stimulation of the subthalamic nucleus of Parkinson's patients with a stereotactically placed electrode results in alleviation of many of the motor symptoms of this disease (*31*).

Clearly, CIs and ABIs not only are of benefit to profoundly deaf individuals but also continue to provide insight into information processing in the auditory nervous system. And certainly, each new understanding achieved in basic scientific research will result in improvements to the technology of auditory prostheses, and increased benefits for patients.

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VIEWPOINT

Repairing the Injured Spinal Cord

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Certain cell, molecular, and bioengineering strategies for repairing the injured spinal cord are showing encouraging results (either alone or in combination) in animal models, with limited recovery of mobility being reported in some cases.

Our spinal cord is a finger-thick strand of nervous tissue that is tightly enclosed in the bony vertebrae of the spinal column. The spinal cord receives sensory information from the skin, the muscles, the joints, and other tissues of the body. It transmits this information in the form of electrical impulses to the brain, along millions of nerve fibers that are grouped together in bundles. The motor commands that are subsequently generated in the brain are sent to the spinal cord along fast-conducting nerve fibers, which terminate in local spinal motor circuits. From here, the electrical impulses that will direct coordinated muscle contraction reach the muscles via the peripheral nerves. A sharp blow to the spinal column can cause dislocation of individual vertebrae and severe damage to the spinal cord, including its complete severance. Clinically, the result of an incomplete or complete spinal cord lesion is either paraplegia (paralysis of the lower body) or quadriplegia (paralysis of the body from the neck down), depending on whether the injury was sustained in the thoracic/lumbar region or neck region of the spinal column, respectively.

Destruction of the spinal cord can be compared to a bomb exploding in a computer center, and repairing the spinal cord is as complicated as trying to rebuild all of the computer connections. In the last few years, there has been encouraging progress in animal models, with sufficient regeneration of the damaged spinal cord to enable some recovery of motor ability. When the spinal cord is injured, the first phase of injury involves mechanical tissue destruction. It is followed by a second phase of tissue loss, which is principally caused by a severe local disturbance of the blood supply (*1, 2*). There have been attempts to minimize this secondary damage with neuroprotective agents, but, so far, only high-dose methylprednisolone (a synthetic corticosteroid) given within the first hours after injury is in use clinically (*2, 3*). Within several weeks of the injury, macrophages migrating from the bloodstream have cleared the tissue debris at the lesion site, resulting in fluid-filled cysts surrounded by scar tissue (Fig. 1). Whether this inflammatory reaction leads to additional damage of spinal cord tissue that is still intact remains a matter of debate.

Remarkably, images of the lesioned spinal cord in paraplegic or quadriplegic patients show that complete anatomical separation of the spinal cord is very rare. Instead, bridges of nerve tissue (tracts) connecting regions above and below the lesion often persist, mostly at the peripheral edges of the spinal cord (*4*). This type of anatomically incomplete spinal cord lesion has been recreated in rats and other animals, either by microsurgical transection of defined regions of the spinal cord or by crushing the cord with metal rods of different weights. These animal models are valuable tools with which to test various spinal cord repair strategies.

There are four principal strategies for repairing spinal cord lesions: (i) promoting the regrowth of interrupted nerve fiber tracts, using nerve growth stimulatory factors or molecules that suppress inhibitors of neuronal extensions (neurites); (ii) bridging spinal cord lesions with scaffolds that are impregnated with nerve growth factors, which promote axon growth and reduce the barrier caused by scar tissue; (iii) repairing damaged myelin (the insulating sheath that surrounds axons) and restoring nerve fiber impulse conductivity in the lesion area; and (iv) enhancing central nervous system (CNS) plasticity by promoting compensatory growth of spared, intact nerve fibers above and below the lesion.

Regeneration of Nerve Fiber Tracts

Crushed or transected nerve fibers in the CNS of the adult often react with a spontaneous,

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but short-lived and ultimately abortive, attempt at repair called regenerative sprouting. In vitro studies have revealed that spontaneous regenerative sprouting is short-lived because the adult CNS (particularly the myelin sheaths of adult nerves) produces specific inhibitory proteins that block neurite outgrowth (*5*). Since this discovery, there have been numerous attempts to ablate or neutralize these inhibitory factors in order to promote regenerative sprouting of the lesioned spinal cord. Ten years ago, in vivo studies showed that preventing myelin formation or using a monoclonal antibody (mAb IN-1) that neutralized the activity of the myelin protein Nogo-A (*5, 6*) promoted regeneration of corticospinal fibers (which connect the cerebral cortex and the spinal cord) in the lesioned spinal cords of adult rats (*2, 7, 8*). These observations were confirmed by immunizing lesioned animals with CNS myelin, lysing myelin with antibody and complement in vivo, or enhancing myelin clearance by injecting activated macrophages (*9–11*). Functional improvements observed in such animals strongly indicated that nerve fibers allowed to regrow in an adult spinal cord can still recognize and connect with their correct targets.

Current efforts are aimed at blocking Nogo-A as well as other growth-inhibitory molecules by the in vivo application of antibodies against these molecules, by blocking the receptors to which they bind, or by pharmacologically manipulating the downstream signaling pathways induced by these inhibitory signals in growing neurites (*12, 13*). One way to deliver such agents is by subcutaneous pumps that inject antibodies or other blocking molecules directly into the cerebrospinal fluid that bathes the spinal cord. Such pumps are routinely used in the clinic for infusing drugs, e.g., into chronic pain patients.

Neurotrophic factors are small proteins secreted by a variety of different cell types that enhance nerve fiber outgrowth during embryonic development. Local application of neurotrophic factors such as neurotrophin-3 (NT-3) to lesioned fiber tracts of the spinal cord can directly promote sprouting, and, in some cases, can induce long-distance regeneration of lesioned fibers (*14, 15*). The specificities of neurotrophic factors for particular nerve cell populations during embryonic development are well established. However, as yet, such specificities have not been well worked out for the adult CNS. Indeed, the regenerative effects of nerve growth factor (NGF) on peripheral nerves, for example, have turned out to be clinically useless because NGF affects pain-sensitive neurons, resulting in hyperalgesia (increased sensitivity to pain). Although more than 30 neurotrophic factors are known, fewer than six of them have been investigated as potential treatments for lesioned spinal cords in animal models (*15*). Injections and pumps can be used to deliver neurotrophic factors to the lesion site. However, other strategies have also been tried, such as implanting cells engineered to secrete these factors directly into the lesion site, or using gene therapy with viral constructs containing neurotrophic factor genes to locally produce the factors where they are needed (*15*).

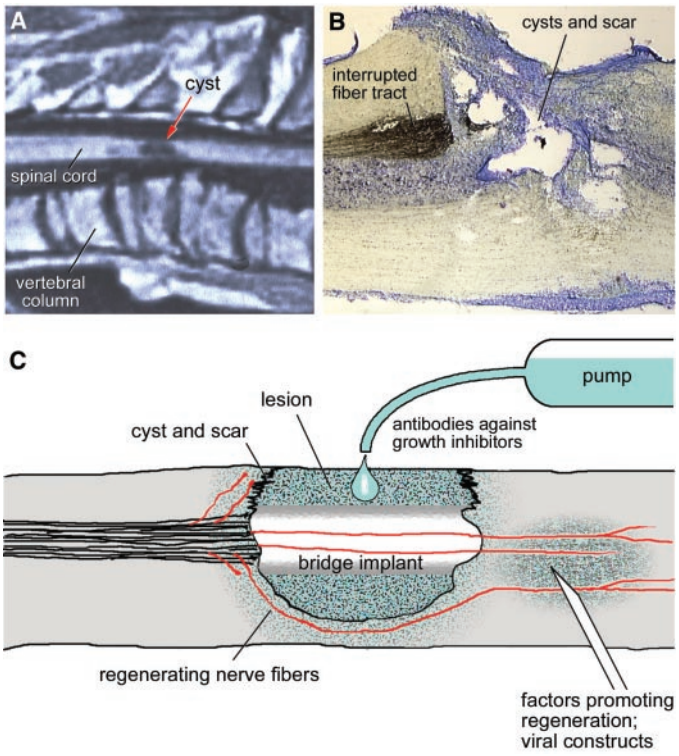

Fig. 1. Spinal cord lesions in human and rat. (**A**) Magnetic resonance image of a human spinal column showing the spinal cord lying within the central canal. Bone fragments from a burst fracture of the middle vertebral bodies have contused the spinal cord, resulting in a fluid-filled cyst (dark) at the site of tissue destruction. (**B**) Longitudinal histological section through the lesion site of an injured rat spinal cord. Cysts and scar tissue are prominent at the injury site. The corticospinal tract (black), the bundle of nerve fibers connecting the cerebral cortex to the spinal cord, is fully interrupted by the lesion, depriving the lower spinal cord of its cortical input for motor control. (**C**) Strategies to repair the injured spinal cord include implanting scaffolds to bridge scars and cysts, treating the lesion site with antibodies or other agents that counteract the effects of neurite growth-inhibitory factors, applying neurite growth-promoting molecules or nerve attractants by injection pump, or gene delivery to increase nerve fiber sprouting and nerve regeneration.

Bridging Cysts and Scars

In anatomically incomplete spinal cord lesions, regenerating nerve fibers are able to bypass the injury site by using persisting tissue bridges (Fig. 1). But sprouting nerve fibers often do not seem eager to cross this stretch of foreign territory, in particular because scar tissue at the injury site contains scar-associated neurite growth-inhibitory molecules such as the chondroitin sulfate proteoglycans (*16*). Enzymatic digestion of chondroitin sulfate proteoglycans enhances the regenerative growth of CNS fibers in a brain lesion rat model (*17*). Scar formation is a natural reaction of the lesioned CNS tissue, and attempts to prevent it have not been successful. The complex interplay between inflammatory cells and astrocytes, the glial cells of the nervous system that are the principal contributors to scar formation, is still poorly understood.

Bridges that form a growth-permissive scaffold within the lesion site should greatly facilitate regenerative axon growth. Many types of cells, tissues, or artificial materials have been implanted as bridges into the injured spinal cord (*18*). The success of these experiments is limited, often because astrocytes "wall off" the foreign object, thus greatly restricting access of regenerating fibers to the implants. Important exceptions to this rather deceiving picture are implants made of Schwann cells (the glial cells that produce the myelin sheaths surrounding peripheral nerves) or precisely placed peripheral nerve grafts, which are invaded by regenerating axons and can serve as bridges across even anatomically complete lesions (*18, 19*). In a spinal cord lesion rat model, implanted olfactory nerve glial cells align themselves with the lesion site, migrate long distances into the anterior and posterior spinal cord stumps, and guide regenerating axons through the lesion (*20*). The migratory behavior of these specialized glial cells, which are also known to produce a variety of growth factors and growth-permissive extracellular matrix molecules, may be part of their success. However, these glial cells may also damage intact nervous tissue, because they are foreign to the spinal cord and may promote an immunological reaction, thus negating the possibility of implanting them in human patients.

Several labs are currently exploring the potential use of other cell types as bridging material, including neural stem cells and

cells genetically engineered to allow manipulation of their behavior or their ablation once their bridging function is complete (*14, 18*). Neural stem cells can be obtained by expanding a small biopsy of brain or bone marrow tissue in culture. These cells could then be induced to form growth-permissive astrocytes, which could be implanted into the spinal cord lesion cavity (Fig. 1). If such cells misbehave, for example, by inducing formation of dense scars or tumors, they could be ablated by activation of an inbuilt suicide gene. For repair of lesioned spinal cord tissue, fibrin or hydrogels loaded with growth factors that attract regenerating neurites and keep scar formation under control show promise. The principal obstacle to be overcome with all of these bridges is how to integrate them into the spinal cord tissue without inducing scar formation.

Myelin Repair

In all fast-conducting nerves, the nerve fibers are surrounded by a myelin sheath. Local loss of myelin often occurs in surviving bundles of nerve fibers at the site of the spinal cord lesion (*2, 4*), leading to disruption of electrical impulse conductivity. The adult spinal cord seems unable to efficiently replace either lost myelin or loss of oligodendrocytes, the glial cells that produce myelin in the CNS. Neural stem cells, obtained from adult animals or human brain biopsies (and in the future possibly from adult bone marrow) and expanded in culture, could be primed with the correct growth factor cocktail to become oligodendrocytes, which could then be implanted into lesion sites to promote myelin production. Successful remyelination by such cells has been shown to occur in the spinal cord of adult rats (*21–23*). Repair of the myelin sheath and subsequent restoration of impulse conductivity in nerve fibers that have survived the lesion would enable patients to make much better use of their surviving nerve fiber tracts.

Enhancing CNS Plasticity

After spinal cord injury, the remaining intact nerve fibers react to the imbalance of the neural circuitry by sprouting compensatory fibers. Although pronounced before and just after birth, this plasticity (that is, the ability of one group of nerve fibers to take over the role of another injured group) is much less prominent in the adult CNS (*24*). Antibodies against neurite growth-inhibitory factors have been shown to enhance compensatory sprouting of nerve fibers in the partially lesioned brain stem and spinal cord of the adult rat. This resulted in an almost complete functional restoration of fine paw movements in these animals, as demonstrated by the food pellet reaching test (*25, 26*). Several of the interventions that promote regeneration of damaged nerve fibers (neurotrophic factors, antibodies) will almost certainly also enhance compensatory growth of nonlesioned nerve fibers. In addition, the flow of electrical impulses in a particular neural circuit is known to strengthen connections, or even to induce sprouting and the formation of new connections (*24*). Here, specific rehabilitation strategies may come into play. The effects of activity on the molecular machinery of nerve fiber growth are currently under investigation, as are the effects of combining growth factors with specific training programs for treating spinal cord injuries.

A few years ago, the prognosis for recovery after spinal cord injury was bleak, and this field of research was labeled a lost cause. Now, at least from the research perspective, the situation has changed radically. Some of the new strategies to repair spinal cord injuries, either alone or in combination, offer the possibility of clinically effective therapies for paraplegic and quadriplegic patients in the not too distant future.

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