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JOURNAL OF THE SPINAL RESEARCH FOUNDATION

THE JOURNAL OF THE SPINAL RESEARCH FOUNDATION
A multidisciplinary journal for patients and spine specialists

From the Editor

Brian R. Subach, M.D., F.A.C.S.

Welcome to the 2008 Spring Edition of the Journal of the Spinal Research Foundation. As we begin our third year of publication, there have been some very exciting things going on at the Spinal Research Foundation (SRF) headquarters. In addition to our resident Ph.D. and managing editor, Dr. Anne G. Copay, we welcome Marcus M. Martin Ph.D. to the SRF team. Dr. Martin recently completed his post-doctoral work at the University of Florida with an extensive background in both immunology and virology. He has been hired to spearhead both the effort to set up the SRF laboratory facility and to take command of the SRF Chronic Neuropathy Study (CNS). To manage the tremendous amount of work and organization associated with prospective data collection and other research efforts, Ashley Holmberg B.S. has been brought on board as well.

In addition to the expansion of the SRF staff, I am excited to introduce a novel investigation known as the Chronic Neuropathy Study (CNS). We have embarked upon a landmark, multicenter collaborative effort designed to identify the mechanism of spinal nerve injury which often results in disabling extremity pain, numbness and weakness. Through the efforts of more than a dozen individual SRF Regional Research Centers across the United States, we hope to identify the mechanism of neural injury, explore the time course of damage and finally, develop realistic strategies for successful intervention which may limit or reverse the process.

The Spinal Research Foundation has initiated this study focused upon identifying the causes of chronic spinal nerve damage and attempting to identify interventions and treatment options for affected patients, due to the widespread nature of the problem. Millions of people suffer from the disabling pain and numbness associated with damage to the cervical and lumbar spinal nerves. This may be due to direct traumatic injury, nerve compression from degenerative arthritis or disc herniation and ineffective surgical treatment which alters the blood supply to the supporting tissues around the nerve and often leads to the formation of dense scar tissue. It is difficult to understand how minimally-invasive surgery, even with the most advanced techniques, may result in persistent or permanent symptoms. Successful alterations in the progression of neuropathy have been generally focused upon early identification and early intervention, although the optimal timing for such intervention remains unclear.

In unveiling the new CNS effort, it seems only reasonable to focus this issue upon neural injury and dysfunction. Dr. Vishal Kancherla, both a specialist in the field of Physical Medicine and Rehabilitation and an expert in the electrical diagnosis of nervous system disorders, presents an outstanding summary of normal nerve function and the effect of the pathologic processes which lead to nerve damage or destruction.

Dr. Marcus Martin has coordinated the Research Update section which brings the most recent laboratory and clinical advances to you in an abbreviated format.

I would like to make one final point. Over the years of doing research, it has become clear that progress in the field of spinal disorders would quite simply not be possible if not for two groups: our patients and our donors. Without the participation of our patients in the collaborative research effort, there would be no progress. In the name of research, patients fill out detailed computer data forms and return for office evaluations and x-rays long after their incisions have healed. I would also like to acknowledge our corporate and private donors for their generosity in supporting this most worthy cause. Through donations, we have been able to add research personnel, expand the number of ongoing research projects and continue publishing the results of our work in both community-based forums as well as medical journals.

This journal shows you what we do every day. Our research is performed to improve the lives of our patients and to increase the public awareness of the magnitude of the problem. I consider our efforts a success every time a person spends a few moments reading this publication and hopefully learns something new about spinal disorders.

Spine Tale

David De Hora first arrived at the spinal surgeon's office in October 2006. As a thirty-nine year old software engineer, he spent a significant amount of time sitting in front of a computer. He found that over the past few years the pain he was experiencing in his back and his right leg had been gradually increasing. His symptoms really began to worsen acutely one day. There was no injury. There was no car accident. There was no fall from a rooftop. He did have a family history of spinal problems in that his sister and his brother both had similar disease with disc herniations and low back pain.

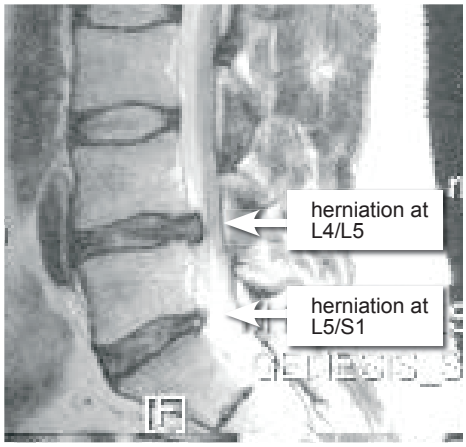
The pain was surprising; David had always found himself to be physically fit. He did a little cardiovascular activity, worked on flexibility and strength training and overall was in fairly good health with the exception of smoking a few cigarettes.

The pain began to affect his life. He found it difficult to function in his activities of daily living. He found it difficult to work. He described this pain as 80% in the back and 20% into the back of the thigh and back of the calf in a typical pain pattern associated with a ruptured lumbar disc. When asked to rate his pain on a scale of 0 (none) to 10 (worst), he stated that the average pain was generally a 6; however, he experienced significant flare ups as high as a 10.

David De Hora

He had tried physical therapy, working on core muscular strengthening and flexibility. He had tried anti-inflammatory agents and had seen even an orthopaedic surgeon for evaluation and was told that nothing could be done. He was seen by a pain management specialist who tried epidural steroid injections, which did very little to alleviate his symptoms. He had heard about artificial disc replacements and found himself sitting in the office waiting to meet Dr. Subach in October 2006 hoping for a solution. When asked to describe the symptoms, Mr. De Hora stated that the pain was significant in the back, across the small of his back at the junction between the lumbar spine and the tailbone. The pain that radiated down into his leg involved the right posterior thigh, posterior calf and into the bottom surface of the foot. His left leg was really unaffected. The right leg had numbness in the posterior calf and into the bottom of the foot. His symptoms were clearly worse at different times throughout the day, occasionally worse when he was standing in one position for too long or sitting at his computer for too long. He found that driving for prolonged periods of time was also very uncomfortable. Any types of recreation, such as activities in the gym, walking on the treadmill, were being curtailed by the severity of his pain. He was unable to even stand and walk any significant distance without pain as high as an 8 on the scale of 10.

He had tried everything that he could think of to ease the pain. He had been through anti-inflammatory agents, even narcotic pain medications. His exercise program had always been aggressive until he found that the pain prevented him from exercising. He had tried working with a physical therapist to do a trunk stabilization program to alleviate the pain from degeneration in the low back. He had tried using a TENS Unit, which is electrical stimulation of the muscles. The epidural steroid injections had all failed. He was very much frustrated with his care and its results.



MRI showing disc herniation at L4/L5 and L5/S1

Dr. Subach reviewed his imaging studies, including x-rays and a lumbar spine MRI scan. The lumbar MRI scan, which was done earlier in 2006, demonstrated evidence of disc herniations at both L4/5 and L5/S1 with obvious degenerative changes in the two lumbar discs at these levels. It appeared to the doctors that his low back pain was coming from degeneration of the lumbar discs at these two lowest levels (L4/5 and L5/S1). A relatively large disc herniation at L4/5 seemed to cause significant pressure on the exiting nerve roots at that level, which would explain the leg pain he was

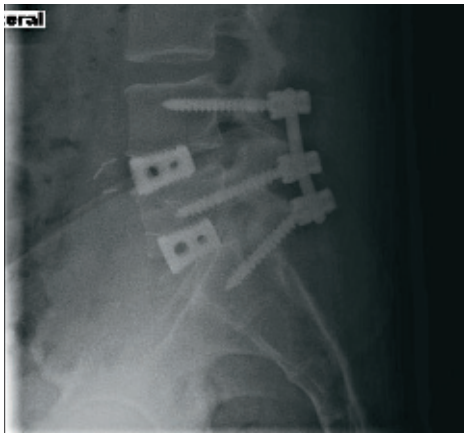
Spine Tale

having. When the doctors examined him he had no difficulty bending forward to touch his toes, however, arching his back in extension was extremely painful. The doctors identified atrophy or wasting of the calf musculature on the right leg, indicative of a longstanding process which was causing nerve damage. He had lost the reflex at the right ankle and had difficulty standing on the tiptoe of his right leg secondary to the weakness.

After his imaging studies and his examination had been reviewed, it was recommended that he consider lumbar discography. Lumbar discography is a test which identifies weakness in the discs themselves, which may be the source of back pain. Unfortunately, many patients with similar symptoms of back pain and leg symptoms are often recommended a lumbar laminectomy or resection of the disc herniation. Most people don't realize that simply removing a disc herniation may take the pressure off the offended nerve relieving the leg symptoms, but will do nothing for low back pain. Discography will help to identify the source of low back pain by pressurizing individual discs with contrast dye. By using x-ray guidance the discs can essentially be inflated to see if they provoke the discomfort that bothers a person on a daily basis, while actually seeing how the dye flows in and around the disc space itself.

On October 25, 2006, Mr. De Hora showed up at Reston Hospital for lumbar discography. He had never been one for surgical procedures and was not excited about having a needle placed into his back. He found that, with a little sedation and a little local anesthetic, he actually was able to tolerate three small needles placed directly into the discs at L3/4, L4/5, and L5/S1. Each disc was sequentially injected with the contrast dye and pressurized. At L3/4, he had a pressure sensation but really no discomfort. The dye demonstrated normal disc space anatomy consistent with a normal healthy disc. At L4/5 and L5/S1, however, the pain was much different. At each of these levels, when the dye was injected, this stretched and filled up the disc causing the dye to flow from one side to the other in a clearly disrupted fashion. The injection elicited right-sided low back pain which caused radiation down his right leg into the calf in the usual pain distribution which bothered him on a daily basis. At L4/5 and L5/S1, both levels reproduced his typical low back pain while L4/5 reproduced his typical right leg symptoms.

After carefully considering his options, David decided to pursue surgery. He had truly failed every conservative management strategy which could be devised and, at this point, his life was being altered by the pain. On December 13, 2006, he underwent a staged operation. The first stage approached his lumbar spine through an abdominal incision removing the degenerative disc material and reconstructing the spine with titanium cages with genetically-engineered bone morphogenetic protein (BMP), essentially putting his posture back into normal alignment and making his spine approximately one-half inch taller.



Side x-ray after the fusion surgery

When that operation was complete, the operating table was then turned so that he was lying face down. Through a minimally invasive approach he underwent decompression of the exiting nerve roots as well as a fusion along the side of the spine using two small screws. In a matter of a few hours his procedure was complete and he was resting comfortably in his hospital bed.

Prior to surgery, he had stated that his pain was 6 on the visual analog pain scale of 10. When he returned to the office, two weeks after the surgical procedure, his pain was already down to 2 out of 10. He noticed an immediate difference in the pain he was having in his low back. The leg pain was completely gone at this point. He described mostly soreness around the area of the incision, however, he felt much better. He was started on a gentle physical therapy regimen, given some mild narcotic pain medications and was seen back approximately six weeks after surgery. By May 2007, he was off all pain medications except for anti-inflammatories. He was essentially three months out from his fusion procedure and felt that his pain was 95% improved compared to prior to surgery.

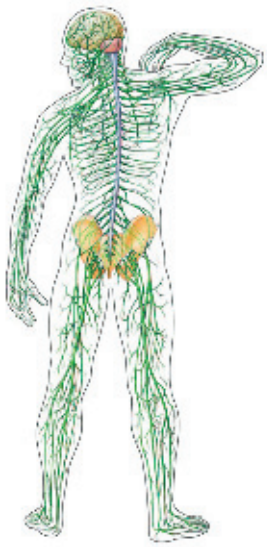
"Hitting the Right Nerve": Spine and Nerve Pathology

By Anne G. Copay, Ph.D.

1 - Anatomy of the nervous system

Nerves form a vast network that reaches into all the recesses of our body. Damage to a nerve is potentially felt through different body areas.

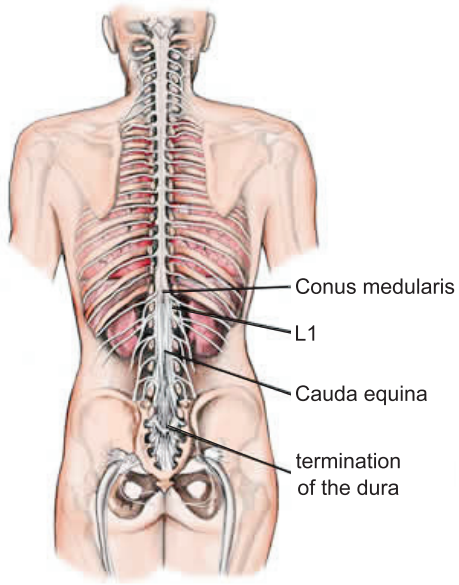
The nervous system is comprised of the central nervous system (brain and spinal cord) and the peripheral nervous system (spinal nerves and autonomous nervous system). Damage to the central nervous system is irreversible so that paralysis due to a spinal cord injury is typically permanent. On the other hand, it is possible to recover from damage to the peripheral nervous system.



The nervous system

(picture courtesy DK Images)

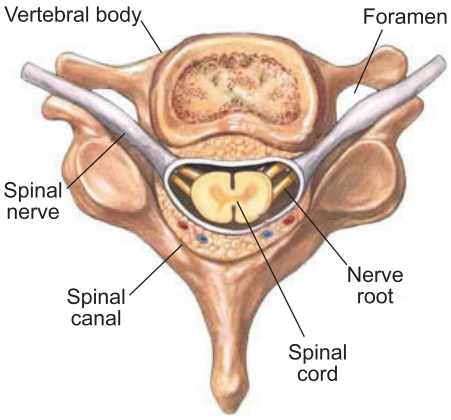
The spinal cord runs inside the spinal canal formed by the stacking of the vertebrae. The spinal cord ends in the lumbar area at the level of the first or second lumbar vertebra. The ending of the spinal cord is called the conus medullaris. Below the conus medullaris, the spinal cord continues through the spinal canal in the form of spinal nerves. Because of its resemblance to a horse's tail, the collection of these nerves at the end of the spinal cord is called the cauda equina.



Spinal cord and spinal nerves

(picture courtesy Medtronic)

The spinal nerves leave the spinal cord and pass through openings between the vertebrae. These openings are called intervertebral foramen. The nerves leaving the spinal cord in the neck send and receive signals to the upper extremities and the nerves leaving the spinal cord in the lower back area send and receive signals to the lower extremities.



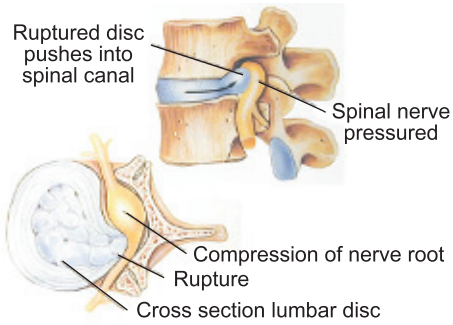
Spinal nerve leaving the spinal canal

(picture courtesy Medtronic)

2 - Changes in the spine affect the spinal cord and spinal nerves

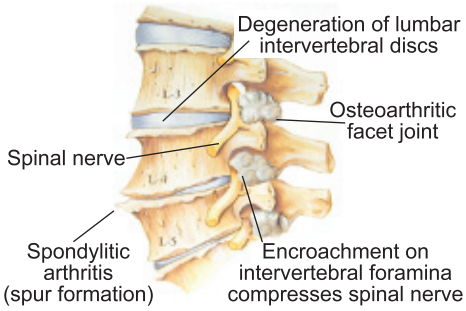
The spine encases and protects the spinal cord and the nerve roots. However, injuries and degenerative changes of the spine may cause the spine to compress and injure the spinal cord and nerves.

- **Disc herniation:** a herniated disc may press against the spinal cord and the nerve.



Herniated disc

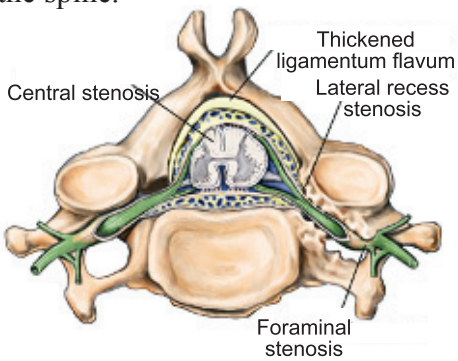
- **Several degenerative changes** combine to narrow the spinal canal and intervertebral foramen: degeneration of the intervertebral disc with loss of disc height, arthritis of the facet joints, bone spur, and thickening of ligaments.



Degeneration of the spine

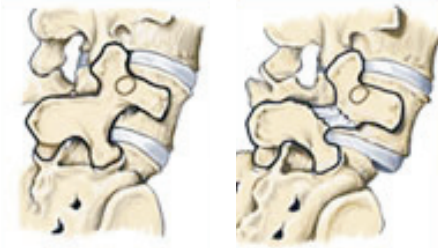
The result is a narrowing of the space occupied by the nervous system. Narrowing is called **stenosis** and typically occurs in 3 areas.

Central stenosis is the narrowing of the spinal canal and causes compression of the spinal cord. *Lateral recess stenosis* is the narrowing of the space where the nerve root exits the spinal canal. *Foraminal stenosis* is the narrowing of the intervertebral foramen where the nerve root leaves the spine.



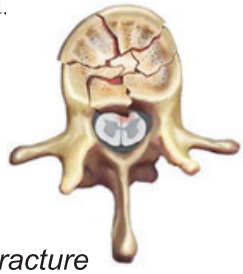
Stenosis
(picture courtesy Medtronic)

- **Spondylolisthesis** is the slippage of a vertebra. The slippage also can compress the spinal cord and nerves.



Spondylolisthesis
(picture courtesy Medtronic)

- **Injury** to the spine can directly injure the nervous system or injure parts of the spine that will damage the nervous system. For instance, a fractured vertebra can compress the spinal cord.



Fracture
(picture courtesy Medtronic)

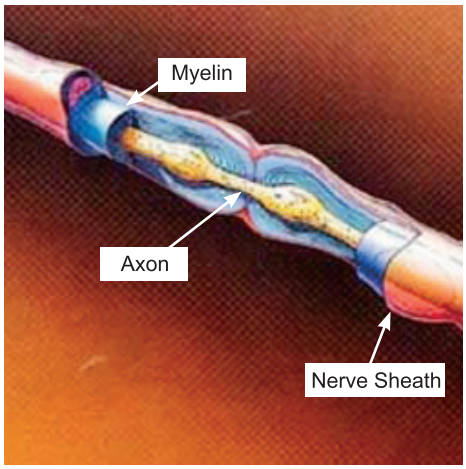
3 - The Anatomy of Nerve Damage: Changes in Structure Affect Function

By Vishal Kancherla, D.O.

Could true love cause a wrist drop? Honeymooner's palsy is the coined term that demonstrates the potential fate of a lover's arm placed under the head of their significant other. The unexpected victim who had willingly lent an arm as head support is now left with a radial wrist drop, the inability to cock up the wrist. This is a symptom of nerve damage resulting from prolonged compression of the radial nerve. Fortunately, the nerve has an inherent ability to heal itself when the compression is removed. In most situations, the person's wrist strength should return to full strength but perhaps not the willingness to lend a loving arm.

The anatomy of a nerve is very similar in structure to a coaxial cable wire, an outer covering with a complex wiry architecture within. The covering is called myelin and serves a dual purpose: insulating the nerve and facilitating conduction of an electrical signal. The inner part of the nerve is composed of bundles of axons, responsible for the transmission of the electrical signal. The longest axons in the human body are those found in the sciatic nerve which runs continuously from the spine to the big toe.

The nerve also has a blood supply which is responsible for the transport of nutrition and is essentially the life force of the nerve. Nerves are very vulnerable to changes in vascular supply so that an interference in circulation will rapidly lead to sensory and motor disturbances. Compromise of sensory nerves most commonly leads to symptoms such as numbness, tingling and burning. A sensation that is anything but normal is called a paresthesia. Compromise of motor nerves may lead to complete motor paralysis. Paresthesias are the first to occur because the sensory nerves are smaller and more vulnerable to compression while motor nerves require longer duration and a higher magnitude of injury to be compromised.



Healthy nerve
(picture courtesy Mackinnon & Dellon)

Mechanisms of nerve damage

Several mechanisms can cause injury to the nerve: metabolic disease (such as diabetes mellitus), transection (such as a knife wound), traction (a forceful pull on a nerve or group of nerves that may occur in a motorcycle accident or high velocity accident), or compression. Compression to the nerve may occur anywhere along its path. When compression occurs close to the origin or root of the nerve, it is called radiculopathy. When compression occurs at the periphery it is labeled entrapment (as in carpal tunnel syndrome of the wrist or ulnar neuropathy at the cubital tunnel.)

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"Hitting the Right Nerve" : Spine and Nerve Pathology

3 - Anatomy of Nerve Damage

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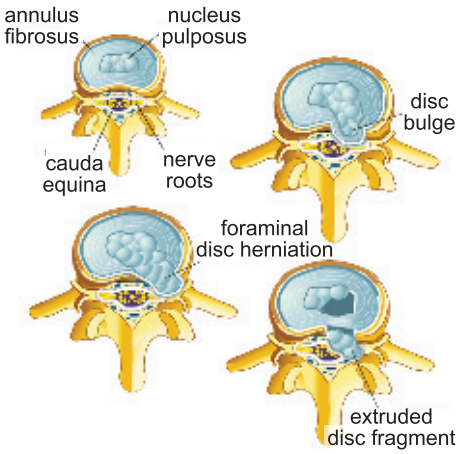
Due to its physical proximity to the nerve roots, changes in the spine are most likely to pinch a nerve close to its root.



Lumbar disc herniation

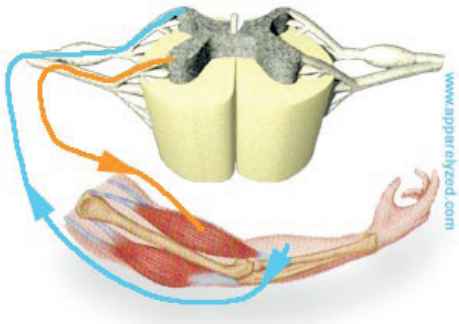
Let's take, for instance, a common spine pathology, the herniated disc. The axonal transport, an efficient energy dependent system that allows communication along the entire length of the nerve, has been abated at the level of the herniation.

Depending on the characteristics of the lesion, the symptoms may present as radicular pain (commonly known as sciatica) described as burning, electrical, or pins and needles type pain in a predictable pattern. The area or band of skin that receives its sensation from a particular nerve root is called a **dermatome** *(see picture on page 8)*. Those with an S1 nerve root lesion might have pain that radiates into the back of their leg, calf, and along the lateral aspect of their foot.

The injury may progress to weakness in the distribution of the muscle groups that the particular nerve supplies. For instance, if the L5 nerve root was impinged, there would be a deficit in L5 innervated muscles such as the muscle that extend the big toe and foot. A group of muscles primarily innervated by the motor fibers of a single nerve root is called a myotome. Often, treatment strategies are defined by singling out a particular nerve or group of nerves based on their myotomal and dermatomal pattern.

Classification of nerve damage

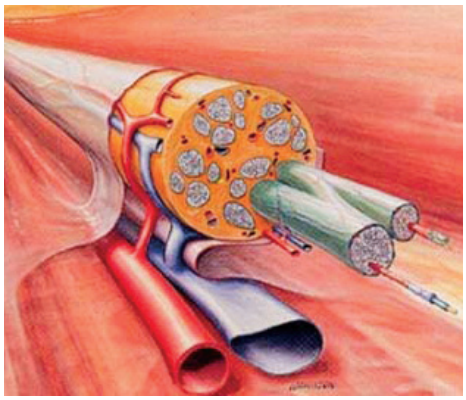
Many factors play into the severity of a lesion, such as magnitude, duration, and character of the compression. The consequences of nerve compression at the level of the spine may vary from slight paresthesia to numbness to even paralysis and muscle atrophy. Mild compression, such as that seen in Honeymooner's palsy will likely result in complete resolution after a few days to weeks. Local arrest of circulation is typically immediately reversed when the compression is removed. As in the phenomenon of having one's arm or hand "fall asleep".



Orange arrow: C5 myotome (innervation to the biceps). Blue arrow: C5 dermatome

What is a disc?

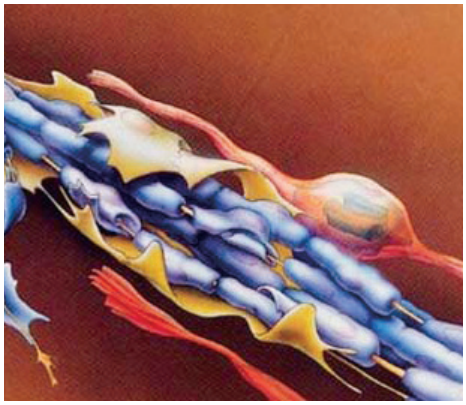
A spinal disc is the ligamentous structure that attaches one vertebra (a spinal bone) to the adjacent vertebra. The purpose of the disc is to allow motion of the spine. Many people consider the disc to be a "shock absorber" between the bones of the spine (vertebrae); however, this is just one purpose of the disc. The more important function of the disc is to allow for motion in the spine



Healthy nerve and its blood supply

(picture courtesy Mackinnon & Dellon)

When compression of a higher magnitude is applied to a nerve or nerve root, a local conduction block lasting weeks or even months may occur. The basis is local damage to myelin sheath (the outer part of the coaxial cable wire) with the axons remaining intact and is called **neuropraxia**. A neuropraxic lesion is usually reversible within three months if the compression is removed. Surgery is usually not indicated in a neuropraxic lesion.



Neuropraxia

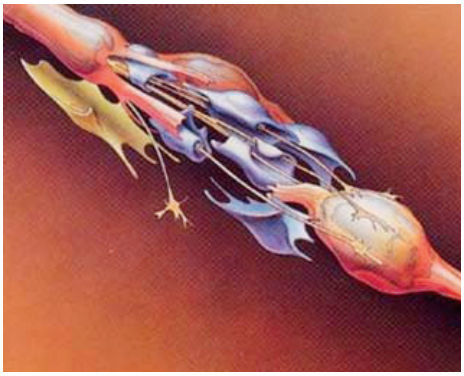
(picture courtesy Mackinnon & Dellon)

Classification of nerve damage

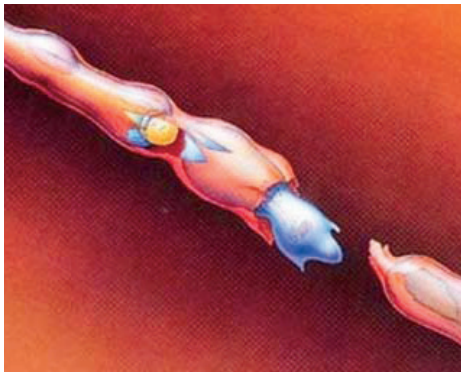
Injury	Comment	Rate of recovery	Recovery Pattern	Type of lesion
Neuropraxia	Mild injury to the myelin sheath of the nerve with transient symptoms	Rapid: days to weeks	Reversible and complete- Between 2 minutes and 4 weeks	Carpal tunnel syndrome, Honeymooner's palsy
Axonotmesis	Moderate to severe injury to both the myelin and axon sparing the connective tissue framework so regeneration can occur	1-2 mm per day	Reversible and complete- Between 6-8 weeks	Moderate to severe crush injuries or prolonged compressive lesions
Neurotmesis	Severe nerve injury that disrupts the entire nerve resulting in permanent neurologic deficit without repair	1-2 mm/day after repair or surgery	Irreversible without surgery	Transection injuries (knife laceration), avulsion of nerve roots, severe prolonged compression

If there is moderate to severe compression of a nerve root, there will likely be involvement of both the axon and the myelin resulting in **axonotmesis**. This type of injury results in more pronounced functional deficits including motor weakness and takes much longer for restoration and recovery. Surgery may or may not be required in axonotmesis as some of the roadwork is intact for regrowth, depending on the degree of injury. However, patience certainly is required, as nerves regenerate at the slow rate of 1-2mm/day.

The most severe of lesions is **neurotmesis**, when there is loss of continuity between the connective tissue and axons. Not only has the axon been damaged but also the encapsulating connective tissue. There is severe internal disruption of the architecture of the nerve. Neurotmetic type injuries typically require surgery.



Axonotmesis
(picture courtesy Mackinnon & Dellon)



Neurotmesis (transection)
(picture courtesy Mackinnon & Dellon)

What are common causes of back pain?

Wear and tear conditions, such as degenerative arthritis and degenerative disc disease, are some of the most common causes. Low back joint restrictions and/or sacroiliac joint restrictions, muscle pulls and tears can cause back pain. Also weak or de-conditioned muscles, lack of flexibility, and poor posture all aggravate underlying conditions and worsen symptoms. Uncommon causes of pain include infection, cancer, fractures, aneurysms, and/or internal organ problems.

continued on page 8

"Hitting the Right Nerve" : Spine and Nerve Pathology

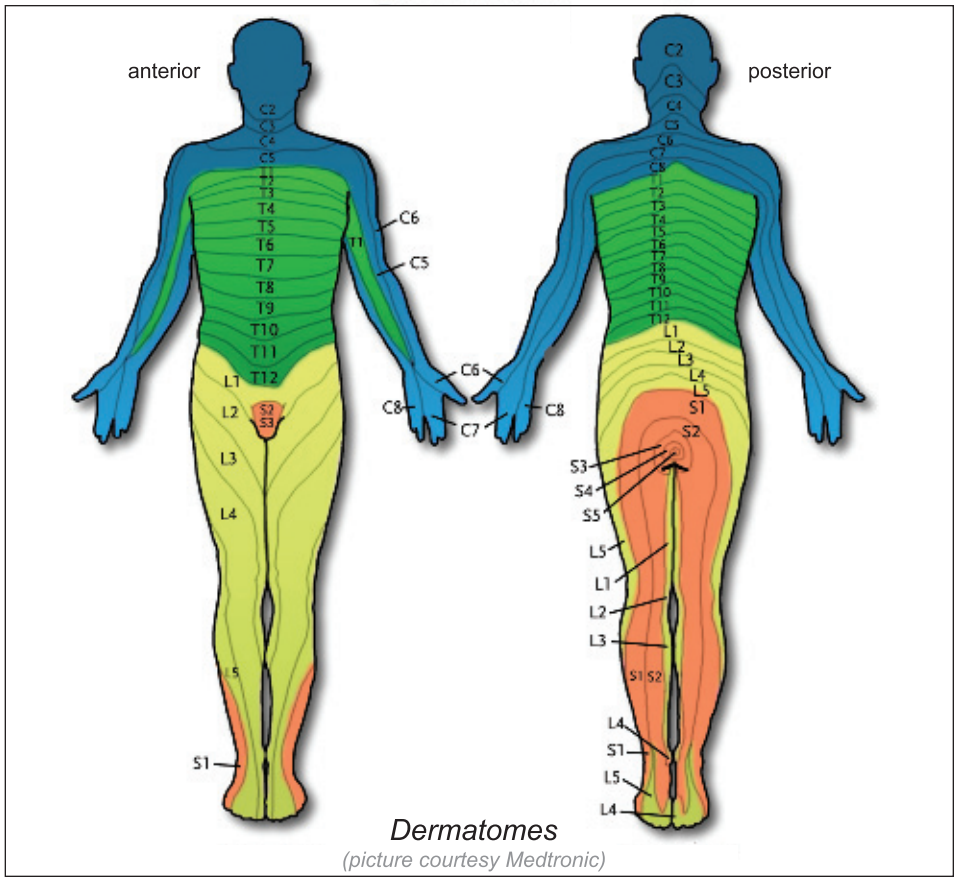
(continued from page 7)

4. Symptoms

General symptoms

Typical symptoms of nerve damage are pain, weakness (up to loss of function), and paresthesia (abnormal sensations such as numbness, tingling, pricking, or burning). If a specific nerve or nerve root is damaged, the affected body parts will be those innervated by the nerve. The location of the pain, motor deficit, and paresthesia is used to identify which nerve or nerve root is damaged.

A dermatome is an area of the skin supplied by nerve fibers originating from a single dorsal nerve root. Abnormal skin sensations in a specific skin area indicate which nerve root is affected.

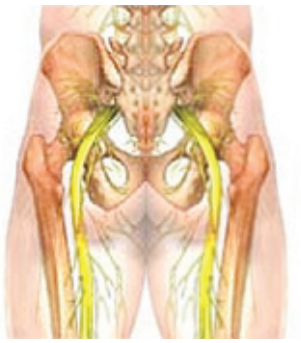


Dermatomes
(picture courtesy Medtronic)

Specific symptoms

Sciatica

Sciatica is the pain or discomfort associated with the sciatic nerve. The sciatic nerve is the largest and longest nerve in the body: from the lower back, down the back of the leg, to the foot. The most common symptom of true sciatica is pain in the posterior thigh, lower leg or foot that can be much worse than the accompanying lower back pain. Usually a patient will experience moderate to severe pain, which begins in the buttocks and runs down through the leg or foot. Often lower back pain begins a few days or weeks before the leg pain occurs, then the leg pain becomes worse than the back pain, and in some cases the back pain will completely disappear.



Sciatic nerve
(picture courtesy NLM)

True sciatica will produce pain that radiates beyond the knee. However, in the case of longstanding history of sciatica, the pain may gradually become localized to the buttocks and back of the leg. In this situation, the patient may have a vague aching pain that does not reach all the way to the lower leg or foot, though it may have done so earlier in the course of the disease.

Often there is no specific traumatic event or motion associated with the onset of sciatica. Standing, sitting, heavy lifting, sneezing, or having a bowel movement may aggravate the pain. Lying down is usually the most comfortable position.

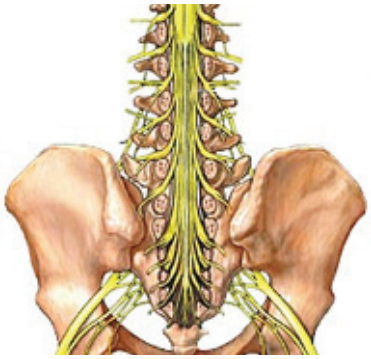
Neurogenic claudication

Claudication is pain in the leg and difficulty of walking. Neurogenic claudication is due to stenosis (causing compression of nerves in the lower back). Hence, some positions can alleviate the symptoms of spinal stenosis by increasing the amount of space available for the nerves. These positions usually involve flexion of the lumbar spine and bending forward. For instance, patients with spinal stenosis can ride a bike and walk up an incline or flight of stairs without any pain. They can often walk for extended distances if they have something to lean on, like a

shopping cart. However, if they are walking down an incline or flight of stairs, or if they have to give up the shopping cart, their symptoms will often reappear.

Cauda equina syndrome

The cauda equina syndrome results from the impairment of the nerves in the cauda equina, the bundle of spinal nerve roots that arise from the lower end of the spinal cord. The syndrome is characterized by dull pain in the lower back and upper buttocks and lack of feeling in the buttocks, genitalia and thigh, together with disturbances of bowel and bladder function.



Cauda equina
(picture courtesy NLM)

Neuropathy: injury or disease of a nerve.

Myelopathy: injury or disease of the spinal cord.

Radiculopathy: injury or disease of a spinal nerve root. Radiculopathy is a spinal nerve root dysfunction (not just irritation) presenting with pain, altered reflex, weakness, and nerve-conduction abnormalities. Pain is not always present with radiculopathy but is always present with radiculitis.

Radiculitis: irritation of the nerve root that causes pain.

Radiating pain: pain traveling from its original location to another area of the body. Radiculopathic pain typically radiates from the spine to the arms, legs, or trunk.

Referred pain: pain originating from an internal organ but interpreted by the brain as originating from another body part. For instance, pain from a heart attack is felt in the upper chest, left shoulder, arm, or hand.

Nerve compression in an area remote from the spine may cause numbness, pain, weakness, or paresthesia of the extremities or trunk (similarly to radiculopathy). Hence, the location of the symptoms does not immediately indicate the location of the compression (at the nerve root or at a location distant from the spine).

Two types of claudication

	Neurogenic claudication	Intermittent (or Vascular) claudication
Caused by	Pressure on spinal cord or nerves in the lower back	Narrowing of the arteries supplying blood to the legs
Pain pattern	Pain starts in the back then goes down the leg	Pain starts in the lower leg and then goes up the leg toward the lower back
Pain increased by	Standing and walking	Exercise such as walking, particularly uphill
Pain relieved by	Positions where the spine is flexed such as sitting and lying down in fetal position	Resting

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"Hitting the Right Nerve" : Spine and Nerve Pathology

(continued from page 9)

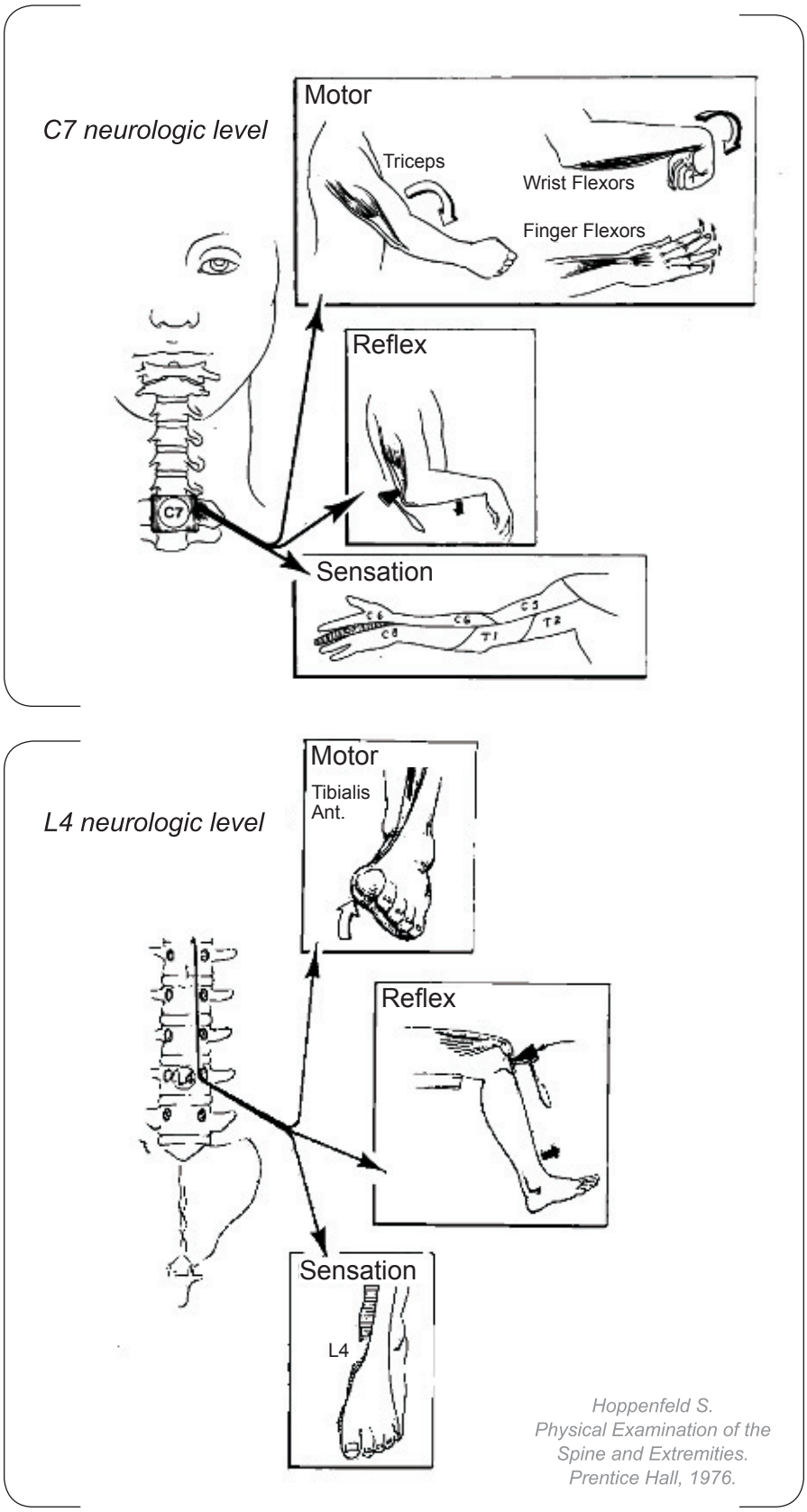
5. Diagnosis

Physical examination

The examination of motor function (myotomes), reflexes, and sensation in specific parts of the body (dermatomes) help identify the injured nerve root. For example, C7 radiculopathy (the nerve root at the level of the 7th cervical vertebra) is characterized by weak triceps and wrist extensor muscles and a numb middle finger. L4 radiculopathy (at the level of the 4th lumbar vertebra) is characterized by decreased kneecap reflex, loss of sensation and/or pain in the big toe side of the foot, and weakness in the muscles of the anterior lower leg.

How do disc injuries cause back pain?

The torn outer portion of an injured disc may irritate the nerves that innervate the outer edge of the disc. The injured disc may begin to degenerate, producing enzymes irritating the surrounding nerves, a common cause of chronic back pain. The injured disc is often weakened and allows abnormal motion of one vertebra in relation to the next causing irritation of the nerves that innervate the disc, surrounding facet joints and supporting tissues. An injured disc can also cause a piece of disc tissue to break off and compress the surrounding nerves, usually causing leg pain if the pinch is in the low back, or arm pain if it is in the neck; however, depending upon the position of compression, they may also cause central pain in the neck or in the low back.

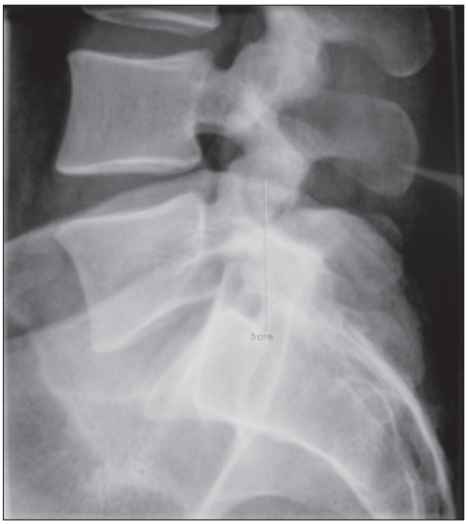


Hoppenfeld S. Physical Examination of the Spine and Extremities. Prentice Hall, 1976.

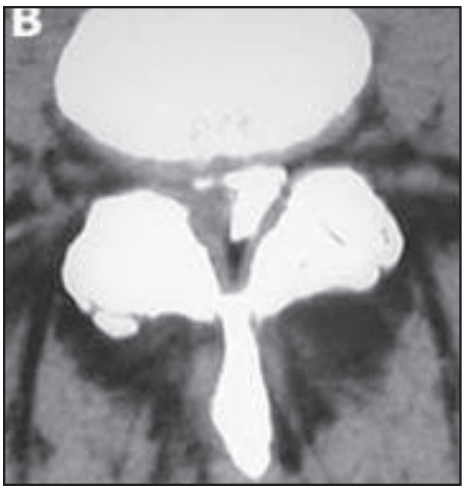
Radiographic studies

Images help identify the structure of the spine potentially responsible for the damage to the nerve. Some imaging techniques provide a better view of the bones while others provide a better view of soft tissues.

X-rays - Painless, non-invasive imaging process that utilizes photographic film to absorb electromagnetic radiation. X-rays give an excellent overview of the bones of the spine and skeleton.

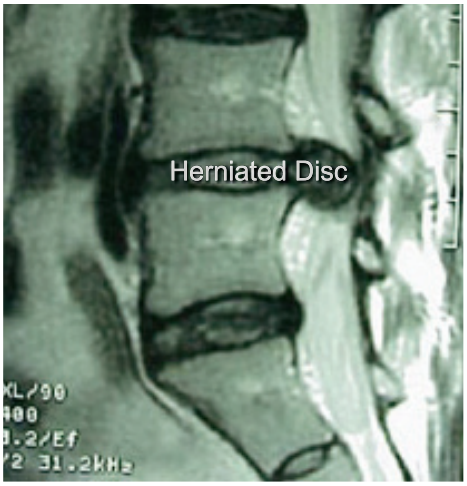


X-ray



CT Scan

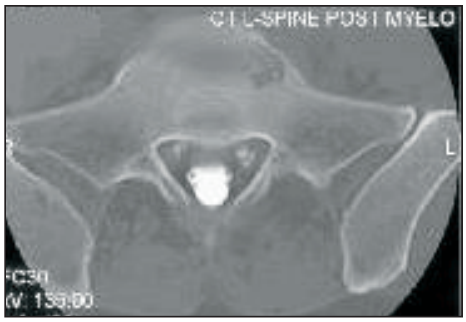
CAT Scan (computed axial tomography scan), also called a CT scan (computed tomography scan) - Another painless imaging technique that utilizes a computer to produce three-dimensional images from X-rays taken from different angles. CAT scans provide very detailed images of bones and soft tissue but emit high doses of radiation.



MRI showing a herniated disc

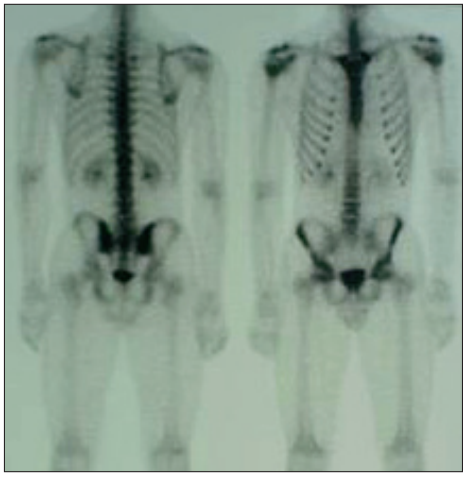
MRI in progress

MRI (magnetic resonance imaging) - Non-invasive technique that utilizes a magnetic field. MRI gives outstanding details of soft tissues such as the intervertebral disc, ligaments, and nerves.



Myelogram

Myelogram - A test procedure that involves injecting a radiographic contrast media (dye) into the sac (dura) surrounding the spinal cord and nerves, and then taking X-rays of the spine. This allows the radiologist to specifically X-ray the nerve roots. In this way, any abnormalities within the spinal canal can potentially be identified to aid in the diagnosis of certain spinal problems, such as nerve compression or a disc rupture.



Bone scan

Bone Scan - A test procedure that involves intravenously injecting a small quantity of a radiographic marker into the patient, and then running a scanner over the area of concern. A bone scan is utilized when there is suspicion of tumor, inflammation, infection, or small fracture.

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"Hitting the Right Nerve" : Spine and Nerve Pathology

5 - Diagnosis

(continued from page11)

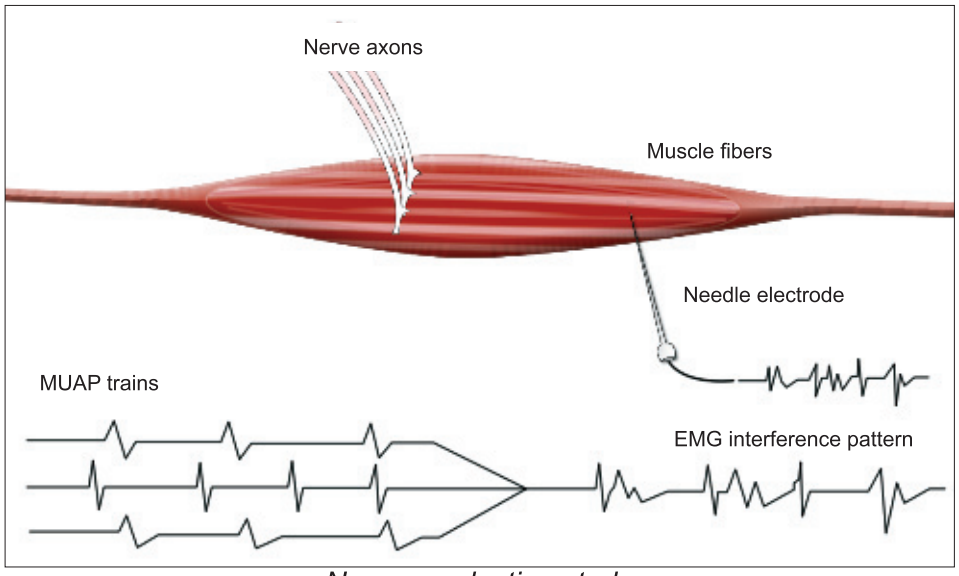
Electrodiagnostic medicine

by Vishal Kancherla, D.O.

The electrical qualities of the human nerve give us vital information about the health of the nerve. For instance, electrical signals travel at the speed of 50 meters per second in the nerves of the upper extremities. Abnormalities in these electrical characteristics indicate a problem with the nerve. Nerves transmit electrical signals to muscles making them contract or relax. Disease or injury to a nerve or muscle changes their electrical environment. The changes in the electrical characteristics of nerve and muscle are evaluated through electrodiagnostic tests. These tests identify the source of symptoms such as muscle weakness, numbness, spasms, paralysis, and pain. The tests also help delineate whether the problem involves nerves, muscles, spinal cord, or brain. For instance, a variety of muscle or nerve disorders can be detected by electromyography (EMG).

There are two parts to the electrodiagnostic study: nerve conduction study (NCS) and needle electromyography (EMG). NCS measures a nerve's electrical qualities and EMG measures a muscle's response. These two tests provide information about the function of individual muscle fibers and the nerve fibers that supply those muscles, and they aid to identify disease processes causing neurologic deficit. By combining data found on NCS and EMG, the location, duration, severity, and prognosis of the nerve lesion can be determined.

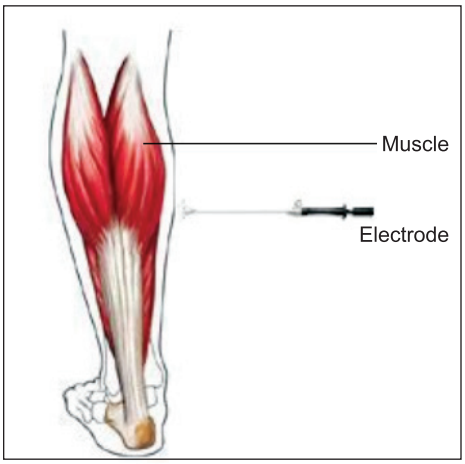
The **nerve conduction study** is the first part of the evaluation. An electrode is placed over the nerve to be studied and transmits an electrical signal to the nerve. The electrical signal is sent either up or down the nerve to a distant recording electrode that picks up electrical information. The process is repeated on the asymptomatic side of the body. The electric signal is then compared side to side and to normative data. Normative data for most of the major nerves in the body have been established through careful clinical research. The most commonly tested parameters of a nerve include the nerve conduction velocity (the speed at which the signal travels along the nerve), amplitude (the strength of the signal), and latency (the amount of time it takes for the response to arrive at the recording electrode). A deviation from the normal values of one or more of the above mentioned parameters would suggest damage to the nerve. Each specific abnormality indicates a specific diagnosis. For example, slowed conduction velocity of the sensory or motor nerve across the wrist would suggest carpal tunnel syndrome.



Nerve conduction study

Late responses tests are special tests of nerve conduction. For instance, the H-reflex is a special nerve conduction test that can determine if the reflex at the Achilles' heel is intact in its path from the foot to the spinal cord and back. If it is abnormal one might suspect an S1 nerve root lesion. F-responses are another special study of the integrity of the motor neuron, plexus, and nerve root of the upper and lower extremities.

The needle **EMG** is the second part of the study which detects disease or injury of the muscle or to the nerve that supplies it. During the test, a small needle electrode is inserted directly into the muscle. The electrical activity is picked up through the electrode and is displayed on an oscilloscope, a monitor that displays electrical



EMG

Common conditions referred for EMG

CONDITION	COMMENT
Radiculopathy(pinched nerve in the lumbar or cervical region)	Due to injury , ruptured disk, or other conditions causing nerve root injury
Peripheral Nerve entrapments	Carpal tunnel syndrome Pressure on the median nerve at the wrist causing pain in the hands
Primary Muscle Disorders	Myopathy, a disease process that causes the muscles to waste away
Neuromuscular Disorders	For instance, Myasthenia gravis, a defect in nerve impulses which causes chronic muscle weakness
Metabolic Disorders	For instance, Diabetes Mellitus
Nerve Disorders	For instance, Amyotrophic lateral sclerosis (Lou Gehrig's disease)

activity in the form of waveforms. An audio amplifier allows the electrical activity to be heard. Both sound and waveform are integral part in the interpretation of the electrical signals. The study is performed with the muscle at rest and in a contracted state. A healthy muscle at rest will be electrically inactive when a needle is inserted. Electrical activity upon insertion of the needle into a resting muscle signifies acute or new onset nerve damage. After testing the muscle at rest the patient will be asked to contract with slight contraction and forceful contraction. Testing the muscle when it is active gives the operator insight into the severity of the lesion and whether the nerve damage is old (chronic), resolving, and whether or not there has been repair. For example, a patient who suffers from a drop foot from a new onset large disc herniation would exhibit increased electrical activity when the muscle is at rest, if the test is done shortly after the injury. This would indicate an acute or new process. If the nerve is given a chance to repair itself after the lesion is removed through surgery and physical therapy, the motor function should slowly return. At this point in time, an EMG performed with the muscle in a contracted state would show evidence of re-innervation and healing of the nerve.

The physical examination, history, and provisional diagnosis help decide which nerves should be examined with electrodiagnostic studies. Based on that information, the electromyographer decides which nerves to include in the NCS. The results of the NCS add further insight to help decide which muscles to examine in through EMG.

The EMG/NCS is an invaluable tool in distinguishing between spinal related pathology and other etiologies of nerve damage. When used in conjunction with a thorough history and neurologic exam it helps the health care provider make an accurate diagnosis and develop an effective plan of care to optimize patient outcome.

Vishal S. Kancherla, D.O.

Dr. Kancherla is a board certified, fellowship trained Doctor of Osteopathic Medicine.

Dr. Kancherla specializes in interventional physiatry, the use of minimally invasive spinal procedures and electrodiagnostic nerve testing (EMG)in the evaluation, diagnosis and management of spine related pain syndromes.

"Hitting the Right Nerve" : Spine and Nerve Pathology

(continued from page13)

6. Treatments

Medications

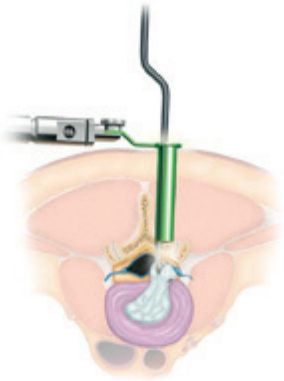
Analgesic (pain killer) medications are typically not very effective at relieving nerve pain. Better pain relief can be achieved with two types of medications: steroids and anti-convulsants. Steroids decrease inflammation and swelling, which indirectly decreases pain. Anti-convulsants modify the transmission of nerve signals and help calm down overactive nerves.

Injections

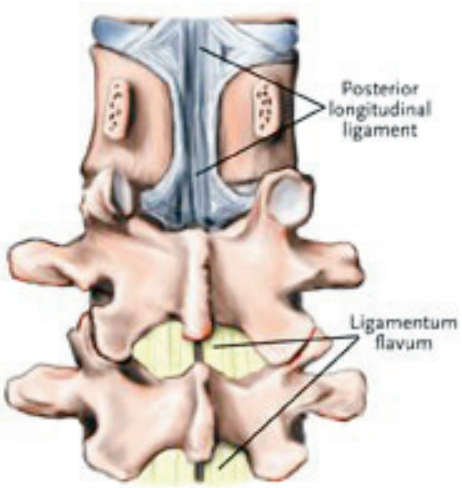
Medications may also be injected directly onto or near nerves. The main purpose of these injections is to deliver the medicine close to the source of pain and avoid the side-effects of oral medications. Depending on the location of the injection, the injections are called epidural, nerve block, or facet block. Two types of drugs are injected: analgesic and steroids. Analgesic drugs are similar to those used at the dentist: they will numb the painful area but wear off within hours. The immediate relief of pain confirms that the area targeted by the injection is the actual source of pain. Steroids will decrease inflammation and swelling but their effect will not be felt for about a week. With the use of injections, some patients are able to get relief from pain and even avoid surgery altogether[1].

Surgery

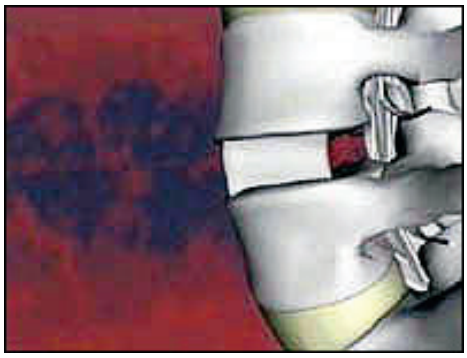
The rationale of surgery for radiculopathy is to remove the spinal structure causing damage to the nerve. If the source of the radiculopathy is a herniated disc, the part of the disc impinging on the nerve will be removed (discectomy). If spinal stenosis is the cause, several structures may have to be removed (laminectomy, foraminotomy). If there is slippage of the vertebrae, a fusion may be needed to realign the vertebrae and keep them in place.



Microdiscectomy
(picture courtesy Medtronic)



Laminectomy
(picture courtesy Medtronic)



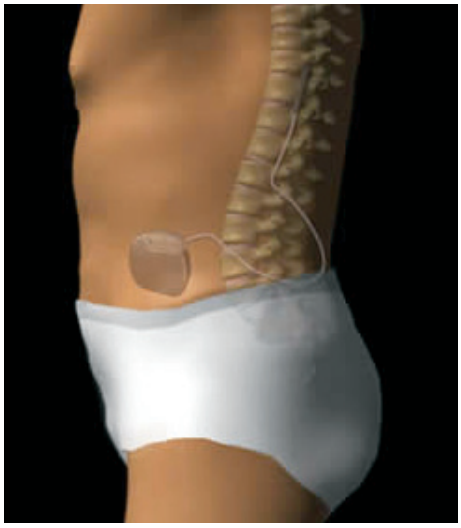
Fusion

Rigorous studies have compared non-surgical to surgical treatments and found surgery to be more effective at relieving pain due to herniated disc[2, 3], stenosis[4-6], and spondylolisthesis[7, 8].

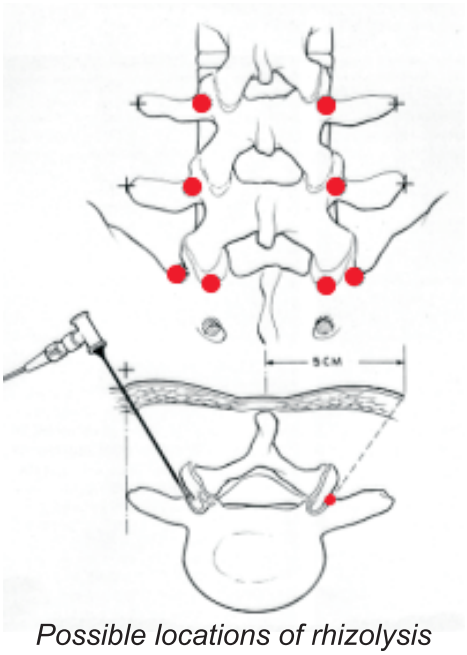
Spinal cord stimulator

The rationale of spinal cord stimulator is to mask the pain signals. Electrodes are implanted on the spinal cord. Those electrodes send low-level electrical signals that override the pain signals. Spinal cord stimulators have helped person who were not able to find relief with other therapies, including surgery. Persons considering a spinal cord stimulator will have a trial period: the signal generator is worn on a belt and the stimulation settings are adjusted. If the trial stimulation proves to help in pain reduction, the stimulator is implanted under the skin.

Trial spinal cord stimulator worn on a belt



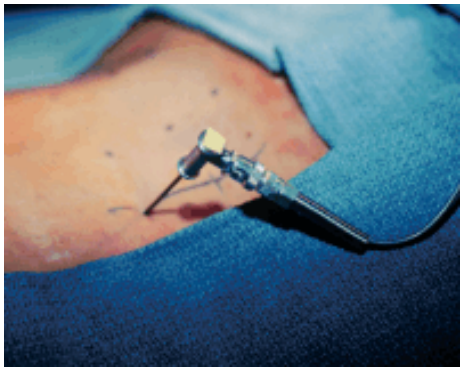
Spinal cord stimulator implanted under the skin



Possible locations of rhizolysis

Rhizolysis (also called rhizotomy or ablation)

Rhizolysis is the destruction of the nerve root assumed to be responsible for the pain. A probe is inserted and the nerve is burned through radio-frequency waves. The benefits of rhizolysis are debated but it appears that rhizolysis decreases pain and disability in some patients[9, 10]. The exact source of pain should be localized through injections or blocks before rhizolysis is undertaken.



Rhizolysis probe

1. Abdi S, Sukdeb D, Trescot A, et al. Epidural Steroids in the management of Chronic Spinal pain: A Systematic Review. Pain Physician. 2007;10:185-212.
2. Butterman GR. Treatment of Lumbar Disc Herniation: Epidural Steroid Injection Compared with Discectomy. The Journal of Bone and Joint Surgery. 2004;86-A(4):670-679.
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4. Atlas SJ, Keller RB, Robson D, Deyo RA, Singer DE. Surgical and Nonsurgical Management of Lumbar Spinal Stenosis. Spine. 2000;25(5):556-562.
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9. Van Kleef M, Barendse GAM, Kessels A, Voets HM, Weber WEJ, de Lange S. Randomized Trial of Radiofrequency Lumbar Facet Denervation for Chronic Low Back Pain. Spine. 1999;24(18):1937-1942.
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Are all bulging discs and/or herniated discs painful?

Many people have discs that are degenerative or abnormal and yet experience no symptoms. It is also possible that they may have had symptoms at one time, but they improved without any specific intervention. Many times, these degenerative discs are not painful at all until some significant injury or trauma damages them further, leading to significant instability and pain. The bottom line is just because a disc is abnormal does not mean it has to be painful.

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Physical Therapy for Nerve Pathology

By Richard Banton, PT, T-DPT, ATC and Larry Grine, MSPT, ATC

Physical therapy inventions such as manual therapy, neural mobilization, proprioceptive neuromuscular facilitation, and functional electrical stimulation (FES) have proven to be successful in relieving pain from nerve damage and facilitating the healing process.

Neural Tension Testing

Physical therapy interventions for nerve pathology have come a long way throughout the years. In the early 1900s surgeons would make an incision at the sciatic notch and actually grab the sciatic nerve with their hands. The debate was not if the nerve could be mobilized but how hard should you pull on it. Fortunately techniques to improve neural mobility have improved over the years.

When therapists choose to incorporate neural tension testing as part of their evaluation or intervention they are studying the nervous systems ability to dynamically move. Our neuroanatomical design must allow for features such as[1]:

- Sliding, gliding and strain, e.g. the sciatic nerve as you touch your toes
- Compression, e.g. the ulnar nerve compressing into the humerus during elbow flexion
- Strength, e.g. the sciatic nerve during a football kick
- Selectivity, e.g. reaction to fluids and chemicals that have access to neurons.

When performing neural tension tests, therapists aim to reproduce the patient's symptoms. A positive test indicates poor dynamic mobility of the nervous system. Neural tension testing does not give a therapist an exact reason for this loss in mobility, but only the knowledge that the system is not functioning at an optimal level. A more comprehensive examination and diagnostic testing is needed to determine the underlying mechanism.

The rationale behind the use of neural mobilization as an intervention is the assumption that the techniques can improve axonal transport, thereby improving nerve conduction velocity. The rational behind using neural mobilization as a diagnostic test can be explained using the straight leg raise test (SLR) as an example *(see picture on page 19)*. When SLR is severely limited, it is considered diagnostic for a disk herniation. The SLR produces a posterior shear and some motion in the lumbar spine. When the leg is raised between 30 and 70 degrees, the spinal nerves, their dural sleeves, and the roots of the L4-S2 segments are tensioned. The SLR test is positive when the patient's buttock, thigh, or leg pain is reproduced. When the leg is raised beyond 70 degrees, other structures such as hamstrings, lumbar facet joints, gluteal muscles, and sacroiliac joints are stressed and may also trigger pain in the buttock, thigh, or leg.

Nerves and their vascular supply are extremely sensitive to changes in tension, friction, and compression forces. If nerve tissue or dura becomes adherent, excessive stress may be produced in the areas of the adhesion, thus increasing the dura beyond its normal tension threshold. If nerves can not glide they have the ability to limit range of motion available to a joint. Therefore, a decrease in mobility of a nerve along its entire length makes the nerve vulnerable to additional injuries during repetitive movements.

Mobilization of the nervous system has a mechanical effect that provides increased vascularization to unhealthy tissues, improves transports of nutrients and oxygen to nerves, and prevents unnecessary scarring of connective tissues. Some literature has suggested that it may also facilitate regeneration of nervous tissue. It should be easy to imagine how a nerve compressed by edema or dura mater surrounded by blood would benefit from movement or mobilization. When nerves are compressed, they are deprived of oxygen and nutrients, which leads to damaged neural tissue, and thus scarring. Scarring interferes with normal biomechanics or movement of nerves. Restoration of normal mechanics of nerves after injury lessens the possibility of the nerve becoming entrapped and thus prevents further damage to other healthy connective tissues. Neural mobilization may promote the release of nerve growing cells and enzymes necessary for nerve regeneration and growth.

Examples of Positive SLR Test

Hip Range of Motion is Limited by Spasm Before 70 Degrees
Reproduction of Leg and Back Pain
Reproduction of Neurologic Pain Following Appropriate Dermatome

A comprehensive neurological evaluation can provide a moderately accurate diagnosis. The three diagnostic signs are muscle weakness, decreased sensation, and decreased reflexes. One sign by itself does not offer much, but three signs are usually indicative of pathology in a specific region. For instance, weakness of ankle plantar flexion, diminished sensation in the lateral foot and posterior calf, and an absent Achilles reflex indicates S1 nerve pathology. Add a positive SLR test to this examination and the sensitivity for a disc herniation at the L5-S1 becomes 95%. Physical therapists have become so adapt at identifying serious pathology such as nerve damage, tumors, and systemic pathology that they have been granted direct access in over 40 states. Direct access implies that patients can go directly to a physical therapist for treatment of their conditions without being evaluated by a physician first.

A neurological examination should be performed with all patients even if non-neural tissue is involved. The nervous system plays an enormous role in conveying, interpreting, and expressing impulses related to injury. Table 1 identifies pathology of the nervous system and which intervention would be most appropriate to use in treatment.

Contraindications to performing neural tension tests include malignancy involving the nervous system or vertebral column, acute inflammatory infections, acute disorders that have unstable neurologic signs, cauda equina lesions evident by alteration in bowel and bladder function or perineal sensation alteration, or injury to the spinal cord.

Precautions include acutely injured lumbar discs or cervical zygophyseal joints, spinal stenosis or spondylosis, highly irritable neural conditions, worsening disorders that have developed rapidly such as leg pain that developed in last 24 hrs, neurologic disease processes such as with AIDS or multiple sclerosis (MS), complaints of dizziness, circulatory disturbances in the area being tested.

Table 1: Pathology of Nervous System and Most Appropriate Intervention

Pathology	Description	Intervention
Inflammation from Acute Nerve Irritation	Burning, lancination pain	Ice, Bracing, Anti-Inflammatory Medication
Paresthesia from Nerve Entrapment	Numbness or tingling	Gentle Neural Mobilization, Manual Traction, Active Exercise
Scarring of Nerve from Chronic Nerve Irritation	Burning, lancination pain lasting longer than six weeks	Vigorous Neural Mobilization, Electrical Stimulation-TENS, Aerobic Exercise, Desensitization Massage
Radiculopathy from Nerve Cell Death	Decreased ROM with radiating pain, weakness and or numbness over distinct region	Gentle Neural Mobilization, Manual Traction
Neuropathy from Degeneration of Nerve	Decreased ROM with radiating pain, weakness and or numbness over multiple regions	Vigorous Neural Mobilization, Proprioceptive Neuromuscular Reeducation (PNF), Electrical Stimulation-FES

continued on page 18

Physical Therapy for Nerve Pathology

(continued from page17)

Electrical Stimulation (TENS And FES)

It has been known for nearly a quarter of a century that a nerve's membrane is electrically charged. In the presence of inflammation and swelling, this charge becomes more positively charged on the outside resulting in decreased neural output. Therefore, the patient may report a feeling of numbness or tingling. Compression that remains chronic, as with a disc herniation or chronic inflammation, may cause a nerve to become ischemic (decreased blood supply). Ischemic nerve roots cause burning, lancinating pain and may also result in weakness of the involved tissue. If inflammation is not treated early and is allowed to become chronic, scarring may develop around the nerve root. Scarring results in decreased mobility of the nervous system and will limit the patient's range of motion and functional ability.

Electrical stimulation (ES) has multiple uses for nerve injury that range from pain modulation to nerve reeducation, muscle pumping to reduce inflammation and retarding muscle atrophy. Nerves are classified as one of three types, A, B, or C. Table 2 lists some characteristics between the three types.

Generally, the larger the fiber type then the faster its velocity. Therefore, because nerve fibers function at different speeds, treatment with electrical stimulation must account for this fact by using different frequencies, wavelengths, and pulse widths.

Transcutaneous Electrical Nerve Stimulation (TENS) is an example of how electrical stimulation is used to treat nerve pathology. By delivering TENS at wave of 100-500 msec pulse per second, physical therapists are able to stimulate the large, myelinated A fibers, which in turn inhibit the slower unmyelinated C fibers that are sending pain signals to the brain. TENS also provides pain relief by the release of enkephalin from local sites within the central nervous system, and the release of endorphins from the pituitary gland into the cerebrospinal fluid. This effect of TENS has proven to be quite successful in relieving pain associated with reflex sympathetic dystrophy (RSD) and other sympathetic nervous system dysfunction. RSD is an example of a complex regional pain syndrome in which the body's sympathetic nervous system fails to regulate itself. Increased levels of adrenaline surrounds nerve cells causing hypersentivity, vasoconstriction to involved tissues, and an increase in sensory information relayed by type C pain fibers. The enhanced sensitivity to touch makes this condition very difficult to treat. The therapist's primary goal is to achieve desensitization of the tissue by any means possible. Interventions may include ice, TENS, or gentle massage techniques. Care must be taken not to increase pain in the tissues as this will stimulate the release of more inflammatory agents.

Another example of electrical stimulation is known as functional electrical stimulation (FES). When electrical current passes through muscle tissue it forces nerves to depolarize and thus contract the muscle. The choice of wavelength, pulse width, and intensity determines what type of nerve will be stimulated and, thus, determines the physiological effect. Studies have shown that for post-surgical or acutely injured patients, FES can be more effective than isometric exercises to prevent muscle atrophy. Although, the effects of FES are short term, it serves as a pain reducer in the early stages of rehabilitation and initiates the beginning of neuromuscular re-education.

A physical therapy intervention is most effective when it addresses facts learned from the evaluation of patients, addresses patient's functional needs, and is designed from a combination of therapist experience and scientific research. Science has shown that early intervention is most critical when treating nerve pathology.

Table 2. Types of Nerve Fibers

Fiber Type	Fiber Size	Velocity	Origin	Function
A Fiber	Large	Fast	Tendons, Muscle Skin	Motor
B Fiber	Small	Slow	Sympathetic Ganglion	Sympathetic Response
C Fiber	Smallest	Slowest	Muscle and Skin	Pain

Tests to evaluate the ability of the nervous system to elongate[1]

Straight Leg Raise (SLR) (L4-S2)

Method: passively lift testing leg from ankle with one hand above knee to maintain knee extension. Leg is lifted until symptoms are provoked or end range of motion. Note location of symptoms and range of motion attained. Compare to contralateral side.

Indications: routine for all spinal and radicular leg symptoms.

Prone Knee Bend (L1-3)

Method: therapist passively flexes knee to point of maximum resistance or onset of symptoms. Note location of symptoms and range of motion attained. Compare to contralateral side.

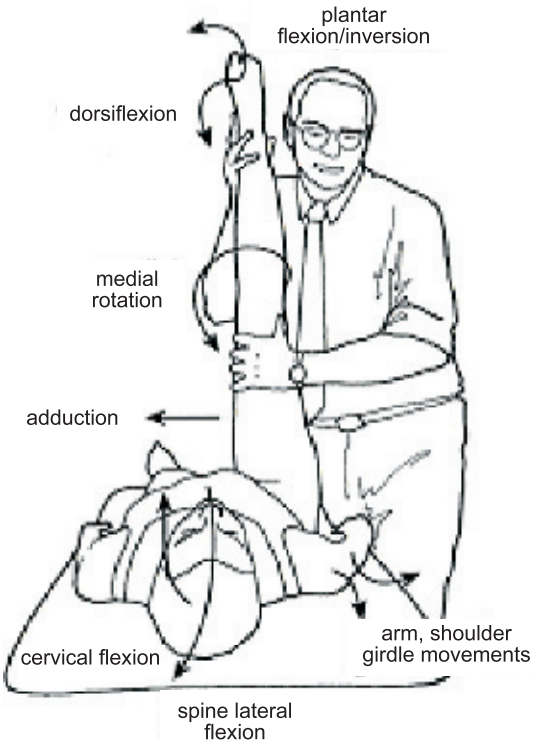
Indications: patients with knee, anterior thigh and hip and upper lumbar symptoms.

Slump Test

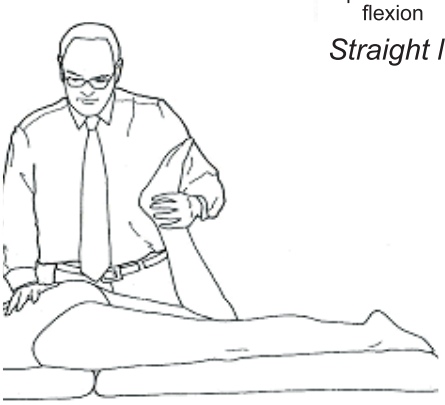
Method: (1) Patient asked to 'slump' or 'sag' while the examiner maintains the cervical spine in neutral. Apply overpressure to the lumbar and thoracic flexion to further 'bow' the spine. Assess response. Maintaining spinal flexion, ask the patient to take their chin to their chest and apply some overpressure. Assess response.

Ask patient to extend knee actively. Then have patient dorsiflex the ankle to see if symptoms are elicited or worsened. Repeat other leg. Compare the two and assess response.

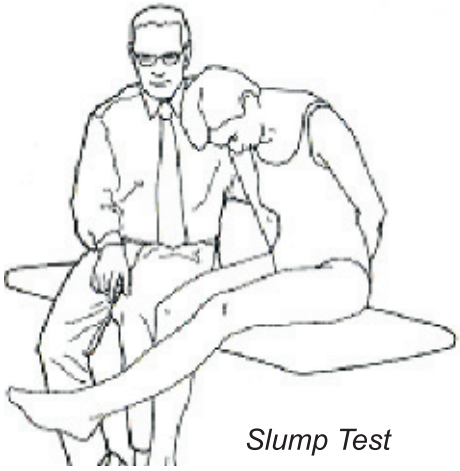
** If any of the positions elicit pain, release the neck flexion component to see if symptoms are alleviated.



Straight leg Raise



Prone Knee Bend



Slump Test

If so, these symptoms can be interpreted as neurogenic in origin.

Indications: when there are spinal symptoms, to assess treatments using nerve mobilizations such as SLR.

ULTT1 (Median Nerve Dominant)

Method: use hand closest to patient to maintain neutral shoulder girdle position by depressing shoulder during testing, the other hand is used to control the patient's hand on the side being tested with access to control the finger tips and thumb. This position is easier to maintain by resting pt's arm on PT's thigh (stage 1). Abduct patient's arm 110° (stage 2), supinate forearm and extend wrist and fingers (stage 3), laterally rotate shoulder (stage 4), and extend elbow (stage 5). Be sure all components are maintained

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Physical Therapy for Nerve Pathology

(continued from page 19)

throughout testing. Cervical flexion toward and away from the examiner can be added (stage 6). Assess the range attained before onset of symptoms and if patient's symptoms are reproduced.

Individuals without pathology will experience a deep stretch or ache in the cubital fossa that extends down the forearm, a tingling sensation in the thumb and 1st 3 fingers, or stretch in anterior shoulder. Symptoms will typically be worse with lateral flexion away from the therapist and ease with lateral flexion toward.

Indications: patients with symptoms anywhere in wrist, arm, head, neck and thoracic spine. This neural mobilization technique is effectively used to treat carpal tunnel syndromes.

ULTT2 (Radial Nerve Dominant)

Method: using the thigh, depress shoulder girdle with the arm in approximately 10° abduction, extend elbow (stage 1), medially rotate entire arm (stage 2), flex wrist (stage 3), thumb and finger flexion (stage 4). If the patient has more distal symptoms, the shoulder depression can be released to see if symptoms are relieved. If more proximal symptoms are present, the wrist can be moved to see if alteration in symptoms.

Indications: should be examined in cervical, thoracic, and upper limb disorders especially where disorders involving the radial nerve exist such as in tennis elbow.

ULTT3 (Ulnar Nerve Dominant)

Method: extend wrist and supinate forearm (stage 2), fully flex elbow (stage 3), shoulder depression and lateral rotation (stage 4), shoulder abduction to bring patient's hand over the ear (stage 5). Lateral flexion of the neck away from the therapist can be added (stage 6).

Patient may feel burning or tingling in ulnar nerve distribution or at medial elbow. Always compare to contralateral side, assess tension, and where in range of motion symptoms or tension begin.

Indications: when any suspicion of ulnar nerve involvement exists in patient's symptoms such as golfer's elbow.

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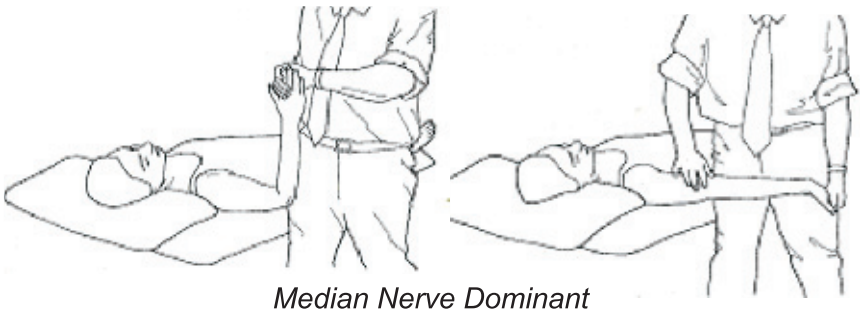
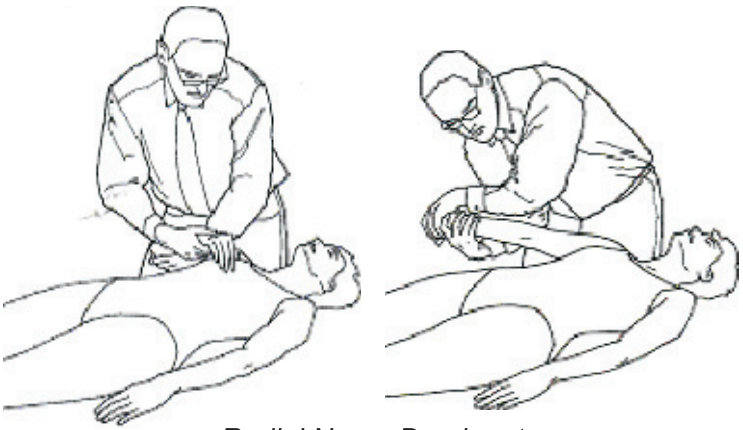
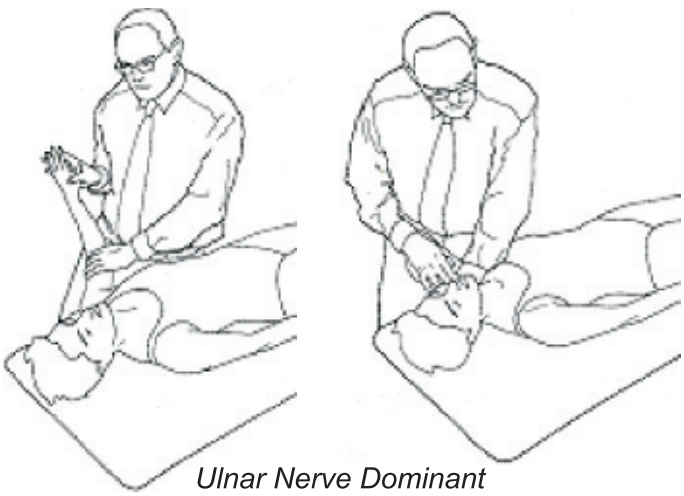


Median Nerve Dominant



Radial Nerve Dominant



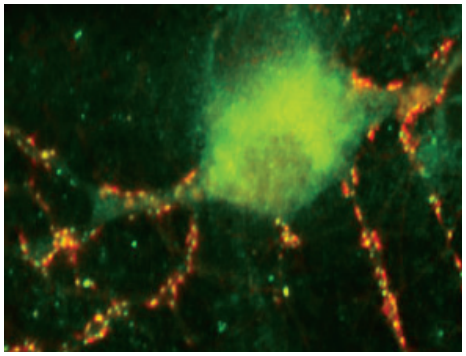
Ulnar Nerve Dominant

The Future of Nerve Repair

By Marcus M. Martin, Ph.D.

Introduction

The treatment of spinal cord injury (SCI) remains a major challenge to modern medicine. Currently, the only options available when treating these injuries are to halt the progression of the damage and then promote rehabilitation. The option of repairing the spinal cord was accepted as improbable because of the limited regenerative ability of spinal cord tissue.



Nerve Cells

cmbi.bjmu.edu.cn/news/0605/123.htm
Image provided by Dr. S. Wojcik, Max Planck Institute of Experimental Medicine, Göttingen, Germany

However, several promising advances are being made on the frontiers of spinal research which have the potential to dramatically change the long accepted treatment approach. They aim to include nerve regeneration as a potential treatment for spinal cord injury. This review outlines some of the major scientific developments in the treatment of SCI. The investigation into this area tends to fall into two main categories. The first involves the transplant of cells and tissues into the damaged areas of the central nervous system and the second is to enhance the latent regenerative ability of the nerve cells at the site of trauma[1-3].

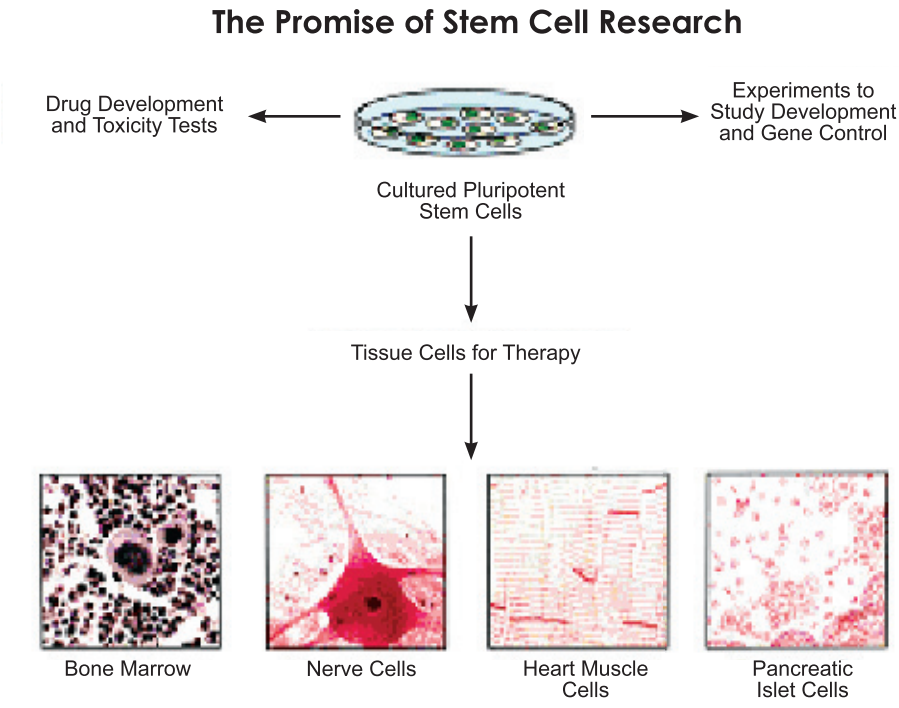
Cell and Tissue Transplant

Stem Cells

Stem cell therapy presents the exciting possibility that transplanted cells will compensate for cell loss due to injury and restore tissue function. The success of this approach has already been demonstrated in mice, where the use of embryonic stem cells and neural progenitor cells facilitated functional recovery in rodent spinal injury models. However, this field of research faces several hurdles. Transplantation of fetal CNS tissue faces opposition on ethical grounds, as well as the practical difficulty of obtaining adequate human cells to infuse at the site for therapeutic effect. Stem cell therapy has gained great momentum following the successful isolation and culture of pluripotent neural cell lines from bone marrow and umbilicord derived human cells along with encouraging results from rodent studies. This has led to the anticipation that this approach might work with human spinal cord injuries. There is still a lot of work to be done in the area of stem cell therapy. To date, there is no verified report of human recovery due to a stem cell transplant, but new approaches are emerging based on current research[4-6].

Schwann Cell Implants

Schwann cells are instrumental in the repair of peripheral nerves. These cells express neurotrophic factors and aid in the proliferation and myelination of regenerating axons. When a spinal cord injury occurs, Schwann cells migrate to the site of the injury where they produce extracellular matrix molecules and several growth factors.



Stem cell differentiation

http://stemcells.nih.gov/staticresources/info/media/DSC_1188.jpg

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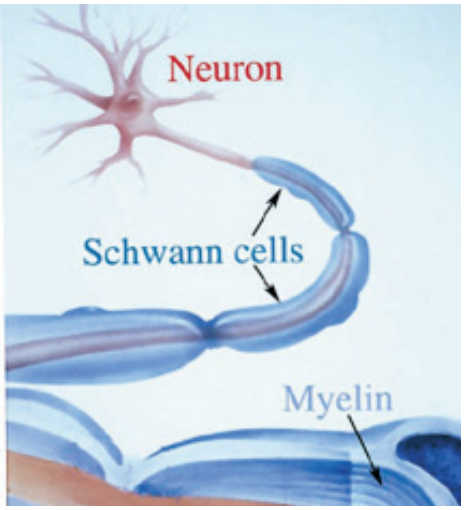
The Future of Nerve Repair

(continued from page 21)

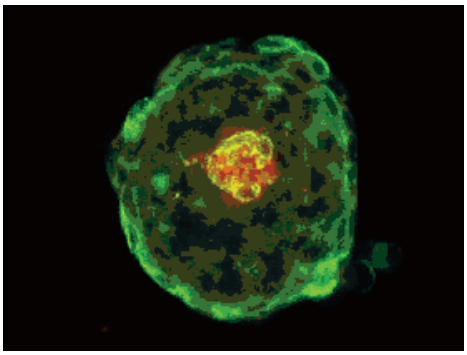
In animal models, the grafting of Schwann cells to spinal cord lesions has demonstrated stimulation of axonal regeneration and myelination. It is clear that these cells can contribute to the repair of injured spinal cords. They may need to be optimized in combination with other approaches to facilitate the connection of the cord segments adjacent to the gap[7, 8].



Schwann cells
(courtesy Dr. J. Salzer, NYU Scool of Medicine)

Olfactory Ensheathing Cells (OEC)

Olfactory ensheathing cells usually facilitate the regeneration of the olfactory nerve of mammals. There is a significant body of scientific evidence which suggests that they could be useful in the treatment of CNS injury. Recent studies in rats demonstrate that olfactory ensheathing cell transplantation promotes the improvement of hind limb stepping in paraplegic rats[9]. Experiments performed in rats showed that sensory axons grew from the dorsal roots of lesions into the spinal cord after OEC implant into the spinal tissue proximal to the dorsal root entry zone[10, 11]. The injured axons were able to regenerate beyond the spinal cord bridge or across a complete transection.



Olfactory ensheathing cells
www.vet.cam.ac.uk/.../neurosciences/mechcns.html

The results to date are encouraging, however, more studies need to be performed using these cells before we can determine if this approach can be utilized in human treatment[11, 12].

Molecular Enhancement of Regenerative Ability

It is generally believed that the functional specialization of CNS cells results in the limitation of their reparative ability. This belief suggests that a complete severance of the spinal cord at any point would preclude the potential to regenerate cells and bridge the gap. Observation of spinal cord regeneration in amphibian physiology and neonatal mammals led some researchers to consider that it might be possible to facilitate the restoration of regenerative ability to adult human spinal cord cells after injury. Currently, there is a considerable amount of research which aims to understand the process of restoration of the regenerative capacity of CNS cells. This area of research includes the use of inhibitory molecules, extracellular matrix manipulation, nerve growth factors and inhibition of glial scarring[13].

Inhibitory Molecules

Recently some inhibitory molecules to myelin have been isolated. The antagonists to these molecules appear to promote recovery from spinal injuries in experimental rat systems. One of these inhibitory molecules, NoGo, is considered to have strong potential as a therapeutic target. The use of IN-1, a monoclonal antibody, and NEP 1-40 which blocks the receptor for NoGo have been demonstrated to show long tract generation in rats. Another molecule, myelin associated glycoprotein (MAG) is also implicated in the inhibition of the regeneration of neural cells. Both molecules are referred to as myelin-derived growth-inhibiting proteins. Blockage of the Rho pathway also believed to allow axons to overcome inhibitory signaling by NoGo and other inhibitor molecules present in glial scars. Clinical trials of both NoGo and C3Rho inhibitors are underway to determine the potential of this therapy. If these studies are successful, they could lead to the development of therapies to stop the activity of nerve growth inhibitors[14-16].

NoGo, oligodendrocyte-myelin glycoprotein (OMgp), myelin-associated glycoprotein (MAG) and repulsive guidance molecule (RGM) are all identified as inhibitors of CNS neural regeneration. These molecules send inhibitory signals utilizing other molecules such as RhoA and other effector Rho kinases. In experimental models, the inhibition of this pathway promotes the regeneration of axons and functional recovery in damaged CNS tissue of rodents. Inhibition of this pathway is a very promising potential drug target[17-19].

Extracellular matrix manipulation

During the early part of neural development, several molecules are produced which promote the growth of neural cells. These are later down regulated in the adult CNS promoting the stability of the circuitry. It is believed that this leads to a shift in the balance from the factors which support neurite growth toward the expression of inhibitory molecules. Extracellular matrix proteins chondroitin sulfate and proteoglycans are believed to contribute to the arrest of spinal cord generation. Studies performed with rats show functional recovery in rats with dorsal column lesions which were treated with intrathecal infusion of chondroitinase ABC which blocks chondroitin sulfate activity. Therefore in order to stimulate the activity of the down regulated molecules, chondroitin sulfate removal may be beneficial[2].

Nerve growth factors

Identification and administration of neutrophins have the potential to stimulate axonal growth in areas of nerve injury. Nerve growth factors NGFs have been identified which stimulate the growth of fine primary afferent nerve fiber systems. Neurotrophin 3 (NT-3) has been

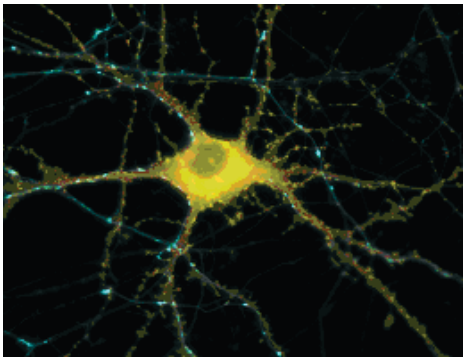
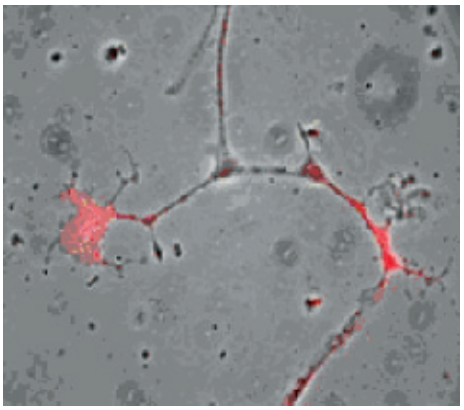


Image of neuron showing actin formation in response to stimulation.

http://ucsdnews.ucsd.edu/graphics/images/nervecell.jpg



A growing sensory axon in culture has the putative inhibitor of axonal growth (Nogo-A, red) in its growth cones

www.anat.ucl.ac.uk/research/anderson/index.shtml

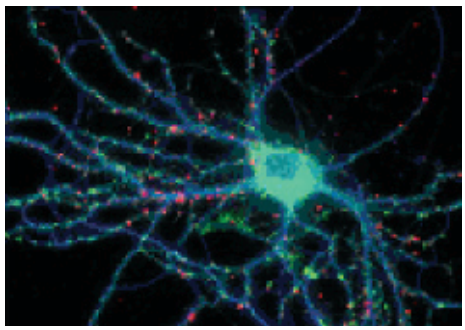
shown to stimulate corticospinal growth. Glial derived neutrophic factors and brain derived neutrophic factors have shown some success in stimulating the regrowth of cut dorsal roots in the dorsal root entry zone. This approach could possibly be refined to stimulate similar nerve growth in humans[20, 21].

Inhibition of glial scarring

After spinal cord trauma the affected axons may die by necrosis or later by apoptosis. The surviving neurons initiate abortive neurite regeneration. It has been demonstrated that after grafting with peripheral nerves the cut spinal cord may grow to the full length of the distal stump but lack the ability to reconnect with the distal stump. The regenerative capacity of these cells may be physically inhibited by the glial scar tissue. Recent work done in mice indicate that CHL1is a component of glial scars which may restrict posttraumatic axonal growth and the remodeling of spinal circuit binding mechanisms. The research focus in this area is designed to restrict the scar formation in an attempt to foster the reconnection of the severed ends. In experiments aimed at blocking the glial scar combined with the inhibition of the activity of growth factors and their receptors there has been enhanced axonal regeneration[2, 22-24].

Neuro-protective agents

Neuro-protective drugs are agents which limit or reduce the amount of nerve injury caused following the initial trauma. Following a nerve injury most damage is done to the spinal cord during the inflammatory reaction at the site of injury. Current research indicates that as little as 10% of the spinal cord white matter tracts when left intact can allow rats to retain mo-



Fixed Neuron: A multi-wavelength, three dimensional, wide-field immunofluorescence image of a fixed neuron.

www.wadsworth.org/cores/alm/gallery.htm

tor ability[1]. The reduction of this secondary inflammatory reaction could preserve a large amount of spinal cord tissue. Recent studies based on the off-label effects of statin drugs show great promise in animal studies for reducing post operative nerve damage. Hydralazine a drug once commonly used to treat high blood pressure appears to also have some neuroprotective properties. Researchers at Perdue University showed that this drug may also help repair nerve damage from spinal cord injury by preventing the cascade of cell death which usually

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The Future of Nerve Repair

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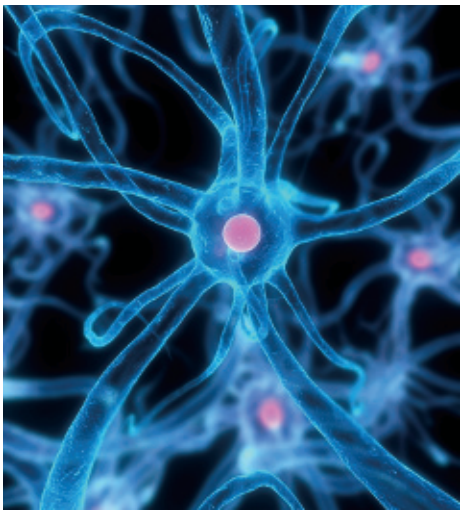
occurs around the injury site. Since hydralazine can pass through the blood brain barrier into the CNS it could possibly be administered by a single injection in the arm. Before these drugs can be used as neuroprotective agents in humans more research needs to be done in this area. However, research done in rats shows great promise.

Nanotechnology

Another promising area of spinal cord research is nanotechnology. In order to address spinal repair it would likely require preservation of the tissue, growth across the gap, growth promotion and reconnection by plasticity. The use of synthetic self assembling nanofiber scaffolds to create this environment is a possibility. Using a mechanical model researchers were able to stimulate the regeneration of nerve tissue promoting the restoration of vision shown by orientation behavior. Neuroprotective compounds delivered using nanowires showed a higher level of protection of sensory motor function, cord pathology, edema formation and blood-spinal cord barrier breakdown compared to the parent compounds delivered systemically. The nanowire administered compounds might have greater accessibility within the cord than the parent compounds independently. This technology promises to provide a structure to facilitate nerve regeneration as well as an advance system of drug delivery to enhance the activity of neuroprotective drugs[25].

Conclusion

Though several of these methods show great promise, it is not certain if one of these approaches will prove to be enough to stimulate nerve repair. It is more likely that a combination of different approaches may be required to provide conditions which facilitate axonal regeneration. Nevertheless it is undeniable that we are moving ever closer to the goal of CNS nerve repair and regeneration. This offers hope to many of the millions of persons afflicted with spinal cord injury. In our enthusiasm about these advancements it must be remembered that many of these potential treatments are still in the early stages of development. However, the future of spinal cord research and repair looks very hopeful.



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Research Notes

by Marcus M. Martin, Ph.D.

Development of combination strategies to repair the injured spinal cord

By Mary Bartlett Bunge, Ph.D.

The goal of our research is primarily to foster regeneration of axons across and beyond the area of injury. This has been an objective since moving to Miami in 1989. To improve regeneration of axons after spinal cord injury(SCI), we are investigating increases in cyclic AMP levels, interference with proteoglycans (molecules that inhibit axonal growth), transplantation of Schwann cells and/or olfactory ensheathing glia, and genetic engineering of these cells before transplantation to improve their neurotrophic factor-secreting capability. We have also initiated a new microarray study to explore gene differences between neurons that are able to regrow onto a cellular bridge placed in the area of injury and those that do not grow onto the bridge. Because the reactions of the tissue to spinal cord injury are many and varied, I espouse the concept that a combination strategy will be necessary to adequately improve outcome after spinal cord injury.

A main contribution of our laboratory has been to introduce the novel use of a cellular (Schwann cell) bridge across a complete transection gap in the adult rat spinal cord. We have tried a number of combination strategies, and the spinal cord injured animal has improved. For example, when neurotrophins, brain-derived neurotrophic factor and neurotrophin-3, are introduced along with Schwann cell bridges, there are more regrowing fibers on the bridge and there is an increased variety of fibers on the bridge, including some from distant neuronal somata positioned in the brain stem. Fibers also exit the bridge after a combination strategy, such as the transplantation of olfactory ensheathing glia at either end of the Schwann cell bridge. This combination also led to long-distance axonal regeneration in the adult rat spinal cord. We also have tested combination strategies in a spinal cord contusion model. We have demonstrated that a combination strategy with either lesion model is consistently more effective than transplanting Schwann cells alone. Also, more recent studies have been initiated to assess transplanted Schwann cell survival, how to improve it, and to investigate modes of presenting the Schwann cells in the spinal cord from a bioengineering perspective.

It is hoped that this work will lead to the development of treatments that result in the repair of damaged spinal cords. If perfected, these strategies for CNS regeneration could allow those immobilized due to spinal cord injury to be able to regain sensation and motor ability in paralyzed limbs.

Mary Bartlett Bunge, Ph.D
University of Miami
Leonard M. Miller School of Medicine,
The Miami Project to Cure Paralysis.

Dr. Bunge has made significant scientific contributions in the area of understanding nerve injury and axonal regeneration.

Selected Publications
Golden KL, Pearse DD, Blits B, Garg M, Oudega M, Wood PM, Bunge MB (2007) Transduced Schwann cells promote axon growth and myelination after spinal cord injury. Exp Neurol. 207:203-217.
Hill CE, Hurtado A, Blits B, Bahr BA, Wood PM, Bunge MB (2007) Early necrosis and apoptosis of Schwann cells transplanted into the injured rat spinal cord. Europ J Neurosci. 26:1433-1445.
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When do most people develop significant low back pain?

The usual age of onset of severe lower back pain is between 30 and 50 years old. It is also common in this age group for individuals to be very preoccupied with their life and occupation so that they may not take as good care of themselves as when they are younger. This leads to increased stress on the disc thereby predisposing them to injury and significant pain. The incidence of low back pain is equal between males and females.

Research Notes

Biomechanics of the Interspinous Spacers Appropriate for use with Minimally Invasive Surgical Procedures

By Vijay K. Goel, Ph.D.

Interspinous spacers have gained prominence for the treatment of spinal stenosis and other related issues. The thrust, at present, is to develop spacers suitable for minimally invasive surgical procedures (MIS). We have tested two such spacers in a cadaver model.

Fifteen fresh frozen L1-S1 ligamentous spine specimens were used for the two-part study. In part I, the specimens were potted and sequentially tested for the load-displacement behavior for the intact, and Vertiflex interspinous spacers placed at L3-4, and L2-3 and L3-4 levels. A maximum moment of 10 Nm with a 400 N follower load was applied in flexion, extension, lateral bending and axial rotation. The data for the stabilized cases was compared with the intact motion data. In part II, motion segments were implanted with a Vertiflex or Synthes spacer and subjected to 30,000/50,000 cycles of flexion-extension (10°/5°) or lateral bending (+7.5°) plus axial rotation (+3°). The moments and torque variations over time were recorded. Specimens were radiographed and CT scanned pre and post cyclic tests. Following testing, specimens were dissected to visually assess damage to the spacer and tissue around the spacer site.

The motion decreased in extension while in other modes there were no significant differences with the intact motion data. There were no significant decreases in moments/torque during cyclic loading.

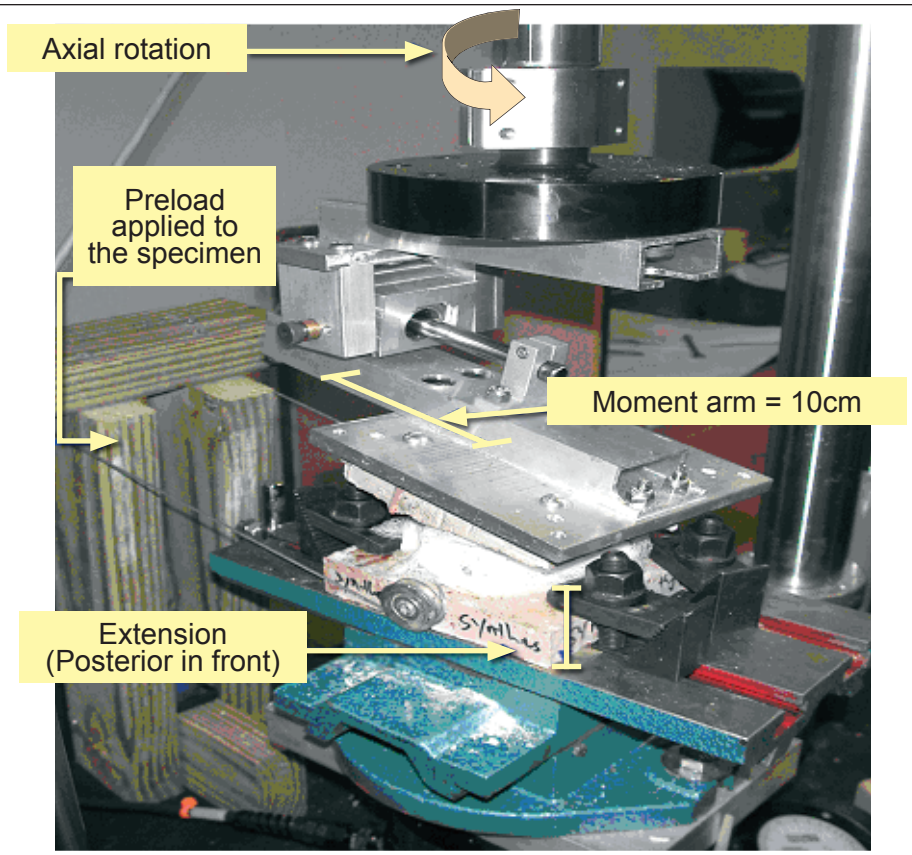

Figure showing a ligamentous motion segment in an MTS Test set up for cyclic testing in flexion-extension and axial rotation.

We did not see any noteworthy damage to the spinal elements around the spacers or to the spacers themselves. The reduction in motion in extension was similar to the data reported in the literature for the conventional interspinous spacers.

In conclusion, the Vertiflex and Synthes spacers were found to limit the motion in extension and can withstand complex cyclic loading without any significant damage to the spacers or the surrounding tissue.

Acknowledgements: Work supported in part by grants from Orthokinetic Technologies, LLC and Synthes Spine, Inc.

Vijay K. Goel, Ph.D.

Department of Orthopedic Surgery
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As a researcher, Professor Goel has made several noteworthy contributions in the area of spinal biomechanics.

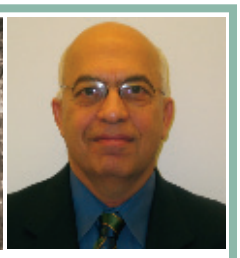
Design of Advanced Biomaterials to Repair the Injured Spinal Cord

By Dr. Penelope Georges and Dr. Noshir A. Langrana

As biomedical engineers, our approach to remedy medical pathology involves building and design. In the event of traumatic spinal cord damage, there are repairs that require engineering of replacement spinal discs or functional bone and cartilage tissue. Very often, however, damage necessitates the construction and design of replacement nervous tissue of the spinal cord, a venture that has yet to be definitively accomplished. Spinal cord injury (SCI) often results in damage to axons in the white matter of the spinal cord and subsequent interruption of neuronal communication. The re-establishment of neural circuitry via regeneration of axons is a critical process in reversing the effects of SCI. While numerous biological therapies (i.e. stem cell transplantation, various pharmacological agents) are being pursued to enhance spinal cord regeneration, tissue-engineering strategies have emerged as alternatives and/or compliments to other approaches. Many tissue engineering strategies introduce a biomaterial to serve as a bridge or scaffold to support the growth of regenerating axons from proximal to the injury site to their distal target[1] and aim to mimic the nervous system during axiogenesis.

Biomaterials are implanted at the site of SCI to support axonal regeneration through the normally harmful microenvironment that appears following injury. Such biomaterials can be improved by introducing chemical and structural modifications that mask inhibitory cues and the intrinsic ability for spinal cord axons to regenerate and present trophic ones[2, 3]. Environmental cues that stimulate and direct growth cone migration during neuronal development are incorporated into biomaterials. Much progress has been made in using diffusible growth factors[4], supporting cells[4, 5], and adhesion molecules[6, 7] in improving the regenerative environment. Our lab studies how the mechanical properties of matrices could also affect native and transplanted cell growth. The recent work of our laboratory occurs at the interface of novel, "active" biomaterials as well as established neuroscience and cell biology techniques to establish a replacement network of nerve tissue from dissociated spinal cord cells. The contribution of our work to the field of neural tissue engineering is the development of DNA-cross-linked hydrogels. These gels have not only been adapted for neural cell growth, but are force-actuating: a time-dependent, controlled force can be applied to the cells grown on them as well as tissue or other biomaterials attached to them.

Various polymers have been tested for use as guidance channels for nerve regeneration in the injured spinal cord[1]. A good example is a multicomponent polymer implant modeled after the intact spinal cord consisting of poly(lactic-co-glycolic acid) seeded with neural stem cells and found to improve motor function and reduce glial scarring[8]. Other scaffolds containing both matrix components and cell lines supporting neuronal regeneration after spinal cord injury have been designed to be either biodegradable using poly-beta-hydroxybutyrate (PHB) fibers[9] or mechanically stable using poly(2-hydroxyethyl methacrylate)[10]. However, despite much progress made, none of these devices have completely repaired spinal cord injury.



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Dr. Georges expertise is in the area of cellular interaction with advanced biomaterials.

Dr. Langrana is internationally recognized for his work on spinal biomechanics.

Tissue engineering solutions described above facilitate spinal cord regeneration by enticing neurite outgrowth through a biomaterial scaffold. Other strategies that have only been used in cell culture physically induce growth by applying tension to axons. Our group is in the design stage of a hydrogel device that will incorporate both methods, by applying controlled tension to a culture of spinal cord cells cultured on a permissive biomaterial that conjoins two severed sections of a spinal cord. The goal of this material is to achieve uniaxial, elongated cellular tracts within an implantable matrix, similar to the tracts severed during a spinal cord injury. There are two design objectives for our device: first, to identify optimal static mechanical properties of the biomaterial scaffold, or the most favorable stiffness at which we can achieve optimal cellular growth and function and, second, to identify optimal dynamic mechanical properties of the scaffold, or the magnitude and rate at which to "stretch" neurons that were cultured on a previously static hydrogel.

continued on page 28

Research Notes

Design of Advanced Biomaterials (continued from page 27)

Static Mechanical Conditions Ideal for Spinal Cord Neural Cell Growth

Our work is motivated by the findings of the past decade that cellular response to mechanical cues can have as large an influence on structure and function as chemical signals[11, 12]. These mechanical cues are not limited to active forces applied to the cells, but include the mechanical properties of the extracellular environment that cells are sensing around them[13]. Neuronal cells are dynamic and can reorganize their cytoskeleton in response to a variety of external signals. Most efforts to maximize neuronal growth have focused on identifying growth-promoting or inhibitory chemical signals, but the mechanical properties of plastic substrates with elastic moduli in the GPa range also contrast with the mechanical properties of the brain which has elastic moduli in the few hundred Pa range[14, 15].

Using hydrogels as cell substrates, our group investigated the cellular response to substrate compliance of spinal cord neural cells. Substrates used spanned a large range of stiffnesses including above and below that of brain and spinal cord tissue. Gels that closely match the stiffness of nervous tissue are designated "soft" while those that are over an order of magnitude stiffer are designated "hard". Spinal cord neurons adhered well to both soft and hard gels, and neurite length was constant with stiffness. Glia adhered best to hard gels stiffer than physiological tissue. Extensive glial aggregation at the site of injury has been found to counter the ability of neurons to regenerate across the injury site [16-19]. By varying the stiffness of materials on which CNS cells are grown, we have shown that it is possible to attain neuronal cell survival and extension while minimizing attachment of glial cells, which comprise the majority of non-neuronal cells in the CNS[20]. Altering the matrix stiffness to values above and below physiological levels shifts the resulting cell populations on the gel surface [20, 21]; neuron are proportionally more prevalent on soft gels, while glia spread and adhere better to stiff materials (Figure 1), a feature that we intend to exploit in the design of our implantable hydrogel device. The substrate mechanical stiffness effect on neurite extension and branching, as well as glial attachment and growth, suggest that an implantable hydrogel scaffold should ideally have mechanical stiffness that is soft and most closely matches that of native central nervous system tissue. Functional neuronal tests of spinal cord cells on gels, however, complicate the design parameters. The functional implications of varying the stiffness of the matrix and consequentially altering cellular populations were examined by testing the differential effects of the known neurotoxin, glutamate, based on gel compliance. Glutamate is a major neurotransmitter of the spinal cord. Glia function to clear extracellular glutamate after an injury, presumably preventing neuronal toxicity. Glia are necessary in culture to prevent glutamate toxicity[22-24]. In our hydrogel system in which small changes can alter the resulting population of neurons or glia in a mixed culture, we also observe variations in neuronal resistance to glutamate (Figure 2A). Neurons are most resistant to glutamate treatment in co-cultures where a high proportion of glia are present, namely on gels harder than nervous tissue (Figure 2B). The greater number of glia on hard gels could impart more protection on neurons, therefore preventing glutamate toxicity compared to neurons in soft gel cultures where glia are not as prevalent. It is also possible that neurons are not as well attached to soft materials as to hard and that aggravating agents will cause more cells to detach from the culture. Our results conclude that neurons are dependent on glia in a co-culture system for functional protective effects, though not for cell adhesion and morphological development (Figure 1).

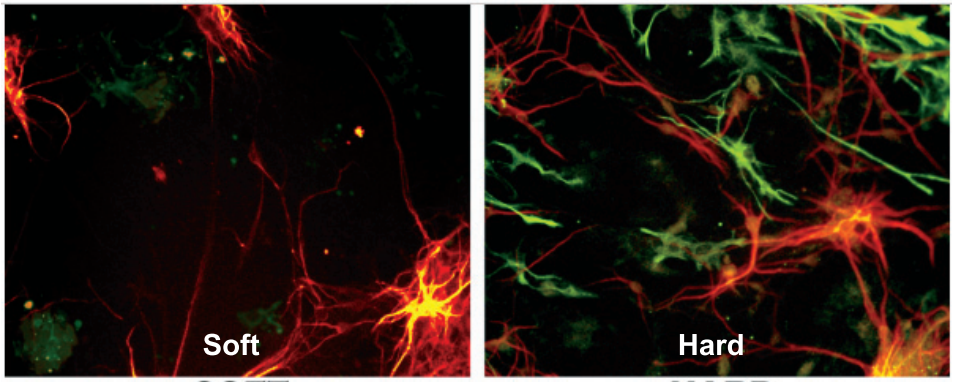

Figure 1. Spinal cord dissociations cultured on soft and hard hydrogels were immunostained for neuron-specific microtubule-associated protein (MAP2, red) and glial-specific glial acidic fibrillary protein (GFAP, green).

Further characterization will be performed in vivo to examine static stiffness effects in such and environment. It could be that in order to achieve both form and function, a scaffold whose stiffness

matches indigenous nervous tissue should be used and the chemical protection conveyed by glia should be supplemented into the mesh of the scaffold. Alternatively, design characteristics of scaffold hydrogels may require two phases of culture conditions, first to allow maximal neurite extension, and second to induce controlled glial expansion. It is probable based on the results detailed above that the mechanical stiffness necessary for each phase of growth is unique. Reversible polymerization of DNA-crosslinked gels that are inducible towards more or less compliant material properties through the addition of complementary DNA strands [25] will be exploited in our future designs to provide an innovative approach to control each growth phase.

Principles of DNA-Crosslinked Hydrogels for Use as Neural Cell Scaffolds

The aforementioned DNA-crosslinked hydrogels are generated by modifying a synthesized oligonucleotide so that it can incorporate with a polymer during its polymerization process. The result is a DNA-crosslinked hydrogel that can be reversibly assembled and disassembled through the application of particular strands of DNA. Two distinct "side-branch" DNA strands – SA1 and SA2 – make up the polymer strands, while a third crosslinking strand – L2 – is complementary with both side-branch strands and hybridizes to crosslink the gel (Figure 3). Finally, when a fourth strand that is fully complementary to the crosslinking strand is added, the gel disassembles. The mechanical stiffness of these gels can be varied like most polymer gels, by varying the degree of gel crosslinking. Since DNA-crosslinked hydrogels can be easily directed to assemble and disassemble – allowing the release of captured drugs or molecules, or disappearance after serving as a scaffold for cellular growth – they are attractive candidate materials for various biomedical engineering applications, particularly in drug delivery or in vivo cellular transplantation.

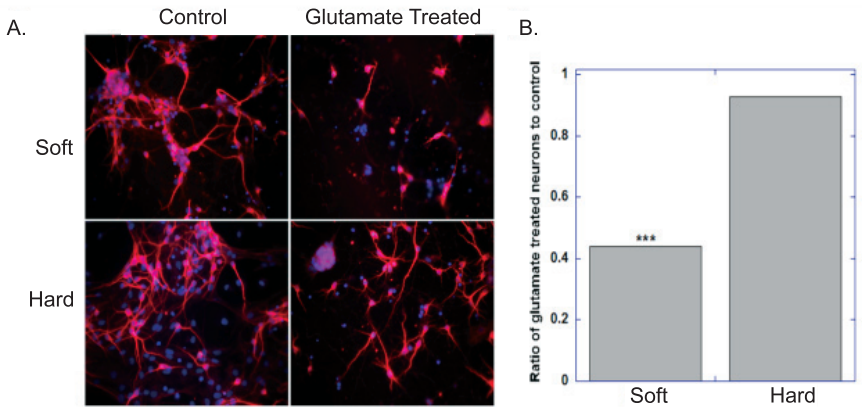

*Figure 2. Population of neurons surviving 500 mm glutamate treatment for 24 hours compared to untreated control cultures on soft 500 Pa and hard 25 kPa hydrogels. ***p < 0.001 by ANOVA followed by Tukey's test for multiple comparisons against 0.3 kPa gels.*

Dynamic Force Actuation on Neural Cells

The concept of applying controlled tension to physiological tissues to grow or expand the tissues is not new. For example, "limb lengthening" via the application of controlled traction to long bones is commonly employed in achondroplastic patients[26, 27]. Skin grafts are expanded to provide increased autologous tissue for reconstructive surgery following burns and trauma[28]. In vitro blood vessel expansion has been investigated for vascular tissue engineering [29]. However, to our knowledge, this mechanism has not been implemented in vivo to extend the spinal cord to produce regeneration following injury. Neurons are particularly susceptible to induced growth via towing or pulling[30]. The phenomenon of towed growth is currently being characterized by several groups[3, 31, 32]. It has been shown that there is a critical force that must be applied to induce growth; below this threshold value, axons do not grow, and above the threshold, axons presumably fail mechanically[31]. Under proper conditions, neurons are able to increase production of proteins to stabilize the neo-axoplasm. Force-extension principles have been used to physically stretch and grow groups of axons by culturing neurons on adjacent coverslips and slowly pulling them apart under controlled stretch, thereby lengthening the axons and forming a nerve-like structure[33]. Our device employs a similar principle, but by stretching neuronal tracts on a hydrogel, the result will be an implantable biopolymer, which can also be induced to dissolve using the DNA-crosslinked gel technology, once transplanted cellular tracts have incorporated with native tissue.

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Research Notes

Design of Advanced Biomaterials (continued from page 29)

Implantable Biomaterial Design for Repair of Spinal Cord Injury

The final design of our biomaterial will stimulate spinal cord regeneration in vivo both by inducing axon extension on a mechanically permissive hydrogel and by applying mechanical tension to the spinal cord (Figure 4). The biomaterial comprises a polymer based hydrogel that is crosslinked and stabilized by complementary DNA strands. By functionalizing the biomaterial with extracellular matrix molecules that foster neurite attachment and growth, we can employ the biomaterial as a tissue scaffold. Moreover, by dynamically modulating the stiffness of the hydrogel by adding crosslinking DNA strands, we can force the tissue scaffold to shrink, thereby exerting traction on the emerging neurites and physically expanding the tissue. The inherent elasticity and deformability of the hydrogel allow it to change shape to accommodate changes in the size of the injured space.

Preliminary testing of the feasibility of this design has begun in the form of force transduction testing of the contracting polymer. A calibrated force transducer was attached to the DNA-crosslinked hydrogel and gels were allowed to swell. Gels were 50% crosslinked with complementary DNA strands, followed by slow addition of DNA crosslinks into the gel. They were added in controlled increments of 10% over time to 100%. The graph of actuating force with respect to percentage crosslinks is shown in Figure 5. A maximum contraction of approximately 25% was observed at 90% crosslink density. The corresponding force generated was 249μN. These forces are comparable to those employed by Smith et al[33]. As stated above, the ongoing research has identified the relationship between the net concentration of crosslinked DNA strands, the stiffness of the polymer hydrogels, and the amount of force generated by the hydrogel as it shrinks.

In summary, with invaluable support from the National Institutes of Health (Grant # EB004919-01) and The New Jersey Commission on Spinal Cord Research (Grant# 05-3041-SCR-E-0), we have begun design and in vitro experimentation on an implantable bifunctional hydrogel construct for spinal cord repair. The construct connects two static hydrogel scaffolds on which transplanted neuronal cells are grown and a dynamic gel to which the actuating force is applied. By adding controlled amounts of DNA crosslinks to polymer hydrogels, we demonstrate that we will be capable of inducing tension-mediated axonal growth within the critical range to engage the towed growth mechanism in neurons[3, 30, 31, 33]. Characterization of the design not only confirms that the mechanical stiffness of the substrate impacts neuronal and astroglial survival and growth, but it also reveals the functional consequences and the individual cell type response to mechanical stimuli are altered in the presence and absence of interaction with one another. The results from this study provide important information toward a novel device for SCI repair that exploits the mechanical aspects of cellular-ECM interactions and axonal extension.

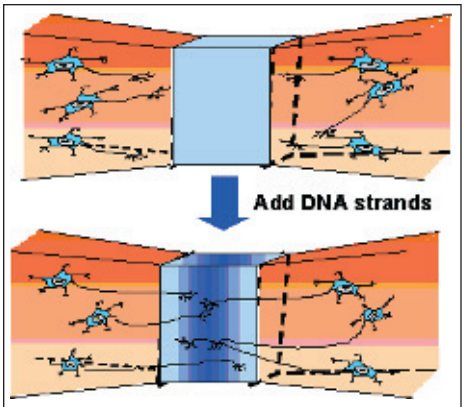

Figure 4. Schematic of bifunctional force-actuating gel design. DNA crosslinked hydrogels is implanted in injury cavity of nerves. It provides mechanical support and inductive environment. Upon introduction of additional DNA crosslinks,traction forces are created to stimulate axonal growth.

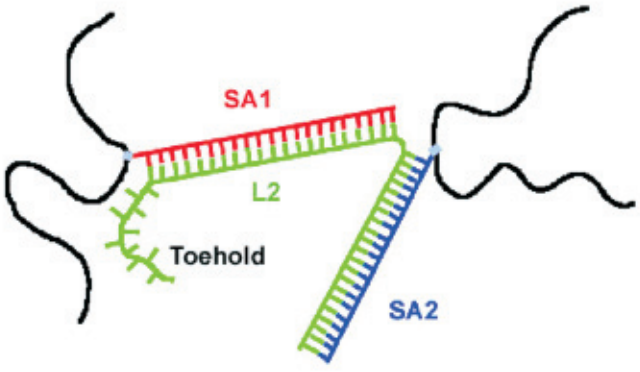

Figure 3. Two polymer chains crosslinked by three DNA strands. The DNA side branch strands labeled SA1 and SA2 branch off of the polymer backbone. The crosslinking L2 strand has sections complementary to SA1 and SA2, and includes extra nucleotides as a "toehold". A fourth DNA strand, fully complementary to L2 (SA1 + SA2 + Toehold) uncrosslinks L2 and degrades the gel.

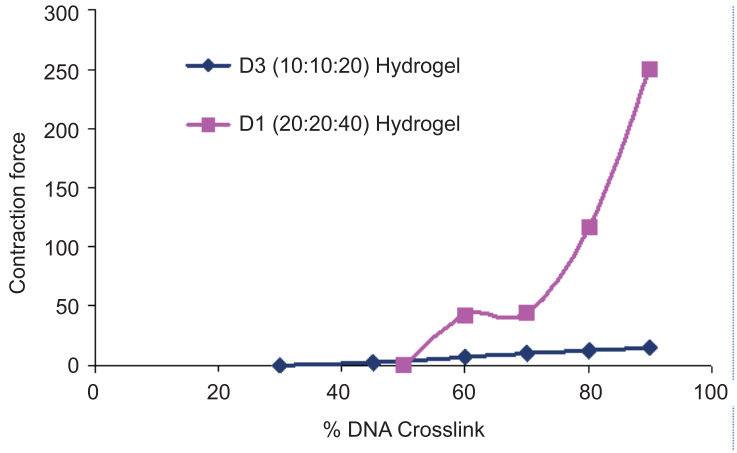

Figure 5. The calculated force generated over time in DNA crosslinked gel. Force increases as complementary DNA strands are increased by 10% every hour.

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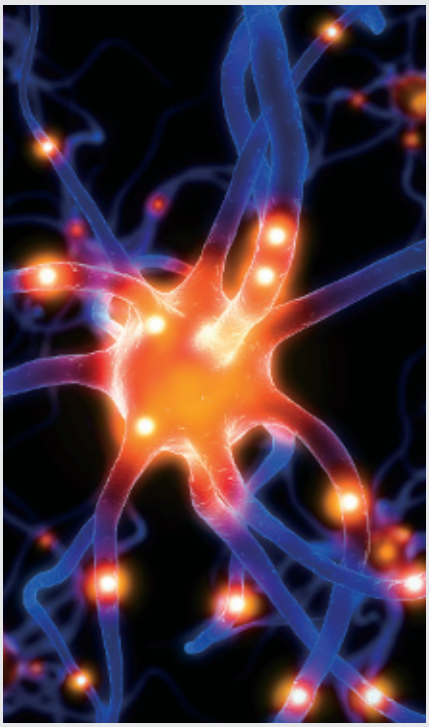

Giving

The Spinal Research Foundation is an international non-profit organization dedicated to improving spinal health care through research and education. The Foundation collaborates with spinal research centers of excellence around the world to prove the success of traditional approaches, as well as develop new techniques and technologies. These results are shared with both the medical profession and the general public to improve the overall quality and understanding of optimal spinal health care.

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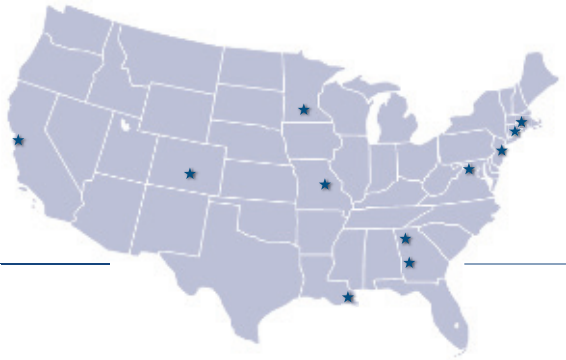

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The Spinal Research Foundation is an international non-profit organization dedicated to improving spinal health care through research and education. The foundation collaborates with spinal research centers of excellence around the world to prove the success of traditional approaches, as well as develop new techniques and technologies. These results are shared with the medical profession and the general public to improve the overall quality and understanding of optimal spinal health care.

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