual dysfunction in people with spinal cord injury. *Physical Therapy* 82(6): 601-612.

Bethea JR, Castro M, Keane RW, Lee TT, Dietrich WD, Yezierski RP. 1998. Traumatic spinal cord injury induces nuclear factor-kappaB activation. *Journal of Neuroscience* 18(9): 3251-3260.

Bhadra N, Kilgore KL, Peckham PH. 2001. Implanted stimulators for restoration of function in spinal cord injury. *Medical Engineering & Physics* 23(1): 19-28.

Bowsher D. 1996. Central pain: Clinical and physiological characteristics. *Journal of Neurology, Neurosurgery & Psychiatry* 61(1): 62-69.

Bracken MB, Holford TR. 2002. Neurological and functional status 1 year after acute spinal cord injury: Estimates of functional recovery in National Acute Spinal Cord Injury Study II from results modeled in National Acute Spinal Cord Injury Study III. *Journal of Neurosurgery* 96(3 Suppl): 259-266.

Bracken MB, Collins WF, Freeman DF, Shepard MJ, Wagner FW, Silten RM, Hellenbrand KG, Ransohoff J, Hunt WE, Perot PL. 1984. Efficacy of methylprednisolone in acute spinal cord injury. *Journal of the American Medical Association* 251(1): 45-52.

Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, Eisenberg HM, Flamm E, Leo-Summers L, Maroon J, et al. 1990. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the second National Acute Spinal Cord Injury Study. *New England Journal of Medicine* 322(20): 1405-1411.

Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, Fehlings M, Herr DL, Hitchon PW, Marshall LF, Nockels RP, Pascale V, Perot PL Jr, Piepmeier J, Sonntag VKH, Wagner F, Wilberger JE, Winn HR, Young W. 1997. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury: Results of the third National Acute Spinal Cord Injury randomized controlled trial. *Journal of the American Medical Association* 277(20): 1597-1604.

Burchiel KJ, Hsu FP. 2001. Pain and spasticity after spinal cord injury: Mechanisms and treatment. *Spine* 26(24 Suppl): S146-160.

Burns AS, Rivas DA, Ditunno JF. 2001. The management of neurogenic bladder and sexual dysfunction after spinal cord injury. *Spine* 26(24 Suppl): S129-136.

Canavero S, Bonicalzi V, Pagni CA, Castellano G, Merante R, Gentile S, Bradac GB, Bergui M, Benna P, Vighetti S, Coletti Moia M. 1995. Propofol analgesia in central pain: Preliminary clinical observations. *Journal of Neurology* 242(9): 561-567.

Cardenas DD, Mayo ME. 1987. Bacteriuria with fever after spinal cord injury. *Archives of Physical Medicine and Rehabilitation* 68(5 Pt 1): 291-293.

Cardenas DD, Warms CA, Turner JA, Marshall H, Brooke MM, Loeser JD. 2002. Efficacy of amitriptyline for relief of pain in spinal cord injury: Results of a randomized controlled trial. *Pain* 96(3): 365-373.

Cavuoto J. 2002. *NeuroControl Exit Leaves Hole in Spinal Injury Market*. [Online]. Available: http://www.neurotechreports.com/pages/SCImarket.html [accessed February 8, 2005].

Charlifue SW, Gerhart KA, Menter RR, Whiteneck GG, Manley MS. 1992. Sexual issues of women with spinal cord injuries. *Paraplegia* 30(3): 192-199.

Chen D, Apple DF Jr, Hudson LM, Bode R. 1999. Medical complications during acute rehabilitation following spinal cord injury—Current experience of the model systems. *Archives of Physical Medicine and Rehabilitation* 80(11): 1397-1401.

Chen YL, Tang FT, Chang WH, Wong MK, Shih YY, Kuo TS. 1999. The new design of an infrared-controlled human-computer interface for the disabled. *IEEE Transactions on Rehabilitation Engineering* 7(4): 474-481.

Chiou-Tan FY, Eisele SG, Song JX, Markowski J, Javors M, Robertson CS. 1999. Increased norepinephrine levels during catheterization in patients with spinal cord injury. *American Journal of Physical Medicine and Rehabilitation* 78(4): 350-353.

Creasey GH, Dahlberg JE. 2001. Economic consequences of an implanted neuroprosthesis for bladder and bowel management. *American Journal of Physical Medicine and Rehabilitation* 82(11): 1520-1525.

Creasey GH, Kilgore KL, Brown-Triolo DL, Dahlberg JE, Peckham PH, Keith MW. 2000. Reduction of costs of disability using neuroprostheses. *Assistive Technology* 12(1): 67-75.

Creasey GH, Grill JH, Korsten M, U HS, Betz R, Anderson R, Walter J, Implanted Neuroprosthesis Research Group. 2001. An implantable neuroprosthesis for restoring bladder and bowel control to patients with spinal cord injuries: A multicenter trial. *Archives of Physical Medicine and Rehabilitation* 82(11): 1512-1519.

Davidoff G, Guarracini M, Roth E, Sliwa J, Yarkony G. 1987. Trazodone hydrochloride in the treatment of dysesthetic pain in traumatic myelopathy: A randomized, double-blind, placebo-controlled study. *Pain* 29(2): 151-161.

Davis JA Jr, Triolo RJ, Uhlir JP, Bhadra N, Lissy DA, Nandurkar S, Marsolais EB. 2001. Surgical technique for installing an eight-channel neuroprosthesis for standing. *Clinical Orthopaedics and Related Research* 385: 237-252.

Demirel G, Yllmaz H, Gencosmanoglu B, Kesiktas N. 1998. Pain following spinal cord injury. *Spinal Cord* 36(1): 25-28.

Derry F, Hultling C, Seftel AD, Sipski ML. 2002. Efficacy and safety of sildenafil citrate (Viagra) in men with erectile dysfunction and spinal cord injury: A review. *Urology* 60(2 Suppl 2): 49-57.

Dietz V, Harkema SJ. 2004. Locomotor activity in spinal cord-injured persons. *Journal of Applied Physiology* 96(5): 1954-1960.

Dimar JR II, Glassman SD, Raque GH, Zhang YP, Shields CB. 1999. The influence of spinal canal narrowing and timing of decompression on neurologic recovery after spinal cord contusion in a rat model. *Spine* 24(16): 1623-1633.

DiMarco AF. 1999. Diaphragm pacing in patients with spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation* 5(1): 6-20.

DiMarco AF, Onders RP, Kowalski KE, Miller ME, Ferek S, Mortimer JT. 2002. Phrenic nerve pacing in a tetraplegic patient via intramuscular diaphragm electrodes. *American Journal of Respiratory and Critical Care Medicine* 166(12 Pt 1): 1604-1606.

Dobkin BH. 2000. Spinal and supraspinal plasticity after incomplete spinal cord injury: Correlations between functional magnetic resonance imaging and engaged locomotor networks. *Progress in Brain Research* 128: 99-111.

Dobkin BH, Havton LA. 2004. Basic advances and new avenues in therapy of spinal cord injury. *Annual Review of Medicine* 55: 255-282.

Dobkin BH, Apple D, Barbeau H, Basso M, Behrman A, Deforge D, Ditunno J, Dudley G, Elashoff R, Fugate L, Harkema S, Saulino M, Scott M. 2003a. Methods for a randomized trial of weight-supported treadmill training versus conventional training for walking during inpatient rehabilitation after incomplete traumatic spinal cord injury. *Neurorehabilitation & Neural Repair* 17(3): 153-167.

Dobkin BH, Apple D, Barbeau H, Basso M, Behrman A, Deforge D, Ditunno J, Dudley G, Elashoff R, Fugate L, Harkema S, Saulino M, Scott M. 2003b. Randomized trial of weight-supported treadmill training versus conventional training for walking during patient rehabilitation after incomplete traumatic spinal cord injury. *Journal of Rehabilitation Research & Development* 40(6 Suppl 3): 32.

Dobkin BH, Apple D, Barbeau H, Basso M, Behrman A, Deforge D, Ditunno J, Dudley G, Elashoff R, Fugate L, Harkema S, Saulino M, Scott M. 2004. Walking-related gains over the first 12 weeks of rehabilitation for incomplete traumatic spinal cord injury: The SCILT randomized clinical trial. *Neurologie & Rehabilitation* 10(4): 179-187.

Drewes AM, Andreasen A, Poulsen LH. 1994. Valproate for treatment of chronic central pain after spinal cord injury: A double-blind cross-over study. *Paraplegia* 32(8): 565-569.

Edgerton VR, Leon RD, Harkema SJ, Hodgson JA, London N, Reinkensmeyer DJ, Roy RR, Talmadge RJ, Tillakaratne NJ, Timoszyk W, Tobin A. 2001. Retraining the injured spinal cord. *Journal of Physiology* 533(1): 15-22.

Edgerton VR, Tillakaratne NJT, Bigbee AJ, de Leon RD, Roy RR. 2004. Plasticity of the spinal circuitry after injury. *Annual Review of Neuroscience* 27: 145-167.

Eide PK, Stubhaug A, Stenehjem AE, Hodge CJ, Burchiel KJ. 1995. Central dysesthesia pain after traumatic spinal cord injury is dependent on N-methyl-D-aspartate receptor activation. *Neurosurgery* 37(6): 1080-1087.

Elliot S. 2002. Sexual dysfunction and infertility in men with spinal cord disorders. In: Lin V, Cardenas DD, Cutter NC, Frost FS, Hammond MC, Lindblom LB, Perkash I, Waters R, eds. *Spinal Cord Medicine: Principles and Practice*. New York: Demos Medical Publishing. Pp. 349-368.

Escher DJ, Furman S, Solomon N, Schwedel JB. 1966. Transvenous pacing of the phrenic nerves. *American Heart Journal* 72(2): 283-284.

Faden AI, Jacobs TP, Holaday JW. 1981. Thyrotropin-releasing hormone improves neurologic recovery after spinal trauma in cats. *New England Journal of Medicine* 305(18): 1063-1067.

Fehlings MG, Spine Focus Panel. 2001. Summary statement: The use of methylprednisolone in acute spinal cord injury. *Spine* 26(24 Suppl): S55.

Fehlings MG, Sekhon LH, Tator C. 2001. The role and timing of decompression in acute spinal cord injury: What do we know? What should we do? *Spine* 26(24 Suppl): S101-110.

Field-Fote EC. 2001. Combined use of body weight support, functional electric stimulation, and treadmill training to improve walking ability in individuals with chronic incomplete spinal cord injury. *Archives of Physical Medicine and Rehabilitation* 82(6): 818-824.

Finnerup NB, Jensen TS. 2004. Spinal cord injury pain—Mechanisms and treatment. *European Journal of Neurology* 11(2): 73-82.

Finnerup NB, Sindrup SH, Bach FW, Johannesen IL, Jensen TS. 2002. Lamotrigine in spinal cord injury pain: A randomized controlled trial. *Pain* 96(3): 375-383.

Friehs GM, Zerris VA, Ojakangas CL, Fellows MR, Donoghue JP. 2004. Brain-machine and brain-computer interfaces. *Stroke* 35(11 Suppl 1): 2702-2705.

Garfin SR, Shackford SR, Marshall LF, Drummond JC. 1989. Care of the multiply injured patient with cervical spine injury. *Clinical Orthopaedics and Related Research* 239: 19-29.

Garraway SM, Petruska JC, Mendell LM. 2003. BDNF sensitizes the response of lamina II neurons to high threshold primary afferent inputs. *European Journal of Neuroscience* 18(9): 2467-2476.

Geisler FH, Coleman WP, Grieco G, Poonian D, Sygen Study Group. 2001. Recruitment and early treatment in a multicenter study of acute spinal cord injury. *Spine* 26(24 Suppl): S58-67.

Glickman S, Kamm MA. 1996. Bowel dysfunction in spinal-cord-injury patients. *Lancet* 347(9016): 1651-1653.

Graupe D, Kohn KH. 1998. Functional neuromuscular stimulator for short-distance ambulation by certain thoracic-level spinal-cord-injured paraplegics. *Surgical Neurology* 50(3): 202-207.

Hachen HJ. 1974. Emergency transportation in the event of acute spinal cord lesion. *Paraplegia* 12(1): 33-37.

Hains BC, Klein JP, Saab CY, Craner MJ, Black JA, Waxman SG. 2003. Upregulation of sodium channel $Na_v1.3$ and functional involvement in neuronal hyperexcitability associated with central neuropathic pain after spinal cord injury. *Journal of Neuroscience* 23(26): 8881-8892.

Harkema SJ, Hurley SL, Patel UK, Requejo PS, Dobkin BH, Edgerton VR. 1997. Human lumbosacral spinal cord interprets loading during stepping. *Journal of Neurophysiology* 77(2): 797-811.

Herman RM, D'Luzansky SC, Ippolito R. 1992. Intrathecal baclofen suppresses central pain in patients with spinal lesions. A pilot study. *Clinical Journal of Pain* 8(4): 338-345.

Hesse S. 1999. Treadmill training with partial body weight support in hemiparetic patients: Further research needed. *Neurorehabilitation & Neural Repair* 13(3): 179-181.

Hobby J, Taylor PN, Esnouf J. 2001. Restoration of tetraplegic hand function by use of the neurocontrol Freehand system. *Journal of Hand Surgery—British* 26(5): 459-464.

Hulsebosch CE. 2002. Recent advances in pathophysiology and treatment of spinal cord injury. *Advances in Physiology Education* 26(1-4): 238-255.

Hulsebosch CE. 2003. Central sensitization and pain after spinal cord injury. *Seminars in Pain Medicine* 1(3): 159-170.

Hurlbert RJ. 2000. Methylprednisolone for acute spinal cord injury: An inappropriate standard of care. *Journal of Neurosurgery: Spine* 93(1 Suppl): 1-7.

Jackson AB, Wadley V. 1999. A multicenter study of women's self-reported reproductive health after spinal cord injury. *Archives of Physical Medicine and Rehabilitation* 80(11): 1420-1428.

Kaplan SA, Chancellor MB, Blaivas JG. 1991. Bladder and sphincter behavior in patients with spinal cord lesions. *Journal of Urology* 146(1): 113-117.

Kawasaki Y, Kohno T, Zhuang Z-Y, Brenner GJ, Wang H, Van Der Meer C, Befort K, Woolf CJ, Ji R-R. 2004. Ionotropic and metabotropic receptors, protein kinase A, protein kinase C, and Src contribute to C-fiber-induced ERK activation and cAMP response element-binding protein phosphorylation in dorsal horn neurons, leading to central sensitization. *Journal of Neuroscience* 24(38): 8310-8321.

Keirn ZA, Aunon JI. 1990. A new mode of communication between man and his surroundings. *IEEE Transactions on Biomedical Engineering* 37(12): 1209-1214.

Kennedy P, Rogers BA. 2000. Anxiety and depression after spinal cord injury: A longitudinal analysis. *Archives of Physical Medicine and Rehabilitation* 81(7): 932-937.

Kerr BJ, Bradbury EJ, Bennett DL, Trivedi PM, Dassan P, French J, Shelton DB, McMahon SB, Thompson SW. 1999. Brain-derived neurotrophic factor modulates nociceptive sensory inputs and NMDA-evoked responses in the rat spinal cord. *Journal of Neuroscience* 19(12): 5138-5148.

Kirk PM, King RB, Temple R, Bourjaily J, Thomas P. 1997. Long-term follow-up of bowel management after spinal cord injury. *SCI Nursing* 14(2): 56-63.

Kirshblum S. 1999. Treatment alternatives for spinal cord injury related spasticity. *Journal of Spinal Cord Medicine* 22(3): 199-217.

Kirshblum S. 2004. New rehabilitation interventions in spinal cord injury. *Journal of Spinal Cord Medicine* 27(4): 342-350.

Klose KJ, Jacobs PL, Broton JG, Guest RS, Needham-Shropshire BM, Lebwohl N, Nash MS, Green BA. 1997. Evaluation of a training program for persons with SCI paraplegia using the Parastep 1 ambulation system. Part 1. Ambulation performance and anthropometric measures. *Archives of Physical Medicine and Rehabilitation* 78(8): 789-793.

Loubser PG, Donovan WH. 1991. Diagnostic spinal anaesthesia in chronic spinal cord injury pain. *Paraplegia* 29(1): 25-36.

Mao J, Price DD, Mayer DJ. 1995. Mechanisms of hyperalgesia and morphine tolerance: A current view of their possible interactions. *Pain* 62(3): 259-274.

McDonald JW, Becker D. 2003. Spinal cord injury: Promising interventions and realistic goals. *American Journal of Physical Medicine and Rehabilitation* 82(10 Suppl): S38-49.

Mirza SK, Chapman JR. 2001. Principles of management of spine injury. In: Rockwood CA, Green DP, Heckman JD, Bucholz RW, eds. *Rockwood and Green's Fractures in Adults*. 5th ed. Philadelphia: Lippincott Williams & Wilkins. Pp. 1295-1324.

NIH (National Institutes of Health). 2004. *Clinical Trials*. [Online]. Available: http://www.clinicaltrials.gov/ [accessed August 18, 2004].

Onders RP, Aiyar H, Mortimer JT. 2004. Characterization of the human diaphragm muscle with respect to the phrenic nerve motor points for diaphragmatic pacing. *American Surgeon* 70(3): 241-247.

Peckham PH, Keith MW, Kilgore KL, Grill JH, Wuolle KS, Thrope GB, Gorman P, Hobby J, Mulcahey MJ, Carroll S, Hentz VR, Wiegner A, Implantable Neuroprosthesis Research Group. 2001. Efficacy of an implanted neuroprosthesis for restoring hand grasp in tetraplegia: A multicenter study. *Archives of Physical Medicine and Rehabilitation* 82(10): 1380-1388.

Peckham PH, Kilgore KL, Keith MW, Bryden AM, Bhadra N, Montague FW. 2002. An advanced neuroprosthesis for restoration of hand and upper arm control using an implantable controller. *Journal of Hand Surgery* 27(2): 265-276.

Pitts LH, Ross A, Chase GA, Faden AI. 1995. Treatment with thyrotropin-releasing hormone (TRH) in patients with traumatic spinal cord injuries. *Journal of Neurotrauma* 12(3): 235-243.

Polacek L, Wuolle KS, Van Doren CL, Bryden AM, Peckham HP, Keith MW, Kilgore KL, Grill JH. 1999. Satisfaction with and usage of a hand neuroprosthesis. *Archives of Physical Medicine and Rehabilitation* 80(2): 206-213.

Postans NJ, Hasler JP, Granat MH, Maxwell DJ. 2004. Functional electric stimulation to augment partial weight-bearing supported treadmill training for patients with acute incomplete spinal cord injury: A pilot study. *Archives of Physical Medicine and Rehabilitation* 85(4): 604-610.

Protas EJ, Holmes SA, Qureshy H, Johnson A, Lee D, Sherwood AM. 2001. Supported treadmill ambulation training after spinal cord injury: A pilot study. *Archives of Physical Medicine and Rehabilitation* 82(6): 825-831.

PVA (Paralyzed Veterans of America). 1998. *Consortium for Spinal Cord Medicine—Depression Following Spinal Cord Injury: A Clinical Practice Guideline for Primary Care Physicians.* Washington, DC: Paralyzed Veterans of America.

PVA. 2000. *Consortium for Spinal Cord Medicine—Pressure Ulcer Prevention and Treatment Following Spinal Cord Injury: A Clinical Practice Guideline for Healthcare Professionals.* Washington, DC: Paralyzed Veterans of America.

PVA. 2001. *Consortium for Spinal Cord Medicine—Acute Management of Autonomic Dysreflexia: Individuals with Spinal Cord Injury Presenting to Health-Care Facilities.* Washington, DC: Paralyzed Veterans of America.

PVA. 2002. *Consortium for Spinal Cord Medicine*. [Online]. Available: http://www.pva.org/res/cpg/devgde.htm [accessed January 11, 2004].

Siddall PJ, Molloy AR, Walker S, Mather LE, Rutkowski SB, Cousins MJ. 2000. The efficacy of intrathecal morphine and clonidine in the treatment of pain after spinal cord injury. *Anesthesia & Analgesia* 91(6): 1493-1498.

Sidi AA, Becher EF, Reddy PK, Dykstra DD. 1990. Augmentation enterocystoplasty for the management of voiding dysfunction in spinal cord injury patients. *Journal of Urology* 143(1): 83-85.

Silber JS, Vaccaro AR. 2001. Summary statement: The role and timing of decompression in acute spinal cord injury: Evidence-based guidelines. *Spine* 26(24 Suppl): S110.

Sipski ML, Rosen RC, Alexander CJ, Hamer RM. 2000. Sildenafil effects on sexual and cardiovascular responses in women with spinal cord injury. *Urology* 55(6): 812-815.

Sonksen J, Sommer P, Biering-Sorensen F, Ziebe S, Lindhard A, Loft A, Andersen AN, Kristensen JK. 1997. Pregnancy after assisted ejaculation procedures in men with spinal cord injury. *Archives of Physical Medicine and Rehabilitation* 78(10): 1059-1061.

Spinal Cord Medicine Consortium. 1998. Clinical practice guidelines: Neurogenic bowel management in adults with spinal cord injury. *Journal of Spinal Cord Medicine* 21(3): 248-293.

Tai Q, Kirshblum S, Chen B, Millis S, Johnston M, DeLisa JA. 2002. Gabapentin in the treatment of neuropathic pain after spinal cord injury: A prospective, randomized, double-blind, crossover trial. *Journal of Spinal Cord Medicine* 25(2): 100-105.

Tator CH, Fehlings MG. 1991. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. *Journal of Neurosurgery* 75(1): 15-26.

Tator CH, Duncan EG, Edmonds VE, Lapczak LI, Andrews DF. 1993. Changes in epidemiology of acute spinal cord injury from 1947 to 1981. *Surgical Neurology* 40(3): 207-215.

Taylor DM, Tillery SIH, Schwartz AB. 2002. Direct cortical control of 3D neuroprosthetic devices. *Science* 296(5574): 1829-1832.

Vierck CJ Jr, Siddall P, Yezierski RP. 2000. Pain following spinal cord injury: Animal models and mechanistic studies. *Pain* 89(1): 1-5.

von Heijne M, Hao JX, Sollevi A, Xu XJ, Wiesenfeld-Hallin Z. 2000. Marked enhancement of anti-allodynic effect by combined intrathecal administration of the adenosine A1-receptor agonist R-phenylisopropyladenosine and morphine in a rat model of central pain. *Acta Anaesthesiologica Scandinavica* 44(6): 665-671.

Wernig A, Muller S, Nanassy A, Cagol E. 1995. Laufband therapy based on "rules of spinal locomotion" is effective in spinal cord injured persons. *European Journal of Neuroscience* 7(4): 823-829.

Wernig A, Nanassy A, Muller S. 1998. Maintenance of locomotor abilities following Laufband (treadmill) therapy in para- and tetraplegic persons: Follow-up studies. *Spinal Cord* 36(11): 744-749.

Wiesenfeld-Hallin Z, Aldskogius H, Grant G, Hao JX, Hokfelt T, Xu XJ. 1997. Central inhibitory dysfunctions: Mechanisms and clinical implications. *Behavioral and Brain Sciences* 20(3): 420-425.

Wirz M, Colombo G, Dietz V. 2001. Long term effects of locomotor training in spinal humans. *Journal of Neurology, Neurosurgery & Psychiatry* 71(1): 93-96.

Wolpaw JR, McFarland DJ. 2004. Control of a two-dimensional movement signal by a noninvasive brain-computer interface in humans. *Proceedings of the National Academy of Sciences (U.S.A.)* 101(51): 17849-17854.

Yang CH, Chuang LY, Yang CH, Luo CH. 2003. Morse code application for wireless environmental control systems for severely disabled individuals. *IEEE Transactions on Neural Systems & Rehabilitation Engineering* 11(4): 463-469.

Yarkony GM, Heinemann AW. 1995. Pressure ulcers. In: Stover SL, DeLisa JA, Whiteneck GG, eds. *Spinal Cord Injury: Clinical Outcomes from the Model Systems*. Gaithersburg, MD: Aspen Publications.

Yezierski RP. 2000. Pain following spinal cord injury: Pathophysiology and central mechanisms. *Progress in Brain Research* 129: 429-449.

Yezierski RP. 2000. Pain following spinal cord injury: Pathophysiology and central mechanisms. *Progress in Brain Research* 129: 429-449.

Zehnder Y, Risi S, Michel D, Knecht H, Perrelet R, Kraenzlin M, Zach GA, Lippuner KJ. 2004. Prevention of bone loss in paraplegics over 2 years with alendronate. *Journal of Bone and Mineral Research* 19(7): 1067-1074.

Spinal Cord Injuries: An Overview

1. Because the spinal cord is encased in the protective armor of the vertebrae, investigation of the site of the injury or the effects of potential therapies has required the development of a diverse set of research tools. In the past 40 years the rapid progress in the technologies available to perform experiments has largely been responsible for the great strides that have been made in understanding the basic principles of _____.
    - anatomy
    - genetics
    - neuroscience
    - None of the above
2. Recent advances in imaging techniques and methods for investigation of the actions of genes have advanced the understanding of spinal cord injuries even further. They also provide researchers with the tools that they need to examine changes in the spinal cord at the molecular and structural levels, for example, improving knowledge of the _____ that serve as barriers to neuronal regeneration.
    - inhibitory conditions
    - autonomic dysreflexias
    - pathological changes
    - None of the above
3. In 1978, the _____ was developed by researchers to simulate the continual pressure and displacement of the spinal cord common in spinal cord injuries, which is not reproduced in contusion injuries. This procedure has provided researchers with a great deal of information about the pathophysiology of the spinal cord during the acute stages of the injury; the timing, necessity, and effectiveness of releasing the pressure from the spinal cord; and potential therapies.
    - decompressioin technique
    - clip compression technique
    - axonal elongation technique
    - None of the above
4. Techniques have been developed that allow researchers to isolate and grow populations of neurons to investigate the effects of specific proteins and molecules on neuronal injury and repair. Neurons can be grown in isolation or with glial cells such as oligodendrocytes or Schwann cells to study the processes of axonal outgrowth and myelination. Investigators use molecular biology-based techniques, such as DNA or protein analysis, that can be used to easily visualize or analyze outcomes.
    - True
    - False

5. Animal models allow in-depth investigation of the anatomical and molecular changes that occur in response to a spinal cord injury at a level of detail that would not be possible or ethical in studies with humans. These insights are critical for the design and interpretation of the results of studies with humans. Without the knowledge gleaned from studies with animals, the spinal cord would remain the equivalent of a black box and therapies aimed at restoring function would be limited.

    - True
    - False

6. It is important that researchers use standardized animal models and that they use them consistently. In _____, The National Institute of Neurological Disorders and Stroke (NINDS), in recognition of the need to train researchers who work on spinal cord injuries, collaborated with Ohio State University to design a course that emphasizes competency in the technical approaches required for standard animal care and treatment and experimental design.

    - 1968
    - 1984
    - 1994
    - 2004

7. Because of the variations in the severity and the nature of the outcomes that individuals with spinal cord injuries experience, it is often difficult for health care professionals and researchers to assess the success of a particular intervention. Similarly, it is difficult for preclinical researchers to consistently assess progress in laboratory animal experiments and to determine the amount of progress, if any, that results from _____.

    - natural recovery
    - drug therapy
    - surgical intervention
    - All of the above

8. Clinicians have available more than _____ assessment tests and surveys that they can use to examine individuals with spinal cord injuries, including the American Spinal Injury Association (ASIA) scale and measures that assess all the major complications associated with spinal cord injuries. Each of these measures assesses a specific aspect of recovery from spinal cord injury or evaluates the individual's quality of life and is not designed to examine all the major complications that arise because of a spinal cord injury.

    - 10
    - 30
    - 67
    - 100

9. The expression profile of a biomarker, especially proteins, could provide clinicians with information that aids in establishment of a diagnosis and a prognosis of a patient's injury. For instance, the progression of multiple sclerosis (MS) can be determined by examining the levels of a major myelin component, myelin basic protein, whose concentration increases in the cerebrospinal fluid in response to a demyelinating episode.

    - True
    - False

10. Of the imaging technologies for the detection of abscesses or other masses near the spinal cord and is to monitor patients with chronic compression injuries, _____ is superior technology.

    - PET
    - CT
    - MRI
    - None of the above

11. _____ scan technology is being developed to inform clinicians about whether drugs can bind to the appropriate targets. For example, clinicians are using these scans to determine if treatments are effective by looking at the uptake of glucose, which tumors need to nourish their growth. These effects can be observed before structural changes in the tumor can be detected.

    - MRI
    - CT
    - PET
    - None of the above

12. In an attempt to examine the activities of specific neuronal circuits, imaging markers that mimic neurotransmitters and receptors that are nonradioactive are being created, including the iron analog annexin V, the fluorescent marker Cy5.5, and markers that do not become active until they reach their target. Future modification and adaptation of these technologies could be used to examine specific stages of regeneration, including those designed to detect _____.

    - neurite outgrowth
    - oligodendrocyte myelination
    - immunological response
    - All of the above

13. Beginning at the accident scene, immobilization of the spine prevents or reduces the severity of a spinal cord injury, and advances in emergency response have improved the medical care for other urgent and life-threatening problems often associated with spinal cord injuries, such as _____.

    - significant blood loss
    - blocked respiratory pathways
    - major head or body system trauma
    - All of the above

14. Decompression of the spinal cord, if it is performed during the appropriate time window, may provide a benefit to individuals with spinal cord injuries. In many patients, surgery is performed soon after the injury to remove _____ that compress the spinal cord. The goal is to alleviate pressure and to improve the circulation of blood and cerebrospinal fluid, particularly for those with central cervical spinal cord injuries.

    - the tissue debris
    - bone
    - fluid
    - All of the above

15. As a result of recent advances in science and technology, individuals with a spinal cord injury have _____.

    - improved survival rates
    - increased opportunities for independent living
    - longer life spans
    - All of the above

16. Chronic pain, one of the most common sequelae of spinal cord injuries, is not adequately controlled by currently available treatments. Inadequately controlled pain erodes _____, but also can lead to depression and, most tragically, suicide. Some clinicians have been slow to recognize that chronic pain is real, has serious consequences, and should not be dismissed as grounds for psychiatric referral.

    - quality of life
    - functioning
    - mood
    - All of the above

17. Primary sensory neurons (also known as primary afferents) in the spinal cord convey pain information from the primary sensory neuron to the brain. After a spinal cord injury, these neurons become hyperexcitable; namely, they fire more readily than before the injury.

    - True
    - False

18. Neuropathic pain results from direct damage to neural tissue, whereas nociceptive pain is caused by damage to nonneural tissues (_____). Nociceptive pain is what most healthy people are familiar with, and it is more treatable and controllable with standard pain therapies like anti-inflammatory agents and analgesics. Neuropathic pain is often treated with antidepressants and anticonvulsants, but their efficacies specifically for the treatment of spinal cord injury-associated pain are weak.

    - bone
    - muscles
    - ligaments
    - All of the above

19. Spasticity refers to the debilitating muscle spasms and other types of increased muscle tone that occur after a spinal cord injury. Spasticity is similar to pain in that both are highly common after spinal cord injuries and have multiple possible mechanisms that might account for their onset. The key difference between them is that spasticity results from the heightened activity of reflex pathways (proprioceptive sensory neurons and motor neurons), whereas pain reflects the heightened activities of pain pathways.

    - True
    - False

20. Thromboembolism is a potentially life-threatening condition frequently encountered in the early weeks after a spinal cord injury. Deep vein thromboses (DVTs) are blood clots that form deep within the veins, usually in the legs and thighs, and result from slowed or halted blood flow (venous stasis) in immobilized individuals with spinal cord injuries. The most feared complication of DVT is_____, which can bring sudden death.

    - autonomic dysreflexia
    - pulmonary embolism
    - autonomic hyperreflexia
    - None of the above