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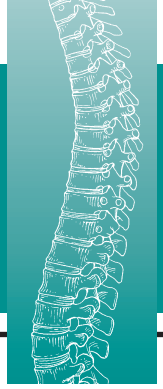

# Clinical Utility of Mesenchymal Stem Cells In the Treatment of Spinal Cord Injury

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**LEARNING OBJECTIVES:** After participating in this CME activity, the spine surgeon should be better able to:

1. Discuss the basics of stem cell biology and their mechanism of action in the treatment of spinal cord injuries.
2. Identify theoretical predictors of clinical outcomes after stem cell treatment in patients with spinal cord injury.
3. Assess the relative efficacy of stem cells in the treatment of spinal cord injury according to recent literature.

**Key Words:** Mesenchymal stem cells, Spinal cord injury

Mesenchymal stem cells (MSCs) have theoretical potential in the treatment of spinal cord injury (SCI) because of their known neuroregenerative properties. This article provides an overview of stem cell biology, an introduction to the clinical uses of MSCs, and a review of recent literature on stem cell treatment of SCI. Studies have demonstrated that numerous factors affect the efficacy of stem cell treatment of SCI, including baseline level of injury, spinal level of injury, and timing of surgical intervention. The literature with regard to stem cell treatment of SCI mainly comprises low-level evidence and is largely inconclusive with regard to efficacy. A careful review of recent literature suggests that more studies should be conducted to provide grades I and II levels of evidence and enable better determination of treatment efficacy.

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## BACKGROUND

Numerous interventions aimed at clinical improvement in neurologic deficits after SCI have, so far, demonstrated little efficacy. The extent of disability and patient suffering after SCI, as well as the high cost of care, continue to motivate research into effective interventions. Societal fear of paralysis associated with SCI and desire for hope of successful treatment results in a robust emotional and economic investment in the search for effective therapies, with associated bias present in SCI research.

In addition to psychosocial issues, the patient population is fragmented, with variable mechanism and degree of neurologic injury. Clinical challenges include nonuniform treatment protocols, difficulty with injury classification, and a low overall incidence of SCI at any one center. Research efforts in pharmacologic, biologic, and procedural interventions have made some strides, with large multicenter studies such as the National Acute Spinal Cord Injury Study (NASCIS), Austrian Spinal Cord Injury Study (ASCIS), and other prospective studies. This review discusses MSC therapies that conceptually address the fundamental problem of cellular injury and subsequent loss of motor and sensory function resulting from SCI.

## BASELINE INJURY VARIABILITY

Studies have been published describing the use of MSC therapies in both incomplete and complete SCI.[1-3] Most available studies also report the mechanism of injury as blunt trauma, penetrating trauma, or ischemic or iatrogenic SCI. Clear delineation of the degree of baseline injury and cause of injury is necessary to compare results of published trials; however, this information is not always readily available. The majority of published studies stratify patients according to the American Spinal Injury Association (ASIA) impairment scale (Table 1).[4] Studies in patients with incomplete injuries demonstrate greater variation in the degree of recovery and greater probability of a positive clinical outcome,[1] in contrast to patients with ASIA grade A injuries,

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**Table 1. American Spinal Injury Association (ASIA) Impairment Scale[5]**

| ASIA Grade | Clinical Manifestation Below Level of Injury |
|---|---|
| A (complete) | No preservation of sensory or motor function in the sacral segments (S4–S5) |
| B (incomplete) | Sensory but no motor function is preserved below the neurologic level and in the sacral segments S4–S5 |
| C (incomplete) | Motor function is preserved below the neurologic level, and more than half of the key muscles below the neurologic level have a muscle grade of less than 3 |
| D (incomplete) | Motor function is preserved below the neurologic level, and at least half of the key muscles below the neurologic level have a muscle grade of at least 3 or more |
| E (normal) | Sensory and motor functions are normal |

because of a variable baseline probability of spontaneous improvement.[6-8] Owing to this variable spontaneous recovery, injuries graded B and C on the ASIA scale are not typically reported in high-quality articles analyzing the efficacy of MSCs.[4]

In addition to classifying the severity of the lesion, spinal level of injury is reported in evaluating cellular therapy outcomes because the cervical and thoracic spinal cords have differing natural history with regard to spontaneous neurologic improvement after injury. Chernykh et al[9] and Saberi et al[10] demonstrated that greater neurologic improvement in both motor and sensory function is associated with injury to the cervical spinal cord compared with injury to the thoracic spinal cord. Other studies have demonstrated that injuries to the thoracic spinal cord display a more robust response to bone marrow therapy than injuries to the cervical spinal cord.[11]

## TIMING OF INTERVENTION

Delay between injury and intervention is a key factor in evaluating the efficacy of MSC treatment. The definition of early intervention varies among researchers, ranging from 14 days to 2.6 years.[11,12] Despite the variability of time to intervention in published research, an overwhelming majority of the literature proposes that early MSC intervention promotes greater neurologic improvement.[11-14,15,16] Bhanot[17] postulates that in chronic SCI, the chemokine signals are too weak to direct stem cells toward the site of injury.

This continuing education activity is intended for orthopaedic and neurologic surgeons and other physicians with an interest in spine surgery.

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Conceptually, early intervention can potentially ameliorate the injury before reactive processes of scar formation destroy the cytoskeletal framework.[17] Primary lesions are thought to prelude a secondary injury via a more extensive inflammatory reaction, potentially extending the zone of injury. Oligodendrocyte products NI250, MAG, and tenascin-R; oligodendrocyte precursor products NG2 DsD-1/phosphacan and versican;[18] lack of appropriate trophic support;[19,20] and proliferation of fibroblasts, astrocytes, microglia, and endothelial cells are thought to create a less salvageable tissue environment.[21] This provides a tissue barrier that impedes MSCs from accessing the lesion. This, in theory, can limit the effectiveness of MSC therapies.

The efficacy of MSC treatment alone has not been defined. MSCs may be part of a broader treatment plan that includes other developing interventions. In addition to cellular therapy, acute surgical intervention,[10-14,17-24] pharmacologic therapy,[25-28] and biologic interventions[29] are being evaluated for treatment of SCI.

## CLINICAL USE OF STEM CELLS

Adult hematopoietic stem cell transplantation has been integrated successfully into the practice of regenerative medicine. Unrelated donor hematopoietic cells have been used in the treatment of leukemia and lymphoma for the past 25 years.[30] Modern advances in cell culture technology, directed differentiation, and long-term propagation have improved the clinical results of cellular transplantation therapy.[31] In addition to leukemia and lymphoma, stem cells are used to treat patients after cancer therapy and patients with severe burns.[32]

## STEM CELL BIOLOGY

MSCs arise from the mesoderm of the epiblast (SCiS). Unlike embryonic stem cells, MSCs have limited capacity for regeneration and can give rise to muscle, vascular, and nerve tissue; hematopoietic cells; and osteocytes. Animal studies have demonstrated that MSCs are more likely to differentiate into neuronal cells when in the presence of other neuronal cells.[33] Despite the high capacity of MSCs for tissue repair,[34,35] the problem lies in directing the injected cells to the lesion site. MSCs are easily harvested from bone marrow, umbilical cord blood, peripheral blood, and body fat.[36] Harvesting protocols and isolating techniques for MSCs vary between laboratories. In several reports, the MSCs are aspirated from the posterior iliac crest and collected in containers with citrate phosphate dextrose ascorbic acid. Preparation, preservation, and injection techniques dramatically vary among studies,[4] which can lead to variation in outcomes. The MSCs are immunoprivileged and do not activate alloreactive T cells[37,38] because they do not display costimulatory molecules such as B7-1, B7-2, CD40, CD40L, or HLA II[39,40] on their cell surface.

Olfactory-ensheathing cells are a subtype of glial-restricted progenitor cells that also have potential in regenerative cellular therapy. They are harvested from the olfactory bulb and have demonstrated the ability to promote neural recovery and repair in animal models of SCI[41] by supporting continual axon process extension.[42-44] They are unique in that they have the ability to wrap around groups of nonmyelinated sensory axons from the peripheral nervous system to the central nervous system.[45-47]

## CURRENT LITERATURE

Systematic reviews of the literature on MSC treatment of SCI are available and emphasize the necessity for expanded clinical trials. In a recent review by Harrop et al,[4] no conclusion regarding efficacy was assessed on the basis of available literature. In the authors' evaluation, they excluded studies with fewer than 10 patients and studies in which more than 20% of the patients had non-SCI disorders or SCI that resulted from tumor or infection. The authors note that smaller studies have shed valuable insight on the potential therapeutic effect of MSCs in SCI treatment, briefly citing studies by Feron et al and Mackay-Sim et al.

Several subsequent studies are available in the literature on the topic of MSC therapy. Vawda and Fehlings[4] conducted a mini-review of the literature, stressing the importance of MSCs' ability to modulate inflammatory reactions and provide trophic support to the damaged axon.

The most recent clinical study to date was conducted by Dai and colleagues[49] who analyzed treatment of complete and chronic cervical SCI. Forty patients were randomized to either bone marrow-derived MSC transplantation or control. Abbreviated Injury Scale (AIS) and ASIA scores, residual urine volume, and neurophysiologic function were assessed at baseline and 6 months postintervention. Significant improvements in motor function, light touch, pin-prick sensation, and residual urine volume were documented in 10 of the patients who received cellular intervention. Furthermore, 9 patients had changes in their AIS scores. The control group did not show improvement in any variables of interest.[49]

Similarly, Jiang et al[50] treated 20 patients with SCI with autologous bone marrow-derived MSCs. As assessed by ASIA scale, improvement was noted 30 days postintervention in 15 patients in sensory, motor, and autonomic nerve function.

Karamouzian et al[51] conducted a nonrandomized clinical trial to determine the potential adverse effects or risks associated with MSC transplantation in subacute thoracic SCI. Lumbar puncture introduced the MSCs directly into the site of injury, and patients were followed up for 12 to 23 months after intervention. Although functional recovery was not statistically significant, no adverse effects or complications were reported in either the experimental or the control group.[51]

Park et al[52] evaluated the long-term results of MSC cellular therapy in patients who received 3 MSC injections at 4-week intervals. Motor power grade, MRI, and electrophysiological recordings were used as outcome measures. Six of 10 patients improved motor power of upper extremities; of these, 3 improved in activities of daily living. MRI demonstrated a decrease in cavity size and fiber-like low-signal intensity streaks.[52] A summary of the aforementioned studies is provided in Table 2.

## CONCLUSION

SCI remains a devastating diagnosis associated with grave disability, adverse effects, and poor patient outcomes. The costs

**Table 2. Literature on Stem Cell Treatment of Spinal Cord Injury**

| First Author (Year) | Sample Size (n) | Treatment | Follow-up Time | Reported Outcomes | Level of Evidence |
|---|---|---|---|---|---|
| Dai et al[49] | 40 | Bone marrow-derived MSCs | 6 mos | 50% of patients in the treated group experienced clinical improvement | 3 |
| Jiang et al[50] | 20* | Bone marrow-derived MSCs | 30 d | 75% of those treated experienced clinical improvement | 4 |
| Karamouzian et al[51] | 31 | Bone marrow-derived MSCs | 12–33 mos | 45.5% of those treated experienced substantial recovery, but this result may be statistically marginal | 3 |
| Park et al[52] | 10* | Bone marrow-derived MSCs | 6 mos | 30% of patients treated with MSCs exhibited significant improvement at follow-up | 4 |

MSCs, mesenchymal stem cells.

*Sample size does not include the control group.

of care for patients with these disabilities can be staggering. There are limited treatment options to restore spinal cord function after injury. MSCs have a theoretical role in the treatment of SCI. The studies available in the literature generally provide lower levels of evidence with bias, diverse patient populations, and varying degrees of injury limiting any definitive conclusions about efficacy. In addition, techniques for collection, source of collection, culture, and delivery have not been uniformly established, with the result that there is little consensus among studies with regard to methods of therapy. On the other hand, with a cumulatively large number of treatment reports, there have been limited reports of serious adverse effects related to the various treatment methods used in MSC therapy. Further research will build on treatment techniques and establishing efficacy through randomized prospective studies.

## REFERENCES


1. Kishk NA, Gabr H, Hamdy S, et al. Case control series of intrathecal autologous bone marrow mesenchymal stem cell therapy for chronic spinal cord injury. *Neurorehabil Neural Repair*. 2010; 24:702-708.
2. Huang H, Chen L, Wang H, et al. Safety of fetal olfactory ensheathing cell transplantation in patients with chronic spinal cord injury. A 38-month follow-up with MRI. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2006;20:439-443.
3. Mehta T, Feroz A, Thakkar U, et al. Subarachnoid placement of stem cells in neurological disorders. *Transplant Proc*. 2008;40:1145-1147.
4. Harrop J, Hashimoto R, Norvell D, et al. Evaluation of clinical experience using cell-based therapies in patients with spinal cord injury: a systematic review. *J Neurosurg Spine*. 2012;17(suppl 1):230-246.
5. Geffner LF, Santacruz P, Izurieta M, et al. Administration of autologous bone marrow stem cells into spinal cord injury patients via multiple routes is safe and improves their quality of life: comprehensive case series. *Cell Transplant*. 2008;17:1277-1293.
6. Burns AS, Lee BS, Ditunno JF, Jr, et al. Patient selection for clinical trials: the reliability of the early spinal cord injury examination. *J Neurotrauma*. 2003;20:477-482.
7. Kirshblum S, Millis S, McKinley W, et al. Late neurologic recovery after traumatic spinal cord injury. *Arch Phys Med Rehabil*. 2004;85:1811-1817.
8. Marino RJ, Ditunno JF, Jr, Donovan WH, et al. Neurologic recovery after traumatic spinal cord injury: data from the Model Spinal Cord Injury Systems. *Arch Phys Med Rehabil*. 1999;80:1391-1396.
9. Chernykh ER, Stupak VV, Muradov GM, et al. Application of autologous bone marrow stem cells in the therapy of spinal cord injury patients. *Bull Exp Biol Med*. 2007;143:543-547.
10. Saberi H, Firouzi M, Habibi Z, et al. Safety of intramedullary Schwann cell transplantation for postrehabilitation spinal cord injuries: 2-year follow-up of 33 cases. Clinical article. *J Neurosurg Spine*. 2011;15: 515-525.
11. Kumar AA, Kumar SR, Narayanan R, et al. Autologous bone marrow derived mononuclear cell therapy for spinal cord injury: a phase I/II clinical safety and primary efficacy data. *Exp Clin Transplant*. 2009;7:241-248.
12. Yoon SH, Shim YS, Park YH, et al. Complete spinal cord injury treatment using autologous bone marrow cell transplantation and bone marrow stimulation with granulocyte macrophage-colony stimulating factor: phase I/II clinical trial. *Stem Cells*. 2007;25:2066-2073.
13. Sykova E, Homola A, Mazanec R, et al. Autologous bone marrow transplantation in patients with subacute and chronic spinal cord injury. *Cell Transplant*. 2006;15:675-687.
14. Mehta T, Feroz A, Thakkar U, et al. Subarachnoid placement of stem cells in neurological disorders. *Transplant Proc*. 2008;40:1145-1147.
15. Fehlings MG, Vaccaro AR, Wilson JR, et al. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). *PLoS One*. 2012;7(2):e32037.
16. Chikuda H, Ohtsu H, Ogata T, et al. OSCIS investigators. Optimal treatment for spinal cord injury associated with cervical canal stenosis (OSCIS): a study protocol for a randomized controlled trial comparing early versus delayed surgery. *Trials*. 2013;14:245.
17. Bhanot Y, Rao S, Ghosh D, et al. Autologous mesenchymal stem cells in chronic spinal cord injury. *Br J Neurosurg*. 2011;25(4):516-522.
18. Fawcett JW, Asher RA. The glial scar and central nervous system repair. *Brain Res Bull*. 1999;49:377-391.
19. Skene JH. Axonal growth-associated proteins. *Ann Rev Neurosci*. 1989;12:127-156.
20. Widenfalk J, Lundstromer K, Jubran M, et al. Neurotrophic factors and receptors in the immature and adult spinal cord after mechanical injury or kainic acid. *J Neurosci*. 2001;21:3457-3475.
21. Fu-jiang C, Shi-qing F. Human umbilical cord mesenchymal stem cells and the treatment of spinal cord injury. *Chin Med J*. 2009;122(2):225-231.
22. Furlan JC, Noonan V, Cadotte DW, et al. Timing of decompressive surgery of spinal cord after traumatic spinal cord injury: an evidence-based examination of pre-clinical and clinical studies. *J Neurotrauma*. 2011;28(8):1371-1399.
23. Chikuda H, Ohtsu H, Ogata T, et al. OSCIS investigators. Optimal treatment for spinal cord injury associated with cervical canal stenosis (OSCIS): a study protocol for a randomized controlled trial comparing early versus delayed surgery. *Trials*. 2013;14:245.
24. van Middendorp JJ, Barbagallo G, Schuetz M, et al. Design and rationale of a prospective, observational European multicenter study on the efficacy of acute surgical decompression after traumatic spinal cord injury: the SCI-POEM study. *Spinal Cord*. 2012;50(9):686-694.
25. McKerracher L, Anderson KD. Analysis of recruitment and outcomes in the phase I/IIa Cethrin clinical trial for acute spinal cord injury. *J Neurotrauma*. 2013;30(21):1795-1804.
26. Forgione N, Fehlings MG. Rho-ROCK Inhibition in the treatment of spinal cord injury. *World Neurosurg*. 2014;82(3-4):e535-e539.

27. Grossman RG, Fehlings MG, Frankowski RF, et al. A prospective, multicenter, phase I matched-comparison group trial of safety, pharmacokinetics, and preliminary efficacy of riluzole in patients with traumatic spinal cord injury. *J Neurotrauma*. 2013;31(3):239-255.
28. Fehlings MG, Vawda R. Cellular treatments for spinal cord injury: the time is right for clinical trials. *Neurotherapeutics*. 2011;8:704-720.
29. Takahashi H, Yamazaki M, Okawa A, et al. Neuroprotective therapy using granulocyte colony-stimulating factor for acute spinal cord injury: a phase I/IIa clinical trial. *Eur Spine J*. 2012;21(12):2580-2587.
30. Karanes C, Nelson GO, Chitphakdithai P, et al. Twenty years of unrelated donor hematopoietic cell transplantation for adult recipients facilitated by the National Marrow Donor Program. *Biol Blood Marrow Transplant*. 2008;14(9 suppl):8-15.
31. Singec I, Jandial R, Crain A, et al. The leading edge of stem cell therapeutics. *Annu Rev Med*. 2007;58:313-328.
32. Blanpain C, Daley G, Hochedlinger K, et al. Stem cells assessed. *Nature*. 2012;13:471-476.
33. Abouelfetouh A, Kondoh T, Ehara K, et al. Morphological differentiation of bone marrow stromal cells into neuron-like cells after co-culture with hippocampal slice. *Brain Res*. 2004;1029:114-119.
34. Akiyama Y, Radtke C, Kocsis JD. Remyelination of the rat spinal cord by transplantation of identified bone marrow stromal cells. *J Neurosci*. 2002;22:6623-6630.
35. Lu D, Mahmood A, Wang L, et al. Adult bone marrow stromal cells administered intravenously to rats after traumatic brain injury migrate into brain and improve neurological outcome. *Neuroreport*. 2001;12:559-563.
36. Gómez Bello RM. Stem Cells in Spine. In: Bhave A, ed. *Emerging Techniques in Spine Surgery*. 1st ed. New Delhi, IN: Jaypee Brothers Medical Publishers Ltd; 2009:273-286.
37. Di Nicola M, Carlo-Stella C, Magni M, et al. Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. *Blood*. 2002;99:3838-3843.
38. Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. *Blood*. 2005;105:1815-1822.
39. Deans RJ, Moseley AB. Mesenchymal stem cells: biology and potential clinical uses. *Exp Hematol*. 2000;28:875-884.
40. Le Blanc K, Tammik C, Rosendahl K, et al. HLA expression and immunologic properties of differentiated and undifferentiated mesenchymal stem cells. *Exp Hematol*. 2003;31:890-896.
41. Ramón-Cueto A, Nieto-Sampedro M. Regeneration into the spinal cord of transected dorsal root axons is promoted by ensheathing glia transplants. *Exp Neurol*. 1994;127:232-244.
42. King-Robson J. Encouraging regeneration in the central nervous system: is there a role for olfactory ensheathing cells? *Neurosci Res*. 2011;69:263-275.
43. Mackay-Sim A, St John JA. Olfactory ensheathing cells from the nose: clinical application in human spinal cord injuries. *Exp Neurol*. 2011;229:174-180.
44. Ramón-Cueto A, Muñoz-Quiles C. Clinical application of adult olfactory bulb ensheathing glia for nervous system repair. *Exp Neurol*. 2011;229:181-194.
45. Doucette JR, Kiernan JA, Flumerfelt BA. The re-innervation of olfactory glomeruli following transection of primary olfactory axons in the central or peripheral nervous system. *J Anat*. 1983;137(Pt 1):1-19.
46. Doucette JR. The glial cells in the nerve fiber layer of the rat olfactory bulb. *Anat Rec*. 1984;210(2):385-391.
47. Raisman G. Specialized neuroglial arrangement may explain the capacity of vomeronasal axons to reinnervate central neurons. *Neuroscience*. 1985;14(1):237-254.
48. Vawda R, Fehlings MG. Mesenchymal cells in the treatment of spinal cord injury: current and future perspectives. *Curr Stem Cell Res Ther*. 2013;8(1):25-38.
49. Dai G, Liu X, Zhang Z, et al. Transplantation of autologous bone marrow mesenchymal stem cells in the treatment of complete and chronic cervical spinal cord injury. *Brain Res*. 2013;1533:73-79.
50. Jiang PC, Xiong WP, Wang G, et al. A clinical trial report of autologous bone marrow-derived mesenchymal stem cell transplantation in patients with spinal cord injury. *Exp Ther Med*. 2013;6(1):140-146.
51. Karamouzian S, Nematollahi-Mahani SN, Nakhaee N, et al. Clinical safety and primary efficacy of bone marrow mesenchymal cell transplantation in subacute spinal cord injured patients. *Clin Neurol Neurosurg*. 2012;114(7):935-939.
52. Park JH, Kim DY, Sung IY, et al. Long-term results of spinal cord injury therapy using mesenchymal stem cells derived from bone marrow in humans. *Neurosurgery*. 2012;70(5):1238-1247.

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**1.** Human MSCs arise from which one of the following germ layers?
- A. Endoderm
- B. Mesoderm of the epiblast
- C. Ectoderm of the epiblast
- D. Mesoderm of the hypoblast

**2.** MSCs can give rise to all of the following tissues and/or cells *except*
- A. osteocytes
- B. myocytes
- C. neurons
- D. hepatocytes

**3.** Olfactory-ensheathing cells have been discovered to promote neural recovery and repair primarily through which one of the following mechanisms?
- A. Differentiation into neuronal cells while in the presence of neurons
- B. Suppression of harmful inflammatory reaction that occurs with primary lesions
- C. Support of continual axon process extension and provision of trophic support
- D. Phagocytosis of axonal debris

**4.** According to the literature, clinical factors that may affect the efficacy of MSC treatment in patients with SCI include
- A. degree of baseline injury
- B. spinal level of injury
- C. timing of intervention
- D. all of the above

**5.** A patient sustained severe SCI (ASIA grade A) approximately 5 years previously. If the patient were to be treated now via administration of MSCs, what might you predict about neurologic recovery on the basis of recent clinical evidence?
- A. Little neurologic improvement because of relatively late intervention and injury severity
- B. Some improvement in neurologic function primarily because of the timing of intervention
- C. Great improvement in neurologic function because of the baseline level of injury
- D. Some improvement in neurologic function because of the potency of Cethrin treatment

**6.** Which one of the following does *not* contribute to tissue barrier formation that impedes MSC access to the lesion site?
- A. Inflammatory reaction that occurs with primary injury
- B. Disturbance in mitochondrial function
- C. Accumulation of oligodendrocyte products such as NI250, MAG, and tenascin-R
- D. Proliferation of fibroblasts, astrocytes, microglia, and endothelial cells

**7.** Which one of the following statements regarding olfactory-ensheathing cells is *true*?
- A. They are a type of microglia also known as olfactory Schwann cells.
- B. They are present only in the central nervous system.
- C. They are cells that help maintain the olfactory mucosa.
- D. They can wrap around groups of nonmyelinated sensory axons from the peripheral nervous system to the central nervous system.

**8.** A patient presents with SCI at the cervical level. Could a general outcome be predicted simply on the basis of level of injury?
- A. No. Recent findings are inconclusive with regard to which level of SCI may have greater potential for recovery. It is assumed that the level of injury may impact recovery because of the differing natural histories of the cervical and thoracic spines.
- B. Yes. Recent evidence indicates that patients with cervical SCI may have better outcomes than those with thoracic SCI.
- C. Yes. Recent findings support the notion that patients with thoracic injury experience greater improvement in motor and sensory function than those with cervical injury.
- D. No. There is no correlation between level of injury and outcomes after SCI.

**9.** According to evidence presented in recent literature, which one of the following patients could potentially have the *best* prognosis if treated with MSCs?
- A. Patient with an incomplete SCI who receives late treatment
- B. Patient with a complete SCI who receives early treatment
- C. Patient with an incomplete SCI who receives early treatment
- D. Patient with a complete SCI who receives late treatment

**10.** All of the following are accepted clinical uses for MSCs *except*
- A. treatment of leukemia and lymphoma
- B. restoration of skin after severe burns
- C. engraftment (replacement of blood cells) after cancer therapy
- D. treatment of SCI