SCIENTIFIC AMERICAN

Features - November 6, 2008

Repairing the Damaged Spinal Cord

Once little more than a futile hope, some restoration of the injured spinal cord is beginning to seem feasible

By John W. McDonald

Editor's Note: This story, originally printed in the September 1999 issue of Scientific American*, is being posted due to a new study showing that nerve cells can be regenerated by knocking out genes that typically inhibit their growth.*

For Chinese gymnast Sang Lan, the cause was a highly publicized headfirst fall during warm-ups for the 1998 Goodwill Games. For Richard Castaldo of Littleton, Colo., it was bullets; for onetime football player Dennis Byrd, a 1992 collision on the field; and for a child named Samantha Jennifer Reed, a fall during infancy. Whatever the cause, the outcome of severe damage to the spinal cord is too often the same: full or partial paralysis and loss of sensation below the level of the injury.

Ten years ago doctors had no way of limiting such disability, aside from stabilizing the cord to prevent added destruction, treating infections and prescribing rehabilitative therapy to maximize any remaining capabilities. Nor could they rely on the cord to heal itself. Unlike tissue in the peripheral nervous system, that in the central nervous system (the spinal cord and brain) does not repair itself effectively. Few scientists held out hope that the situation would ever change.

Then, in 1990, a human trial involving multiple research centers revealed that a steroid called methylprednisolone could preserve some motor and sensory function if it was administered at high doses within eight hours after injury. For the first time, a therapy had been proved to reduce dysfunction caused by spinal cord trauma. The improvements were modest, but the success galvanized a search for additional therapies. Since then, many investigators—including us— have sought new ideas for treatment in studies of why an initial injury triggers further damage to the spinal cord and why the disrupted tissue fails to reconstruct itself.

In this article we will explain how the rapidly burgeoning knowledge might be harnessed to help people with spinal cord injuries. We should note, however, that workers have also been devising strategies that compensate for cord damage instead of repairing it. In the past two years, for example, the U.S. Food and Drug Administration has approved two electronic systems that regulate muscles by sending electrical signals through implanted wires. One returns certain hand movements (such as grasping a cup or a pen) to patients who have shoulder mobility; another restores a measure of control over the bladder and bowel.

A different approach can also provide grasping ability to certain patients. Surgeons identify tendons that link paralyzed forearm muscles to the bones of the hand, disconnect them from those muscles and connect them to arm muscles regulated by parts of the spine above the injury (and thus still under voluntary control). Further, many clinicians suspect that initiating rehabilitative therapy early—exercising the limbs almost as soon as the spine is stabilized—may enhance motor and sensory function in limbs. Those perceptions have not been tested rigorously in people, but animal studies lend credence to them.

The Cord at Work

The organ receiving all this attention is no thicker than an inch but is the critical highway of communication between the brain and the rest of the body. The units of communication are the nerve cells (neurons), which consist of a bulbous cell body (home to the nucleus), trees of signal-detecting dendrites, and an axon that extends from the cell body and carries signals to other cells. Axons branch toward their ends and can maintain connections, or synapses, with many cells at once. Some traverse the entire length of the cord.

The soft, jellylike cord has two major systems of neurons. Of these, the descending, motor pathways control both smooth muscles of internal organs and striated muscles; they also help to modulate the actions of the autonomic nervous system, which regulates blood pressure, temperature and the body's circulatory response to stress. The descending pathways begin with neurons in the brain, which send electrical signals to specific levels, or segments, of the cord. Neurons in those segments then convey the impulses outward beyond the cord.

The other main system of neurons— the ascending, sensory pathways—transmit sensory signals received from the extremities and organs to specific segments of the cord and then up to the brain. Those signals originate with specialized, "transducer" cells, such as sensors in the skin that detect changes in the environment or cells that monitor the state of internal organs. The cord also contains neuronal circuits (such as those involved in reflexes and certain aspects of walking) that can be activated by incoming sensory signals without input from the brain, although they can be influenced by messages from the brain.

The cell bodies in the trunk of the cord reside in a gray, butterfly-shaped core that spans the length of the spinal cord. The ascending and descending axonal fibers travel in a surrounding area known as the white matter, so called because the axons are wrapped in myelin, a white insulating material. Both regions also house glial cells, which help neurons to survive and work properly. The glia include star-shaped astrocytes, microglia (small cells that resemble components of the immune system) and oligodendrocytes, the myelin producers. Each oligodendrocyte myelinates as many as 40 different axons simultaneously.

The precise nature of a spinal cord injury can vary from person to person. Nevertheless, certain commonalities can be discerned.

When Injury Strikes

When a fall or some other force fractures or dislocates the spinal column, the vertebral bones that normally enclose and protect the cord can crush it, mechanically killing and damaging axons. Occasionally, only the gray matter in the damaged area is significantly disrupted. If the injury ended there, muscular and sensory disturbances would be confined to tissues that send input to or receive it from neurons in the affected level of the cord, without much disturbing function below that level.

For instance, if only the gray matter were affected, a cervical 8 (C8) lesion— involving the cord segment where the nerves labeled C8 originate—would paralyze the hands without impeding walking or control over the bowel and bladder. No signals would go out to, or be received from, the tissues connected to the C8 nerves, but the axons conveying signals up and down the surrounding white matter would keep working.

In contrast, if all the white matter in the same cord segment were destroyed, the injury would now interrupt the vertical signals, stopping messages that originated in the brain from traveling below the damaged area and blocking the flow to the brain of sensory signals coming from below the wound. The person would become paralyzed in the hands and lower limbs and would lose control over urination and defecation.

Sadly, the initial insult is only the beginning of the trouble. The early mechanical injury triggers a second wave of damage—one that, over the subsequent minutes, hours and days, progressively enlarges the lesion and thus the extent of functional impairment. This secondary spread tends to occur longitudinally through the gray matter at first before expanding into the white matter (roughly resembling the inflation of a footballshaped balloon). Eventually the destruction can encompass several spinal segments above and below the original wound.

The end result is a complex state of disrepair. Axons that have been damaged become useless stumps, connected to nothing, and their severed terminals disintegrate. Often many axons remain intact but are rendered useless by loss of their insulating myelin. A fluid-filled cavity, or cyst, sits where neurons, other cells and axons used to be. And glial cells proliferate abnormally, creating clusters termed glial scars. Together the cyst and scars pose a formidable barrier to any cut axons that might somehow try to regrow and connect to cells they once innervated. A few axons may remain whole, myelinated and able to carry signals up or down the spine, but often their numbers are too small to convey useful directives to the brain or muscles.

First, Contain the Damage

If all these changes had to be fully reversed to help patients, the prospects for new treatments would be grim. Fortunately, it appears that salvaging normal activity in as little as 10 percent of the standard axon complement would sometimes make walking possible for people who would otherwise lack that capacity. In addition, lowering the level of injury by just a single segment (about half an inch) can make an important difference to a person's quality of life. People with a C6 injury have no power over their arms, save some ability to move their shoulders and flex their elbows. But individuals with a lower, C7 injury can move the shoulders and elbow joints and extend the wrists; with training and sometimes a tendon transfer, they can make some use of their arms and hands.

Because so much damage arises after the initial injury, clarifying how that secondary destruction occurs and blocking those processes are critical. The added wreckage has been found to result from many interacting mechanisms.

Within minutes of the trauma, small hemorrhages from broken blood vessels appear, and the spinal cord swells. The blood vessel damage and swelling prevent the normal delivery of nutrients and oxygen to cells, causing many of them to starve to death.

Meanwhile damaged cells, axons and blood vessels release toxic chemicals that go to work on intact neighboring cells. One of these chemicals in particular triggers a highly disruptive process known as excitotoxicity. In the healthy cord the end tips of many axons secrete minute amounts of glutamate. When this chemical binds to receptors on target neurons, it stimulates those cells to fire impulses. But when spinal neurons, axons or astrocytes are injured, they release a flood of glutamate. The high levels overexcite neighboring neurons, inducing them to admit waves of ions that then trigger a series of destructive events in the cells—including production of free radicals. These highly reactive molecules can attack membranes and other components of formerly healthy neurons and kill them.

Until about a year ago, such excitotoxicity, also seen after a stroke, was thought to be lethal to neurons alone, but new results suggest it kills oligodendrocytes (the myelin producers) as well. This effect may help explain why even unsevered axons become demyelinated, and thus unable to conduct impulses, after spinal cord trauma.

Prolonged inflammation, marked by an influx of certain immune system cells, can exacerbate these effects and last for days. Normally, immune cells stay in the blood, unable to enter tissues of the central nervous system. But they can flow in readily where blood vessels are damaged. As they and microglia become activated in response to an injury, the activated cells release still more free radicals and other toxic substances.

Methylprednisolone, the first drug found to limit spinal cord damage in humans, may act in part by reducing swelling, inflammation, the release of glutamate and the accumulation of free radicals. The precise details of how it helps patients remain unclear, however.

Studies of laboratory animals with damaged spinal cords indicate that drugs able to stop cells from responding to excess glutamate could minimize destruction as well. Agents that selectively block glutamate receptors of the so-called AMPA class, a kind abundant on oligodendrocytes and neurons, seem to be particularly effective at limiting the final extent of a lesion and the related disability. Certain AMPA receptor antagonists have already been tested in early human trials as a therapy for stroke, and related compounds could enter safety studies in patients with spinal cord injury within several years.

Much of the early cell loss in the injured spinal cord occurs by necrosis, a process in which cells essentially become passive victims of murder. In the past few years, neurobiologists have also documented a more active form of cell death, somewhat akin to suicide, in the cord. Days or weeks after the initial trauma, a wave of this cell suicide, or apoptosis, frequently sweeps through oligodendrocytes as many as four segments from the trauma site. This discovery, too, has opened new doors for protective therapy. Rats given apoptosisinhibiting drugs retained more ambulatory ability after a traumatic spinal cord injury than did untreated rats.

In the past few years, biologists have identified many substances, called neurotrophic factors, that also promote neuronal and glial cell survival. A related substance, GM-1 ganglioside (Sygen), is now being evaluated for limiting cord injury in humans. Ultimately, interventions for reducing secondary damage in the spinal cord will probably enlist a variety of drugs given at different times to thwart specific mechanisms of death in distinct cell populations.

The best therapy would not only reduce the extent of an injury but also repair damage. A key component of that repair would be stimulating the regeneration of damaged axons—that is, inducing their elongation and reconnection with appropriate target cells.

Although neurons in the central nervous system of adult mammals generally fail to regenerate damaged axons, this lapse does not stem from an intrinsic property of those cells. Rather the fault lies with shortcomings in their environment. After all, neurons elsewhere in the body and in the immature spinal cord and brain regrow axons readily, and animal experiments have shown that the right environment can induce axons of the spinal cord to extend quite far.

Then, Induce Regeneration

One shortcoming of the cord environment turns out to be an overabundance of molecules that actively inhibit axonal regeneration—some of them in myelin. The scientists who discovered these myelin-related inhibitors have produced a molecule named IN-1 (inhibitorneutralizing antibody) that blocks the action of those inhibitors. They have also demonstrated that infusion of mouse-derived IN-1 into the injured rat spinal cord can lead to long-distance regrowth of some interrupted axons. And when pathways controlling front paw activity are severed, treated animals regain some paw motion, whereas untreated animals do not. The rodent antibody would be destroyed by the human immune system, but workers are developing a humanized version for testing in people.

Many other inhibitory molecules have now been found as well, including some produced by astrocytes and a number that reside in the extracellular matrix (the scaffolding between cells). Given this array, it seems likely that combination therapies will be needed to counteract or shut down the production of multiple inhibitors at once.

Beyond removing the “brakes” on axonal regrowth, a powerful tactic would supply substances that actively promote axonal extension. The search for such factors began with studies of nervous system development. Decades ago scientists isolated nerve growth factor (NGF), a neurotrophic factor that supports the survival and development of the peripheral nervous system. Subsequently, this factor turned out to be part of a family of proteins that both enhance neuronal survival and favor the outgrowth of axons. Many other families of neurotrophic factors with similar talents have been identified as well. For instance, the molecule neurotrophin- 3 (NT-3) selectively encourages the growth of axons that descend into the spinal cord from the brain.

Luckily, adult neurons remain able to respond to axon-regenerating signals from such factors. Obviously, however, natural production of these substances falls far short of the amount needed for spinal cord repair. Indeed, manufacture of some of the compounds apparently declines, instead of rising, for weeks after a spinal trauma occurs. According to a host of animal studies, artificially raising those levels after an injury can enhance regeneration. Some regeneration- promoting neurotrophic factors, such as basic fibroblast growth factor, have been tested in stroke patients. None has been evaluated as an aid to regeneration in people with spinal cord damage, but many are being assessed in animals as a prelude to such studies.

Those considering neurotrophic factors for therapy will have to be sure that the agents do not increase pain, a common long-term complication of spinal cord injury. This pain has many causes, but one is the sprouting of nascent axons where they do not belong (perhaps in a failed attempt to address the injury) and their inappropriate connection to other cells. The brain sometimes misinterprets impulses traveling through those axons as pain signals. Neurotrophic factors can theoretically exacerbate that problem and can also cause pain circuits in the spiral cord and pain-sensing cells in the skin to become oversensitive.

After axons start growing, they will have to be guided to their proper targets, the cells to which they were originally wired. But how? In this case, too, studies of embryonic development have offered clues.

During development, growing axons are led to their eventual targets by molecules that act on the leading tip, or growth cone. In the past five years especially, a startling number of substances that participate in this process have been uncovered. Some, such as a group called netrins, are released or displayed by neurons or glial cells. They beckon axons to grow in some directions and repel growth in others. Additional guidance molecules are fixed components of the extracellular matrix. Certain of the matrix molecules bind well to specific molecules (cell adhesion molecules) on the growth cones and thus provide anchors for growing axons. During development, the required directional molecules are presented to the growth cones in specific sequences.

Establish Proper Connections

At the moment, no one knows how to supply all the needed chemical road signs in the right places. But some findings suggest that regeneration may be aided by supplying just a subset of those targeting molecules—say, a selection of netrins and components from the extracellular matrix. Substances already in the spinal cord may well be capable of supplying the rest of the needed guidance.

A different targeting approach aims to bridge the gap created by cord damage. It directs injured axons toward their proper destinations by supplying a conduit through which they can travel or by providing another friendly scaffolding able to give physical support to the fibers as they try to traverse the normally impenetrable cyst. The scaffolding can also serve as a source of growth-promoting chemicals.

For instance, researchers have implanted tubes packed with Schwann cells into the gap where part of the spinal cord was removed in rodents. Schwann cells, which are glia of the peripheral nervous system, were chosen because they have many attributes that favor axonal regeneration. In animal experiments, such grafts spurred some axonal growth into the tubes.

A second bridging material consists of olfactory-ensheathing glial cells, which are found only in the tracts leading from the nose to the olfactory bulbs of the brain. When those cells were put into the rat spinal cord where descending tracts had been cut, the implants spurred partial regrowth of the axons over the implant. Transplanting the olfactory-ensheathing glia with Schwann cells led to still more extensive growth.

In theory, a biopsy could be performed to obtain the needed olfactory ensheathing glia from a patient. But once the properties that enable them (or other cells) to be competent escorts for growing axons are determined, researchers may instead be able to genetically alter other cell types if desired, giving them the required combinations of growthpromoting properties.

Fibroblasts (cells common in connective tissue and the skin) are among those already being engineered to serve as bridges. They have been altered to produce the neurotrophic molecule NT-3 and then transplanted into the cut spinal cord of rodents. The altered fibroblasts have resulted in partial regrowth of axons. Along with encouraging axonal regrowth, NT-3 stimulates remyelination. In these studies the genetically altered fibroblasts have enhanced myelination of regenerated axons and improved hind limb activity.

Replace Lost Cells

Other transplantation schemes would implant cells that normally occur in the central nervous system. In addition to serving as bridges and potentially releasing proteins helpful for axonal regeneration, certain of these grafts might be able to replace cells that have died.

Transplantation of tissue from the fetal central nervous system has produced a number of exciting results in animals treated soon after a trauma. This immature tissue can give rise to new neurons, complete with axons that travel long distances into the recipient's tissues (up and down several segments in the spinal cord or out to the periphery). It can also prompt host neurons to send regenerating axons into the implanted tissue. In addition, transplant recipients, unlike untreated animals, may recover some limb function, such as the ability to move the paw in useful ways. What is more, studies of fetal tissue implants suggest that axons can at times find appropriate targets even in the absence of externally supplied guidance molecules. The transplants, however, are far more effective in the immature spinal cord than in the injured adult cord—an indication that young children would probably respond to such therapy much better than adolescents or adults would.

Some patients with long-term spinal cord injuries have received human fetal tissue transplants, but too little information is available so far for drawing any conclusions. In any case, application of fetal tissue technology in humans will almost surely be limited by ethical dilemmas and a lack of donor tissue. Therefore, other ways of achieving the same results will have to be devised. Among the alternatives is transplanting stem cells: immature cells that are capable of dividing endlessly, of making exact replicas of themselves and also of spawning a range of more specialized cell types.

Various kinds of stem cells have been identified, including ones that generate all the cell types in the blood system, the skin, or the spinal cord and brain. Stem cells found in the human adult central nervous system have, moreover, been shown capable of producing neurons and all their accompanying glia, although these so-called neural stem cells seem to be quiescent in most regions of the system. In 1998 a few laboratories also obtained much more versatile stem cells from human tissue. These human embryonic stem cells (in common with embryonic stem cells obtained previously from other vertebrates) can be grown in culture and, in theory, can yield almost all the cell types in the body, including those of the spinal cord.

Stem Cell Strategies

How might stem cells aid in spinal cord repair? A great deal will be possible once biologists learn how to obtain those cells readily from a patient and how to control the cells' differentiation. Notably, physicians might be able to withdraw neural stem cells from a patient's brain or spinal cord, expand the numbers of the still undifferentiated cells in the laboratory and place the enlarged population in the same person's cord with no fear that the immune system will reject the implant as foreign. Or they might begin with frozen human embryonic stem cells, coax those cells to become precursors, or progenitors, of spinal cells and implant a large population of the precursors. Studies proposing to examine the effects on patients with spinal cord injuries of transplanting neural stem cells (isolated from the patients' brains by biopsy) are being considered.

Simply implanting progenitor cells into the cord may be enough to prod them to multiply and differentiate into the needed lineages and thus to replace useful numbers of lost neurons and glial cells and establish the proper synaptic connections between neurons. Stem cells transplanted into the normal and injured nervous systems of animals can form neurons and glia appropriate for the region of transplantation. Combined with the fetal tissue results, this outcome signifies that many important cues for differentiation and targeting preexist in the injured nervous system. But if extra help is needed, scientists might be able to deliver it through genetic engineering. As a rule, to be genetically altered easily, cells have to be able to divide. Stem cells, unlike mature neurons, fit that bill.

Scenarios involving stem cell transplants are admittedly futuristic, but one day they themselves may become unnecessary, replaced by gene therapy alone. Delivery of genes into surviving cells in the spinal cord could enable those cells to manufacture and release a steady supply of proteins able to induce stem cell proliferation, to enhance cell differentiation and survival, and to promote axonal regeneration, guidance and remyelination. For now, though, technology for delivering genes to the central nervous system and for ensuring that the genes survive and work properly is still being refined.

Until, and even after, cell transplants and gene therapies become commonplace for coping with spinal cord injury, patients might gain help through a different avenue—drugs that restore signal conduction in axons quieted by demyelination. Ongoing clinical tests are evaluating the ability of a drug called 4-aminopyridine to compensate for demyelination. This agent temporarily blocks potassium

ion channels in axonal membranes and, in so doing, allows axons to transmit electrical signals past zones of demyelination. Some patients receiving the drug have demonstrated modest improvement in sensory or motor function.

At first glance, this therapy might seem like a good way to treat multiple sclerosis, which destroys the myelin around axons of neurons in the central nervous system. Patients with this disease are prone to seizures, however, and 4-aminopyridine can exacerbate that tendency.

Neurotrophic factors, such as NT-3, that can stimulate remyelination of axons in animals could be considered for therapy as well. NT-3 is already entering extensive (phase III) trials in humans with spinal cord injury, though not to restore myelin. It will be administered by injection in amounts capable of acting on nerves in the gut and of enhancing bowel function, but the doses will be too low to yield high concentrations in the central nervous system. If the drug proves to be safe in this trial, though, that success could pave the way for human tests of doses large enough to enhance myelination or regeneration.

The Years Ahead

Clearly, the 1990s have seen impressive advances in understanding of spinal cord injury and the controls on neuronal growth. Like axons inching toward their targets, a growing number of investigators are pushing their way through the envelope of discovery and generating a rational game plan for treating such damage. That approach will involve delivery of multiple therapies in an orderly sequence. Some treatments will combat secondary injury, some will encourage axonal regrowth or remyelination, and some will replace lost cells.

When will the new ideas become real treatments? We wish we had an answer. Drugs that work well in animals do not always prove useful in people, and those that show promise in small human trials do not always pan out when examined more extensively. It is nonetheless encouraging that at least two human trials are now under way and that others could start in the next several years.

Limiting an injury will be easier than reversing it, and so treatments for ameliorating the secondary damage that follows acute trauma can be expected to enter human testing most quickly. Of the repair strategies, promoting remyelination will be the simplest to accomplish, because all it demands is the recoating of intact axons. Remyelination strategies have the potential to produce meaningful recovery of function, such as returning control over the bladder or bowel— abilities that uninjured people take for granted but that would mean the world to those with spinal cord injuries.

Of course, tendon-transfer surgery and advanced electrical devices can already restore important functions in some patients. Yet for many people, a return of independence in daily activities will depend on reconstruction of damaged tissue through the regrowth of injured axons and the reconnection of disrupted pathways.

So far, few interventions in animals with well-established spinal cord injuries have achieved the magnitude of regrowth and synapse formation that would be needed to provide a hand grasp or the ability to stand and walk in human adults with long-term damage. Because of the great complexities and difficulties involved in those aspects of cord repair, we cannot guess when reconstructive therapies might begin to become available. But we anticipate continued progress toward that end.

Traditionally, medical care for patients with spinal cord injury has emphasized compensatory strategies that maximize use of any residual cord function. That focus is now expanding, as treatments designed to repair the damaged cord and restore lost function—science fiction only a decade ago—are becoming increasingly plausible.

Further Reading

Impact and the Brain
Sparking Recovery with Brain "Pacemakers"
Putting Thoughts into Action: Implants Tap the Thinking Brain
Neural Light Show: Scientists Use Genetics to Map and Control Brain Functions

Remember: Memory Record and Replay Handled by Same Cells
Can one neuron release more than one neurotransmitter? Why is it comforting to discuss problems with others?
Is It Time to Give Up on Therapeutic Cloning? A Q&A with Ian Wilmut
Why Migraines Strike