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Therapeutic strategies in multiple sclerosis. II. Long–term repair

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THE ROYAL SOCIETY

Therapeutic strategies in multiple sclerosis. II. Long-term repair

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Spontaneous myelin repair in multiple sclerosis (MS) provides a striking example of the brain's inherent capacity for sustained and stable regenerative tissue repair—but also clearly emphasizes the limitations of this capacity; remyelination ultimately fails widely in many patients, and disability and handicap accumulate. The observation of endogenous partial myelin repair has raised the possibility that therapeutic interventions designed to supplement or promote remyelination might have a useful and significant impact both in the short term, in restoring conduction, and in the long term, in safeguarding axons. Therapeutic remyelination interventions must involve manipulations to either the molecular or the cellular environment within lesions; both depend crucially on a detailed understanding of the biology of the repair process and of those glia implicated in spontaneous repair, or capable of contributing to exogenous repair.

Here we explore the biology of myelin repair in MS, examining the glia responsible for successful remyelination, oligodendrocytes and Schwann cells, their 'target' cells, neurons and the roles of astrocytes. Options for therapeutic remyelinating strategies are reviewed, including glial cell transplantation and treatment with growth factors or other soluble molecules. Clinical aspects of remyelination therapies are considered—which patients, which lesions, which stage of the disease, and how to monitor an intervention—and the remaining obstacles and hazards to these approaches are discussed.

Keywords: remyelination; human oligodendrocytes; oligodendrocyte precursor; myelin repair

1. INTRODUCTION

The characteristic pathological processes of inflammation and demyelination in multiple sclerosis (MS), described in detail in papers in this issue, in essence reflect a targeted immune process directed against the oligodendrocyte and its myelin sheath. While the morphology of lesions is clearly not uniform, and there are undoubtedly variations in the intensity of cell injury, in the mechanisms implicated in tissue damage, and perhaps in the precise target, a defining ultimate characteristic of many brain lesions in MS is oligodendrocyte death accompanied by myelin loss. The astrogliotic or sclerotic plaque, with relative axon preservation, is historically described as the response of the central nervous system (CNS) to this inflammatory tissue damage.

However, classical principles of general pathology delineate two fundamentally different ways in which tissue may repair following damage. The first is regenerative repair, with successful remodelling leading to the stable restoration of normal structure and function. The superficial layers of the skin and the liver exhibit an inherent capacity for regenerative repair. The second response to tissue damage is that of repair by scar formation, with fibrous tissue deposition safeguarding tissue integrity, but failing to restore specialized function.

Conventional neuropathological wisdom has it that the CNS repairs only by scar formation, a general rule classically attributed to Cajal and summarized in his immortal aphorism, 'everything may die, nothing may regenerate' (Cajal 1913). However, in describing loss of 'the founts of regeneration' in the CNS, Cajal was no more than summarizing others' positions—perhaps the better to emphasize the radical nature of his own proposals. Drawing on his extensive experimental observations, he suggested that the CNS did indeed possess some capacity for regenerative repair, but that this process often proved abortive or ill-sustained.

Interestingly, our evolving understanding and interpretation of the myelin pathology of MS shows this disorder can offer exemplary illustrations of both positions. Early pathological descriptions of disseminated sclerosis, defining the eponymous chronic sclerotic plaque, interpreted lesions as clear instances of repair by scar formation (Dawson 1916). The last two or three decades of neuropathological research in MS have, however, confirmed that this is not the only CNS tissue response to inflammatory demyelination. Spontaneous myelin repair was described in MS in 1965 by Perier & Gregoire, only a few years after the first demonstration of spontaneous CNS remyelination (Bunge *et al.* 1961). It was confirmed

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by contemporary pathologists (Lassmann *et al.* 1997; Prineas & Connell 1979; Raine & Traugott 1985), whose studies have indicated that the classically described 'shadow plaque' (Markschattenherde)—present in acute cases, comprising areas of pale-staining myelin either on the edge of a plaque, or in normal unaffected white matter, and originally felt to represent a young and active or incompletely demyelinated lesion (Dawson 1916)—in fact contains large numbers of uniformly thin myelin sheaths, implying successful repair of myelin across whole plaques—an attractive anatomical substrate for clinical recovery. Remyelination is now widely accepted as perhaps the most striking example of the brain's inherent capacity for sustained, stable regenerative tissue repair.

Nevertheless, spontaneous remyelination in MS is only partial; it has been estimated that 40% of plaques exhibit remyelination extending over more than 10% of the lesion area during ongoing inflammation (Prineas *et al.* 1993; Raine & Wu 1993); fewer chronic plaques show evidence of myelin repair (Ozawa *et al.* 1994). Much acute myelin damage is therefore not repaired, and clinical experience emphasizes that myelin repair ultimately fails widely in many patients as disability and handicap accumulate. Nevertheless, the observations that spontaneous myelin repair occurs in MS, and is initially successful and useful, but ultimately limited and very partial, have profound conceptual implications for considering treatment in MS. They raise the possibility that therapeutic interventions designed to supplement or promote remyelination might have a useful and significant impact both in the short term, in restoring conduction, and in the long term, in safeguarding axons. These pathological findings redefine the goal as the promotion of an endogenous process, rather than necessarily initiating repair *de novo*. Strategies for promoting remyelination in order to prevent, ameliorate or delay neurological impairment have attracted increasing interest recently (Compston 1996) as improved immunotherapies permit some control over the occurrence of repeated episodes of inflammation, especially since these treatments exert very little impact on the progression of disability (Rudick *et al.* 1997). The first trials of systemic therapy intended to promote remyelination in MS (both using intravenous immunoglobulin) have now been completed, albeit with negative results (Noseworthy *et al.* 1997), while centres with expertise in experimental glial biology and remyelination have declared that they will conduct clinical trials transplanting human cells into patients with de- or dysmyelinating disease, the first apparently to commence during 1999.

Therapeutic remyelination interventions must involve manipulations to either the molecular or the cellular environment within lesions (Scolding 1997). The former approach would aim to increase the provision or activity of factors positively influencing resident oligodendrocyte progenitor function, and/or to override endogenous barriers to spontaneous repair, while the latter would centre on artificially supplementing populations of remyelinating cells by glial transplantation. Self-evidently, both the development and implementation of such therapeutic strategies depend crucially on a detailed understanding of the biology of the repair process and of those glia implicated in spontaneous repair, or capable of contributing to exogenous repair.

2. THE CELL BIOLOGY OF MYELIN REPAIR IN MULTIPLE SCLEROSIS

(a) *Myelinating glia*

(i) *Oligodendrocytes*

Oligodendrocytes were first discovered only 80 years ago by Rio Hortega (1921); he also described their only function, the synthesis of myelin in the CNS. We now know that they develop from a progenitor cell whose properties have been much studied since culture techniques offered new opportunities for cell biological investigations. The progenitor was originally named an O-2A progenitor because of its ability *in vitro* to generate either oligodendrocytes or so-called 'type 2' astrocytes (Raff *et al.* 1983), although subsequent studies, while confirming the presence of this cell in the developing and the mature rodent CNS (ffrench Constant & Raff 1986), cast doubt on whether the astrocyte differentiation pathway is adopted during normal development (reviewed by Skoff 1996). It seems more likely that bipotentiality *in vivo* may rather be exhibited as a response to injury, not during normal development, and therefore represent glial plasticity, rather than lineage (Skoff 1996; Franklin & Blakemore 1995). The growth factors responsible for the proliferation, survival, differentiation and maturation of oligodendrocyte lineage cells have been minutely defined (Compston *et al.* 1997; Woodruff & Franklin 1997); few cell types have been so intensively studied.

In MS, it has not been clear which cell is responsible for spontaneous myelin repair. As mentioned in the others papers in this issue, there is significant pathological heterogeneity in MS, and some controversy concerning the fate of oligodendrocytes in acute lesions, but it is certainly the case that oligodendrocytes are absent from many types of lesion. Furthermore, experimental studies in the rodent indicate that mature oligodendrocytes in fact have a profoundly limited capacity for recapitulating their developmental activities and laying down new myelin sheaths to replace old (Warrington *et al.* 1993; Kierstead & Blakemore 1997). These experimental rodent studies rather indicate that the oligodendrocyte progenitor, a cell whose simple bipolar morphology may help to explain its marked migratory capacity, and which has the ability to proliferate in response to a variety of mitotic growth factors, is a much more efficient remyelinating cell, capable of substantial myelin repair (Carroll *et al.* 1990; Duncan 1996; Franklin & Blakemore 1997; Rosenbluth 1996).

However, until recently, few of the available data on the rodent oligodendrocyte lineage have been substantiated by direct investigation of human glia, the study of which is seriously hampered by difficult and limited access to human oligodendrocyte lineage cells, and by the very small numbers of progenitors present in normal tissue. No human oligodendrocyte precursor had been identified in adult CNS tissue until Armstrong *et al.* (1992) demonstrated a cell intermediate in phenotype between the proliferative (rodent O-2A) progenitor and a fully differentiated cell—a cell they termed the pre-oligodendrocyte. Later studies in Cambridge provided evidence that cells more closely equivalent to the proliferative rodent oligodendrocyte are present in the adult human brain, identifiable both in cell culture and *in situ*

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using wet-mount 'tissue print' preparations (Scolding *et al.* 1995, 1999). These cells have a morphology, immunophenotype, and bipotential capacity for differentiation *in vitro* similar to those of the rodent progenitor, but their proliferative response appears to differ; while both rodent and human oligodendrocyte progenitors proliferate when growing on astrocyte monolayers, thus far we (and others) have failed to induce proliferation of human progenitors by exposure to those mitogens known to trigger neonatal rodent progenitor mitosis, including platelet-derived growth factor (PDGF), basic fibroblast growth factor (FGF-2), and neurotrophin-3 (Armstrong *et al.* 1992; Prabhaker *et al.* 1995). More recent studies have allowed the identification of this cell in (fresh frozen) tissue, confirming its presence in normal adult white matter, and also demonstrating that acute and chronic lesions from patients dying with MS also contain small numbers of these immature glial progenitors (Scolding *et al.* 1998).

(ii) *Schwann cells*

Oligodendrocytes, however, are not the only glia capable of remyelinating CNS axons. It has long been recognized that inwardly migrating Schwann cells are responsible for a significant proportion of spontaneous myelin repair in MS. This is particularly true in the spinal cord (Feigin & Popoff 1966; Ludwin 1988; Itoyama *et al.* 1983, 1985), although the extent to which this occurs in the brain has not been exhaustively assessed. It has been assumed that these cells migrate into the CNS either from the dorsal root entry zones, or out of the nerve fascicles supplying small blood vessels in the parenchyme; we have some evidence that the latter may be more than sufficient (C. Behan and N. Scolding, unpublished observations).

Much is known from rodent studies of the behaviour and properties of Schwann cells, and of their interactions with other neural elements (see §2(b)(ii)) (Ludwin 1988; Jessen & Mirsky 1997; Mirsky & Jessen 1999; Bunge 1987; Duncan & Hoffman 1997; Reynolds & Woolf 1993), although (thus far) the biology of human Schwann cells has been less intensively explored; whether, as in the embryonic rodent (Jessen & Mirsky 1997), Schwann cell precursors are present in the human nervous system has not been ascertained. Importantly, however, there is good understanding of those growth factors which trigger Schwann cell proliferation—including that of human cells (Rutkowski *et al.* 1995; Van den Berg *et al.* 1995). Glial growth factors (neuregulins) are particularly important in this respect (Mirsky & Jessen 1999); they have also been implicated in the proliferation of adult rodent oligodendrocytes (Shi *et al.* 1998).

(b) *Other neural cells*

(i) *Astrocytes*

Proliferation and hypertrophy of astrocytes are classically described features of MS lesions; the chronic astrogliotic plaque (which additionally contains fibroblasts and meningeal cells from the surrounding vasculature) has been mentioned above. *In vitro* studies indicate that astrocytes inhibit oligodendrocyte myelination, and it is commonly accepted that the dense network of astroglial fibres within chronic plaques presents a profound barrier to the inward migration of oligodendrocyte precursors and to remyelination (Rosen *et al.* 1989).

Direct investigations of remyelination and of astrocyte biology indicate that the picture is (predictably) more complex than this. Acutely reactive astrocytes synthesize and release pro-migratory and proliferative growth factors for oligodendrocyte progenitors (Eddelston & Mucke 1993); astrocytosis accompanying various toxic or even inflammatory demyelinating models offers no discernible obstacle to remyelination (Raine & Traugott 1985; Ludwin 1980), and it has indeed been suggested that a vigorous astrocyte response is an important prerequisite of successful oligodendrocyte remyelination. There is clear experimental evidence that glial progenitors transplanted with astrocytes achieve more remyelination than progenitors alone (Franklin *et al.* 1991). It has recently been shown that astrocyte synthesis of the growth factors basic fibroblast growth factor (bFGF) and PDGF occurs in MS lesions (Malik *et al.* 1999); these act (at least with respect to rat cells) as oligodendrocyte progenitor mitogens and chemoattractant signals.

Very similar observations apply to Schwann cell remyelination. There is persuasive evidence that astrocytes present an insurmountable barrier to inward migration of (and therefore myelination by) Schwann cells (Harrison 1985; Franklin & Blakemore 1993), and it is suggested that Schwann cell remyelination in MS occurs only in an astrocyte-free environment (Itoyama *et al.* 1985; Yamamoto *et al.* 1991). However, others have found cohabiting astrocytes and Schwann cells in lesions which exhibit 'peripheral' myelin repair (Itoyama *et al.* 1983; Ogata & Feigin 1975), while in experimental studies, extensive Schwann cell migration and remyelination occurs unimpeded by large numbers of host or purified transplanted astrocytes (Duncan & Hoffman 1997; Franklin *et al.* 1992).

It is therefore increasingly apparent that astrocytes play highly influential but paradoxical roles in CNS remyelination. Whether different astrocyte populations are responsible for these conflicting roles, or whether the same cells exhibit markedly different activities as lesions develop remains wholly unexplored, but it is clear that an understanding of the processes of astrocyte reactivity and gliosis will have important implications for reconstructive therapies.

(ii) *Neurons*

While the primary insult in MS is directed against the oligodendrocyte–myelin unit, there is much evidence for additional loss of axons. This of course represents an important consideration—therapeutic attempts to repair myelin within a lesion which has no useful axons would not be fruitful.

However, axonal loss has long been recognized and studied in MS, and in important studies over 50 years ago was very carefully quantified; in these studies it was clear that major degrees of axon loss, 80% or more, were only apparent in a very small proportion of lesions (Greenfield & King 1936). Since in most axon tracts it is estimated that 80–85% of axons must be lost before serious permanent functional loss is induced (Sabel 1997), then it may well be that the degree of axon loss in many lesions in MS is not sufficient to account for extensive functional loss. The timing of axon loss remains a matter

for further exploration. Although it is now clear that some axon damage does occur in acute lesions (Ferguson *et al.* 1997; Trapp *et al.* 1998), functionally important loss of axons would of course be difficult to reconcile with the usual remitting course of most acute clinical events in MS.

The cause of axon loss in MS is also relevant. Inflammatory insults may play a significant role (Ferguson *et al.* 1997; Trapp *et al.* 1998), but another attractive possibility is that axons which have become demyelinated are no longer robust (Raine & Cross 1989); they are dependent upon their myelin sheaths, and degenerate without them (Griffiths *et al.* 1998). In lesions with persistent, demyelination-induced, conduction block, it is possible that axons may degenerate as a direct consequence of their enforced and prolonged electrical silence—as is known to happen throughout the CNS, including electrically inactive retinal ganglion cells (Lipton 1986), whose (myelinated) axons, of course, constitute the optic nerve. Oligodendrocytes secrete trophic factors important for neuronal survival (Meyer-Franke 1995), and their loss might also contribute directly to secondary axonal degeneration. Axon loss might thus be prevented if lesions were repopulated with oligodendrocytes.

Schwann cells also exhibit a complex and intricate relationship with neurons (Reynolds & Woolf 1993). Axons promote Schwann cell survival; they arrest migration, and provide proliferative signals for Schwann cells (Jessen & Mirsky 1997; Reynolds & Woolf 1993); Schwann cells are known to promote the survival of peripheral nerve axons and anterior horn cells (Reynolds & Woolf 1993; Scherer 1999), although the important question (in the current context) of whether they nurture central axons remains to be explored.

Far from undermining the rationale for remyelination therapy, these experimental observations may therefore provide a further imperative for pursuing therapeutic strategies that help to restore normal CNS cellular environments and promote remyelination; repopulating lesions and reinvesting axons with myelin sheaths may in fact help to preserve axons.

3. ENHANCING REMYELINATION

(a) *Soluble factors to encourage myelin repair*

(i) *Immunoglobulins*

Rodriguez and his colleagues have systematically explored the role of immunoglobulins in promoting remyelination. In experimental animals, whole antiserum, or purified IgG directed against spinal cord homogenate, promotes myelin repair (Rodriguez *et al.* 1987; Rodriguez & Lennon 1990). Investigations into the underlying mechanisms showed that polyclonal immunoglobulins against myelin basic protein achieved this effect (Rodriguez *et al.* 1996), as did a monoclonal antibody directed against a partially characterized oligodendrocyte surface antigen (Asakura *et al.* 1996*a*). The antibody belongs to the class of 'natural autoantibodies' (Asakura *et al.* 1996*b*)—naturally occurring polyreactive antibodies of uncertain function and significance (Coutinho *et al.* 1995). It has been speculated that antibody binding to oligodendrocytes might stimulate myelinating function, but direct observation suggests this is not the case (Stangel *et al.* 1999), and it appears more likely that immunological consequences of immunoglobulin treatment might encourage remyelination (Miller *et al.* 1995). While further experimental studies continue, two trials of intravenous immunoglobulin in MS patients with fixed disabilities (motor and visual) have been completed at the Mayo Clinic, the first specifically to explore remyelination and its promotion. Both, unfortunately, have now provisionally reported negative results (Noseworthy *et al.* 1997).

(ii) *Growth factors*

Growth factor treatment to promote remyelination has considerable superficial attractions, but it is increasingly clear that the complex and dynamic requirements for multiple and different factors during the sequential phases of oligodendrocyte progenitor proliferation, migration, differentiation and myelination (Woodruff & Franklin 1997), the clear but yet incompletely explored differences between the growth factor requirements of human oligodendrocyte progenitors compared with those of the rat (Scolding 1998), the potentially deleterious (oligodendrocytotoxic) effects of the exposure of post-mitotic oligodendrocytes to mitogenic growth factors (Muir & Compston 1996), and difficulties of direct, sustained and controlled peptide delivery all mitigate against this approach.

PDGF is a key growth factor for oligodendrocyte progenitors, and recent evidence indicates that PDGF antagonists inhibit remyelination (McKay *et al.* 1997). Perhaps the most exhaustively and systematically investigated candidate in this context is insulin-like growth factor (IGF). IGF promotes the synthesis of myelin-like membranes *in vitro*; transgenic mice overexpressing IGF-I show increased myelin synthesis, and IGF-I reduces clinical deficits and increases myelin basic protein synthesis in experimental allergic encephalomyelitis (Carson *et al.* 1993; McMorris *et al.* 1990; McMorris & McKinnon 1996; Yao *et al.* 1996). However, it is reported that the first trial of systemically delivered IGF-I in MS was unsuccessful and has very recently been terminated, and attention is increasingly turning towards glial cell transplantation as a more promising therapeutic approach.

(b) *Glial cell transplantation in demyelination*

(i) *Oligodendrocytes*

Laboratory studies devoted to exploring and providing an experimental infrastructure to clinical therapeutic remyelination have so far focused largely on studying the applied biology of the cell type mainly responsible for remyelination in MS, the oligodendrocyte and its lineage. There is an inherent logic in concentrating on these cells. They are the cells lost in MS; it is their normal function to myelinate the CNS, and spontaneous oligodendrocyte remyelination in MS bears witness to their substantial inherent capacity for remyelinating damaged areas of the brain (Lassmann *et al.* 1997; Prineas & Connell 1979). This reparative ability is clearly not unlimited, and studying their cell biology might illuminate the reasons for incomplete remyelination in MS.

Successful remyelination by transplanted oligodendroglia in a variety of experimental animals, developing and adult, demyelinated or dysmyelinated, has been confirmed by numerous laboratories (Duncan 1996; Rosenbluth 1996; Archer *et al.* 1997; Blakemore & Franklin

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1991; Franklin 1993). Improved conduction in the rat spinal cord following remyelination by transplanted oligodendrocytes has been shown (Utzschneider *et al.* 1994), and it is now clear that transplantation also improves functional impairment (Jeffery 1999).

The remyelinating capacity of glial cells is dependent upon a number of biological properties, but two which are particularly important are the ability of a transplanted cell to migrate, and its proliferative capacity (Franklin & Blakemore 1995, 1997; Warrington *et al.* 1993; Kierstead & Blakemore 1997; Rosenbluth *et al.* 1990). These qualifications clearly favour immature oligodendrocyte progenitors as that stage within the oligodendrocyte lineage most likely to succeed.

Procuring a transplantable human oligodendrocyte progenitor, however, presents certain practical and other difficulties. Investigations—limited, to date—of human CNS glia have consistently shown there to be fundamental biological differences from rodent cells; data from rodent studies cannot be directly extrapolated to human glia (Scolding 1998). Cells derived from fragments of abortion-derived foetal human CNS include glia similar in phenotype to rodent oligodendrocyte progenitors, but of dissimilar (and as yet undetermined) growth factor responsiveness (Aloisi *et al.* 1992; Kennedy & Fok Seang 1986; Satoh & Kim 1994). Implanted into the dysmyelinated rodent CNS, they can (even post-cryopreservation) synthesize myelin—although ultrastructural evidence of myelin compaction is awaited (Seilhean *et al.* 1996). However, developing a therapy which is wholly dependent for its implementation upon the induced termination of human foetal life, while in most Western countries (including the UK; Polkinghorne 1989) not illegal, is nevertheless open to as yet unresolved ethical criticism (Keown 1993; Scolding 1996)—and harvesting aborted foetuses on a therapeutic scale is unlikely ever to be practically possible or ethically or socially acceptable. Spontaneously aborted tissue has yielded cells capable of functionally useful neural repair after transplantation (into rodent Parkinson's and Huntington's models) (Kondoh *et al.* 1996; Pundt *et al.* 1995). The practical difficulties of this ethically more robust approach are greater than those applying to suction abortions, but epidemiological and technical evidence of large-scale applicability has been presented (Low *et al.* 1994).

Proliferative oligodendrocyte progenitors have also been demonstrated in the adult human brain (Scolding *et al.* 1995, 1999; Scolding 1998). They are present only in modest numbers, but may be responsible for spontaneous remyelination in MS (Scolding *et al.* 1998), the extent of which provides eloquent testament to their remyelinating capacity (Lassmann *et al.* 1997; Prineas & Connell 1979). Experimental studies of the myelinating potential of the adult human oligodendrocyte *in vitro*, using a syngeneic system employing a human neural cell line (Compston *et al.* 1997), and *in vivo*, transplanting into demyelinated lesions in the rodent spinal cord (Targett *et al.* 1996), disclosed disappointingly little myelin formation in either system. These observations may be linked to the very limited proliferative capacity of the human progenitor lineage (Armstrong *et al.* 1992; Scolding *et al.* 1995; Prabhakar *et al.* 1995), so that the identification of mitogens for adult human oligodendrocyte progenitors has become emphatically a priority—critically, the very substantial but controlled proliferation possible in rodent cells by exposure to (then withdrawal of) FGF-2 and PDGF (Wolswijk & Noble 1992), has not been achieved with adult human (or foetal) oligodendrocyte progenitors, and neither has it proved possible thus far to induce adult human progenitors to mimic their rodent counterparts in reverting to neonatal behaviour under appropriate growth factor stimulation (Wolswijk & Noble 1992). However, new insights into the proliferative signals for adult rodent oligodendrocytes (Shi *et al.* 1998) provide continued impetus for this search.

Ex vivo studies of MS lesions suggest that the growth factor environment of lesions is indeed important in determining the success or otherwise of remyelination (Malik 1999). The adult human oligodendrocyte progenitor is the only cell type with a proven capacity to effect large-scale myelin repair in the human brain, and it is premature to reject it as a potentially useful therapeutic tool.

(ii) *Stem cells*

Pluripotential and highly proliferative neural stem cells are present in the foetal and adult rodent nervous system (Gritti *et al.* 1996; Reynolds & Weiss 1996; Weiss *et al.* 1996; McKay 1997); such cells transplanted into normal adult brain may differentiate into oligodendrocytes (as well as astrocytes or neurons) (Weiss *et al.* 1996; Gage *et al.* 1995); thus far, we have failed to culture stem cells from adult human brain. Nevertheless, methods for generating oligodendrocytes from neural precursors from experimental animals, both developing and adult, are now described (Avellana-Adid *et al.* 1996; Zhang *et al.* 1998, 1999), and this approach may present valuable opportunities for generating myelinating glia for human transplantation.

(iii) *Immortalized cell lines*

The practical problems of obtaining sufficient numbers of human oligodendrocyte progenitors having been mentioned, are there other means of generating pharmaceutical quantities of human glia? Immortalized cell lines clearly offer one potential solution (Snyder 1994). Conditionally immortalized neonatal rodent oligodendrocyte progenitors repair myelin after transplantation (Barnett *et al.* 1993; Franklin *et al.* 1995; Groves *et al.* 1993; Tontsch *et al.* 1994; Trotter *et al.* 1991). We have recently generated a human immortalized oligodendrocyte progenitor line using the temperature-sensitive SV40 virus (Wilson *et al.* 1999). This line is distressingly potent in its proliferative behaviour, however, and despite the availability of increasingly elegant and apparently foolproof techniques to prevent malignant transformation (Martinez-Serrano & Bjorklund 1995), the potential hazards of mitotic escape and tumour formation present a serious hurdle to the therapeutic use of cell lines.

(iv) *Xenogeneic transplantation*

Successful remyelination by transplanted glia (probably dependent upon immunosuppression) is found across experimental animal species (Archer *et al.* 1997; Crang & Blakemore 1991; Rosenbluth *et al.* 1993). The development and availability of genetically engineered pigs designed to escape human rejection (Platt 1996; Edge *et al.* 1998)

presents a potentially abundant source of remyelinating cells for transplantation, although the fears of retroviral or other host infection, recently much publicized in the UK (Anonymous 1997), may delay clinical experimental trials; nevertheless, patients with Parkinson's disease have received porcine xenografts in the USA (Deacon *et al.* 1997).

(v) *Schwann cells*

In addition to the practical, ethical and cell biological (unresolved proliferative signals) difficulties concerning human oligodendrocyte transplantation, is the conceptual problem that the grafted cells would most likely be susceptible to continuing disease processes. Secure (and justifiable) transplantation ought therefore await more successful disease-arresting therapies; these, unfortunately, are not on the horizon. By contrast, transplanted Schwann cells and their myelin membranes should be resistant to MS processes. Inwardly migrating Schwann cells, as mentioned above, are responsible for a significant proportion of spontaneous myelin repair in MS, particularly in the spinal cord (Feigin & Popoff 1966; Ludwin 1988; Itoyama *et al.* 1983, 1985). Dissociated Schwann cells were in fact implanted into the rodent CNS before oligodendrocyte transplantation studies were carried out (Harrison 1980), and both endogenous (Felts & Smith 1992) and exogenous (transplanted) Schwann cells restore normal central conduction to the demyelinated rodent spinal cord (Honmou *et al.* 1996). Experimental methods for preparing proliferating cultures of adult human Schwann cells are well established (Rutkowski *et al.* 1995). Autotransplantation—harvesting Schwann cells from peripheral nerve biopsies of patients with MS for self-grafting—should avoid allogeneic graft rejection (and obviously with much less hazard than putative autotransplants of oligodendrocyte precursors via brain biopsy).

Schwann cells therefore represent an attractive candidate for human glial transplantation. Human Schwann cells can form compact myelin *in vitro*, although myelination appears less efficient than that observed in homotypic rat co-cultures (Morrissey *et al.* 1995*a*,*b*). Myelin synthesis after transplantation into a mouse mutant (Levi & Binge 1994) is also reported. We have begun to explore the behaviour of adult human Schwann cells in primary demyelinating lesions *in vivo* (C. Behan, W. Blakemore and N. Scolding, unpublished observations). Preliminary results suggest that, in addition to limited myelin formation, tumours may develop—a consistent hazard worryingly described when rodent Schwann cells immortalized by growth factor expansion are transplanted (Langford *et al.* 1988); this obviously presents an imposing barrier to the clinical application of Schwann cell transplants.

(vi) *Olfactory glia*

Olfactory ensheathing glia are found in the olfactory bulb, nerves and olfactory epithelium (Ramon & Avila 1998). They ensheath the axons emanating from olfactory epithelial neurons, and penetrate the olfactory bulb, providing a local environment which facilitates entry of these axons and allows them to navigate through the normally hostile CNS parenchyme to reach and synapse with their target neurons. Their ability to promote CNS axon regeneration, and their capacity for ensheathing and myelinating areas of experimentally demyelinated axons unimpeded by the astrocytic environment (Franklin *et al.* 1996) (in contrast with Schwann cells), has excited considerable interest in olfactory glia in the field of CNS repair (Ramon & Avila 1998).

4. THERAPEUTIC GLIAL CELL TRANSPLANTATION?

Studies in experimental animals have therefore provided detailed support for this therapeutic approach—as far as they are able. There are, however, serious limitations not only resulting from the concentration thus far on rodent glia, whose properties, as repeatedly mentioned above, cannot with impunity be extrapolated to human cells, but also to the animal models exploited. The majority of transplantation studies have been performed using either myelin-deficient animals, or chemically demyelinated areas, neither of which closely mimics the relapsing–remitting inflammatory environment of the MS lesion.

Most studies have also explored the effects of single-sited glial implantation. One often-rehearsed obstacle to transplantation in MS is the enormous number of demyelinated lesions which patients with MS steadily accumulate. Clearly to repair by direct injection of glial cells even a significant proportion of these lesions would be beyond the bounds of any current experimental surgical approach. However, it should be borne in mind that the majority of lesions in most patients are in fact clinically silent; conversely small numbers of lesions, particularly those in the spinal cord, optic nerve and brainstem, contribute disproportionately to clinical disability, so that repairing small numbers of lesions in these sites might yield a useful therapeutic dividend (Compston 1996; Scolding 1997).

Relatively little attention has thus far been directed towards patient management after remyelinating intervention. Early results in Parkinson's disease transplantation indicate better neural cell survival in immunosuppressed patients (Remy *et al.* 1995); the same is likely to apply to patients receiving glial cell allografts, and certainly xenografts. However, in MS, the primary disease-suppressing treatment might help prevent rejection. The anti-leucocyte humanized monoclonal antibody Campath-1H, currently under investigation for the treatment of both (solid organ) transplant rejection and MS (Hale & Waldmann 1996; Moreau *et al.* 1994) is particularly promising in this respect. Nevertheless, if cell implantation is adopted, there may be a risk, despite immunosuppression, of inciting new anti-oligodendrocyte immune reactions which not only destroy the graft, but also augment underlying disease processes; the patient becomes worse. Autografting might avoid this.

Assessing the therapeutic and biological efficacy of the remyelinating treatment also requires attention. In addition to well-validated clinical outcomes, measures of function, disability and handicap, tailored to relevant patient groups, and serial clinical electrophysiological means of monitoring conduction in the targeted pathway(s) need to be developed. Magnetic-resonance-imaging-based strategies will be important for localizing targeted lesions and investigating new myelin formation after therapy.

Some of these potential hazards of neural cell transplantation are not specific to MS, and yet the approach

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of attempting CNS repair by transplantation has, of course, already been adopted for experimental clinical trial work in Parkinson's and indeed Huntington's disease, with variable but very often promising results. Clearly there are still some very serious difficulties which must be overcome before this approach can safely and responsibly be adopted in patients with MS, and the unwisdom (and unkindness) of exaggerating the exciting potential while overlooking the uncertainties, hazards and unsolved obstacles of the approach cannot be stressed too often. It seems inevitable, however, that, within the foreseeable future, such strategies will be applied to patients; whether they will successfully translate from laboratory to clinical therapeutic neurology will subsequently emerge.

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES