



## Spinal Cord Injury: Hope Through Research

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### Introduction

Until World War II, a serious spinal cord injury (SCI) usually meant certain death. Anyone who survived such injury relied on a wheelchair for mobility in a world with few accommodations and faced an ongoing struggle to survive secondary complications such as breathing problems, blood clots, kidney failure, and pressure sores. By the middle of the twentieth century, new antibiotics and novel approaches to preventing and treating bed sores and urinary tract infections revolutionized care after spinal cord injury. This greatly expanded life expectancy and required new strategies to maintain the health of people living with chronic *paralysis*. New standards of care for treating spinal cord injuries were established: reposition the spine, fix the bones in place to prevent further damage, and rehabilitate disabilities with exercise.

Today, improved emergency care for people with spinal cord injuries, antibiotics to treat infections, and aggressive rehabilitation can minimize damage to the nervous system and restore function to varying degrees. Advances in research are giving doctors and people living with SCI hope that spinal cord injuries will eventually be repairable. With new surgical techniques and developments in spinal nerve regeneration, cell replacement, neuroprotection, and neurorehabilitation, the future for spinal cord injury survivors looks brighter than ever.

### Facts and Figures about Spinal Cord Injury

- ▶ There are an estimated 12,000 spinal cord injuries every year in the United States alone.
- ▶ More than a quarter of a million Americans are currently living with spinal cord injuries.
- ▶ The cost of managing the care of spinal cord injury patients is \$3 billion each year.
- ▶ The largest proportion of spinal cord injuries (36.5 percent) occurs during car accidents; more than a quarter are the result of falls; and the rest are due to acts of violence (primarily gunshot wounds), sporting accidents, and other less common causes.
- ▶ The average age at injury has risen and is now 42.6 years.
- ▶ 80 percent of spinal cord injury patients are men.

### How does the spinal cord work?

To understand what can happen as the result of a spinal cord injury, it is important to understand the anatomy of the spinal cord and its normal functions.

The spinal cord is a tight bundle of neural cells (*neurons* and *glia*) and nerve pathways (*axons*) that extend from the base of the brain to the lower back. It is the primary information highway that receives sensory information from the skin, joints, internal organs, and muscles of the trunk, arms, and legs, which is then relayed upward to the brain. It also carries messages downward from the brain to other body systems. Millions of nerve cells situated in the spinal cord itself also coordinate complex patterns of movements such as rhythmic breathing and walking. Together, the spinal cord and brain make up the central nervous system (CNS), which controls most functions of the body.

The spinal cord is made up of neurons, glia, and blood vessels. The neurons and their dendrites (branching projections that receive input from axons of other neurons) reside in an H-shaped or butterfly-shaped region called gray matter. The gray matter of the cord contains *lower motor neurons*, which branch out from the cord to muscles, internal organs, and tissue in other parts of the body and transmit information commands to start and stop muscle movement that is under voluntary control. *Upper motor neurons* are located in the brain and send their long processes (axons) to the spinal cord neurons. Other types of nerve cells found in dense clumps of cells that sit just outside the spinal cord (called sensory ganglia) relay information such as temperature, touch, pain, vibration, and joint position back to the brain.

The axons carry signals up and down the spinal cord and to the rest of the body. Thousands of axons are bundled into pairs of spinal nerves that link the spinal cord to the muscles and the rest of the body. The function of these nerves reflects their location along the spinal cord.

- ▶ *Cervical* spinal nerves (C1 to C8) emerge from the spinal cord in the neck and control signals to the back of the head, the neck and shoulders, the arms and hands, and the diaphragm.
- ▶ *Thoracic* spinal nerves (T1 to T12) emerge from the spinal cord in the upper mid-back and control signals to the chest muscles, some muscles of the back, and many organ systems, including parts of the abdomen.
- ▶ *Lumbar* spinal nerves (L1 to L5) emerge from the spinal cord in the low back and control signals to the lower parts of the abdomen and the back, the buttocks, some parts of the external genital organs, and parts of the leg.
- ▶ *Sacral* spinal nerves (S1 to S5) emerge from the spinal cord in the low back and control signals to the thighs and lower parts of the legs, the feet, most of the external genital organs, and the area around the anus.

The outcome of any injury to the spinal cord depends upon the level at which the injury occurs in the neck or back and how many and which axons and cells are damaged; the more axons and cells that survive in the injured region, the greater the amount of function recovery. Loss of neurologic function occurs below the level of the injury, so the higher the spinal injury, the greater the loss of function.

A whitish mixture of proteins and fat-like substances called *myelin* covers the axons and allows electrical signals to flow quickly and freely. Myelin is much like the insulation around electrical wires. It is formed by axon-insulating cells called *oligodendrocytes*. Because of its whitish color, the outer section of the spinal cord—which is formed by bundles of myelinated axons—is called white matter.

The spinal cord, like the brain, is enclosed in three membrane layers called meninges: the dura mater (the tougher, most protective, outermost layer); the arachnoid (middle layer); and the pia mater (innermost and very delicate). The soft, gel-like spinal cord is protected by 33 rings of bone called *vertebrae*, which form the spinal column. Each vertebra has a circular hole, so when the rung-like bones are stacked one on top of the other there is a long hollow channel, with the spinal cord inside that channel. The vertebrae are named and numbered from top to bottom according to their location along the backbone: seven cervical vertebrae (C1-C7) are in the neck; twelve thoracic vertebrae (T1-T12) attach to the ribs; five lumbar vertebrae (L1-L5) are in the lower back; and, below them, five sacral vertebrae (S1-S5) that connect to the pelvis. The adult spinal cord is shorter than the spinal column and generally ends at the L1-L2 vertebral body level. A thick set of nerves from the lumbar and sacral cord form the “cauda equina” in the spinal canal below the cord.

The spinal column is not all bone. Between the vertebrae are *discs* of semi-rigid cartilage and narrow spaces called foramen that act as passages through which the spinal nerves travel to and from the rest of the body. These are places where the spinal cord is particularly vulnerable to direct injury.

### What is a spinal cord injury?

The vertebrae normally protect the soft tissues of the spinal cord, but they can be broken or dislocated in a variety of ways that puts harmful pressure on the spinal cord. Injuries can occur at any level of the spinal cord. The segment of the cord that is injured, and the severity of the damage to the nervous tissue, will determine which body functions are compromised or lost. An injury to a part of the spinal cord causes physiological consequences to parts of the body controlled by nerves at and below the level of the injury.

Motor vehicle accidents and catastrophic falls are the most common causes of physical trauma that breaks, crushes, or presses on the vertebrae and can cause irreversible damage at the corresponding level of the spinal cord and below. Severe trauma to the cervical cord results in paralysis of most of the body, including the arms and legs, and is called *tetraplegia* (though the older term, *quadriplegia*, is still in common use). Trauma to the thoracic nerves in the upper, middle, or lower back results in paralysis of the trunk and lower extremities, called *paraplegia*.

Penetrating injuries, such as gunshot or knife wounds, damage the spinal cord; however, most traumatic injuries do not completely sever the spinal cord. Instead, an injury is more likely to cause fractures and compression of the vertebrae, which then crush and destroy the axons that carry signals up and down the spinal cord. A spinal cord injury can damage a few, many, or almost all of the axons that cross the site of injury. A variety of cells located in and around the injury site may also die. Some injuries in which there is little or no nerve cell death but only pressure-induced blockage of nerve signaling or only demyelination without axonal damage will allow almost complete recovery. Others in which there is complete cell death across even a thin horizontal level of the spinal cord will result in complete paralysis.

### What happens when the spinal cord is injured?

Traumatic spinal cord injury usually begins with a sudden, mechanical blow or rupture to the spine that fractures or dislocates vertebrae. The damage begins at the moment of **primary injury**, when the cord is stretched or displaced by bone fragments or disc material. Nerve signaling stops immediately but may not return rapidly even if there is no structural damage to the cord. In severe injury, axons are cut or damaged beyond repair, and neural cell membranes are broken. Blood vessels may rupture and cause bleeding into the spinal cord's central tissue, or bleeding can occur outside the cord, causing pressure by the blood clot on the cord.

Within minutes, the spinal cord near the site of severe injury swells within the spinal canal. This may increase pressure on the cord and cut blood flow to spinal cord tissue. Blood pressure can drop, sometimes dramatically, as the body loses its ability to self-regulate. All these changes can cause a condition known as *spinal shock* that can last from several hours to several days.

There is some controversy among neurologists about the extent and impact of spinal shock, and even its definition in terms of physiological characteristics. It appears to occur in approximately half of the cases of spinal cord injury and is usually directly related to the size and severity of the injury. During spinal shock, the entire spinal cord below the lesion becomes temporarily disabled, causing complete paralysis, loss of all reflexes, and loss of sensation below the affected cord level.

The primary injury initiates processes that continue for days or weeks. It sets off a cascade of biochemical and cellular events that kills neurons, strips axons of their protective myelin covering, and triggers an inflammatory immune system response. This is the beginning of the **secondary injury** process. Days, or sometimes even weeks later, after this second wave of damage has passed, the area of destruction has increased—sometimes to several segments above and below the original injury.

- ▶ **Changes in blood flow cause ongoing damage.** The major reduction in blood flow to the site following the initial injury can last for as long as 24 hours and become progressively worse if there is continued compression of the cord due to swelling or bleeding. Because of the greater blood flow needs of gray matter, the impact is greater on the central cord than on the outlying white matter. Blood vessels in the gray matter also become leaky, sometimes as early as 5 minutes after injury, which initiates spinal cord swelling. Cells that line the still-intact blood vessels in the spinal cord also begin to swell, and this further reduces blood flow to the injured area. The combination of leaking, swelling, and sluggish

blood flow prevents the normal delivery of oxygen and nutrients to neurons, causing many of them to die.

- ▶ **Excessive release of neurotransmitters kills nerve cells.** After the injury, an excessive release of *neurotransmitters* (chemicals that allow neurons to signal each other) can cause additional damage by over-stimulating nerve cells. The neurotransmitter glutamate is commonly used by axons in the spinal cord to stimulate activity in other neurons. But when spinal cells are injured, their axons flood the area with glutamate and trigger additional nerve cell damage. This process kills neurons near the injury site and the myelin-forming oligodendrocytes at and beyond the injured area.
- ▶ **An invasion of immune system cells creates inflammation.** Under normal conditions, the blood-brain barrier keeps potentially destructive immune system cells from entering the brain or spinal cord. This barrier is a naturally-occurring result of closely spaced cells along the blood vessels that prevent many substances from leaving the blood and entering brain tissues. But when the blood-brain barrier breaks down, immune system cells—primarily white blood cells—can invade the spinal cord tissue and trigger an inflammatory response. This inflammatory response can cause additional damage to some neurons and may kill others.
- ▶ **Free radicals attack nerve cells.** Another consequence of inflammation is the increased production of highly reactive forms of oxygen molecules called free radicals—chemicals that modify the chemical structure of other molecules in damaging ways, for example, damaging cell membranes. Free radicals are produced naturally as a by-product of normal oxygen metabolism in small enough amounts that they cause no harm. But injury to the spinal cord causes cells to overproduce free radicals, which destroy critical molecules of the cell.
- ▶ **Nerve cells self-destruct.** For reasons that are still unclear, spinal cord injury sets off apoptosis—a normal process of cell death that helps the body get rid of old and unhealthy cells. Apoptosis kills oligodendrocytes in damaged areas of the spinal cord days to weeks after the injury. Apoptosis can strip myelin from intact axons in adjacent ascending and descending pathways, causing the axons to become dysfunctional and disrupting the spinal cord's ability to communicate with the brain.
- ▶ **Scarring occurs.** Following a spinal cord injury, astrocytes (star-shaped glial cells that support the brain and spinal cord) wall off the injury site by forming a scar, which creates a physical and chemical barrier to any axons which could potentially regenerate and reconnect. Even if some intact myelinated axons remain, there may not be enough to convey any meaningful information to or from the brain.

Researchers are especially interested in studying the mechanisms of this wave of secondary damage because finding ways to stop it could save spinal cord tissue and thereby enable greater functional recovery.

### What immediate treatments are available?

Injury to the spine isn't always obvious. Any injury that involves the head and neck, pelvic fractures, penetrating injuries in the area of the spine, or injuries that result from falling from heights should raise concerns regarding an unstable spinal column. Until imaging of the spine is done at an emergency or trauma center, people who might have spine injury should be cared for as if any significant movement of the neck or back could cause further damage.

At the accident scene, emergency personnel will immobilize the head and neck to prevent movement, put a rigid collar around the neck, and carefully place the person on a rigid backboard to prevent further damage to the spinal cord. Sedation may be given to relax the person and prevent movement. A breathing tube may be inserted if the injury is to the high cervical cord and the individual is at risk of respiratory arrest.

At the hospital or trauma center, realigning the spine using a rigid brace or axial traction (using a mechanical force to stretch the spine and relieve pressure on the spinal cord) is usually done as soon as possible to stabilize the spine and prevent additional damage. Fractured vertebrae, bone fragments, herniated discs, or other objects compressing the spinal column may need to be surgically removed. Spinal decompression surgery to relieve pressure within the spinal column also may be necessary in the days after injury. Results of a neurosurgical study show that, in some cases, earlier surgery is associated with better functional recovery.

### How are spinal cord injuries diagnosed?

The emergency room physician will test the individual to see if there is any movement or sensation at or below the level of injury. Methods to assess autonomic function also have been established (American Spinal Injury Association, or ASIA, Autonomic Standards Classification). Emergency medical tests for a spinal cord injury include:

- ▶ Magnetic resonance imaging (MRI), which uses computer-generated radio waves and a powerful magnetic field to produce detailed three-dimensional images of body structures, including tissues, organs, bones, and nerves. It can document brain and spinal trauma from injury, as well as aid in diagnosing brain and spinal cord tumors, herniated disks, vascular (blood vessel) irregularities, bleeding and inflammation that might compress the spine and spinal cord, and injury to the ligaments that support the cervical spine.
- ▶ Computerized tomography (CT) provides rapid, clear two-dimensional x-ray images of organs, bones, and tissues. Neurological CT scans are used to view the brain and spine. CT is excellent in detecting bone fractures, bleeding, and spinal stenosis (narrowing of the spinal canal), but CT has less ability to image the spinal cord or identify ligament injury associated with an unstable spine than MRI.
- ▶ Plane x-rays (which demonstrate the planes of bone on bone) of the person's chest and skull are often taken as part of a neurological work-up. X-rays can be used to view most parts of the body, such as a joint or major organ system. In a conventional x-ray, a concentrated burst of low-dose ionized radiation is passed through the body and onto a photographic plate. Since calcium in bones absorbs x-rays more easily than soft tissue or muscle, the bony structure appears white on the film. Vertebral misalignment or fracture can be seen within minutes. X-rays taken in different neck positions (i.e., flexion and extension views) detect instability of the cervical spine. Tissue masses such as injured ligaments or a bulging disc are not visible on conventional x-rays.

### How are spinal cord injuries classified?

Once the swelling from within and around the spinal cord has eased a bit—usually within a week to 10 days—physicians will conduct a complete neurological exam to classify the injury as complete or incomplete. An **incomplete injury** means that the ability of the spinal cord to convey messages to or from the brain is not completely lost. People with incomplete injuries retain some sensory function and may have voluntary motor activity below the injury site. A **complete injury** prevents nerve communications from the brain and spinal cord to parts of the body below the injury site. There is a total lack of sensory and motor function below the level of injury, even if the spinal cord was not completely severed. Studies have shown that people with incomplete injuries have a greater chance of recovering some function in the affected limbs than those with a complete injury.

Physicians use the International Standards of Neurologic Classification of Spinal Cord Injury (ISNCSCI) to measure the extent of neurologic injury following a spinal cord injury. The ASIA Impairment Scale (AIS) is used to categorize the degrees of injury into different groups.

American Spinal Injury Association Impairment Scale = AIS \*

Classification	Description
A	Complete: no motor or sensory function is preserved below the level of injury, including the sacral segments S4-S5
B	Incomplete: sensory, but not motor, function is preserved below the neurologic level and some sensation in the sacral segments S4-S5
C	Incomplete: motor function is preserved below the neurologic level, however, more than half of key muscles below the neurologic level have a muscle grade less than 3 (i.e., not strong enough to move against gravity)
D	Incomplete: motor function is preserved below the neurologic level, and at least half of key muscles below the neurologic level have a muscle grade of 3 or more (i.e., joints can be moved against gravity)
E	Normal: motor and sensory functions are normal

\* Used with permission of the American Spinal Injury Association

### How does a spinal cord injury affect the rest of the body and how is it treated?

People who survive a spinal cord injury often have medical complications resulting in bladder, bowel, and sexual dysfunction. They may also develop chronic pain, autonomic dysfunction, and spasticity (increased tone in and contractions of muscles of the arms and legs), but this is highly variable and poorly understood. Higher levels of injury may have an increased susceptibility to respiratory and heart problems.

- ▶ **Breathing.** A spinal cord injury high in the neck can affect the nerves and muscles in the neck and chest that are involved with breathing. Respiratory complications are often an indication of the severity of spinal cord injury. About one-third of those with injury to the neck area will need help with breathing and require respiratory support via intubation, which involves inserting a tube connected to a machine that pushes oxygen into the lungs and removes carbon dioxide) through the nose or throat and into the airway. This may be temporary or permanent depending upon the severity and location of injury. Any injury to the spinal cord between the C1-C4 segments, which supply the phrenic nerves leading to the diaphragm, can stop breathing. (The phrenic nerves cause the diaphragm to move and the lungs to expand.) People with these injuries need immediate ventilatory support. People with high cervical cord injury may have trouble coughing and clearing secretions from their lungs. Special training regarding breathing and swallowing may be needed.
- ▶ **Pneumonia.** Respiratory complications are the leading cause of death in people with spinal cord injury, commonly as a result of pneumonia. Intubation increases the risk of developing ventilator-associated pneumonia; individuals with spinal cord injury who are intubated have to be carefully monitored and treated with antibiotics if symptoms of pneumonia appear. Attention to clearing secretions and preventing aspiration of mouth contents into the lungs can prevent pneumonia.
- ▶ **Circulatory problems.** Spinal cord injuries can cause a variety of changes in circulation, including blood pressure instability, abnormal heart rhythms (arrhythmias) that may appear days after the injury, and blood clots. Because the brain's control of the cardiac nerves is cut off, the heart can beat at a dangerously slow pace, or it can pound rapidly and irregularly. Arrhythmias are more common and severe in the most serious injuries. Low blood pressure also often occurs due to changes in nervous system control of blood vessels, which then widen, causing blood to pool in the small arteries far away from the heart. Blood pressure needs to be closely monitored to keep blood and oxygen flowing through the spinal cord tissue, with the understanding that baseline blood pressure can be significantly lower than usual in people living with spinal cord injuries. Since muscle movement contributes to moving blood back to the heart, people with spinal cord injuries are at triple the usual risk for blood clots due to stagnation of blood flow in the large veins in the legs. Treatment includes anticoagulant drugs and compression stockings to increase blood flow in the lower legs and feet.
- ▶ **Spasticity and muscle tone.** When the spinal cord is damaged, information from the brain can no longer regulate reflex activity. Reflexes may become exaggerated over time, causing muscle spasticity. Muscles may waste away or diminish due to underuse. If spasms become severe enough, they may require medical treatment. For some, spasms can be as much of a help as they are a hindrance, since spasms can tone muscles that would otherwise waste away. Some people can even learn to use the increased tone in their legs to help them turn over in bed, propel them into and out of a wheelchair, or stand.
- ▶ **Autonomic dysreflexia.** The autonomic nervous system controls involuntary actions such as blood pressure, heartbeat, and bladder and bowel function. Autonomic dysreflexia is a life-threatening reflex action that primarily affects those with injuries to the neck or upper back. It happens when there is an irritation, pain, or stimulus to the nervous system below the level of injury. The irritated area tries to send a sensory signal to the brain, but the signal may be misdirected, causing a runaway reflex action in the spinal cord that has been disconnected from the brain's regulation. Unlike spasms that affect muscles, autonomic dysreflexia affects blood vessels and organ systems controlled by the sympathetic nervous system. Anything that causes pain or irritation can set off autonomic dysreflexia, including a full bladder, constipation, cuts, burns, bruises, sunburn, pressure of any kind on the body, or tight clothing. Symptoms of its onset may include flushing or sweating, a pounding headache, anxiety, sudden increase in blood pressure, vision changes, or goose bumps on the arms and legs. Emptying the bladder or bowels and removing or loosening tight clothing are just a few of the possibilities that should be tried to relieve whatever is causing the irritation. If possible, the person should be kept in a sitting position, rather than lying flat, to keep blood flowing to the lower extremities and help reduce blood pressure.
- ▶ **Pressure sores (or pressure ulcers).** Pressure sores are areas of skin tissue that have broken down because of continuous pressure on the skin and reduced blood flow to the area. People with paraplegia and tetraplegia are susceptible to pressure sores because they may lose all or part of skin sensations and cannot shift their weight. As a result, individuals must be shifted periodically by a caregiver if they cannot shift

positions themselves. Good nutrition and hygiene can also help prevent pressure sores by encouraging healthy skin. Special motorized rotating beds may be used to prevent and treat sores.

- ▶ **Pain.** Some people who have spinal cord nerve are paralyzed often develop neurogenic pain—pain or an intense burning or stinging sensation may be unremitting due to hypersensitivity in some parts of the body. It can either be spontaneous or triggered by a variety of factors and can occur even in parts of the body that have lost normal sensation. Almost all people with spinal cord injury are prone to normal musculoskeletal pain as well, such as shoulder pain due to overuse of the shoulder joint from using a wheelchair. Treatments for chronic pain include medications, acupuncture, spinal or brain electrical stimulation, and surgery. However, none of these treatments are completely effective at relieving neurogenic pain.
- ▶ **Bladder and bowel problems.** Most spinal cord injuries affect bladder and bowel functions because the nerves that control the involved organs originate in the segments near the lower end of the spinal cord and lose normal brain input. Although the kidneys continue to produce urine, bladder control may be lost and the risk of bladder and urinary tract infections increases. Some people may need to use a catheter to empty their bladders. The digestive system may be unaffected, but people recovering from a spinal cord injury may need to learn ways to empty their bowels. A change in diet may be needed to help with control.
- ▶ **Sexual function.** Depending on the level of injury and recovery from the trauma, sexual function and fertility may be affected. A urologist and other specialists can suggest different options for sexual functioning and health.
- ▶ **Depression.** Many people living with a spinal cord injury may develop depression as a result of lifestyle changes. Therapy and medicines may help treat depression.

Once someone has survived the injury and begins to cope psychologically and emotionally, the next concern is how to live with disabilities. Doctors are now able to predict with reasonable accuracy the likely long-term outcome of spinal cord injuries. This helps people experiencing SCI set achievable goals for themselves, and gives families and loved ones a realistic set of expectations for the future.

### How does rehabilitation help people recover from spinal cord injuries?

No two people will experience the same emotions after surviving a spinal cord injury, but almost everyone will feel frightened, anxious, or confused about what has happened. It's common for people to have very mixed feelings: relief that they are still alive, but disbelief at the nature of their disabilities.

Rehabilitation programs combine physical therapies with skill-building activities and counseling to provide social and emotional support. The education and active involvement of the newly injured person and his or her family and friends is crucial.

A rehabilitation team is usually led by a doctor specializing in physical medicine and rehabilitation (called a physiatrist), and often includes social workers, physical and occupational therapists, recreational therapists, rehabilitation nurses, rehabilitation psychologists, vocational counselors, nutritionists, a case worker, and other specialists.

In the initial phase of rehabilitation, therapists emphasize regaining communication skills and leg and arm strength. For some individuals, mobility will only be possible with the assistance of devices such as a walker, leg braces, or a wheelchair. Communication skills such as writing, typing, and using the telephone may also require adaptive devices for some people with tetraplegia.

Physical therapy includes exercise programs geared toward muscle strengthening. Occupational therapy helps redevelop fine motor skills, particularly those needed to perform activities of daily living such as getting in and out of a bed, self-grooming, and eating. Bladder and bowel management programs teach basic toileting routines. People acquire coping strategies for recurring episodes of spasticity, autonomic dysreflexia, and neurogenic pain.

Vocational rehabilitation includes identifying the person's basic work skills and physical and cognitive capabilities to determine the likelihood for employment; identifying potential work places and any assistive equipment that will be needed; and arranging for a user-friendly workplace. If necessary, educational training is provided to develop skills for a new line of work that may be less dependent upon physical abilities and more dependent upon computer or communication skills. Individuals with disabilities that prevent them from returning to the workforce are encouraged to maintain productivity by participating in activities that provide a sense of satisfaction and self-esteem, such as educational classes, hobbies, memberships in special interest groups, and participation in family and community events.

Recreation therapy encourages people with SCI to participate in recreational sports or activities at their level of mobility, as well as achieve a more balanced and normal lifestyle that provides opportunities for socialization and self-expression.

Adaptive devices also may help people with spinal cord injury to regain independence and improve mobility and quality of life. Such devices may include a wheelchair, electronic stimulators, assisted gait training, *neural prostheses*, computer adaptations, and other computer-assisted technology.

### What research is being done?

Scientists continue to investigate new ways to better understand and treat spinal cord injuries.

Much of this research is supported by the National Institute of Neurological Disorders and Stroke (NINDS), a part of the National Institutes of Health (NIH). Other NIH components, as well as the Department of Veterans Affairs, other Federal agencies, research institutions, and voluntary health organizations, also fund and conduct basic to clinical research related to improvement of function in paralyzed individuals.

Many hospitals have developed specialized centers for spinal cord injury care. Many of these bring together spinal cord injury researchers from a variety of disciplines for partnerships regarding basic and clinical research, clinical care, and knowledge translation.

Current research is focused on advancing our understanding of four key principles of spinal cord repair:

- ▶ Neuroprotection—protecting surviving nerve cells from further damage
- ▶ Regeneration—stimulating the regrowth of axons and targeting their connections appropriately
- ▶ Cell replacement—replacing damaged nerve or glial cells

► Retraining CNS circuits and plasticity to restore body functions

A spinal cord injury is complex. Repairing it has to take into account all of the different kinds of damage that occur during and after the injury. Because the molecular and cellular environment of the spinal cord is constantly changing from the moment of injury until several weeks or even months later, combination therapies will have to be designed to address specific types of damage at different stages of the injury.

### Neuroprotection

Strategies involving neuroprotection are aimed at preventing cell death, limiting or reducing inflammation, and stopping over-excitability of certain cells and their functions. Investigators are looking at ways to reduce inflammation within or near the injured spinal cord, which can restrict blood flow, affect nerve signal transmission, and increase cell death. One approach is using steroid drugs to reduce nerve cell damage and suppress activities of immune cells. One clinical trial identified slight improvement in motor function among some individuals who were given a steroid within 8 hours after injury. However, other trials showed the drug's modest benefit did not outweigh serious side effects. Steroid therapy has not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute spinal cord injury.

Antibiotics, which can cross the protective blood-brain barrier, have been shown to improve motor function, restoration, decrease lesion size, and reduce cell death in animal models of SCI.

The kidney hormone erythropoietin promotes the growth of new red blood cells and increases oxygen levels in the blood. Studies in animal models have shown that erythropoietin can reduce inflammation in the brain, improve blood flow to the brain, and reduce nerve cell death following brain injury. It also aids in the recovery of motor function. However, other trials in animal models show conflicting results regarding the drug's usefulness in preventing inflammation and cell death. Researchers continue to study the drug in preclinical models.

Therapeutic hypothermia (controlled lowering of the body's core temperature) can protect cells from damage following cardiac arrest, stroke, and traumatic brain injury. Therapeutic hypothermia has been shown to reduce the swelling and inflammation that presses on the spinal cord following injury in animal models and in small, limited human studies. It also can reduce damage to susceptible neurons following the primary injury, reduce damage to spinal cord microvasculature, and improve functional outcome. Researchers are studying the safety and effectiveness of different durations of hypothermia following spinal cord injury.

Researchers are trying to manipulate *macrophages*—a type of white blood cell that travels to the injury site during the inflammatory response—to promote nerve cell growth without causing further tissue damage. Following a spinal cord injury, macrophages at the site of injury begin to remove cellular debris and receive signals that help them promote the growth of axons. But, within a few days post-injury, the collection of macrophages increases inflammation, scarring, and toxicity, which can worsen the damage. Scientists hope to learn how to signal macrophages to continue their restorative function while turning off their damaging consequences.

The buildup of sodium and glutamate in cells following a spinal cord injury can lead to cell damage and impaired or blocked cell signaling. The drug riluzole, which slows the progression of the disease amyotrophic lateral sclerosis, has shown in animal models to improve motor function and reduce cell death loss caused by decreased blood flow following spinal cord injury. The experimental drug HP 184 blocks the entry of sodium into cells (which can impair nerve function) and may enhance cell signaling in surviving axons that have had their protective myelin cover either destroyed or damaged following spinal cord injury. Other scientists are examining drugs that target glutamate, whose release is greatly increased following a spinal injury. Excess glutamate leads to cell death and blocked transmission of signals across nerve synapses. Researchers are studying different drugs that may reduce glutamate binding among cells following spinal cord injury, which could reduce secondary cell death, improve motor function outcome, and reduce long-term hypersensitive pain post-injury.

### Regeneration

Neurons have a limited capacity to regenerate. As nerve cells are either damaged or destroyed by injury, and as others die naturally during development, the number of chemical interactions between adjacent nerve cells (synapses) decreases. Nerve cells can die when they do not make enough synapses, leaving large numbers of supporting glial cells in the area of damage. Glial cells are thought to support tissue after injury to the spinal cord but also inhibit the growth of axons.

Approaches to repairing damaged axons through remyelination and new growth include:

Some anti-inflammatory drugs have been shown to encourage axonal regeneration by stimulating CNS nerve axons to grow and by inhibiting amino acid toxicity and cell death that occurs after the initial injury. Two such nonsteroidal anti-inflammatory drugs are ibuprofen and indomethacin. The drug rolipram was shown to encourage axonal regeneration in an animal model of spinal cord injury. Preclinical studies are examining the effectiveness of rolipram in combination with other drugs given at different delivery times post-injury.

Antibodies are proteins made by immune cells and are designed to attach themselves to specific foreign proteins (called antigens) and disable them. Therapeutically, antibodies can be made that target specific proteins that inhibit repair of the body after injury. Monoclonal antibodies, produced in a laboratory, may promote nerve fiber regeneration by blocking proteins in the myelin debris that inhibit regeneration after spinal cord injury. Scientists are testing monoclonal antibodies at the site of the spinal cord injury in animal models in an attempt to block anti-regeneration activity of cells in the damaged central nervous system and improve nerve function and recovery. For example, researchers are using a Nogo-A monoclonal antibody to block proteins that inhibit the sprouting and regeneration of axons following a spinal injury. Other antibodies, called anti-MAG (myelin associated glycoproteins), are designed to counteract protein-sugar molecules on myelin-forming debris at the site of injury.

A number of other targets are being tested to overcome inhibition to regeneration. Cethrin, a recombinant protein that blocks activation of rho (a protein that inhibits axon regeneration), has been tested clinically. A drug that targets Nogo-receptors is being developed to promote regeneration after spinal cord injury and stroke. Recent animal studies showing that inhibition of the tumor-suppressing gene PTEN can promote growth of upper motor neurons has led to active research into strategies to promote regeneration after spinal cord and optic nerve injuries. Finally, the histone deacetylases (HDAC) are a class of compounds that are involved in the regulation of gene expression and negatively affect cell structure following a traumatic spinal cord injury. Preclinical studies are examining ways to inhibit HDAC activity as a way to protect and allow axons to overcome inhibition in regions of a spinal injury.

To get past the glial scar that forms after a spinal cord injury and be able to transmit signals from the cell body, an axon has to advance between the tangles of long, branching molecules made up of inhibitory proteins and sugars that surround the cells. Experiments have successfully used a bacterial enzyme, chondroitinase ABC, to clear away the tangles so that axons could grow in animal models of injury. Researchers are looking at ways to combine chondroitinase ABC with other treatments, such as cell transplants, to increase functional recovery.

Other researchers are using a tissue-engineered highway-like matrix that is implanted onto the spinal cord to help axons "bridge" the lesion that forms at the injury site and to rebuild neural circuits. They also will look at using the matrix as a way of delivering growth factors that can promote nerve cell survival and inhibit proteins associated with the glial scar.

## Cell Replacement

Controversy exists over potential benefits and possible harmful consequences of cell replacement and cell transplants. The potential of several cell types, including *stem cells* and glial cells, to treat spinal cord injury is being investigated eagerly, but there are many things about stem cells that researchers still need to understand. For example, researchers know there are many different kinds of chemical signals that tell a stem cell what to do. Some of these are internal to the stem cell, but many others are external—within the cellular environment—and will have to be recreated in the transplant region to encourage proper growth and differentiation. Because of the complexities involved in stem cell treatment, researchers expect these kinds of therapies to be possible only after much more research is done. Preclinical research results are limited but show cell transplants can regenerate neuronal growth and create new connections between neurons.

Scientists are experimenting with a variety of cells for effectiveness and safety in increasing connectivity and restoring function following a spinal cord injury:

- ▶ Human oligodendrocyte progenitor cells have been shown to reduce secondary damage following a spinal cord injury and promote functional recovery and remyelination. Researchers are expanding trials to better determine optimal cell delivery windows and evaluate potential risks of transplants, such as the formation of tumors and inflammatory reactions.
- ▶ Schwann cells surround and insulate peripheral nerves, and often grow into the spinal cord after injury. Schwann cells that have been transplanted at the site of the spinal cord injury can produce growth factors and reinsulate damaged nerve axons. They are not stem cells in that their fate as Schwann cells is determined before transplantation. Schwann cells can be taken from the individual's own body, which reduces the need for immune-suppressing drugs and the risk of tumor formation, but this requires several weeks after injury before grafting can be done. Preclinical studies are examining their potential in safely treating both acute and chronic spinal cord injury.
- ▶ Bone marrow stromal cells, taken from the tissue found inside bones, have been shown in some studies to increase recovery from an injury to the spinal cord. Scientists are studying the injection of these cells into the cerebrospinal fluid (fluid that bathes the brain and spinal cord) to promote proteins needed to grow and maintain nerves and increase nerve signaling across the glial scarring that forms post-injury.
- ▶ Nasal olfactory ensheathing cells, taken from the lining of the nose, are special types of glial cells that have been shown to promote axon regeneration and remyelination at the injury site. The transplanted cells have been shown to permit regrowth of axons in both the peripheral and central nervous systems, and improve functional outcome in animal models of spinal cord injury. Early-stage trials in humans are being conducted overseas.

## Retraining CNS circuits and plasticity

Recovery from a spinal cord injury may occur for quite some time after the initial injury, as part of the brain's ability to reorganize or form new nerve connections and pathways following injury or cell death (called neuroplasticity).

### Active rehabilitation and exercise

Specific training can improve function, coordination of fine muscle movements, and overall strength and health. Scientists are comparing the relative effectiveness of an intensive task-specific motor training program added to standard rehabilitation compared with standard rehabilitation alone for improving hand function and clinical outcomes in people with recent tetraplegia.

Much as in the general population, cardiovascular disease (CVD) is a leading cause of death in persons with spinal cord injury. After the injury, the opportunity to actively exercise large muscles affected by paralysis is limited or may require assistive technologies. Researchers have recently shown that such injuries increase the risk of CVD, along with other muscle atrophy and effects of deconditioning. Since CVD occurs earlier in life for those with a spinal cord injury, researchers are assessing the impact of acute exercise, conditioning, and dietary supplementation on measures of fitness, function, and CVD risk factors/modifiers in individuals with tetraplegia. Other scientists are examining an add-on group exercise program to the usual physical therapy delivered in the hospital to see if it improves the participant's overall outlook on exercise and recovery, and to promote physical activity as part of a healthy lifestyle.

### Epidural Stimulation

In May 2011, scientists funded in part by the National Institutes of Health reported that after intensive physical therapy and electrical stimulation to the spine, a man with a paralyzing spinal cord injury from the chest down had recovered the ability to stand and move paralyzed muscles at will when the stimulator is active. The man participated in a pilot study that combined epidural stimulation and locomotor training—involving his being suspended for hours a day in a harness, walking on a treadmill while physical therapists moved his legs in stepping motions. Two years of locomotor training following his injury did not improve his ability to walk or stand. But he did improve after December 2009, when electrodes were surgically implanted over the paralyzed area of his spinal cord and began sending rhythmic electrical bursts to neurons in the spinal cord during the locomotor training sessions. This epidural stimulation imitates the brain's sending signals to the spinal cord to begin movement. He gradually became able to stand and fully bear his own weight for a few minutes at a time. Although he can't walk without assistance, he can bend one leg at the knee and flex his ankle when the stimulator is active. Locomotor training without any epidural stimulation is routinely used as a rehabilitative technique for people with spinal cord injuries—which allows some individuals to retain the ability to move and feel below the injury. Meanwhile, a form of epidural stimulation is used to relieve pain for some individuals. The researchers and NIH scientists caution that this finding was in only one person, and further study is required to confirm these early, promising results and to understand exactly how the stimulation is working.

### Functional Electric Stimulation

Exciting and promising results in restoring or assisting function in individuals with chronic spinal cord injury have been shown in studies using *functional electric stimulation* (FES). FES devices use a computer system and electrodes to deliver small bursts of a low-level electrical current to paralyzed muscles, to generate muscle contractions. Researchers are working to improve the electrode and computer interfaces so they can produce more natural yet complex movements. FES is being used to restore breathing without a ventilator, cough unassisted, enhance bladder and bowel control, increase hand movement and grasping, and improve blood flow to the skin.

Several studies continue to investigate the use of FES in restoring or improving function following a spinal cord injury. Researchers are using FES to help individuals with tetraplegia move paralyzed muscles to restore voluntary grasping function. Others are attempting to stimulate recovery with the goal of being able to grasp objects without stimulation once the treatment program is completed. This approach has been shown to be useful for people who have had a stroke.

A NINDS-supported clinical trial demonstrated that FES of the diaphragm and intercostal muscles (muscles between adjacent ribs that help move the chest wall) can produce effective cough in persons with high tetraplegia. The ability to cough at will eliminates the need for assistance in suctioning secretions and reduces the risk of lung disease. These researchers are now working to improve electrode design to allow for a less invasive surgical implantation.

One study is using a surgically implanted FES to facilitate exercise, standing, stepping, and/or balance in people with various degrees of paralysis. A related study is using a surgically implanted FES to facilitate stability of the trunk and hips, and to evaluate how stabilizing and stiffening the trunk can change the way spinal cord injured volunteers sit, breathe, reach, push a wheelchair, or roll in bed.

Transcranial Direct Current Stimulation (tDCS) is another form of electric stimulation that is being tested experimentally to improve patient outcomes after a spinal cord injury. tDCS is a noninvasive procedure that delivers continuous low electrical current to areas of the brain involved with movement via small electrodes placed on the scalp. Researchers are investigating if combining tDCS with exercise therapy for the affected hand will increase performance over exercise therapy alone. Other researchers hope to determine if tDCS can decrease chronic pain in people with spinal cord injury.

#### Robotic-assisted therapy

Most recovery following SCI takes place within six months after injury. Substantial recovery after 12 months is unusual, but researchers continue to test ways to restore function in persons with chronic paralysis. In one very small study involving patients one year after injury, scientists are testing the safety and efficacy of a type of robotic therapy device known as the AMES device. The aim of this study is to investigate the use of assisted movement and enhanced sensation (AMES) technology in the rehabilitation of the legs of participants with incomplete spinal cord injury. The AMES device rotates the ankle over a range of 30 degrees while vibrators stimulate the tendons attached to muscles that move the leg. The subject's task is to assist the motion of the device.

In another study, researchers will determine the effect of using body-weight supported treadmill training and a robotic gait trainer on functional movement from place to place (ambulation) in people with an incomplete spinal cord injury. The person is suspended in a harness and onto a treadmill, and the robotic legs are strapped to the person. A computer controls the pace of the walking. The effect of the therapy will be evaluated by analyzing changes in ambulation and gait patterns during walking.

#### Brain-computer interfaces (BCI)

The goal of *brain-computer interface* technology is to bypass the damaged nerve circuits in the spinal cord and establish a direct link between the brain and an assistive implanted device which may restore an individual's control of voluntary muscle movement and coordination of paralyzed muscles.

Most individuals with tetraplegia have intact brain function but are unable to move due to injury or disease affecting the spinal cord. Brain-computer interface technology is based on the finding that with intact brain function, neural signals for movement are generated in the brain and can be used to control computer-assisted devices. By implanting electrodes in the brain, individuals can be trained to practice thoughts and thereby generate neural signals that are interpreted by a computer and translated to movement which can then be used to control a variety of devices or computer displays.

Researchers are working to develop BCI technology to offer individuals with upper limb paralysis a natural and rich control signal for prosthetic arms or FES device to re-animate paralyzed arms. The study uses electrocorticographic (ECoG) electrodes that interface with neurons in the brain's cortex (the part of the brain that is responsible for higher thought and motor control) to measure brain activity. Participants will learn to control computer cursors, virtual reality environments, and assistive devices such as hand orthotics and FES devices using neural activity recorded with the ECoG sensor.

Another preliminary study is assessing the safety and effectiveness of a brain-computer interface to give people with tetraplegia the ability to control a computer cursor and other assistive devices with their thoughts. A small electrode array is inserted into the part of the brain's surface that controls movements. Using the very precise signals this device records, researchers are working to improve the computer's ability to interpret the person's intent and transfer that to the display screen.

### How can I help with research?

Clinical trials offer hope for many people and an opportunity to help researchers find better ways to safely detect, treat, or prevent disease, but trials can be done only if people volunteer to participate. Many neurological disorders don't have good treatment options. By participating in a clinical trial, you—as a healthy individual or someone with an illness or disease—can greatly affect the lives of people affected by a neurological disorder. To learn more and to volunteer in a clinical trial or learn more about clinical trials, For information about finding and participating in clinical trials, visit NIH Clinical Research Trials and You at <http://www.nih.gov/health/clinicaltrials/>. Use search terms such as "spinal cord injury" and "tetraplegia" to access current and completed trials involving spinal injury.

Other centers maintain registries of people interested in participating in ongoing or future clinical research studies. A multi-site network supported by the Christopher and Dana Reeve Foundation called the NeuroRecovery Network also accepts volunteer research participants. For more information, see [http://www.christopherreeve.org/site/c.ddJFKRNoFiG/b.5399929/k.6F37/NeuroRecovery\\_Network.htm](http://www.christopherreeve.org/site/c.ddJFKRNoFiG/b.5399929/k.6F37/NeuroRecovery_Network.htm)

### Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN  
P.O. Box 5801  
Bethesda, MD 20824  
(800) 352-9424  
<http://www.ninds.nih.gov>

Information also is available from the following organizations:

**[Christopher and Dana Reeve Foundation](#)**  
636 Morris Turnpike  
Suite 3A  
Short Hills, NJ 07078  
[informations@christopherreeve.org](mailto:informations@christopherreeve.org)  
<http://www.christopherreeve.org>  
Tel: 973-379-2690 800-225-0292  
Fax: 973-912-9433

**[Miami Project to Cure Paralysis/ Buoniconti Fund](#)**  
P.O. Box 016960  
R-48  
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**[National Spinal Cord Injury Association](#)**  
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 Tel: 202-245-7460 202-245-7316 (TTY)

## Glossary

**axon** - the long, thin extension of a nerve cell that conducts impulses away from the cell body.

**brain-computer interface** - a device with a sensor to monitor brain signals linked to computer software and hardware that turn these signals into commands for external devices. The interface bypasses nerves that have been damaged by injury or other means.

**cervical** - the part of the spine in the neck region.

**complete injury** – the injury prevents nerve communications from the brain and spinal cord to parts of the body below the injury site.

**discs** - round, spongy pads of cartilage found between the vertebrae that act like shock absorbers throughout the spinal column and allow for flexibility in the back.

**functional electrical stimulation (FES)** - the therapeutic use of low-level electrical current to stimulate muscle movement and restore useful movements such as standing or stepping; also called functional neuromuscular stimulation.

**glia** - supportive cells in the brain and spinal cord. Glial cells are the most abundant cell types in the central nervous system. There are three types: astrocytes, oligodendrocytes, and microglia.

**incomplete injury** – the ability of the spinal cord to convey some messages is not completely lost following injury.

**lower motor neurons** - nerve cells found in the brain stem and spinal cord that directly stimulate movement in the arms, legs, chest, face, throat, and tongue.

**lumbar** - the part of the spine in the middle back, below the thoracic vertebrae and above the sacral vertebrae.

**macrophage** - a type of white blood cell that engulfs foreign material. Macrophages also release substances that stimulate other cells of the immune system.

**myelin** - a structure of cell membranes that forms a sheath around axons, insulating them and speeding conduction of nerve impulses.

**neural prostheses** - devices that provide electrical stimulation to activate paralyzed muscles in a coordinated manner to supplement or restore functional movement.

**neuron** - also known as a nerve cell; the structural and functional unit of the nervous system. A neuron consists of a cell body and its processes: an axon and one or more dendrites.

**neuroplasticity** – the brain's ability to form new nerve connections and pathways following injury or cell death

**neurotransmitters** – chemicals that allow neurons to signal each other.

**oligodendrocyte** - a type of glial cell in the brain and spinal cord that wraps around and insulates axons and speeds the conduction of nerve impulses.

**paralysis** - the inability to control movement of a part of the body.

**paraplegia** - a condition involving paralysis of the legs.

**quadriplegia** - also known as tetraplegia, a condition involving paralysis of the legs and partial or complete paralysis of the arms.

**sacral** - refers to the part of the spine in the hip area.

**spinal shock** - a temporary physiological state that can occur after a spinal cord injury in which all sensory, motor, and sympathetic functions of the nervous system are lost below the level of injury. Spinal shock can lower blood pressure to dangerous levels and cause temporary paralysis.

**stem cells** - cells that have the ability to grow into any one of the body's many cell types. Unlike mature cells, which are permanently committed to their fate, stem cells can both renew themselves and create cells of other tissues.

**tetraplegia** - also called quadriplegia, this refers to paralysis of the legs and partial or complete paralysis of the arms.

**thoracic** - the part of the spine at the upper-back to mid-back level.

**upper motor neurons** - nerve cells in the brain that direct lower motor neurons to produce movements such as walking or chewing.

**vertebrae** - the 33 bones that make up the spinal column, characterized by a round opening through which the spinal cord passes and three flat projections to which muscles of the back attach.

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