Prospects for the treatment of spinal cord and peripheral nerve injury

After severe musculoskeletal trauma it is usually possible to reconstruct the skeletal elements of the injury, but any significant neurological damage may limit the functional outcome. For this reason injuries to the nervous system require careful management to maximise recovery. Despite new knowledge of such injuries and the potential for regeneration, there is need for further research.

Peripheral nerves are known to be able to regenerate; divided axons can grow distally and reconnect with target organs. This may occur spontaneously when the nerve is in continuity and there is no severe damage to its connective-tissue elements, but after division or severe damage, surgical repair is indicated. Research on the biology of peripheral nerve regeneration has led to the identification of neurotrophic factors which influence the process (Lundborg et al 1982; Lundborg 1988; Loughlin and Fallon 1992). It has not yet been possible to make use of these growth factors. Determining which factors are clinically important is very difficult and the method, timing, extent, site, and duration of delivery remain to be established. Experimental work suggests a potential role for these factors in nerve repair but has not yet derived enough firm data for clinical use.

Successful axonal regeneration requires the presence of these neurotrophic factors, largely produced by proliferating Schwann cells in the distal stump, and of a basement-membrane matrix containing certain macromolecules to which axons can attach. The beneficial effect of the distal segment of nerve helps to explain the widely accepted observation that early repair of a nerve increases the chance of satisfactory outcome (Birch 1992). To provide a suitable basement membrane across a gap in peripheral nerve freeze-thawed muscle grafts have been developed as an alternative to nerve grafts (Glasby et al 1986, 1990). These give a similar basement-membrane matrix, but their effectiveness is limited by the lack of Schwann cells and hence of any neurotrophic factors.

In contrast to the peripheral nervous system, axons in the central nervous system (CNS) do not show any functionally significant regeneration. There has been considerable research on the pathophysiology of CNS damage, particularly in the spinal cord. It is now known that axons in the CNS do have the ability to regenerate, but are inhibited by the microenvironment provided by non-neuronal cells (Felthings and Tator 1988). Two new approaches to spinal-cord repair have been reported. Schnell et al (1994) have used a combination of the growth factor, neurotrophin-3, and antibodies against inhibitory proteins; they showed enhanced regeneration of corticospinal axons in the spinal cord of the adult rat. Iwashita, Kawaguchi and Murata (1994) found some functional recovery after using fetal spinal cord to repair the spinal cord of neonatal rats. These results are encouraging but any clinical application is clearly a long way off.

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The spinal nerve roots at the interface between the central and peripheral nervous systems are of considerable interest. These have received little attention since useful regeneration of the dorsal roots would require fibres to grow into the spinal cord and make new connections with the CNS. This cannot occur, at least in adult animals (Cullheim et al 1989). It is known, however, that axons in the ventral roots, with their cell bodies in the anterior horn of the spinal cord, can regenerate distally in a similar manner to those in a peripheral nerve (Kilvington 1907; Tower 1943; Carlstedt et al 1986; Hems and Glasby 1992). There is also evidence that motor fibres can regenerate into ventral roots after avulsion (Tower 1943; Jamieson and Eames 1980), but these early experiments have not been followed up until recently. It has now been confirmed that motor fibres can regenerate out of the spinal cord into ventral roots after repair of an avulsion (Carlstedt et al 1986; Hems, Clutton and Glasby 1994).

The evidence for the establishment of functional connections after such a repair raises the possibility of surgical repair of cervical ventral roots damaged by traction injuries of the brachial plexus. It has also been shown that CNS fibres can regenerate into peripheral nerve grafts (David and Aguayo 1981). In both these circumstances the CNS-derived axons are exposed to the environment and growth factors of peripheral nerves. It therefore seems possible that peripheral nerve grafts could be used to repair some injuries of the cauda equina and distal spinal cord, and an approach to this has been reported in the Russian literature by Yumachev et al (1987). They found an improvement in motor function in about a quarter of the patients who had late reconstruction with nerve grafts. There is certainly a need for further evaluation of this type of work.

The possibilities for improvement of the surgical treatment of nerve injuries have potential, but there is a need to identify those patients who may benefit. Intervention is not indicated when there is a good chance of spontaneous recovery, but experience with peripheral nerves has shown a better outcome after early repair. This suggests that expectant management is not ideal. Help with these decisions may come from the new imaging technologies and also from electrodiagnosis. It should be possible to develop better methods for the early prediction of outcome from nerve injuries.

Major advances in the management of neurological injury are likely to come from increased knowledge of molecular and cell biology, but the possibilities available with present technology have not yet been fully exploited, particularly with respect to repair at the interface of the central and peripheral nervous systems.

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REFERENCES


