Repairing the Damaged Spinal Cord

SPINAL CORD (at center in human figure and enclosed by vertebrae in detail) is the central highway for signals traveling between the brain and the rest of the body. It receives sensory information from, and conveys motor commands to, the periphery via the nerves branching from it. A cord injury can disrupt activity and sensation in all tissues below the damage. Hence, injury in the neck area can erase control over most of the body and often necessitates use of a respirator for breathing. The background depicts nerve cells (neurons).
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 [see box on pages 72 and 73].

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.

Four divisions of the spinal cord and their associated nerves serve specific areas of the body. In general, the cervical nerves link to the neck, the arms and the respiratory apparatus; the thoracic nerves control posture and many internal organs; the lumbar nerves work the legs; and the sacral nerves regulate the bladder and the bowel and play a role in sexual function.
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 football-shaped 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

SEGMENT OF CORD (a) reveals the butterfly-shaped gray matter at the core and a ring of white matter. The main components of the gray matter (b) are neuronal cell bodies, but so-called glial cells (such as astrocytes and microglia) and blood vessels are present as well. The white matter (c) also contains astrocytes and blood vessels, but it consists mostly of axons (signal-carrying neuronal projections), which travel up and down the cord, and of oligodendrocytes—glial cells that wrap axons in white, insulating myelin. Axonal tracts that ascend in the cord, such as the red one in a, convey sensory messages received from elsewhere in the body; the descending tracts, such as that shaded blue, carry motor commands to muscles.
A spinal injury often affects a small area at first, but it triggers secondary processes that expand the destruction. Many axons then end up either cut or partly shorn of their insulating myelin and unable to propagate signals past the affected areas (diagram).

Axons normally do not regrow or become adequately remyelinated. But even if they did, they would still meet critical barriers to full repair. One is an impenetrable, fluid-filled cavity—a cyst—that forms where cells have died and axons have been cut away. This cyst is often surrounded by glial “scars”—clusters of activated glial cells that are physically penetrable but release or display substances that inhibit axonal growth. In many people, only a small fraction of axons at the periphery of the cord remain in service.

Eventually therapy is likely to include a combination of several treatments, such as those listed below. Most treatments would be delivered directly into the injured area. Limiting destruction will be easier than repairing it. And once the damage is established, compensating for demyelination will be easier than coaxing axons to regrow and to form appropriate synapses.

—J.W. McD.

### Targets for Therapy

- **Compensate for Demyelination**
  - Supply chemicals that prevent nerve impulses from dissipating at demyelinated areas
  - Provide agents that spur surviving oligodendrocytes to remyelinate axons
  - Replenish lost oligodendrocytes (see “Replace Dead Cells” box on next page)

- **Promote Axonal Regeneration**
  - Deliver agents that overcome natural inhibitors of regeneration
  - Administer compounds that induce axonal regrowth

- **Direct Axons to Proper Targets**
  - Somehow supply needed guidance molecules at the right sites
  - Administer compounds that induce surviving cells to produce or display guidance molecules

***Note:*** The diagram illustrates the path of axons and the zones of demyelination and injury. The zone lacking myelin is an area where axons are disrupted and unable to propagate signals. The cyst (fluid-filled cavity) represents a barrier to axonal regeneration. The demyelinated axons are those that have lost their myelin sheaths and are unable to propagate signals. The severed axons are those that have been cut and are unable to regrow. Normal conductance and signal fail to propagate past the demyelinated area.

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 un severed 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 dam-

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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 apoptosis-inhibiting 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.

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imal experiments have shown that the
right environment can induce axons of
the spinal cord to extend quite far.

Then, Induce Regeneration

O
e shortcoming of the cord envi-
ronment turns out to be an over-
abundance of molecules that actively in-
hit axonal regeneration—some of them
in myelin. The scientists who discovered
these myelin-related inhibitors have pro-
duced a molecule named IN-1 (inhibitor-
neutralizing 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 re-
growth of some interrupted axons. And
when pathways controlling front paw
activity are severed, treated animals re-
gain some paw motion, whereas untreat-
ed animals do not. The rodent antibody
would be destroyed by the human im-
une system, but workers are develop-
ing 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 combina-
tion therapies will be needed to coun-
teract or shut down the production of
multiple inhibitors at once.

Beyond removing the “brakes” on ax-
onal 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 sci-
entists isolated nerve growth factor
(NGF), a neurotrophic factor that sup-
ports the survival and development of
the peripheral nervous system. Subse-
quently, 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 neu-
rotrophin-3 (NT-3) selectively encour-
ges 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
depends, instead of rising, for weeks af-
ther a spinal trauma occurs. According
to a host of animal studies, artificially
raising those levels after an injury can
enhance regeneration. Some regenera-
tion-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 fac-
tors for therapy will have to be sure that
the agents do not increase pain, a com-
mon 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 prob-
lem and can also cause pain circuits in
the spinal cord and pain-sensing cells in
the skin to become oversensitive.

After axons start growing, they will
have to be guided to their proper tar-
gets, the cells to which they were origi-
nally wired. But how? In this case, too,
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. 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.

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

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studies of embryonic development have offered clues.

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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
Advances in Electronics

What if implanted electrodes could stimulate nerves quieted by spinal cord injury and thereby restore function to certain paralyzed muscles? In fact, such devices already exist, and two meant to increase independence have recently gained the approval of the U.S. Food and Drug Administration. One enables certain people who retain shoulder mobility to use a hand (illustration). Particular movements by the opposite shoulder activate a detector that sends signals to an external control unit. That unit, in turn, relays the signals to an implanted transmitting coil connected to wires that terminate on selected arm and hand muscles.

The other device, long used in England before being tested in the U.S., aims primarily to enable people to urinate on demand. An external transmitter activates an implanted pacemakerlike device that sends electrical signals to nerves feeding into the bladder. In response, the bladder and its sphincter contract, after which the sphincter relaxes, enabling the bladder to empty. The system also stimulates the nerves to the bowel and aids in its evacuation.

Other electrical devices that are available or under study include systems that allow people to stand (for easier transfer between, say, a wheelchair and a bed or toilet), exercise the heart and lungs, assist breathing, induce coughing, improve circulation or reduce spasticity.

—Ricki L. Rusting, staff writer

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 regeneration 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.

The Authors

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