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PROGRESS IN BRAIN RESEARCH

Autonomic Dysfunction After Spinal Cord Injury

EDITED BY
L.C. WEAVER
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Dedication

"Spinal cord injury is a ferocious assault on the body that leaves havoc in its wake. Paralysis is certainly part of its legacy, but there are other equally devastating consequences including autonomic dysfunction: compromised cardiovascular, bowel, bladder, and sexual function. Treatments and cures for these losses would greatly improve the quality of life for all of us living with spinal cord injury. I am hopeful that the multi-faceted and collaborative approach to spinal cord repair evidenced by this book and its contributors means that there will be effective therapies for autonomic dysfunction in the not too distant future."

Christopher Reeve, September 30, 2004

Christopher Reeve sent this endorsement to us only 10 days before his death. His passionate advocacy for research that would better the lives of all who have suffered spinal cord injury has affected all of us who work in this field. We dedicate this book to Christopher Reeve and to all, who like him, strive to overcome the tragedy of spinal cord injury. As Canadian editors, we particularly would like to thank and acknowledge the efforts of our advocates, Mr. Rick Hansen and Ms. Barbara Turnbull for their tireless efforts to bring awareness, expertise and funding to the field of spinal cord injury research, in all of its dimensions. Finally, we dedicate this book to everyone who has sustained a spinal cord injury and lives courageously, hoping that the efforts of science will bring timely rewards.

Lynne Weaver and Canio Polosa
on behalf of the contributors,
March 1, 2005

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Foreword

Autonomic dysfunction after spinal cord injury: the perspective of a person with a spinal cord injury.

> "Something's wrong. I'm hot. No, wait, now I'm cold. But why am I sweating? I never sweat. My legs won't stop jumping. Now my hands are in tight fists and my torso is tight as well. Why does my scalp itch? Oh no, the headache is starting. I'm getting dysreflexic. What is causing it? My catheter seems okay, I don't feel any kinks. But why isn't there any urine in the leg bag? Oh no, is the catheter clogged up? The headache is getting worse. It feels like a nail is being hammered into my head. What am I going to do? It's going to get worse. I know it, I know what's going to happen. But I'm all alone. I can't reach anyone to ask for help. How am I going to fix this? I'm going to have to drive myself to the doctor. I'm trying to adjust everything, but it's not working. My head, it hurts so bad. I can't think straight. Everything looks a little bit blurry. It's hard to breathe now, the spasms are so severe. I feel like I'm going to throw up. Why is this happening to me? Why? I'm crying now, I'm so afraid. I know what can happen if I don't stop this. My heart is beating wildly, my head is hurting more and more. It feels like it's going to explode. I have to hurry to the doctor before it's too late. I could die from this …"

This is what happened to me a few years ago during one of my worst attacks of autonomic dysreflexia. Fortunately, I was able to make it to the doctor's office and convince him of the urgency of the situation. He changed the catheter, which was indeed clogged with sediment, and within a matter of seconds after the volume of my bladder was reduced, the grossly obvious symptoms vanished. There are after effects from such an episode, however. The biggest being extreme exhaustion, which is not trivial when you're paralyzed.

For a little background on my spinal cord injury, I'm classified as a C5 ASIA grade B and was injured in a motor vehicle accident in December of 1988. The most prominent source of my autonomic dysreflexia stems from my bladder. While in the hospital, I tried various methods of managing my bladder and finally settled on using a suprapubic catheter. This provides me with the greatest level of independence, comfort, and reliability. I do use an anti-cholinergic medication to reduce spasticity in my bladder. This is a very important point to stress. If I miss my medication or am delayed in taking it, I experience a continuous state of mild dysreflexia. That consists of increased spasticity in my body, hot/cold flashes, and an itchy scalp. I do not develop the severe headache, however, but I also do not know what fluctuations are occurring with my blood pressure when in that state. These symptoms disappear shortly after I resume the medication.

Just as every spinal cord injury is different, the primary stimulus and pattern of symptoms of autonomic dysreflexia experienced by each individual are different. The two most common stimuli appear to be bladder or bowel distension. One anecdotal observation is that the onset and intensity of the symptoms seem to occur faster and more severely with increasing time post-injury. I have experienced this first-hand and have been told the same thing by many other people with spinal cord injury. Is this truly common among the majority of people who develop autonomic dysreflexia? If so, what is the underlying biological mechanism? And, what long-term damage develops in people with chronic spinal cord injury who repeatedly experience episodes of dysreflexia? These are but a few of the problems that need to be addressed in the scientific and clinical settings.

Aside from acute autonomic dysreflexia episodes, there are many autonomic *dysfunctions* that present difficulties that people with any level of spinal cord injury have to deal with on a daily basis. Some of the most prominent problems include impairments in bladder and bowel control, sexual function, body temperature regulation, cardiovascular control, and metabolism. Any of these dysfunctions can significantly reduce a person's quality of life.

Now, in addition to being a quadriplegic, I am also a scientist and, when I first entered the field of spinal cord injury science in 2000, I observed that research regarding autonomic dysfunctions resulting from spinal cord injury was not very prevalent. Yet these are problems that everybody with cord injury experiences to some degree. This is a perplexing paradox. In an effort to address this issue, I conducted a study to determine what areas of functional recovery were most important to people living with spinal cord injury. Regaining bladder/bowel function and eliminating autonomic dysreflexia was the first or second highest priority for approximately 40% of quadriplegics and paraplegics and, similarly, regaining sexual function was the first or second highest priority to 28.3% of quadriplegics and 45.5% of paraplegics (Anderson, 2004). These results demonstrate that research regarding autonomic dysfunctions is extremely important. To that end, this book has been written about what is already known and to serve as a platform for fueling future research.

After all, it is all of these autonomic functions that we take for granted when we have them and that dominate our lives when we lose them.

References

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Kim Anderson

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Introduction

This book was inspired by a gathering of basic and clinical scientists, and healthcare providers, for a workshop on autonomic dysfunction after spinal cord injury held in Banff, Alberta, Canada in July, 2003. The discussions in this meeting highlighted the contrast between the high priority assigned by people with spinal cord injury to finding a cure for their autonomic dysfunctions, and the limited awareness of these issues or attention given to them by the scientific and medical community, other than care providers who interact with cord-injured people regularly. Research is needed to gain greater understanding of the mechanisms of these problems and to develop treatments and prevention strategies for them. To provide a foundation for such endeavours, this book contains a compilation of what is known about bladder, cardiovascular, bowel and sexual dysfunction after spinal cord injury, as it relates to the changes within the autonomic nervous system control of these functions.

The book is organized into sections that focus on each of the affected visceral functions: urinary bladder, cardiovascular, gastrointestinal and sexual. The book begins with a description of the time course of autonomic dysfunctions and their ramifications from the first hours after a spinal cord injury to the more stable chronic states. The next section contains three chapters that address anatomical findings that may provide some of the foundation for autonomic dysfunctions in many of the systems. The system-specific chapters then follow in four sections. Each section begins with a chapter or two defining the clinical problems experienced by people with cord injury. The following chapters present research, basic and clinical, that address the autonomic dysfunctions.

We have noted themes that transcend the different sections and can pertain to bladder, bowel, cardiovascular and sexual functions. For example, sprouting of axons, including the central processes of sensory neurons, within the injured spinal cord can be advantageous or detrimental, depending on the amount, location and potential for new contacts of this sprouting. This may also pertain to changes in the autonomic ganglia outside the central nervous system. Another theme is loss of coordination and balance of parasympathetic, sympathetic and somatic systems in the absence of modulatory influences from supraspinal neuronal systems. Bladder dyssynergia and autonomic dysreflexia, with its episodic hypertension, have much in common. Lack of coordinated control of pelvic neurons leads to failure of defaecation and ejaculation. Spinal cord injury affects more than spinal neurons; it impacts on peripheral ganglia and target tissues such as blood vessels and the wall of the urinary bladder. Growth factors that one would think should be advantageous to repair of the injured spinal cord, may actually promote development of circuits that impair rather than support recovered function. Many other themes also thread through this book.

Finally, we would like to acknowledge several people who have helped us during the preparation of this book. Ms. Bibi Pettypiece organized the meeting in Banff that started this project and was in communication with all of the contributing authors to coordinate the details that can so easily become a burden. Her assistance was invaluable. Ms. Eilis Hamilton applied her considerable skill with graphic presentation to many of the illustrations in this book, adding to their clarity. The authors who have benefited from her assistance are very appreciative. Mr. Tom Merriweather and Ms. Maureen Twaig from Progress in Brain Research, Elsevier, have been encouraging and helpful throughout our effort. Lastly, we realize that we have not included all of the work that has been done on the subject of autonomic dysfunction after spinal

cord injury. Excellent work is being done in addition to that described in these chapters, and we apologize to those who did not have the opportunity to contribute to this book.

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Overview

Autonomic dysfunction in spinal cord injury: clinical presentation of symptoms and signs

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Abstract: Spinal cord injury and especially cervical spinal cord injury implies serious disturbances in autonomic nervous system function. The clinical effects of these disturbances are striking. In the acute phase, the autonomic imbalance and its effect on cardiovascular, respiratory system and temperature regulation may be life threatening. Serious complications such as over-hydration with the risk of pulmonary edema or hyponatremia are seen. The cord-injured person suffers from autonomic nervous system dysfunction also affecting bladder and bowel control, renal and sexual function. Paralytic ileus may cause vomiting and aspiration, which in turn interferes with respiratory function in those with cervical spinal cord injury. The cord-injured person is at risk to develop pressure sores from the moment of the accident. Two to three months post-injury the cord-injured person with a lesion level above the fifth thoracic segment may develop autonomic dysreflexia, characterised by sympathetically mediated vasoconstriction in muscular, skin, renal and presumably gastrointestinal vascular beds induced by an afferent peripheral stimulation below lesion level. The reaction might cause cerebrovascular complications and has effects on metabolism. Some of the autonomic disturbances are transient and a new balance is reached months post-injury, while others persist for life.

Spinal cord injury, in a moment, dramatically changes the life of the affected person. The loss of control of skeletal muscle, as well as of sensations from below the injury, together with the impairment of thermoregulation, urinary bladder and bowel function produce a profound deterioration in the quality of life for people after spinal cord injury. Tetraplegic subjects rank improvement in hand function as the most important factor to enhance quality of life (Anderson, 2004). However, paraplegic subjects give normal sexual function the highest priority and, when the first and second choice was combined, recovery of normal bladder and bowel function were given the highest priority in both groups of subjects. This shows that people with spinal cord injury consider the disturbances in autonomic nervous system function even more devastating than the loss of motor and sensory function.

The moment of the accident

A cervical spinal cord injury may be life threatening. When the level of lesion is above the third cervical segment (C3), the injured person needs immediate assistance of respiration due to the loss of the supraspinal excitatory drive of the phrenic motor neurons located at C3–C4. Even when the level of the lesion is below C3, the cord-injured person may suffer from life-threatening conditions due to autonomic nervous system dysfunction. Cardiac arrest may be one of the causes of death in

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the first few minutes following a cervical spinal cord injury due to the disruption of central sympathetic control and the concomitant unopposed vagal outflow. The incidence of this complication is difficult to estimate, although some data indicate a decreasing incidence during the last decades. The number of patients who reach hospital alive has increased more than twofold from the 1940s to the late 1970s. This probably reflects improved skill in treatment of a potential spinal cord injury by the first aid team, since unskilled handling of an unstable neck might result in an ascending neurological level of the lesion, making it life threatening.

In the emergency room

When arriving at the hospital the person with a cervical spinal cord injury presents with the following symptoms: flaccid paresis, exclusively diaphragmatic respiration, low blood pressure and mostly bradycardia. It is well recognized that spinal cord injury implies inability to empty the bladder voluntary and, accordingly, an indwelling catheter is always placed in the urinary bladder in the emergency room when a spinal cord injury is suspected. At this stage, new risks appear. Because the spinal cord injury is often part of a multitrauma the low blood pressure after cervical spinal cord injury may be misinterpreted as consequent to extensive blood loss. A treatment with rapid infusion of intravenous fluids might lead to pulmonary edema. On the other hand, the cord-injured person may be bleeding in the abdomen and this may be difficult to diagnose because of the pre-existing low blood pressure, absence of tonic contraction of the abdominal muscles (guarding reaction) and absence of pain. For this and other reasons, the cord-injured person needs to be carefully investigated by computerized tomography scanning and magnetic resonance imaging. An unstable fracture in the spinal column with the risk of deterioration of the neurological outcome sometimes results in placing the patient on a hard table, a so-called ''spine board.'' Then the patient can be moved from the emergency room to X-ray or to the intensive care unit without having to be moved from bed to examination tables and back. However, if the injured person lies more than 2 h in the same position on a hard spine board, he/she is at risk of developing pressure sores. This risk is attributed to the loss of sensory inputs to the brain from below the level of the lesion, but this may not be the whole explanation since unconscious patients without spinal cord injury do not seem to be at as high risk of developing pressure sore as are the cord injury patients, conscious or unconscious. Regulation of blood flow in the skin exposed to pressure seems to be deranged in the decentralized areas of the body, even though subcutaneous adipose tissue blood flow during resting conditions shows no difference when compared to that in able-bodied people (Karlsson et al., 1997a).

Blood pressure control and the syndrome of inappropriate anti-diuretic hormone secretion

After the extent of the injury is visualized radiographically, the injured patient is transported either to an operating theatre, an intensive care unit or to a spinal cord injury unit. Careful monitoring of blood pressure, heart rate, respiratory rate and body temperature begins. A mean arterial blood pressure above 80 mmHg is recommended (Hadley, 2002), and this level is sometimes maintained by intravenous fluid supply and/or by the use of pressor agents. Urine output in the cord-injured patient usually is low during the first days post-injury, probably due to an inappropriate secretion of anti-diuretic hormone. Three to six days post-injury urine output reaches 5–6 l/day; the accumulated water is excreted. If urine output is strictly monitored daily, this polyuria may be misinterpreted as a sign of inability to concentrate the urine, and if the loss of water is fully substituted by intravenous fluids, or vasopressin is given, hyponatremia may develop. Some years ago a 28-year-old man sustained a C7 spinal cord injury resulting in tetraplegia and developed a serious hyponatremia with concomitant loss of vision (Karlsson and Krassioukov, 2004). His cervical fracture was stabilized surgically and during the day of surgery he received 8.6 l of fluid intravenously. When his urine output some days later increased to 6 l, it was misinterpreted as inability to concentrate the urine

and vasopressin was given. Serum sodium concentration decreased to 121 mmol/l (at the lowest level), and he was treated by restriction of fluid intake and by mineral corticoids. His sodium level normalized slowly. As soon as his water intake exceeded 0.7 l/day his serum level of sodium decreased. As a result of these problems, he had a partial loss of vision that was permanent. Urine output must be calculated for a longer period than the previous day to avoid this risk of overcompensation.

Bradycardia

Another effect of the loss of supraspinal control of the sympathetic nervous system is the bradycardia that is seen sometimes during the first 2–3 weeks post-injury. An example of this is a man, who at the age of 39 years sustained a spinal cord injury at the C5 level, an ASIA C type injury. He was treated in the intensive care unit for 2 days and his condition was uncomplicated except for bradycardia. At the spinal cord injury unit, he showed signs of a decreased arterial oxygen tension a tracheal suction induced a cardiac arrest. He was transferred to the intensive care unit, where he stayed for 12 days. He had a prolonged period of bradycardia with a mean heart rate of 48 bpm that lasted for 2–3 weeks. The cardiologist was consulted and he prescribed a 24 h electrocardiogram recording. The recording showed sinus bradycardia with a mean rate of 48 bpm and the installation of a pacemaker was suggested. However, a week later the bradycardia resolved spontaneously and during the next 2 weeks the heart rate increased to a mean of 57 bpm. This imbalance in the acute phase seems to be replaced by a new balance later since, when measuring heart rate variability in the chronic phase, no difference is found when comparing cord-injured subjects to able-bodied subjects (Gao et al., 2002).

Respiratory system

In the first weeks post-injury there is a risk of respiratory failure in the cervical spinal cord injury patient. This is sometimes due to obvious reasons such as simultaneous injuries in the chest. However, the 40% loss of vital capacity, due to the paralysis of the inter-costal muscles, is also of importance. The loss of sympathetically mediated bronchial dilatation may add further to the risk of developing respiratory failure. Inhalation of bronchodilators is usually used in the acute phase following spinal cord injury. In spite of this treatment, excessive mucus production and stagnation of secretion is seen. The autonomic nervous system imbalance might be life threatening during this condition, since a person with cervical injury who has a tendency to hypoxia might sustain a severe bradycardia or heart arrest during tracheal suctioning. Irritation of the trachea is a heavy stimulus of vagal outflow even in able-bodied people and the reaction in cord-injured patients might be an exaggeration of this reaction due to the loss of supraspinal control of the sympathetic nervous system. Pretreatment with anti-cholinergic drugs is sometimes needed before tracheal suctioning.

Temperature regulation

The respiratory problems might lead to pneumonia with high fever. Then the cord-injured patient is faced with another effect of autonomic disturbances: that is the inability to lose excess heat by sweating. This inability might be life threatening during high fever or in an extremely warm climate. Several years ago a young man was treated at Sahlgrenska University Hospital. He had sustained a C4 spinal cord injury and had an aspiration of fluid into his lungs during the transport to hospital. He developed pneumonia and his temperature increased from 41.0 to 42.4° C and, at this high temperature, he died of a cardiac arrest.

Even though central temperature control is unaffected by cervical spinal cord injury, we sometimes see a prolonged period of increased temperature in newly injured patient. Careful examination reveals no signs of infection or inflammation and 3–6 weeks post-injury, the temperature normalizes. Some people with cervical spinal cord injury complain of feeling very cold. This is very marked after a shower, when the patient sometimes needs a heating quilt or a heater to feel

comfortable. The ability to increase temperature by shivering is lost below the lesion level and may explain some of the sensation. However, some patients suffer from coldness all the time.

Blood pressure and mobilization

When the fracture is stabilized and the neurological level of lesion is stable, the person with spinal cord injury needs to be mobilized. The low blood pressure and the inability to increase blood pressure by vasoconstriction below lesion level make mobilization of the person with cervical injury difficult. It has to be done gradually by tilting the patient 10°/day while blood pressure and neurological status are continuously monitored. When the patient tolerates a 40° tilt, they are usually able to sit in a wheelchair. Age at injury seems to affect the ability to mobilize the patients, since the elderly usually need more time to become mobilized. Whether this is due to a lower tolerance to low blood pressure or to greater decreases in blood pressure during mobilization is not known. The renin–angiotensin system plays a role in blood pressure control in cervical spinal cord injury (Johnson et al., 1971; Sutters et al., 1992). This was clearly demonstrated when we treated a man in his 40 s with a cervical injury who had suffered from renal failure prior to his injury. His mobilization was prolonged and he suffered from symptoms of low blood pressure for several months after his injury.

Skin and sensation

Very few patients are able to lie or sit more than 4 h in the same position without getting redness in the skin of areas used for body support; this is the first sign of pressure sores. The patient needs to be turned every fourth hour even during a skull traction period. Four to five caregivers are needed to do a safe log-roll of the patient. When the patient is mobilized to a wheel chair sitting position, selection of cushions is of great importance in order to avoid pressure sores. The risk of developing pressure sores persists in the cord-injured person and is increased during severe infections with increased body temperature. Under these circumstances the patient needs to be turned every second hour in order to avoid skin problems. What makes the skin more vulnerable to pressure during fever is not known.

Another problem with the skin, seen during the first months post-injury, is acne vulgaris that sometimes flares up in the person with cervical injury. This condition is not life threatening and occurs above as well as below lesion level. Whether this is due solely to hormonal disturbances elicited by a stress reaction or to a combination with autonomic dysfunction is not known.

Urinary system, bladder control

The autonomic nervous system dysfunction involves the urinary system during the initial post-injury stage of "spinal shock" and for the lifetime of the person. The dysfunction entails loss of control of the urinary outlet and, during spinal shock, loss of sensation from the bladder wall making the patient at risk of over-distension of the bladder. During spinal shock the bladder is atonic irrespective of level of lesion. When the stage of spinal shock is past, which may take 3–4 months, people with cervical or thoracic lesions develop a spinal reflex bladder that expels urine under high intravesical pressure at a certain amount of bladder filling, a condition categorized as upper motor neuron lesion. People with lower lumbar and/or sacral levels of lesion retain an atonic bladder, a lower motor neuron lesion. Regulation of bladder emptying appears rather robust and might be normalized even if the person suffers from some degree of paresis and loss of sensation. In a retrospective chart review of 249 patients with upper motor neuron lesions who had been treated at the Spinal Cord Injury Unit in Göteborg, we found that almost 30% of the individuals recovered normal micturition and most of them had injuries classified as ASIA C and D (Karin Pettersson, personal communication).

Urinary system, renal function

Renal dysfunction has previously been the major cause of death following spinal cord injury. The mortality rate due to renal failure has decreased

from about 40% in the late 1940s (Whiteneck et al., 1992) to 3–5% during the last decade (Webb et al., 1984). This dramatic change is probably due to improvements in bladder emptying regime as well as to the introduction of antibiotics to treat urinary tract infections. Even better, it seems that renal function has a capacity to improve during the first years post-injury. In a retrospective chart review, we found that glomerular filtration rate was low in those with cervical spinal cord injury in the first months after injury. However, at a follow-up 2–3 years later we found that the glomerular filtration rate had increased, at least in the group who emptied the bladder by clean intermittent catheterization (Karin Pettersson, personal communication).

Gastrointestinal system

The gastrointestinal system is also affected by the spinal cord injury. Newly injured patients are at increased risk of developing stress related gastric ulcers and are regularly offered anti-acid treatment. It might be that the unopposed vagal outflow plays a role and increases the risk of ulcer formation. Other problems from the intestinal system are obvious to the patient soon after injury. The bowel is silent and the voluntary control of bowel emptying is lost. This paralytic ileus ceases within 1–2 weeks, but if liquids or solid food is given prior to this there is a clear risk of a prolonged period of paralytic ileus, with the concomitant risk of nausea and vomiting. A patient who is placed in skull traction is hard to manage properly during vomiting and there is a great risk of aspiration. Furthermore, a paralytic ileus could give rise to a meteoristic abdomen, which might interfere with respiration by interference with the breathing movement of the diaphragm.

Programs for bowel emptying must be introduced and we choose a rather conservative way of treatment initially: no ingestion of food or drink until the bowel has been emptied. In people with lesions at the cervical and thoracic level this takes about 3–6 days, but in the low lumbar lesion level the emptying might be further delayed by several days. By this regime, the risk of vomiting and aspiration and the influence on respiration are controlled. The pathogenesis of this temporary paralytic ileus is unclear and the time frame for return of bowel activity does not correspond to return of reflex activity in the bladder or return of tonus and reflexes in the skeleto-muscular system. Even though a program for bowel emptying is introduced, the evacuation of stool may be protracted. This might be due to the new balance of parasympathetic control, with an intact innervation of the ascending colon via the vagus nerve and the loss of supraspinal control of the sacral parasympathetic supply to the colon.

When the bowel program has started the cord-injured person may face new problems. There is a risk of developing anal incontinence, and the risk is highest with lesions in the lower lumbar level due to a low tonus in the external anal sphincter. This is perhaps one of the most devastating effects of the injury to the spinal cord and may be one important reason why cord-injured people do not return to work after their injury.

The higher tonus and the uninhibited activity in the anal sphincter after cervical and thoracic lesions might give rise to severe pain that seems to originate from the anal sphincter. The pain is made worse by anal fissures and hemorrhoids, and this pain, as well as anal incontinence and constipation, might later lead to colostomy. However, the pain problem is not always resolved even though the rectum and anal region are bypassed.

Sexual function

Some cord-injured men already in the intensive care unit ask about their ability to have an active sex life and become fathers. The erectile dysfunction in men after spinal cord injury has different characteristics depending on level of lesion, and mainly follows the pattern of bladder dysfunction. The person with an upper motor neuron lesion usually has the capacity for reflex erection by tactile stimulation. The person with a lower motor neuron lesion has loss of all erectile function. The capacity of psychogenic erection is lost in all cord-injured men with a complete lesion. Retrograde ejaculation is the rule when there is an ejaculation