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ORIGINAL ARTICLE

Autonomic function and spinal cord injury: are we at a crossroads?

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Study design: This presentation was originally given as 'The Sullivan Lecture' at the International Spinal Cord Society Meeting in Reykjavik, Iceland on 30 June 2007.
Setting: Named lecture at an international meeting.
Results: The development of the autonomic component standards of the International Standards for the Neurologic Classification is described. Research pertaining to sexual responses after spinal cord injury is presented as a model for ways the impact of varying patterns of spinal cord injuries on other organ systems could be studied. Future challenges and opportunities facing the field of spinal cord injury are also discussed.
Conclusion: The addition of a standard form of communicating the impact of spinal cord injury on autonomic responses should improve clinical care and research related to spinal cord injury. Using the knowledge that can be obtained from detailed assessment of persons with spinal cord injuries will help provide increased understanding of neuroanatomy in the able-bodied persons. This added value from studying persons with spinal cord injuries provides further justification for research in this area.
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It has been 25 years[1] since the initial development of the International Standards for the Neurologic Classification of Spinal Cord Injury (ISNCSCI). In this time the ISNCSCI has evolved to allow description of the impact of specific spinal cord injuries (SCIs) on motor and sensory functions. Although originally designed for clinical use, the ISNCSCI has also been used in retrospective research[2] and in clinical trials[3,4] as a means of assessment of the remaining neurologic abilities of persons with SCIs.

Recently, the importance of adding an accurate description of remaining autonomic function to the ISNCSCI has been increasingly acknowledged. Over the past 2 years an international panel of experts has collaborated to draft the international standards to document remaining autonomic function after SCI (Figure 1). These standards have been available for review at the American Spinal Injury Association (ASIA) and International Spinal Cord Society (ISCoS) websites and it is believed that the successful completion, validation and implementation of these standards will provide a common terminology to discuss the autonomic effects of SCI. The original draft of the standards suggests the institution of an anatomic diagnosis for SCI including supraconal, conal and cauda equina as options in addition to providing a detailed format for the description of remaining bladder, bowel, sexual, cardiovascular, sudomotor and thermoregulatory functions after SCI. It is anticipated that online feedback will be accepted with respect to the standards through the summer of 2007 at which point the committee will evaluate the recommendations and finalize the first draft of the standards so that they can be submitted for publication in 2008.

The ISNCSCI has now been through five revisions. This first draft of the autonomic component to the standards is an important addition to our ability to communicate and educate ourselves and others about the impact of specific SCIs on specific autonomic responses. However, we must realize that this initiative is a start of a long process that should ultimately provide us with an improved understanding of the neurologic effects of SCIs on specific autonomic responses. Moreover, once we have a better understanding of the neurologic effects of SCIs on specific autonomic responses we will be able to develop more targeted treatments and outcome measures to assess the effects of treatments.

Once the standards are agreed upon and published, we will need to develop a specific plan for training regarding the standards. At present ASIA and ISCoS are developing an online training program for the ISNCSCI. Likewise, there has

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Figure 1 Participants in Original Autonomic Standards International Committee.

been agreement among the boards of the two organizations to develop an online training program for the autonomic standards. It will be important to ensure widespread dissemination and use of the autonomic standards for both clinical care and research related to persons with SCIs. This will also serve a secondary benefit of improving general awareness of the variability of specific autonomic responses and their relationship to specific SCIs.

Another aspect of the development of autonomic standards is reliability and validity testing. This will undoubtedly take years and will need to be performed internationally. Moreover, it is likely that reliability and validity testing will take place concomitantly with the development of second and even third revisions of the autonomic component of the ISNCSCI. Under ideal circumstances, reliability testing would be performed before dissemination of information regarding these standards; however, in this case the immediate need for common terminology supersedes the need for ideal sequence of procedures.

Perhaps the most important long-term goal of the development of these standards will be the ability to map out how specific patterns of autonomic function relate to the specific patterns of SCI. It is my belief that once we begin systematically classifying the impact of specific injuries on autonomic function we will notice patterns of alteration of autonomic responses and how they correlate with remaining neurologic function. For instance, we may be able to perform detailed assessments of patients with specific injury patterns and determine whether a specific injury pattern correlates with hypo- and hyperhidrosis. We are also optimistic that this data will ultimately allow us to appropriately select subjects for targeted treatments for specific aspects of autonomic function. For example, in this case, a drug that is targeting improved sexual responses might not work with certain injury patterns and might be expected to work better with others. Hence, a trial would be limited to those subjects who are likely to respond to the treatment. Another long-term goal of development of these standards is to assist in determination of whether therapies targeting SCI as a whole have an impact on autonomic responses. For instance, researchers studying a drug targeting neurologic recovery would be able to better analyze the effects of their drug on a person's bowel program because some subjects would be documented to have no neurologic control of bowel function and others might start out with partial control.

A specific example of how this has already been done is to look at the model to study the neurologic control of sexual response after SCI in humans that was developed in my laboratory.[5,6] The principle behind the development of this model was that to be able to understand the impact of SCIs on sexual responses we would need to eliminate as many variables as possible. Thus, the subject would need to be tested without a partner and in a laboratory. Moreover, the neurologic assessment of subjects and the outcomes monitored would need to be as specific as possible. Thus, with regard to sexual responses we chose to study psychogenic arousal, reflex arousal and orgasm via separate protocols. Additionally, we used the ASIA assessment to document neurologic status along with analysis of blood pressure, heart rate, psychogenic sexual arousal and vaginal photoplethysmography[7] or penile plethysmography.[8]

I hypothesized that as determined by the ISNCSCI, the degree of remaining sensation in the T11–L2 dermatomes would be predictive of the ability to achieve psychogenic genital arousal.[9] The genesis for this hypothesis involved work in a number of different areas. Ditunno *et al*.[10] hypothesized that because of the proximity of the spinothalamic tracts and the corticospinal tracts you could correlate preserved pinprick sensation with recovery of motor function post-SCI, thus describing how the arrangement of fibers in a cross section of the spinal cord could be utilized to predict neurologic recovery. Comarr[11] indicated that one could determine the potential for psychogenic erection based upon the ability to perceive pinprick sensation in the penile, scrotal and perianal area. Thus, correlating degree of injury with preservation of specific aspects of sexual responses and studies in able-bodied women documented that the sympathetic nervous system has an impact upon psychogenic genital arousal.[12–14] Based on the combined knowledge of these researchers, I hypothesized that by studying the degree of incompleteness in T11–L2 there would be able to find a correlation of preserved sensation with psychogenic lubrication. This is because there would likely be preservation of the sympathetic cell bodies contributing to the hypogastric nerve if other sensory function at this level of the spinal cord was mostly preserved.

To test this hypothesis, we have conducted numerous assessments of sexual responsiveness in the laboratory.[5,6,9,15–18] A laboratory-based 78 min protocol with baseline periods alternating with audiovisual erotic stimulation and audiovisual combined with manual erotic stimulation was the basis for most of the studies related to arousal. In summary, one can predict the potential for psychogenic genital responsiveness based upon the preservation of the ability to perceive combined pinprick and light touch sensation in the T11–L2 dermatomes. With regard to

determining the impact of various patterns of injury on the ability to achieve orgasm, a laboratory-based 75 min protocol was utilized whereby individuals stimulated themselves to orgasm via any means they chose. Results revealed the capacity for orgasm persists in people with SCIs provided they have intact bulbocavernosus and or anal wink reflexes and/or some sort of preserved neurologic function in the S2–5 area.[9,18] This information is currently being utilized in an ongoing study of women with multiple sclerosis to determine if similar impacts of neurologic lesions on sexual responses will be observed in this population.

For research to be considered valid by multiple audiences it is important to demonstrate similar findings in both human and animal models. Thus, I was fortunate to develop a collaboration with a basic scientist, Dr Lesley Marson to perform reverse translational research from humans to animals. Dr Marson has noted similar findings to those in my laboratory in humans with SCIs in a rodent model. To assess the impact of injury on arousal, nerve cuts of the hypogastric, pelvic and pudendal sensory nerves were performed in spinal transected female rats and vaginal blood flow responses were monitored.[19] With respect to orgasm, the urethrogenital reflex observed in spinalized rodents is considered the most valid animal model of human orgasm,[20] and further testing of the urethrogenital reflex in rats with selected nerve injuries is also ongoing in Dr Marson's laboratory. While, the original purpose of our research program has been to assess the impact of injury on sexual responses, it has been refreshing to see that these findings may prove useful in deciphering the neurologic physiology of sexual response in the able-bodied.[21] It is my belief that this reverse translational research will also be useful as findings from persons with SCIs are utilized to understand autonomic neuroanatomy and neurophysiology in the able-bodied.

It is important to understand the impact of SCIs on sexual responses and sexuality; however, there are many more aspects of autonomic nervous system control and neuroanatomy that require assessment after SCI. Neurogenic bladder, bowel, cardiovascular, sudomotor and respiratory function changes need to be understood. Currently, we cannot adequately describe when individuals with incomplete SCIs have retention of partial control of bowel and bladder function. If we develop an appropriate means to communicate this information it may be possible to better predict these functions based upon the neurologic injuries that persons sustain. Once we have this information it is also theoretically possible that we will be able to develop more targeted treatments for recovery of neurologic control of these responses. Currently, it is difficult to distinguish between pathology at the organ level that leads to a lack of voluntary control of organ system functions (for example, urinary tract infection leading to incontinence) and neurogenic causes resulting in a lack of voluntary control. At present we are also unable to determine whether there exists a link between pattern of injury and components of dysreflexia. It is possible that through detailed study of the impact of injury on autonomic function we would be able to determine an association between the occurrence of dysreflexia, altered sudomotor and thermoregulatory function, and pattern of injury. Further, detailed study of correlations between remaining autonomic function and somatic neurologic function will be beneficial to determine whether other relationships exist. Moreover, we may find information here that will be enlightening with regard to these issues and autonomic functioning in the able-bodied.

The twenty-first century will bring many changes to the world. It is hypothesized that climate change will make obtaining shelter, food and water more difficult for many able-bodied people around the world.[22] As the world begins to realize the need for alternative energy sources as a means to battle climate change, it will be important that professionals working in the field of SCI constantly refine our work and make sure that we are judiciously using our resources. It is possible that in the future the basic funding available to address the clinical concerns of persons with SCIs will become limited, particularly if developing countries need to develop a 'survival of the fittest' policy. Moreover, funds available for research for SCI may also become limited in developed countries.

Despite the negative possibilities that loom over the horizon with regard to climate change, there are significant positive developments in the field of SCI that we can capitalize on, to assure our patients continue receive optimal care. In this regard the realization that autonomic function is as important as general motor and sensory function to persons with SCIs is important. As we have shown with neurogenic sexual function, there is also much to be learned about able-bodied neurophysiology from the study of SCI and we can use this caveat to help justify our studies to funding agencies.

Additionally, the field of SCI and our ability to create successful collaborations can be a model to other areas of medicine. Recently ASIA, ISCOS, the International Campaign for the Cures of Paralysis and a number of federal and private organizations have agreed to develop the Spinal Cord Outcomes Project Endeavor (SCOPE). The primary goals of SCOPE include improving communication between basic scientists, clinicians, researchers, academics, industry and government partners so that the work we are doing in SCI is targeted, does not waste resources and remains timely as we pursue treatments for SCIs. Our field is setting an example for others that the time is now to pool our resources with regard to research, clinical care and conservation of resources. I believe others will look to follow in our footpaths in the future.

In conclusion, we are at an exciting time with regard to autonomic function and SCI. By performing detailed assessments not only of the neurologic function of persons with SCIs in conjunction with their autonomic function, we will be able to increase our awareness and ability to treat the autonomic consequences of SCIs. We will also be able to use this information to learn more about the impact of injury on physiologic function and to understand autonomic responses in the able-bodied. These actions and others such as the development of SCOPE will help professionals and consumers in the field of SCI as we are seen as a worldwide model of how to work together to maximize our resources

and develop mutually beneficial solutions for persons with SCIs and humanity.

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