Whilst few neuroscientists doubt that stem cell technology does indeed have enormous future potential, those with perhaps the most experience in neural transplantation note the ‘danger [of] the rush to apply stem cell or fetal cell therapies in patients’, citing epilepsy and stroke as diseases where a poverty of experimental justification has not prevented clinical experiments implanting embryonic cells – porcine or human teratocarcinoma – into patients (Bjorklund & Lindvall 2000). Regenerative cell implantation as an approach to treating Alzheimer’s disease is at present little more than experimental speculation.

Conversely, transplantation in Parkinson’s disease is considered a more respectable pursuit, for several reasons: a distinct subpopulation of cells degenerates; their striatal target is (relatively) discrete and accessible; and there are well-characterized models of the disease. Animal studies have long-illustrated benefits following implantation of embryonic dopaminergic neural cells into diseased basal ganglia. Following the serious hiccup of adrenal medullary cell implantation into Parkinson’s Disease patients, a now abandoned approach, significant progress has been made since the late 1980s. Many patients around the world have now received implants of fetal mesencephalic (not stem) cells, with evidence of functional survival of the implanted cells offered by PET studies and in a few cases by autopsy. Moderate improvement in motor performance is commonly reported, which some consider ‘remarkable … considering the complexity of the circuits … the lack of standards regarding the amount and handling of tissue to be transplanted, the placement (caudate or putamen, unilateral or bilateral), the criteria for the selection of patients and the duration of follow up’ (Fischbach & McKhann 2001). A placebo-controlled (by sham surgery) trial has now been reported (Freed et al 2001), with much negative publicity, but the consensus view remains that certain subgroups of Parkinson’s disease patients might benefit (perhaps particularly those under 60 years of age).

Quite how or why benefit occurs remains obscure. Such major surgery induces a pronounced and prolonged placebo effect (Freed et al 2001), but this is unlikely to explain the recorded clinical benefit lasting up to a decade, while reported correlations between clinical improvement and quantitative PET changes likewise defy this facetious explanation – though not all have found this relationship (Freed et al 2001). The more

EDITORIAL

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IT is a sobering thought that at present not a single neurodegenerative disorder can be reversed, none halted, and the evidence that any can even be slowed down is very slight. Useful interventions for more acute CNS injury – trauma, established stroke – are little better. This unimpressive therapeutic armoury has helped stimulate the search for more imaginative, regenerative treatments, generally based on cell implantation. The complexity of brain structure and function presents daunting challenges to this approach, but decades of animal studies have illustrated real potential, and early clinical studies show promise. The advent of embryonic stem cell technology has loudly focused public attention on regenerative medicine, but will stem cells imminently – or ever – unleash their ‘huge power to end suffering’ and ‘prove the Holy Grail in finding treatments for cancer, Parkinson’s disease, diabetes, osteoporosis, spinal cord injuries, Alzheimer’s disease, leukaemia and multiple sclerosis’?
recent sham-controlled surgery of course helps exclude the placebo effect. Implanted neurones do act as a source of dopamine, and may also establish local connections. Restoration of normal circuitry is unlikely, not least because the cells are implanted not at the site of cell loss, the (atrophic) nigra being too difficult a target by far, but in the more amenable striatum. Surprisingly, however, host cortex and striatum may acquire some measure of control over implanted neurones (Bjorklund & Lindvall 2000).

Multiple sclerosis shares some pertinent characteristics with Parkinson’s disease: a highly specific target cell population and a range of informative animal models. Perhaps surprisingly (considering how far clinical translation lags behind that of Parkinson’s disease), the justification and rationale for cell implantation in multiple sclerosis is in many ways more powerful (Blakemore et al 2000; Halfpenny et al 2002). First, the relative preservation of axons reduces the complexity of repair – to regenerating myelin sheaths, not reconstructing circuits. Second, spontaneous myelin repair, albeit partial, does occur in multiple sclerosis, so the challenge becomes that of promoting an endogenous process rather than imposing repair de novo. Third, animal studies prove that implantation of a variety of glial cells can not only remyelinate axons, but also restore conduction and function.

Serious obstacles remain (Halfpenny et al 2002). These include the timing of implantation, bearing in mind the reversibility of acute deficits, the irreversible axonal loss of chronic lesions, and the perhaps yet more worrying molecular changes in (preserved) demyelinated axons rendering them apparently quite repulsive to the ensheathing advances of remyelinating cells (Charles et al 2000). Second, the site of implantation is problematic in such a widely disseminated disease. Choosing single, eloquent lesions, accessible to surgeons and to post-implant functional and structural interrogation, is one approach to provide proof of principal (Compston 1996). The means of assessing the success (or reasons for failure) of an implant also remain obscure – there are no specific MRI parameters for confirming remyelination. Finally, the optimum cell type is not yet clear. Oligodendrocytes, Schwann cells, stem cells and olfactory cells all have their advocates. In the only clinical experiments so far publicised, autologous Schwann cells were implanted into non-symptomatic lesions, their activity to be assessed by later biopsy (www.myelin.org/schwann_cells.html).

Finally, to apply stem cell technologies to these clinical problems – or other disorders where implantation is already being explored, such as Huntington’s disease – does not necessarily require the use of human embryonic cells as recently legalised uniquely in the UK. All sources of human embryonic stem cells carry serious ethical and practical difficulties (Scolding 2001), and rejection would remain a problem unless each and every patient requiring a transplant were first cloned to create autologous cells (which seems unrealistic). It is now clear that adult bone marrow-derived stem cells are pluripotent, and their progeny includes neurones and myelinating glia. Methods for expanding these cells indefinitely are now reported, and such a source plainly could avoid rejection. Stromal or mesenchymal stem cells will (inadvertently) have been implanted into thousands of bone marrow transplant recipients, which as a long-standing practice offers a wealth of data concerning safety and techniques for handling tissue. Importantly, direct implantation of bone marrow cells has now been shown to achieve successful remyelination in the rodent spinal cord (Sasaki et al 2001).

REFERENCES