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Priorities for Research in Spinal Cord Injury

Research on spinal cord injuries aims to prevent, minimize, or repair neural tissue damage, reduce the sequelae of injury, and improve function. While animals have been used by a number of investigators, other avenues of research have demonstrated great potential. A few particularly promising research modalities are described below.

Clinical Therapies. At the Banner Good Samaritan Medical Center in Phoenix, Arizona, Dr. Richard Herman has shown that, through a process of retraining the neuromuscular circuitry, some partially paralyzed patients are able to walk again.[1,2] This research combines weight-bearing therapy on a treadmill and electrical stimulation of the spinal cord by a device surgically implanted into the epidural area (between the spinal cord and spine). Partial weight-bearing therapy "trains" the body in a regular gait and reduces spasticity of the muscles, while the electrical stimulation device reduces the energetic cost of walking. The training periods and treatment parameters must be individualized, taking into account each patient's clinical status. While still in its early stages, this combination of therapies appears promising. Herman et al.[1] first reported the progress of a wheelchair-dependent individual who had sub-functional motor strength in lower limb muscles and some large fiber sensation. The patient was classified as being at an ASIA C [on a scale of A (complete injury) to E (normal)] level of function, according to the nomenclature of the American Spinal Injury Association. After several months of training, this individual was able to walk for at least 250 meters, and the patient's ability to perform independent tasks was increased substantially. A second patient had similar results, doubling his walking speed and covering distances of at least 325 meters.[2]

Patients with a spinal cord injury are often at risk for aliments that can result from activity restriction, such as bone and muscle loss, weight gain, cardiovascular disease, diabetes mellitus, and circulatory dysfunction.[3-5] A number of researchers are working to develop training programs and devices to counteract such conditions.

Scientists in Miami are conducting a number of studies with patients with varying levels of injury and fitness. Several studies have found that training programs emphasizing upper body exercises, such as neuromuscular stimulation-assisted arm crank ergometry (ACE)[6] or circuit resistance training ACE,[7,8] can increase patients' physical fitness levels and upper body strength and lower patients' plasma triglycerides and cholesterol, lessening cardiovascular risk. One study found that neuromuscular stimulation allowed patients to increase arm strength above and beyond standard ergometry.[6]

Patients with incomplete spinal injuries can also benefit from assisted lower body exercise. Functional electric stimulation (FES), body weight support (BWS), and treadmill training are training strategies being tested for improvements in walking speed, leg strength, intralimb coordination, and cardiovascular benefits.[9-11] University of Miami clinicians developed the Parastep 1 ambulation system, which has since been shown to increase resting lower extremity blood flow and alleviate vascular occlusion in paraplegic patients,[5] increase patients' abilities to complete other exercise programs,[12] allow patients with complete thoracic spinal injuries to ambulate short distances, and over time increased lower body muscle tissue.[13] The system consists of an electronic stimulator and a modified walking frame with switches controlled by the operator's fingers, allowing the user to control the stimulation parameters and activate the stepping. Use of Parastep 1 was also shown to increase a patient's sense of physical self and decrease depression scores on standard tests.[14]

Those with chronic spinal cord injuries often report pain that is difficult to characterize or treat. Clinicians in Miami are working to develop comprehensive physical and verbal evaluation tools to both classify patients' pain sensations and determine the best treatments. Widerstrom-Noga et al.[15] were able to identify common clinical patterns of pain, grouping survey respondents' responses into three groups. The groupings will make potential treatments easier to develop, classify, and test clinically. Widerstrom-Noga and Turk[16] found that respondents who sought "physical therapies" (massage, etc.) to control pain reported alleviation of symptoms more often than those who were taking prescription medications. In fact, those taking medication reported more intense pain symptoms. Muscle spasticity is another common problem for which clinicians are searching for answers. While currently used medications like botox or tizanidine continue to

be evaluated,[17] University of Miami researchers are collaborating with other hospitals to test anecdotal evidence that vibratory stimulation can alleviate muscle spasticity. A case study series done in the United Kingdom highlights the importance of considering psychological factors: all four patients reported improvements in somatic complaints—including unexplained pain, spasm, pressure sores, constipation, and other minor physical problems—with resolutions in psychosocial issues.[18]

Efforts to improve the quality of life for SCI patients also include studies to determine ways to improve sexual dysfunction. Scientists in the UK have found that sildenafil citrate (Viagra) can improve sexual function in those with incomplete and complete injuries.[19] University of Miami researchers investigated genital, subjective, and autonomic responses to visual and manual sexual stimuli, in order to better characterize the sexual potential of women with spinal injuries.[20]

According to Cardenas et al.,[21] patients with paraplegia are most likely to be rehospitalized after their injury for pressure ulcers. Pressure ulcers, or sores, in the skin are a result of long periods of inactivity of certain parts of the body; they can be particularly insidious because the patient cannot sense the ulcer and so has no idea it exists.[22] Without treatment, the ulcer can injure surrounding skin and muscle and result in fatal systemic infections. A number of strategies for early detection of pressure sores have been tested, including self-inspection[23] and temperature difference measurement.[24] Both interventions were able to detect developing pressure sores earlier than controls. Vitamin supplementation to prevent pressure ulcers and improve overall health is being investigated in Texas.[25] For some patients, carbon fiber implants placed at past or future pressure sore sites help augment skin tissue and are well tolerated.[26]

Quality of life for spinal cord injury patients can also be affected by difficulty with urinary and colonic evacuation. Constipation, incontinence, and impaction can lead to significant distress and affect a patient's ability to overcome other health issues they may face.[27] Korsten et al.[27] found that compared to able-bodied controls, colonic pressure activity for study volunteers was depressed during sleep. Authors also found that an abdominal belt with electrodes implanted into patients' abdominal wall musculature improved time to first stool and total bowel care time versus controls. A multi-center trial coordinated in Cleveland[28] evaluated the efficacy and safety

of a neuroprosthesis implanted in patients with complete suprasacral SCIs. This externally controlled device stimulated the sacral nerves, improving overall evacuation continence and decreasing drug use, urinary tract infections, catheter use, and time spent with bowel management. Schurch et al.,[29] however, found no improvement in five patients after sacral nerve stimulation for five days, suggesting that treatments must be individualized to be effective.

Neural and Stem Cell Culture. *In vitro* research using neural and stem cell cultures or whole spinal cord culture, while still in its infancy, can provide information about the efficacy and toxicity of novel therapies as well about the pathology of tissue injury. For example, a group of London researchers found that damage to spinal cord neurons in cell culture was prevented by inhibiting a specific nuclear enzyme apparently involved in peroxynitrite-induced cell damage after injury.[30] A procedure to create human motoneuron cell lines in culture was developed in 2000.[31] Researchers found the cloned neurons displayed normal neuronal processes, including immunoreactivity and action potential firing, and researchers were also able to coax clonal precursor cells into multiple types of spinal cord neurons.[31] Genetic microarrays, used extensively in clinical cancer research, can reveal genetic changes in neural cells at specific time points after injury or during a course of treatment.

Flow cytometry helped Basu et al.[32] characterize the degree of leukocytospermia in men with SCI by comparing patients' semen samples to those of men without SCI. They found that, when compared to men without SCI, the semen of men with SCI showed increased numbers of activated, mature granulocytes and lymphocytes, most of which were T cells. These immunologically active cells may provide an explanation for the abnormally low sperm motility often seen in men with SCI.

Imaging and Electrodiagnostic Studies. Non-invasive imaging techniques, such as PET, SPECT, and fMRI, as well as more invasive cerebrospinal fluid studies, can be used to visualize neural pathology at various time points after injury and monitor the effects of experimental therapies. Electromyography and auditory, visual, or somatosensory evoked potentials measure the extent of spinal cord injuries and have demonstrated that reconnection and regeneration of nerves in humans is possible.[33,34] Further, by studying neuromuscular connections in both

uninjured and spinal cord-injured patients, University of Miami School of Medicine scientists have found mechanisms in the spinal cord that are responsible for coordinating opposing muscle movements.[35]

Evidence-Driven Injury Modeling. In Miami, researchers are collaborating on the Human Spinal Cord Injury Model project. This project is studying spinal cord injured patients, both pre- and post-mortem, to build a more realistic understanding of human spinal cord injury. Post-mortem spinal cord tissue can be compared to MRIs to determine histopathological changes in cells and tissues.[36,37] By correlating neurological function, neurophysiological status, imaging studies, and histopathology, researchers can design more rational therapies to help improve the quality of life of injured patients, prevent further damage after acute injury, and restore function in chronic victims.

Educating Future Scientists. The instruction of scientists interested in spinal cord injury research should be as broad as the methods and programs delineated here. There are several ways in which a course that prepares students for the spinal injury research field could be conducted. A particularly apt program could involve shadowing a number of researchers from different disciplines as they conduct their research. While we do not recommend continued reliance on experimental animal models, when techniques using animals are perceived as necessary, animal care, surgical techniques, and methodologies can be taught without using additional animals. A host of non-animal learning tools are available. Video films showing animal care principles, microsurgical techniques, and transplantation procedures can offer a valuable learning experience, and a number of comprehensive models are also available. One example is the PVC rat model, available from the Microsurgical Developments Foundation, that allows students to practice 25 different surgical techniques, and includes a computer-based supplement to teach students how to handle anesthetic care and emergency situations that may arise. The University of Arkansas has developed a cadaver head model, complete with blood flow capabilities, for teaching microsurgery to aspiring neurosurgeons. Information on these models, as well as suggested MedLine search terms to find published research, can be found on the Web at http://www.vetmed.ucdavis.edu/Animal_Alternatives/lab_an_protocol.htm**.**

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