CLINICAL IMPLICATIONS OF BASIC RESEARCH

Stem Cells and Spinal Cord Repair

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For the past couple of decades, clinicians have watched the stem-cell field with a mixture of anticipation and skepticism. No group of patients has been more expectant than those with spinal cord injuries. Therapies for spinal cord injury have been promised almost since the dawning of the stem-cell field. The recent launch — and abrupt termination — of a phase 1 clinical trial for acute spinal cord injury by the biotechnology company Geron whetted the appetite, and then fueled the frustration, of these patients.

A recent study by Sakai et al.[1] is one of a series in this field. It is important in that it embraces concepts that were first introduced a decade ago[2]: namely, that spinal cord injury is not a monolithic entity but rather a series of concurrent and interacting pathological processes[3]; that multimodal actions will be required to combat the various facets of this malady; that stem cells, in fulfilling their fundamental teleologic role of maintaining homeostasis in a perturbed system, may be capable of intrinsically exerting many of these requisite multifaceted actions[4]; and that the stem cell may serve as the glue that bonds and focuses many of these multidisciplinary approaches. The authors observed that implantation of stem cells derived from human tooth pulp (a neural-crest derivative) into transected rat spinal cords led to functional improvement by reducing the death of neurons and glia, preserving axons and myelin sheaths, promoting regeneration of transected axons by down-regulating multiple growth inhibitors, and spurring the differentiation of stem cells into myelinating cells. Although such observations are not new to the neural stem-cell field, the appeal of the approach used by Sakai et al. lies in exploiting a stem-cell source that is both readily accessible from a living patient and is immunologically matched to the potential recipient, precluding the need for immunosuppressive drugs.

Although this study, like many in the field of spinal cord injury, is not without flaws, it provides an opportunity to coach clinicians (who can then inform their patients) about why research in spinal cord injury is so challenging. The cascade of pathological processes that characterize spinal cord injury unfolds in the context of a neuroanatomy that is complex, with connections and functions that have been rendered regionally discrete within a span of millimeters, if not microns, during a finely tuned process that is part of embryonic development. Despite attempts to standardize experimental models, procedures, readouts, and instruments, there can nevertheless be variability from animal to animal and investigator to investigator. The presence of spared fibers after transaction is often difficult to detect. Substantial degrees of spontaneous recovery that are not related to treatment can occur for reasons not entirely known or controllable. Certainly, much of this spontaneous recovery is attributable to the resolution of processes such as edema, inflammation, altered perfusion, shock, and transient channelopathies. It is also probably due to gradual behavioral compensation by the animal, redundancy in connections, and the disinhibition of certain intraspinal reflexive movements (so-called locomotion pattern generators[5]).

The field itself is inherently vulnerable to observer bias because it lacks adequate varieties of truly objective, quantifiable, discrete measures of spinal function attributable purely to single pathways. Other confounders include related maladies (e.g., pain, bladder and bowel dysfunction, muscle atrophy, osteopenia, skin breakdown, and fatigue); the unmonitored effects of learning, environmental stimulation, motivation, and rehabilitation; the effect of immunosuppressant drugs or use of experimental animals with immunodeficiency; the sex and strain of experimental animals; and in stem-cell transplantation, the

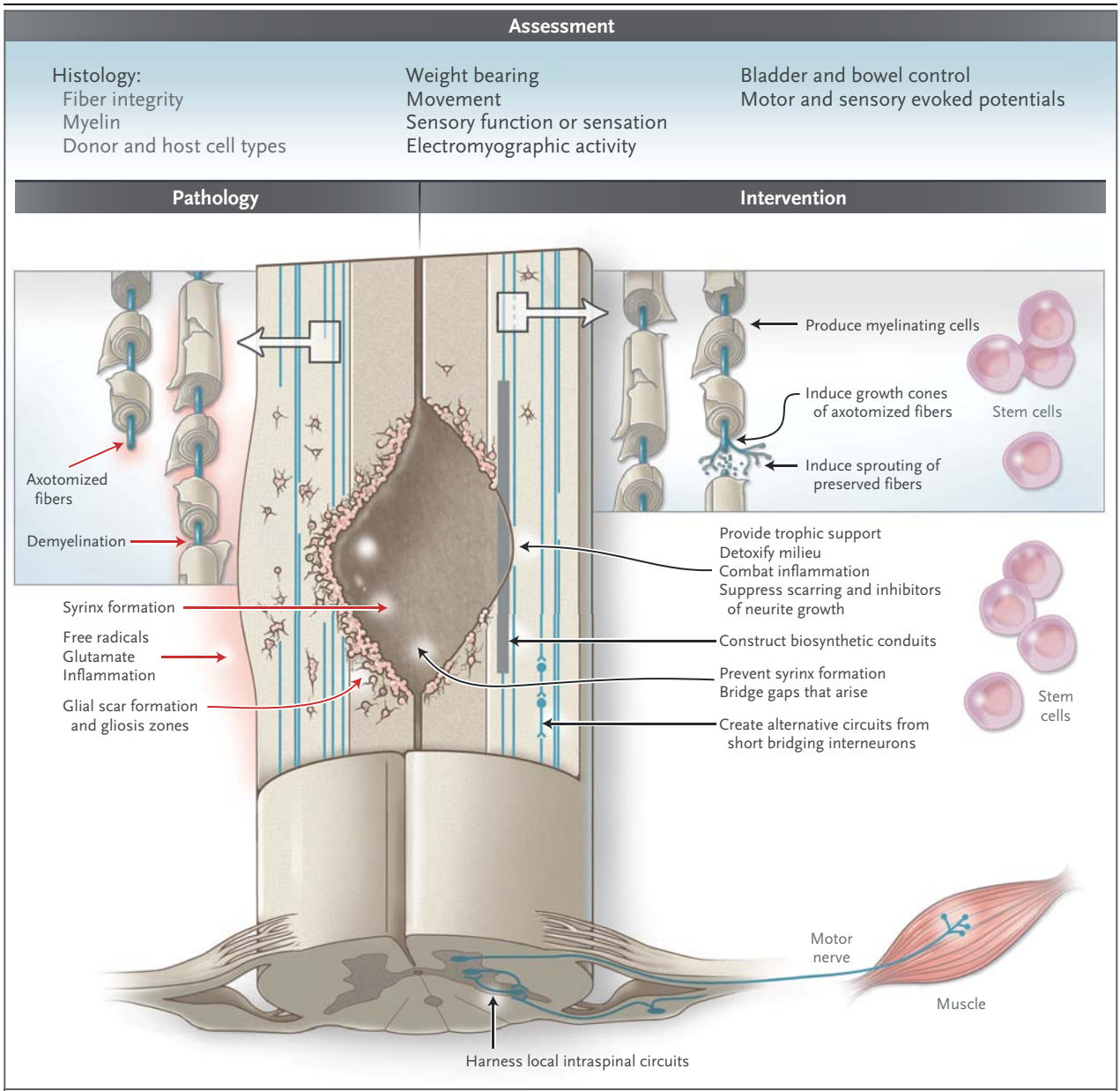

Figure 1. Approaches to Repairing Spinal Cord Injury.

The left side of the enlarged view of the spinal cord shows some of the multiple pathophysiological processes that unfold after acute injury. The right side of the cord illustrates some of the multiple ways in which implanted stem cells may have a favorable effect on these processes. Some strategies for assessing spinal function are also listed.

fusion of donor cells with host cells, leading to the mistaken identification of a host cell as having come from the graft.

In addition, the field is plagued by an incomplete knowledge of the relative contributions of the multiple pathological events that unfold after trauma and thus is poorly guided as to which processes should be combated in order to restore or preserve function. Although it is clear that the crux of spinal cord injury is the interruption of cortical involvement in spinal-mediated processes through ascending sensory and de-

Questions About Experimental Treatments for Spinal Cord Injury.

Were assessments of lesions, interventions, and other evaluations performed in a blinded fashion by multiple observers?

Were animals showing a rate of recovery that was too rapid for regeneration (or even rescue) or were lesions that were incorrectly staged eliminated from the data set?

Were observation periods carried out for at least 4 months after the intervention?

Were the longitudinal fibers of the cord traced both before and after a lesion to distinguish preexisting (unsevered) tracts versus recreated or reclaimed tracts?

Were the tracts or cells that were credited with recovery then removed experimentally to show that their elimination returned the animal to the pretreatment state? Was there plausible molecular, cellular, and histologic evidence of a sufficiently robust regenerative process?

Were measures of open-field behavior analyzed with appropriate statistical rigor and an appreciation for the pitfalls of that type of assessment?

Were approaches other than open-field testing used to evaluate spinal function?

Were improvements in cortically recorded motor and sensory evoked potentials documented?

Are the results reproducible?

If transplanted cells are required, can they be isolated, characterized, and safely scaled up within a timeframe that can produce an effect on a freshly injured human spinal cord?

scending motor connections, it is far more daunting to re-create circuitry than to preserve the intricate connections established during embryonic development. Interventions may be directed at providing trophic support or neutralizing toxins to prevent the death or impairment of neural tissue from secondary injury processes[3] (e.g., excessive extracellular glutamate, inflammation, free radicals, ischemia, and impaired axonal transport); redressing conduction deficits by protecting or regenerating myelin sheaths or inducing the growth cones of axotomized fibers; suppressing scarring and inhibitors to neurite growth; preventing the formation of syrinx or bridging gaps; circumventing the injury through the promotion of alternative routes to the muscles, including sprouting from preserved neural fibers, replacing long connections with multiple shorter ones created from interneurons, harnessing local circuits within the cord,[5] and constructing biosynthetic conduits[2]; and re-creating a supportive niche, including adequate vascularization (Fig. 1). Appealingly, the use of stem cells — in conjunction with other approaches — can mediate many of these therapeutic actions by virtue of the inherent biologic properties of such cells.[2,4]

Claims of functional advantage that has been gained by a given therapeutic intervention should be judged on the basis of a series of important questions (see box). There is a long route between concept and practice, along which these questions must be answered. Although the length of the route frustrates patients, clinicians, venture capitalists, and politicians, careful navigation of the steps will ultimately ensure both safety and meaningful, reproducible improvement. As to what constitutes improvement in a patient with spinal cord injury, the reacquisition of even one or two spinal segments of function can be life-changing. Finally, it must not be forgotten that most patients with spinal cord injury have been in a wheelchair for years. Interventions to treat chronic spinal cord injury, the "third rail" in neurorepair, are likely to be even more challenging. Indeed, interventions that seem promising for acute spinal cord injury tend to falter when applied, without modification, to the long-injured spinal cord.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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