

Regenerating myelin

Forty years ago, Mary and the late Dick Bunge provided the first unequivocal evidence that spontaneous myelin repair occurred in the mammalian central nervous system (Bunge *et al.*, 1961). Their observations had implications for neurobiology and for clinical neuroscience of immense and lasting consequence. First, they gave the lie to conventional neuropathological wisdom, which held that the CNS could repair only by scar formation, a general rule classically attributed to Ramon y Cajal ('everything may die, nothing may regenerate': an unfortunate attribution given that Cajal was largely summarizing others' positions, perhaps the better to emphasize the radical nature of his own experimental observations and conclusions, which proposed rather that the CNS did indeed possess some capacity for regenerative repair, but that this process often proved abortive or ill-sustained).

The second consequence related to the treatment of patients with demyelinating disease. Spontaneous repair, however partial or limited, raised the possibility that therapeutic interventions designed to supplement remyelination might be feasible. Promoting an endogenous process appeared an eminently more realistic and achievable end than attempting to impose repair *ab initio*—and one to which the Bunges continued to make fundamental contributions over the next four decades. Press releases indicating that the first remyelinating cell implantation into the CNS of a patient with multiple sclerosis has now been performed (<http://www.myelin.org/pressrelease.htm>; July 22, 2001) make it timely to revisit this topic.

Obstacles and difficulties in developing reparative cell implantation treatments for multiple sclerosis and other diseases of myelin are neither trivial nor few in number, and have been widely articulated. Nevertheless, as the interesting and tantalizing paper from Mitome and colleagues in this issue of *Brain* (Mitome *et al.*, 2001) illustrates, they are being systematically addressed, and many have proved soluble. They may be summarized as *when?*, *where?*, *with what?* and *what then?*

Optimizing the timing of any such therapy remains problematic. The intuitive temptation is to treat early, not least to place remyelinating cells in a lesion before the formation of astrogliotic scarring, which seriously impedes their activity. But this is tempered by the unpredictable natural history of the disease—might not the lesion satisfactorily repair itself without intervention?—and by the

knowledge that inflammation will inevitably be continuing and could, indeed should, rapidly see off the precious and hitherto carefully nurtured implant. Accompanying the remyelinating intervention with a pulse of hefty immunotherapy might help; then again, recent findings that macrophage depletion diminishes remyelination (Kotter *et al.*, 2001), and other findings implying that inflammatory processes may be beneficial for repair, mitigate against this approach.

The issue of axon loss adds to the complexity of timing. There is growing consensus over two points: (i) that, while clearly occurring in acute lesions (Ferguson *et al.*, 1997; Trapp *et al.*, 1998), axon loss carries greater functional significance in chronic and accumulating disability (Scolding and Franklin, 1998; Bjartmar and Trapp, 2001); (ii) this chronic and progressive axonal fallout may well be a direct consequence of myelin and oligodendrocytes loss, rather than inflammatory damage (Bitsch *et al.*, 2000; Kornek *et al.*, 2000). Thus, axon loss offers a greater, not lesser, imperative to developing treatments designed to restore a normal glial-axonal environment in lesions (Scolding and Franklin, 1998).

Where should an implant be placed? Most experimental studies explore the effects of single-sited glial implantation, but in multiple sclerosis many demyelinated lesions were present. However, since the majority of plaques in most patients are clinically silent, repairing a very small number of lesions carefully chosen for their site, e.g. the spinal cord, optic nerve or brainstem, might yield a useful therapeutic dividend (Compston, 1996).

Oligocentric implantation of remyelinating cells offers little for patients with (diffuse) dysmyelinating disease, and it is this problem that the study described in this issue seeks to address. The authors used a genetically mutant form of mouse, the shiverer, in which the myelin basic protein gene harbours a sizeable deletion. They implanted cells into the lateral ventricle of post-natal mice and/or into the cisterna magna. Engrafted cells were found to migrate exclusively into and around white matter tracts, and to differentiate into astrocytes and oligodendrocytes but not neurones. Successful myelin sheath formation occurred in those areas re-populated by implanted oligodendrocytes. In novel studies, the authors injected cells into both lateral ventricles and into the cisterna magna at post-natal day 1, and then repeated this procedure on day 3. They report extensive partial remyelination in central white matter tracts throughout the brain 8–12 weeks

after implantation in 100% of transplanted mice. Whilst not specifically designed to assess behavioural improvements in the transplanted mice, none, nevertheless, were observed. This is the first time a double implantation has been reported, and the results plainly carry encouraging implications for the development of treatments for infants with inherited myelin disorders. Whether similar dissemination of cells by double-implantation can be achieved in the adult CNS was not tested, but seems unlikely.

To the 'with what?' question, there are several potential answers (Scolding and Franklin, 1997). The current authors implanted embryonic sub-ventricular-zone-derived neural stem cells after growth factor expansion, as others have done also with success. Autologous Schwann cells are being used in the two or three multiple sclerosis patients so far transplanted in the reported United States trial. They have the advantages of being readily accessible from the patient (via peripheral nerve biopsy), easily expanded and purified *in vitro* after which they remain capable of very successful remyelination provided they are first purified (Brierley *et al.*, 2001), and they are likely to be resistant to multiple sclerosis-related disease activity. Significant spontaneous Schwann cell remyelination is seen in the spinal cord of patients with multiple sclerosis. However, their ability to function within the astrocytic environment of most multiple sclerosis lesions does represent a serious obstacle. Olfactory glia may have advantages in this respect, but stem cells currently command most attention.

Stem cells from embryos cloned for the purpose (by cell nuclear transfer) from the patient needing an implant, as recently legalized uniquely in the UK, would, like autologous Schwann cells, avoid rejection—an advantage over stem cells derived from aborted fetuses or from embryos surplus to IVF (*in vitro* fertilization) treatment requirements. However, all sources of human embryonic stem cells carry serious ethical and practical difficulties, and the proposal that every patient requiring a transplant would first have to be cloned seems quite unrealistic. More recent work showing the presence of neural stem cells in the adult human brain, and also that adult bone-marrow-derived stem cells have neural and glial potential, may offer a potential solution. Importantly, direct implantation of bone marrow cells has now been shown to achieve successful remyelination in the rodent spinal cord (Sasaki *et al.*, 2001).

Finally, what then? Assessing the therapeutic and biological efficacy of the remyelinating treatment also requires attention. Improved clinical measures of function, disability and handicap tailored to relevant patient groups are appearing. Serial clinical electrophysiological means of monitoring conduction in the targeted pathway(s) need to be developed. Better MRI-based strategies are required to demonstrate new myelin formation after therapy.

Step by cautious step, most, but not all, forward, clinical

neuroscientists are leading the work started by the Bunges to therapeutic fruition, and are meeting Cajal's bequeathed challenge concerning the lack of successful CNS regeneration: '. . . it is for the science of the future to change this harsh decree'.

Neil Scolding
Frenchay Hospital,
University of Bristol,
Bristol, UK

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